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Trading *N* and *O*: asymmetric syntheses of β-hydroxy-α-amino acids via α-hydroxy-β-amino esters

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ABSTRACT

Both diastereoisomers of 2-amino-3-hydroxybutanoic acid and 2-amino-3-hydroxy-3-phenylpropanoic acid have been prepared from enantiopure α-hydroxy-β-amino esters via the intermediacy of the corresponding *cis*- and *trans*-aziridines. Aminohydroxylation of two α,β-unsaturated esters produced enantiopure 2,3-*anti*-α-hydroxy-β-amino esters in >99:1 dr. Subsequent epimerisation at the C(2)-position via a sequential oxidation/diastereoselective reduction protocol gave the corresponding enantiopure 2,3-*syn*-α-hydroxy-β-amino esters in >99:1 dr. These *syn*- and *anti*-substrates were then converted into the corresponding *N*-Boc protected *cis*- and *trans*-aziridines, respectively, via a three step reaction sequence: (i) hydrogenolysis and in situ *N*-Boc protection; (ii) OH-activation; and (iii) aziridine formation. Subsequent regioselective ring-opening of the C(3)-methyl-aziridines with Cl_3CCO_2H proceeded with inversion of configuration to give the corresponding 2-amino-3-trichloroacetate esters, whereas the analogous reaction with the C(3)-phenyl-aziridines resulted in rearrangement to the corresponding oxazolidin-2-ones with retention of configuration. In each case, hydrolysis of the products from these ring-opening reactions produced the corresponding enantiopure β-hydroxy-α-amino acids as single diastereoisomers.

1. Introduction

Enantiopure aziridines are important building blocks in synthetic organic chemistry as they can be prepared readily from the corresponding vicinal amino alcohols via a range of methods,[1] and can be used to access many chiral nitrogen containing compounds via regio- and stereoselective ring-opening reactions.[1,2] For example, Tomasini and Vecchione have reported that the Lewis acid-promoted rearrangement of *N*(1)-*tert*-butoxycarbonyl-2-carboxymethyl aziridines gives the corresponding 4-carboxymethyloxazolidin-2-ones, which can then be hydrolysed to give β-hydroxy-α-amino acids.[3,4]

In order to extend the scope and utility of our conjugate addition methodology[5–8] to include the preparation of enantiopure β-hydroxy-α-amino acids,[9] it was envisaged that a range of enantiopure *trans*-aziridines **6** could be accessed utilising our diastereoselective aminohydroxylation protocol.[8,10,11] This reliably yields the corresponding 2,3-*anti*-α-hydroxy-β-amino esters **4** [upon treatment of α,β-unsaturated esters **1** with enantiopure lithium amides, such as **2**, followed by oxidation of the intermediate enolate with camphorsulfonyloxaziridine (CSO) **3**] with a high and predictable sense of diastereocontrol. Subsequent tandem hydrogenolysis and *N*-Boc protection of **4** would then give the corresponding *N*-Boc protected α-hydroxy-β-amino esters **5**, which could be converted to the corresponding *trans*-aziridines **6** by conversion of the hydroxyl moiety to a leaving group.[12] Application of a sequential oxidation/reduction protocol to the 2,3-*anti*-α-hydroxy-β-amino esters **4** would give the corresponding 2,3-*syn*-diastereoisomers **8** and therefore allow access to the epimeric *cis*-aziridines **10** via an analogous reaction sequence. Regioselective ring-opening of aziridines **6** and **10**, and subsequent global deprotection would then provide access to the corresponding β-hydroxy-α-amino acids **7** and **11** (Fig. 1).

2. Results and discussion

2.1. Preparation of enantiopure aziridines

As many different methods are known for the formation of enantiopure aziridines from the corresponding vicinal amino alcohols (or activated derivatives, such as mesylates),[1] we set out to prepare a range of *N*-Boc protected α-hydroxy-β-amino esters and the corresponding mesylates to screen the optimum conditions for aziridine formation for this class of compounds. Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **2** to both *tert*-butyl cinnamate **12** and *tert*-butyl crotonate **13**, followed by in situ oxidation of the intermediate lithium (*Z*)-β-amino enolates[13]

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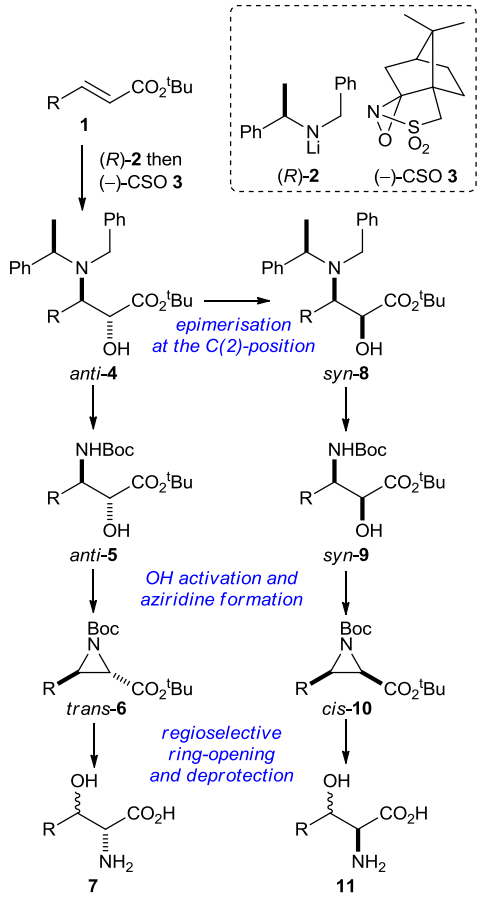
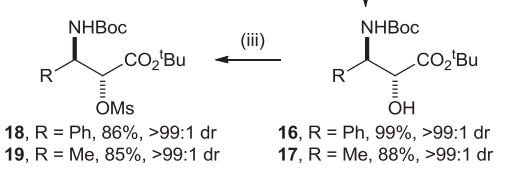


Fig. 1. Synthetic strategy to access β-hydroxy-α-amino acids **7** and **11**.

with (−)-CSO **3** gave the known α-hydroxy-β-amino esters **14**[10a] and **15**[10a] as single diastereoisomers (>99:1 dr), which were isolated in 93 and 91% yield, respectively. Tandem hydrogenolysis/*N*-Boc protection of **14** gave **16** in 99% yield and >99:1 dr, then mesylation of the hydroxyl group within **16** gave **18** in 86% yield and >99:1 dr (Scheme 1). Single crystal X-ray diffraction analyses[14] of both **16** and **18** confirmed the assigned configurations within these substrates. Furthermore, the determination of a Flack *x* parameter[15] of 0.00(6) for the crystal structure of **18** was also consistent with its assigned absolute configuration (Fig. 2). An analogous reaction sequence was then applied to **15**, which gave **19**[16] in 75% overall yield for the two-step procedure (Scheme 1).



Scheme 1. Reagents and conditions: (i) (*R*)-**2**, THF, −78 °C, 2 h then (−)-CSO **3**, −78 °C to rt, 15 h; (ii) $Pd(OH)_2/C$, H_2 (5 atm), Boc_2O, EtOAc, rt, 15 h; (iii) MsCl, Et_3N, DMAP, CH_2Cl_2, rt, 15 h.

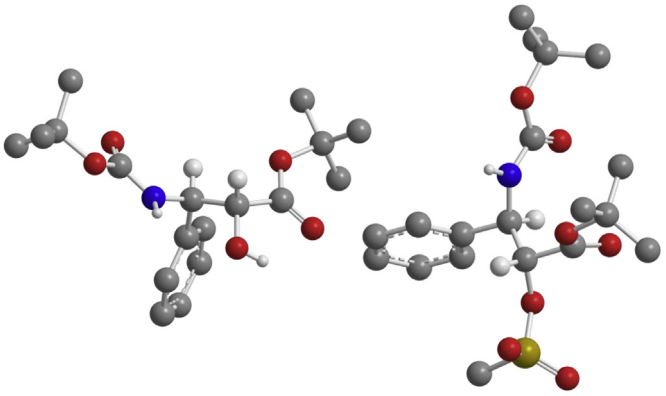
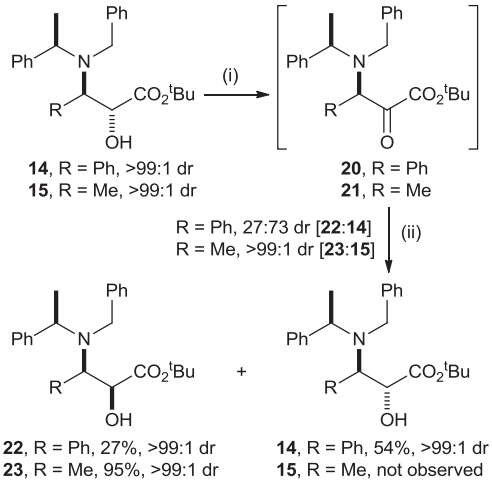


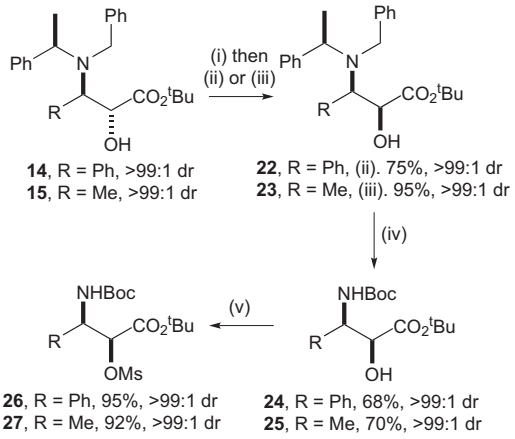
Fig. 2. X-ray crystal structures of **16** [left] and **18** [right] (selected H atoms are omitted for clarity).

The corresponding 2,3-*syn*-configured mesylates were targeted next. It was envisaged that epimerisation of **14** and **15** at the C(2)-position could be achieved via a sequential Swern oxidation/diastereoselective reduction protocol, which we have previously employed to good effect to access a 2,3-*syn*-α-hydroxy-β-amino ester in a related system.[17] Swern oxidation of **15** (R=Me) gave **21** and reduction of **21** with $NaBH_4$ gave **23** as a single diastereoisomer (>99:1 dr) in 95% isolated yield. Application of these conditions to **14** (R=Ph) gave **20**;[18] however, poor diastereoselectivity was observed upon reduction of **20** with $NaBH_4$, which actually favoured formation of the 2,3-*anti*-product **14** giving a mixture of **22** and **14** in 27:73 dr, respectively (Scheme 2).[19]



Scheme 2. Reagents and conditions: (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 30 min, then Et_3N, −78 °C to rt, 30 min; (ii) $NaBH_4$, MeOH, −20 °C, 2 h.

A range of different reaction conditions was therefore screened for the reduction of **20**. The levels of diastereoselectivity were found to be extremely variable with the 2,3-*anti*-diastereoisomer **14** predominating in most cases; however, it was found that reduction of **20** with DIBAL-H in THF at −20 °C for 2 h gave exclusively 2,3-*syn*-**22**. Upon scale-up, application of these optimised conditions gave **22** in >99:1 dr and 75% yield (from **14**) after chromatographic purification (Scheme 3). Single crystal X-ray



Scheme 3. Reagents and conditions: (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 30 min, then Et_3N, −78 °C to rt, 30 min; (ii) DIBAL-H, THF, −20 °C, 2 h; (iii) $NaBH_4$, MeOH, −20 °C, 2 h; (iv) $Pd(OH)_2/C$, H_2 (5 atm), Boc_2O, EtOAc, rt, 15 h; (v) MsCl, Et_3N, DMAP, CH_2Cl_2, rt, 15 h.

diffraction analysis[20] confirmed the assigned 2,3-*syn*-configuration within **22**, with the absolute (2*S*,3*R*,α*R*)-configuration within **22** being assigned relative to the known configuration of the *N*-α-methylbenzyl fragment (Fig. 3). Subsequent tandem hydrogenolysis and *N*-Boc protection of both **22** and **23**, followed by mesylation of the hydroxyl groups within **24** and **25** gave mesylates **26** and **27** in 65 and 64% overall yield, respectively, from 2,3-*syn*-β-amino esters **22** and **23** (Scheme 3). Single crystal X-ray diffraction analyses[21] confirmed the assigned 2,3-*syn*-configurations within **24**, **26** and **27** (Fig. 4).

