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Asymmetric synthesis of *anti*-(2*S*,3*S*)- and *syn*-(2*R*,3*S*)-diaminobutanoic acid †

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Conjugate addition of homochiral lithium *N*-benzyl-*N*-α-methylbenzylamide to *tert*-butyl (*E*)-cinnamate or *tert*-butyl (*E*)-crotonate and *in situ* amination with trisyl azide results in the exclusive formation of the corresponding 2-diazo-3-amino esters in >95% de. Amination of the lithium (*E*)-enolates of *tert*-butyl (3*S*,α*R*)-3-*N*-benzyl-*N*-α-methylbenzylamino-3-phenylpropanoate or *tert*-butyl (3*S*,α*S*)-3-*N*-benzyl-*N*-α-methylbenzylaminobutanoate with trisyl azide gives the (2*R*,3*R*,α*R*)- and (2*S*,3*S*,α*S*)-*anti*-2-azido-3-amino esters in good yields and in 85% de and >95% de respectively. Alternatively, *tert*-butyl *anti*-(2*S*,3*S*,α*S*)-2-hydroxy-3-*N*-benzyl-*N*-α-methylbenzylaminobutanoate may be converted selectively to *tert*-butyl *anti*-(2*S*,3*S*,α*S*)-2-azido-3-*N*-benzyl-*N*-α-methylbenzylaminobutanoate by aziridinium ion formation and regioselective opening with azide. Deprotection of *tert*-butyl (2*S*,3*S*,α*S*)-2-azido-3-aminobutanoate *via* Staudinger reduction, hydrogenolysis and ester hydrolysis furnishes *anti*-(2*S*,3*S*)-diaminobutanoic acid in 98% de and 98% ee. The asymmetric synthesis of the diastereomeric *syn*-(2*R*,3*S*)-diaminobutanoic acid (98% de and 98% ee) was accomplished *via* functional group manipulation of *tert*-butyl *anti*-(2*S*,3*S*,α*S*)-2-hydroxy-3-*N*-benzyl-*N*-α-methylbenzylaminobutanoate in a protocol involving azide inversion of *tert*-butyl (2*S*,3*S*)-2-mesyloxy-3-*N*-Boc-butanoate and subsequent deprotection.

Introduction

2,3-Diamino acids are a naturally occurring and diverse set of bioactive compounds that have attracted considerable commercial and academic interest.[1] This simple, polyfunctional motif can be incorporated into peptide chains and utilised to stabilise specific conformations,[2] and can be used in the preparation of 3-amino-2-azetidinones, a medically important class of β-lactam antibiotics.[3] Furthermore, they can be utilised in the production of imidazolines for use as amide bond replacements in peptidomimetic design,[4] although the interest in these diamino acids resides primarily with their occurrence in a number of peptide antibiotics. For instance (*S*)-2,3-diaminopropanoic acid **1** is a component of the neurotoxin (*S*)-2-*N*-oxalyl-2,3-diaminopropanoic acid,[5] as well as capreomycin,[6] and the antifungal dipeptides Sch37137 and A19009.[7] A family of 2,3-diamino acids bearing a C(3)-stereogenic centre have also been identified, with (2*S*,3*S*)-2,3-diaminobutanoic acid **2** a component of a variety of peptide antibiotics including lavendomycin,[8] glumamycin,[9] antrimycin,[10] and cirratiomycin,[11] and has been shown to occur with its C(2)-epimer, *syn*-(2*R*,3*S*)-**3**, in the antibiotics amphomycin[12] and aspartocin.[13] Further examples include (2*S*,3*R*)-2,3-diamino-4-phenylbutanoic acid **4**, the amino acid of aminodeoxybestatin,[14] while (2*R*,3*S*)-2,3-diamino-3-phenylpropanoic acid **5** has been considered as an alternative sidechain of the anticancer drug Taxol (Fig. 1).[15]

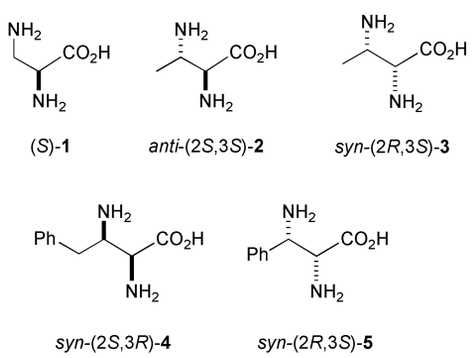

Fig. 1 Homochiral 2,3-diaminoacids.

A range of methodologies for the asymmetric synthesis of this class of amino acid have been reported, with perhaps the most popular involving manipulation of pre-existing stereodefined functionality within material available from the chiral pool. For instance, Mitsunobu reaction[16] or functional group transformations of either threonine[17] or serine[18] derivatives have been applied to the synthesis of 2,3-diaminoacids, while Rapoport *et al.* have shown that the (2*S*,3*S*)- and (2*S*,3*R*)-diastereoisomers of 2,3-diamino-4-phenylbutanoic acid may be prepared by alkylation of an aspartic acid derivative.[19] An alternative route to this molecular class has been reported by Merino *et al.*, who have shown that the addition of Grignard reagents to nitrones derived from L-serine offers an efficient route to protected *syn*- or *anti*-3-substituted 2,3-diaminoacids.[20] A variety of other syntheses of this class of diamino acid have also been reported, including the preparation of the four diastereoisomers of *N*,*N*-protected 2,3-diaminobutanoic acid using an asymmetric Rh(I)-phosphine-catalysed hydrogenation of diastereomeric enamides,[21] azide opening of *cis*-3-alkylaziridene-2-carboxylates,[22] application of an asymmetric Strecker reaction,[23] epoxidation of 1-tolylthio-1-nitroalkenes and trapping with ammonia,[24] and the application of Sharpless asymmetric aminohydroxylation to α,β-unsaturated enones and subsequent functional group manipulation.[25] Previous work from this laboratory has demonstrated that the conjugate addition of homochiral lithium amides derived from α-methylbenzylamine to α,β-unsaturated acceptors and subsequent deprotection offers an efficient and versatile route for the asymmetric synthesis of a range of β-amino acid derivatives. Furthermore, this methodology allows for the synthesis of *anti*-α-alkyl-β-amino esters[26] and *anti*-α-hydroxy-β-amino esters[27] by elaboration of β-amino ester enolates through reaction with either an alkyl halide or oxaziridine respectively (Scheme 1).

† This is one of a number of contributions from the current members of the Dyson Perrins Laboratory to mark the end of almost 90 years of organic chemistry research in that building, as all its current academic staff move across South Parks Road to a new purpose-built laboratory.

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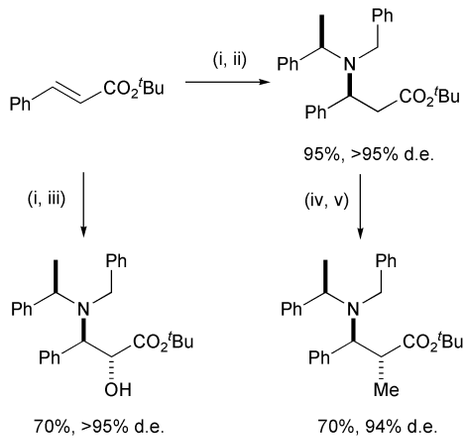


Scheme 1 *Reagents and conditions*: (i). lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide, THF, −78 °C; (ii). NH_4Cl (aq); (iii). (−)-camphorsulfonyloxaziridine, THF, −78 °C to rt; (iv). LDA, THF, −78 °C; (v). MeI, −78 °C to rt.

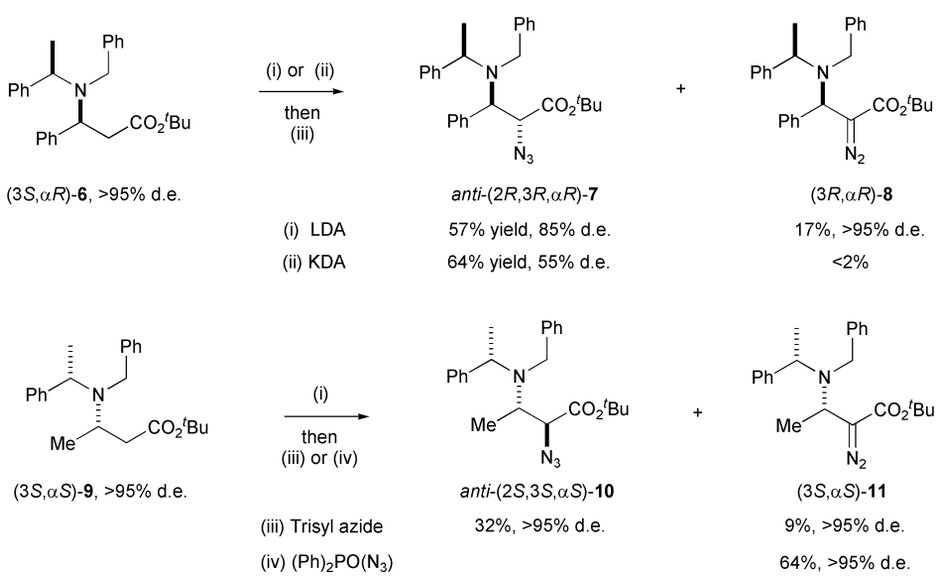
The extension of this methodology to the synthesis of 2,3-diamino acids *via* amination of the enolates of β-amino esters with an electrophilic nitrogen source is described herein, with application to the synthesis of *anti*-(2*S*,3*S*)- and *syn*-(2*R*,3*S*)-diaminobutanoic acid. Part of this work has been the subject of a preliminary communication.[28]

