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Asymmetric syntheses of 3,4-*syn*- and 3,4-*anti*-3-substituted-4-aminopiperidin-2-ones: application to the asymmetric synthesis of (+)-(3*S*,4*R*)-cisapride

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ABSTRACT

The conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to δ-(*N*-allylamino)-α,β-unsaturated esters, followed by N-deallylation and cyclisation of the resultant β,δ-diamino esters, gives the corresponding 4-aminopiperidin-2-ones as single diastereoisomers (>99:1 dr). Subsequent deprotonation with LiHMDS and functionalisation of the resultant lithium enolate gives 3,4-*anti*-3-substituted-4-aminopiperidin-2-ones in >99:1 dr. Alternatively, in situ oxidation of the intermediate lithium (*Z*)-β-amino enolates formed upon conjugate addition gives α-hydroxy-β,δ-diamino esters, which after N-deallylation and cyclisation gives the corresponding 3,4-*syn*-3-hydroxy-4-aminopiperidin-2-ones in >99:1 dr. The utility of this methodology was successfully demonstrated in a concise asymmetric synthesis of the gastroprokinetic agent (+)-(3*S*,4*R*)-cisapride {(+)-(3*S*,4*R*)-*N*(1)-[3′-(4″-fluorophenoxy)propyl]-3-methoxy-4-(2‴-methoxy-4‴-amino-5‴-chlorobenzamido)piperidine} in nine steps from commercially available starting materials with an overall yield of 19%.

1. Introduction

3-Substituted-4-aminopiperidines are important targets in organic synthesis as they are common building blocks for potential therapeutic agents.[1] For example, *trans*-3,4-disubstituted piperidine **1** has recently been found to have anti-fungal activity,[2] dihydroxylated piperidine **2** is a potential building block for HIV protease inhibitors,[3] and *cis*-3-methylfentanyl **3** and (3*R*,4*S*,2′*S*)-ohmefentanyl **4** are derivatives of the analgesic fentanyl,[4] with both having greatly increased potency compared to fentanyl itself (Fig. 1).

A key point to address in any synthetic route to enantiopure piperidines is the construction of the azacyclic skeleton in such a manner to enable the desired substitution pattern to be introduced stereoselectively. A large variety of different methods exist to achieve this goal, including the reduction of pyridines,[5] ring-closing metathesis,[6] aza-Diels-Alder reactions[7] and via intramolecular aza-Michael additions,[8] and the synthesis of piperidines has been extensively reviewed.[9]

Previous investigations from our laboratory have demonstrated that the conjugate addition of enantiopure secondary lithium amides (derived from α-methylbenzylamine) to α,β-unsaturated esters represents a general and efficient synthetic protocol for the synthesis of β-amino esters and their derivatives.[10] This methodology has found numerous applications, including the total syntheses of natural products,[11] molecular recognition phenomena[12] and resolution protocols,[13] and has been reviewed.[14] As part of our ongoing research programme in this area we became interested in the application of this methodology for the preparation of enantiopure azacyclic scaffolds. We have previously demonstrated the asymmetric

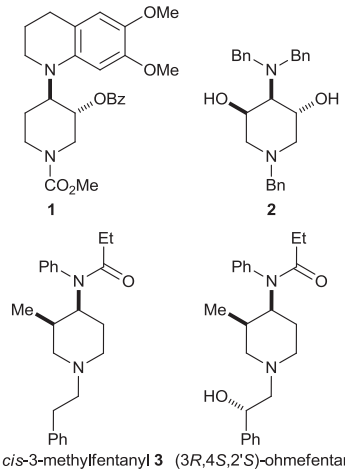

Fig. 1. Biologically active 3-substituted-4-aminopiperidines **1**–**4**.

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syntheses of 3,4-*anti*- and 3,4-*syn*-3-methoxy-4-aminopyrrolidines **11** and **18** via conjugate addition of lithium (*S*)-*N*-methyl-*N*-(α-methylbenzyl)amide (*S*)-**12** to methyl 4-(*N*-allyl-*N*-benzylamino) but-2-enoate **5**.[15,16] For the preparation of 3,4-*anti*-substituted pyrrolidine **11**, β-amino ester **6** was formed via conjugate addition of (*S*)-**12** to **5** followed by treatment with satd aq NH_4Cl, which gave **6** in 91% yield and >99:1 dr. N-Deallylation of **6** and subsequent cyclisation was achieved with $Pd(PPh_3)_4$ and *N*,*N*-dimethyl barbituric acid (DMBA) as an allyl cation scavenger, followed by treatment of the resultant β,γ-diamino ester with SiO_2 to induce cyclisation to give 4-aminopyrrolidin-2-one **7** in 89% yield and >99:1 dr. Deprotonation of **7** with lithium tetramethylpiperidide (LiTMP), followed by enolate oxidation upon treatment with (+)-camphorsulfonyloxaziridine [(+)-CSO] **13**[17] gave 3,4-*anti*-3-hydroxy-4-aminopyrrolidin-2-one **8** in 86% yield and >99:1 dr. Sequential O-methylation of **8**, reduction of **9** with $LiAlH_4$, and hydrogenolysis of **10** gave 3,4-*anti*-3-methoxy-4-(*N*-methylamino)pyrrolidine **11** (which was isolated as the corresponding TsOH salt) in 65% overall yield from **8**. The complementary synthesis of 3,4-*syn*-3-methoxy-4-aminopyrrolidine **18** proceeds via conjugate addition of (*S*)-**12** to **5** and in situ oxidation of the intermediate lithium (*Z*)-β-amino enolate with (+)-CSO **13** to give α-hydroxy-β-amino ester **14** in 92% yield and >99:1 dr. Sequential O-methylation of **14**, N-deallylation of **15**, and cyclisation gave pyrrolidin-2-one **16** in 41% yield over two steps. Reduction of **16** with $LiAlH_4$, and subsequent hydrogenolysis of **17** gave 3,4-*syn*-3-methoxy-4-(*N*-methylamino)pyrrolidine **18** (which was isolated as the corresponding HCl salt) in 84% yield from **16** (Scheme 1).

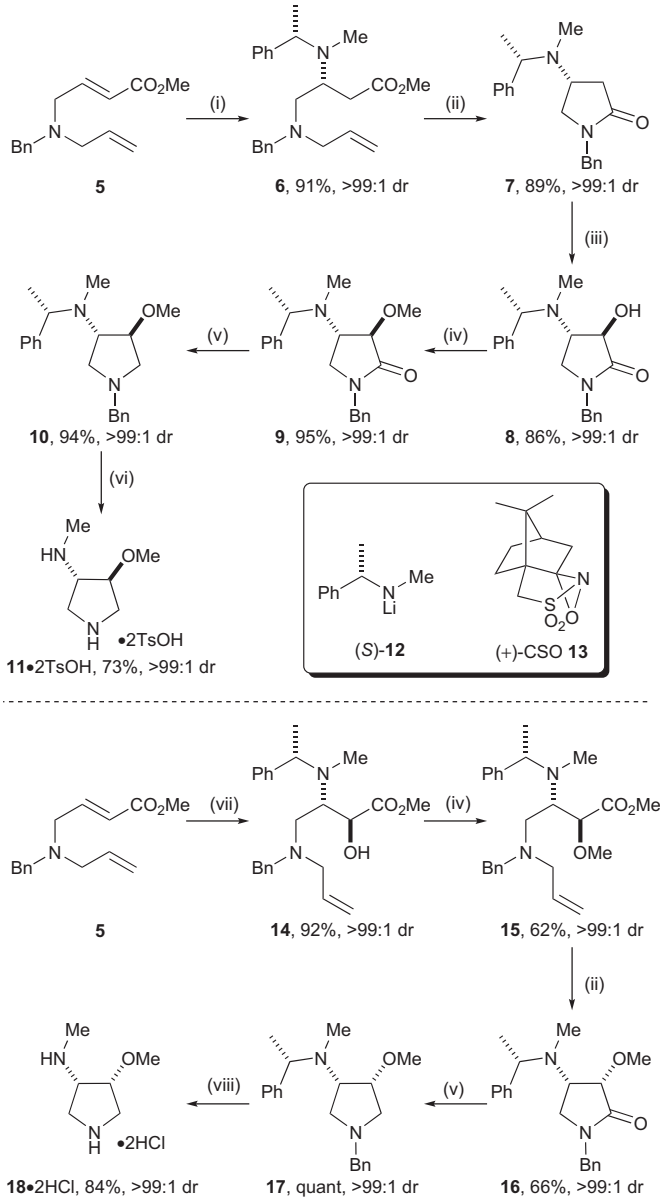
We envisaged that this approach could also be used for the synthesis of 3,4-*syn*- and 3,4-*anti*-3-substituted-4-aminopiperidines from δ-amino-α,β-unsaturated esters and delineate herein our full investigations within this area. Part of this work has been communicated previously.[18]

2. Results and discussion

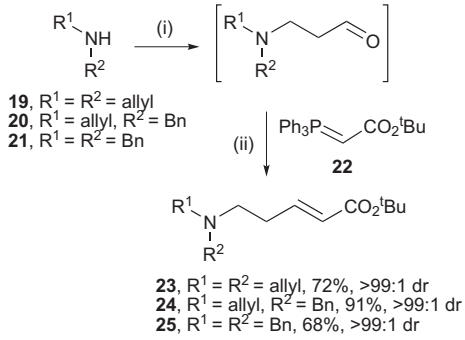
2.1. Asymmetric synthesis of 3-substituted-4-aminopiperidin-2-ones

A range of *N*,*N*-diprotected δ-amino-α,β-unsaturated esters **23**–**25** was required for the synthesis of 3-substituted-4-aminopiperidin-2-ones; the nature of the δ-amino protecting groups within **23**–**25** were chosen to provide orthogonal or complementary protection to the β-amino substituent that would be introduced upon conjugate addition of the lithium amide reagent. Using a one-pot procedure developed by Chesney and Markó for the synthesis of an analogous δ-amino-α,β-unsaturated ester,[19] conjugate addition of amines **19**–**21** to acrolein and Wittig olefination of the in situ formed β-amino aldehydes[20] with *tert*-butyl (triphenylphosphoranylidene)acetate **22** gave α,β-unsaturated esters **23**–**25** in 68–91% yield, and in >99:1 dr in each case (Scheme 2).[21] The (*E*)-configurations within **23**–**25** were confidently assigned from the diagnostic values of the olefinic coupling constants (**23**: $J_{2,3}$=15.7 Hz; **24**: $J_{2,3}$=15.7 Hz; **25**: $J_{2,3}$=15.5 Hz).

With δ-amino-α,β-unsaturated esters **23**–**25** in hand, the conjugate addition of lithium (*R*)-*N*-benzyl-(*N*-α-methylbenzyl)amide (*R*)-**32**[22] to **23**–**25** was undertaken and gave, after treatment of the reaction mixture with satd aq NH_4Cl, β-amino esters **26**–**28** as single diastereoisomers (>99:1 dr) in 52–88% isolated yield. The absolute (*R*,*R*)-configurations within β-amino esters **26**–**28** were initially assigned by reference to the transition state mnemonic developed by us to rationalise the diastereofacial selectivity of this class of lithium amide reagents upon conjugate addition.[23] The synthesis of 3,4-*syn*-3-substituted-4-aminopiperidin-2-ones from **23**–**25** required the stereoselective introduction of the C(3)-substituent prior to cyclisation, which could be performed via either a 'tandem' or a 'stepwise' conjugate addition/enolate functionalisation protocol.[17c] By analogy

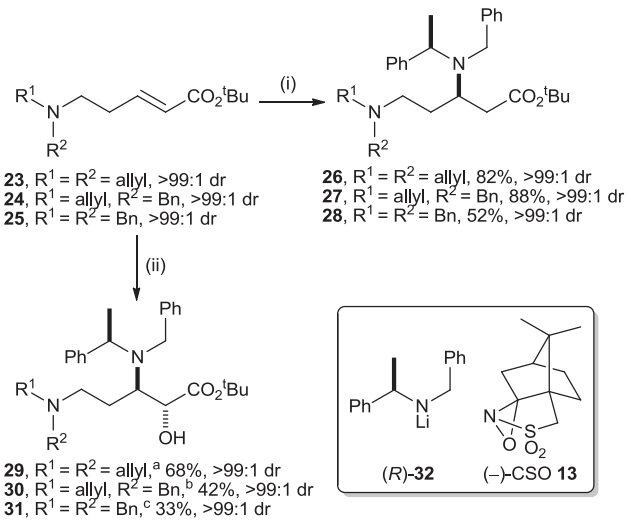


Scheme 1. Reagents and conditions: (i) lithium (*S*)-*N*-methyl-*N*-(α-methylbenzyl) amide (*S*)-**12**, THF, −78 °C, 2 h; (ii) $Pd(PPh_3)_4$, DMBA, CH_2Cl_2, rt, 16 h then SiO_2, CH_2Cl_2; (iii) LiTMP, THF, −78 °C, 2 h then (+)-CSO **13**, THF, −78 °C to rt, 16 h; (iv) NaH, THF, 0 °C, 1 h then MeI, 0 °C to rt, 12 h; (v) $LiAlH_4$, THF, reflux, 12 h; (vi) H_2 (5 atm), $Pd(OH)_2$/C, MeOH, 48 h then TsOH; (vii) lithium (*S*)-*N*-methyl-*N*-(α-methylbenzyl)amide (*S*)-**12**, THF, −78 °C, 2 h then (+)-CSO **13**, −78 °C to rt, 12 h; (viii) H_2 (5 atm), $Pd(OH)_2$/C, MeOH, 48 h then HCl.