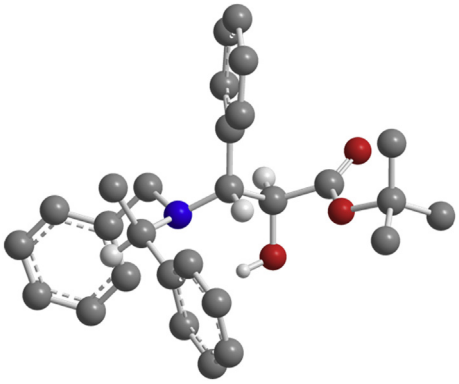


Fig. 3. X-ray crystal structure of **22** (selected H atoms are omitted for clarity).

With samples of *N*-Boc protected amino alcohols **16**, **17**, **24** and **25**, and the corresponding mesylates **18**, **19**, **26** and **27** in hand, investigations into aziridine formation from these substrates were undertaken. It has been reported that some of the most successful aziridine forming reactions from *N*-Boc protected vicinal amino alcohols use a strategy first published by Wessig et al.[22] in which tosylation of the α-hydroxyl group is followed by in situ aziridine formation in the presence of KOH. These conditions were first trialled on **16** and resulted in a 61:34:5 mixture of three major products, which were assigned as aziridines **28** and **29**, and oxazolidin-2-one **30**, respectively, from which only **28** and **29** were isolated in 34 and 28% yield (Scheme 4). The relative configurations within *trans*-**28** and *cis*-**29** were initially established by a combination of ^{1}H NMR NOE and ^3J coupling constants analyses,[23] and these assignments were later confirmed by single crystal X-ray diffraction analyses of both **28** and **29** (Fig. 5).[24] Although the ^{1}H NMR ^3J coupling constants observed between the C(4)*H* and C(5)*H* protons within 4,5-disubstituted oxazolidin-2-ones are also diagnostic of their relative configuration,[25] the identity of oxazolidin-2-one **30** was established unambiguously via the preparation of authentic samples of **30** and its C(5)-epimer **32**: hydrogenolysis of **14** and **22**, and treatment of the resultant β-amino esters **31** and **33** with CDI gave **32** and **30** in 22 and 15% overall yield, respectively (Scheme 4). In this case, single crystal X-ray diffraction analysis[24] of **30** allowed its relative configuration to be unambiguously confirmed (Fig. 5). The ^{1}H NMR spectroscopic data for this sample of **30** were found to be identical to those for the sample prepared from **16** upon attempted aziridine formation and distinctly different to those for **32**. The formation of both **28** and **30** is consistent with a mechanistic pathway in which intramolecular displacement of the tosylate group within **16** by either the N or O atom within the carbamate functionality proceeds with inversion of configuration, and in the case of **30** this is followed by concomitant loss of the *tert*-butyl group.[26]

Other attempts at the direct formation of aziridines from *N*-Boc protected amino alcohols **16**, **17**, **24** and **25** were not successful, therefore further studies were carried out on the corresponding mesylates **18**, **19**, **26** and **27**. Treatment of **18** with a variety of bases under various reaction conditions revealed four main strategies, which gave good conversion to *trans*-**28**. Heating a solution of **18** in DMF at 50 °C in the presence of Cs_2CO_3 gave an 81:10:9 ratio of **28**, **29** and **30**, respectively, from which **28** was isolated in 51% yield and >99:1 dr. Improved selectivity was observed when **18** was treated with NaH under the same reaction conditions, which gave a 98:2 mixture of **28** and **29**, respectively, from which **28** was isolated in 72% yield and >99:1 dr. For the reactions in THF with NaH as the base, the addition of 15-crown-5 greatly improved the reaction selectivity in favour of the formation of **28**. However, little difference was observed when 15-crown-5 ether was used in the corresponding reaction in DMF (Scheme 5).

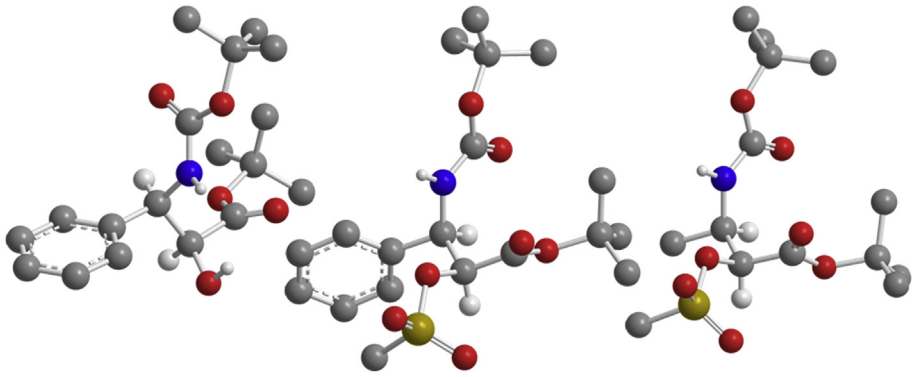
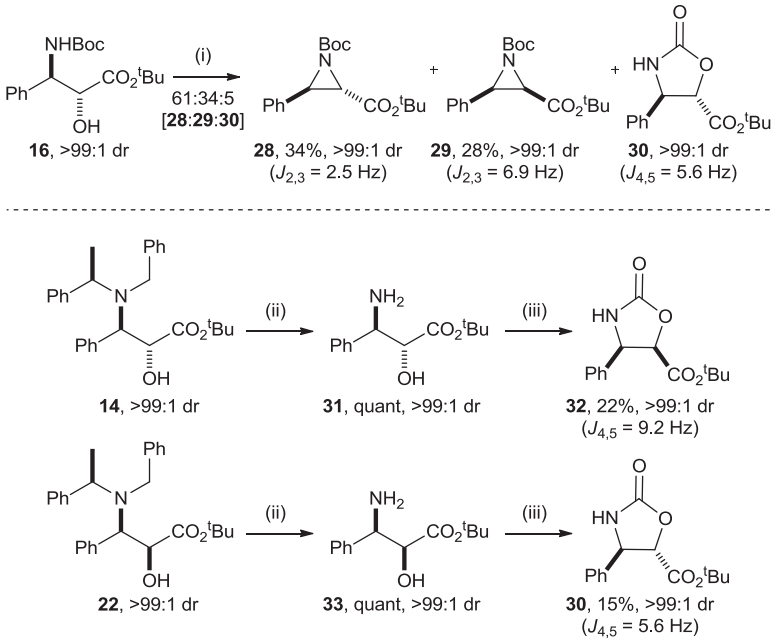


Fig. 4. X-ray crystal structures of **24** [left], **26** [centre] and **27** [right] (selected H atoms are omitted for clarity).



Scheme 4. Reagents and conditions: (i) KOH, TsCl, Et_2O, 40 °C, 15 h; (ii) H_2 (5 atm), $Pd(OH)_2/C$, MeOH, rt, 15 h; (iii) CDI, DMAP, THF, rt, 12 h.

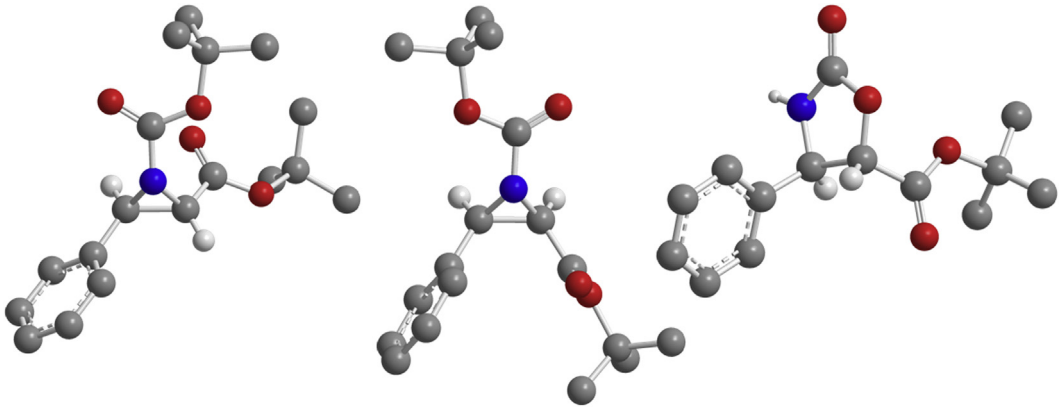
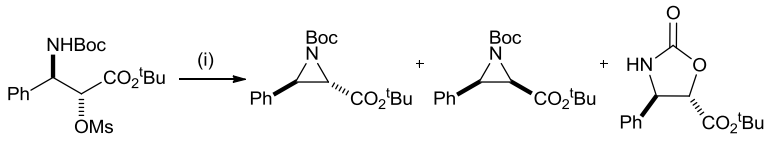


Fig. 5. X-ray crystal structures of **28** [left], **29** [centre] and **30** [right] (selected H atoms are omitted for clarity).

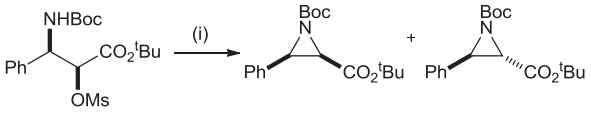


base (equiv)	other reagents	temp (°C)	time (h)	product distribution [18:28:29:30]	yield of 28 (%)[a]	yield of 29 (%)[a]	yield of 30 (%)[a]
Et_3N (5.0)	THF	20	15	53:13:0:34	0	0	25
MeMgBr (1.05)	THF	–78 to 20	15	95:0:0:5	–	–	–
^{t}BuOK (1.05)	THF	20	15	0:51:49:0	30	27	0
NaH (1.2)	THF	20	15	0:58:41:1	28	14	0
TBAF (5.0)	THF	20	15	0:42:32:26	–	–	–
n/a	DMF	50	3	80:0:0:20	–	–	–
Cs_2CO_3 (3.0)	DMF	50	3	0:81:10:9	51	10	0
NaH (1.2)	DMF	50	3	0:98:2:0	72	0	0
NaH (1.2)	15-crown-5, DMF	50	3	0:90:4:6	62	2	0
NaH (1.2)	15-crown-5, THF	20	15	0:90:7:3	56	6	0

Scheme 5. Reagents and conditions: (i) see table. [[a]Isolated yields correspond to single diastereoisomers (>99:1 dr)].

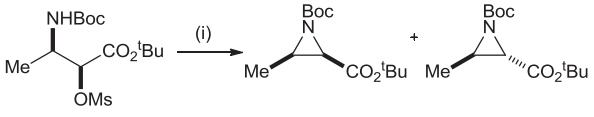
Subjecting **19** to Cs_2CO_3 in DMF gave a 66:14:20 mixture of three major products: aziridines **34** and **35**, and oxazolidin-2-one **36**,[10c] which were isolated in 23, 8 and 20% yield, respectively (Scheme 6). ^{1}H NMR ^3J coupling constant analysis enabled the relative configurations within aziridines **34** ($J_{2,3}$=2.7 Hz) and **35** ($J_{2,3}$=6.8 Hz) to be assigned, although both **34** and **35** were found to be crystalline and therefore subsequent single crystal X-ray diffraction analyses[27] enabled these assignments to be unambiguously confirmed (Fig. 6). Furthermore, in the case of *cis*-**35**, the determination of a Flack *x* parameter of −0.06(7) allowed the assigned absolute (*R*,*R*)-configuration within **35** to be confirmed, establishing that epimerisation at the α-centre was responsible for the formation of *cis*-aziridine **35**. The assigned relative configuration within oxazolidin-2-one **36** was also confirmed unambiguously via single crystal X-ray diffraction analysis (Fig. 6),[27] and the absolute configuration within **36** was established by comparison of the specific rotation of this sample with that of a literature value for the antipode {$[\alpha]_D^{25}$ +27.3 (*c* 1.0 in $CHCl_3$); lit.[10c] for *ent*-**36**: $[\alpha]_D^{25}$ −22.6 (*c* 0.5 in $CHCl_3$)}. Further optimisation revealed that reaction with NaH in DMF produced *trans*-**34** in 48% isolated yield and >99:1 dr (Scheme 6).