Results and discussion

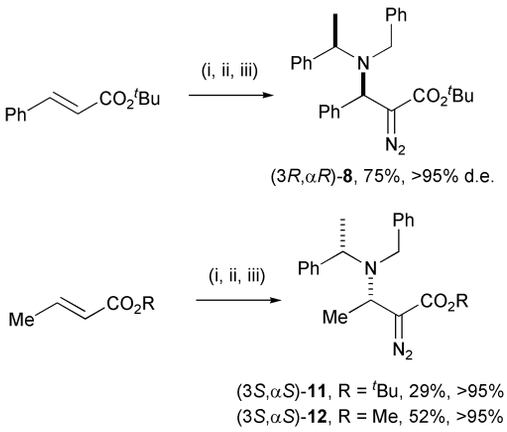
Amination of β-amino ester enolates: asymmetric synthesis of *anti*-2-azido-3-amino esters

Initial investigations concentrated upon an evaluation of the diastereoselectivity observed upon the amination of crotonate and cinnamate derived β-amino enolates, with trisyl azide used as an electrophilic nitrogen source for the installation of azide at C(2) within β-amino esters.[29] Treatment of *tert*-butyl (3*S*,α*R*)-3-*N*-benzyl-*N*-α-methylbenzylamino-3-phenylpropanoate **6** (>95% de)[30] with LDA and subsequent reaction of the lithium (*E*)-β-amino enolate of (3*S*,α*R*)-**6** with trisyl azide gave a mixture of two distinct components. The major isolated product from the reaction was the desired *anti*-(2*R*, 3*R*, α*R*)-2-azido-3-amino ester **7** in 57% yield and 85% de, indicating that the amination procedure proceeded with high levels of selectivity upon formation of the new stereogenic centre at C(2). The (3*R*,α*R*)-2-diazo-3-amino ester **8** was also isolated from this procedure in 17% yield and in >95% de, consistent with the stereochemical integrity of the C(3) stereocentre arising from diastereoselective conjugate addition remaining intact during this transformation. As Evans *et al.* have demonstrated that the use of potassium enolates minimises the extent of diazo transfer in the reaction of trisyl azide with oxazolidinone enolates,[31] application of this protocol to generate the potassium β-amino enolate of (3*S*,α*R*)-**6** was attempted. Deprotonation of (3*S*,α*R*)-**6** with KDA and amination with trisyl azide gave essentially exclusive azido transfer, furnishing an inseparable diastereoisomeric mixture of *anti*-(2*R*,3*R*,α*R*)- and *syn*-(2*S*,3*R*,α*R*)-2-azido-3-amino esters **7** in 64% yield but in only 55% de, indicating that although the use of the potassium enolate in this reaction manifold has the desired effect upon minimisation of diazo-transfer, it also has a detrimental effect upon reaction diastereoselectivity (Scheme 2). In the crotonate series, application of this amination protocol *via* generation of the lithium (*E*)-β-amino enolate of *tert*-butyl (3*S*,α*S*)-3-*N*-benzyl-*N*-α-methylbenzylaminobutanoate **9** (>95% de) by treatment with LDA and subsequent reaction with trisyl azide gave, at 70% conversion, the desired *anti*-(2*S*,3*S*,α*S*)-2-azido-3-amino ester **10** in 32% yield (43% yield based upon recovered starting material) and in >95% de, and the (3*S*,α*S*)-2-diazo-3-amino ester **11** in 9% yield (>95% de) respectively. Attempts to improve the yield of *anti*-(2*S*,3*S*,α*S*)-2-azido-3-amino ester **10** *via* the use of an alternative electrophilic azide source was examined, but reaction with the lithium (*E*)-β-amino enolate of (3*S*,α*S*)-**9** with diphenylphosphoryl azide gave exclusively the (3*S*,α*S*)-2-diazo-3-amino ester **11** in 64% yield (>95% de).[32] In each case, the C(2)–C(3) *anti* relative configuration within the 2-azido-3-amino esters **7** and **10** was assigned by analogy to the known *anti*-selectivity noted upon hydroxylation of β-amino enolate **6** (Scheme 2).

Having demonstrated that trisyl azide allows the incorporation of nitrogen in the 2-position of lithium (*E*)-β-amino enolates, the efficiency of a tandem conjugate addition–amination protocol was next examined. Thus, conjugate addition of homochiral lithium *N*-benzyl-*N*-α-methylbenzylamide to *tert*-butyl cinnamate, *tert*-butyl crotonate or methyl crotonate generated the requisite (*Z*)-β-amino enolates, and subsequent addition of trisyl azide, gave, in each case, the 2-diazo-3-amino esters **8**, **11** and **12** in >95% de, consistent with the stereochemical integrity of the C(3) stereocentre from conjugate addition remaining intact (Scheme 3). Although this tandem conjugate addition–amination protocol allows for three component coupling and the diastereoselective synthesis of



Scheme 2 *Reagents and conditions*: (i). LDA, THF, −78 °C; (ii). KO^{t}Bu, ^{i}Pr$_2$NH, *n*-BuLi, THF; (iii). trisyl azide, −78 °C then AcOH; (iv). diphenylphosphoryl azide, −78 °C then AcOH.



Scheme 3 *Reagents and conditions*: (i). lithium (*R*)- or (*S*)-*N*-benzyl-*N*-α-methylbenzylamide, THF, −78 °C; (ii). trisyl azide, −78 °C; (iii). AcOH.

homochiral 2-diazo-3-amino esters, it is not applicable for the synthesis of 2-azido-3-amino esters.

Although the synthesis of *anti*-2-azido-3-aminobutanoates may be achieved with high levels of diastereoselectivity by enolate amination with trisyl azide, an alternative strategy for the synthesis of this motif was devised. It was envisaged that *in situ* aziridinium ion formation following neighbouring group participation of the C(3)-amino substituent onto an activated form of the known *anti*-2-hydroxy-3-amino ester **13**,[27] coupled with subsequent regioselective ring opening would install the desired C(2)-amino functionality with overall retention of configuration (Fig. 2).

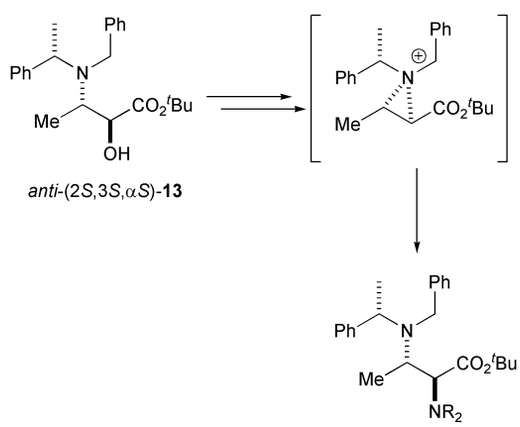
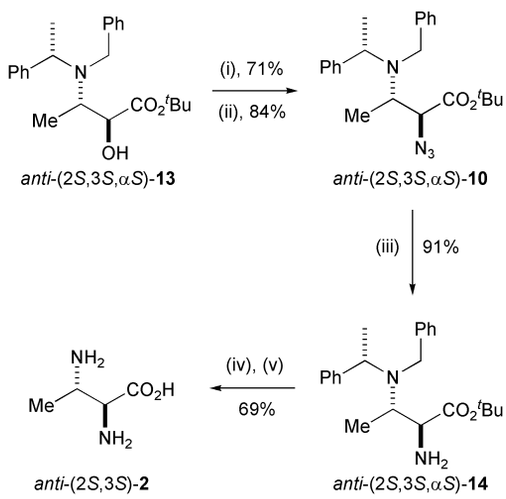