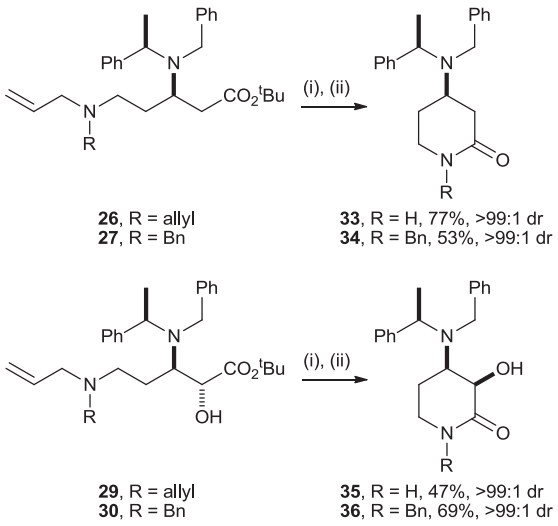
Scheme 2. Reagents and conditions: (i) acrolein, DBU, THF, −15 °C, 40 min; (ii) $Ph_3P{=}CHCO_2{}^tBu$ **22**, −15 °C to rt, 16 h.

to our synthesis of 3,4-*syn*-substituted pyrrolidine **18**, the 'tandem' lithium amide conjugate addition of (*R*)-**32** to **23**, and subsequent in situ oxidation of the intermediate lithium (*Z*)-β-amino enolate[24] with (−)-CSO **13**, was attempted first. Conjugate addition of (*R*)-**32** to **23** followed by treatment with (−)-CSO **13** gave **29** in 68% isolated yield and >99:1 dr. These conditions were then successfully applied to substrates **24** and **25** to give **30** and **31** in 42 and 33% yield, respectively, and >99:1 dr in both cases (Scheme 3).[25] The absolute (*R*,*R*,*R*)-configurations within **29**–**31** were assigned by analogy to the well established stereochemical outcome of this *anti*-amino-hydroxylation protocol.[17a,c,26]



Scheme 3. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl) amide (*R*)-**32**, THF, −78 °C, 2 h then NH_4Cl (satd aq); (ii) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**32**, THF, −78 °C, 2 h then (−)-CSO **13**, −78 °C to rt, 16 h. [a**26** was also isolated in 7% yield; b**27** was also isolated in 36% yield; c**28** was also isolated in 47% yield].

The attempted formation of α-alkyl-β-amino esters via 'tandem' conjugate addition of (*R*)-**32** to **23**–**25** and in situ alkylation of the intermediate lithium (*Z*)-β-amino enolates[24] with either MeI or *tert*-butyl bromoacetate (using our previously reported protocol[24c]) was not successful, as the intermediate lithium (*Z*)-β-amino enolates proved inert to alkylation giving complex mixtures of products within which only **26**–**28** could be identified. A 'stepwise' protocol was therefore investigated whereby deprotonation of **26**–**28** with LDA was followed by addition of either MeI or *tert*-butyl bromoacetate. However, the intermediate lithium (*E*)-β-amino enolates[24] derived from β,δ-diamino esters **26**–**28** also proved inert to alkylation under these conditions. Our synthetic endeavours therefore focussed upon the N-deprotection and cyclisation of β-amino esters **26**–**31**. Unfortunately, attempted hydrogenolysis of δ-(*N*,*N*-dibenzylamino)-β-amino esters **28** and **31** in the presence of Pearlman's catalyst [$Pd(OH)_2$/C] gave poor mass return. N-Deallylation of β-amino esters **26** and **27**, however, upon treatment with $Pd(PPh_3)_4$ (0.01 equiv per allyl group) and DMBA (3.0 equiv per allyl group),[15] was successful although attempts to isolate the intermediate amines gave poor mass return. The crude reaction mixture obtained from deallylation of **26** was therefore dissolved in toluene and the resultant solution was treated with $PhCO_2H$ (0.1 equiv) and heated at 80 °C for 16 h, which gave 4-aminopiperidin-2-one **33** in 77% yield (over two steps) and >99:1 dr. This procedure was subsequently applied to **27**, **29** and **30**, using either 0.05 or 0.1 equiv of $PhCO_2H$, to give the corresponding 4-aminopiperidin-2-ones **34**–**36** as single diastereoisomers (>99:1 dr) in 47–69% isolated yield (Scheme 4). The relative configuration within **36** was unambiguously established by single crystal X-ray diffraction analysis, with the absolute (*R*,*R*,*R*)-configuration within **36** being assigned relative to the known configuration of the (*R*)-α-methylbenzyl stereogenic centre (Fig. 2).[27] This analysis also allowed the assigned absolute (*R*,*R*,*R*)-configuration within α-hydroxy-β-amino ester **30** and the absolute (*R*,*R*)-configurations within **27** and **34** to be unambiguously confirmed. The absolute (*R*,*R*)-configurations within **26** and **33**, and the absolute (*R*,*R*,*R*)-configurations within **29** and **35** were therefore assigned by analogy.



Scheme 4. Reagents and conditions: (i) $Pd(PPh_3)_4$, DMBA, CH_2Cl_2, 35 °C, 3 h; (ii) $PhCO_2H$, toluene, 80 °C, 16 h.

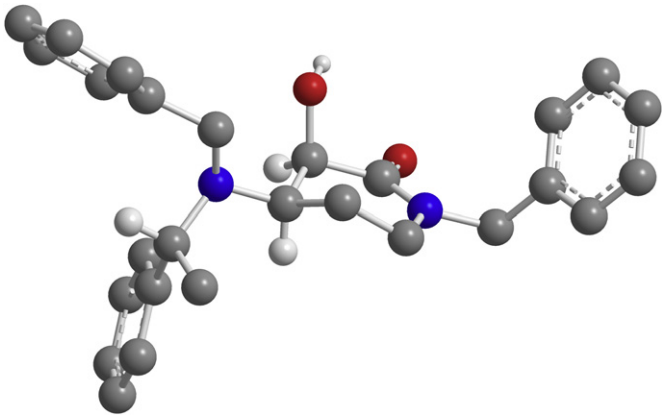
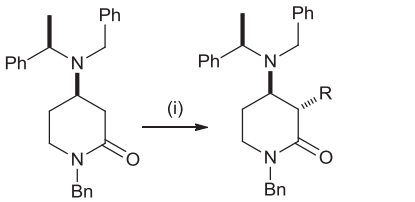


Fig. 2. Chem 3D representation of the single crystal X-ray diffraction structure of **36** (selected H atoms are omitted for clarity).

It was anticipated that alkylation of enolates derived from 4-aminopiperidin-2-one **34** would give predominantly 3,4-*anti*-3-alkyl-4-aminopiperidin-2-ones as a result of alkylation on the face opposite the bulky C(4)-*N*-benzyl-*N*-(α-methylbenzyl)amino substituent. A variety of strong bases have previously been used in the alkylation of piperidin-2-ones, including ^{t}BuLi,[28] LiTMP[15] and LDA.[29] However, treatment of 4-aminopiperidin-2-one **34** with either LiTMP (1.5 equiv), LDA (1.5 equiv), or KHMDS (2.0 equiv), followed by treatment of the resultant enolate with MeI (3.0 equiv) gave returned starting material exclusively. The use of either NaHMDS (2.0 equiv) or LiHMDS (1.5 equiv) as the base, however, gave 3,4-*anti*-3-methyl-4-aminopiperidin-2-one **37** in >99:1 dr, although the reaction conversions were very low (10 and 26% conversion, respectively). Increasing the equivalents of LiHMDS was found to significantly increase the reaction conversion and under optimised conditions the use of 3.0 equiv of LiHMDS was found to give quantitative conversion to **37** (>99:1 dr), which was

isolated in 67% yield after chromatographic purification (Scheme 5). No evidence of dialkylation was noted in the ^{1}H NMR spectrum of the crude reaction mixture. The relative configuration within **37** was unambiguously assigned by single crystal X-ray diffraction analysis, with the absolute (3*S*,4*R*,α*R*)-configuration within **37** assigned from the known configuration of the (*R*)-α-methylbenzyl stereogenic centre (Fig. 3).[27] This optimised procedure was also applied to the alkylation of **34** with *tert*-butyl bromoacetate, although only 20% conversion to **38** (80:20 dr) was noted in this case; after purification **38** was isolated in 12% yield and >99:1 dr. The configuration at C(3) within **38** was assigned by analogy to that unambiguously established for **37** upon alkylation with MeI.



Scheme 5. Reagents and conditions: (i) LiHMDS, −78 °C, 1 h, then MeI or $BrCH_2CO_2{}^tBu$, THF, −78 °C to rt, 16 h.

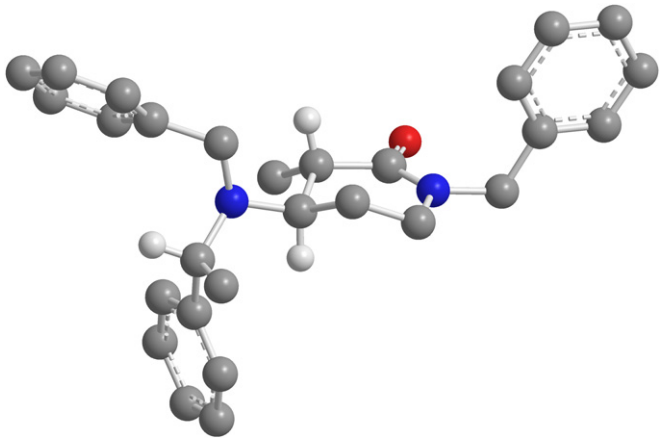
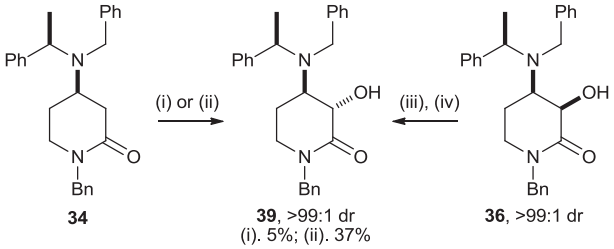


Fig. 3. Chem 3D representation of the single crystal X-ray diffraction structure of **37** (selected H atoms are omitted for clarity).

The corresponding 3,4-*anti*-3-hydroxy-4-aminopiperidin-2-one **39** was produced upon treatment of **34** with LiHMDS (3.0 equiv), followed by oxidation of the intermediate lithium enolate with either (+)- or (−)-CSO **13**, which gave 15 and 47% conversion to **39**,[30] which was isolated as a single diastereoisomer (>99:1 dr) in 5 and 37% yield, respectively (Scheme 6). The relative 3,4-*anti*-configuration within **39** was initially assigned by analogy to the stereochemical outcome of enolate alkylation. The diagnostic ^{1}H NMR ^3J coupling constants observed between the C(3)*H* and C(4)*H* protons, however, were supportive of this assignment (for 3,4-*syn*-3-substituted-4-aminopiperidin-2-ones **35** and **36**, $^3J_{3,4}$=6.0–6.3 Hz; for 3,4-*anti*-3-substituted-4-aminopiperidin-2-ones **37**–**39**, $^3J_{3,4}$=10.1–11.0 Hz). Furthermore, an authentic sample of 3,4-*anti*-**39** was prepared via Mitsunobu reaction of 3,4-*syn*-**36** upon treatment with PPh_3, DEAD and *p*-nitrobenzoic acid, followed by transesterification of the resultant *p*-nitrobenzoate ester. The sample so produced displayed identical spectroscopic data to the sample of 3,4-*anti*-**39** which was prepared by oxidation of the enolate derived from **34** (Scheme 6).



Scheme 6. Reagents and conditions: (i) LiHMDS, THF, −78 °C, 1 h then (+)-CSO **13**, −78 °C to rt, 16 h; (ii) LiHMDS, THF, −78 °C, 1 h then (−)-CSO **13**, −78 °C to rt, 16 h; (iii) PPh_3, DEAD, *p*-nitrobenzoic acid, THF, 0 °C, 6 h; (iv) K_2CO_3, MeOH, rt, 16 h.

Although the alkylation/enolate oxidation of these substrates proved to be somewhat troublesome, this strategy readily provided access to both 3,4-*syn*- and 3,4-*anti*-3-hydroxy-4-aminopiperidin-2-ones **36** and **39** in >99:1 dr. We therefore sought to demonstrate the utility of this protocol in the asymmetric synthesis of a 3-substituted-4-aminopiperidine, and selected (+)-(3*S*,4*R*)-cisapride as a suitable target.

2.2. Asymmetric synthesis of (+)-(3*S*,4*R*)-cisapride

(±)-(*RS*,*SR*)-Cisapride {(±)-(*RS*,*SR*)-*N*(1)-[3′-(4″-fluorophenoxy)-propyl]-3-methoxy-4-(2‴-methoxy-4‴-amino-5‴-chlorobenzamido)-piperidine} **40** is a gastroprokinetic agent[31] that was developed by Janssen Pharmaceutica in the 1980s[32] (Fig. 4). The racemate was marketed (from 1993 onwards) under the trade name Propulsid® as a treatment for gastroesophageal reflux disease,[33] although it has also been used successfully in the treatment of other gastrointestinal diseases such as chronic bowel constipation and irritable bowel syndrome.[34] However, the adverse gastrointestinal (e.g., abdominal pain and diarrhoea) and cardiovascular effects associated with taking this medication can be severe.[35] Between 1993 and 1999 there were 341 cases of cardiac dysrhythmia attributed to the use of Propulsid®, as well as 80 reported deaths, which ultimately led to the voluntary withdrawal of the drug from market in the USA in 2000, pending further research.[36] It has been reported that administration of the (+)-(3*S*,4*R*)-eutomer substantially reduces the adverse effects associated with the racemate,[37] and the biological screening of compounds related to cisapride **40** is still an active area of research.[38] As such, there is continued interest in the development of methods to enable the efficient syntheses of analogues of cisapride **40**.