Reaction of the corresponding *syn*-mesylates **26** and **27** under the same conditions typically proceeded with higher diastereoselectivity and gave *cis*-aziridines **29** and **35** in superior yields. Under the optimal conditions treatment of **26** and **27** with Cs_2CO_3 in DMF at 50 °C gave *cis*-aziridines **29** and **35** in >99:1 dr, and 99 and 73% isolated yield, respectively, and >99:1 dr after purification. The corresponding oxazolidin-2-ones were not observed in any of these reactions (Scheme 7).



26, >99:1 dr **29** **28**

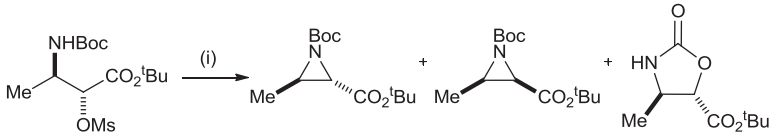
base (equiv)	other reagents	dr [29:28]	yield of 29 (%)[a]
Cs_2CO_3 (3.0)	DMF	>99:1	99
NaH (1.2)	DMF	93:7	–
NaH (1.2)	15-crown-5, DMF	76:24	–



27, >99:1 dr **35** **34**

base (equiv)	other reagents	dr [35:34]	yield of 35 (%)[a]
Cs_2CO_3 (3.0)	DMF	>99:1	73
NaH (1.2)	DMF	>99:1	32
NaH (1.2)	15-crown-5, DMF	83:17	–

Scheme 7. Reagents and conditions: (i) 50 °C, 3 h, see table. [[a]Isolated as a single diastereoisomers (>99:1 dr)].



19, >99:1 dr **34** **35** **36**

base (equiv)	other reagents	temp (°C)	time (h)	product distribution [34:35:36]	yield of 34 (%)	yield of 35 (%)	yield of 36 (%)
Cs_2CO_3 (3.0)	DMF	50	3	66:14:20	23[a]	8[a]	20[a]
NaH (1.2)	DMF	50	3	93:0:7	48[a]	0	0
NaH (1.2)	15-crown-5, DMF	50	3	95:5:0	45[a]	0	0
NaH (1.2)	15-crown-5, THF	20	15	96:4:0	5[b]	0	0

Scheme 6. Reagents and conditions: (i) see table. [[a]Isolated as a single diastereoisomer (>99:1 dr); [b]an 84:16 mixture of **34** and **35** was also isolated in 20% combined yield].

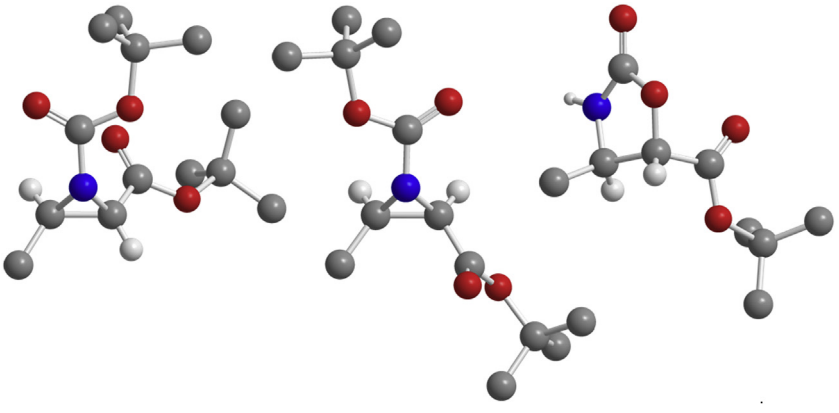


Fig. 6. X-ray crystal structures of **34** [left], **35** [centre] and **36** [right] (selected H atoms are omitted for clarity).

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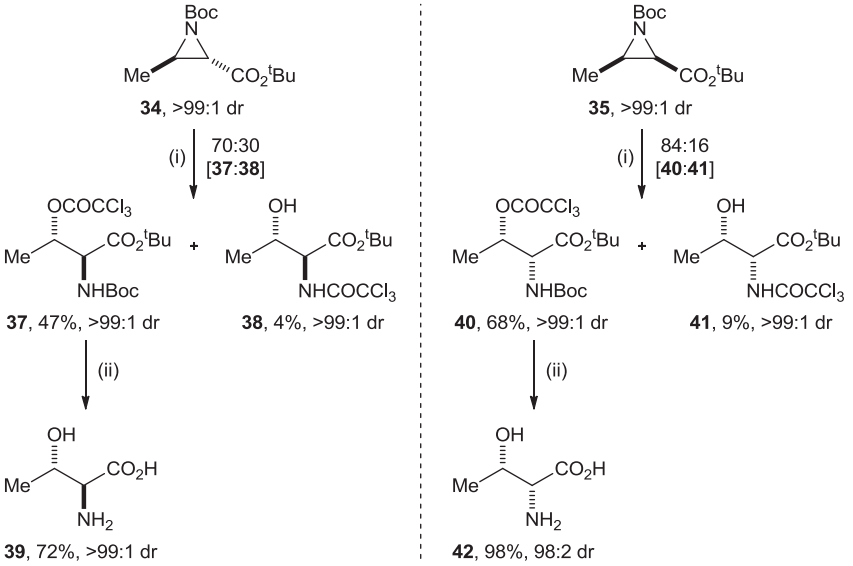
2.2. Elaboration to β-hydroxy-α-amino acids

We have previously reported the ring-opening of a range of epoxides with Cl_3CCO_2H in which regioselective attack of the trichloroacetate ion occurs at the position distal to an electron withdrawing ammonium group.[28] It was therefore envisaged that regioselective ring-opening of aziridines **28**, **29**, **34** and **35** with Cl_3CCO_2H would occur selectively at the C(3)-position. Indeed, treatment of *trans*-C(3)-methyl substituted aziridine **34** with Cl_3CCO_2H gave rise to a 70:30 mixture of two products, which were identified as **37** and **38**, and isolated in 47 and 4% yield, respectively. Likewise, reaction of *cis*-**35** with Cl_3CCO_2H gave an 84:16 mixture of **40** and **41**, which were isolated in 68 and 9% yield, respectively (Scheme 8). The regiochemistries within **37**, **38**, **40** and **41** were assigned via ^{1}H NMR COSY analyses (in which coupling between the C(2)*H* and N*H* protons was observed) and ^{1}H–^{13}C NMR HMBC analyses. Furthermore, single crystal X-ray diffraction analyses[29] of **37** and **41** enabled unambiguous confirmation of their relative configurations, and the determination of Flack *x* parameters[15] of −0.017(15) and −0.023(13) for the crystal structures of **37** and **41**, respectively, allowed the assigned absolute (*S*,*S*)-configuration within **37** and (2*R*,3*S*)-configuration within **41** to be confirmed unambiguously (Fig. 7). The formation of these products is in both cases consistent with regioselective S_N2-type ring-opening of the aziridine at C(3) by the trichloroacetate ion, with inversion of configuration. The formation of **38** and **41** is consistent with hydrolysis of the *N*-Boc group, under the acidic reaction conditions, followed by *O* to *N* transfer of the trichloroacetyl group.[30] In support of this hypothesis, a sample of **37** was re-subjected to the reaction conditions for 15 h; this produced a 59:41 mixture of **37** and **38**, respectively, confirming the intermediacy of **37** in the formation of **38**. For both **37** and **40**, global deprotection upon treatment with 6.0 M aq HCl at 60 °C for 24 h gave β-hydroxy-α-amino acids (*S*,*S*)-*allo*-threonine **39** and (2*R*,3*S*)-threonine **42**, respectively, which were isolated in 72% yield and >99:1 dr, and 97% yield and 98:2 dr, after purification on Dowex 50WX8 ion exchange resin (Scheme 8). The spectroscopic data, including specific rotations, for the samples of (*S*,*S*)-**39** {mp 240–250 °C (dec); $[\alpha]_D^{20}$ +7.5 (*c* 1.0 in H_2O); lit.[9c] mp 264–266 °C; lit.[9c] $[\alpha]_D^{20}$ +8 (*c* 1.1 in H_2O)} and (2*R*,3*S*)-**42** {mp 250–260 °C (dec); $[\alpha]_D^{20}$ +23.2 (*c* 1.0 in H_2O); lit.[31] mp 264 °C; lit.[32] $[\alpha]_D$ +26.1 (*c* 1.0 in H_2O)} were in excellent agreement with literature values.[9c,33,34]

For the C(3)-phenyl substituted aziridines **28** and **29**, however, treatment with Cl_3CCO_2H induced rearrangement to give the corresponding oxazolidin-2-ones: upon treatment of *cis*-aziridine **29** with Cl_3CCO_2H a 92:8 mixture of *cis*- and *trans*-oxazolidin-2-ones



Scheme 8. Reagents and conditions: (i) Cl_3CCO_2H, CH_2Cl_2, rt, 15 h; (ii) HCl (6.0 M aq), 90 °C, 24 h.

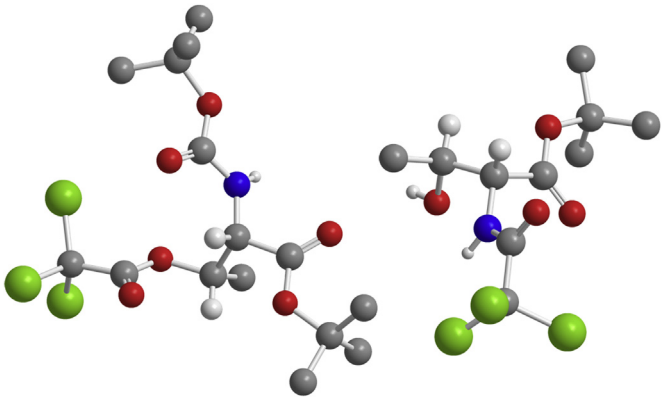


Fig. 7. X-ray crystal structures of **37** [left] and **41** [right] (selected H atoms are omitted for clarity).

43 ($J_{4,5}$=9.2 Hz) and **44** ($J_{4,5}$=5.3 Hz) was produced, and **43** and **44** were subsequently isolated in 74 and 4% yield, respectively, after purification of the crude reaction mixture. Identical treatment of the epimeric *trans*-aziridine **28** produced *trans*-oxazolidin-2-one *ent*-**44** exclusively, which was isolated in 77% yield and >99:1 dr (Scheme 9). For both **43** and *ent*-**44** single crystal X-ray diffraction analyses[35] enabled unambiguous confirmation of the relative configurations within these compounds, and the determination of Flack *x* parameters[15] of −0.03(19) and −0.08(16) for the crystal structures of **43** and *ent*-**44**, respectively, allowed the absolute (*R*,*R*)-configuration within **43** and (4*S*,5*R*)-configuration within *ent*-**44** to be assigned unambiguously (Fig. 8). These stereochemical outcomes (i.e., retention of configuration) are consistent with a mechanism whereby Cl_3CCO_2H promotes S_N1-type ring-opening of aziridines **28** and **29** to generate the corresponding benzylic carbonium ions, which then undergo rapid intramolecular reaction with the carbamate functionality to form the oxazolidin-2-one ring