Fig. 2

The regioselectivity of aziridinium ion ring opening has been investigated by a variety of research groups,[33] with monosubstituted aziridinium ions generally undergoing nucleophilic attack at the least sterically hindered position,[34] although this regioselectivity is dependent upon the nature of the nucleophile.[35] Chuang and Sharpless have also recently demonstrated that ring opening at the benzylic C(3)-position of C(2)-ester and C(3)-aryl *bis*-substituted aziridinium ions is favoured, giving β-aryl-α,β-diamino esters in good yields and with high selectivity.[36] To investigate the efficiency of the proposed double inversion protocol, it was envisaged that Mitsunobu activation of *anti*-2-hydroxy-3-amino ester (2*S*,3*S*,α*S*)-**13** would result in aziridinium formation, with displacement using an azide source giving the *anti*-2-azido-3-amino ester. Thus, treatment of (2*S*,3*S*,α*S*)-**13** (98% de) with PPh_3, DEAD and diphenylphosphoryl azide gave selectively the *anti*-(2*S*,3*S*,α*S*)-2-azido-3-amino ester **10**, in 71% isolated yield and 98% de, with identical spectroscopic properties to that prepared from azidation of the lithium (*E*)-enolate of (3*S*,α*S*)-**9**. A similar reaction with hydrazoic acid as the nitrogen nucleophile gave (2*S*,3*S*,α*S*)-**10** in 84% isolated yield and 98% de. With *anti*-(2*S*,3*S*,α*S*)-2-azido-3-amino ester **10** in hand from both amination and double inversion protocols, reduction to the corresponding *anti*-(2*S*,3*S*,α*S*)-2,3-diamino ester **14** by application of the Staudinger reaction was followed,[37] giving diamine (2*S*,3*S*,α*S*)-**14** in 91% yield and in 98% de. *N*-Deprotection *via* hydrogenolysis and subsequent ester hydrolysis, followed by purification by ion exchange chromatography, gave *anti*-(2*S*,3*S*)-2,3-diaminobutanoic acid **2** {$[a]_D^{26}$ +12.3 (*c* 0.37, 6 M HCl]; lit.[38] $[a]_D^{22}$ +10.3 (*c* 1.0, 6 M HCl)} in 98% de and 98% ee, having spectroscopic data consistent with that of the literature. This assignment serves to confirm not only the sense of asymmetric induction upon amination of the (*E*)-β-amino enolate of (3*S*,α*S*)-**9** with trisyl azide, but also the regioselectivity of nucleophilic attack during the double inversion protocol (Scheme 4).

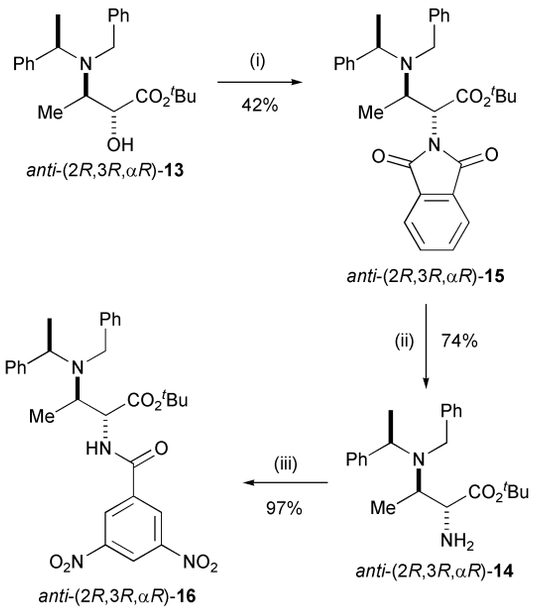


Scheme 4 *Reagents and conditions*: (i). DEAD (2 eq.), PPh_3 (2 eq.), diphenylphosphoryl azide (15 eq.), THF, rt; (ii). hydrazoic acid (4.5 eq.), PPh_3 (4.3 eq.), DEAD (4.3 eq.), benzene, rt; (iii). PPh_3, THF–H_2O, rt; (iv). $Pd(OH)_2$ on C, EtOH, H_2 (5 atm), 55 °C; (v). TFA, rt then 1 M $HCl_{(aq)}$ then Dowex 50X8-200.

The efficiency of this double inversion protocol using phthalimide as the nitrogen source was similarly investigated, with reaction of *anti*-2-hydroxy-3-amino ester (2*R*,3*R*,α*R*)-**13** (98% de) with phthalimide in the presence of PPh_3 and DEAD giving (2*R*,3*R*,α*R*)-2-phthalimido-3-amino ester **15** in 42% yield and 98% de. Deprotection with hydrazine[39] gave diamine (2*R*,3*R*,α*R*)-**14**, which was characterised as its 3,5-dinitrobenzoyl derivative **16** (Scheme 5). Although this approach allows for the synthesis of the *anti*-2,3-diamino ester **14**, the use of diphenylphosphoryl azide or hydrazoic acid as the nitrogen source in this double inversion protocol are much more efficient procedures, allowing the synthesis of the target diamino acid in good yield.

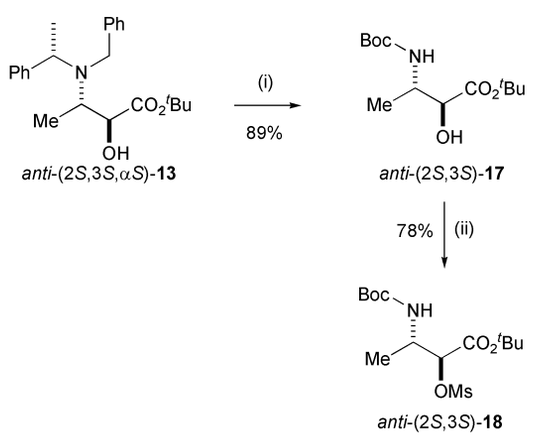
Asymmetric synthesis of *syn*-2-azido-3-amino esters

Having demonstrated an efficient asymmetric synthesis of *anti*-(2*S*,3*S*)-2,3-diaminobutanoic acid *via* either enolate amination or functional group manipulation, synthesis of the diastereoisomeric *syn*-(2*R*,3*S*)-2,3-diaminobutanoic acid was attempted. Previous investigations from within this laboratory have shown that Mitsunobu inversion of 2-hydroxy-3-amino ester (2*S*,3*S*,α*S*)-**13** may be controlled efficiently by neighbouring group participation of a C(3)-*N*-benzoyl group upon treatment with PPh_3 and DEAD and hydrolysis of the resultant oxazoline.[40] In order to install nitrogen functionality at C(2) with inversion of configuration, aziridinium ion formation from C(3)-*N*-participation, or oxazoline formation from participation of an *N*-acyl fragment had to be prevented. It was predicted that a protecting group combination of *N*-Boc at C(3), coupled with C(2)-hydroxy activation *via* mesylation would allow direct S_N2



Scheme 5 *Reagents and conditions*: (i). DEAD (2 eq.), PPh_3 (2 eq.), phthalimide (7.5 eq.), THF, rt; (ii). hydrazine monohydrate (3.5 eq.), EtOH, 0 °C then AcOH, 0 °C to rt; (iii). 3,5-dinitrobenzoyl chloride, NEt_3, DCM, rt.

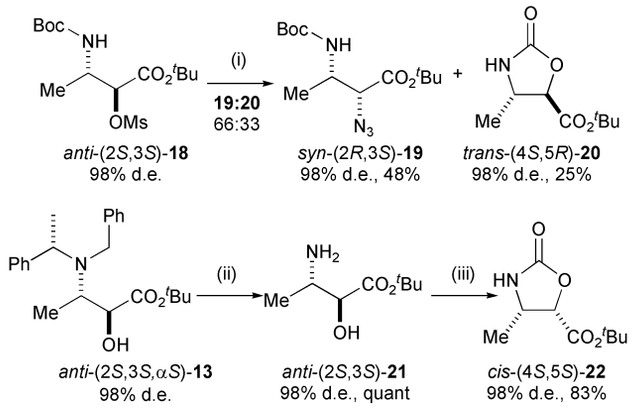
displacement at C(2) with azide.[41] The 2-hydroxy-3-amino ester (2*S*,3*S*,α*S*)-**13** was first *N*-debenzylated and trapped *in situ* with Boc_2O, giving *anti*-(2*S*,3*S*)-2-hydroxy-3-*N*-Boc ester **17** in 89% yield and 98% de. Mesylate (2*S*,3*S*)-**18** (98% de) was subsequently isolated in 78% yield by treatment of 3-*N*-Boc ester (2*S*,3*S*)-**17** with methanesulfonyl chloride and NEt_3 (Scheme 6).



Scheme 6 *Reagents and conditions*: (i). $Pd(OH)_2$ on C, H_2 (5 atm), Boc_2O (3.7 eq.), EtOAc, rt; (ii). $MeSO_2Cl$ (1.1 eq.), NEt_3 (1.5 eq.), DCM, 0 °C (30 min) then rt.

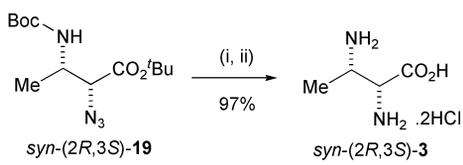
Attempted displacement of mesylate (2*S*,3*S*)-**18** with sodium azide gave, at 75% conversion, a 66 : 33 mixture of two separable components, identified as the *syn*-2-azido-3-*N*-Boc ester (2*R*,3*S*)-**19** (the product of direct azide displacement) in 48% isolated yield and 98% de (64% yield based on recovered starting material), and *trans*-oxazolidinone (4*S*,5*R*)-**20** (the product of neighbouring group *N*-Boc participation) in 25% isolated yield and 98% de. The (4*S*,5*R*)-configuration within *trans*-oxazolidinone **20** was confirmed by the preparation of an authentic sample of the epimeric *cis*-oxazolidinone from the known 2-hydroxy-3-amino ester (2*S*,3*S*,α*S*)-**13** *via* hydrogenolysis to amino alcohol (2*S*,3*S*)-**21** (quantitative yield, 98% de) and subsequent treatment with diphosgene, giving *cis*-(4*S*,5*S*)-**22** in 98% de and in 83% yield (Scheme 7).