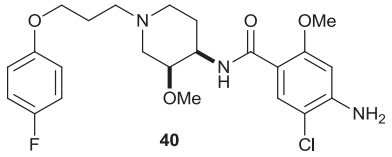
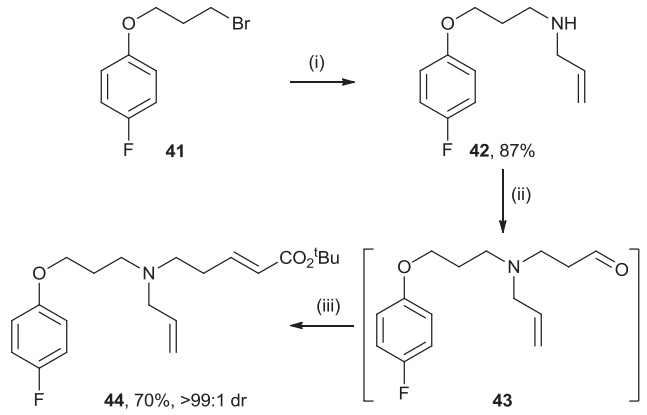


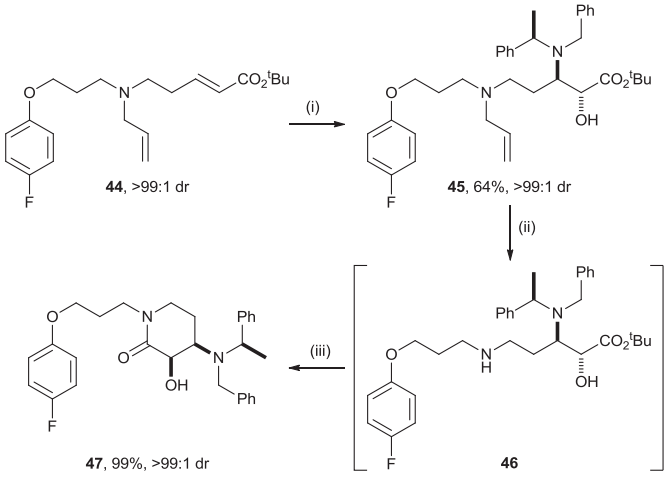
Fig. 4. Structure of (+)-(3*S*,4*R*)-cisapride **40**.

It was envisaged that the asymmetric synthesis of (+)-(3*S*,4*R*)-cisapride **40**[39,40] could be achieved from the corresponding 3-hydroxy-4-aminopiperidin-2-one, which in turn could be derived from *N*-[3-(4′-fluorophenoxy)propyl]-*N*-allylamine **42**. Secondary amine **42** was therefore produced by treatment of commercially available 1-(4′-fluorophenoxy)-3-bromopropane **41** with allylamine, which gave **42** in 87% yield.[41] Subsequent conversion of **42** into α,β-unsaturated ester **44** was achieved (following the procedure of Chesney and Markó)[19] by conjugate addition of **42** to acrolein at −15 °C to give β-amino aldehyde **43** that was trapped by in situ Wittig reaction with *tert*-butyl (triphenylphosphoranylidene)acetate **22** to give a 77:23 mixture of (*E*) and (*Z*) geometric isomers. Purification gave diastereoisomerically pure (*E*)-**44** ($J_{2,3}$=16.2 Hz) in 70% yield (Scheme 7).



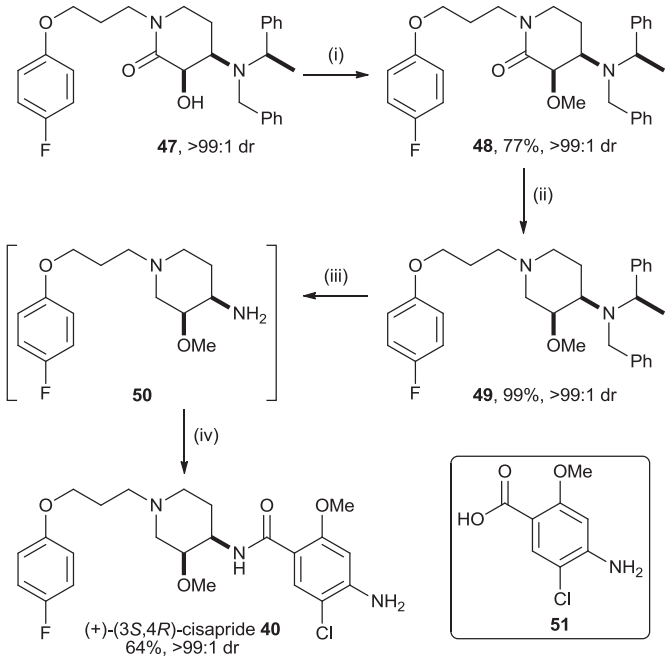
Scheme 7. Reagents and conditions: (i) allylamine, K_2CO_3, NaI, THF, 45 °C, 16 h; (ii) acrolein, DBU, THF, −15 °C, 40 min; (iii) $Ph_3P{=}CHCO_2{}^tBu$ **22**, THF, −15 °C to rt, 16 h.

Diastereoselective conjugate addition of lithium amide (*R*)-**32** to α,β-unsaturated ester **44** was followed by in situ enolate oxidation upon treatment with (−)-CSO **13** to give α-hydroxy-β-amino ester **45** as a single diastereoisomer (>99:1 dr), which was isolated in 64% yield and >99:1 dr after chromatographic purification. The absolute (*R*,*R*,*R*)-configuration within **45** was again assigned by analogy to the well established stereochemical outcome of our aminohydroxylation process.[17a,c] Following the previously optimised procedures, N-deallylation of **45** and subsequent cyclisation of **46** to give the corresponding 3-hydroxy-4-aminopiperidin-2-one **47** was achieved by sequential treatment with $Pd(PPh_3)_4$ in the presence of DMBA, followed by heating a solution of the crude reaction mixture in toluene at 80 °C in the presence of $PhCO_2H$ (0.05 equiv). After chromatographic purification, 3,4-*syn*-3-hydroxy-4-aminopiperidine-2-one **47** was isolated in 99% yield over the two steps and in >99:1 dr (Scheme 8).



Scheme 8. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl) amide (*R*)-**32**, THF, −78 °C, 2 h, then (−)-CSO **13**, −78 °C to rt, 12 h; (ii) $Pd(PPh_3)_4$, DMBA, CH_2Cl_2, 35 °C, 3 h; (iii) $PhCO_2H$, toluene, 80 °C, 16 h.

O-Methylation of **47** was achieved upon sequential treatment with NaH then MeI, which gave **48** in 77% isolated yield and >99:1 dr. Subsequent reduction of **48** with $LiAlH_4$ in THF at reflux gave 3,4-*syn*-3-methoxy-4-aminopiperidine **49** in 99% isolated yield (Scheme 9). The relative configuration within **49** was unambiguously assigned by single crystal X-ray diffraction analysis, with the absolute (3*S*,4*R*,α*R*)-configuration within **49** being assigned from the known configuration of the (*R*)-α-methylbenzyl stereogenic centre (Fig. 5).[27] Hydrogenolytic N-debenzylation of **49** in the presence of Pearlman's catalyst [$Pd(OH)_2$/C] gave primary amine **50**, and subsequent coupling of **50** with 2-methoxy-4-amino-5-chlorobenzoic acid **51** was achieved via treatment of **51** with ethyl chloroformate and Et_3N, followed by addition of **50** to the reaction flask.[32,42] Chromatographic purification of the crude reaction mixture gave (+)-(3*S*,4*R*)-cisapride **40** in 64% isolated yield over the two steps and >99:1 dr (Scheme 9). This sample of cisapride **40** displayed identical spectroscopic data to those of an authentic sample. The total asymmetric synthesis of (+)-(3*S*,4*R*)-cisapride **40** from commercially available starting materials was therefore achieved in nine steps with an overall yield of 19%. This synthetic strategy can be applied to the preparation of either enantiomer of cisapride **40**, and should be readily amenable to diversification.



Scheme 9. Reagents and conditions: (i) NaH, THF, 0 °C, 1 h, then MeI, 0 °C to rt, 16 h; (ii) $LiAlH_4$, THF, 60 °C, 16 h; (iii) H_2, $Pd(OH)_2$/C, MeOH, rt, 16 h; (iv) **51**, $ClCO_2Et$, Et_3N, THF, rt, 16 h.

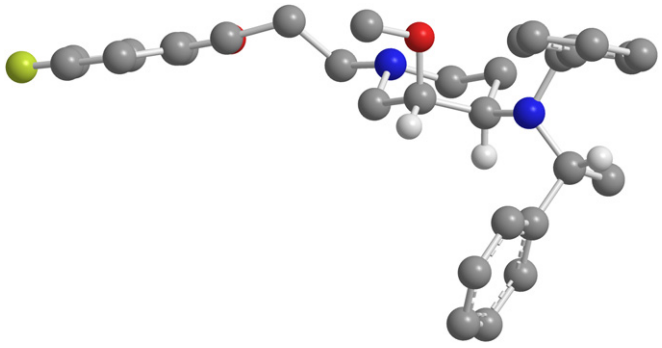


Fig. 5. Chem 3D representation of the single crystal X-ray diffraction structure of **49** (selected H atoms are omitted for clarity).

3. Conclusion

The conjugate addition of lithium (*R*)-*N*-benzyl-(*N*-α-methylbenzyl)amide to δ-(*N*-allylamino)-α,β-unsaturated esters, followed by N-deallylation and cyclisation of the resultant β,δ-diamino esters, gives the corresponding 4-aminopiperidin-2-ones as single diastereoisomers (>99:1 dr). Subsequent deprotonation with LiHMDS and functionalisation of the resultant lithium enolate gives 3,4-*anti*-3-substituted-4-aminopiperidin-2-ones in >99:1 dr. Alternatively, in situ oxidation of the intermediate lithium (*Z*)-β-amino enolates formed upon conjugate addition gives α-hydroxy-

β,δ-diamino esters which, after N-deallylation and cyclisation, gives the corresponding 3,4-*syn*-3-hydroxy-4-aminopiperidin-2-ones in >99:1 dr. The utility of this methodology was successfully demonstrated in a concise asymmetric synthesis of the gastroprokinetic agent (+)-(3*S*,4*R*)-cisapride in nine steps from commercially available starting materials with an overall yield of 19%.

4. Experimental

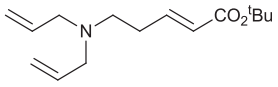
4.1. General experimental

Reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. BuLi was purchased from Sigma–Aldrich (as a solution in hexanes) and titrated against diphenylacetic acid before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[43] Water was purified by an Elix® UV-10 system. All other reagents were used as supplied without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Elemental analyses were recorded by the microanalysis service of the London Metropolitan University, U.K. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer on an ATR module. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. Spectra were recorded at rt. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20–250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m×0.25 mm) using amyl acetate as a lock mass.

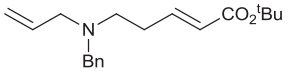
4.2. Experimental details

4.2.1. *tert*-Butyl (*E*)-5-(*N*,*N*-diallylamino)pent-2-enoate **23**.



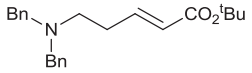
Acrolein (3.44 mL, 51.5 mmol) was added dropwise to a stirred solution of DBU (23 μL, 0.15 mmol) and *N*,*N*-diallylamine **19** (6.35 mL, 51.5 mmol) in THF (20 mL) at −15 °C. The reaction mixture was stirred at −15 °C for 40 min then **22** (19.4 g, 51.5 mmol) was added portionwise and the reaction mixture was stirred at −15 °C for 20 min. The resultant mixture was allowed to warm to rt over 16 h, then concentrated in vacuo to give **23** in 91:9 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **23** as a yellow oil (2.33 g, 72%, >99:1 dr); ν_{max} (ATR) 3077, 3006, 2978, 2931, 2806 (C–H), 1713 (C=O), 1651 (C=C); δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, CMe_3), 2.28–2.36 (2H, m, C(4)H_2), 2.57 (2H, t, *J* 7.5, C(5)H_2), 3.09 (4H, d, *J* 6.3, N(CH_2CH=CH_2)$_2$), 5.08–5.21 (4H, m, N(CH_2CH=CH_2)$_2$), 5.75 (1H, d, *J* 15.7, C(2)*H*), 5.78–5.89 (2H, m, N(CH_2C*H*=CH_2)$_2$), 6.81 (1H, dt, *J* 15.7, 7.0, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 28.1 (CMe_3), 29.6 (*C*(4)), 51.6 (*C*(5)), 56.8 (N(CH_2CH=CH_2)$_2$), 80.0 (*C*Me$_3$), 117.5 (N(CH_2CH=CH_2)$_2$), 123.8 (*C*(2)), 135.5 (N(CH_2C*H*=CH_2)$_2$), 145.8 (*C*(3)), 165.9 (*C*(1)); *m*/*z* (ESI$^+$) 274 ([M+Na]$^+$, 88%), 252 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{15}H_{26}NO_2^+$ ([M+H]$^+$) requires 252.1958; found 252.1955.

4.2.2. *tert*-Butyl (*E*)-5-(*N*-allyl-*N*-benzylamino)pent-2-enoate **24**.