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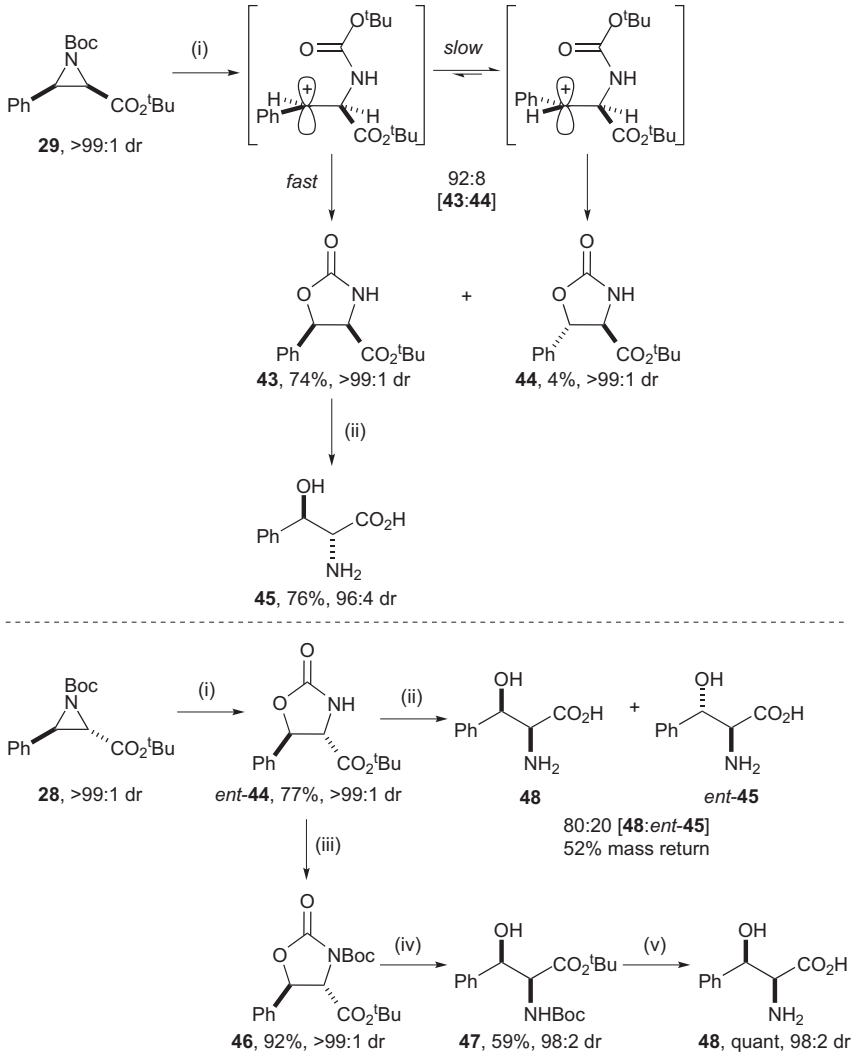

Scheme 9. Reagents and conditions: (i) Cl_3CCO_2H, CH_2Cl_2, rt, 15 h; (ii) HCl (6.0 M aq), 90 °C, 24 h; (iii) Boc_2O, Et_3N, DMAP, THF, rt, 15 h; (iv) LiOH, dioxane/H_2O (5:1), rt, 45 min; (v) CH_2Cl_2/TFA (4:1), rt, 2 h.

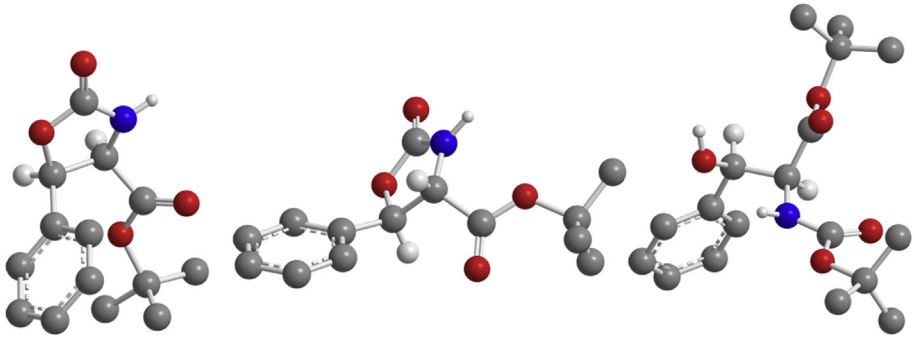

Fig. 8. X-ray crystal structures of **43** [left], *ent*-**44** [centre] and **47** [right] (selected H atoms are omitted for clarity).

with concomitant loss of the *tert*-butyl group; in the case of **29** the corresponding benzylic carbonium ion presumably undergoes C–C bond rotation (to minimise the interaction between the phenyl and ester substituents) at a competitive rate, giving rise to the formation of the minor diastereoisomer **44**.[36] Hydrolysis of **43**, upon treatment with aqueous HCl, produced the corresponding β-hydroxy-α-amino acid **45** in 76% yield and 96:4 dr after purification on Dowex 50WX8 ion exchange resin. However, in the case of *ent*-**44**, application of identical hydrolysis conditions produced an 80:20 mixture of the epimeric β-hydroxy-α-amino acids **48** and *ent*-**45**, respectively, in 52% mass return.[37] Conversion of *ent*-**44** to the corresponding *N*(3)-Boc protected compound **46** followed by hydrolysis with LiOH in dioxane[38] gave **47** in 71% overall yield and 98:2 dr after purification (Scheme 9). The relative configuration within **47** was established unambiguously via single crystal X-ray diffraction analysis,[35] and the determination of a Flack

x parameter[15] of −0.06(14) for the crystal structure of **47** allowed the assigned absolute (2*S*,3*R*)-configuration within **47** to be confirmed (Fig. 8). Finally, hydrolysis of both the *tert*-butyl ester and *N*-Boc groups within **47** was achieved upon treatment with TFA, which gave **48** in quantitative yield and 98:2 dr after purification on Dowex 50WX8 ion exchange resin (Scheme 9). The spectroscopic data, including specific rotations, for both samples of (*R*,*R*)-**45** {mp 189–192 °C (dec); $[\alpha]_D^{20}$ −2.4 (*c* 1.0 in H_2O); lit.[9a] mp 174 °C (dec); lit.[39] $[\alpha]_D$ −4.3 (*c* 1.1 in H_2O)} and (2*S*,3*R*)-**48** {mp 201–202 °C; $[\alpha]_D^{20}$ −28.9 (*c* 1.0 in H_2O); lit.[40] mp 192–195 °C; lit.[9c] $[\alpha]_D^{20}$ −30 (*c* 1.0 in H_2O)} were in excellent agreement with literature values.[41]

3. Conclusion

In conclusion, a range of enantiopure α-hydroxy-β-amino esters were converted into the corresponding *N*-Boc protected aziridines and subsequently used in the syntheses of β-hydroxy-α-amino acids. The β-amino ester substrates were prepared upon conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to the corresponding α,β-unsaturated esters, followed by oxidation of the intermediate lithium (*Z*)-β-amino enolate with (−)-CSO, which gave diastereoisomerically pure 2,3-*anti*-configured products. Epimerisation of these substrates was achieved using an oxidation/diastereoselective reduction approach, which (under optimised conditions) gave the corresponding 2,3-*syn*-configured products in >99:1 dr. The *syn*- and *anti*-substrates were then converted into the corresponding *N*-Boc protected mesylates followed by base-promoted aziridine formation. Subsequent regioselective ring-opening of the C(3)-methyl substituted aziridines with Cl_3CCO_2H proceeded with inversion of configuration at C(3) (i.e., an S_N2-type process), and reaction of the analogous C(3)-phenyl substituted aziridines with Cl_3CCO_2H produced the corresponding oxazolidin-2-ones with retention of configuration (i.e., an S_N1-type process). In each case, hydrolysis of the products from these ring-opening reactions produced the corresponding diastereoisomerically pure (>95:5 dr) β-hydroxy-α-amino acids.

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 et al.[42] Water was purified by an Elix® UV-10 system. All other reagents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$ or $NaSO_4$. 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.

Melting points were recorded on a Gallenkamp Hot Stage apparatus. 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 using 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. $^1H-^1H$ COSY, $^1H-^{13}C$ HSQC and $^1H-^{13}C$ HMBC analyses were used to establish atom connectivity. 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. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 14

BuLi (2.5 M in hexanes, 15.2 mL, 38.0 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl) amine[43] (8.26 g, 39.1 mmol, >99:1 er) in THF (100 mL) at −78 °C and stirring was continued at −78 °C for 30 min. A solution of **12**[44] (5.00 g, 24.5 mmol, >99:1 dr) in THF (100 mL) was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. (−)-CSO **3** (8.97 g, 39.1 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 15 h. Satd aq NH_4Cl (5 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (100 mL) and 10% aq citric acid (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (3×40 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated in vacuo. The residue was dissolved in Et_2O (100 mL), the insoluble CSO residues were filtered off, and the filter cake was washed with Et_2O (2×50 mL). The filtrate was concentrated in vacuo and the process was repeated. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **14** as a pale yellow solid (9.77 g, 93%, >99:1 dr);[30b] mp 85–88 °C; {lit.[45] mp 87–88 °C}; $[\alpha]_D^{23}$ −26.7 (*c* 1.0 in $CHCl_3$); {lit.[45] $[\alpha]_D^{25}$ −27.2 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.26–1.29 (12H, m, C(α)*Me*, *CMe*$_3$), 2.91 (1H, br s, O*H*), 3.92 (1H, d, *J* 14.9, NCH_AH_BPh), 4.22 (1H, d, *J* 14.9, NCH_AH_BPh), 4.27–4.33 (2H, m, C(α)*H*, C(3)*H*), 4.49 (1H, d, *J*, 3.0, C(2)*H*), 7.21–7.61 (15H, m, *Ph*).

4.3. *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]butanoate 15

BuLi (2.4 M in hexanes, 4.54 mL, 10.9 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl) amine[43] (2.39 g, 11.3 mmol, >99:1 er) in THF (60 mL) at −78 °C and stirring was continued at −78 °C for 30 min. A solution of **13** (1.00 g, 7.03 mmol, >99:1 dr) in THF (60 mL) was then added via cannula and the resultant mixture was stirred at −78 °C for 2 h. (−)-CSO **3** (2.59 g, 11.3 mmol) was then added and stirring was continued as the reaction mixture was allowed to warm to rt over 15 h. Satd aq NH_4Cl (5 mL) was added and the reaction mixture was stirred at rt for 5 min then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (100 mL) and 10% aq citric acid (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (3×40 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated in vacuo. The residue was dissolved in Et_2O (100 mL), the insoluble CSO residues were filtered off, and the filter cake was washed with Et_2O (2×50 mL). The filtrate was concentrated in vacuo and the process was repeated. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **15** as a yellow solid (2.29 g, 91%, >99:1 dr);[45] mp 89–94 °C; {lit.[45] mp 88–89 °C}; $[\alpha]_D^{23}$ −35.5 (*c* 1.0 in $CHCl_3$); {lit.[45] $[\alpha]_D^{25}$ −35.2 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.08 (3H, d, *J* 7.0, C(4)H_3), 1.32 (3H, d, *J* 6.8, C(α)*Me*), 1.36 (9H, s, *CMe*$_3$), 2.92 (1H, app d, *J* 6.5, O*H*), 3.25 (1H, qd, *J* 7.0, 2.6, C(3)*H*), 3.87 (1H, d, *J* 14.7, NCH_AH_BPh), 3.97–4.04 (3H, m, C(2)*H*, C(α)*H*, NCH_AH_BPh), 7.18–7.50 (10H, m, *Ph*).

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4.4. *tert*-Butyl (*R*,*R*)-2-hydroxy-3-[*N*-(*tert*-butoxycarbonyl)-amino]-3-phenylpropanoate 16

$Pd(OH)_2/C$ (500 mg, 25% w/w) was added to a degassed solution of **14** (2.00 g, 4.64 mmol, >99:1 dr) and Boc_2O (1.11 g, 7.66 mmol) in EtOAc (40 mL) and the resultant mixture was stirred under H_2 (5 atm) at rt for 15 h. The reaction mixture was then filtered through Celite® (eluent EtOAc) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **16** as a white solid (1.54 g, 99%, >99:1 dr); mp 75–79 °C; $[\alpha]_D^{23}$ −25.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3400 (N–H), 3292 (O–H), 2976, 2933 (C–H), 1707, 1687 (2× C=O); δ_H (400 MHz, $CDCl_3$) 1.36 (9H, s, C*Me*$_3$), 1.43 (9H, s, C*Me*$_3$), 1.57 (1H, br s, O*H*), 4.44–4.51 (1H, m, C(2)*H*), 5.06 (1H, dd, *J* 8.9, 3.3, C(3)*H*), 5.60 (1H, d, *J* 8.9, N*H*), 7.26–7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.9, 28.4 (2× C*Me*$_3$), 56.3 (*C*(3)), 73.0 (*C*(2)), 79.8, 83.6 (2× *C*Me$_3$), 127.9, 128.1, 128.2 (*o*,*m*,*p*-*Ph*), 137.2 (*i*-*Ph*), 155.0 (NCO), 171.0 (*C*(1)); *m*/*z* (ESI^+) 360 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{18}H_{27}NNaO_5^+$ ($[M+Na]^+$) requires 360.1781; found 360.1767.