Subequent *N*-Boc deprotection and ester hydrolysis of *syn*-2-azido-3-*N*-Boc ester (2*R*,3*S*)-**19** gave the desired *syn*-diamino



Scheme 7 *Reagents and conditions*: (i). NaN_3 (4.6 eq.), DMF, 55 °C; (ii). $Pd(OH)_2$ on C, H_2 (5 atm), rt; (iii). diphosgene, toluene, activated charcoal, rt.

acid (2*R*,3*S*)-**3** as its dihydrochloride salt {$[\alpha]_D^{25}$ −34.5 (*c* 1.15, 6 M HCl); lit.[38] (i). $[\alpha]_D^{22}$ −38.1 (*c* 1.0, 6 M HCl), (ii). lit.[25] $[\alpha]_D^{25}$ −34.3 (*c* 1.0, 6 M HCl)} in 98% de and 98% ee, with NMR spectroscopic properties consistent with those reported in the literature (Scheme 8).[42]



Scheme 8 *Reagents and conditions*: (i). Pd/C, H_2 (5 atm), EtOAc, rt; (ii). TFA, rt overnight then 1 M $HCl_{(aq)}$, rt.

In conclusion, the asymmetric synthesis of *anti*-(2*S*,3*S*)- and *syn*-(2*R*,3*S*)-2,3-diaminobutanoic acid has been completed *via* a strategy involving the conjugate addition of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide to *tert*-butyl crotonate. As both enantiomers of *N*-benzyl-*N*-α-methylbenzylamine are readily available in homochiral form, all four stereoisomers of 2,3-diaminobutanoic acid should be readily available by application of this synthetic strategy, which represents a general and efficient route to this class of compound. Furthermore, the identification of methodology for the asymmetric synthesis of α-diazo-β-amino esters with excellent diastereoselectivity has also been achieved. The application of this methodology for the synthesis of libraries of homochiral 2,3-diamino acids, and the utilisation of homochiral aziridinium ions for natural product synthesis is currently underway within our laboratory.

Experimental

General experimental

Melting points were determined using either Gallenkamp or Koffler hot stage apparatus and are uncorrected. Specific rotations were recorded using a Perkin-Elmer 241 polarimeter with a thermally jacketed 10 cm cell; [α] values are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were obtained on a Perkin-Elmer 781 or Perkin-Elmer 1750 spectrophotometer with solution spectra generally being recorded in chloroform using 0.1 mm or 1.0 mm NaCl cells, with selected peaks reported in cm^{-1}. ^1H NMR spectra were recorded on Varian Gemini 200, Bruker AC200, Bruker WH300, Bruker DPX-400 Bruker AM-500 or Bruker AMX-500 spectrometers with ^{13}C NMR spectra recorded with DEPT editing as necessary. Chemical shifts (δ_C) are quoted in ppm and referenced using residual solvent peaks with coupling constants (*J*) measured in Hertz. Mass spectra were recorded on a VG MASSLAB VG 20–250 instrument using the chemical ionisation (CI) technique, or on a Waters 2790-Micromass LCT electrospray ionisation mass

spectrometer operating at a resolution of 5000 full width half height. Positive ion spectra were calibrated relative to PEG with tetraoctylammonium bromide as the internal lock mass. Elemental analyses were performed by the Dyson Perrins Laboratory analytical department. Flash column chromatography was performed on silica gel (Kieselgel 60), with tlc performed on Merck aluminium sheets coated with 0.2 mm silica gel 60 F_{254}. THF was distilled from sodium–benzophenone ketyl under an atmosphere of dry nitrogen. For moisture sensitive reactions, standard vacuum line techniques were used, using glassware that was flame dried and cooled under nitrogen. Reactions involving lithium amides were performed under an atmosphere of dry nitrogen and reaction diastereoselectivities were determined by integration of the appropriate peaks in the ^{1}H NMR spectrum of the crude reaction product.

tert-Butyl (3*S*,α*S*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-butanoate **9**,[30] *tert*-butyl (3*R*,α*S*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-phenylpropanoate **6**[30] and *tert*-butyl (2*S*,3*S*, α*S*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-2-hydroxybutanoate **13**[27] were prepared according to their respective literature procedures.

Preparation of (2*R*,3*R*,α*R*)-*tert*-butyl 2-azido-3-(*N*-benzyl-*N*-α-methylbenzylamino)-3-phenylpropanoate 7

n-BuLi (1.5 M, 0.6 ml, 0.90 mmol) was added dropwise to a stirred solution of diisopropylamine (97 mg, 0.96 mmol) in THF (10 ml) at 0 °C. After 20 minutes, the solution was cooled to −78 °C before the addition of (3*S*,α*R*)-**6** (250 mg, 0.60 mmol) in THF (3 ml) and stirred for 1 h before the addition of trisyl azide (279 mg, 0.90 mmol) in THF (4 ml). After 2 min, AcOH (166 mg, 2.77 mmol) in anhydrous THF (2 ml) was added and the reaction mixture was warmed to rt overnight. After concentration *in vacuo*, the residue was treated with saturated aqueous sodium bicarbonate (20 ml), extracted with DCM (3 × 30 ml), dried and concentrated *in vacuo*. Purification by flash chromatography on silica gel (5% Et_2O : petrol) gave **7** as a colourless oil (158 mg, 57%); found: C, 73.9; H, 6.75; N, 12.0%; $C_{28}H_{32}N_4O_2$ requires C, 73.7; H, 7.1; N, 12.3%; $[\alpha]_D^{25}$ −15.6 (*c* 1.03, $CHCl_3$); ν_{max} ($CHCl_3$) 2115 (N_3), 1733 (C=O); δ_H (300 MHz; $CDCl_3$) 7.43–7.25 (15H, m, *Ph*), 4.47 (1H, d, *J* 7.7, C(2)*H*), 4.15 (1H, q, *J* 6.9, C(α)*H*), 4.05 (1H, d, *J* 7.7, C(3)H), 3.88, 3.73 (2H, AB system, J_{AB} 14.6, NCH_2Ph), 1.39 (9H, s, $CO_2C(CH_3)_3$), 1.21 (3H, d, *J* 6.9, C(α)*Me*); δ_C (126 MHz; $CDCl_3$) 168.2 (C(1)), 143.8, 140.7, 137.1 (Ph: C_{ipso}), 129.7, 128.5, 128.2, 128.1, 128.0 (Ph: C_{ortho}, C_{meta}, C_{para}), 82.6 ($CO_2C(CH_3)_3$], 65.0, 63.1 (*C*(3), *C*(2)), 58.2 (*C*(α)H), 51.6 (N*C*H_2Ph), 27.9 ($CO_2C(CH_3)_3$), 15.9 (C(α)*Me*); *m*/*z* (CI) 457 (MH^+, 100%). Further elution gave the more polar diazo compound (3*R*,α*R*)-**8** as a pale yellow oil (45 mg, 17%).

Preparationof*tert*-butyl(3*R*,α*R*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-2-diazo-3-phenylpropanoate 8

n-BuLi (1.5 M, 0.5 ml, 0.74 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (166 mg, 0.78 mmol) in THF (10 ml) at −78 °C. After 1 hour, *tert*-butyl (*E*)-cinnamate (100 mg, 0.490 mmol) in THF (5 ml) was added and stirred for a further 2 hours before the addition of trisyl azide (227 mg, 0.74 mmol) in THF (5 ml) at −78 °C. After 2 min, acetic acid (147 mg, 2.45 mmol) in anhydrous THF (3 ml) was added, and the mixture allowed to warm to rt overnight. After dilution with DCM (30 ml) and neutralisation with saturated aqueous sodium bicarbonate (20 ml), the solution was partitioned between H_2O and DCM (3 × 40 ml), dried and concentrated *in vacuo*. Purification by flash chromatography on silica gel (5% Et_2O : petrol) gave **8** as a yellow oil (162 mg, 75%); found: C, 76.2; H, 7.2; N, 9.3%; $C_{28}H_{31}N_3O_2$ requires C, 76.2; H, 7.1; N, 9.5%; $[\alpha]_D^{25}$ +94.1 (*c* 0.92, $CHCl_3$); ν_{max} ($CHCl_3$) 2098 (N_2), 1674 (C=O); δ_H (300 MHz; $CDCl_3$) 7.54–7.13 (15H, m, *Ph*), 4.96 (1H, s, C(3)*H*), 4.06 (1H, q, *J* 6.7, C(α)*H*), 3.84–3.61 (2H, AB system, J_{AB} 15.0, NCH_2Ph), 1.44 (3H, d, obscured, C(α)*Me*), 1.43 (9H, s, $CO_2C(CH_3)_3$); δ_C (126 MHz; $CDCl_3$) 165.7 (*C*(1)), 143.8, 142.1, 140.1 (Ph: C_{ipso}), 129.0, 128.4, 128.1, 128.0, 127.8, 127.2, 126.8, 126.5, 126.1 (Ph: C_{ortho}, C_{meta}, C_{para}), 81.1 ($CO_2C(CH_3)_3$); 61.5, 57.0 (*C*(3), *C*(α)H), 51.2 (N*C*H_2Ph), 28.5 ($CO_2C(CH_3)_3$), 10.7 (C(α)*Me*); *m*/*z* (CI) 442 (MH^+, 10%).