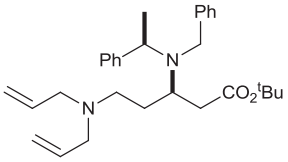
Acrolein (3.16 mL, 47.5 mmol) was added dropwise to a stirred solution of DBU (72 μL, 0.48 mmol) and *N*-allyl-*N*-benzylamine **20** (7.00 g, 47.5 mmol) in THF (20 mL) at −15 °C. The reaction mixture was stirred at −15 °C for 40 min then **22** (12.8 g, 34.0 mmol) was added portionwise and the reaction mixture was stirred at −15 °C for 20 min. The resultant mixture was allowed to warm to rt over 16 h, then concentrated in vacuo to give **24** in 94:6 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O/Et_3N, 50:50:1) gave **24** as colourless oil (13.0 g, 91%, >99:1 dr); ν_{max} (ATR) 3064, 3028, 3005, 2977, 2931, 2802 (C–H), 1713 (C=O), 1651 (C=C), 1603 (C=C, aromatic); δ_H (400 MHz, $CDCl_3$) 1.49 (9H, s, CMe_3), 2.36 (2H, app q, *J* 6.8, C(4)H_2), 2.60 (2H, t, *J* 6.8, C(5)H_2), 3.11 (2H, d, *J* 6.3, NCH_2CH=CH_2), 3.60 (2H, s, NCH_2Ph), 5.11–5.24 (2H, m, NCH_2CH=CH_2), 5.74 (1H, dt, *J* 15.7, 1.5, C(2)*H*), 5.82–5.93 (1H, m, NCH_2C*H*=CH_2), 6.79–6.88 (1H, dt, *J* 15.7, 6.8, C(3)*H*), 7.20–7.35 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.2 (CMe_3), 29.8 (*C*(4)), 51.8 (*C*(5)), 56.7 (NCH_2CH=CH_2), 58.0 (NCH_2Ph), 80.0 (*C*Me$_3$), 117.4 (NCH_2CH=CH_2), 123.8 (*C*(2)), 126.9 (*p*-*Ph*), 128.2, 128.8 (*o*,*m*-*Ph*), 135.7 (NCH_2C*H*=CH_2), 139.4 (*i*-*Ph*), 146.0 (*C*(3)), 165.9 (*C*(1)); *m*/*z* (ESI$^+$) 324 ([M+Na]$^+$, 100%), 302 ([M+H]$^+$, 92%); HRMS (ESI$^+$) $C_{19}H_{28}NO_2^+$ ([M+H]$^+$) requires 302.2115; found 302.2107.

4.2.3. *tert*-Butyl (*E*)-5-(*N*,*N*-dibenzylamino)pent-2-enoate **25**.



Acrolein (1.69 mL, 25.3 mmol) was added dropwise to a stirred solution of DBU (37 μL, 0.21 mmol) and *N*,*N*-dibenzylamine **21** (4.90 mL, 25.3 mmol) in THF (20 mL) at −15 °C. The reaction mixture was stirred at −15 °C for 40 min then **22** (12.8 g, 34.0 mmol) was added portionwise and the reaction mixture was stirred at −15 °C for 20 min. The resultant mixture was allowed to warm to rt over 16 h, then concentrated in vacuo to give **25** in 89:11 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 4:1) gave **25** as a yellow oil (6.07 g, 68%, >99:1 dr); ν_{max} (ATR) 3062, 3028, 2977, 2931, 2799 (C–H), 1710 (C=O), 1652 (C=C); δ_H (400 MHz, $CDCl_3$) 1.54 (9H, s, CMe_3), 2.40 (2H, app q, *J* 7.2, C(4)H_2), 2.60 (2H, t, *J* 7.2, C(5)H_2), 3.61 (4H, s, N(CH_2Ph)$_2$), 5.74 (1H, app d, *J* 15.5, C(2)*H*), 6.85 (1H, dt, *J* 15.5, 7.4, C(3)*H*), 7.22–7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.2 (CMe_3), 29.8 (*C*(4)), 51.9 (*C*(5)), 58.2 (N(CH_2Ph)$_2$), 80.0 (*C*Me$_3$), 123.8 (*C*(2)), 126.9 (*p*-*Ph*), 128.3, 128.7 (*o*,*m*-*Ph*), 139.5 (*i*-*Ph*), 146.2 (*C*(3)), 165.9 (*C*(1)); *m*/*z* (ESI$^+$) 374 ([M+Na]$^+$, 98%), 352 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{30}NO_2^+$ ([M+H]$^+$) requires 352.2271; found 352.2258.

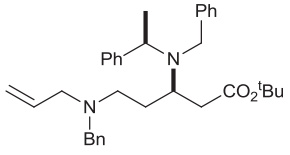
4.2.4. *tert*-Butyl (*R*,*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-(*N*′,*N*′-diallylamino)pentanoate **26**.



BuLi (2.5 M, 2.80 mL, 7.00 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.46 mL, 7.00 mmol) in THF (5 mL) at −78 °C and the resultant mixture was

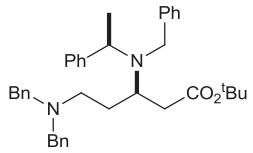
stirred at this temperature for 30 min. A solution of **23** (1.10 g, 4.38 mmol) in THF (15 mL) at −78 °C was then added dropwise. The reaction mixture was stirred at −78 °C for 2 h then satd aq NH_4Cl (2 mL) was added. The resultant mixture was diluted with Et_2O (40 mL) and washed with 10% aq citric acid (2×30 mL). The aqueous layer was extracted with Et_2O (2×40 mL) and the combined organic extracts were washed with satd aq $NaHCO_3$ (50 mL) and brine (50 mL), then dried and concentrated in vacuo to give **26** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O/Et_3N, 50:50:1) gave **26** as a yellow oil (1.67 g, 82%, >99:1 dr); $[\alpha]_D^{22}$ +3.4 (*c* 1.2 in $CHCl_3$); ν_{max} (ATR) 3063, 3026, 3004, 2971, 2930 (C–H), 1725 (C=O),1642 (C=C); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, d, *J* 6.8, C(α)*Me*), 1.42 (9H, s, C*Me*$_3$), 1.48–1.59 (1H, m, C(4)H_A), 1.60–1.73 (1H, m, C(4)H_B), 1.89–1.94 (2H, m, C(2)H_2), 2.44 (1H, td, *J* 11.6, 5.3, C(5)H_A), 2.94 (1H, td, *J* 11.6, 4.6, C(5)H_B), 3.08 (2H, dd, *J* 13.9, 6.8, N′(CH_AH$_B$CH=CH$_2$)$_2$), 3.18 (2H, dd, *J* 13.9, 6.2, N′(CH$_A$H$_B$CH=CH$_2$)$_2$),3.33–3.39 (1H, m, C(3)*H*), 3.50 (1H, d, *J* 14.7, NCH_AH$_B$Ph), 3.72–3.86 (2H, m, NCH$_A$H$_B$Ph, C(α)*H*), 5.13–5.25 (4H, m, N′(CH$_2$CH=CH$_2$)$_2$), 5.83–5.97 (2H, m, N′(CH$_2$CH=CH$_2$)$_2$), 7.22–7.46 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.2 (C(α)*Me*), 28.1 (C*Me*$_3$), 30.0 (*C*(4)), 37.8 (*C*(2)), 50.1 (NCH$_2$Ph), 51.4 (*C*(5)), 52.5 (*C*(3)), 56.8 (N(CH$_2$CH=CH$_2$)$_2$), 58.0 (*C*(α)), 80.0 (*C*Me$_3$), 117.9 (N′(CH$_2$CH=CH$_2$)$_2$), 126.6, 127.0, 127.9, 128.1, 128.2, 128.3 (*o*,*m*,*p*-*Ph*), 135.2 (N′(CH$_2$CH=CH$_2$)$_2$), 141.5, 147.7 (*i*-*Ph*), 171.9 (*C*(1)); *m*/*z* (ESI$^+$) 463 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{43}N_2O_2^+$ ([M+H]$^+$) requires 463.3319; found 463.3302.

*4.2.5. tert-Butyl (R,R)-3-[N-benzyl-N-(α-methylbenzyl)amino]-5-(N′-allyl-N′-benzylamino)pentanoate **27**.*



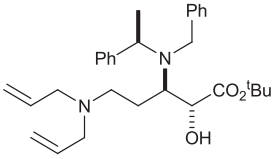
BuLi (2.5 M, 26.5 mL, 66.4 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (13.9 mL, 66.4 mmol) in THF (40 mL) at −78 °C and the resultant mixture was stirred at this temperature for 30 min. A solution of **24** (12.5 g, 41.5 mmol) in THF (150 mL) at −78 °C was then added dropwise. The reaction mixture was stirred at −78 °C for 2 h then satd aq NH_4Cl (15 mL) was added. The resultant mixture was diluted with Et_2O (250 mL) and washed with 10% aq citric acid (2×150 mL). The aqueous layer was extracted with Et_2O (2×200 mL) and the combined organic extracts were washed with satd aq $NaHCO_3$ (500 mL) and brine (500 mL), then dried and concentrated in vacuo to give **27** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O/Et_3N, 66:34:1) gave **27** as a colourless oil (18.7 g, 88%, >99:1 dr); $[\alpha]_D^{22}$ −2.9 (*c* 1.3 in $CHCl_3$); ν_{max} (ATR) 3062, 3027, 2975, 2930, 2801 (C–H), 1723 (C=O), 1643, (C=C), 1602 (C=C, aromatic); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 7.1, C(α)*Me*), 1.44 (9H, s, C*Me*$_3$), 1.55–1.65 (1H, m, C(4)H_A), 1.66–1.76 (1H, m, C(4)H_B), 1.87–1.96 (2H, m, C(2)H_2), 2.39–2.51 (1H, m, C(5)H_A), 2.86–2.99 (1H, m, C(5)H_B), 3.06 (1H, dd, *J* 13.9, 6.8, N′CH_AH$_B$CH=CH$_2$), 3.19 (1H, dd, *J* 13.9, 5.9, N′CH$_A$H$_B$CH=CH$_2$), 3.32–3.42 (1H, m, C(3)*H*), 3.51 (1H, d, *J* 14.9, NCH_AH$_B$Ph), 3.53 (1H, d, *J* 13.5, N′CH_AH$_B$Ph), 3.70 (1H, d, *J* 13.5, N′CH$_A$H$_B$Ph), 3.78–3.86 (2H, m, NCH$_A$H$_B$Ph, C(α)*H*), 5.16–5.29 (2H, m, N′CH$_2$CH=CH_2), 5.89–6.02 (1H, m, N′CH$_2$C*H*=CH$_2$), 7.20–7.45 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.2 (C(α)*Me*), 28.1 (C*Me*$_3$), 30.4 (*C*(4)), 37.9 (*C*(2)), 50.1 (NCH$_2$Ph), 51.7 (*C*(5)), 52.6 (*C*(3)), 56.9 (N′CH$_2$CH=CH$_2$), 58.0 (*C*(α)Me), 58.3 (N′CH$_2$Ph), 80.0 (*C*Me$_3$), 117.2 (N′CH$_2$CH=*C*H$_2$), 126.6, 126.8, 127.0 (*p*-*Ph*), 128.0, 128.1, 128.2, 128.3, 128.3, 129.0 (*o*,*m*-*Ph*), 136.1 (N′CH$_2$*C*H=CH$_2$), 139.6, 141.6, 142.8 (*i*-*Ph*), 172.0 (*C*(1)); *m*/*z* (ESI$^+$) 513 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{45}N_2O_2^+$ ([M+H]$^+$) requires 513.3476; found 513.3460.

*4.2.6. tert-Butyl (R,R)-3-[N-benzyl-N-(α-methylbenzyl)amino]-5-(N′,N′-dibenzylamino)pentanoate **28**.*



BuLi (2.5 M, 1.82 mL, 4.55 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (0.95 mL, 4.55 mmol) in THF (5 mL) at −78 °C and the resultant mixture was stirred at this temperature for 30 min. A solution of **25** (1.00 g, 2.85 mmol) in THF (15 mL) at −78 °C was then added dropwise. The reaction mixture was stirred at −78 °C for 2 h then satd aq NH_4Cl (2 mL) was added. The resultant mixture was diluted with Et_2O (30 mL) and washed with 10% aq citric acid (2×20 mL). The aqueous layer was extracted with Et_2O (2×30 mL) and the combined organic extracts were washed with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated in vacuo to give **28** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O/Et_3N, 80:20:1) gave **28** as a colourless oil (838 mg, 52%, >99:1 dr); $[\alpha]_D^{25}$ −9.0 (*c* 1.8 in $CHCl_3$); ν_{max} (ATR) 3061, 3027, 2971, 2930, 2798 (C–H), 1724 (C=O), 1601 (C=C); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 7.1, C(α)*Me*), 1.46 (9H, s, C*Me*$_3$), 1.62–1.71 (1H, m, C(4)H_A), 1.71–1.83 (1H, m, C(4)H_B), 1.89–1.96 (2H, m, C(2)H_2), 2.45 (1H, ddd, *J* 12.6, 10.4, 5.1, C(5)H_A), 2.95 (1H, ddd, *J* 12.6, 10.6, 5.1, C(5)H_B), 3.32–3.41 (1H, m, C(3)*H*), 3.46–3.56 (3H, m, NCH_AH$_B$Ph, N′(CH_AH$_B$Ph)$_2$), 3.70–3.86 (4H, m, C(α)*H*, NCH$_A$H$_B$Ph, N′(CH$_A$H$_B$Ph)$_2$), 7.24–7.47 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.2 (C(α)*Me*), 28.1 (C*Me*$_3$), 30.6 (*C*(4)), 37.9 (*C*(2)), 50.2 (NCH$_2$Ph), 51.9 (*C*(5)), 52.8 (*C*(3)), 58.0 (*C*(α)), 58.4 (N′(*C*H$_2$Ph)$_2$), 80.0 (*C*Me$_3$), 126.6, 126.8, 127.0 (*p*-*Ph*), 128.0, 128.2, 128.2, 128.3, 128.9, 129.0 (*o*,*m*-*Ph*), 139.9, 141.6, 142.9 (*i*-*Ph*), 172.1 (*C*(1)); *m*/*z* (ESI$^+$) 563 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{38}H_{47}N_2O_2^+$ ([M+H]$^+$) requires 563.3632; found 563.3628.

