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Doubly diastereoselective conjugate addition of enantiopure lithium amides to enantiopure *N*-enoyl oxazolidin-2-ones: a mechanistic probe

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Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

ABSTRACT

The doubly diastereoselective conjugate addition of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to a range of enantiopure *N*-enoyl oxazolidin-2-ones has been used as a mechanistic probe to determine that the reactive conformation is the *anti-s-cis* form. The β-amino carbonyl products resulting from these conjugate addition reactions are useful templates for further elaboration into an α,β,α-pseudotripeptide.

1. Introduction

The conjugate addition of nucleophiles to α,β-unsaturated carbonyl compounds plays a fundamental role in the stereoselective formation of β-functionalised carbonyl compounds. Stereocontrol in these reactions has been achieved by the use of chiral nucleophiles ('donors'), chiral α,β-unsaturated carbonyl compounds ('acceptors') and chiral catalysts.[1,2] Within this arena, the diastereoselective conjugate addition of organocuprates to *N*-enoyl derivatives of oxazolidin-2-one chiral auxiliaries (e.g., **1**) has been used extensively, with Lewis acids traditionally employed to facilitate reactivity.[3] It is possible for an *N*-enoyl oxazolidine-2-one derivative to undergo diastereoselective 1,4-addition via any of the four possible *syn*- or *anti*- and *s-cis* or *s-trans* conformations **3A**–**3D**. An intriguing mechanistic dichotomy exists in this system, since the expected favoured nucleophilic attack on the face of the double bond opposite to the C(4)-stereodirecting group of the oxazolidin-2-one scaffold in either the *syn-s-cis* **3A** or the *anti-s-trans* **3C** conformation leads to the same stereochemical result; the same argument may be applied to the *anti-s-cis* **3B** or the *syn-s-trans* **3D** pair of conformers. In single asymmetric transformations an assessment of the product distribution does not therefore allow conclusive determination of the reactive conformation of these systems. It has been proposed however that the diastereoselective conjugate addition of organocuprates occurs preferentially via the (Lewis acid chelated) *syn-s-cis* conformation **3A**,[4] with the reaction diastereoselectivity postulated to reflect the populations of the reactive conformers of these substrates;[5] however, the *anti-s-cis* conformation **3B** has been proposed to account for the reversal of selectivity noted in TMSI-promoted additions of monoorganocuprates,[6] and a similar reversal of selectivity has been reported in conjugate addition reactions promoted by Et_2AlCl and $TiCl_4$.[7] The conjugate addition of nucleophiles other than copper-based species to *N*-enoyl oxazolidin-2-ones **3** has been less widely explored[8,9] (Scheme 1).

We have demonstrated extensively that the conjugate addition of secondary lithium amides such as lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **4** to α,β-unsaturated esters and amides represents a versatile and efficient method for the preparation of β-amino esters and β-amino amides and their derivatives.[10] This methodology has found numerous synthetic applications, including the total synthesis of natural products,[11] molecular recognition phenomena[12] and resolution protocols.[13] We envisaged that this reaction protocol could be extended to encompass *N*-enoyl oxazolidin-2-ones **3** as chiral α,β-unsaturated carbonyl components. In addition to these synthetic studies, it was anticipated that an evaluation of the levels of double asymmetric induction[14] displayed upon conjugate addition of enantiopure lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **4** to a chiral *N*-enoyl oxazolidin-2-one **3** might serve as a tool with which to examine the reactive conformation of the oxazolidinone systems, given the established requirement for lithium amides to add to (*E*)-α,β-unsaturated esters and amides exclusively in the *s-cis* conformation,[15] conjugate addition to an *N*-enoyl oxazolidin-2-one **3** may be expected to occur only via either the *syn*- or *anti-s-cis* conformation **3A** or **3B**, respectively. Furthermore, elaboration of the conjugate addition products **5** would facilitate the preparation of a series of α,β-pseudopeptides **6** by unmasking the oxazolidin-2-one auxiliary as a latent α-amino acid. The results of these studies are delineated herein; part of this work has been communicated previously[16] (Fig. 1).

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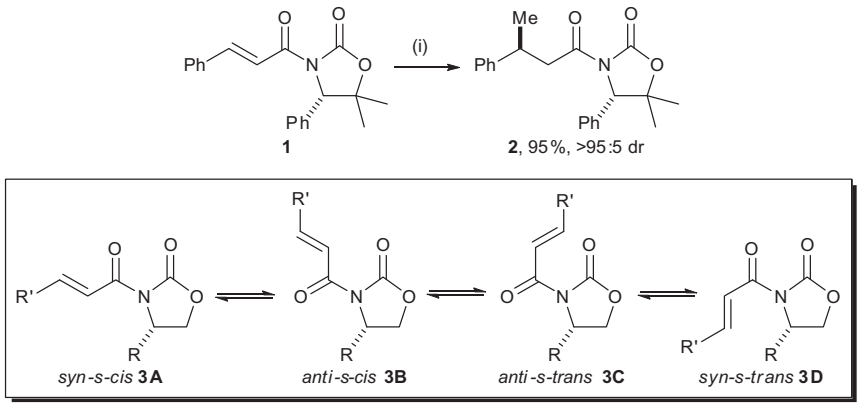


Scheme 1. Reagents and conditions: (i) CuBr·DMS, MeMgBr, $BF_3{\cdot}Et_2O$, DMS, THF, −40 °C to rt.

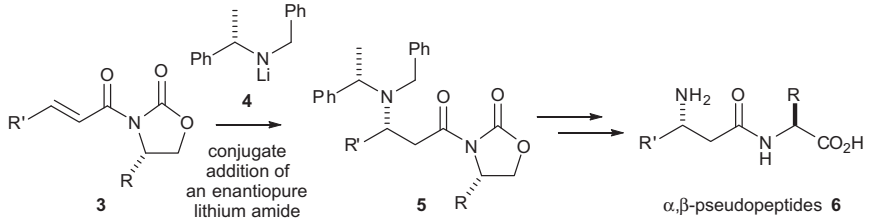


Figure 1. Conjugate addition of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **4** to enantiopure *N*-enoyl oxazolidin-2-ones **3** as a mechanistic probe, and elaboration of the 1,4-addition products **5** to α,β-pseudopeptides **6**.

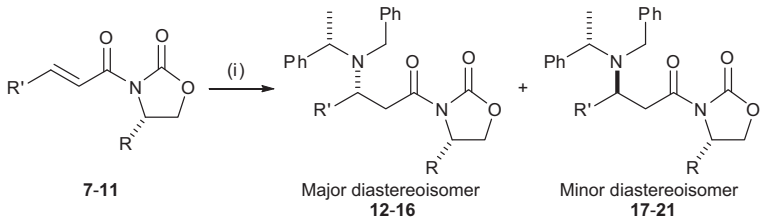
2. Results and discussion

2.1. Conjugate addition of lithium amides to *N*-enoyl oxazolidin-2-ones

The conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**4** to a range of *N*-enoyl (*S*)-4-benzyl- and (*S*)-4-phenyl-oxazolidin-2-ones **7**–**11** proceeded with excellent levels of diastereoselectivity (⩾94:6 dr) to furnish **12**–**16** as the major products. Initial attempts to purify **12**–**16** proved difficult, as it was found that a retro conjugate addition reaction to return the corresponding starting materials occurred readily on extended exposure to silica gel. Nevertheless, filtration through a pad of silica gave mixtures of diastereoisomers **12**–**21** in ⩾72% yield, with further purification by crystallisation or chromatography giving access to the major diastereoisomers **12**–**16** in >99:1 dr and in moderate to good isolated yields (Scheme 2).

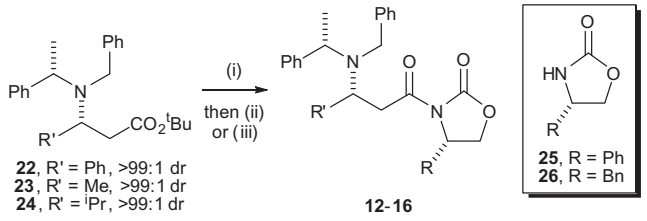
The configurations at C(3′) within *N*-3′-aminoacyl oxazolidin-2-ones **12**–**16** were established unambiguously by a separate chemical synthesis in each case. The β-amino esters **22**–**24** obtained from the conjugate addition of lithium amide (*S*)-**4** to the corresponding α,β-unsaturated *tert*-butyl esters were treated with TFA to give the corresponding carboxylic acids which were coupled with (*S*)-4-benzyl- and (*S*)-4-phenyl-oxazolidin-2-ones **25** and **26** to give **12**–**16**. The spectroscopic properties, including specific rotation values, of the samples of **12**–**16** prepared in this manner were identical to the major diastereoisomers arising from the conjugate addition of lithium amide (*S*)-**4** to the *N*-enoyl oxazolidin-2-ones **7**–**11**, providing unequivocal evidence of the sense of stereoinduction observed in these reaction pairings (Scheme 3).

The conjugate addition reaction of the enantiomeric lithium amide (*R*)-**4** to *N*-enoyl oxazolidin-2-ones **7**–**11** under identical reaction conditions furnished 1,4-addition products **27**–**36** exclusively although with only modest levels of diastereoselectivity



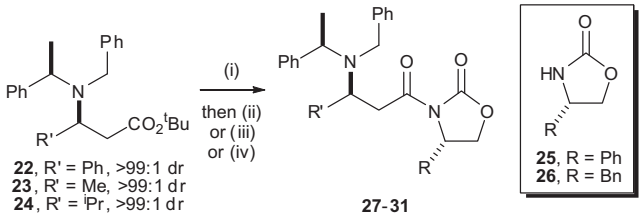
	R	R′	dr[a]	yield %[b]
7	Ph	Ph	**12**:**17**, 96:4	79 (64)
8	Ph	Me	**13**:**18**, 95:5	75 (53)
9	Bn	Ph	**14**:**19**, >99:1	(84)
10	Bn	Me	**15**:**20**, 96:4	73 (51)
11	Bn	^{i}Pr	**16**:**21**, 94:6	72 (51)

Scheme 2. Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**4**, THF, −78 °C, 2 h [[a] Diastereoisomeric ratios determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield of purified mixture of diastereoisomers after chromatography (isolated yield of major diastereoisomer, in >99:1 dr, after further purification)].



	R	R'	method	product	yield %
22	Ph	Ph	(i), (ii)	12	48
23	Me	Ph	(i), (ii)	13	26
22	Ph	Bn	(i), (iii)	14	90
23	Me	Bn	(i), (iii)	15	56
24	iPr	Bn	(i), (iii)	16	59

Scheme 3. Reagents and conditions: (i) TFA, CH_2Cl_2, rt, 2 h; (ii) $(COCl)_2$, DMF, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h, then **25**, BuLi, THF, −78 °C to rt, 3 h; (iii) pivaloyl chloride, Et_3N, −30 °C, 2 h, then **26**, LiCl, THF, −30 °C to rt, 12 h.



	R	R'	method	product	yield %
22	Ph	Ph	(i), (ii)	27	25
23	Me	Ph	(i), (ii)	28	31
22	Ph	Bn	(i), (iii)	29	34
23	Me	Bn	(i), (iii)	30	22
24	iPr	Bn	(i), (iv)	31	43

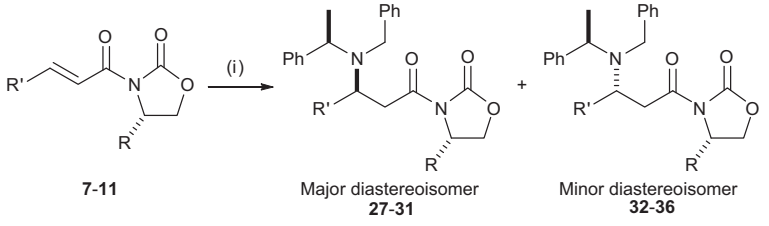
Scheme 5. Reagents and conditions: (i) TFA, CH_2Cl_2, rt, 2 h; (ii) $(COCl)_2$, DMF, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h, then **25**, BuLi, THF, −78 °C to rt, 3 h; (iii) $(COCl)_2$, DMF, Et_3N, CH_2Cl_2, 0 °C to rt, 1 h, then **26**, BuLi, THF, −78 °C to rt, 3 h; (iv) pivaloyl chloride, Et_3N, −30 °C, 2 h, then **26**, LiCl, THF, −30 °C to rt, 12 h.

(~85:15 dr in each case), as determined by ^{1}H NMR analysis of the crude reaction mixtures. The adducts **27**–**36** were similarly difficult to purify due to their instability with respect to retro conjugate addition upon prolonged exposure to silica, and mixtures of diastereoisomers were obtained in 52–74% yield after chromatography (Scheme 4).

The C(3′)-configurations within the major diastereoisomers **27**–**31** arising from the addition of lithium amide (*R*)-**4** to the *N*-enoyl oxazolidin-2-ones **7**–**11** were also confirmed by a separate chemical synthesis in each case. β-Amino esters **22**–**24** obtained from the conjugate addition of (*R*)-**4** to the requisite α,β-unsaturated *tert*-butyl esters were transformed into the corresponding carboxylic acids followed by coupling with either (*S*)-4-benzyl- or (*S*)-4-phenyl-oxazolidin-2-one **25** or **26** to give authentic samples of **27**–**31** (Scheme 5).