4.5. *tert*-Butyl (*R*,*R*)-2-hydroxy-3-[*N*-(*tert*-butoxycarbonyl)-amino]butanoate 17

$Pd(OH)_2/C$ (1.00 g, 25% w/w) was added to a degassed solution of **15** (4.00 g, 10.8 mmol, >99:1 dr) and Boc_2O (2.60 g, 11.9 mmol) in EtOAc (50 mL) and the resultant mixture was stirred under H_2 (5 atm) at rt for 15 h. The reaction mixture was then filtered through Celite® (eluent EtOAc) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **17** as a colourless oil (2.62 g, 88%, >99:1 dr);[10c] $[\alpha]_D^{23}$ −10.4 (*c* 1.0 in $CHCl_3$); {lit.[10c] for *ent*-**17**: $[\alpha]_D^{23}$ +10.8 (*c* 2.4 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.02 (3H, d, *J* 6.7, C(4)H_3), 1.45 (9H, s, C*Me*$_3$), 1.50 (9H, s, C*Me*$_3$), 3.04 (1H, d, *J* 5.5, O*H*), 4.05–4.15 (1H, m, C(3)*H*), 4.21 (1H, m, C(2)*H*), 4.90 (1H, d, *J* 8.9, N*H*).

4.6. *tert*-Butyl (*R*,*R*)-2-methanesulfonyloxy-3-[*N*-(*tert*-butoxycarbonyl)amino]-3-phenylpropanoate 18

MsCl (1.37 mL, 17.8 mmol), Et_3N (5.90 mL, 44.5 mmol) and DMAP (5 mg, cat.) were added to a stirred solution of **16** (3.00 g, 8.89 mmol, >99:1 dr) in CH_2Cl_2 (270 mL) and the resultant solution was stirred at rt for 15 h. H_2O (180 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (2×90 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (200 mL), satd aq $NaHCO_3$ (200 mL) and brine (200 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1) gave **18** as a yellow solid (3.16 g, 86%, >99:1 dr); mp 113–116 °C; $[\alpha]_D^{23}$ −17.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3381 (N–H), 3064, 3034, 2974, 2936, 2872 (C–H), 1740, 1695 (2× C=O); δ_H (400 MHz, $CDCl_3$) 1.32 (9H, s, C*Me*$_3$), 1.45 (9H, s, C*Me*$_3$), 3.15 (3H, s, SO_2Me), 5.22–5.32 (2H, m, C(3)*H*, N*H*), 5.41–5.46 (1H, m, C(2)*H*), 7.31–7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.7, 28.3 (2× C*Me*$_3$), 39.1 (SO_2Me), 55.2 (*C*(3)), 79.0 (*C*(2)), 80.4, 83.9 (2× *C*Me$_3$), 128.1, 128.6, 128.6 (*o*,*m*,*p*-*Ph*), 135.8 (*i*-*Ph*), 154.8 (NCO), 165.5 (*C*(1)); *m*/*z* (ESI^+) 438 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{19}H_{29}NNaO_7S^+$ ($[M+Na]^+$) requires 438.1557; found 438.1574.

4.7. *tert*-Butyl (*R*,*R*)-2-methanesulfonyloxy-3-[*N*-(*tert*-butoxycarbonyl)amino]butanoate 19

MsCl (0.56 mL, 7.26 mmol), Et_3N (2.41 mL, 18.2 mmol) and DMAP (3 mg, cat.) were added to a stirred solution of **17** (1.00 g, 3.63 mmol, >99:1 dr) in CH_2Cl_2 (110 mL) and the resultant solution was stirred at rt for 15 h. H_2O (60 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2×40 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (100 mL), satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **19** a pale yellow oil (1.10 g, 85%, >99:1 dr);[10c] $[\alpha]_D^{23}$ +35.5 (*c* 1.0 in $CHCl_3$); {lit.[10c] for *ent*-**19**: $[\alpha]_D^{25}$ −38.4 (*c* 1.05 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.13 (3H, d, *J* 7.0, C(4)H_3), 1.45 (9H, s, C*Me*$_3$), 1.51 (9H, s, C*Me*$_3$), 3.17 (3H, s, SO_2Me), 4.23–4.34 (1H, m, C(3)*H*), 4.75 (1H, d, *J* 8.7, N*H*), 5.20 (1H, d, *J* 2.7, C(2)*H*).

4.8. *tert*-Butyl (2*S*,3*R*,α*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 22

Step 1: DMSO (0.17 mL, 2.32 mmol) was added to a stirred solution of $(COCl)_2$ (0.20 mL, 2.32 mmol) in CH_2Cl_2 (15 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 5 min. A solution of **14** (500 mg, 1.16 mmol, >99:1 dr) in CH_2Cl_2 (15 mL) was added via cannula and the resultant mixture was stirred at −78 °C for 30 min. Et_3N (0.62 mL, 4.64 mmol) was added and the reaction mixture was allowed to warm to rt. H_2O (20 mL) was then added, the reaction mixture was extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts were dried and concentrated in vacuo to give **20** (498 mg, >99:1 dr).

Step 2: DIBAL-H (1.0 M in THF, 1.16 mL, 1.16 mmol) was added to a stirred solution of **20** (498 mg, >99:1 dr) in THF (13 mL) at −20 °C and the resultant mixture was stirred at −20 °C for 2 h. MeOH (1 mL) was added and the reaction mixture was then allowed to warm to rt. Satd aq Rochelle's salt (1 mL) was added and the resultant suspension was stirred at rt for 15 h, then filtered through Celite® (eluent MeOH) and concentrated in vacuo to give **22** in >99:1 dr. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 7:1) gave **22** as a white solid (375 mg, 75%, >99:1 dr); mp 110–114 °C; $[\alpha]_D^{23}$ −25.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3492 (O–H), 3085, 3062, 3028, 2976, 2934, 2879, 2842 (C–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.08 (9H, s, C*Me*$_3$), 1.10 (3H, d, *J* 6.9, C(α)*Me*), 3.66 (1H, d, *J* 13.3, NCH_AH_BPh), 3.84 (1H, br s, O*H*), 3.90 (1H, d, *J* 9.9, C(3)*H*), 4.07 (1H, d, *J* 13.3, NCH_AH_BPh), 4.21 (1H, q, *J* 6.9, C(α)*H*), 4.47 (1H, d, *J* 9.9, C(2)*H*), 7.24–7.42 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.7 (C(α)*Me*), 27.4 (C*Me*$_3$), 50.4 (NCH_2Ph), 56.0 (*C*(α)), 64.4 (*C*(3)), 71.0 (*C*(2)), 81.0 (*C*Me$_3$), 127.3, 127.4, 127.9, 128.1, 128.2, 128.6, 128.7, 129.1, 130.0 (*o*,*m*,*p*-*Ph*), 136.7, 139.3, 143.2 (*i*-*Ph*), 171.2 (*C*(1)); *m*/*z* (ESI^+) 432 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{28}H_{34}NO_3^+$ ($[M+H]^+$) requires 432.2533; found 432.2518.

4.9. *tert*-Butyl (2*S*,3*R*,α*R*)-2-hydroxy-3-[*N*-benzyl-*N*(α-methylbenzyl)amino]butanoate 23

Step 1: DMSO (0.58 mL, 8.13 mmol) was added to a stirred solution of $(COCl)_2$ (0.69 mL, 8.13 mmol) in CH_2Cl_2 (50 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 5 min. A solution of **15** (1.50 g, 4.06 mmol, >99:1 dr) in CH_2Cl_2 (50 mL) was added via cannula and the resultant mixture was stirred at −78 °C for 30 min. Et_3N (2.18 mL, 16.2 mmol) was added and the reaction mixture was allowed to warm to rt. H_2O (80 mL) was then added, the reaction mixture was extracted with CH_2Cl_2 (3×50 mL) and combined organic extracts were dried and concentrated in vacuo to give **21** (1.49 g, >99:1 dr).

Step 2: $NaBH_4$ (154 mg, 4.06 mmol) was added to a solution of **21** (1.49 g, >99:1 dr) in MeOH (105 mL) and the resultant solution was cooled to −20 °C and stirred at −20 °C for 2 h, then allowed to warm to rt and concentrated in vacuo. The reaction mixture was then partitioned between Et_2O (50 mL) and H_2O (30 mL) and the aqueous layer was extracted with Et_2O (2×20 mL). The combined organic extracts were then dried and concentrated in vacuo to give **23** as a colourless oil (1.42 g, 95%, >99:1 dr); $[\alpha]_D^{23}$ −68.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3501 (O–H), 3086, 3062, 3028, 2975, 2935, 2881

(C–H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6.8, C(4)H_3), 1.43 (9H, s, CMe_3), 1.47 (3H, d, *J* 6.9, C(α)*Me*), 3.07 (1H, dq, *J* 8.3, 6.8, C(3)*H*), 3.65–3.72 (2H, m, C(2)*H*, NCH_AH_BPh), 3.78 (1H, br s, O*H*), 3.81 (1H, d, *J* 13.6, NCH_AH_BPh), 4.06 (1H, q, *J* 6.9, C(α)*H*), 7.19–7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.6 (*C*(4)), 14.4 (C(α)*Me*), 27.9 (CMe_3), 49.6 (NCH_2Ph), 54.9 (*C*(3)), 57.1 (*C*(α)), 73.5 (*C*(2)), 81.3 (*C*Me$_3$), 127.3, 127.3, 127.7, 128.4, 128.5, 129.1 (*o*,*m*,*p*-*Ph*), 139.8, 143.0 (*i*-*Ph*), 172.2 (*C*(1)); *m*/*z* (ESI$^+$) 370 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{32}NO_3^+$ ([M+H]$^+$) requires 370.2377; found 370.2364.

4.10. *tert*-Butyl (2*S*,3*R*)-2-hydroxy-3-[*N*-(*tert*-butoxycarbonyl)-amino]-3-phenylpropanoate 24

$Pd(OH)_2$/C (150 mg, 40% w/w) was added to a degassed solution of **22** (375 mg, 0.870 mmol, >99:1 dr) and Boc_2O (189 mg, 0.870 mmol) in EtOAc (10 mL) and the resultant mixture was stirred under H_2 (5 atm) at rt for 15 h. The reaction mixture was then filtered through Celite® (eluent EtOAc) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **24** as a white solid (163 mg, 68%, >99:1 dr);[46] mp 106–107 °C; $[\alpha]_D^{23}$ −9.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3447 (N–H), 3392 (O–H), 3091, 3065, 3032, 2978, 2933 (C–H), 1716 (2× C=O); δ_H (400 MHz, $CDCl_3$) 1.42 (9H, s, CMe_3), 1.52 (9H, s, CMe_3), 3.27 (1H, br s, O*H*), 4.31–4.39 (1H, m, C(2)*H*), 5.20–5.26 (1H, m, C(3)*H*), 5.41–5.49 (1H, m, N*H*), 7.22–7.43 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.9, 28.3 (2× CMe_3), 55.7 (*C*(3)), 73.7 (*C*(2)), 79.6, 83.7 (2× *C*Me$_3$), 126.7, 127.5, 128.5 (*o*,*m*,*p*-*Ph*), 139.7 (*i*-*Ph*), 155.0 (NCO), 172.1 (*C*(1)); *m*/*z* (ESI$^+$) 360 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{27}NNaO_5^+$ ([M+Na]$^+$) requires 360.1781; found 360.1769.