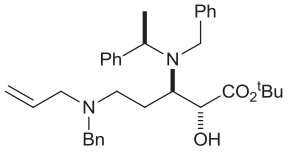
*4.2.7. tert-Butyl (R,R,R)-2-hydroxy-3-[N-benzyl-N-(α-methylbenzyl)amino]-5-(N′,N′-diallylamino)-pentanoate **29**.*



BuLi (2.5 M, 1.27 mL, 3.18 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (0.66 mL, 3.18 mmol) in THF (10 mL) at −78 °C and the resultant mixture was stirred at this temperature for 30 min. A solution of **23** (500 mg, 1.99 mmol) in THF (10 mL) at −78 °C was then added dropwise. The reaction mixture was stirred at −78 °C for 2 h then (−)-CSO **13** (1.19 g, 3.98 mmol) was added. The reaction mixture was allowed to warm to rt over 16 h, H_2O (5 mL) was added, then the organic layer was dried and concentrated in vacuo to give **29** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1) gave **26** as a colourless oil (64 mg, 7%, >99:1 dr). Further elution gave **29** as a pale yellow oil (532 mg, 68%, >99:1 dr); $[\alpha]_D^{25}$ −5.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3502 (O–H), 3063, 3027, 2975, 2931, 2809 (C–H), 1720 (C=O); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 7.0, C(α)*Me*), 1.47 (9H, s, C*Me*$_3$), 1.43–1.52 (1H, m, C(4)H_A), 1.70–1.81 (1H, m, C(4)H_B), 2.32–2.43 (1H, m, C(5)H_A), 2.75–2.83 (1H, m, C(5)H_B), 3.03–3.16 (4H, m, N′(CH_2CH=CH$_2$)$_2$), 3.29 (1H, ddd, *J* 7.8, 5.3, 2.8, C(3)*H*), 3.71 (1H, d, *J* 15.4, NCH$_A$H$_B$Ph), 3.87 (1H, d, *J* 2.8, C(2)*H*), 3.96 (1H, q, *J* 7.0, C(α)*H*), 4.24 (1H, d, *J* 15.4, NCH$_A$H$_B$Ph), 3.13–3.21 (4H, m, N′(CH$_2$CH=CH_2)$_2$), 5.81–5.93 (2H, m, N′(CH$_2$C*H*=CH$_2$)$_2$), 7.21–7.51 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.3 (C(α)*Me*), 25.0 (*C*(4)), 28.0

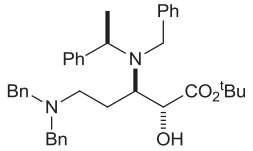
(CMe_3), 51.0 (NCH_2Ph), 51.2 (*C*(5)), 56.7 (N′($CH_2CH{=}CH_2$)$_2$), 58.4, 58.7 (*C*(3), *C*(α)), 71.6 (*C*(2)), 82.1 (CMe_3), 117.7 ($NCH_2CH{=}CH_2$), 126.4, 127.0 (*p-Ph*), 128.1, 128.2, 128.4, 128.5 (*o,m-Ph*), 135.4 (N′($CH_2CH{=}CH_2$)$_2$), 142.2, 143.2 (*i-Ph*), 174.2 (*C*(1)); *m/z* (ESI^+) 479 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{30}H_{43}N_2O_3^+$ ($[M+H]^+$) requires 479.3268; found 479.3250.

*4.2.8. tert-Butyl (R,R,R)-2-hydroxy-3-[N-benzyl-N-(α-methylbenzyl) amino]-5-(N′-allyl-N′-benzyl)pentanoate **30**.*



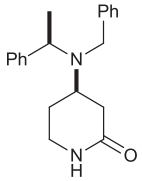
BuLi (2.5 M, 3.18 mL, 7.96 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.67 mL, 7.96 mmol) in THF (15 mL) at −78 °C and the resultant mixture was stirred at this temperature for 30 min. A solution of **24** (1.50 g, 4.98 mmol) in THF (10 mL) at −78 °C was then added dropwise. The reaction mixture was stirred at −78 °C for 2 h then (−)-CSO **13** (2.98 g, 9.96 mmol) was added. The reaction mixture was allowed to warm to rt over 16 h, H_2O (5 mL) was added, then the organic layer was dried and concentrated in vacuo to give **30** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc/Et_3N, 100:10:1) gave **27** as a colourless oil (925 mg, 36%, >99:1 dr). Further elution gave **30** as a colourless oil (1.10 g, 42%, >99:1 dr); $[\alpha]_D^{25}$ −27.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3500 (O–H), 3083, 3063, 3027, 3004, 2976, 2932, 2808 (C–H), 1719 (C=O), 1601 (C=C, aromatic); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, d, *J* 7.0, C(α)*Me*), 1.49 (9H, s, CMe_3), 1.52–1.62 (1H, m, C(4)H_A), 1.83–1.94 (1H, m, C(4)H_B), 2.46 (1H, ddd, *J* 13.4, 8.8, 6.6, C(5)H_A), 2.89 (1H, ddd, *J* 13.4, 8.8, 5.1, C(5)H_B), 3.11 (1H, dd, *J* 14.2, 6.6, N′C$H_A$$H_B$CH=$CH_2$), 3.20 (1H, dd, *J* 14.2, 6.1, N′C$H_A$$H_B$CH=$CH_2$), 3.32–3.38 (1H, m, C(3)*H*), 3.50 (1H, d, *J* 13.6, N′C$H_A$$H_B$Ph), 3.71 (1H, d, *J* 13.6, N′C$H_A$$H_B$Ph), 3.76 (1H, d, *J* 15.4, NC$H_A$$H_B$Ph), 3.90 (1H, d, *J* 1.5, C(2)*H*), 4.00 (1H, q, *J* 7.0, C(α)*H*), 4.32 (1H, d, *J* 15.4, NC$H_A$$H_B$Ph), 5.21–5.30 (2H, m, N′CH_2CH=CH_2), 5.99 (1H, app ddt, *J* 17.0, 10.4, 6.4, N′CH_2C*H*=CH_2), 7.25–7.53 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.4 (C(α)*Me*), 25.1 (*C*(4)) 28.1 (CMe_3), 51.2 (NCH_2Ph), 51.5 (*C*(5)), 56.5 (N′CH_2CH=CH_2), 58.1 (*C*(3)), 58.1 (N′CH_2Ph), 58.5 (*C*(α)), 71.4 (*C*(2)), 82.2 (CMe_3), 117.6 (N′CH_2CH=CH_2), 126.5, 127.0, 127.1 (*p-Ph*), 128.2, 128.2, 128.2, 128.3, 128.3, 129.1 (*o,m-Ph*), 135.7 (N′CH_2CH=CH_2), 139.2, 142.3, 143.2 (*i-Ph*), 174.3 (*C*(1)); *m/z* (ESI^+) 529 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{34}H_{45}N_2O_3^+$ ($[M+H]^+$) requires 529.3425; found 529.3426.

*4.2.9. tert-Butyl (R,R,R)-2-hydroxy-3-[N-benzyl-N-(α-methylbenzyl) amino]-5-(N′,N′-dibenzylamino)pentanoate **31**.*



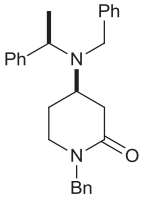
BuLi (2.5 M, 2.73 mL, 6.83 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (1.43 mL, 6.83 mmol) in THF (10 mL) at −78 °C and the resultant mixture was stirred at this temperature for 30 min. A solution of **25** (1.50 g, 4.27 mmol) in THF (10 mL) at −78 °C was then added dropwise. The reaction mixture was stirred at −78 °C for 2 h then (−)-CSO **13** (2.56 g, 8.54 mmol) was added. The reaction mixture was allowed to warm to rt over 16 h, H_2O (5 mL) was added, then the organic layer was dried and concentrated in vacuo to give **31** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 10:1) gave **28** as a colourless oil (1.14 g, 47%, >99:1 dr). Further elution gave **31** as a colourless oil (812 mg, 33%, >99:1 dr); $[\alpha]_D^{25}$ −22.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3500 (O–H), 3062, 3027, 2973, 2798 (C–H), 1719 (C=O), 1602 (C=C, aromatic); δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.8, C(α)*Me*), 1.42 (9H, s, CMe_3), 1.46–1.48 (1H, m, C(4)H_A), 1.83–1.94 (1H, m, C(4)H_B), 2.40 (1H, ddd, *J* 12.7, 10.0, 5.4, C(5)H_A), 2.86 (1H, ddd, *J* 12.7, 10.0, 4.9, C(5)H_B), 3.24 (1H, ddd, *J* 8.3, 4.6, 1.8, C(3)*H*), 3.53 (2H, d, *J* 13.6, N′($CH_A$$H_B$Ph)$_2$), 3.67 (2H, d, *J* 13.6, N′($CH_A$$H_B$Ph)$_2$), 3.68 (1H, d, *J* 15.4, NC$H_A$$H_B$Ph), 3.79 (1H, d, *J* 1.8, C(2)*H*), 3.90 (1H, q, *J* 6.8, C(α)*H*), 4.24 (1H, d, *J* 15.4, NC$H_A$$H_B$Ph), 7.23–7.44 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.1 (C(α)*Me*), 25.0 (*C*(4)), 28.0 (CMe_3), 51.2 (*C*(5)), 51.8 (NCH_2Ph), 57.9, 58.1 (*C*(2), *C*(3)), 58.1 (N′(CH_2Ph)$_2$), 71.3 (*C*(α)), 82.4 (CMe_3), 126.4, 126.9, 127.0 (*p-Ph*), 128.1, 128.1, 128.2, 128.3, 128.9, 129.0 (*o,m-Ph*), 139.5, 142.1, 143.0 (*i-Ph*), 174.3 (*C*(1)); *m/z* (ESI^+) 579 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{38}H_{47}N_2O_2^+$ ($[M+H]^+$) requires 579.3581; found 579.3581.

*4.2.10. (R,R)-4-[N-Benzyl-N-(α-methylbenzyl)amino]piperidin-2-one **33**.*



$Pd(PPh_3)_4$ (57 mg, 50 μmol) was added to a mixture of **26** (1.15 g, 2.49 mmol) and DMBA (2.33 g, 14.9 mmol) in de-gassed CH_2Cl_2 (50 mL) at 35 °C. The reaction mixture was then stirred for 3 h at 35 °C in the dark, then concentrated in vacuo. The residue was then dissolved in toluene (50 mL) and $PhCO_2H$ (30 mg, 0.25 mmol) was added. The resultant solution was stirred at 80 °C for 16 h then 2.0 M aq Na_2CO_3 (25 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic extracts were washed with brine (50 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc/Et_3N, 50:50:1) gave **33** as a pale yellow oil (593 mg, 77%, >99:1 dr); $[\alpha]_D^{25}$ +65.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3457 (N–H), 3026, 3016, 2970, 2947, 2868 (C–H), 1738 (C=O); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.6, C(α)*Me*), 1.74 (1H, qd, *J* 12.3, 5.5, C(5)H_A), 2.00 (1H, dd, *J* 12.3, 2.0, C(5)H_B), 2.37 (2H, app d, *J* 8.8, C(3)H_2), 3.03–3.17 (2H, m, C(4)*H*, C(6)H_A), 3.22–3.29 (1H, m, C(6)H_B), 3.79 (1H, d, *J* 15.0,NC$H_A$$H_B$Ph), 3.83 (1H, d, *J* 15.0, NC$H_A$$H_B$Ph), 3.99 (1H, q, *J* 6.6, C(α)*H*), 6.13 (1H, br s, N*H*),7.20–7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.3 (C(α)*Me*), 27.7 (*C*(5)), 36.0 (*C*(3)), 40.2 (*C*(6)), 49.6 (NCH_2Ph), 51.6 (*C*(4)), 57.1 (*C*(α)), 126.7, 126.9 (*p-Ph*), 128.0, 128.1, 128.3, 128.3 (*o,m-Ph*), 141.3, 144.1 (*i-Ph*), 172.8 (*C*(2)); *m/z* (ESI^+) 947 ($[3M+Na]^+$, 70%), 639 ($[2M+Na]^+$, 100%), 309 ($[M+H]^+$, 20%); HRMS (ESI^+) $C_{20}H_{25}N_2O^+$ ($[M+H]^+$) requires 309.1961; found 309.1951.

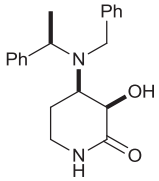
*4.2.11. (R,R)-N(1)-Benzyl-4-[N-benzyl-N-(α-methylbenzyl)amino]piperidin-2-one **34**.*



$Pd(PPh_3)_4$ (184 mg, 0.160 mmol) was added to a mixture of **27** (8.19 g, 15.97 mmol) and DMBA (7.48 g, 47.91 mmol) in de-gassed CH_2Cl_2 (80 mL) at 35 °C. The reaction mixture was then stirred for 3 h at 35 °C in the dark, then concentrated in vacuo. The residue was then dissolved in toluene (80 mL) and $PhCO_2H$ (195 mg, 1.60 mmol) was added. The resultant solution was stirred at 80 °C for 16 h then 2.0 M aq Na_2CO_3 (50 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2×50 mL). The combined organic extracts

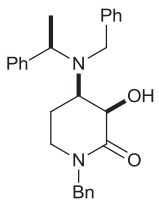
were washed with brine (80 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 75:25) gave **34** as a yellow solid (3.24 g, 53%, >99:1 dr); mp 74–75 °C; $[\alpha]_D^{25}$ +51.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3084, 3061, 3028, 2969, 2931 (C–H), 1644 (C=O); δ_H (400 MHz, $CDCl_3$) 1.42 (3H, d, *J* 6.7, C(α)*Me*), 1.75 (1H, qd, *J* 12.1, 5.3, C(5)H_A), 2.02 (1H, app d, *J* 12.1, C(5)H_B), 2.55 (1H, dd, *J* 17.4, 10.9, C(3)H_A), 2.62 (1H, dd, *J* 17.4, 5.8, C(3)H_B), 3.01–3.22 (3H, m, C(6)H_2, C(4)*H*), 3.83 (2H, s, NCH_2Ph), 4.04 (1H, q, *J* 6.7, C(α)*H*), 4.27 (1H, d, *J* 14.7, N(1)CH_AH$_B$Ph), 4.84 (1H, d, *J* 14.7, N(1)CH$_A$$H_B$Ph), 7.19–7.52 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.2 (C(α)*Me*), 28.5 (*C*(5)), 36.9 (*C*(3)), 45.3 (*C*(6)), 49.6, 49.7 (NCH$_2$Ph, N(1)CH$_2$Ph), 52.0 (*C*(4)), 57.0 (*C*(α)), 126.8, 126.9, 127.4 (*p-Ph*), 127.5, 128.0, 128.1, 128.3, 128.4, 128.7 (*o,m-Ph*), 137.1, 141.5, 144.2 (*i-Ph*), 169.8 (*C*(2)); *m/z* (FI^+) 398 ($[M]^+$, 100%); HRMS (FI^+) $C_{27}H_{30}N_2O^+$ ($[M]^+$) requires 398.2353; found 398.2347.