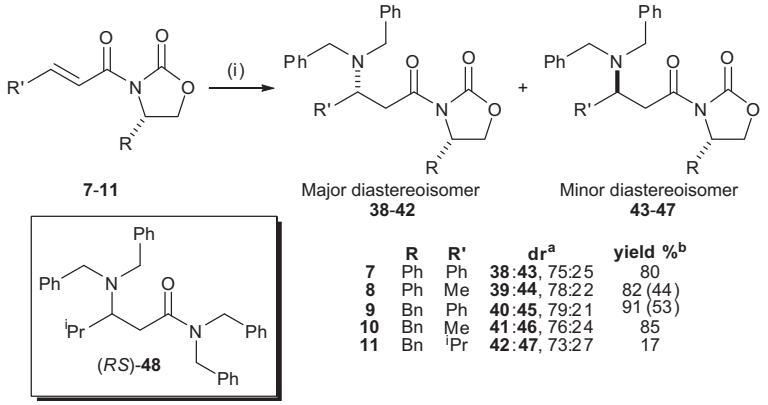
Comparison of the diastereoselectivities observed for conjugate addition of the enantiomeric lithium amides (*S*)-**4** and (*R*)-**4** to *N*-enoyl oxazolidin-2-ones (*S*)-**7**–**11** revealed that the additions of lithium amide (*S*)-**4** represent the 'matched' reaction pairings, and the additions of lithium amide (*R*)-**4** are the 'mismatched' pairings. Furthermore, the sense of asymmetric induction observed for the additions of both (*S*)-**4** and (*R*)-**4** to the *N*-enoyl oxazolidin-2-ones (*S*)-**7**–**11** is consistent with the stereocontrol of the lithium amides, not the oxazolidin-2-one chiral auxiliary, dominating the reaction selectivity. In order to enable a more complete understanding of the levels of selectivity displayed in this system, the conjugate addition of an achiral lithium amide to the range of *N*-enoyl (*S*)-4-benzyl- and (*S*)-4-phenyl-oxazolidin-2-ones (*S*)-**7**–**11** was next investigated to determine the sense and magnitude of stereoinduction by the C(4)-substituent of the oxazolidin-2-one framework. Addition of lithium dibenzylamide **37** to the range of *N*-enoyl oxazolidin-2-ones **7**–**11** proceeded, in each case, with modest levels of diastereoselectivity (~75:25 dr) to furnish a diastereoisomeric mixture of the corresponding 1,4-addition products **38**–**47**. In the case of addition to C(3′)-isopropyl substituted **11**, the conjugate addition reaction was accompanied by the formation of racemic **48**,[17] which is presumably a result of the steric bulk of the C(3′)-substituent retarding the conjugate addition reaction and promoting a competitive 1,2-addition pathway with subsequent cleavage of the *N*-enoyl fragment from the chiral auxiliary followed by 1,4-addition to the resultant achiral α,β-unsaturated amide. The 1,4-addition products **38**–**47** exhibited some instability upon prolonged exposure to silica gel chromatography, but good yields (80–91%) of purified mixtures of diastereoisomers were obtained. Subsequent recrystallisation facilitated the isolation of major diastereoisomers **39** and **40** in 44% and 53% yield, respectively, and >99:1 dr in each case. The similarity in the observed reaction diastereoselectivities indicated that there is no significant difference in terms of selectivity for the conjugate addition to chiral *N*-enoyl oxazolidin-2-ones with different substitution patterns (Scheme 6).

The configuration at C(3′) within **40** (>99:1 dr) was determined by deprotection via sequential hydrolysis and hydrogenolysis, giving the β-amino acid (*R*)-β-phenylalanine **50** {$[\alpha]_D^{22} = +6.2$ (*c* 0.6, H_2O); lit.[18] $[\alpha]_D^{19} = +6.5$ (*c* 1.0, H_2O)} in 86% yield after purification by ion exchange chromatography (Scheme 7). The configurations within the major 1,4-addition products **38**, **39**, **41** and **42** were assigned by analogy. The substrate directed addition of the lithium amide nucleophile to the *Re* face of the α,β-unsaturated system is therefore consistent with the facial selectivity displayed by the



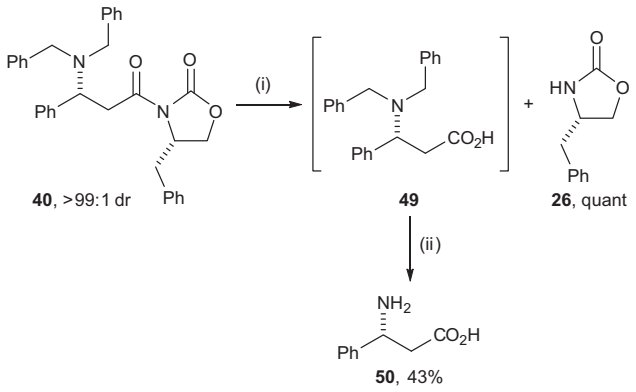
	R	R'	dr[a]	yield %[b]
7	Ph	Ph	**27**:**32**, 80:20	52
8	Ph	Me	**28**:**33**, 89:11	74
9	Bn	Ph	**29**:**34**, 83:17	64
10	Bn	Me	**30**:**35**, 80:20	64
11	Bn	iPr	**31**:**36**, 85:15	64

Scheme 4. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*R*)-**4**, THF, −78 °C, 2 h [[a] Diastereoisomeric ratios determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield of purified mixture of diastereoisomers after chromatography].

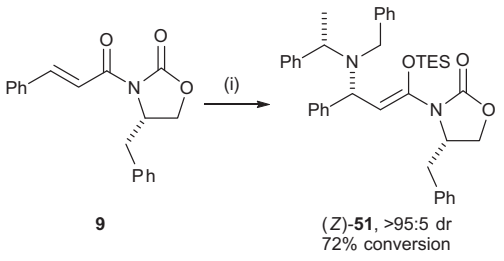


	R	R'	dr[a]	yield %[b]
7	Ph	Ph	**38**:**43**, 75:25	80
8	Ph	Me	**39**:**44**, 78:22	82 (44)
9	Bn	Ph	**40**:**45**, 79:21	91 (53)
10	Bn	Me	**41**:**46**, 76:24	85
11	Bn	^{i}Pr	**42**:**47**, 73:27	17

Scheme 6. Reagents and Conditions: (i) lithium dibenzylamide **37**, THF, −78 °C, 2 h [[a] Diastereoisomeric ratios determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield of purified mixture of diastereoisomers after chromatography (isolated yield of major diastereoisomer, in >99:1 dr, after further purification)].



Scheme 7. Reagents and Conditions: (i) LiOH, H_2O_2, THF/H_2O (v:v, 3:1), 0 °C to rt, 16 h; (ii) H_2, Pd(OH)$_2$/C, MeOH/H_2O/AcOH (v:v:v, 40:4:1), rt, 12 h, then HCl (1 M, aq), then Dowex 50WX8-200 ion exchange chromatography.



Scheme 8. Reagents and conditions: (i) lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **4** (1.6 equiv), THF, −78 °C, 3 h, then TESCl, −78 °C to rt, 5 h.

substrate and reagent in the doubly diastereoselectively 'matched' conjugate addition of lithium amide (*S*)-**4** to the range of *N*-enoyl oxazolidin-2-ones (*S*)-**7**–**11**.

It was envisaged that the reactive conformation of these systems could be further investigated by examining the geometry of the lithium enolate arising from the conjugate addition procedure, as such an analysis would differentiate between the possible *s-cis* and *s-trans* conformations, as a (*Z*)-enolate would arise from addition to an *s-cis* conformer and an (*E*)-enolate via addition to an *s-trans* conformer. The doubly diastereoselective 'matched' conjugate addition of lithium amide (*S*)-**4** to *N*-cinnamoyl-4-benzyl-oxazolidin-2-one (*S*)-**9** followed by treatment of the resultant enolate with triethylsilylchloride gave 72% conversion to the silyl enol ether (*Z*)-**51** exclusively, the geometry of which was established by ^{1}H NMR NOE experiments, and which is consistent with other enolate trapping studies of this class of conjugate addition reactions[15,19] (Scheme 8).

These data from the enolate trapping study determine conclusively that the addition of homochiral lithium amide (*S*)-**4** to *N*-enoyl oxazolidin-2-one (*S*)-**9** proceeds via an *s-cis* conformation. Considering the double asymmetric induction observed upon addition to *N*-cinnamoyl (*S*)-4-benzyl-oxazolidin-2-one (*S*)-**9**, in the 'matched' case the addition of lithium amide (*S*)-**4** to (*S*)-**9** results in the preferential formation of **14** in >99:1 dr. In the 'mismatched' case, conjugate addition of lithium amide (*R*)-**4** to (*S*)-**9** results in the formation of **29**:**34** in 83:17 dr. This empirical 'matched' and 'mismatched' product distribution cannot be achieved if the reaction were to proceed through the *syn-s-cis* conformation **9A**, but is consistent with addition of lithium amides (*S*)-**4** and (*R*)-**4** to (*S*)-**9** in the *anti-s-cis* conformation **9B**. In this model, the preferential addition of lithium amide (*S*)-**4** to the *Re* face of the double bond (reagent control) coincides with addition opposite to the stereodirecting C(4)-benzyl group of the oxazolidin-2-one auxiliary (substrate control), and is consistent with the formation of **14** in the 'matched' case. The formation of **29** as the major diastereoisomer in the 'mismatched' case most likely occurs via approach of the lithium amide (*R*)-**4** on the same face as the stereodirecting C(4)-benzyl group in the *anti-s-cis* conformation **9B**, although these data do not discount the possibility that the formation of **29** may occur via preferential addition of lithium amide (*R*)-**4** to (*S*)-**9** in the *syn-s-cis* conformation **9A**. In order to investigate this possibility, the conjugate addition reactions of lithium amides (*S*)-**4** and (*R*)-**4** to **9** were repeated in the presence of the Lewis acids LiBr, MeMgBr, Ti(O^{i}Pr)$_3$Cl and Zn(OTf)$_2$: under these conditions, the carbonyl groups of the *N*-enoyl oxazolidinone **9** may be expected to be held in the *syn* conformation. However, although 70–90% of the starting material was recovered even upon extended reaction times (up to 48 h), the observed levels of diastereoselectivity remained unchanged in both cases [>99:1 dr for 'matched' addition of (*S*)-**4**; 83:17 dr for 'mismatched' addition of (*R*)-**4**]. Thus, assuming that addition of a Lewis acid increases the ratio of *syn*:*anti* conformers, a change in the level of diastereoselectivity upon addition of both lithium amides (*S*)-**4** and (*R*)-**4** would have been expected, which was not observed, suggesting that the *syn-s-cis* conformation **9A** is less reactive towards conjugate addition of the lithium amides, and providing further evidence that the formation of **29** as the major diastereoisomer from the 'mismatched' addition of lithium amide (*R*)-**4** to (*S*)-**9** more than likely derives from reaction through the *anti-s-cis* conformation **9B** (Fig. 2).

These results were then considered in the context of the low diastereoselectivities observed for the 1,4-conjugate addition of

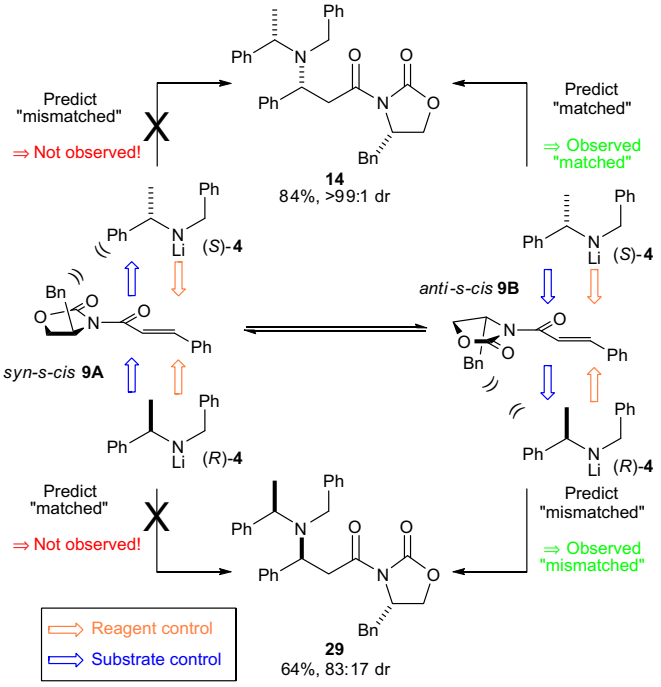


Figure 2. Model to rationalise the observed 'matched' and 'mismatched' double asymmetric induction; given the observed 'matched' and 'mismatched' reaction pairing from the double asymmetric induction, the reactive conformation cannot be *syn-s-cis* **9A**.