Preparation of *tert*-butyl (2*S*,3*S*,α*S*)-2-azido-3-(*N*-benzyl-*N*-α-methylbenzylamino)butanoate 10

n-BuLi (1.6 M, 1.6 ml, 2.6 mmol) was added dropwise to a stirred solution of diisopropylamine (0.4 ml, 2.57 mmol) in THF (5 ml) at 0 °C. After 20 minutes, the solution was cooled to −78 °C before the addition of (3*S*,α*S*)-**9** (0.6 g, 1.7 mmol) in THF (5 ml) and stirred for 1 h before the addition of trisyl azide (709 mg, 2.6 mmol) in THF (4 ml). After 2 min, AcOH (0.6 ml, 10.5 mmol) in anhydrous THF (3 ml) was added and the reaction mixture was warmed to rt overnight. After concentration *in vacuo*, the residue was treated with saturated aqueous sodium bicarbonate (20 ml), extracted with DCM (3 × 30 ml), dried and concentrated *in vacuo*. Purification by flash chromatography on silica gel (1% Et_2O : petrol) gave **10** as a colourless oil (0.21 g, 32%); found: C, 70.2; H, 7.4; N, 14.1%; $C_{23}H_{30}N_4O_2$ requires C, 70.1; H, 7.6; N, 14.2%; $[\alpha]_D^{23}$ −77.4 (*c* 1.9, $CHCl_3$); ν_{max} (film) 2108 (N_3), 1735 (C=O); δ_H (200 MHz; $CDCl_3$) 7.46 (2H, m, *Ph*), 7.41–7.27 (8H, m, *Ph*), 4.01 (1H, q, *J* 6.8, C(α)*H*), 3.92 (2H, br s, NCH_2Ph), 3.61 (1H, d, *J* 4.9, C(2)*H*), 3.52 (1H, m, C(3)*H*), 1.45 (9H, s, $CO_2C(CH_3)_3$), 1.38 (3H, d, *J* 6.8, C(α)*Me*), 1.12 (3H, d, *J* 6.7, C(4)H_3); δ_C (126 MHz; $CDCl_3$) 168.5 (*C*(1)), 143.4, 141.5 (Ph: C_{ipso}), 128.4, 128.2 128.1, 127.8, 126.8, 126.7 (Ph: C_{ortho}, C_{meta}, C_{para}), 82.3 ($CO_2C(CH_3)_3$), 67.4 (*C*(2)), 58.7 (*C*(α)H), 53.9 (*C*(3)H), 50.2 (N*C*H_2Ph), 27.9 ($CO_2C(CH_3)_3$), 16.4 (C(α)*Me*), 13.1 (*C*(4)); *m*/*z* (CI) 395 (MH^+, 8%). Further elution gave (3*S*,α*S*)-**11** (58 mg, 9%) and recovered starting material (0.10 g, 26%).

Preparation of *tert*-butyl (3*S*,α*S*)-2-diazo-3-(*N*-benzyl-*N*-α-methylbenzyl)aminobutanoate 11

n-BuLi (1.6 M, 3.3 ml, 5.3 mmol) was added dropwise to a stirred solution of (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (1.2 g, 5.6 mmol) in THF (10 ml) at −78 °C. After 1 hour, *tert*-butyl (*E*)-crotonate (500 mg, 3.5 mmol) in THF (5 ml) was added and stirred for a further 2 hours before the addition of trisyl azide (1.7 g, 5.6 mmol) in THF (5 ml) at −78 °C. After 2 min, acetic acid (1 ml) in anhydrous THF (5 ml) was added, and the mixture allowed to warm to rt overnight. After dilution with DCM (40 ml) and neutralisation with saturated aqueous sodium bicarbonate (20 ml), the solution was partitioned between H_2O and DCM (3 × 40 ml), dried and concentrated *in vacuo*. Purification by flash chromatography on silica gel (3% Et_2O : petrol) gave **11** as a yellow oil (0.38 g, 29%); found: C, 72.55; H, 7.9; N, 10.9%; $C_{23}H_{29}N_3O_2$ requires C, 72.8; H, 7.65; N, 11.1%; $[\alpha]_D^{23}$ −53.7 (*c* 1.45, $CHCl_3$); ν_{max} (film) 2081 (N_2), 1687 (C=O); δ_H (200 MHz; $CDCl_3$) 7.60–7.15 (10H, m, *Ph*), 4.14 (1H, q, *J* 6.9, C(3)*H*), 4.02 (1H, q, *J* 6.9, C(α)*H*), 3.85, 3.70 (2H, AB system, J_{AB} 15.4, NCH_2Ph), 1.49 (9H, s, $CO_2C(CH_3)_3$), 1.39 (3H, d, *J* 6.9, C(4)H_3), 1.32 (3H, d, *J* 6.9, C(α)*Me*); δ_C (50 MHz; $CDCl_3$) 166.1 (*C*(1)), 144.8, 142.4 (Ph: C_{ipso}), 128.1, 127.7, 127.4, 126.8, 126.2 (Ph: C_{ortho}, C_{meta}, C_{para}), 80.8 ($CO_2C(CH_3)_3$], 59.3 (*C*(3)), 51.2 (*C*(α)H), 50.4 (N*C*H_2Ph), 28.4 ($CO_2C(CH_3)_3$), 18.4, 17.6 (*C*(4)H_3, C(α)*Me*); *m*/*z* (CI) 380 (MH^+, 24%).

Preparation of methyl (3*S*,α*S*)-2-diazo-3-(*N*-benzyl-*N*-α-methylbenzylamino)butanoate 12

n-BuLi (1.5 M, 3.4 ml, 5.1 mmol) was added dropwise to a stirred solution of (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (1.1 g, 5.4 mmol) in THF (10 ml) at −78 °C. After 1 hour, methyl (*E*)-crotonate (340 mg, 3.4 mmol) in THF (5 ml) was added and stirred for a further 2 hours before the addition of

trisyl azide (1.6 g, 5.1 mmol) in THF (5 ml) at −78 °C. After 20 min, acetic acid (1 ml) in anhydrous THF (5 ml) was added, and the mixture allowed to warm to rt overnight. After dilution with DCM (40 ml) and neutralisation with saturated aqueous sodium bicarbonate (20 ml), the solution was partitioned between H_2O and DCM (3 × 40 ml), dried and concentrated *in vacuo*. Purification by flash chromatography on silica gel (10% Et_2O : petrol) gave **12** as a yellow oil (0.59 g, 52%); found: C, 71.5; H, 6.7; N, 12.45%; $C_{20}H_{23}N_3O_2$ requires C, 71.2; H, 6.8; N, 12.5%; $[\alpha]_D^{21}$ −69.9 (*c* 1.1, $CHCl_3$); ν_{max} (film) 2083 (N_2), 1696 (C=O), 1602 (Ph); δ_H (200 MHz; $CDCl_3$) 7.47–7.20 (10H, m, *Ph*), 4.11 (1H, q, *J* 6.7, C(α)*H*), 4.01 (1H, q, *J* 6.9, C(3)*H*), 3.83, 3.70 (2H, AB system, J_{AB} 15.2, NCH_2Ph), 3.70 (3H, s, O*Me*), 1.32 (6H, app d, *J* 6.9, C(4)H_3 and C(α)*Me*); δ_C (126 MHz; $CDCl_3$) 167.2 (*C*(1)), 144.9, 142.2 (Ph: C_{ipso}), 128.1, 127.6, 127.4, 126.8, 126.4 (Ph: C_{ortho}, C_{meta}, C_{para}), 59.4 (*C*(3)), 51.6 (N*C*H_2Ph), 51.2 (*C*(α)H), 50.6 (O*Me*), 18.9, 17.7 (*C*(4), C(α)*Me*); *m*/*z* (Electrospray) 338 (MH^+, 100%).

Preparation of *tert*-butyl (3*S*,α*S*)-2-diazo-3-(*N*-benzyl-*N*-α-methylbenzylamino)butanoate 11 from diphenylphosphoryl azide quench of the enolate derived from *tert*-butyl (3*S*,α*S*)-3-(*N*-benzyl-*N*-α-methylbenzylamino)butanoate 9

n-BuLi (1.1 M, 1.2 ml, 1.4 mmol) was added dropwise to a stirred solution of diisopropylamine (0.2 ml, 1.4 mmol) in THF (4 ml) at 0 °C. After 20 minutes, the solution was cooled to −78 °C before the addition of (3*S*,α*S*)-**9** (0.3 g, 0.85 mmol) in THF (5 ml) and stirred for 1.75 h before the addition of diphenylphosphoryl azide (0.4 ml, 1.7 mmol) in THF (3 ml). After 30 min, AcOH (0.2 ml) in anhydrous THF (3 ml) was added and the reaction mixture was warmed to rt overnight. After concentration *in vacuo*, the residue was treated with saturated aqueous sodium bicarbonate (20 ml), extracted with DCM (3 × 30 ml), dried and concentrated *in vacuo*. Purification by flash chromatography on silica gel (10% Et_2O : petrol) gave **11** as a colourless oil (0.21 g, 64%).