4.2.12. (R,R,R)-3-Hydroxy-4-[N-benzyl-N-(α-methylbenzyl)amino] piperidin-2-one ***35****.*



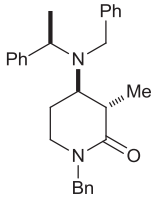
$Pd(PPh_3)_4$ (40 mg, 40 μmol) was added to a mixture of **29** (834 mg, 1.74 mmol) and DMBA (1.64 g, 10.45 mmol) in de-gassed CH_2Cl_2 (25 mL) at 35 °C. The reaction mixture was then stirred for 3 h at 35 °C in the dark, then concentrated in vacuo. The residue was then dissolved in toluene (20 mL) and $PhCO_2H$ (106 mg, 0.87 mmol) was added. The resultant solution was stirred at 80 °C for 16 h then 2.0 M aq Na_2CO_3 (15 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2×15 mL). The combined organic extracts were washed with brine (50 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent EtOAc/Et_3N, 100:1) gave **35** as a white solid (265 mg, 47%, >99:1 dr); mp 73–77 °C; $[\alpha]_D^{25}$ +45.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3245 (O–H), 3061, 3027, 2969, 2874 (C–H), 1648 (C=O); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.8, C(α)*Me*), 1.85–2.06 (2H, m, C(5)H_2), 3.06 (1H, app td, *J* 11.7, 4.1, C(6)H_A), 3.20 (1H, dtd, *J* 13.1, 5.5, 2.2, C(6)H_B), 3.31 (1H, app q, *J* 7.3, C(4)*H*), 3.71 (1H, d, *J* 14.2, NCH_AH$_B$Ph), 3.79 (1H, d, *J* 14.2, NCH$_A$$H_B$Ph), 3.86 (1H, br dd, *J* 6.0, 2.8, C(3)*H*), 4.03 (1H, br d, *J* 2.8, O*H*), 4.10 (1H, q, *J* 6.8, C(α)*H*), 7.17–7.50 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.8 (C(α)*Me*), 24.6 (*C*(5)), 38.4 (*C*(6)), 51.4 (NCH$_2$Ph), 54.2 (*C*(4)), 57.0 (*C*(α)), 68.7 (*C*(3)), 127.1, 127.1 (*p-Ph*), 127.6, 128.4, 128.5, 128.7 (*o,m-Ph*), 140.8, 143.5 (*i-Ph*), 174.2 (*C*(2)); *m/z* (ESI^+) 671 ($[2M+Na]^+$, 100%), 325 ($[M+H]^+$, 10%); HRMS (ESI^+) $C_{20}H_{25}N_2O_2^+$ ($[M+H]^+$) requires 325.1911; found 325.1913.

4.2.13. (R,R,R)-N(1)-Benzyl-3-hydroxy-4-[N-benzyl-N-(α-methylbenzyl)amino]piperidin-2-one ***36****.*



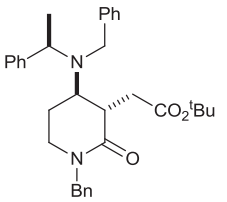
$Pd(PPh_3)_4$ (17 mg, 20 μmol) was added to a mixture of **30** (800 mg, 1.51 mmol) and DMBA (711 mg, 4.54 mmol) in de-gassed CH_2Cl_2 (12 mL) at 35 °C. The reaction mixture was then stirred for 3 h at 35 °C in the dark, then concentrated in vacuo. The residue was then dissolved in toluene (20 mL) and $PhCO_2H$ (100 mg, 0.82 mmol) was added. The resultant solution was stirred at 80 °C for 16 h then 2.0 M aq Na_2CO_3 (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic extracts were washed with brine (30 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc/Et_3N, 100:25:1) gave **36** as a white solid (435 mg, 69%, >99:1 dr); mp 109–112 °C; $[\alpha]_D^{25}$ +45.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3294 (O–H), 3085, 3062, 3027, 2970 (C–H), 1634 (C=O); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, d, *J* 6.8, C(α)*Me*), 1.85–2.01 (2H, m, C(5)H_2), 3.05–3.18 (2H, m, C(6)H_2), 3.35 (1H, app dt, *J* 8.6, 6.9, C(4)*H*), 3.76 (1H, d, *J* 14.9, N(1)CH_AH$_B$Ph), 3.86 (1H, br s, O*H*), 3.89 (1H, d, *J* 14.9, N(1)CH$_A$$H_B$Ph), 4.06 (1H, d, *J* 6.3, C(3)*H*), 4.24 (1H, q, *J* 6.8, C(α)*H*), 4.36 (1H, d, *J* 14.7, NCH_AH$_B$Ph), 4.76 (1H, d, *J* 14.7, NCH$_A$$H_B$Ph), 7.18–7.51 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.1 (C(α)*Me*), 24.9 (*C*(5)), 43.6 (*C*(6)), 50.0 (NCH$_2$Ph), 51.3 (N(1)CH$_2$Ph), 54.8 (*C*(4)), 57.8 (*C*(α)), 69.9 (*C*(3)), 126.8, 127.0, 127.6 (*p-Ph*), 127.7, 128.2, 128.3, 128.3, 128.4, 128.7 (*o,m-Ph*), 136.6, 141.6, 144.0 (*i-Ph*), 171.8 (*C*(2)); *m/z* (ESI^+) 852 ($[2M+Na]^+$, 100%), 415 ($[M+H]^+$, 18%); HRMS (ESI^+) $C_{27}H_{30}N_2NaO_2^+$ ($[M+Na]^+$) requires 437.2199; found 437.2195.

4.2.14. (3S,4R,αR)-N(1)-Benzyl-3-methyl-4-[N-benzyl-N-(α-methylbenzyl)amino]piperidin-2-one ***37****.*



LiHMDS (1.0 M in toluene, 0.78 mL, 0.78 mmol) was added dropwise to a solution of **34** (103 mg, 0.26 mmol) in THF (10 mL) at −78 °C and the resultant mixture was stirred at this temperature for 1 h. MeI (50 μL, 0.78 mmol) was then added and the reaction mixture was allowed to warm to rt over 16 h. Satd aq NH_4Cl (1 mL) was then added and the resultant mixture was diluted with Et_2O (25 mL) and washed with 10% aq citric acid (25 mL). The aqueous layer was extracted with Et_2O (2×25 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (2×50 mL) and brine (50 mL), then dried and concentrated in vacuo to give **37** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:50) gave **37** as a white solid (72 mg, 67%, >99:1 dr); mp 135–137 °C; $[\alpha]_D^{25}$ +2.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3028, 2971, 2930 (C–H), 1636 (C=O); δ_H (400 MHz, $CDCl_3$) 1.07 (3H, d, *J* 7.1, C(3)*Me*), 1.41 (3H, d, *J* 7.0, C(α)*Me*), 1.79 (1H, dddd, *J* 12.9, 11.5, 11.0, 5.3, C(5)H_A), 2.05 (1H, app qd, *J* 12.9, 3.4, C(5)H_B), 2.45 (1H, dq, *J* 10.1, 7.1, C(3)*H*), 2.70 (1H, ddd, *J* 11.5, 10.1, 3.4, C(4)*H*), 3.10 (1H, app td, *J* 11.9, 3.8, C(6)H_A), 3.16–3.23 (1H, m, C(6)H_B), 3.69 (1H, d, *J* 13.9, N(1)CH_AH$_B$Ph), 3.85 (1H, d, *J* 13.9, N(1)CH$_A$$H_B$Ph), 4.03 (1H, q, *J* 7.0, C(α)*H*), 4.31 (1H, d, *J* 14.7, NCH_AH$_B$Ph), 4.74 (1H, d, *J* 14.7, NCH$_A$$H_B$Ph), 7.14–7.44 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 15.7 (C(3)*Me*), 26.9 (*C*(5)), 41.6 (*C*(3)), 45.1 (*C*(6)), 49.9, 50.1 (N(1)CH$_2$Ph, NCH$_2$Ph), 56.2 (*C*(α)), 57.6 (*C*(4)), 126.8, 127.0, 127.3 (*p-Ph*), 127.9, 128.0, 128.1, 128.3, 128.6, 128.8 (*o,m-Ph*), 137.3, 140.6, 143.7 (*i-Ph*), 173.3 (*C*(2)); *m/z* (ESI^+) 848 ($[2M+Na]^+$, 100%), 435 ($[M+Na]^+$, 18%), 413 ($[M+H]^+$, 42%); HRMS (ESI^+) $C_{28}H_{33}N_2O^+$ ($[M+H]^+$) requires 413.2587; found 413.2574.

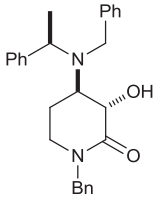
4.2.15. (3S,4R,αR)-N(1)-Benzyl-3-(2′-tert-butoxy-2′-oxoethyl)-[N-benzyl-N-(α-methylbenzyl)amino]piperidin-2-one ***38****.*



LiHMDS (1.0 M in toluene, 0.75 mL, 0.75 mmol), was added dropwise to a solution of **34** (100 mg, 0.25 mmol) in THF (10 mL)

at −78 °C and the resultant mixture was stirred at this temperature for 1 h. $BrCH_2CO_2{}^tBu$ (0.11 mL, 0.75 mmol) was then added and the reaction mixture was allowed to warm to rt over 16 h. Satd aq NH_4Cl (1 mL) was then added and the resultant mixture was diluted with Et_2O (25 mL) and washed with 10% aq citric acid (25 mL). The aqueous layer was extracted with Et_2O (2×25 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (2×25 mL) and brine (25 mL), then dried and concentrated in vacuo to give **38** in 80:20 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 50:50) gave **38** as a colourless oil (15 mg, 12%, >99:1 dr); $[\alpha]_D^{25}$ −34.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3463 (O–H), 3086, 3064, 3029, 2971, 2934 (C–H), 1724, 1638 (C=O); δ_H (400 MHz, $CDCl_3$) 1.35 (9H, s, CMe_3), 1.44 (3H, d, *J* 6.8, C(α)*Me*), 1.84 (1H, app qd, *J* 12.2, 5.0, C(5)H_A), 2.07 (1H, app dq, *J* 12.8, 3.1, C(5)H_B), 2.44 (1H, dd, *J* 17.0, 4.4, C(1′)H_A), 2.60 (1H, app dt, *J* 11.0, 4.4, C(3)*H*), 2.78 (1H, dd, *J* 17.0, 4.6, C(1′)H_B), 3.11–3.28 (3H, m, C(4)*H*, C(6)H_2), 3.65 (1H, d, *J* 13.9, N(1)C$H_A$$H_B$Ph), 3.83 (1H, d, *J* 13.9, N(1)C$H_A$$H_B$Ph), 3.99 (1H, q, *J* 6.8, C(α)*H*), 4.46 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 4.63 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 7.17–7.33 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.6 (C(α)*Me*), 27.0 (*C*(5)), 28.1 (C*Me*$_3$), 33.6 (*C*(1′)), 43.4 (*C*(3)), 44.9 (*C*(6)), 49.6 (N(1)*C*H_2Ph), 50.1 (NCH_2Ph), 54.6 (*C*(4)), 56.1 (*C*(α)), 79.9 (*C*Me$_3$), 126.9, 127.1, 127.2 (*p-Ph*), 127.9, 128.1, 128.1, 128.3, 128.4, 128.9 (*o,m-Ph*), 137.3, 140.4, 143.5 (*i-Ph*), 171.9, 172.0 (*C*(2), *C*(2′)); *m/z* (FI^+) 512 ([M^+], 100%); HRMS (FI^+) $C_{33}H_{40}N_2O_3^+$ ([M^+]) requires 512.3033; found 512.3016.

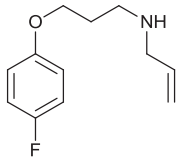
*4.2.16. (3S,4R,αR)-N(1)-Benzyl-3-hydroxy-4-[N-benzyl-N-(α-methylbenzyl)amino]piperidin-2-one **39**.*



Method A: LiHMDS (1.0 M in toluene, 0.45 mL, 0.45 mmol) was added dropwise to a solution of **34** (60 mg, 0.15 mmol) in THF (10 mL) at −78 °C and the resultant mixture was stirred at this temperature for 1 h. (+)-CSO **13** (103 mg, 0.45 mmol) was then added and the reaction mixture was allowed to warm to rt over 16 h. Satd aq NH_4Cl (1 mL) was then added and the resultant mixture was diluted with Et_2O (25 mL) and washed with 10% aq citric acid (25 mL). The aqueous layer was extracted with Et_2O (2×25 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (2×25 mL) and brine (25 mL), then dried and concentrated in vacuo to give an 85:15 mixture of **34** and **39**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 75:25) gave **39** (3 mg, 5%, >99:1 dr); ν_{max} (ATR) 3433 (O–H), 3084, 3060, 3027, 2970, 2931, 2868 (C–H), 1638 (C=O), 1603 (C=C, aromatic); δ_H (500 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.9, C(α)*Me*), 1.78 (1H, app qd, *J* 11.4, 6.0, C(5)H_A), 1.92–2.02 (1H, m, C(5)H_B), 2.99–3.08 (2H, m, C(4)*H*, C(6)H_A), 3.09–3.16 (1H, m, C(6)H_B), 3.60 (1H, s, O*H*), 3.89 (1H, d, *J* 15.0, N(1)C$H_A$$H_B$Ph), 3.93 (1H, d, *J* 15.0, N(1)C$H_A$$H_B$Ph), 4.16 (1H, d, *J* 10.7, C(3)*H*), 4.26–4.33 (2H, m, C(α)*H*, NC$H_A$$H_B$Ph), 4.71 (1H, d, *J* 15.0, NC$H_A$$H_B$Ph), 7.15–7.50 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$), 18.3 (C(α)*Me*), 25.8 (*C*(5)), 44.8 (*C*(6)), 49.2 (N(1)CH_2Ph), 50.2 (NCH_2Ph), 57.9 (*C*(4)), 58.9 (*C*(α)), 70.4 (*C*(3)), 126.8, 126.9, 127.7 (*p-Ph*), 127.8, 128.2, 128.2, 128.3, 128.4, 128.7 (*o,m-Ph*), 136.4, 141.7, 144.8 (*i-Ph*), 172.0 (*C*(2)); *m/z* (ESI^-) 413 ([M−H]$^-$, 25%); HRMS (ESI^+) $C_{27}H_{30}N_2NaO_2^+$ ([M+Na]$^+$) requires 437.2199; found 437.2191.