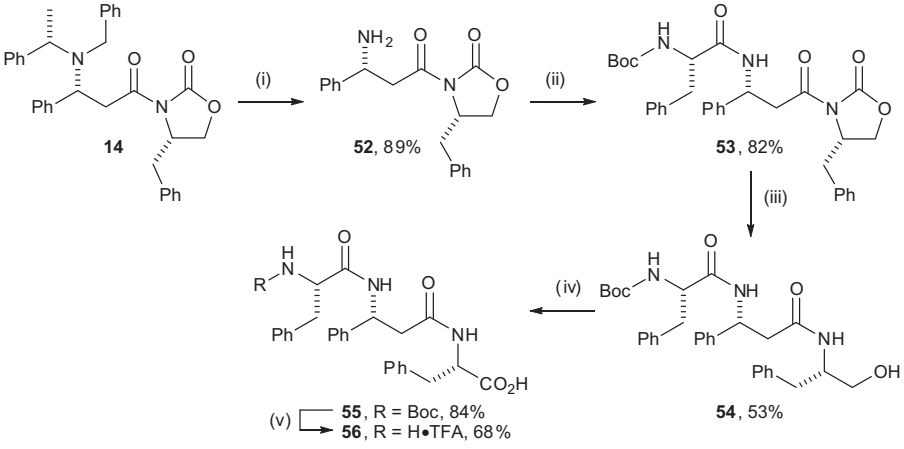
the achiral lithium amide **37** to the range of chiral *N*-enoyl oxazolidin-2-one systems. As an example, the observed product distribution upon addition of lithium dibenzylamide **37** to (*S*,*E*)-*N*-cinnamoyl-4-benzyl-oxazolidin-2-one **9** may arise from a number of mechanistic scenarios: (1) addition of lithium dibenzylamide **37** occurs with exclusive facial selectivity (opposite to the C(4)-stereodirecting benzyl group) to an unequilibrating 79:21 mixture of *anti-s-cis* to *syn-s-cis* conformers of (*S*)-**9**; (2) addition of lithium dibenzylamide **37** occurs with unknown facial selectivity to both *anti-s-cis* and *syn-s-cis* conformers of (*S*)-**9** which are rapidly equilibrating; (3) addition of lithium dibenzylamide **37** occurs with moderate (79:21) facial selectivity via exclusive addition to the *anti-s-cis* conformation of (*S*)-**9**; or (4) a combination of any of these scenarios. If the reaction proceeded under scenario (1), addition of neither lithium amide (*S*)-**4** nor (*R*)-**4** would result in high levels of diastereoselectivity; the product distributions arising from double asymmetric induction clearly demonstrate that this is not the case. The observation of 'matched' and 'mismatched' reaction pairings in these reactions also eliminates the possibility that the reaction proceeds under Curtin-Hammett control [scenario (2)]. In this mechanistic scheme, reaction with both lithium amides (*S*)-**4** and (*R*)-**4** would have been 'matched' and would have progressed with equal and high levels of diastereocontrol. Therefore, by process of elimination, it is determined that the reaction must proceed with moderate facial selectivity via exclusive addition of lithium dibenzylamide **37** to the *anti-s-cis* conformation of *N*-enoyl oxazolidine-2-one **9** [scenario (3)].

2.2. Synthetic application: preparation of pseudopeptides

Elaboration of the β-amino acid moieties resulting from these conjugate addition reactions was envisaged as part of a novel asymmetric approach towards the preparation of pseudopeptides. In this strategy, the protected functionality within the oxazolidine-2-one chiral auxiliary would be unmasked as a latent α-amino acid equivalent via endocyclic cleavage of the auxiliary, a process that typically predominates under standard hydrolysis conditions of either bulky α-substituted or β-heteroatom derivatives of oxazolidin-2-ones.[20] Following this plan, treatment of **14** with Pearlman's catalyst in glacial acetic acid under hydrogen gave primary amine **52** in 89% yield. Amine **52** was coupled with *N*-Boc phenylalanine to give **53** in 82% yield. Endocyclic cleavage of the oxazolidin-2-one auxiliary upon treatment with LiOH gave alcohol **54** in 53% yield. Oxidation of **54** to the corresponding acid with the Jones reagent followed by *N*-Boc deprotection of **55** furnished α,β,α-tri(phenylalanine) **56** in 68% yield, isolated as its TFA salt, after purification (Scheme 9).

3. Conclusion

The doubly diastereoselective conjugate additions of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to a range of enantiopure *N*-enoyl oxazolidin-2-ones has been used as a mechanistic probe to determine that the reactive conformation is the *anti-s-cis* form. The synthetic utility of these β-amino carbonyl products resulting from conjugate has been demonstrated by the elaboration to the α,β,α-pseudotripeptide α,β,α-triphenylalanine.



Scheme 9. Reagents and conditions: (i) H_2 (5 atm), $Pd(OH)_2/C$, AcOH, rt, 24 h; (ii) Boc-Phe, DCC, THF, 0 °C, 3 h; (iii) LiOH (4.8 equiv), THF/H_2O (2:1), 60 °C, 5 h; (iv) CrO_3, H_2SO_4, acetone, 0 °C, 3 h; (v) TFA/CH_2Cl_2 (1/1), rt, 2 h, then purification on RP-18 gel.

4. Experimental

4.1. General experimental

All 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. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[21] Water was purified by an Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$ or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica or neutral alumina.

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

4.2. General experimental procedures

4.2.1. General procedure 1: N-acylation of oxazolidin-2-ones

Method A: BuLi (1.1 equiv) was added to a solution of either **25** or **26** (1 equiv) in THF at −78 °C. After 20 min, the requisite acid chloride (1.3 equiv) was added. The reaction mixture was allowed to warm to rt over 12 h, followed by addition of satd aq NH_4Cl. The resultant mixture was extracted three times with EtOAc and the combined organic extracts were washed with satd aq $NaHCO_3$, then dried and concentrated in vacuo.

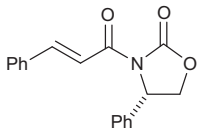
Method B:[22] A solution of the requisite carboxylic acid derivative (1 equiv) in THF at −30 °C was treated with Et_3N (3 equiv) and pivaloyl chloride (1.1 equiv). The resultant suspension of mixed anhydride was stirred for 2 h, followed by the addition of LiCl (1.2 equiv) and either **25** or **26** (1.1 equiv). The reaction mixture was allowed to warm to rt over 12 h, followed by addition of satd aq NH_4Cl. The resultant mixture was extracted three times with EtOAc and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ and brine, then dried and concentrated in vacuo.

Method C: A solution of the requisite carboxylic acid derivative (1 equiv) in CH_2Cl_2 at 0 °C was treated with $(ClCO)_2$ (1.5 equiv) and one drop of DMF. The reaction mixture was allowed to warm to rt over 1 h, then one drop of Et_3N was added, which gave a white suspension. The suspension was concentrated in vacuo and the residue was suspended in THF. In a separate vessel, BuLi (3 equiv) was added to a solution of either **25** or **26** (3 equiv) in THF at −78 °C. After 20 min, the acid chloride suspension was added via cannula, and the reaction mixture was allowed to warm to rt over a further 3 h, followed by addition of satd aq NH_4Cl. The resultant mixture was extracted three times with EtOAc and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ and brine, then dried and concentrated in vacuo.

4.2.2. General procedure 2: lithium amide conjugate addition

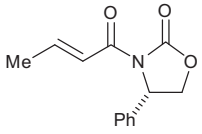
BuLi (1.55 equiv) was added to a solution of the requisite amine (1.6 equiv) in THF at −78 °C. After 30 min, a solution of the requisite *N*-enoyl oxazolidin-2-one (1 equiv) in THF at −78 °C was added via cannula and the reaction mixture was stirred for a further 2 h, followed by the addition of satd aq NH_4Cl and warming to rt. The resultant mixture was extracted three times with EtOAc and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and washed sequentially with 10% aq citric acid, satd aq $NaHCO_3$, and brine, then dried and concentrated in vacuo.

4.3. (*S*,*E*)-*N*(3)-(3′-Phenylpropenoyl)-4-phenyloxazolidin-2-one 7



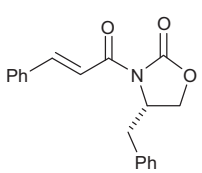
Following *general procedure 1A*, a solution of **25** (132 mg, 0.81 mmol) in THF (5 mL) at −78 °C was treated with BuLi (1.38 M, 0.64 mL, 0.89 mmol) and *trans*-cinnamoyl chloride (175 mg, 1.00 mmol). Purification via flash column chromatography (silica, eluent 30–40 °C petrol/EtOAc, 4:1) gave **7** as a white solid (185 mg, 78%);[23] mp 167–168 °C; {lit.[23] mp 169–171 °C}; $[\alpha]_D^{22} = +3.5$ (*c* 0.75, $CHCl_3$); {lit.[23] $[\alpha]_D^{22} = +3.4$ (*c* 0.7, $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 4.34 (1H, dd, *J* 8.8, 3.9, C(5)H_A), 4.76 (1H, app t, *J* 8.8, C(5)H_B), 5.57 (1H, dd, *J* 8.8, 3.9, C(4)*H*), 7.33–7.43 (8H, m, *Ph*), 7.59–7.62 (2H, m, *Ph*), 7.80 (1H, d, *J* 15.7, C(2′)*H*), 7.95 (1H, d, *J* 15.7, C(3′)*H*).

4.4. (*S*,*E*)-*N*(3)-But-2′-enoyl-4-phenyloxazolidin-2-one 8



Following *general procedure 1A*, a solution of **25** (1.00 g, 6.13 mmol) in THF (20 mL) at −78 °C was treated with BuLi (1.51 M, 4.06 mL, 6.13 mmol) and *trans*-crotonoyl chloride (705 mg, 6.74 mmol). Purification via flash column chromatography (silica, eluent 30–40 °C petrol/EtOAc, 7:3) gave **8** as a white solid (731 mg, 53%);[23] mp 76–78 °C; {lit.[23] mp 77–79 °C}; $[\alpha]_D^{23} = +121.4$ (*c* 1.1, $CHCl_3$); {lit.[23] $[\alpha]_D^{22} = +111.8$ (*c* 1.1, $CHCl_3$)}; δ_H (200 MHz, $CDCl_3$) 1.95 (3H, d, *J* 6.6, C(4′)H_3), 4.28 (1H, dd, *J* 8.8, 3.9, C(5)H_A), 4.71 (1H, dd, *J* 8.8, 8.7, C(5)H_B), 5.50 (1H, dd, *J* 8.7, 3.9, C(4)*H*), 7.05–7.20 (2H, m, C(2′)*H*, C(3′)*H*), 7.26–7.45 (5H, m, *Ph*).

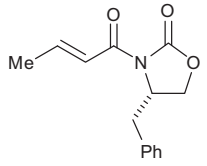
4.5. (*S*,*E*)-*N*(3)-(3′-Phenylpropenoyl)-4-benzyloxazolidin-2-one 9



Following *general procedure 1A*, a solution of **26** (4.95 g, 28.0 mmol) in THF (60 mL) at −78 °C was treated with BuLi (1.54 M, 22.4 mL, 33.6 mmol) and *trans*-cinnamoyl chloride (5.13 g, 30.8 mmol). Purification via recrystallisation (EtOAc/

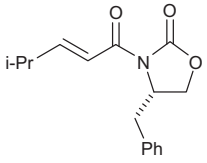
hexane) gave **9** as white needles (6.54 g, 76%);[24] mp 117–118 °C; {lit.[24] mp 122–123 °C}; $[\alpha]_D^{25} = +51.3$ (*c* 1.0, $CHCl_3$); {lit.[24] $[\alpha]_D^{20} = +56.3$ (*c* 1.8, $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 2.83–2.91 (1H, m, CH_AH$_B$Ph), 3.37–3.42 (1H, m, CH$_A$H$_B$Ph), 4.20–4.30 (2H, m, C(5)H_2), 4.79–4.84 (1H, m, C(4)*H*), 7.25–7.43 (8H, m, *Ph*), 7.65–7.66 (2H, m, *Ph*), 7.93–7.95 (2H, m, C(2′)*H*, C(3′)*H*).

4.6. (*S*,*E*)-*N*(3)-But-2′-enoyl-4-benzyloxazolidin-2-one 10



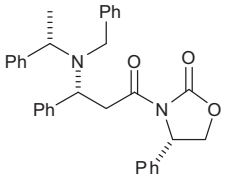
Following *general procedure 1A*, a solution of **26** (1.00 g, 5.64 mmol) in THF (25 mL) at −78 °C was treated with BuLi (1.50 M, 4.51 mL, 6.77 mmol) and *trans*-crotonoyl chloride (649 mg, 6.21 mmol). Purification via recrystallisation (Et_2O) gave **10** as a white solid (910 mg, 66%);[25] mp 86–87 °C; {lit.[25] mp 85–86 °C}; $[\alpha]_D^{23} = +77.1$ (*c* 1.0, $CHCl_3$); {lit.[25] $[\alpha]_D^{25} = +77.9$ (*c* 2.0, $CHCl_3$)}; δ_H (200 MHz, $CDCl_3$) 2.00 (3H, d, *J* 5.1, C(4′)H_3), 2.80 (1H, dd, *J* 13.3, 9.5, CH_AH$_B$Ph), 3.34 (1H, dd, *J* 13.3, 2.9, CH$_A$H$_B$Ph), 4.15–4.26 (2H, m, C(5)H_2), 4.68–4.79 (1H, m, C(4)*H*), 7.16–7.39 (7H, m, C(2′)*H*, C(3′)*H*, *Ph*).

4.7. (*S*,*E*)-*N*(3)-(4′-Methylpent-2-′enoyl)-4-benzyloxazolidin-2-one 11



Following *general procedure 1B*, a solution of (*E*)-4-methylpent-2-enoic acid (600 mg, 5.26 mmol) in THF (25 mL) at −30 °C was treated with Et_3N (2.20 mL, 15.8 mmol) and pivaloyl chloride (0.7 mL, 5.78 mmol), followed after 2 h by LiCl (270 mg, 6.31 mmol) and **26** (1.00 g, 5.78 mmol). Purification via flash column chromatography (silica, eluent 30–40 °C petrol/EtOAc, 10:1) gave **11** as a white solid (1.06 g, 76%); $C_{16}H_{19}NO_3$ requires C, 70.3; H, 7.0; N, 5.1; found C, 70.0; H, 7.5; N, 5.1; mp 59–60 °C; $[\alpha]_D^{25} = +59.0$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.11–1.13 (6H, m, C(4′)Me_2), 2.54–2.62 (1H, m, C(4′)*H*), 2.79 (1H, dd, *J* 13.4, 9.7, CH_AH$_B$Ph), 3.36 (1H, dd, *J* 13.4, 3.2, CH$_A$H$_B$Ph), 4.16–4.24 (2H, m, C(5)H_2), 4.74 (1H, app dq, *J* 13.1, 3.5, C(4)*H*), 7.15–7.37 (7H, m, C(2′)*H*, C(3′)*H*, *Ph*); δ_C (125 MHz, $CDCl_3$) 21.1, 21.2 (C(4′)Me_2), 31.4 (*C*(4′)), 37.8 (*C*H$_2$Ph), 55.2 (*C*(4)), 66.0 (*C*(5)), 117.7 (*C*(2′)), 127.2, 128.8, 129.3 (*Ph*$_{o,m,p}$), 135.3 (*Ph*$_i$), 153.3 (*C*(2)), 157.7 (*C*(3′)), 165.3 (*C*(1′)); ν_{max} (film) 1781 (C=O$_{endo}$), 1683 (C=O$_{exo}$), 1634 (C=C); *m*/*z* (ESI$^+$) 332 ([M+59]$^+$, 100%), 274 ([M+H]$^+$, 30%); HRMS (ESI$^+$) $C_{16}H_{20}NO_3^+$ ([M+H]$^+$) requires 274.1438; found 274.1454.