4.11. *tert*-Butyl (2*S*,3*R*)-2-hydroxy-3-[*N*-(*tert*-butoxycarbonyl)-amino]butanoate 25

$Pd(OH)_2$/C (78 mg, 25% w/w) was added to a degassed solution of **23** (313 mg, 0.847 mmol, >99:1 dr) and Boc_2O (203 mg, 0.932 mmol) in EtOAc (10 mL) and the resultant mixture was stirred under H_2 (5 atm) at rt for 15 h. The reaction mixture was then filtered through Celite® (eluent EtOAc) and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **25** as a yellow solid (164 mg, 70%, >99:1 dr); mp 65–80 °C; $[\alpha]_D^{23}$ +17.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3449 (N–H), 3391 (O–H), 2978, 2934 (C–H), 1714 (2× C=O); δ_H (400 MHz, $CDCl_3$) 1.24 (3H, d, *J* 7.1, C(4)H_3), 1.40 (9H, s, CMe_3), 1.49 (9H, s, CMe_3), 3.12–3.26 (1H, m, O*H*), 3.98 (1H, app br s, C(2)*H*), 4.13–4.24 (1H, m, C(3)*H*), 4.70–4.79 (1H, m, N*H*); δ_C (100 MHz, $CDCl_3$) 18.5 (*C*(4)), 27.8, 28.3 (2× CMe_3), 48.3 (*C*(3)), 73.4 (*C*(2)), 79.1, 83.3 (2× *C*Me$_3$), 154.9 (NCO), 172.6 (*C*(1)); *m*/*z* (ESI$^+$) 298 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{25}NNaO_5^+$ ([M+Na]$^+$) requires 298.1625; found 298.1626.

4.12. *tert*-Butyl (2*S*,3*R*)-2-methanesulfonyloxy-3-[*N*-(*tert*-butoxycarbonyl)amino]-3-phenylpropanoate 26

MsCl (34 μL, 0.45 mmol), Et_3N (0.14 mL, 1.0 mmol) and DMAP (1 mg, cat.) were added to a solution of **24** (30 mg, 0.09 mmol, >99:1 dr) in CH_2Cl_2 (3 mL) and the resultant solution was stirred at rt for 15 h. H_2O (1.5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (3 mL), satd aq $NaHCO_3$ (3 mL) and brine (3 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1 then increased to 1:1) gave **26** as a colourless oil (35 mg, 95%, >99:1 dr); $[\alpha]_D^{23}$ −5.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3065, 2980, 2936 (C–H), 1749, 1717 (2× C=O); δ_H (400 MHz, $CDCl_3$) 1.42, (9H, s, CMe_3), 1.51 (9H, s, CMe_3), 2.72 (3H, s, SO_2Me), 5.05–5.14 (1H, m, C(2)*H*), 5.35–5.44 (1H, m, N*H*), 5.46–5.53 (1H, m, C(3)*H*), 7.28–7.42 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.8, 28.2 (2× CMe_3), 38.6 (SO_2Me), 55.1 (*C*(3)), 81.5 (*C*(2)), 84.2 (2× *C*Me$_3$), 126.4, 128.2, 128.8 (*o*,*m*,*p*-*Ph*), 137.7 (*i*-*Ph*), 154.6 (NCO), 165.6 (*C*(1)); *m*/*z* (ESI$^+$) 438 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{29}NNaO_7S^+$ ([M+Na]$^+$) requires 438.1557; found 438.1544.

4.13. *tert*-Butyl (2*S*,3*R*)-2-methanesulfonyloxy-3-[(*tert*-butoxycarbonyl)amino]butanoate 27

MsCl (0.26 mL, 3.31 mmol), Et_3N (1.10 mL, 8.30 mmol) and DMAP (3 mg, cat.) were added to a stirred solution of **25** (456 mg, 1.66 mmol, >99:1 dr) in CH_2Cl_2 (50 mL) and the resultant solution was stirred at rt for 16 h. H_2O (40 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2×25 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (50 mL), satd aq $NaHCO_3$ (50 mL) and brine (50 mL), then dried and concentrated in vacuo to give **27** as a yellow solid (473 mg, 92%, >99:1); mp 97–106 °C; $[\alpha]_D^{20}$ +4.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3388 (N–H), 2981, 2966, 2935, 2866 (C–H), 1750, 1722 (2× C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.8, C(4)H_3), 1.42 (9H, s, CMe_3), 1.49 (9H, s, CMe_3), 3.19 (3H, s, SO_2Me), 4.39–4.50 (1H, m, C(3)*H*), 4.65–4.75 (1H, m, C(2)*H*), 4.88 (1H, d, *J* 2.3, N*H*); δ_C (100 MHz, $CDCl_3$) 18.3 (*C*(4)), 27.8, 28.3 (2× CMe_3), 39.3 (SO_2Me), 47.6 (*C*(3)), 81.0 (*C*(2)), 79.7, 83.9 (2× *C*Me$_3$), 154.6 (NCO), 166.2 (*C*(1)); *m*/*z* (ESI$^+$) 376 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{14}H_{27}NNaO_7S^+$ ([M+Na]$^+$) requires 376.1400; found 376.1384.

4.14. Di-*tert*-butyl (2*S*,3*R*)-3-phenylaziridine-*N*(1),2-dicarboxylate 28

NaH (60% dispersion in mineral oil, 323 mg, 8.09 mmol) was added to a stirred solution of **18** (2.80 g, 6.74 mmol, >99:1 dr) in DMF (100 mL) and the resultant solution was heated at 50 °C for 3 h. Et_2O (60 mL) was then added and the resultant mixture was washed with H_2O (4×40 mL), then dried and concentrated in vacuo to give a 98:2 mixture of **28** and **29**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 20:1) gave **28** as a white solid (1.55 g, 72%, >99:1 dr); mp 120–128 °C; $[\alpha]_D^{23}$ +69.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3064, 3036, 2986, 2967, 2933 (C–H), 1729, 1717 (2× C=O); δ_H (500 MHz, $CDCl_3$) 1.48 (9H, s, CMe_3), 1.52 (9H, s, CMe_3), 3.01 (1H, d, *J* 2.5, C(2)*H*), 3.74 (1H, d, *J* 2.5, C(3)*H*), 7.27–7.37 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 27.9, 28.1 (2× CMe_3), 44.5 (*C*(3)), 45.1 (*C*(2)), 82.0, 82.7 (2× *C*Me$_3$), 126.5, 128.2, 128.5 (*o*,*m*,*p*-*Ph*), 135.7 (*i*-*Ph*), 158.6 (NCO), 166.4 ($CO_2{}^tBu$); *m*/*z* (ESI$^+$) 342 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{25}NNaO_4^+$ ([M+Na]$^+$) requires 342.1676; found 342.1674.

4.15. Di-*tert*-butyl (*R*,*R*)-3-phenylaziridine-*N*(1),2-dicarboxylate 29

Cs_2CO_3 (299 mg, 0.918 mmol) was added to a stirred solution of **26** (127 mg, 0.306 mmol, >99:1 dr) in DMF (6.2 mL) and the resultant mixture was heated at 50 °C for 3 h. Et_2O (5 mL) was then added and the resultant mixture was washed with H_2O (4×3 mL), then dried and concentrated in vacuo to give **29** as a white solid (97 mg, 99%, >99:1 dr); mp 121–124 °C; $[\alpha]_D^{25}$ −18.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3065, 3034, 3007, 2976, 2959, 2926, 2853 (C–H), 1736, 1724 (2× C=O); δ_H (500 MHz, $CDCl_3$); 1.16 (9H, s, CMe_3), 1.49 (9H, s, CMe_3), 3.33 (1H, d, *J* 6.9, C(2)*H*), 3.77 (1H, d, *J* 6.9, C(3)*H*), 7.25–7.45 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 27.8, 27.9 (2× CMe_3), 43.3 (*C*(2)), 44.2 (*C*(3)), 81.9, 82.2 (2× *C*Me$_3$), 127.6, 127.9, 128.5 (*o*,*m*,*p*-*Ph*), 133.4 (*i*-*Ph*), 160.8 (NCO), 165.1 ($CO_2{}^tBu$); *m*/*z* (ESI$^+$) 342 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{25}NNaO_4^+$ ([M+Na]$^+$) requires 342.1676; found 342.1661.

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4.16. (4*R*,5*S*)-4-Phenyl-5-(*tert*-butoxycarbonyl)oxazolidin-2-one 30

CDI (73 mg, 0.449 mmol) and DMAP (3 mg, cat.) were added to a stirred solution of **33** (77 mg, 0.299 mmol, >99:1 dr) in THF (2.5 mL) and the resultant mixture was stirred at rt for 12 h. Satd aq NH_4Cl (2 mL) was added and the reaction mixture was extracted with EtOAc (3×2 mL). The combined organic extracts were washed with brine (5 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **30** as a white solid (12 mg, 15%, >99:1 dr); mp 145–150 °C; $[\alpha]_D^{25}$ +30.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3287 (N–H), 3037, 3004, 2981, 2932 (C–H), 1760, 1734 (2× C=O); δ_H (500 MHz, $CDCl_3$) 1.54 (9H, s, C*Me*$_3$), 4.64 (1H, d, *J* 5.6, C(5)*H*), 4.93 (1H, d, *J* 5.6, C(4)*H*), 5.78 (1H, br s, N*H*), 7.36–7.46 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 28.0 (C*Me*$_3$), 59.2 (*C*(4)), 80.8 (*C*(5)), 83.8 (*C*Me$_3$), 126.0, 129.1, 129.3 (*o*,*m*,*p*-*Ph*), 139.0 (*i*-*Ph*), 157.7 (*C*(2)), 167.1 ($CO_2{}^tBu$); *m*/*z* (ESI^+) 286 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{14}H_{17}NNaO_4^+$ ($[M+Na]^+$) requires 286.1050; found 286.1041.

4.17. *tert*-Butyl (*R*,*R*)-2-hydroxy-3-amino-3-phenylproanoate 31

$Pd(OH)_2/C$ (27 mg, 25% w/w) was added to a degassed solution of **14** (108 mg, 0.292 mmol, >99:1 dr) in MeOH (5 mL) and the resultant mixture was stirred under H_2 (5 atm) at rt for 15 h. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated in vacuo to give **31** as a colourless oil (55 mg, quant, >99:1 dr);[10a] $[\alpha]_D^{23}$ −27.7 (*c* 1.0 in $CHCl_3$); {lit.[10a] $[\alpha]_D^{23}$ −29.0 (*c* 0.5 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.33 (9H, s, C*Me*$_3$), 3.42–3.47 (3H, br s, NH_2, O*H*), 4.33–4.38 (2H, m, C(2)*H*, C(3)*H*), 7.21–7.36 (5H, m, *Ph*).

4.18. (*R*,*R*)-4-Phenyl-5-(*tert*-butoxycarbonyl)oxazolidin-2-one 32

CDI (205 mg, 1.26 mmol) and DMAP (3 mg, cat.) were added to a stirred solution of **31** (200 mg, 0.843 mmol, >99:1 dr) in THF (7 mL) and the resultant mixture was stirred at rt for 12 h. Satd aq NH_4Cl (5 mL) was added and the reaction mixture was extracted with EtOAc (3×3 mL). The combined organic extracts were washed with brine (5 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **32** as a white solid (49 mg, 22%, >99:1 dr); mp 163–168 °C; $[\alpha]_D^{25}$ −63.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3288 (N–H), 3067, 3036, 2980, 2934 (C–H), 1735 (2× C=O); δ_H (400 MHz, $CDCl_3$) 1.04 (9H, s, C*Me*$_3$), 5.16 (1H, d, *J* 9.2, C(5)*H*), 5.20 (1H, d, *J* 9.2, C(4)*H*), 6.53 (1H, br s, N*H*), 7.23–7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.3 (C*Me*$_3$), 58.4 (*C*(4)), 77.9 (*C*(5)), 83.0 (*C*Me$_3$), 127.5, 128.7, 129.2 (*o*,*m*,*p*-*Ph*), 135.8 (*i*-*Ph*), 158.6 (*C*(2)), 165.0 ($CO_2{}^tBu$); *m*/*z* (ESI^+) 286 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{14}H_{17}NNaO_4^+$ ($[M+Na]^+$) requires 286.1050; found 286.1039.