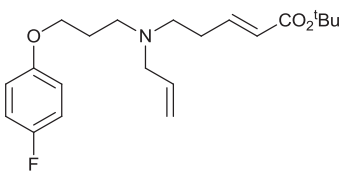
Method B: LiHMDS (1.0 M in toluene, 1.13 mL, 1.13 mmol) was added dropwise to a solution of **34** (150 mg, 0.38 mmol) in THF (10 mL) at −78 °C and the resultant mixture was stirred at this temperature for 1 h. (−)-CSO **13** (338 mg, 1.13 mmol) was then added and the reaction mixture was allowed to warm to rt over 16 h. Satd aq NH_4Cl (1 mL) was then added and the resultant mixture was diluted with Et_2O (25 mL) and washed with 10% aq citric acid (25 mL). The aqueous layer was extracted with Et_2O (2×25 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (2×50 mL) and brine (50 mL), then dried and concentrated in vacuo to give a 53:47 mixture of **34** and **39**. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 75:25) gave **39** as a colourless oil (57 mg, 37%, >99:1 dr).

*4.2.17. N-Allyl-N-[3-(4′-fluorophenoxy)propyl]amine **42**.*



1-(3′-Bromopropoxy)-4-fluorobenzene **41** (7.33 mL, 45.3 mmol), NaI (6.79 g, 45.3 mmol) and K_2CO_3 (25.0 g, 181 mmol) were sequentially added to a solution of allylamine (10.2 mL, 136 mmol) in THF (1.4 L). The reaction mixture was stirred for 16 h at 45 °C. The mixture was allowed to cool to rt then filtered through Celite® (eluent CH_2Cl_2) and the filtrate was concentrated in vacuo. Purification via flash column chromatography (eluent Et_2O/Et_3N, 100:1) gave *N,N*-di-[3-(4′-fluorophenoxy)propyl]-*N*-allylamine as a colourless oil (838 mg, 10%); ν_{max} (ATR) 3075, 2932, 2874, 2809 (C–H), 1504 (C=C); δ_H (400 MHz, $CDCl_3$) 1.87–1.97 (4H, m, 2× C(2)H_2), 2.64 (4H, t, *J* 6.9, 2× C(1)H_2), 3.13 (2H, d, *J* 6.3, NCH_2CH=CH_2), 3.94 (4H, t, *J* 6.3, 2× C(3)H_2), 5.13 (1H, dd, *J* 10.1, 1.5, NCH_2CH=C$H_A$$H_B$), 5.19 (1H, dd, *J* 17.2, 1.5, NCH_2CH=C$H_A$$H_B$), 5.77–5.90 (1H, m, NCH_2CH=CH_2), 6.75–6.82 (8H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 27.0 (2× *C*(2)), 50.0 (2× *C*(1)), 57.2 (NCH_2CH=CH_2), 66.4 (2× *C*(3)), 115.3 (d, *J* 8.0, 2× *C*(2′), 2× *C*(6′)), 115.7 (d, *J* 23.2, 2× *C*(3′), 2× *C*(5′)), 117.4 (NCH_2CH=*C*H_2), 135.6 (NCH_2*C*H=CH_2), 155.1 (d, *J* 1.6, 2× *C*(1′)), 157.1 (d, *J* 237, 2× *C*(4′)); *m/z* ESI^+ 384 ([M+Na]$^+$, 26%), 362 ([M+H]$^+$, 100%); HRMS (ESI^+) $C_{21}H_{26}F_2NO_2^+$ ([M+H]$^+$) requires 362.1926; found 362.1927. Further elution gave **42** as a yellow oil (8.24 g, 87%); ν_{max} (ATR) 3319 (N–H), 3076, 2925, 2873, 2819 (C–H), 1505 (C=C); δ_H (400 MHz, $CDCl_3$) 1.21 (1H, s, N*H*), 1.89–1.98 (2H, m, C(2)H_2), 2.78 (2H, t, *J* 6.8, C(1)H_2), 3.25 (2H, d, *J* 6.1, NCH_2CH=CH_2), 3.97 (2H, t, *J* 6.3, C(3)H_2), 5.07 (1H, dd, *J* 10.4, 1.8, NCH_2CH=C$H_A$$H_B$), 5.16 (1H, dd, *J* 17.2, 1.8, NCH_2CH=$CH_A$$H_B$), 5.83–5.95 (1H, m, NCH_2CH=CH_2), 6.76–6.84 (2H, m, *C*(2′)*H*, *C*(6′)*H*), 6.89–6.98 (2H, m, C(3′)*H*, *C*(5′)*H*); δ_C (100 MHz, $CDCl_3$) 29.7 (*C*(2)), 46.2 (*C*(1)), 52.5 (NCH_2CH=CH_2), 66.9 (*C*(3)), 115.4 (d, *J* 8.0, *C*(2′), *C*(6′)), 115.6 (NCH_2CH=*C*H_2), 115.7 (d, *J* 23.2, *C*(3′), *C*(5′)), 136.9 (NCH_2*C*H=CH_2), 155.1 (d, *J* 1.6, *C*(1′)), 157.1 (d, *J* 238, *C*(4′)); *m/z* (ESI^+) 232 ([M+Na]$^+$, 20%), 210 ([M+H]$^+$, 100%); HRMS (ESI^+) $C_{12}H_{17}FNO^+$ ([M+H]$^+$) requires 210.1289; found 210.1287.

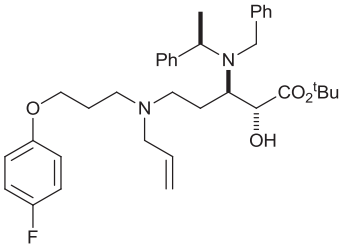
*4.2.18. tert-Butyl (E)-5-[N-allyl-N-3′-(4″-fluorophenoxy)propylamino]pent-2-enoate **44**.*



Acrolein (0.95 mL, 14.1 mmol) was added dropwise to a stirred solution of DBU (21 μL, 0.14 mmol) and **42** (2.96 g, 14.1 mmol) in THF (10 mL) at −15 °C. The reaction was stirred at −15 °C for 40 min then **22** (5.86 g, 15.6 mmol) was added portionwise, and the reaction mixture was stirred at −15 °C for 20 min. The resultant mixture was allowed to warm to rt over

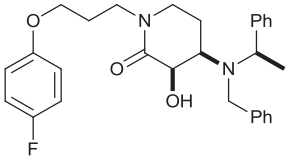
16 h, and then concentrated in vacuo to give **44** in 77:23 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O/Et_3N, 80:20:1) gave **44** as a colourless oil (3.26 g, 70%, >99:1 dr); ν_{max} (ATR) 3077, 2977, 2932, 2811 (C–H), 1710 (C=O), 1652 (C=C); δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, CMe_3), 1.83–1.93 (2H, m, C(2′)H_2), 2.26–2.36 (2H, m, C(4)H_2), 2.54–2.65 (4H, m, C(5)H_2, C(1′)H_2), 3.10 (2H, d, *J* 6.3, NCH_2CH=CH_2), 3.94 (2H, t, *J* 6.3, C(3′)H_2), 5.11 (1H, dd, *J* 10.4, 1.3, NCH_2CH=CH_AH_B), 5.17 (1H, dd, *J* 17.2, 1.3, NCH_2CH=CH_AH_B), 5.74 (1H, d, *J* 16.2, C(2)*H*), 5.77–5.87 (1H, m, NCH_2CH=CH_2), 6.76–6.87 (3H, m, C(3)*H*, *Ar*), 6.90–6.98 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 27.1 (*C*(2′)), 28.1 (CMe_3), 29.8 (*C*(4)), 49.9, 52.2 (*C*(5), *C*(1′)), 57.1 (NCH_2CH=CH_2), 66.5 (*C*(3′)), 80.0 (*C*Me_3), 115.4 (d, *J* 7.2, *C*(2″), *C*(6″)), 115.7 (d, *J* 23.2, *C*(3″), *C*(5″)), 117.3 (NCH_2CH=CH_2), 123.9 (*C*(2)), 135.6 (NCH_2CH=CH_2), 145.9 (*C*(3)), 155.1 (d, *J* 1.6, *C*(1″)), 157.1 (d, *J* 238, *C*(4″)), 165.9 (*C*(1)); *m*/*z* (ESI^+) 386 ($[M+Na]^+$, 27%), 364 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{31}FNO_3^+$ ($[M+H]^+$) requires 364.2282; found 364.2270.

4.2.19. tert-Butyl (R,R,R)-2-hydroxy-3-[N-benzyl-N-(α-methylbenzyl) amino]-5-[N′-allyl-N′-3′-(4″-fluorophenoxy)propylamino]pentanoate ***45****.*



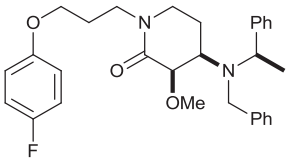
BuLi (2.5 M, 11.7 mL, 29.2 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (6.12 mL, 29.2 mmol) in THF (100 mL) at −78 °C and the resultant mixture was stirred at this temperature for 30 min. A solution of **44** (6.64 g, 18.3 mmol) in THF (80 mL) at −78 °C was then added dropwise. The reaction mixture was stirred at −78 °C for 2 h then (−)-CSO **13** (10.9 g, 36.5 mmol) was added. The reaction mixture was allowed to warm to rt over 16 h, H_2O (10 mL) was added, then the organic layer was dried and concentrated in vacuo to give **45** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc/Et_3N, 66:34:1) gave **45** as a colourless oil (6.91 g, 64%, >99:1 dr); $[\alpha]_D^{25}$ −19.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3502 (O–H), 3062, 3027, 2974, 2933, 2873, 2812 (C–H), 1719 (C=O), 1601, 1505 (C=C, aromatic); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.8, C(α)*Me*), 1.47 (9H, s, CMe_3), 1.44–1.54 (1H, m, C(4)H_A), 1.77 (1H, dtd, *J* 13.5, 8.5, 5.2, C(4)H_B), 1.92 (2H, tt, *J* 7.0, 6.6, C(2′)H_2), 2.39 (1H, ddd, *J* 13.0, 9.6, 6.3, C(5)H_A), 2.63 (2H, td, *J* 7.0, 3.7, C(1′)H_2), 2.74 (1H, ddd, *J* 13.0, 8.8, 4.8, C(5)H_B), 3.06–3.19 (2H, m, N′CH_2CH=CH_2), 3.28 (1H, ddd, *J* 7.6, 5.2, 2.5, C(3)*H*), 3.73 (1H, d, *J* 15.4, NC$H_A$$H_B$Ph), 3.90 (1H, d, *J* 2.5, C(2)*H*), 3.95 (2H, t, *J* 6.6, C(3′)H_2), 3.98 (1H, q, *J* 6.8, C(α)*H*), 4.25 (1H, d, *J* 15.4, NC$H_A$$H_B$Ph), 5.13–5.24 (2H, m, N′CH_2CH=CH_2), 5.81–5.94 (1H, m, N′CH_2C*H*=CH_2), 6.79–7.01 (4H, m, *Ar*), 7.21–7.57 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.4 (C(α)*Me*), 25.1 (*C*(4)), 26.9 (*C*(2′)), 28.0 (CMe_3), 50.1 (*C*(1′)), 51.0 (NCH_2Ph), 52.0 (*C*(5)), 57.0 (N′CH_2CH=CH_2), 58.5 (*C*(3)), 58.8 (*C*(2)), 66.7 (*C*(3′)), 71.5 (*C*(α)), 82.1 (*C*Me_3), 115.4 (d, *J* 8.0, *C*(2″), C(6″)), 115.7 (d, *J* 22.4, *C*(3″), C(5″)), 117.5 (N′CH_2CH=CH_2), 126.5, 127.0 (*p-Ph*), 127.9, 128.1, 128.2, 128.2 (*o*,*m-Ph*), 135.6 (N′CH_2CH=CH_2), 142.3, 143.3 (*i-Ph*), 155.2 (d, *J* 2.4, *C*(1″)), 157.1 (d, *J* 237, *C*(4″)), 174.2 (*C*(1)); *m*/*z* (ESI^+) 591 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{36}H_{48}FN_2O_4^+$ ($[M+H]^+$) requires 591.3593; found 591.3580.