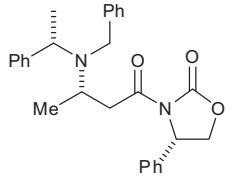
4.8. (4*S*,3′*R*,α*S*)-*N*(3)-{3′-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-3′-phenylpropanoyl}-4-phenyloxazolidin-2-one 12



From **7**: Following *general procedure 2*, a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (115 mg, 0.55 mmol) in THF (10 mL) at −78 °C was treated with BuLi (1.51 M, 0.36 mL, 0.54 mmol) and **7** (100 mg, 0.34 mmol) to give a 96:4 mixture of **12**:**17**. Purification via flash column chromatography (silica, gradient elution, 30–40 °C petrol/EtOAc, 9:1; increased to 30–40 °C petrol/EtOAc, 1:1) gave a 96:4 mixture of **12**:**17** as a colourless oil (135 mg, 79%). Crystallisation from CH_2Cl_2/Et_2O gave **12** as a white solid (102 mg, 64%, >99:1 dr); $C_{33}H_{32}N_2O_3$ requires C, 78.55; H, 6.4; N, 5.55; found C, 78.5; H, 6.4; N, 5.4; mp 73–76 °C; $[\alpha]_D^{21} = +42.7$ (*c* 1.0, $CHCl_3$); ν_{max} (KBr) 1779 (C=O$_{endo}$), 1702 (C=O$_{exo}$); δ_H (500 MHz, $CDCl_3$) 1.28 (3H, d, *J* 6.8, C(α)*Me*), 3.01 (1H, dd, *J* 16.6, 5.0, C(2′)H_A), 3.62 (1H, dd, *J* 16.6, 9.3, C(2′)H_B), 3.73 (1H, d, *J* 15.1, NCH_A), 3.77 (1H, d, *J* 15.1, NCH_B), 4.03 (1H, q, *J* 6.8, C(α)*H*), 4.11 (1H, dd, *J* 8.8, 3.9, C(5)H_A), 4.51 (1H, dd, *J* 8.8, 8.7, C(5)H_B), 4.58 (1H, dd, *J* 9.3, 5.0, C(3′)*H*), 5.24 (1H, dd, *J* 8.7, 3.9, C(4)*H*), 6.95–6.97 (2H, m, *Ph*), 7.18–7.43 (18H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 16.5 (C(α)*Me*), 36.8 (*C*(2′)), 50.8 (NCH_2), 57.0 (*C*(4)), 57.9 (*C*(3′)), 58.9 (*C*(α)), 69.6 (*C*(5)), 125.4, 126.5, 126.8, 127.1, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3, 129.0 (*Ph*$_{o,m,p}$), 138.6, 141.6, 141.6, 144.0 (*Ph*$_i$), 153.4 (*C*(2)), 170.8 (*C*(1′)); *m*/*z* (CI$^+$) 505 ([M+H]$^+$, 100%); HRMS (CI$^+$) $C_{33}H_{33}N_2O_3^+$ ([M+H]$^+$) requires 505.2486; found 505.2488.

From **22**: A solution of (3*R*,α*S*)-**22** (115 mg, 0.28 mmol) in CH_2Cl_2 (5 mL) was treated with TFA (5 mL). After 2 h the reaction mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL), washed with satd aq $NaHCO_3$ (5 mL), dried and concentrated in vacuo. The residue was again dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. Following *general procedure 1C*, the resultant solution was treated with $(ClCO)_2$ (67 mg, 0.53 mmol), one drop of DMF and one drop of Et_3N. A suspension of the resultant acid chloride in THF (5 mL) was added to a solution of **25** (137 mg, 0.84 mmol) and BuLi (1.58 M, 0.53 mL, 0.84 mmol) in THF (10 mL) at −78 °C. Purification via flash column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 1:1) gave **12** as a white solid (67 mg, 48%, >99:1 dr).

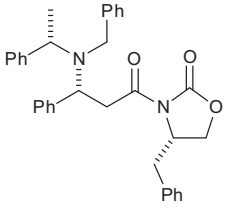
4.9. (*S*,*S*,*S*)-*N*(3)-{3′-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]butanoyl}-4-phenyloxazolidin-2-one 13



From **8**: Following *general procedure 2*, a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (138 mg, 0.65 mmol) in THF (14 mL) at −78 °C was treated with BuLi (1.51 M, 0.43 mL, 0.65 mmol) and **8** (100 mg, 0.43 mmol) to give a 95:5 mixture of **13**:**18**. Purification via flash column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 1:1) gave a 95:5 mixture of **13**:**18** as a white solid (143 mg, 75%). Recrystallisation (Et_2O/30–40 °C petrol) gave **13** as a white solid (102 mg, 53%, >99:1 dr); $C_{28}H_{30}N_2O_3$ requires C, 76.0; H, 6.8; N, 6.3; found C, 75.9; H, 6.7; N, 6.4; mp 130–131 °C; $[\alpha]_D^{21} = +29.2$ (*c* 1.0, $CHCl_3$); ν_{max} (KBr) 1790 (C=O$_{endo}$), 1694 (C=O$_{exo}$); δ_H (500 MHz, $CDCl_3$) 1.03 (3H, d, *J* 6.6, C(4′)H_3), 1.32 (3H, d, *J* 6.9, C(α)*Me*), 2.85 (1H, dd, *J* 16.3, 8.3, C(2′)H_A), 2.90 (1H, dd, *J* 16.3, 5.3, C(2′)H_B), 3.55–3.59 (1H, m, C(3′)*H*), 3.71 (1H, d, *J* 15.0, NCH_A), 3.82 (1H, d, *J* 15.0, NCH_B), 3.91 (1H, q, *J* 6.9, C(α)*H*), 4.20 (1H, dd, *J* 8.8, 3.6, C(5)H_A), 4.55 (1H, dd, *J* 8.8, 8.7, C(5)H_B), 5.29 (1H, dd, *J* 8.7, 3.6, C(4)*H*), 7.19–7.42 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 18.2, 19.5 (*C*(4′), C(α)*Me*), 39.0 (*C*(2′)), 49.7 (*C*(3′)), 49.9 (NCH_2), 57.5 (*C*(4)), 58.5 (*C*(α)), 69.7 (*C*(5)), 125.8, 126.5, 126.7, 127.6, 128.1, 128.6, 129.1 (*Ph*$_{o,m,p}$), 139.1, 142.0, 144.5 (*Ph*$_i$), 153.5 (*C*(2)), 171.4 (*C*(1′)); *m*/*z* (APCI$^+$) 443 ([M+H]$^+$, 100%).

From **23**: A solution of (*S*,*S*)-**23** (595 mg, 1.68 mmol) in CH_2Cl_2 (5 mL) was treated with TFA (5 mL). After 2 h the reaction mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL), washed with satd aq $NaHCO_3$ (5 mL), dried and concentrated in vacuo. The residue was again dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. Following *general procedure 1C*, the resultant solution was treated with $(ClCO)_2$ (319 mg, 2.52 mmol), one drop of DMF and one drop of Et_3N. A suspension of the resultant acid chloride in THF (5.00 mL) was subsequently added to a solution of **25** (823 mg, 5.04 mmol) and BuLi (1.58 M, 3.19 mL, 5.04 mmol) in THF (10 mL) at −78 °C. Purification via flash column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 1:1) gave **13** as a white solid (196 mg, 26%, >99:1 dr).

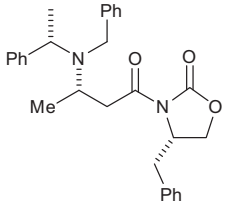
4.10. (4*S*,3′*R*,α*S*)-*N*(3)-{3′-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-3′-phenylpropanoyl}-4-benzyloxazolidin-2-one 14



From **9**: Following *general procedure 2*, a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (2.75 g, 13.0 mmol) in THF (40 mL) at −78 °C was treated with BuLi (1.35 M, 9.60 mL, 13.0 mmol) and **9** (2.50 g, 8.13 mmol) to give **14** in >99:1 dr. Crystallisation from EtOAc/Et_2O gave **14** as a white solid (3.54 g, 84%, >99:1 dr); $C_{34}H_{34}N_2O_3$ requires C, 78.7; H, 6.6; N, 5.4; found C, 78.5; H, 6.9; N, 5.3; mp 140–142 °C; $[\alpha]_D^{21} = +35.6$ (*c* 1.0, $CHCl_3$); ν_{max} (KBr) 1785 (C=O*endo*), 1686 (C=O*exo*); δ_H (500 MHz, $CDCl_3$) 1.30 (3H, d, *J* 6.8, C(α)*Me*), 2.44 (1H, dd, *J* 13.5, 9.7, C(4)C*H*$_A$H$_B$Ph), 2.97 (1H, dd, *J* 13.5, 3.2, C(4)CH$_A$*H*$_B$Ph), 3.07 (1H, dd, *J* 16.6, 5.1, C(2′)*H*$_A$), 3.61 (1H, dd, *J* 16.6, 9.3, C(2′)*H*$_B$), 3.77 (1H, d, *J* 14.9, NC*H*$_A$), 3.83 (1H, d, *J* 14.9, NC*H*$_B$), 4.00–4.05 (2H, m, C(5)*H*$_2$), 4.08 (1H, q, *J* 6.8, C(α)*H*), 4.46–4.50 (1H, m, C(4)*H*), 4.68 (1H, dd, *J* 9.3, 5.1, C(3′)*H*), 7.04–7.07 (2H, m, *Ph*), 7.18–7.39 (14H, m, *Ph*), 7.44–7.48 (4H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 16.2 (C(α)*Me*), 37.1, 37.5 (*C*(2′), C(4)CH_2Ph), 50.8 (NCH_2), 55.1 (*C*(4)), 56.9 (*C*(3′)), 58.9 (*C*(α)), 66.0 (*C*(5)), 126.8, 127.0, 127.2, 127.4, 127.7, 127.9, 128.2, 128.5, 128.9, 129.1, 129.4, 129.6 (*Ph*$_{o,m,p}$), 135.5, 141.8, 142.1, 144.4 (*Ph*$_i$), 153.4 (*C*(2)), 171.6 (*C*(1′)); *m*/*z* (CI^+) 519 ([M+H]$^+$, 100%); HRMS (ESI^+) $C_{34}H_{35}N_2O_3^+$ ([M+H]$^+$) requires 519.2642; found 519.2635.

From **22**: A solution of (3*R*,α*S*)-**22** (1.09 g, 2.62 mmol) in CH_2Cl_2 (10 mL) was treated with TFA (10 mL). After 2 h the reaction mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL), washed with satd aq $NaHCO_3$ (10 mL), dried and concentrated in vacuo. The residue was dissolved in THF (10 mL) and cooled to −30 °C. Following *general procedure 1B*, the resultant solution was treated with Et_3N (1.10 mL, 7.85 mmol) and pivaloyl chloride (0.35 mL, 2.88 mmol), followed after 2 h by LiCl (133 mg, 3.14 mmol) and **26** (510 mg, 2.88 mmol). Trituration with MeOH furnished **14** as a white solid (1.17 g, 90%, >99:1 dr).

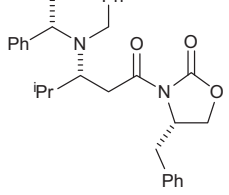
4.11. (*S*,*S*,*S*)-*N*(3)-{3′-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]butanoyl}-4-benzyloxazolidin-2-one 15



From **10**: Following *general procedure 2*, a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (138 mg, 0.65 mmol) in THF (14 mL) at −78 °C was treated with BuLi (1.51 M, 0.43 mL, 0.65 mmol) and **10** (100 mg, 0.41 mmol) to give a 96:4 mixture of **15**:**20**. Purification via flash column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 1:1) gave a 96:4 mixture of **15**:**20** as a colourless oil (136 mg, 73%). Crystallisation from CH_2Cl_2/Et_2O gave **15** as a white solid (98 mg, 51%, >99:1 dr); $C_{29}H_{32}N_2O_3$ requires C, 76.3; H, 7.1; N, 6.1; found C, 76.5; H, 7.2; N, 6.0; mp 88–89 °C; $[\alpha]_D^{21} = +6.6$ (*c* 0.9, $CHCl_3$); ν_{max} (KBr) 1782 (C=O*endo*), 1699 (C=O*exo*); δ_H (500 MHz, $CDCl_3$) 1.22 (3H, d, *J* 6.6, C(4′)*H*$_3$), 1.38 (3H, d, *J* 6.9, C(α)*Me*), 2.60 (1H, dd, *J* 13.3, 10.0, C(4)C*H*$_A$H$_B$Ph), 2.86 (1H, dd, *J* 16.3, 8.0, C(2′)*H*$_A$), 2.95 (1H, dd, *J* 16.3, 5.6, C(2′)*H*$_B$), 3.25 (1H, dd, *J* 13.3, 3.3, C(4)CH$_A$*H*$_B$Ph), 3.64–3.71 (1H, m, C(3′)*H*), 3.77 (1H, d, *J* 14.9, NC*H*$_A$), 3.83 (1H, d, *J* 14.9, NC*H*$_B$), 3.96 (1H, q, *J* 6.9, C(α)*H*), 4.03–4.08 (2H, m, C(5)*H*$_2$), 4.50–4.55 (1H, m, C(4)*H*), 7.18–7.38 (13H, m, *Ph*), 7.43–7.48 (2H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 18.4, 18.9 (*C*(4′), C(α)*Me*), 37.9, 39.4 (*C*(2′), C(4)CH_2Ph), 49.6 (*C*(3′)), 49.9 (NCH_2), 55.2 (*C*(4)), 58.1 (*C*(α)), 66.0 (*C*(5)), 126.5, 126.6, 127.2, 127.3, 127.6, 128.1, 128.2, 128.9, 129.4 (*Ph*$_{o,m,p}$), 135.5, 141.9, 144.6 (*Ph*$_i$), 153.2 (*C*(2)), 171.9 (*C*(1′)); *m*/*z* (CI^+) 457 ([M+H]$^+$, 100%); HRMS (CI^+) $C_{29}H_{33}N_2O_3^+$ ([M+H]$^+$) requires 457.2486; found 457.2490.