4.19. *tert*-Butyl (2*S*,3*R*)-2-hydroxy-3-amino-3-phenylproanoate 33

$Pd(OH)_2/C$ (35 mg, 25% w/w) was added to a degassed solution of **22** (139 mg, 0.322 mmol, >99:1 dr) in MeOH (5 mL) and the resultant mixture was stirred under H_2 (5 atm) at rt for 15 h. The reaction mixture was filtered through Celite® (eluent MeOH) and concentrated in vacuo to give **33** as a colourless oil (77 mg, quant, >99:1 dr); $[\alpha]_D^{23}$ +11.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3363, 3298 (N–H), 3165 (O–H), 3086, 3063, 3030, 3003, 2978, 2932 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, C*Me*$_3$), 2.59 (3H, br s, NH_2, O*H*), 4.15–4.20 (2H, m, C(2)*H*, C(3)*H*), 7.21–7.41 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.9 (C*Me*$_3$), 58.5, 75.3 (*C*(2), *C*(3)), 82.5 (*C*Me$_3$), 127.0, 127.5, 128.4 (*o*,*m*,*p*-*Ph*), 142.2 (*i*-*Ph*), 172.6 (*C*(1)); *m*/*z* (ESI^+) 260 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{13}H_{19}NNaO_3^+$ ($[M+Na]^+$) requires 260.1257; found 260.1250.

4.20. Di-*tert*-butyl (2*S*,3*R*)-3-methylaziridine-*N*(1),2-dicarboxylate 34

Method A: NaH (60% dispersion in mineral oil, 68 mg, 1.69 mmol) was added to a stirred solution of **19** (459 mg, 1.41 mmol, >99:1 dr) in DMF (15 mL) and the resultant mixture was heated at 50 °C for 3 h. Et_2O (15 mL) was then added and the resultant mixture was washed with H_2O (4×10 mL), then dried and concentrated in vacuo to give a 93:7 mixture of **34** and **36**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 15:1) gave **34** as a white solid (185 mg, 48%, >99:1 dr); mp 69–71 °C; $[\alpha]_D^{25}$ −1.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3007, 2980, 2933, 2872 (C–H), 1728, 1718 (2× C=O); δ_H (500 MHz, $CDCl_3$) 1.31 (3H, d, *J* 5.5, C(3)*Me*), 1.46 (9H, s, C*Me*$_3$), 1.49 (9H, s, C*Me*$_3$), 2.68 (1H, d, *J* 2.7, C(2)*H*), 2.75 (1H, qd, *J* 5.5, 2.7, C(3)*H*); δ_C (125 MHz, $CDCl_3$) 16.5 (C(3)*Me*), 28.0, 28.0 (2× C*Me*$_3$), 38.9 (*C*(3)), 42.4 (*C*(2)), 81.5, 82.3 (2× *C*Me$_3$), 159.3 (NCO), 167.4 ($CO_2{}^tBu$); *m*/*z* (ESI^+) 280 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{13}H_{23}NNaO_4^+$ ($[M+Na]^+$) requires 280.1519; found 280.1518.

Method B: Cs_2CO_3 (4.85 g, 17.0 mmol) was added to a stirred solution of **19** (1.76 g, 5.66 mmol, >99:1 dr) in DMF (110 mL) and the resultant mixture was heated at 50 °C for 3 h. Et_2O (50 mL) was added and the resultant mixture was washed with H_2O (4×70 mL), then dried and concentrated in vacuo to give a 66:14:20 mixture of **34**, **35** and **36**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/EtOAc, 30:1) gave **34** as a white solid (342 mg, 23%, >99:1 dr). Further elution gave **35** as a white solid (88 mg, 8%, >99:1 dr). Further elution gave **36** as a white solid (227 mg, 20%, >99:1 dr);[10c] mp 113–122 °C; $[\alpha]_D^{25}$ +27.3 (*c* 1.0 in $CHCl_3$); {lit.[10c] for *ent*-**36** $[\alpha]_D^{25}$ −22.6 (*c* 0.5 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.40 (3H, d, *J* 6.1, C(4)*Me*), 1.49 (9H, s, C*Me*$_3$), 3.88–3.96 (1H, m, C(4)*H*), 4.39 (1H, d, *J* 5.8, C(5)*H*), 6.49–6.59 (1H, m, N*H*).

4.21. Di-*tert*-butyl (*R*,*R*)-3-methylaziridine-*N*(1),2-dicarboxylate 35

Cs_2CO_3 (974 mg, 2.99 mmol) was added to a stirred solution of **27** (352 mg, 0.997 mmol, >99:1 dr) in DMF (9 mL) and the resultant mixture was heated at 50 °C for 3 h. Et_2O (15 mL) was added and the resultant mixture was washed with H_2O (4×10 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent PhMe/Et_2O, 80:1) gave **35** as a white solid (187 mg, 73%, >99:1 dr); mp 61–63 °C; $[\alpha]_D^{25}$ +68.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3041, 2998, 2977, 2933, 2873, 2851 (C–H), 1740, 1712 (2× C=O), 1678 (C–N); δ_H (500 MHz, $CDCl_3$) 1.31 (3H, d, *J* 5.6, C(3)*Me*), 1.44 (9H, s, C*Me*$_3$), 1.47 (9H, s, C*Me*$_3$), 2.62–2.69 (1H, m, C(3)*H*), 3.00 (1H, d, *J* 6.8, C(2)*H*); δ_C (125 MHz, $CDCl_3$) 12.7 (C(3)*Me*), 27.8, 28.1 (2× C*Me*$_3$), 38.5 (*C*(3)), 40.5 (*C*(2)), 81.7, 82.0 (2× *C*Me$_3$), 161.0 (NCO), 166.5 ($CO_2{}^tBu$); *m*/*z* (ESI^+) 280 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{13}H_{23}NNaO_4^+$ ($[M+Na]^+$) requires 280.1519; found 280.1519.

4.22. *tert*-Butyl (*S*,*S*)-2-[*N*-(*tert*-butoxycarbonyl)amino]-3-(trichloroacetoxy)butanoate 37 and *tert*-butyl (*S*,*S*)-2-(trichloroacetamido)-3-hydroxybutanoate 38

Cl_3CCO_2H (1.19 g, 7.26 mmol) was added to a stirred solution of **34** (400 mg, 1.45 mmol, >99:1 dr) in CH_2Cl_2 (9 mL) and the resultant mixture was stirred at rt for 15 h. Satd aq $NaHCO_3$ (5 mL) was then added, the aqueous layer was extracted with CH_2Cl_2 (2×4 mL) and the combined organic extracts were dried and concentrated in

vacuo to give a 70:30 mixture of **37** and **38**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 10:1) gave **37** as a white solid (287 mg, 47%, >99:1 dr); mp 61–63 °C; $[\alpha]_D^{25}$ +36.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3440 (N–H), 2979, 2935 (C–H), 1763, 1743, 1707 (3× C=O); δ_H (400 MHz, C_6D_6) 1.17 (3H, d, *J* 6.6 C(4)H_3), 1.31 (9H, s, CMe_3), 1.47 (9H, s, CMe_3), 4.77–4.84 (1H, m, C(2)*H*), 5.39–5.47 (1H, m, C(3)*H*), 5.48–5.55 (1H, m, N*H*); δ_C (100 MHz, C_6D_6) 15.3 (*C*(4)), 27.7, 28.2 (2× CMe_3), 57.1 (*C*(2)), 77.0 (*C*(3)), 80.0, 82.7 (2× CMe_3), 90.5 (CCl_3), 155.2 (NCO), 161.4 ($COCCl_3$), 167.6 (*C*(1)); *m*/*z* (FI^+) 419 ($[M(^{35}Cl_3)]^+$, 100%); HRMS (FI^+) $C_{15}H_{24}{}^{35}Cl_3NO_6^+$ ($[M(^{35}Cl_3)]^+$) requires 419.0664; found 419.0698. Further elution gave **38** as a colourless oil (14 mg, 4%, >99:1 dr); $[\alpha]_D^{25}$ +4.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3413 (O–H), 2979, 2936 (C–H), 1713 (2× C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.6, C(4)H_3), 1.52 (9H, s, CMe_3), 2.76 (1H, br s, O*H*), 4.20–4.26 (1H, m, C(3)*H*), 4.48 (1H, dd, *J* 7.3, 3.5, C(2)*H*), 7.56–7.63 (1H, m, N*H*); δ_C (100 MHz, $CDCl_3$) 18.9 (*C*(4)), 28.0 (CMe_3), 60.0 (*C*(2)), 68.9 (*C*(3)), 84.0 (CMe_3), 92.1 (CCl_3), 162.3 ($COCCl_3$), 168.0 (*C*(1)); *m*/*z* (ESI^+) 342 ($[M(^{35}Cl_3)+Na]^+$, 100%); HRMS (ESI^+) $C_{10}H_{16}{}^{35}Cl_3NNaO_4^+$ ($[M(^{35}Cl_3)+Na]^+$) requires 342.0037; found 342.0028.

4.23. (*S*,*S*)-2-Amino-3-hydroxybutanoic acid [(*S*,*S*)-*allo*-threonine] 39

A stirred solution of **37** (212 mg, 0.506 mmol, >99:1 dr) in 6.0 M aq HCl (5.7 mL) was heated at 90 °C for 24 h. The reaction mixture was then allowed to cool to rt and concentrated in vacuo. Purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave **39** as a white solid (43 mg, 72%, >99:1 dr);[9c] mp 240–250 °C (dec); {lit.[9c] mp 264–266 °C}; $[\alpha]_D^{20}$ +7.5 (*c* 1.0 in H_2O); {lit.[9c] $[\alpha]_D^{20}$ +8.0 (*c* 1.1 in H_2O)}; δ_H (400 MHz, D_2O) 1.11 (3H, d, *J* 6.6, C(4)H_3), 3.75 (1H, d, *J* 4.1, C(2)*H*), 4.27 (1H, qd, *J* 6.6, 4.1, C(3)*H*); δ_C (100 MHz, D_2O) 16.2 (*C*(4)), 59.7 (*C*(2)), 65.3 (*C*(3)), 171.8 (*C*(1)).

4.24. *tert*-Butyl (2*R*,3*S*)-2-[*N*-(*tert*-butoxycarbonyl)amino]-3-(trichloroacetoxy)butanoate 40 and *tert*-butyl (2*R*,3*S*)-2-(trichloroacetamido)-3-hydroxybutanoate 41

Cl_3CCO_2H (682 mg, 4.18 mmol) was added to a stirred solution of **35** (230 mg, 0.835 mmol, >99:1 dr) in CH_2Cl_2 (5 mL) and the resultant solution was stirred at rt for 15 h. Satd aq $NaHCO_3$ (4 mL) was then added, the aqueous layer was extracted with CH_2Cl_2 (2×3 mL) and the combined organic extracts were dried and concentrated in vacuo to give an 84:16 mixture of **40** and **41**, respectively. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 5:1) gave **40** as a yellow oil (239 mg, 68%, >99:1 dr); $[\alpha]_D^{25}$ −17.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3441 (N–H), 2981, 2936 (C–H), 1767, 1741, 1717 (3× C=O); δ_H (400 MHz, $CDCl_3$) 1.42 (3H, d, *J* 6.5, C(4)H_3), 1.46 (9H, s, CMe_3), 1.49 (9H, s, CMe_3), 4.47 (1H, dd, *J* 9.4, 2.2, C(2)*H*), 5.19 (1H, d, *J* 9.4, N*H*), 5.58 (1H, dq, *J* 6.5, 2.2, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 16.0 (*C*(4)), 27.9, 28.2 (2× CMe_3), 57.2 (*C*(2)), 76.7 (*C*(3)), 80.4, 83.2 (2× CMe_3), 89.6 (CCl_3), 155.9 (NCO), 160.8, 168.0 (*C*(1), $COCCl_3$); *m*/*z* (FI^+) 419 ($[M(^{35}Cl_3)]^+$, 100%); HRMS (FI^+) $C_{15}H_{24}{}^{35}Cl_3NO_6^+$ ($[M(^{35}Cl_3)]^+$) requires 419.0664; found 419.0678. Further elution gave **41** as a brown solid (24 mg, 9%, >99:1 dr); mp 91–111 °C; $[\alpha]_D^{25}$ +3.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3401 (O–H), 3420 (N–H), 2976, 2925, 2852 (C–H), 1737, 1698 (2× C=O); δ_H (400 MHz, C_6D_6) 1.02 (3H, d, *J* 6.3, C(4)H_3), 1.40 (9H, s, CMe_3), 2.32 (1H, br s, O*H*), 4.19 (1H, qd, *J* 6.3, 2.3, C(3)*H*), 4.48 (1H, dd, *J* 8.6, 2.3, C(2)*H*), 7.54–7.60 (1H, m, N*H*); δ_C (100 MHz, C_6D_6) 20.0 (*C*(4)), 28.2 (CMe_3), 59.5 (*C*(2)), 68.0 (*C*(3)), 82.5 (CMe_3), 93.0 (CCl_3), 162.3 ($COCCl_3$), 168.8 (*C*(1)); *m*/*z* (ESI^+) 342 ($[M(^{35}Cl_3)+Na]^+$, 100%); HRMS (ESI^+) $C_{10}H_{16}{}^{35}Cl_3NNaO_4^+$ ($[M(^{35}Cl_3)+Na]^+$) requires 342.0037; found 342.0026.