Preparation of (2*S*,3*S*,α*S*)-10 by treatment of (2*S*,3*S*,α*S*)-13 with diphenylphosphoryl azide

Diphenylphosphoryl azide (2.9 ml, 13.5 mmol) was added to a solution of (2*S*,3*S*,α*S*)-**13** (0.33 g, 0.9 mmol), PPh_3 (0.47 g, 1.8 mmol) and DEAD (0.31 g, 1.8 mmol) in THF (10 ml) and the reaction was stirred at rt for 40 h. Concentration *in vacuo* and purification by flash chromatography on silica gel (25% Et_2O : petrol) gave **10** (0.25 g, 71%) as a colourless oil.

Preparation of (2*S*,3*S*,α*S*)-10 by treatment of (2*S*,3*S*,α*S*)-13 with hydrazoic acid

Hydrazoic acid (0.84 M in benzene, 3.2 ml, 2.7 mmol) was added to a solution of (2*S*,3*S*,α*S*)-**13** (0.23 g, 0.61 mmol) and PPh_3 (0.67 g, 2.6 mmol) in anhydrous benzene (15 ml) before the addition of a solution of DEAD (0.4 ml, 2.6 mmol) in anhydrous benzene (2.5 ml) and the reaction mixture was stirred at rt for 40 min. Concentration *in vacuo* and purification by flash chromatography on silica gel (10% Et_2O : petrol) gave **10** (0.20 g, 84%) as a colourless oil.

tert-Butyl (2*S*,3*S*,α*S*)-2-amino-3-(*N*-benzyl-*N*-α-methylbenzylamino)butanoate 14

PPh_3 (0.5 g, 1.9 mmol) was added to a stirred solution of (2*S*,3*S*,α*S*)-**10** (0.5 g, 1.25 mmol) in anhydrous THF (5 ml) at rt followed by the addition of water (0.8 ml) and stirred at rt overnight. Concentration *in vacuo* and purification by flash chromatography on silica gel (petrol : EtOAc : MeOH, 79 : 20 : 1) gave **14** as a colourless oil (0.42 g, 91%) which solidified on standing; found: C, 75.1; H, 9.0; N, 7.3%; $C_{23}H_{32}N_2O_2$ requires C, 75.0; H, 8.7; N, 7.6%; $[\alpha]_D^{22}$ +22.9 (*c* 1.7, $CHCl_3$); ν_{max} (KBr) 3379 (N–H), 1714 (C=O), 1602 (N–H, deformation); δ_H (500 MHz; $CDCl_3$) 7.44 (2H, m, *Ph*), 7.35–7.20 (8H, m, *Ph*), 4.04 (1H, q, *J* 6.9, C(α)*H*), 3.89 (2H, s, NCH_2Ph), 3.27 (1H, d, *J* 4.2, C(2)*H*), 3.25–3.24 (1H, m, C(3)*H*), 1.39 (9H, s, $CO_2C(CH_3)_3$), 1.37 (3H, d, *J* 6.9, C(α)*Me*), 1.13 (3H, d, *J* 6.8, C(4)H_3); δ_C (126 MHz; $CDCl_3$) 174.4 (*C*(1)), 144.1, 142.0, (Ph: C_{ipso}), 128.5, 128.1, 128.0, 126.7, 126.6, (Ph: C_{ortho}, C_{meta}, C_{para}), 80.7 ($CO_2C(CH_3)_3$), 59.2 (*C*(2)), 57.7 (*C*(α)H), 55.0 (*C*(3)), 50.9 (N*C*H_2Ph), 28.0 ($CO_2C(CH_3)_3$), 15.3 (C(α)*Me*), 13.1 (*C*(4)); *m*/*z* (CI) 369 (MH^+, 100%).

Preparation of (2*S*,3*S*)-2,3-diaminobutanoic acid 2

$Pd(OH)_2$ on C (0.1 g) was added to a stirred solution of (2*S*,3*S*,α*S*)-**14** (0.22 g, 0.6 mmol) in EtOH and the mixture stirred for 19 hours under H_2 (4 atm) at 55 °C. Filtration through Celite, concentration *in vacuo* and trituration (hexane–Et_2O) gave *tert*-butyl (2*S*,3*S*)-2,3-diaminobutanoate as colourless feathers (0.1 g, 88%); mp 129–130 °C; ν_{max} (KBr) 3362 (N–H), 1739 (C=O), 1575 (N–H, deformation), 1166 (C–N); δ_H (500 MHz; $CDCl_3$) 3.92 (1H, d, *J* 3.8, C(2)*H*), 3.82–3.77 (1H, m, C(3)*H*), 1.47 (9H, s, $CO_2C(CH_3)_3$), 1.21 (3H, d, *J* 6.7, C(4)H_3); δ_C (126 MHz; $CDCl_3$) 171.2 (*C*(1)), 82.8 ($CO_2C(CH_3)_3$), 55.6 (*C*(2)), 48.9 (*C*(3)), 28.0 ($CO_2C(CH_3)_3$), 13.0 (*C*(4)); *m*/*z* (CI) 175 (MH^+, 100%), 119 ($MH^+ - C_4H_8$, 97%). TFA (5 ml) was added to *tert*-butyl (2*S*,3*S*)-2,3-diaminobutanoate (85 mg, 0.5 mmol) at 0 °C and warmed to rt overnight. Concentration *in vacuo*, followed by the addition of 1.0 M HCl (5 ml) and stirring at rt for 4.5 h prior to concentration *in vacuo*, gave the hydrochloride salt as a white powdery solid (65 mg). Purification by ion exchange chromatography (Dowex 50X8–200) gave (2*S*,3*S*)-**2** as a white solid (45 mg, 78%); mp 201–202 °C (decomp.); $[\alpha]_D^{22}$ +12.3 (*c* 0.37, 6 M HCl) lit.[22] $[\alpha]_D^{22}$ +10.3 (*c* 1.0, 6 M HCl); ν_{max} (KBr) 3293 (N–H, NH_2), 2987–2152 (N–H, NH_3^+), 1651(N–H deformation, NH_3^+), 1578 (C=O, CO_2^-); δ_H (200 MHz; 2 M DCl) 3.70 (1H, d, *J* 6.1, C(2)*H*), 3.40–3.30 (1H, m, C(3)*H*), 0.74 (3H, d, *J* 7.0, C(4)H_3); δ_C (126 MHz; DMSO-d_6) 167.9 (*C*(1)), 54.6 (*C*(2)), 46.9 (*C*(3)), 14.1 (*C*(4)) {for the DCl salt of (2*S*,3*S*)-**2**}; *m*/*z* (CI) 119 (MH^+, 100).

Preparation of *tert*-butyl (2*R*,3*R*,α*R*)-2-phthalimido-3-(*N*-benzyl-*N*-α-methylbenzylamino)butanoate 15

DEAD (0.36 g, 2.1 mmol) in anhydrous THF (10 ml) was added to a stirred solution of (2*S*,3*S*,α*S*)-**13** (0.38 g, 1.04 mmol), PPh_3 (0.54 g, 2.1 mmol) and phthalimide (2.3 g, 15.6 mmol) in THF (25 ml) and stirred at rt for 44 h, before being filtered, washed with petrol, and concentrated *in vacuo*. Purification by flash chromatography on silica gel (10% Et_2O in petrol) gave **15** as a colourless foam (0.22 g, 42%); $[\alpha]_D^{22}$ +76.1 (*c* 1.7, $CHCl_3$); ν_{max} (film) 1776 (C=O, imide), 1719 (C=O, ester); δ_H (500 MHz; $CDCl_3$) 7.83 (2H, m, *Ph*), 7.71 (2H, m, *Ph*), 7.44–7.19 (11H, m, *Ph*), 4.64 (1H, d, *J* 6.9, C(2)*H*), 4.24 (1H, quintet, *J* 7.0, C(3)*H*), 4.15 (1H, q, *J* 6.9, C(α)*H*), 3.86, 3.76 (2H, AB system, J_{AB}, NCH_2Ph), 1.40 (9H, s, $CO_2C(CH_3)_3$ and 3H, d, *J* 6.9, C(α)*Me*), 1.05 (3H, d, *J* 7.0, C(4)H_3); δ_C (126 MHz; $CDCl_3$) 167.8 (*C*(1)), 167.1 (N*C*O), 143.8, 142.0, 131.7 (Ph: C_{ipso}), 134.0, 128.2, 128.1, 127.8, 126.8, 126.5, 123.3 (Ph: C_{ortho}, C_{meta}, C_{para}), 81.7 ($CO_2C(CH_3)_3$), 60.4 (*C*(2)), 56.7 (*C*(α)H), 53.5 (*C*(3)), 49.3 (N*C*H_2Ph), 27.8 ($CO_2C(CH_3)_3$), 18.2 (C(α)*Me*), 14.2 (*C*(4)); *m*/*z* (CI) 499 (MH^+, 94%).