From **23**: A solution of (*S*,*S*)-**23** (1.97 g, 5.58 mmol) in CH_2Cl_2 (10 mL) was treated with TFA (10 mL). After 2 h the reaction mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL), washed with satd aq $NaHCO_3$ (10 mL), dried and concentrated in vacuo. The residue was dissolved in THF (10 mL) and cooled to −30 °C. Following *general procedure 1B*, the resultant solution was treated with Et_3N (2.30 mL, 16.7 mmol) and pivaloyl chloride (0.76 mL, 6.14 mmol), followed after 2 h by LiCl (280 mg, 6.70 mmol) and **26** (1.09 g, 6.14 mmol). Purification via flash column chromatography (neutral alumina, gradient elution, 30–40 °C petrol/Et_2O, 10:1; increased to 30–40 °C petrol/Et_2O, 5:1) gave **15** as a white solid (1.43 mg, 56%, >99:1 dr).

4.12. (4*S*,3′*R*,α*S*)-*N*(3)-{3′-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-4′-methylpentanoyl}-4-benzyloxazolidin-2-one 16

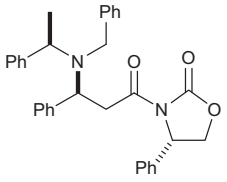


From **11**: Following *general procedure 2*, a solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (247 mg, 1.17 mmol) in THF (20 mL) at −78 °C was treated with BuLi (2.5 M, 0.50 mL, 1.13 mmol) and **11** (200 mg, 0.73 mmol) to give a 94:6 mixture of **16**:**21**. Purification via flash column chromatography (neutral alumina, eluent 30–40 °C petrol/Et_2O, 5:1) gave a 94:6 mixture of **16**:**21** as a pale yellow oil (255 mg, 72%). Further flash column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 1:1) gave **16** as a colourless oil (180 mg, 51%, >99:1 dr); $[\alpha]_D^{20} = +10.4$ (*c* 1.0, $CHCl_3$); ν_{max} (film) 1782 (C=O*endo*), 1700 (C=O*exo*); δ_H (400 MHz, $CDCl_3$) 0.92 (3H, d, *J* 6.7, C(4′)*Me*$_A$), 1.19 (3H, d, *J* 6.5, C(4′)*Me*$_B$), 1.44 (3H, d, *J* 7.4, C(α)*Me*), 1.72–1.81 (1H, m, C(4′)*H*), 2.21 (1H, app d, *J* 18.4, C(2′)*H*$_A$), 2.64 (1H, dd, *J* 13.2, 10.0, C(4)C*H*$_A$H$_B$Ph), 2.90 (1H, dd, *J* 18.4, 8.6, C(2′)*H*$_B$), 3.27 (1H, dd, *J* 13.2, 3.4, C(4)CH$_A$*H*$_B$Ph), 3.49–3.53 (1H, m, C(3′)*H*), 3.64 (1H, d, *J* 15.1, NC*H*$_A$), 3.81 (1H, q, *J* 7.4, C(α)*H*), 3.86 (1H, d, *J* 15.1, NC*H*$_B$), 4.11 (2H, app d, *J* 5.2, C(5)*H*$_2$), 4.53–4.59 (1H, m, C(4)*H*), 7.19–7.41 (13H, m, *Ph*), 7.51–7.53 (2H,

m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.7 (C(α)*Me*), 19.8, 21.7 (C(4′)*Me*$_2$), 32.6 (*C*(4′)), 35.2 (*C*(2′)), 37.9 (C(4)*C*H$_2$Ph), 51.4 (NCH$_2$), 55.2 (*C*(4)), 56.4 (*C*(3′)), 57.1 (*C*(α)), 66.0 (*C*(5)), 126.0, 126.6, 126.8, 127.2, 128.0, 128.4, 128.7, 128.9, 129.4 (*Ph*$_{o,m,p}$), 135.4, 141.2, 141.7 (*Ph*$_i$), 153.2 (*C*(2)), 172.5 (*C*(1′)); *m*/*z* (ESI$^+$) 485 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{37}N_2O_3^+$ ([M+H]$^+$) requires 485.2799; found 485.2817.

From **24**: A solution of (3*R*,α*S*)-**24** (470 mg, 1.23 mmol) in CH_2Cl_2 (10 mL) was treated with TFA (10 mL). After 2 h the reaction mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL), washed with satd aq $NaHCO_3$ (10 mL), dried and concentrated in vacuo. The residue was dissolved in THF (10 mL) and cooled to −30 °C. Following *general procedure 1B*, the resultant solution was treated with Et_3N (0.50 mL, 3.69 mmol) and pivaloyl chloride (0.17 mL, 1.35 mmol), followed after 2 h by LiCl (63 mg, 1.47 mmol) and **26** (240 mg, 1.35 mmol). Purification via flash column chromatography (neutral alumina, gradient elution, 30–40 °C petrol/Et_2O, 10:1; increased to 30–40 °C petrol/Et_2O, 5:1) gave **16** as a colourless oil (350 mg, 59%, >99:1 dr).

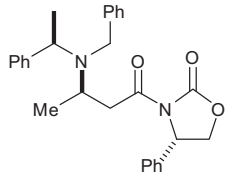
4.13. (4*S*,3′*S*,α*R*)-*N*(3)-{3′-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-3′-phenylpropanoyl}-4-phenyloxazolidin-2-one 27



From **7**: Following *general procedure 2*, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (172 mg, 0.82 mmol) in THF (10 mL) at −78 °C was treated with BuLi (1.5 M, 0.54 mL, 0.81 mmol) and **7** (150 mg, 0.51 mmol) to give an 80:20 mixture of **27**:**32**. Purification via flash column chromatography (neutral alumina, eluent 30–40 °C petrol/Et_2O, 5:1) gave an 80:20 mixture of **27**:**32** as a colourless oil (134 mg, 52%).

From **22**: A solution of (3*S*,α*R*)-**22** (510 mg, 1.23 mmol) in CH_2Cl_2 (5 mL) was treated with TFA (5 mL). After 2 h the reaction mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL), washed with satd aq $NaHCO_3$ (5 mL), dried and concentrated in vacuo. The residue was again dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. Following *general procedure 1C*, the resultant solution was treated with $(ClCO)_2$ (114 mg, 0.90 mmol), one drop of DMF and one drop of Et_3N. A suspension of the resultant acid chloride in THF (5 mL) was subsequently added to a solution of **25** (274 mg, 1.68 mmol) and BuLi (1.58 M, 1.06 mL, 1.67 mmol) in THF (10 mL) at −78 °C. Purification via flash column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 1:1) gave (4*S*,3′*S*,α*R*)-**27** as a white foam (71 mg, 25%, >99:1 dr); $[\alpha]_D^{21} = +63.5$ (*c* 0.65, $CHCl_3$); ν_{max} (film) 1781 (C=O$_{endo}$), 1706 (C=O$_{exo}$); δ_H (500 MHz, $CDCl_3$) 1.23 (3H, d, *J* 6.9, C(α)*Me*), 2.88 (1H, dd, *J* 16.1, 5.0, C(2′)*H*$_A$), 3.55 (1H, dd, *J* 16.1, 9.2, C(2′)*H*$_B$), 3.71 (1H, d, *J* 14.5, NC*H*$_A$), 3.80 (1H, d, *J* 14.5, NC*H*$_B$), 3.99 (1H, q, *J* 6.9, C(α)*H*), 4.16 (1H, dd, *J* 8.8, 3.4, C(5)*H*$_A$), 4.46 (1H, dd, *J* 8.8, 8.7, C(5)*H*$_B$), 4.56 (1H, dd, *J* 9.2, 5.0, C(3′)*H*), 5.17 (1H, dd, *J* 8.7, 3.4, C(4)*H*), 7.19–7.41 (20H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.9 (C(α)*Me*), 37.7 (*C*(2′)), 50.7 (NCH$_2$), 56.4 (*C*(4)), 57.4, 57.9 (*C*(3′), *C*(α)), 69.7 (*C*(5)), 126.0, 126.6, 126.7, 127.1, 127.5, 127.8, 128.1, 128.2, 128.6, 129.0 (*Ph*$_{o,m,p}$), 139.0, 141.2, 141.8, 143.5 (*Ph*$_i$), 153.4 (*C*(2)), 170.4 (*C*(1′)); *m*/*z* (CI$^+$) 505 ([M+H]$^+$, 100%); HRMS (CI$^+$) $C_{33}H_{33}N_2O_3^+$ ([M+H]$^+$) requires 505.2486; found 505.2494.

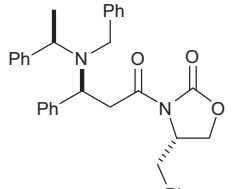
4.14. (4*S*,3′*R*,α*R*)-*N*(3)-{3′-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-butanoyl}-4-phenyloxazolidin-2-one 28



From **8**: Following *general procedure 2*, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (220 mg, 1.04 mmol) in THF (10 mL) at −78 °C was treated with BuLi (1.50 M, 0.68 mL, 1.02 mmol) and **8** (150 mg, 0.65 mmol) to afford an 89:11 mixture of **28**:**33**. Purification via flash column chromatography (neutral alumina, eluent 30–40 °C petrol/Et_2O, 5:1) gave an 89:11 mixture of **28**:**33** as a colourless oil (212 mg, 74%).

From **23**: A solution of (*R*,*R*)-**23** (177 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) was treated with TFA (5 mL). After 2 h the reaction mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL), washed with satd aq $NaHCO_3$ (5 mL), dried and concentrated in vacuo. The residue was again dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. Following *general procedure 1C*, the resultant solution was treated with $(ClCO)_2$ (96 mg, 0.75 mmol), one drop of DMF and one drop of Et_3N. A suspension of the resultant acid chloride in THF (5 mL) was subsequently added to a solution of **25** (245 mg, 1.50 mmol) and BuLi (1.58 M, 0.95 mL, 1.50 mmol) in THF (10 mL) at −78 °C. Purification via flash column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 1:1) gave **28** as a white foam (69 mg, 31%, >99:1 dr); $[\alpha]_D^{21} = +44.6$ (*c* 1.6, $CHCl_3$); ν_{max} (film) 1780 (C=O$_{endo}$), 1706 (C=O$_{exo}$); δ_H (500 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.7, C(4′)*H*$_3$), 1.35 (3H, d, *J* 6.9, C(α)*Me*), 2.73 (1H, dd, *J* 14.2, 7.3, C(2′)*H*$_A$), 2.91 (1H, dd, *J* 14.2, 5.9, C(2′)*H*$_B$), 3.50–3.54 (1H, m, C(3′)*H*), 3.72 (1H, d, *J* 14.2, NC*H*$_A$), 3.82 (1H, d, *J* 14.2, NC*H*$_B$), 3.87 (1H, q, *J* 6.9, C(α)*H*), 4.10 (1H, dd, 8.8, 3.4, C(5)*H*$_A$), 4.40 (1H, dd, *J* 8.8, 8.6, C(5)*H*$_B$), 5.10 (1H, dd, *J* 8.6, 3.4, C(4)*H*), 7.19–7.52 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 16.2, 19.7 (*C*(4′), C(α)*Me*), 41.5 (*C*(2′)), 49.5 (*C*(3′)), 50.0 (NCH$_2$), 57.1, 57.8 (*C*(4), *C*(α)), 70.0 (*C*(5)), 126.2, 126.8, 127.1, 128.2, 128.5, 128.6, 128.9, 129.2, 129.5 (*Ph*$_{o,m,p}$), 139.8, 141.9, 144.8 (*Ph*$_i$), 153.8 (*C*(2)), 171.0 (*C*(1′)); *m*/*z* (CI$^+$) 443 ([M+H]$^+$, 100%); HRMS (CI$^+$) $C_{28}H_{31}N_2O_3^+$ ([M+H]$^+$) requires 443.2329; found 443.2328.

4.15. (4*S*,3′*S*,α*R*)-*N*(3)-{3′-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-3′-phenylpropanoyl}-4-benzyloxazolidin-2-one 29

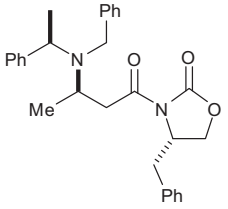


From **9**: Following *general procedure 2*, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (274 mg, 1.30 mmol) in THF (15 mL) at −78 °C was treated with BuLi (1.50 M, 0.86 mL, 1.30 mmol) and **9** (250 mg, 0.81 mmol) to give an 83:17 mixture of diastereoisomers **29**:**34**. Purification via flash column chromatography (neutral alumina, eluent 30–40 °C petrol/Et_2O, 5:1) gave an 83:17 mixture of **29**:**34** as a colourless oil (270 mg, 64%).