4.25. (2*R*,3*S*)-2-Amino-3-hydroxybutanoic acid [(2*R*,3*S*)-threonine] 42

A stirred solution of **40** (160 mg, 0.382 mmol, >99:1 dr) in 6.0 M aq HCl (4.8 mL) was heated at 90 °C for 24 h. The reaction mixture was then allowed to cool to rt and concentrated in vacuo. Purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave **42** as a white solid (44 mg, 98%, 98:2 dr);[34] mp 250–260 °C (dec); {lit.[31] mp 264 °C (dec)}; $[\alpha]_D^{25}$ +23.2 (*c* 1.0 in H_2O); {lit.[47] $[\alpha]_D^{20}$ +26.1 (*c* 1.0 in H_2O)}; δ_H (400 MHz, D_2O) 1.21 (3H, d, *J* 6.6, C(4)H_3), 3.47 (1H, d, *J* 5.0, C(2)*H*), 4.13 (1H, qd, *J* 6.6, 5.0, C(3)*H*); δ_C (100 MHz, D_2O) 19.4 (*C*(4)), 60.4 (*C*(2)), 65.8 (*C*(3)), 172.8 (*C*(1)).

4.26. (*R*,*R*)-5-Phenyl-4-(*tert*-butoxycarbonyl)oxazolidin-2-one 43

Cl_3CCO_2H (826 mg, 5.08 mmol) was added to a stirred solution of **29** (323 mg, 1.01 mmol, >99:1 dr) in CH_2Cl_2 (6.5 mL) and the resultant mixture was stirred at rt for 15 h. Satd aq $NaHCO_3$ (5 mL) was added, the aqueous layer was extracted with CH_2Cl_2 (2×3 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 1:1) gave (4*R*,5*S*)-**44** as a white solid (10 mg, 4%, >99:1 dr); mp 113–127 °C; $[\alpha]_D^{25}$ −33.9 (*c* 1.0 in $CHCl_3$); Further elution gave (*R*,*R*)-**43** as a white solid (197 mg, 74%, >99:1 dr); mp 239–242 °C (dec); $[\alpha]_D^{25}$ −79.0 (*c* 0.5 in $CHCl_3$); ν_{max} (ATR) 3355 (N–H), 2989, 2937 (C–H), 1772, 1745 (2× C=O); δ_H (400 MHz, $CDCl_3$) 1.01 (9H, s, CMe_3), 4.61 (1H, d, *J* 9.2, C(4)*H*), 5.80 (1H, d, *J* 9.2, C(5)*H*), 6.14 (1H, br s, N*H*), 7.30–7.43 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.3 (CMe_3), 59.9 (*C*(4)), 79.2 (*C*(5)), 82.9 (CMe_3), 126.8, 128.5, 129.2 (*o*,*m*,*p*-*Ph*), 134.5 (*i*-*Ph*), 158.9 (*C*(2)), 167.3 (CO_2^tBu); *m*/*z* (ESI^+) 286 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{14}H_{17}NNaO_4^+$ ($[M+Na]^+$) requires 286.1050; found 286.1047.

4.27. (4*S*,5*R*)-5-Phenyl-4-(*tert*-butoxycarbonyl)oxazolidin-2-one *ent*-44

Cl_3CCO_2H (2.14 g, 13.1 mmol) was added to a stirred solution of **28** (839 mg, 2.63 mmol, >99:1 dr) in CH_2Cl_2 (15 mL) and the resultant mixture was stirred at rt for 15 h. Satd aq $NaHCO_3$ (8 mL) was added, the aqueous layer was extracted with CH_2Cl_2 (2×6 mL) and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1) gave (4*S*,5*R*)-**44** (531 mg, 77%, >99:1 dr); mp 109–116 °C; $[\alpha]_D^{25}$ +39.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3279 (N–H), 3067, 3036, 2980, 2934 (C–H), 1764 (2× C=O); δ_H (400 MHz, $CDCl_3$) 1.52 (9H, s, CMe_3), 4.18 (1H, d, *J* 5.3, C(4)*H*), 5.58 (1H, d, *J* 5.3, C(5)*H*), 6.89 (1H, br s, N*H*), 7.33–7.45 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.9 (CMe_3), 62.1 (*C*(4)), 79.6 (*C*(5)), 83.7 (CMe_3), 125.4, 128.9, 129.0 (*o*,*m*,*p*-*Ph*), 138.4 (*i*-*Ph*), 158.6 (*C*(2)), 168.7 (CO_2^tBu); *m*/*z* (ESI^+) 286 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{14}H_{17}NNaO_4^+$ ($[M+Na]^+$) requires 286.1050; found 286.1048.

4.28. (*R*,*R*)-2-Amino-3-hydroxy-3-phenylpropanoic acid 45

A stirred solution of **43** (50 mg, 0.190 mmol, >99:1 dr) in 6.0 M aq HCl (4 mL) was heated at 90 °C for 24 h. The reaction mixture was then allowed to cool to rt and concentrated in vacuo. Purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave **45** as a white solid (26 mg, 76%, 96:4 dr);[41] mp 189–192 °C (dec); {lit.[9a] mp 174 °C (dec)}; $[\alpha]_D^{20}$ −2.4 (*c* 1.0 in H_2O); {lit.[41] $[\alpha]_D^{20}$ −4.3 (*c* 1.1 in H_2O)}; δ_H (400 MHz, D_2O) 4.00 (1H, d, *J* 4.3, C(2)*H*), 5.28 (1H, d, *J* 4.3, C(3)*H*), 7.28–7.41 (5H, m, *Ph*); δ_C (100 MHz, D_2O) 60.4 (*C*(2)), 71.1 (*C*(3)), 126.3, 128.8, 128.8 (*o*,*m*,*p*-*Ph*), 136.8 (*i*-*Ph*), 171.1 (*C*(1)).

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4.29. (4*S*,5*R*)-5-Phenyl-4-(*tert*-butoxycarbonyl)-*N*(3)-(*tert*-butoxycarbonyl)oxazolidin-2-one 46

Et_3N (0.143 mL, 1.08 mmol), Boc_2O (542 mg, 2.49 mmol) and DMAP (20 mg, cat.) were added to a stirred solution of (4*S*,5*R*)-**44** (142 mg, 0.540 mmol, >99:1 dr) in THF (7 mL) and the resultant mixture was stirred at rt for 15 h, then concentrated in vacuo. The residue was partitioned between $CHCl_3$ (10 mL) and $NaHCO_3$ (10 mL) and the organic layer was washed with brine (10 mL), then dried over Na_2SO_4 and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 3:1) gave **46** as a white solid (180 mg, 92%, >99:1 dr); mp 102–104 °C; $[\alpha]_D^{25}$ +15.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2981, 2935 (C–H), 1827, 1747, 1730 (3× C=O); δ_H (400 MHz, $CDCl_3$) 1.43 (9H, s, C*Me*$_3$), 1.47 (9H, s, C*Me*$_3$), 4.42 (1H, d, *J* 4.1, C(5)*H*), 5.26 (1H, d, *J* 4.1, C(4)*H*), 7.28–7.40 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.8, 27.9 (C*Me*$_3$), 64.3 (*C*(4)), 76.1 (*C*(5)), 83.8, 84.5 (*C*Me$_3$), 124.9, 129.2, 129.3 (*o*,*m*,*p*-*Ph*), 137.5 (*i*-*Ph*), 148.5, 151.0 (*C*(2), NCO), 167.5 ($CO_2{}^tBu$); *m*/*z* (ESI^+) 386 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{19}H_{25}NNaO_6^+$ ($[M+Na]^+$) requires 386.1574; found 386.1578.

4.30. *tert*-Butyl (2*S*,3*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-hydroxy-3-phenylpropanoate 47

2.0 M aq LiOH (1.4 mL) was added to a stirred solution of **46** (100 mg, 0.275 mmol, >99:1 dr) in 1,4-dioxane (7 mL) and the resultant mixture was stirred at rt for 45 min, then concentrated in vacuo. The residue was dissolved in $CHCl_3$ (15 mL) and the resultant solution was filtered and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 2:1) gave **47** as a white solid (55 mg, 59%, 98:2 dr); mp 120–125 °C; $[\alpha]_D^{25}$ −8.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3457 (O–H), 2979 (N–H), 1721, 1695 (2× C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (9H, s, C*Me*$_3$), 1.34 (9H, s, C*Me*$_3$), 3.00–3.18 (1H, m, O*H*), 4.28–4.39 (1H, m, C(2)*H*), 4.99-5.04 (1H, m, C(3)*H*), 5.19-5.30 (1H, m, N*H*), 7.16-7.32 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 27.9, 28.2 (2× C*Me*$_3$), 59.9 (*C*(2)), 74.6 (*C*(3)), 79.9, 82.5 (2× *C*Me$_3$), 126.3, 127.9, 128.3 (*o*,*m*,*p*-*Ph*), 140.1 (*i*-*Ph*), 155.8 (NCO), 169.9 (*C*(1)); *m*/*z* (ESI^+) 360 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{18}H_{27}NNaO_5^+$ ($[M+Na]^+$) requires 360.1781; found 360.1785.

4.31. (2*S*,3*R*)-2-Amino-3-hydroxy-3-phenylpropanoic acid 48

A solution of **47** (51 mg, 0.151 mmol, 98:2 dr) in CH_2Cl_2/TFA (4:1, 4 mL) was stirred at rt for 2 h, then concentrated in vacuo. 6.0 M aq HCl (2 mL) was then added and the resultant solution was concentrated in vacuo. Purification via ion exchange chromatography on Dowex-50WX8 resin (hydrogen form, 100–200 mesh, eluent 1.0 M aq NH_4OH) gave **48** as a white solid (20 mg, quant, 98:2 dr);[9c,40] mp 201–202 °C; {lit.[40] mp 192–195 °C}; $[\alpha]_D^{20}$ −28.9 (*c* 1.0 in H_2O); {lit.[9c] $[\alpha]_D^{20}$ −30.0 (*c* 1.0 in H_2O)}; δ_H (500 MHz, D_2O) 3.83 (1H, d, *J* 4.1, C(2)*H*), 5.22 (1H, d, *J* 4.1, C(3)*H*), 7.28–7.45 (5H, m, *Ph*); δ_C (125 MHz, D_2O) 60.9 (*C*(2)), 71.3 (*C*(3)), 125.8, 128.5, 128.9 (*o*,*m*,*p*-*Ph*), 139.1 (*i*-*Ph*), 172.0 (*C*(1)).

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.08.007.

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