Preparation of *tert*-butyl (2*R*,3*R*,α*R*)-2-amino-3-(*N*-benzyl-*N*-α-methylbenzylamino)butanoate 14

Hydrazine monohydrate (30 mg, 0.6 mmol) in EtOH (1 ml) was added to (2*R*,3*R*,α*R*)-**15** (84 mg, 0.17 mmol) in EtOH (10 ml) at 0 °C. After 1 h, AcOH was added, and the mixture stirred for 10 min at 0 °C and then allowed to warm to rt overnight. Concentration *in vacuo* and purification by flash chromatography on silica gel (petrol : EtOAc : MeOH, 79 : 20 : 1) gave **14** as a

pale yellow solid (46 mg, 74%) with identical ^{1}H NMR spectroscopic properties to that previously obtained.

Preparation of *tert*-butyl (2*R*,3*R*,α*R*)-2-(3,5-dinitrobenzoylamino)-3-(*N*-benzyl-*N*-α-methylbenzylamino)butanoate 16

NEt_3 (32 mg, 0.32 mmol) was added to a stirred solution of (2*R*,3*R*,α*R*)-**14** (46 mg, 0.125 mmol) and 3,5-dinitrobenzoyl chloride (58 mg, 0.25 mmol) in anhydrous DCM (15 ml) and the mixture stirred at rt for 26 h. Concentration *in vacuo* and purification by flash chromatography on silica gel (petrol : EtOAc : MeOH, 79 : 20 : 1) gave **16** as a yellow solid (60 mg, 97%); found: C, 64.2; H, 6.1; N, 9.8%; $C_{30}H_{34}N_4O_7$ requires C, 64.1; H, 6.05; N, 10.0%; mp 159–161 °C; ν_{max} (KBr) 3359 (N–H), 1730 (C=O, ester), 1673 (C=O, amide), 1546, 1345 (NO_2); δ_H (500 MHz; $CDCl_3$) 9.17 (1H, d, *J* 2.1, C(4)*H*; $C_6H_3N(NO_2)_2$), 8.69 (2H, d, *J* 2.1, C(2)*H*, C(3)*H*; $C_6H_3N(NO_2)_2$),7.50 (2H, d, *J* 7.2, *Ph*), 7.43 (2H, t, *Ph*), 7.33 (1H, t, *Ph*), 7.09 (2H, d, *J* 7.4, *Ph*), 6.90 (2H, t, *J* 7.4, *Ph*), 6.88 (1H, d, *J* 7.9, CHN*H*CO), 6.70 (1H, t, *J* 7.4, *Ph*), 4.30 (1H, dd, *J* 7.9, 4.9, C(2)*H*), 3.97 (1H, q, *J* 7.0, C(α)*H*), 3.86, 3.66 (2H, AB system, J_{AB} 13.2, NCH_2Ph), 3.43–3.40 (1H, m, C(3)*H*), 1.53 (3H, d, *J* 7.0, C(α)*Me*), 1.45 (9H, s, $CO_2C(CH_3)_3$), 1.40 (3H, d, *J* 7, C(4)H_3); δ_C (126 MHz; $CDCl_3$) 169.7 (*C*(1)), 161.9 (NH*C*O), 148.3, 143.7, 140.0, 137.9 (Ph, C_{ipso}), 129.3, 128.7, 128.3, 127.8, 127.6, 127.3, 126.7, 120.7 (Ph, C_{ortho}, C_{meta}, C_{para}), 82.9 ($CO_2C(CH_3)_3$), 56.7 (*C*(2)), 56.0, 52.2 (*C*(α)H, *C*(3)), 51.1 (N*C*H_2Ph), 28.0 ($CO_2C(CH_3)_3$), 15.2 (C(α)*Me*), 11.8 (*C*(4)); *m*/*z* (CI) 563 (MH^+, 39%).

Preparation of *tert*-butyl (2*S*,3*S*)-2-hydroxy-3-*tert*-butylcarbonyloxyaminobutanoate 17

$Pd(OH)_2$ on C (0.31 g) was added to a stirred solution of (2*S*,3*S*,α*S*)-**13** (0.30 g, 0.76 mmol) and di-*tert*-butyl dicarbonate (0.56 g, 2.58 mmol) in EtOAc (10 ml) and the mixture stirred for 24 hours under H_2 (5 atm) at rt. After filtration through Celite and concentration *in vacuo*, purification by flash chromatography on silica gel (10% Et_2O : petrol) gave **17** (0.19 g, 89%) as a colourless oil; found: C, 56.85%; H, 9.4; N, 4.95%; $C_{13}H_{25}NO_5$ requires C, 56.7; H, 9.1; N, 5.1%; $[\alpha]_D^{23}$ +10.6 (*c* 2.38, $CHCl_3$); ν_{max} (film) 3397 (N–H), 1717 br s (C=O, ester and carbamate); δ_H (200 MHz; $CDCl_3$), 4.92 (1H, d, *J* 8.7, CON*H*), 4.20–4.19 (1H, br m, O*H*), 4.12–4.06 (1H, m, C(3)*H*), 3.06 (1H, d, *J* 5.2, C(2)*H*), 1.49 (9H, s, $CO_2C(CH_3)_3$), 1.45 (9H, s, $NCO_2C(CH_3)_3$), 1.01 (3H, d, *J* 6.8, C(4)H_3); δ_C (126 MHz; $CDCl_3$) 172.1 (*C*(1)), 155.2 ($NCO_2C(CH_3)_3$), 83.2 ($CO_2C(CH_3)_3$), 79.5 ($NCO_2C(CH_3)_3$), 72.7 (*C*(2)), 48.4 (*C*(3)), 28.4 ($CO_2C(CH_3)_3$), 28.0 ($NCO_2C(CH_3)_3$), 14.1 (*C*(4)); *m*/*z* (Electrospray) 293 (MNH_4^+, 5%), 276 (MH^+, 100%).

Preparation of *tert*-butyl (2*S*,3*S*)-2-methanesulfonyloxy-3-*tert*-butylcarbonyloxyaminobutanoate 18

Methanesulfonyl chloride (0.24 ml, 3.13 mmol) in DCM (20 ml) was added dropwise to a stirred solution of (2*S*,3*S*)-**17** (820 mg, 2.98 mmol) in anhydrous DCM (20 ml) and NEt_3 (0.58 ml, 4.17 mmol) at 0 °C. After 40 min the solution was warmed to rt and stirred for a further 24 h before the addition of H_2O (20 ml). The mixture was partitioned between DCM (3 × 30 ml) and H_2O, dried and concentrated *in vacuo* before purification by flash chromatography on silica gel (50% Et_2O : petrol) to give **18** (870 mg, 78%) as a colourless oil; $[\alpha]_D^{21}$ −38.4 (*c* 0.56, $CHCl_3$); ν_{max} (film) 3397 (N–H), 1749 (C=O, ester), 1709 (C=O, carbamate), 1369, 1176 (OSO_2); δ_H (200 MHz; $CDCl_3$), 5.19 (1H, d, *J* 2.5, C(2)*H*), 4.77 (1H, d, *J* 8.2, CON*H*), 4.36–4.26 (1H, m, C(3)*H*), 3.16 (3H, s, OSO_2CH_3), 1.50 (9H, s, $CO_2C(CH_3)_3$), 1.45 (9H, s, $NCO_2C(CH_3)_3$), 1.10 (3H, d, *J* 6.9, C(4)H_3); δ_C (126 MHz; $CDCl_3$) 166.2 (*C*(1)), 154.9 ($NCO_2C(CH_3)_3$), 83.8 ($CO_2C(CH_3)_3$), 80.1 ($NCO_2C(CH_3)_3$), 79.6 (*C*(2)), 47.2 (*C*(3)), 39.1 (OSO_2Me), 28.3 ($CO_2C(CH_3)_3$), 27.9 ($NCO_2C(CH_3)_3$), 14.4 (*C*(4)); *m*/*z* (CI) 354 (MH^+, 1%), 254 ($MH^+ - C_4H_8 - CO_2$, 85%).