From **22**: A solution of (3*S*,α*R*)-**22** (233 mg, 0.56 mmol) in CH_2Cl_2 (5 mL) was treated with TFA (5 mL). After 2 h the reaction mixture was concentrated in vacuo. The residue was dissolved in

CH_2Cl_2 (5 mL), washed with satd aq $NaHCO_3$ (5 mL), dried and concentrated in vacuo. The residue was again dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. Following *general procedure 1C*, the resultant solution was treated with $(ClCO)_2$ (114 mg, 0.90 mmol), one drop of DMF and one drop of Et_3N. A suspension of the resultant acid chloride in THF (5 mL) was subsequently added to a solution of **26** (298 mg, 1.68 mmol) and BuLi (1.58 M, 1.06 mL, 1.67 mmol) in THF (10 mL) at −78 °C. Purification via flash column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 1:1) gave **29** as a white foam (98 mg, 34%, >99:1 dr); $[\alpha]_D^{21} = +44.2$ (*c* 1.0, $CHCl_3$); ν_{max} (film) 1780 (C=O*endo*), 1700 (C=O*exo*); δ_H (500 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.9, C(α)*Me*), 2.60 (1H, dd, *J* 13.4, 9.9, C(4)C*H*$_A$H$_B$Ph), 3.05 (1H, dd, *J* 15.9, 5.2, C(2′)*H*$_A$), 3.19 (1H, dd, *J* 13.4, 3.2, C(4)CH$_A$*H*$_B$Ph), 3.55 (1H, dd, *J* 15.9, 9.2, C(2′)*H*$_B$), 3.75 (1H, d, *J* 14.7, NC*H*$_A$), 3.87 (1H, d, *J* 14.7, NC*H*$_B$), 3.90–3.96 (1H, m, C(5)*H*$_A$), 4.02 (1H, dd, *J* 9.0, 2.6, C(5)*H*$_B$), 4.07 (1H, q, *J* 6.9, C(α)*H*), 4.38–4.43 (1H, m, C(4)*H*), 4.62 (1H, dd, *J* 9.2, 5.2, C(3′)*H*), 7.14–7.47 (20H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.6 (C(α)*Me*), 37.7, 38.1 (*C*(2′), C(4)*C*H$_2$Ph), 50.8 (NCH$_2$), 55.1 (*C*(4)), 56.5 (*C*(3′)), 58.6 (*C*(α)), 65.9 (*C*(5)), 126.6, 126.8, 127.2, 127.9, 128.1, 128.2, 128.3, 128.7, 128.9, 129.3, 129.5, 130.7 (*Ph*$_{o,m,p}$), 135.3, 141.4, 141.8, 143.9 (*Ph*$_i$), 153.1 (*C*(2)), 171.0 (*C*(1′)); *m*/*z* (CI^+) 519 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{34}H_{35}N_2O_3^+$ ($[M+H]^+$) requires 519.2642; found 519.2643.

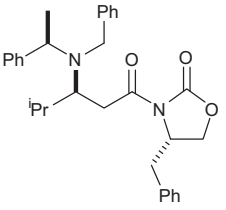
4.16. (4*S*,3′*R*,α*R*)-3-{3′-[*N*-Benzyl-*N*-(α-methylbenzyl)-amino]-butanoyl}-4-benzyloxazolidin-2-one 30



From **10**: Following *general procedure 2*, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (277 mg, 1.31 mmol) in THF (15 mL) at -78 °C was treated with BuLi (1.50 M, 0.86 mL, 1.29 mmol) and **10** (200 mg, 0.82 mmol) to give an 80:20 mixture of **30**:**35**. Purification via flash column chromatography (neutral alumina, eluent 30–40 °C petrol/Et_2O, 5:1) gave an 80:20 mixture of **30**:**35** as a colourless oil (238 mg, 64%).

From **23**: A solution of (*R*,*R*)-**23** (130 mg, 0.37 mmol) in CH_2Cl_2 (5 mL) was treated with TFA (5 mL). After 2 h the reaction mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL), washed with satd aq $NaHCO_3$ (5 mL), dried and concentrated in vacuo. The residue was again dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. Following *general procedure 1C*, the resultant solution was treated with $(ClCO)_2$ (70 mg, 0.56 mmol), one drop of DMF and one drop of Et_3N. A suspension of the resultant acid chloride in THF (5 mL) was subsequently added to a mixture of **26** (197 mg, 1.11 mmol) and BuLi (1.58 M, 0.70 mL, 1.11 mmol) in THF (10 mL) at −78 °C. Purification via flash column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 1:1) gave **30** as a white foam (38 mg, 22%, >99:1 dr); $[\alpha]_D^{21} = +42.9$ (*c* 0.5, $CHCl_3$); ν_{max} (film) 1781 (C=O*endo*), 1700 (C=O*exo*); δ_H (500 MHz, $CDCl_3$) 1.25 (3H, d, *J* 6.6, C(4′)*H*$_3$), 1.39 (3H, d, *J* 6.9, C(α)*Me*), 2.67 (1H, dd, *J* 13.4, 9.6, C(4)C*H*$_A$H$_B$Ph), 2.80 (1H, dd, *J* 14.3, 7.7, C(2′)*H*$_A$), 2.98 (1H, dd, *J* 14.3, 5.7, C(2′)*H*$_B$), 3.23 (1H, dd, *J* 13.4, 3.2, C(4)CH$_A$*H*$_B$Ph), 3.52–3.58 (1H, m, C(3′)*H*), 3.75 (1H, d, *J* 14.2, NC*H*$_A$), 3.88–3.95 (3H, m, C(5)*H*$_A$, C(α)*H*, NC*H*$_B$), 4.00 (1H, dd, *J* 8.9, 2.5, C(5)*H*$_B$), 4.34–4.39 (1H, m, C(4)*H*), 7.18–7.40 (13H, m, *Ph*), 7.54–7.56 (2H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.5, 19.2 (*C*(4′), C(α)*Me*), 37.5, 41.3 (*C*(2′), C(4)CH$_2$Ph), 49.2 (*C*(3′)), 49.6 (NCH$_2$), 54.9 (*C*(4)), 56.5 (*C*(α)), 65.7 (*C*(5)), 126.4, 126.7, 127.3, 127.7, 128.1, 128.2, 128.8, 128.9, 129.4 (*Ph*$_{o,m,p}$), 135.4, 141.4, 144.4 (*Ph*$_i$), 153.1 (*C*(2)), 171.2 (*C*(1′)); *m*/*z* (CI^+) 457 ($[M+H]^+$, 100%); HRMS (CI^+) $C_{29}H_{33}N_2O_3^+$ ($[M+H]^+$) requires 457.2486; found 457.2494.

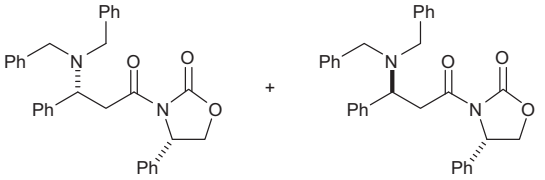
4.17. (4*S*,3′*S*,α*R*)-*N*(3)-{3′-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-4′-methylpentanoyl}-4-benzyloxazolidin-2-one 31



From **11**: Following *general procedure 2*, a solution of (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (247 mg, 1.17 mmol) in THF (10 mL) at −78 °C was treated with BuLi (2.5 M, 0.50 mL, 1.13 mmol) and **11** (200 mg, 0.73 mmol) to give an 85:15 mixture of **31**:**36**. Purification via flash column chromatography (neutral alumina, eluent 30–40 °C petrol/Et_2O, 5:1) gave an 85:15 mixture of **31**:**36** as a pale yellow oil (228 mg, 64%).

From **24**: A solution of (3*S*,α*R*)-**24** (469 mg, 1.23 mmol) in CH_2Cl_2 (5 mL) was treated with TFA (5 mL). After 2 h the reaction mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL), washed with satd aq $NaHCO_3$ (5 mL), dried and concentrated in vacuo. The residue was dissolved in THF (5 mL) and cooled to −30 °C. Following *general procedure 1B*, the resultant solution was treated with Et_3N (0.44 mL, 3.13 mmol) and pivaloyl chloride (0.14 mL, 1.15 mmol), followed after 2 h by LiCl (53 mg, 1.25 mmol) and **26** (204 mg, 1.15 mmol). Purification via flash column chromatography (neutral alumina, gradient elution, 30–40 °C petrol/Et_2O, 10:1; increased to 30–40 °C petrol/Et_2O, 4:1) gave **31** as a colourless oil (216 mg, 43%, >99:1 dr); $[\alpha]_D^{20} = +58.3$ (*c* 1.0, $CHCl_3$); ν_{max} (film) 1781 (C=O*endo*), 1699 (C=O*exo*); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, d, *J* 6.7, C(4′)*Me*$_A$), 1.16 (3H, d, *J* 6.6, C(4′)*Me*$_B$), 1.45 (3H, d, *J* 7.1, C(α)*Me*), 1.70–1.78 (1H, m, C(4′)*H*), 2.13 (1H, dd, *J* 18.2, 1.9, C(2′)*H*$_A$), 2.67 (1H, dd, *J* 13.3, 9.6, C(4)C*H*$_A$H$_B$Ph), 3.03 (1H, dd, *J* 18.2, 8.8, C(2′)*H*$_B$), 3.29 (1H, dd, *J* 13.3, 3.1, C(4)CH$_A$*H*$_B$Ph), 3.59 (1H, app td, *J* 8.8, 1.9, C(3′)*H*), 3.68 (1H, d, *J* 15.0, NC*H*$_A$), 3.80 (1H, q, *J* 7.1, C(α)*H*), 3.84 (1H, d, *J* 15.0, NC*H*$_B$), 4.08–4.13 (2H, m, C(5)*H*$_2$), 4.55–4.61 (1H, m, C(4)*H*), 7.20–7.24 (3H, m, *Ph*), 7.27–7.41 (10H, m, *Ph*), 7.52–7.54 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.4 (C(α)*Me*), 19.7, 20.9 (C(4′)*Me*$_2$), 32.6 (*C*(4′)), 35.6 (*C*(2′)), 37.8 (C(4)*C*H$_2$Ph), 51.5 (NCH$_2$), 55.3 (*C*(4)), 55.9 (*C*(3′)), 57.1 (*C*(α)), 65.8 (*C*(5)), 126.6, 126.9, 127.3, 128.0, 128.1, 128.2, 128,3, 129.0, 129.4 (*Ph*$_{o,m,p}$), 135.3, 141.3, 141.6 (*Ph*$_i$), 153.1 (*C*(2)), 172.3 (*C*(1′)); *m*/*z* (ESI^+) 485 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{31}H_{37}N_2O_3^+$ ($[M+H]^+$) requires 485.2799; found 485.2807.

4.18. (4*S*,3′*R*)- and (*S*,*S*)-*N*(3)-[3′-(*N*,*N*-Dibenzylamino)-3′-phenylpropanoyl]-4-phenyloxazolidin-2-one 38 and 43



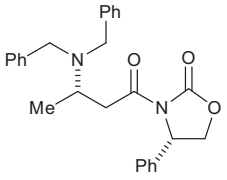
(4*S*,3′*R*)-**38** (*S*,*S*)-**43**

Following *general procedure 2*, a solution of dibenzylamine (0.98 mL, 5.11 mmol) in THF (40 mL) at −78 °C was treated with BuLi (1.58 M, 3.23 mL, 5.10 mmol) and **7** (1.00 g, 3.41 mmol) to

give a 75:25 mixture of **38**:**43**. Purification via flash column chromatography (silica, gradient elution, 30–40 °C petrol/Et_2O, 9:1; increased to 30–40 °C petrol/Et_2O, 1:1) gave a 75:25 mixture of **38**:**43** as a colourless oil (1.31 g, 80%); ν_{max} (film) 1779 (C=O_{endo}), 1702 (C=O_{exo}); *m*/*z* (APCI$^+$) 491 ([M+H]$^+$, 100%).

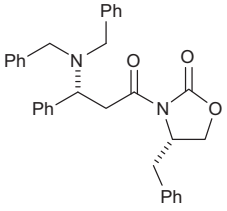
Data for **38**: δ_H (500 MHz, $CDCl_3$) [selected peaks] 1.05 (2H, d, *J* 14.0, N(C$H_A$$H_B$Ph)$_2$), 3.56 (1H, dd, *J* 15.9, 6.1, C(2′)H_A), 3.77 (1H, d, *J* 14.0, N(CH$_A$$H_B$Ph)$_2$), 3.83 (1H, dd, *J* 15.9, 9.1, C(2′)H_B), 4.18 (1H, dd, *J* 8.8, 4.0, C(5)H_A), 4.46 (1H, dd, *J* 9.1, 6.1, C(3′)*H*), 4.59 (1H, dd, *J* 8.8, 8.7, C(5)H_B), 5.37 (1H, dd, *J* 8.7, 4.0, C(4)*H*), 7.21–7.43 (20H, m, *Ph*).