4.2.20. (R,R,R)-N(1)-[3′-(4″-Fluorophenoxy)propyl]-3-hydroxy-4-[N-benzyl-N-(α-methylbenzyl)amino]-piperidin-2-one ***47****.*



$Pd(PPh_3)_4$ (42 mg, 0.04 mmol) was added to a mixture of **45** (2.16 g, 3.65 mmol) and DMBA (1.71 g, 11.0 mmol) in de-gassed CH_2Cl_2 (40 mL) at 35 °C. The reaction mixture was then stirred for 3 h at 35 °C in the dark, then concentrated in vacuo. The residue was then dissolved in toluene (40 mL) and $PhCO_2H$ (20 mg, 0.17 mmol) was added. The resultant solution was stirred at 80 °C for 16 h then 2.0 M aq Na_2CO_3 (25 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic extracts were washed with brine (50 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 50:50) gave **47** as a yellow oil (1.72 g, 99%, >99:1 dr); $[\alpha]_D^{25}$ +32.0 (*c* 0.91 in $CHCl_3$); ν_{max} (ATR) 3307 (O–H), 3083, 3060, 3027, 2970, 2940, 2874 (C–H), 1639 (C=O), 1627 (C=C); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, d, *J* 6.8, C(α)*Me*), 1.92–2.12 (4H, m, C(2′)H_2, C(5)H_2), 3.20–3.26 (2H, m, C(6)H_2), 3.34 (1H, app dt, *J* 8.6, 6.8, C(4)*H*), 3.53 (2H, t, *J* 7.1, C(1′)H_2), 3.78 (1H, d, *J* 14.7, NC$H_A$$H_B$Ph), 3.82–3.91 (4H, m, NCH_AH_BPh, C(3′)H_2, O*H*), 3.96 (1H, dt, *J* 6.3, 3.3, C(3)*H*), 4.23 (1H, q, *J* 6.8, C(α)*H*), 6.71–6.98 (4H, m, *C*(2″), *C*(3″), *C*(5″), *C*(6″)), 7.20–7.50 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.1 (C(α)*Me*), 25.0 (*C*(5)), 27.4 (*C*(2′)), 44.6 (*C*(1′)), 45.0 (*C*(6)), 51.2 (NCH_2Ph), 54.5 (*C*(4)), 57.8 (*C*(α)), 66.0 (*C*(3′)), 69.7 (*C*(3)), 115.4 (d, *J* 8.0, *C*(2″), *C*(6″)), 115.8 (d, *J* 23.2, *C*(3″), *C*(5″)), 126.9, 127.0 (*p-Ph*), 127.7, 128.3, 128.4, 128.4 (*o*,*m-Ph*), 141.5, 144.0 (*i-Ph*), 154.8 (d, *J* 2.4, *C*(1″)), 157.3 (d, *J* 238, *C*(4″)), 171.7 (*C*(2)); δ_F (470 MHz, $CDCl_3$) 123.9 (C(4″)*F*); *m*/*z* (FI^+) 476 ($[M]^+$, 100%); HRMS (FI^+) $C_{29}H_{33}FN_2O_3^+$ ($[M]^+$) requires 476.2470; found 476.2478.

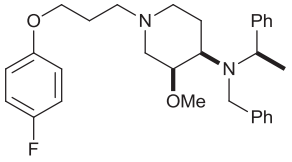
4.2.21. (R,R,R)-N(1)-[3′-(4″-Fluorophenoxy)propyl]-3-methoxy-4-[N-benzyl-N-(α-methylbenzyl)amino]piperidin-2-one ***48****.*



A solution of **47** (1.31 g, 2.76 mmol) in THF (15 mL) was added dropwise via cannula to a solution of NaH (60% in mineral oil, 121 mg, 3.03 mmol) in THF (15 mL) at 0 °C. The reaction mixture was allowed to warm to rt over 1 h, then MeI (0.52 mL, 8.3 mmol) was added dropwise. The resulting solution was stirred at rt for 16 h then H_2O (20 mL) was carefully added. The aqueous layer was extracted with EtOAc (2×40 mL). The combined organic layers were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 50:50) gave **48** as a colourless oil (1.04 g, 77%, >99:1 dr); $[\alpha]_D^{25}$ +46.8 (*c* 0.9 in $CHCl_3$); ν_{max} (ATR) 3060, 3027, 2935, 2827 (C–H), 1638 (C=O), 1601 (C=C, aromatic); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.8, C(α)*Me*), 1.85–1.94 (1H, m, C(5)H_A), 1.96–2.05 (2H, m, C(2′)H_2), 2.34–2.44 (1H, m, C(5)H_B), 2.88 (1H, app dt, *J* 12.4, 3.3, C(4)*H*), 3.15–3.38 (3H, m, C(6)H_A, C(6)H_B, C(1′)H_A), 3.57 (1H, d, *J* 2.5, C(3)*H*), 3.60 (3H, s, O*Me*), 3.61–3.67 (1H, m, C(1′)H_B), 3.87–3.96 (3H, m, C(3′)H_2, NC$H_A$$H_B$Ph), 4.10 (1H, q, *J* 6.8, C(α)*H*), 4.30 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 6.78–7.03 (4H, m, O*Ar*), 7.20–7.54 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$)

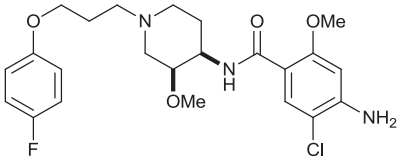
14.4 (C(α)*Me*), 22.7 (*C*(5)), 26.9 (*C*(2′)), 43.8 (*C*(1′)), 46.6 (*C*(6)), 52.0 (NCH_2Ph), 54.4 (*C*(4)), 57.0 (*C*(α)), 59.3 (O*Me*), 66.1 (*C*(3′)), 82.9 (*C*(3)), 115.4 (d, *J* 8.0, *C*(2″), *C*(6″)), 115.8 (d, *J* 22.4, *C*(3″), *C*(5″)), 126.7, 126.8, 127.5, 128.2, 128.3, 128.3 (*o*,*m*,*p*-*Ph*), 142.1, 144.3 (*i*-*Ph*), 154.9 (d, *J* 2.4, C(1″)), 157.3 (d, *J* 238, *C*(4″)), 168.6 (*C*(2)); δ_F (470 MHz, $CDCl_3$) 124.0 (C(4″)*F*); *m*/*z* (ESI^+) 491 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{30}H_{36}FN_2O_3^+$ ($[M+H]^+$) requires 491.2704; found 491.2682.

4.2.22. (3S,4R,αR)-N(1)-(3′-(4″-Fluorophenoxy)propyl)-3-methoxy-4-[N-benzyl-N-(α-methylbenzyl)amino]piperidine ***49****.*



$LiAlH_4$ (1.0 M in THF, 4.57 mL, 4.57 mmol) was added dropwise to a solution of **48** (747 mg, 1.52 mmol) in THF (30 mL) at 0 °C. The reaction was stirred at reflux for 16 h then cooled to 0 °C and quenched by careful addition of 2 M aq NaOH (5 mL). The reaction mixture was diluted with EtOAc (30 mL) and filtered through Celite® (eluent EtOAc). The filtrate was dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc/Et_3N, 50:50:1) gave **49** as a white solid (716 mg, 99%, >99:1 dr); mp 63–67 °C; $[\alpha]_D^{25}$ +50.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3084, 3061, 3027, 2954 (C–H), 1601, 1506 (C=C, aromatic); δ_H (400 MHz, $CDCl_3$) 1.36 (3H, d, *J* 6.8, C(α)*Me*), 1.60 (1H, app br d, *J* 11.9, C(2)H_A), 1.67 (1H, dd, *J* 12.5, 2.7, C(6)H_A), 1.88–2.04 (3H, m, C(2′)H_2, C(5)H_A), 2.25 (1H, qd, *J* 12.5, 3.9, C(6)H_B), 2.35–2.45 (1H, m, C(1′)H_A), 2.47–2.57 (2H, m, C(4)*H*, C(1′)H_B), 3.00 (1H, br d, *J* 10.4, C(5)H_B), 3.08 (1H, dt, *J* 12.5, 2.4, C(2)H_B), 3.17 (1H, s, C(3)*H*), 3.41 (3H, s, O*Me*), 3.90–3.96 (3H, m, C(3′)H_2, NC$H_A$$H_B$Ph), 4.11 (1H, q, *J* 6.8, C(α)*H*), 4.28 (1H, d, *J* 14.3, NC$H_A$$H_B$Ph), 6.78–7.00 (4H, m, *Ar*), 7.18–7.51 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.5 (C(α)*Me*), 25.8 (*C*(6)), 26.9 (*C*(2′)), 51.8 (NCH_2Ph), 54.1 (*C*(5)), 54.4 (*C*(2)), 55.3 (*C*(1′)), 56.5 (*C*(α)), 56.8 (*C*(4)), 56.9 (O*Me*), 67.1 (*C*(3′)), 80.0 (*C*(3)), 115.4 (d, *J* 8.0, *C*(2″), *C*(6″)), 115.7 (d, *J* 22.4, *C*(3″), *C*(5″)), 126.3, 127.7 (*p*-*Ph*), 127.9, 128.1, 128.1, 128.5 (*o*,*m*-*Ph*), 142.9, 145.2 (*i*-*Ph*), 155.1 (d, *J* 2.4, *C*(1″)), 157.1 (d, *J* 238, *C*(4″)); δ_F (376 MHz, $CDCl_3$) 124.2 (C(4″)*F*); *m*/*z* (ESI^+) 477 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{30}H_{38}FN_2O_2^+$ ($[M+H]^+$) requires 477.2912; found 477.2906.

4.2.23. (3S,4R)-N(1)-[3′-(4″-Fluorophenoxy)propyl]-3-methoxy-4-(2‴-methoxy-4‴-amino-5‴-chlorobenzamido)piperidine [(+)-(3S,4R)-cisapride] ***40****.*



Step 1: $Pd(OH)_2/C$ (276 mg) was added to a solution of **49** (552 mg, 1.15 mmol) in de-gassed MeOH (20 mL). The resultant suspension was vigorously stirred under H_2 (1 atm) for 16 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and the filtrate was concentrated in vacuo to give **50** as a colourless oil (296 mg, 91%, >99:1 dr);[32] $[\alpha]_D^{25}$ +24.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3375 (N–H), 2929, 2820 (C–H), 1600, 1505 (C=C, aromatic); δ_H (400 MHz, $CDCl_3$) 1.62–1.80 (2H, m, C(5)H_2), 1.93–2.02 (2H, m, C(2′)H_2), 2.10–2.31 (2H, m, C(2)H_A, C(6)H_A), 2.48–2.62 (2H, m, C(1′)H_2), 2.70–2.80 (1H, br m, C(6)H_B), 2.80–2.89 (1H, br m, C(4)*H*), 2.95–3.11 (1H, br m, C(2)H_B), 3.33–3.37 (1H, m, C(3)*H*), 3.40 (3H, s, O*Me*), 3.99 (2H, t, *J* 6.1, C(3′)H_2), 6.87–7.03 (4H, m, *Ar*); *m*/*z* (ESI^+) 283 ($[M+H]^+$, 50%); HRMS (ESI^+) $C_{15}H_{24}FN_2O_2^+$ ($[M+H]^+$) requires 283.1816; found 283.1813.

Step 2: $ClCO_2Et$ (92 μL, 0.96 mmol) was added dropwise to a solution of **51** (247 mg, 0.86 mmol) and Et_3N (121 μL, 0.88 mmol) in THF (5 mL) at 0 °C, and the reaction mixture was stirred for 2 h. A solution of **50** (194 mg, 0.96 mmol) in THF (1 mL) was then added dropwise via cannula and the reaction was allowed to warm to rt over 16 h. The insoluble residue was filtered, and the filtrate was concentrated in vacuo. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH/Et_3N, 96:3:1) gave **40** as a colourless oil (205 mg, 64% from **49**, >99:1 dr); $[\alpha]_D^{25}$ +3.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3576, 3525, 3469, 3326, 3006, 2970, 2929, 2856, 1738, 1629; δ_H (500 MHz, $CDCl_3$) 1.79–1.92 (2H, m, C(5)H_2), 1.95–2.05 (2H, m, C(2′)H_2), 2.16–2.29 (2H, m, C(2)H_A, C(6)H_A), 2.50–2.61 (2H, m, C(1′)H_2), 2.76–2.88 (1H, m, C(6)H_B), 3.01–3.16 (1H, m, C(2)H_B), 3.44 (3H, s, O*Me*), 3.44–3.47 (1H, m, C(3)*H*), 3.89 (3H, s, O*Me*), 3.93–4.01 (2H, m, C(3′)H_2), 4.17–4.25 (1H, m, C(4)*H*), 4.37 (2H, s, NH_2), 6.30 (1H, s, C(3‴)*H*), 6.80–6.87 (2H, m, C(2″)*H*, C(6″)*H*), 6.93–7.00 (2H, m, C(3″)*H*, C(5″)*H*), 8.11 (1H, s, C(6‴)*H*), 8.21 (1H, d, *J* 8.2, CON*H*); δ_C (125 MHz, $CDCl_3$) 26.8 (*C*(2′)), 27.8 (*C*(5)), 48.0 (*C*(4)), 51.9 (*C*(6)), 53.6 (*C*(2)), 55.2 (*C*(1′)), 56.0, 57.0 (2× O*Me*), 66.9 (*C*(3′)), 76.7 (*C*(3)), 97.9 (*C*(3‴)), 111.6 (*C*(1‴)), 112.9 (*C*(5‴)), 115.4 (d, *J* 7.6, *C*(2″), *C*(6″)), 115.7 (d, *J* 22.9, *C*(3″), *C*(5″)), 133.1 (*C*(6‴)), 146.5 (*C*(4‴)), 155.1 (d, *J* 1.9, *C*(1″)), 157.2 (d, *J* 238, *C*(4″)), 157.5, 163.7 (*C*(2‴), *C*(1‴)CONH); δ_F (470 MHz, $CDCl_3$) 124.2 (C(4″)F); *m*/*z* (ESI^+) 466 ($[M(^{35}Cl)+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{30}{}^{35}ClFN_3O_4^+$ ($[M(^{35}Cl)+H]^+$) requires 466.1903; found 466.1902.

Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.12.084.

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21. The corresponding (*Z*)-diastereoisomers were not isolated.
22. Enantiopure (*R*)-α-methylbenzylamine (99% ee) is commercially available. Reductive alkylation of (*R*)-α-methylbenzylamine upon treatment with benzaldehyde and $NaBH_4$ gave (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine; subsequent deprotonation with BuLi in THF generated a pink solution of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**32**.
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