Preparation of *tert*-butyl (2*R*,3*S*)-2-azido-3-*tert*-butylcarbonyloxyaminobutanoate 19 and *tert*-butyl (4*S*,5*R*)-4-methyloxazolidin-2-one-5-carboxylate 20

Sodium azide (607 mg, 9.34 mmol) was added to a solution of (2*S*,3*S*)-**18** (715 mg, 2.03 mmol) in DMF (50 ml) and heated at 55 °C for 5 h, before cooling to rt and stirring for a further 3 h. After dilution with water (30 ml) and extraction with DCM (2 × 30 ml) the combined organic layers were dried, filtered and concentrated *in vacuo* before purification by flash chromatography on silica gel (50% Et_2O : petrol) giving **19** (295 mg, 48%) as a white solid, mp 56.5–59 °C; $[\alpha]_D^{26}$ +50.0 (*c* 0.3, $CHCl_3$); ν_{max} (film) 3365 (N–H), 2116 (N_3), 1719 br s (C=O, ester and carbamate); δ_H (500 MHz; $CDCl_3$), 4.75 (1H, d, *J* 8.5, CON*H*), 4.24 (1H, m, C(3)*H*), 4.00 (1H, d, *J* 2.7, C(2)*H*), 1.51 (9H, s, $CO_2C(CH_3)_3$), 1.42 (9H, s, $NCO_2C(CH_3)_3$), 1.21 (3H, d, *J* 6.8, C(4)H_3); δ_C (126 MHz; $CDCl_3$) 167.5 (*C*(1)), 154.7 ($NCO_2C(CH_3)_3$), 83.5 ($CO_2C(CH_3)_3$), 79.5 ($NCO_2C(CH_3)_3$), 66.5 (*C*(2)), 47.6 (*C*(3)), 28.3 ($CO_2C(CH_3)_3$), 27.9 ($NCO_2C(CH_3)_3$), 18.5 (*C*(4)); *m*/*z* (CI) 301 (MH^+, 100%); HRMS (CI^+) found, 301.1871; $C_{13}H_{24}N_4O_4$ requires 301.1876. Further elution returned starting material (2*S*,3*S*)-**18** (182 mg, 25%) followed by *tert*-butyl (4*S*,5*R*)-4-methyloxazolidin-2-one-5-carboxylate **20** (100 mg, 25%) as a white solid; R_f 0.18 [1 : 1 30–40 °C petrol : EtOAc]; mp 107 °C [petrol : EtOAc]; found: C, 53.6; H, 7.25; N, 6.9%; $C_9H_{15}NO_4$ requires C, 53.7; H, 7.5; N, 7.0%; $[\alpha]_D^{25}$ −22.6 (*c* 0.5,$CHCl_3$); δ_H (400 MHz; $CDCl_3$) 6.58 (1H, s, N*H*), 4.39 (1H, d, *J* 5.7, C*H*$CO_2C(CH_3)_3$), 3.91–3.94 (1H, m, C*H*CH_3), 1.49 (9H, s, $CO_2C(CH_3)_3$), 1.39 (3H, d, *J* 6.2, CHCH_3); δ_C (100 MHz; $CDCl_3$) 167.5 ($CO_2C(CH_3)_3$), 158.4 (N*C*(O)O), 83.4 ($CO_2C(CH_3)_3$), 79.7 ($CHCO_2C(CH_3)_3$), 52.0 (*C*HCH$_3$), 27.9 ($CO_2C(CH_3)_3$), 21.5 (CH*C*H$_3$); ν_{max} (KBr) 1764, 1731 (C=O); HRMS (Electrospray) found, 202.1084; $C_9H_{16}NO_4$ requires 202.1079; *m*/*z* (CI^+) 202 (MH^+, 85%).

Preparation of *tert*-butyl (2*S*,3*S*)-2-hydroxy-3-aminobutanoate 21[43] and *tert*-butyl (4*S*,5*S*)-4-methyloxazolidin-2-one-5-carboxylate 22

$Pd(OH)_2$ on C (250 mg) was added to a stirred solution of (2*S*,3*S*,α*S*)-**13** (500 mg, 1.36 mmol) in degassed MeOH (10 ml) and stirred at rt under H_2 (5 atm) overnight. After filtration through Celite, concentration *in vacuo* gave (2*S*,3*S*)-**21** (238 mg, quant., identical to a commercially available sample from Evotec OAI); δ_H (400 MHz; $CDCl_3$) 4.33 (1H, d, *J* 2.8, C(2)*H*), 3.68–3.63 (1H, m, C(3)*H*), 1.52 (9H, s, $CO_2C(CH_3)_3$), 1.21 (3H, d, *J* 6.9, C(4)H_3). Diphosgene (0.06 ml, 0.5 mmol) was added dropwise to a stirred suspension of (2*S*,3*S*)-**21** (80 mg, 0.45 mmol) and activated charcoal (20 mg) in toluene (5 ml) at rt before heating at reflux for four hours. After cooling to rt, filtration through Celite and concentration *in vacuo*, the residue was washed with $NH_4Cl_{(aq)}$ (20 ml) and extracted with EtOAc (3 × 20 ml). Concentration *in vacuo* and purification by chromatography on silica (Et_2O) gave (4*S*,5*S*)-**22** as a white solid (81 mg, 83%); mp 103–104 °C [petrol : Et_2O]; $[\alpha]_D^{25}$ −11.6 (*c* 0.8, $CHCl_3$); δ_H (400 MHz; $CDCl_3$) 6.48 (1H, s, N*H*), 4.89 (1H, d, *J* 8.6, C*H*$CO_2C(CH_3)_3$), 4.22 (1H, dq, *J* 8.6, *J* 6.4, C*H*CH_3), 1.51 (9H, s, $CO_2C(CH_3)_3$), 1.25 (3H, d, *J* 6.4, CHCH_3); δ_C (100 MHz; $CDCl_3$) 166.1 ($CO_2C(CH_3)_3$), 158.6 (N*C*(O)O), 83.6 ($CO_2C(CH_3)_3$), 77.0 ($CHCO_2C(CH_3)_3$), 50.1 (*C*HCH$_3$), 28.0 ($CO_2C(CH_3)_3$), 16.7 (CH*C*H$_3$); ν_{max} (KBr) 2983 (N–H), 1756, 1727 (C=O); HRMS (Electrospray) found, 202.1083; $C_9H_{16}NO_4$ requires 202.1079; *m*/*z* (CI^+) 202 (MH^+, 70%).

Preparation of (2*R*,3*S*)-2,3-diaminobutanoic acid 3

Pd on C (42 mg) was added to a stirred solution of (2*S*,3*S*)-**19** (84 mg, 0.27 mmol) in EtOAc (5 ml) and stirred overnight under H_2 (5 atm) at rt. Filtration through Celite and concentration *in*

vacuo gave *tert*-butyl (2*R*,3*S*)-2-amino-3-*tert*-butylcarbonyloxy-aminobutanoate (72 mg, 97%) as a white solid; mp 204–207 °C; $[a]_D^{23}$ −32.8 (*c* 0.54, $CHCl_3$); ν_{max} (KBr) 3426 (N–H, carbamate), 3356 (N–H), 1741 (C=O, ester) 1720 (C=O, carbamate); δ_H (500 MHz; $CDCl_3$), 4.96 (1H, d, *J* 8.0, CON*H*), 4.09 (1H, m, C(3)*H*), 3.42 (1H, br s, C(2)*H*), 1.47 (9H, s, $CO_2C(CH_3)_3$), 1.42 (9H, s, $NCO_2C(CH_3)_3$), 1.16 (3H, d, *J* 6.8, C(4)H_3); δ_C (126 MHz; $CDCl_3$) 122.6 (*C*(1)), 155.1 ($NCO_2C(CH_3)_3$), 81.8 ($CO_2C(CH_3)_3$), 79.0 ($NCO_2C(CH_3)_3$), 58.2 (*C*(2)), 48.9 (*C*(3)), 28.4 ($CO_2C(CH_3)_3$), 28.0 ($NCO_2C(CH_3)_3$), 18.2 (*C*(4)); *m*/*z* (Electrospray) 275 (MH^+, 53%), 219 ($MH^+ - C_4H_8$, 100). TFA (2.5 ml) was added to *tert*-butyl (2*R*,3*S*)-2-amino-3-*tert*-butylcarbonyloxy-aminobutanoate (30 mg, 0.11 mmol) at 0 °C for 10 min and then warmed to rt overnight. Concentration *in vacuo*, followed by the addition of HCl (1.0 M) and stirring for 1.5 h before concentration *in vacuo* gave (2*R*,3*S*)-2,3-diaminobutanoic acid **3** as its dihydrochloride salt; $[a]_D^{25}$ −34.5 (*c* 1.15, 6 M HCl); lit.[38] $[a]_D^{22}$ −38.1 (*c* 1.0, 6 M HCl), lit.[25] $[a]_D^{20}$ −34.3 (*c* 1.0, 6 M HCl)}; δ_H (400 MHz, D_2O) 4.08 (1H, d, *J* 3.2, C*H*CO_2H), 3.85–3.81 (1H, m, C*H*CH_3), 1.31 (3H, d, *J* 6.7, CHCH_3).

Further purification by ion exchange chromatography (Dowex 50X8-200) gave **3** as a white powder (quantitative); $[a]_D^{22}$ −27.2 (*c* 0.18, 6 M HCl); $[a]_D^{25}$ −28.5 (*c* 1.7, 6 M HCl); ν_{max} (KBr) 2971 (N–H, NH_3^+), 2600–2000 (N–H, NH_2), 1654 (C=O, CO_2H), 1590 (C=O, CO_2^-); δ_H (200 MHz; 2 M DCl) 4.15 (1H, d, *J* 3.4, C(2)*H*), 3.66–3.61 (1H, m, C(3)*H*), 1.07 (3H, d, *J* 6.8, C(4)H_3); δ_H (200 MHz; D_2O) 4.19 (1H, d, *J* 3.5, C(2)*H*), 3.93–3.82 (1H, m, C(3)*H*), 1.36 (3H, d, *J* 6.7, C(4)H_3); δ_C {of HCl salt) (126 MHz; D_2O) 169.8 (*C*(1)), 54.1 (*C*(2)), 46.4 (*C*(3)), 12.9 (*C*(4)); *m*/*z* (CI) 119 (MH^+, 100%); HRMS (CI) found, 119.0821; $C_4H_{10}N_2O_2$ requires 119.0821.

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