4.19. (*S*,*S*)-*N*(3)-[3′-(*N*,*N*-Dibenzylamino)butanoyl]-4-phenyloxazolidin-2-one 39



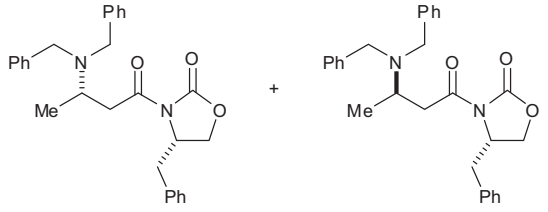
Following *general procedure 2*, a solution of dibenzylamine (0.78 mL, 4.09 mmol) in THF (20 mL) at −78 °C was treated with BuLi (1.58 M, 2.59 mL, 4.09 mmol) and **8** (630 mg, 2.72 mmol) to give a 78:22 mixture of **39**:**44**. Purification via flash column chromatography (silica, gradient elution, 30–40 °C petrol/Et_2O, 9:1; increased to 30–40 °C petrol/Et_2O, 1:1) gave a 78:22 mixture of **39**:**44** as a white solid (957 mg, 82%). Recrystallisation (30–40 °C petrol/Et_2O) gave **39** as a white solid (512 mg, 44%, >99:1 dr); $C_{27}H_{28}N_2O_3$ requires C, 75.7; H, 6.6; N, 6.5; found C, 75.9; H, 6.4; N, 6.5; mp 131–133 °C; $[\alpha]_D^{21} = +50.3$ (*c* 1.0, $CHCl_3$); ν_{max} (KBr) 1792 (C=O_{endo}), 1694 (C=O_{exo}); δ_H (500 MHz, $CDCl_3$) 1.05 (3H, d, *J* 6.6, C(4′)H_3), 3.00 (1H, dd, *J* 15.3, 8.3, C(2′)H_A), 3.33 (1H, dd, *J* 15.3, 5.9, C(2′)H_B), 3.40–3.45 (1H, m, C(3′)*H*), 3.57 (2H, d, *J* 14.0, N(C$H_A$$H_B$Ph)$_2$), 3.65 (2H, d, *J* 14.0, N(CH$_A$$H_B$Ph)$_2$), 4.24 (1H, dd, *J* 8.8, 3.6, C(5)H_A), 4.60 (1H, dd, *J* 8.8, 8.7, C(5)H_B), 5.39 (1H, dd, *J* 8.7, 3.6, C(4)*H*), 7.19–7.22 (2H, m, *Ph*), 7.26–7.40 (13H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.1 (*C*(4′)), 38.4 (*C*(2′)), 51.0 (*C*(3′)), 53.6 (N(*C*H_2Ph)$_2$), 57.7 (*C*(4)), 69.7 (*C*(5)), 126.0, 126.7, 128.1, 128.5, 128.6, 129.1 ($Ph_{o,m,p}$), 139.1, 140.1 (Ph_i), 153.6 (*C*(2)), 171.4 (*C*(1′)); *m*/*z* (CI$^+$) 429 ([M+H]$^+$, 100%).

4.20. (4*S*,3′*R*)-*N*(3)-[3′-(*N*,*N*-Dibenzylamino)-3′-phenylpropanoyl]-4-benzyloxazolidin-2-one 40



Following *general procedure 2*, a solution of dibenzylamine (0.28 mL, 1.46 mmol) in THF (25 mL) at −78 °C was treated with BuLi (1.58 M, 0.92 mL, 1.45 mmol) and **9** (300 mg, 0.98 mmol) to give a 79:21 mixture of **40**:**45**. Purification via flash column chromatography (silica, gradient elution, 30–40 °C petrol/Et_2O, 9:1; increased to 30–40 °C petrol/Et_2O, 1:1) gave a 79:21 mixture of **40**:**45** as a white solid (450 mg, 91%). Recrystallisation (30–40 °C petrol/Et_2O) gave **40** as a white solid (264 mg, 53%, >99:1 dr); $C_{33}H_{32}N_2O_3$ requires C, 78.55; H, 6.4; N, 5.55; found C, 78.6; H, 6.3; N, 5.5; mp 142–144 °C; $[\alpha]_D^{21} = +91.4$ (*c* 1.2, $CHCl_3$); ν_{max} (KBr) 1772 (C=O_{endo}), 1710 (C=O_{exo}); δ_H (500 MHz, $CDCl_3$) 2.53 (1H, dd, *J* 13.4, 9.8, C(4)C$H_A$$H_B$Ph), 3.11 (1H, dd, *J* 13.4, 3.3, C(4)CH$_A$$H_B$Ph), 3.35 (2H, d, *J* 13.9, N(C$H_A$$H_B$Ph)$_2$), 3.61 (1H, dd, *J* 15.9, 6.9, C(2′)H_A), 3.74 (1H, dd, *J* 15.9, 8.4, C(2′)H_B), 3.82 (2H, d, *J* 13.9, N(CH$_A$$H_B$Ph)$_2$), 4.09–4.13 (2H, m, C(5)H_2), 4.55 (1H, dd, *J* 8.4, 6.9, C(3′)*H*), 4.60–4.65 (1H, m, C(4)*H*), 7.10–7.12 (2H, m, *Ph*), 7.22–7.42 (18H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 36.1 (*C*(2′), 37.8 C(4)CH_2Ph), 54.0 (*C*(3′)), 55.2 (*C*(4)), 59.0 (N(*C*H_2Ph)$_2$), 66.0 (*C*(5)), 126.9, 127.2, 127.4, 128.1, 128.2, 128.6, 128.7, 128.9, 129.3 ($Ph_{o,m,p}$), 135.3, 137.9, 139.8 (Ph_i), 153.4 (*C*(2)), 171.0 (*C*(1′)); *m*/*z* (CI$^+$) 505 ([M+H]$^+$, 100%).

4.21. (*S*,*S*)- and (4*S*,3′*R*)-*N*(3)-[3′-(*N*,*N*-Dibenzylamino)butanoyl]-4-benzyloxazolidin-2-one 41 and 46

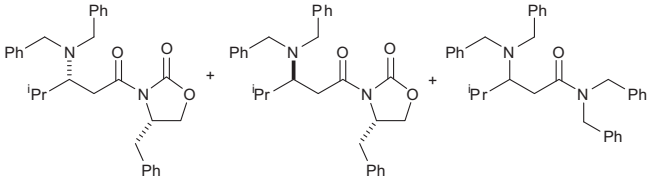


(*S*,*S*)-**41** (4*S*,3′*R*)-**46**

Following *general procedure 2*, a solution of dibenzylamine (1.06 mL, 5.50 mmol) in THF (20 mL) at −78 °C was treated with BuLi (1.58 M, 3.48 mL, 5.50 mmol) and **10** (900 mg, 3.67 mmol) to give a 76:24 mixture of **41**:**46**. Purification via flash column chromatography (silica, gradient elution, 30–40 °C petrol/Et_2O, 10:1; increased to 30–40 °C petrol/Et_2O, 1:1) gave a 76:24 mixture of **41**:**46** as a colourless oil (1.38 g, 85%).

Data for **41**: δ_H (500 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.4, C(4′)H_3), 2.57 (1H, dd, *J* 13.3, 10.1, C(4)C$H_A$$H_B$Ph), 3.02 (1H, dd, *J* 14.9, 7.2, C(2′)H_A), 3.28 (1H, dd, *J* 14.9, 7.1, C(2′)H_B), 3.33 (1H, dd, *J* 13.3, 3.7, C(4)CH$_A$$H_B$Ph), 3.37–3.58 (3H, m, C(3′)*H*, N(C$H_A$$H_B$Ph)$_2$), 3.72 (2H, d, *J* 14.5, N(CH$_A$$H_B$Ph)$_2$), 4.05–4.11 (2H, m, C(5)H_2), 4.60–4.64 (1H, m, C(4)*H*), 7.18–7.34 (15H, m, *Ph*).

4.22. (4*S*,3′*R*)- and (*S*,*S*)-*N*(3)-[3′-(*N*,*N*-Dibenzylamino)-4′-methylpentanoyl]-4-benzyloxazolidin-2-one 42 and 47 and *N*,*N*-dibenzyl (*RS*)-3-(*N*,*N*-dibenzylamino)-4-methylpentanamide 48



(4*S*,3′*R*)-**42** (*S*,*S*)-**47** (*RS*)-**48**

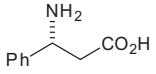
Following *general procedure 2*, a solution of dibenzylamine (0.41 mL, 2.12 mmol) in THF (5 mL) at −78 °C was treated with BuLi (1.6 M, 1.28 mL, 2.05 mmol) and **11** (362 mg, 1.32 mmol) to give a 37:13:50 mixture of **42**:**47**:**48**. Purification via flash column chromatography (silica, gradient elution, 30–40 °C petrol/Et_2O, 9:1; increased to 30–40 °C petrol/Et_2O, 1:1) gave **48** as a colourless oil (200 mg, 31%); ν_{max} (film) 1648 (C=O); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, d, *J* 6.7, C(4)Me_A), 1.04 (3H, d, *J* 6.6, C(4)Me_B), 1.81–1.90 (1H, m, C(4)*H*), 2.47 (1H, dd, *J* 15.9, 7.0, C(2)H_A), 2.70 (1H, dd, *J* 15.9, 3.9, C(2)H_B), 3.27–3.32 (1H, m, C(3)*H*), 3.41 (2H, d, *J* 13.7, C(3)N(C$H_A$$H_B$Ph)$_2$), 3.77 (2H, d, *J* 13.7, C(3)N(C$H_A$$H_B$Ph)$_2$), 4.43–4.81 (4H, m, C(1)N(*C*H_2Ph)$_2$), 7.21–7.45 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.2, 20.9 (C(4)Me_2), 31.2 (*C*(2)), 31.6 (*C*(4)), 48.7, 50.2 (C(1)N(*C*H_2Ph)$_2$),

54.7 (C(3)N(CH_2Ph)$_2$), 61.3 (*C*(3)), 126.5, 126.8, 127.5, 127.7, 128.1, 128.6, 129.0, 129.1 (*Ph*$_{o,m,p}$), 136.9, 137.6, 140.2 (*Ph*$_i$), 173.0 (*C*(1)); *m*/*z* (ESI$^+$) 491 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{38}N_2O^+$ ([M+H]$^+$) requires 491.3057; found 491.3063. Further elution gave a 73:27 mixture of **42**:**47** as a colourless oil (103 mg, 17%); ν_{max} (film) 1780 (C=O$_{endo}$), 1699 (C=O$_{exo}$); *m*/*z* (ESI$^+$) 471 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{35}N_2O_3^+$ ([M+H]$^+$) requires 471.2642; found 471.2650.

Data for **42**: δ_H (400 MHz, $CDCl_3$) 0.90 (3H, d, *J* 6.6, C(4′)*Me*$_A$), 1.07 (3H, d, *J* 6.6, C(4′)*Me*$_B$), 1.92–2.00 (1H, m, C(4′)*H*), 2.65 (1H, dd, *J* 13.2, 10.3, C(4)C*H*$_A$H$_B$Ph), 3.11–3.37 (4H, m, C(2′)*H*$_2$, C(3′)*H*, C(4)CH$_A$*H*$_B$Ph), 3.43 (2H, d, *J* 13.7, N(C*H*$_A$H$_B$Ph)$_2$), 3.83 (2H, d, *J* 13.7, N(CH$_A$*H*$_B$Ph)$_2$), 4.15–4.21 (2H, m, C(5)*H*$_2$), 4.69–4.78 (1H, m, C(4)*H*), 7.22–7.41 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.0, 21.7 (C(4′)*Me*$_2$), 31.5 (*C*(4′)), 32.6 (*C*(2′)), 37.9 (C(4)CH_2Ph), 54.5 (N(CH_2Ph)$_2$), 55.4 (*C*(4)), 60.7 (*C*(3′)), 66.1 (*C*(5)), 126.5, 126.7, 127.3, 128.1, 128.6, 129.0, 129.1, 129.4, 129.5 (*Ph*$_{o,m,p}$), 135.4, 140.0 (*Ph*$_i$), 153.6 (*C*(2)), 172.8 (*C*(1′)).

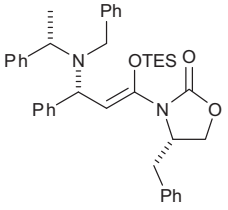
Data for **47**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.14–1.16 (6H, m, C(4′)*Me*$_2$), 2.56–2.64 (1H, m, C(4′)*H*), 2.78–2.84 (1H, m, C(4)C*H*$_A$H$_B$Ph), 3.55 (2H, d, *J* 13.6, N(C*H*$_A$H$_B$Ph)$_2$), 3.77 (2H, d, *J* 13.6, N(CH$_A$*H*$_B$Ph)$_2$), 4.06–4.14 (2H, m, C(5)*H*$_2$), 4.58–4.65 (1H, m, C(4)*H*).

4.23. (*R*)-3-Amino-3-phenyl propanoic acid 50



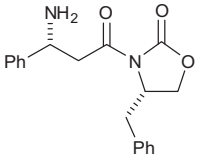
A solution of **40** (100 mg, 0.20 mmol) in THF/H_2O (v:v 3:1, 4 mL) at 0 °C was treated with 35% aq H_2O_2 (0.10 mL, 1.00 mmol) and LiOH (10 mg, 0.40 mmol). After being allowed to warm to rt over 16 h, 10% aq. Na_2SO_4 (5 mL) was added and the reaction mixture was stirred for a further 30 min. The mixture was then basified to pH 9–10 with satd aq $NaHCO_3$ and extracted with CH_2Cl_2 (10 mL). The organic layer was dried and concentrated in vacuo to give **26** (35 mg, quant). The aqueous layer was then acidified to pH 1–2 with 2 M aq. HCl and extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried and concentrated in vacuo. The residue was dissolved in degassed MeOH (5 mL) and Pd(OH)$_2$/C (10 mg) was added. The reaction vessel was flushed with hydrogen and the reaction mixture was left to stir under a hydrogen atmosphere. After 24 h, the reaction mixture was filtered through Celite® (eluent MeOH) and the filtrate was concentrated in vacuo. Purification via ion exchange chromatography (Dowex 50WX8-200, eluent 1 M aq NH_4OH) gave (*R*)-**50** as a white solid (14 mg, 43% from **40**);[26] mp 232–235 °C; {lit.[26] mp 234–237 °C}; $[\alpha]_D^{22} = +6.2$ (*c* 0.6, H_2O); {lit.[18] $[\alpha]_D^{19} = +6.5$ (*c* 1.0, H_2O)}; δ_H (400 MHz, D_2O) 2.71 (1H, dd, *J* 16.2, 6.8, C(2)*H*$_A$), 2.80 (1H, dd, *J* 16.2, 7.9, C(2)*H*$_B$), 4.52 (1H, dd, *J* 7.9, 6.8, C(3)*H*), 7.30–7.37 (5H, m, *Ph*).

4.24. (4*S*,3′*R*,α*S*,*Z*)-*N*(3)-{1′-Triethylsilyloxy-3′-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3′-phenylprop-2′-enyl}-4-benzyloxazolidin-2-one 51



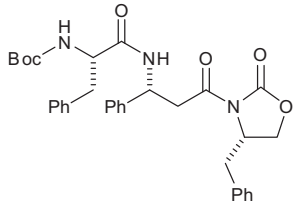
A solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (110 mg, 0.52 mmol) in THF (2 mL) at −78 °C was treated with BuLi (2.5 M, 0.20 mL, 0.50 mmol). After 30 min, a solution of **9** (100 mg, 0.33 mmol) in THF (2 mL) was added via cannula. The mixture was stirred for 3 h at −78 °C, then TESCl was added (78 mg, 0.52 mmol) and the reaction mixture was allowed to warm to rt over 5 h. The solvent was removed in vacuo to give **51** (72% conversion, >95:5 dr); δ_H (500 MHz, $CDCl_3$) 0.46 (6H, q, *J* 7.8, Si(C*H*$_2$CH$_3$)$_3$), 0.79 (9H, t, *J* 7.8, Si(CH$_2$C*H*$_3$)$_3$), 1.24 (3H, d, *J* 6.7, C(α)*Me*), 2.68–2.74 (1H, m, C(4)C*H*$_A$H$_B$Ph), 3.26–3.29 (1H, m, C(4)CH$_A$*H*$_B$Ph), 3.74 (1H, d, *J* 15.3, NC*H*$_A$), 4.03 (1H, d, *J* 15.3, NC*H*$_B$), 4.07–4.10 (2H, m, C(4)*H*, C(5)*H*$_A$), 4.17–4.19 (2H, m, C(5)*H*$_B$, C(α)*H*), 4.86 (1H, d, *J* 8.4, C(3′)*H*), 5.20 (1H, d, *J* 8.4, C(2′)*H*), 7.17–7.39 (16H, m, *Ph*), 7.56–7.59 (4H, m, *Ph*).

4.25. (4*S*,3′*R*)-*N*(3)-(3′-Amino-3′-phenylpropanoyl)-4-benzyloxazolidin-2-one 52



A vigorously stirred solution of **14** (520 mg, 1.00 mmol) in glacial AcOH (5 mL) was treated with Pd(OH$_2$)/C (130 mg). The reaction vessel was flushed with hydrogen and the reaction mixture was left to stir under a hydrogen atmosphere. After 24 h, the reaction mixture was filtered through Celite® (eluent MeOH) and the filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL) and washed with satd aq $NaHCO_3$, then dried and concentrated in vacuo. Crystallisation from Et_2O gave **52** as a white solid (289 mg, 89%); $C_{19}H_{20}N_2O_3$ requires C, 70.35; H, 6.2; N, 8.6; found C, 70.1; H, 6.2; N, 8.6; mp 129–131 °C; $[\alpha]_D^{21} = -49.9$ (*c* 2.1, $CHCl_3$); ν_{max} (KBr) 3442, 3331 (N–H), 1692 (C=O$_{endo}$), 1664 (C=O$_{exo}$); δ_H (500 MHz, $CDCl_3$) 2.62–2.67 (1H, m, C(2′)*H*$_A$), 2.78–2.82 (1H, m, C(2′)*H*$_B$), 3.12 (1H, dd, *J* 13.7, 7.0, C*H*$_A$H$_B$Ph), 3.18 (2H, br s, N*H*$_2$), 3.23 (1H, dd, *J* 13.7, 9.6, CH$_A$*H*$_B$Ph), 3.84 (1H, dd, *J* 11.9, 3.3, C(5)*H*$_A$), 4.02–4.05 (1H, m, C(5)*H*$_B$), 4.37 (1H, app br s, C(3′)*H*), 5.10–5.16 (1H, m, C(4)*H*), 7.18–7.38 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 34.6 (*C*H$_2$Ph), 40.0 (*C*(2′)), 51.0 (*C*(3′)), 56.6 (*C*(4)), 63.4 (*C*(5)), 125.9, 126.6, 128.4, 128.9, 129.3 (*Ph*$_{o,m,p}$), 138.1, 138.6 (*Ph*$_i$), 155.4 (*C*(2)), 169.6 (*C*(1′)); *m*/*z* (CI$^+$) 325 ([M+H]$^+$, 100%).

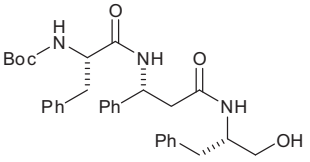
4.26. (4*S*,3′*R*,2″*S*)-*N*(3)-(3′-{*N*′-[2″-*N*″-(*tert*-Butoxycarbonyl)-amino-3″-phenylpropanoyl]amino}-3′-phenylpropanoyl)-4-benzyloxazolidin-2-one 53



A solution of **52** (1.11 g, 3.42 mmol) in THF (5 mL) at 0 °C was treated with *N*-Boc L-phenylalanine (907 mg, 3.42 mmol) and DCC (705 mg, 3.42 mmol). After 3 h, the reaction mixture was filtered and concentrated in vacuo. Purification via flash column chromatography (silica, eluent hexane/EtOAc, 4:1) gave **53** as a white solid (1.61 g, 82%); $C_{33}H_{37}N_3O_6$ requires C, 69.3; H, 6.5; N, 7.35; found C, 69.5; H, 6.6; N, 7.1; mp 200–202 °C (EtOAc/Et_2O); $[\alpha]_D^{21} = +58.2$ (*c* 1.6, $CHCl_3$); ν_{max} (KBr) 3365 (N–H), 1790, 1694, 1661 (C=O); δ_H (500 MHz, $CDCl_3$) 1.42 (9H, s, C*Me*$_3$), 2.62 (1H, dd, *J* 13.6, 9.7, C(4)C*H*$_A$H$_B$Ph), 3.03 (1H, dd, *J* 13.6, 7.7, C(4)CH$_A$*H*$_B$Ph), 3.12–3.15 (2H, m, C(2′)*H*$_A$, C(3″)*H*$_A$), 3.25–3.28 (1H, m, C(2′)*H*$_B$), 3.52 (1H, dd, *J* 16.4, 6.5, C(3″)*H*$_B$), 4.07–4.11 (2H,

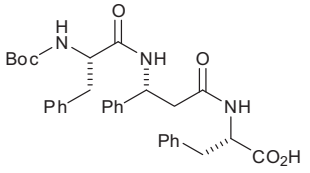
m, C(5)H_2), 4.38 (1H, app br s, C(2″)*H*), 4.52–4.56 (1H, m, C(4)*H*), 5.05 (1H, br s, N*H*), 5.50 (1H, dd, *J* 14.4, 6.3, C(3′)*H*), 6.76 (1H, br s, N*H*), 7.10–7.11 (2H, m, *Ph*), 7.10–7.11 (13H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 28.2, 37.5, 38.4, 40.7, 49.7, 54.9, 55.8, 66.1, 80.1, 126.4, 126.9, 127.3, 127.6, 128.6, 128.7, 128.9, 129.3, 129.4, 135.0, 136.8, 140.3, 153.3, 155.4, 170.2, 170.3; *m*/*z* (CI^+) 572 ($[M+H]^+$, 100%).

4.27. (*S*)-*N*-1′-Hydroxy-3′-phenylpropan-2′-yl (3*R*,2″*S*)-3-{*N*′-[2″-*N*″-(*tert*-butoxycarbonyl)amino-3″-phenylpropanoyl]amino}-3-phenylpropanamide 54



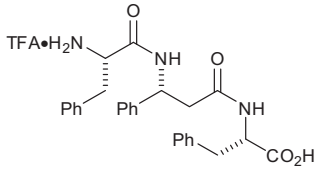
A solution of **53** (1.00 g, 1.75 mmol) in THF/H_2O (v:v 1:1, 12 mL) was treated with LiOH (350 mg, 8.45 mmol) and heated at 60 °C for 5 h. The reaction mixture was concentrated in vacuo and the residue was neutralised by the dropwise addition of 5% aq citric acid. The resultant precipitate was filtered and washed sequentially with cold water (10 mL) and CH_2Cl_2 (10 mL). Purification via flash column chromatography (silica, eluent CH_2Cl_2/MeOH, 9:1) gave **54** as a white solid (506 mg, 53%); mp 202–204 °C; $[\alpha]_D^{21} = -19.1$ (*c* 0.6, DMF); ν_{max} (film) 3309 (N–H, O–H), 1688, 1658 (C=O); δ_H (500 MHz, DMSO-d_6) 1.29 (9H, s), 2.48–2.52 (2H, m), 2.55 (1H, dd, *J* 13.8, 7.8), 2.73–2.78 (2H, m), 2.94 (1H, dd, *J* 13.8, 4.4), 3.17–3.29 (2H, m), 3.82–3.86 (1H, m), 4.16–4.19 (1H, m), 4.73 (1H, br s), 5.17 (1H, dd, *J* 13.1, 6.7), 6.94 (1H, d, *J* 8.6), 7.11–7.29 (15H, m), 7.77 (1H, d, *J* 8.2), 8.43 (1H, d, *J* 8.2); δ_C (125 MHz, DMSO-d_6) 28.3, 36.5, 37.5, 42.1, 49.9, 52.4, 56.0, 62.3, 78.2, 126.0, 126.3, 126.5, 126.8, 128.2, 128.3, 129.2, 138.5, 139.2, 142.6, 155.4, 169.3, 170.9; *m*/*z* (CI^+) 546 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{32}H_{39}N_3NaO_5^+$ ($[M+Na]^+$) requires 568.2782; found 568.2791.

4.28. Boc-[(*S*)-Phe-(*R*)-β-Phe-(*S*)-Phe]-OH 55



Jones reagent (2.2 M, 0.15 mL) was diluted with acetone (2 mL) and added dropwise to a solution of **54** (100 mg, 0.18 mmol) in acetone (10 mL) at 0 °C. After 3 h at 0 °C the reaction mixture changed colour from orange to green; IPA (0.50 mL) was then added, and the reaction mixture was stirred for a further 30 min. The reaction mixture was evaporated in vacuo, and the resultant green solid was dissolved in H_2O (10 mL). The solution was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were concentrated in vacuo. The residue was filtered over Sephadex LH 20® gel, washing with EtOAc/MeOH/H_2O (v:v:v 8:2:1) to remove any traces of chromium. Purification via flash column chromatography (silica, eluent PhMe/MeOH/AcOH, 5:1:1) gave **55** as a white solid (85 mg, 84%); mp 193–194 °C; $[\alpha]_D^{23} = +13.8$ (*c* 0.5, DMF); ν_{max} (KBr) 3329 (N–H, O–H), 1687, 1655 (C=O); δ_H (500 MHz, DMSO-d_6) 1.29 (9H, s), 2.49 (1H, dd, *J* 14.6, 6.8), 2.56 (1H, dd, *J* 14.6, 7.2), 2.74 (1H, dd, *J* 13.8, 10.2), 2.82 (1H, dd, *J* 13.8, 8.4), 2.91–3.34 (2H, m), 4.13–4.17 (1H, m), 4.37–4.41 (1H, m), 5.14–5.19 (1H, m), 6.96 (1H, d, *J* 8.5), 7.08–7.09 (2H, m), 7.16–7.28 (13H, m), 8.24 (1H, d, *J* 7.4), 8.41 (1H, d, *J* 8.3); δ_C (125 MHz, DMSO-d_6) 28.3, 37.0, 37.4, 41.7, 49.7, 53.5, 56.0, 78.2, 126.2, 126.3, 126.7, 126.9, 128.2, 128.3, 128.4, 129.2, 129.4, 137.6, 138.5, 142.5, 155.4, 169.6, 170.9, 172.9; *m*/*z* (CI^+) 560 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{32}H_{38}N_3O_6^+$ ($[M+H]^+$) requires 560.2755; found 560.2767.

4.29. H-[(*S*)-Phe-(*R*)-β-Phe-(*S*)-Phe]-OH trifluoroacetic acid salt 56



A solution of **55** (100 mg, 0.18 mmol) in CH_2Cl_2 (3 mL) was treated with TFA (3 mL). After 2 h the reaction mixture was concentrated in vacuo. Purification via flash column chromatography (RP-18 gel, gradient elution, H_2O (0.1% TFA); increased to H_2O (0.1% TFA)/MeOH, 1:1) gave **56** as a white foam (71 mg, 68%); $[\alpha]_D^{23} = +48.8$ (*c* 0.9, DMF); ν_{max} (KBr) 3411, 3302 (O–H, N–H), 1670 (C=O); δ_H (500 MHz, DMSO-d_6) 2.39 (1H, dd, *J* 14.7, 6.8), 2.56 (1H, dd, *J* 14.7, 8.0), 2.80 (1H, dd, *J* 13.9, 8.3), 2.91 (1H, dd, *J* 13.9, 5.3), 2.96 (1H, dd, *J* 13.9, 7.7), 3.07 (1H, dd, *J* 13.9, 6.3), 4.00 (1H, br s), 4.37–4.41 (1H, m), 5.16–5.23 (1H, m), 7.03–7.07 (2H, m), 7.17–7.36 (13H, m), 8.14 (3H, br s), 8.28 (1H, d, *J* 7.9), 8.87 (1H, d, *J* 8.4); δ_C (125 MHz, DMSO-d_6) 35.1, 35.2, 39.6, 48.3, 51.7, 51.9, 124.8, 125.2, 125.6, 126.6, 126.7, 127.0, 127.4, 128.0, 133.4, 135.7, 140.0, 156.4, 165.4, 167.3, 171.2; *m*/*z* (CI^+) 460 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{30}N_3O_4^+$ ($[M+H]^+$) requires 460.2231; found 460.2246.

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