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Conjugate addition of lithium *N*-*tert*-butyldimethylsilyloxy-*N*-(α-methylbenzyl)-amide: asymmetric synthesis of $\beta^{2,2,3}$-trisubstituted amino acids

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ABSTRACT

Conjugate addition of the homochiral ammonia equivalent lithium *N*-*tert*-butyldimethylsilyloxy-*N*-(α-methylbenzyl)amide to a range of α,β-unsaturated esters gives the corresponding β-amino esters in moderate to good levels of diastereoselectivity. O-Desilylation and cyclisation furnishes homochiral isoxazolidin-5-ones in >99:1 dr after purification. Sequential alkylation of these templates proceeds to give the corresponding 3,4-*anti*-disubstituted and 3,4,4-trisubstituted derivatives as single diastereoisomers after purification. The first alkylation occurs with high levels of diastereoselectivity on the face of the enolate *anti* to the *C*(3)-substituent, whereas the facial selectivity of the second alkylation is governed by a chiral relay effect, which depends upon the relative steric bulk of both the *C*(3)- and *C*(4)-substituents. Subsequent hydrogenolysis promotes cleavage of both the *N*-α-methylbenzyl group and the N–O bond within the isoxazolidin-5-one ring in one pot to give the corresponding $\beta^{2,2,3}$-trisubstituted amino acids directly.

1. Introduction

Isoxazolidin-5-ones are popular synthetic targets due to their desirable biological activity[1] and their utility as homochiral building blocks,[2] for instance in the synthesis of β-amino acids and β- and γ-lactams.[3] Several methods for the synthesis of isoxazolidin-5-ones have been reported, with 1,3-dipolar cycloaddition of a nitrone,[3,4] and conjugate addition of a hydroxylamine to an α,β-unsaturated ester followed by cyclisation[5] representing the most common synthetic strategies. For instance, Sibi et al. employed a chiral Lewis-acid mediated amine conjugate addition protocol for the synthesis of a range of isoxazolidin-5-ones,[5c] whilst Saito et al. utilised the doubly diastereoselective 'thermal' addition of homochiral *N*-α-methylbenzylhydroxylamine **1** to homochiral esters **2** and **3** (derived from L-tartaric acid) to facilitate the synthesis of isoxazolidin-5-ones **6** and **7**.[5a] The elaboration of these templates to the C(4)-mono- and C(4)-disubstituted derivatives **8**–**10** through sequential enolate alkylation reactions was also disclosed, although these reactions failed to proceed to conversion and the reported 59–79% yields 'were corrected for recovered starting material'. The relative stereochemistries within **8**–**10** were assigned on the assumption that the alkylation reactions of the intermediate enolates occur on the face *anti* to the C(3)-stereodirecting group in all cases[5a] (Fig. 1).

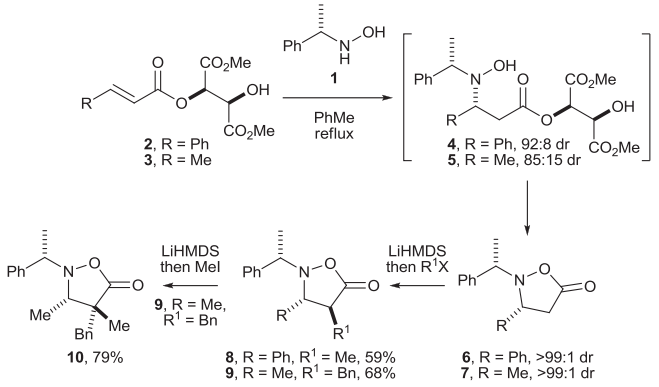

Figure 1. Preparation of isoxazolidin-5-ones **6**–**10** employing the doubly diastereoselective 'thermal' addition of homochiral *N*-α-methylbenzylhydroxylamine **1** to homochiral esters **2** and **3**.

Previous investigations from this laboratory have demonstrated that the conjugate addition of homochiral secondary lithium amides (derived from α-methylbenzylamine) to α,β-unsaturated esters represents a general and efficient synthetic protocol for the synthesis of β-amino esters and their derivatives.[6] This methodology has found numerous applications, including the total synthesis of natural products,[7] molecular recognition phenomena[8] and

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resolution protocols,[9] and has been reviewed.[10] Although the conjugate addition of lithium dialkylamides to α,β-unsaturated carbonyl compounds has been investigated extensively,[10] there is only one report into the analogous reaction employing a lithium *N*-alkoxy-*N*-(α-methylbenzyl)amide: Bew et al. investigated the conjugate addition of lithium (*S*)-*N*-(*tert*-butoxycarbonyloxy)-*N*-(α-methylbenzyl)amide to *tert*-butyl acrylate but did not observe any products of conjugate addition.[11] We wished to extend further our conjugate addition methodology to encompass lithium *N*-alkoxy-*N*-(α-methylbenzyl)amides **12** as we envisaged that the resultant β-*N*-alkoxyamino products **13** would be amenable to selective cleavage of the O–X bond with concomitant cyclisation to generate a range of isoxazolidin-5-ones **14**, which could then be exploited for highly diastereoselective, tandem alkylation reactions, giving 3,4,4-trisubstituted derivatives **15** (Fig. 2). We anticipated that the use of a robust *O*-protecting group would suppress any potential *O*- to *N*-rearrangement, thus promoting the conjugate addition reaction, and we delineate herein our investigations within this area.

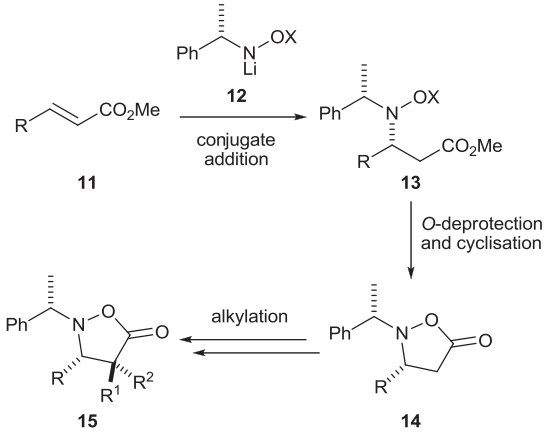
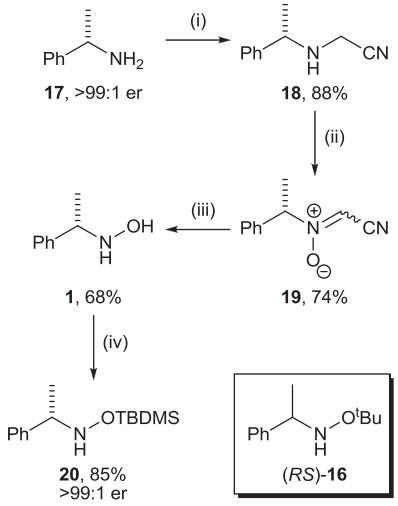


Figure 2. Synthesis and alkylation of isoxazolidin-5-ones **14** utilising conjugate addition of a homochiral lithium *N*-alkoxy-*N*-(α-methylbenzyl)amide **12**. X=Protecting group.

2. Results and discussion

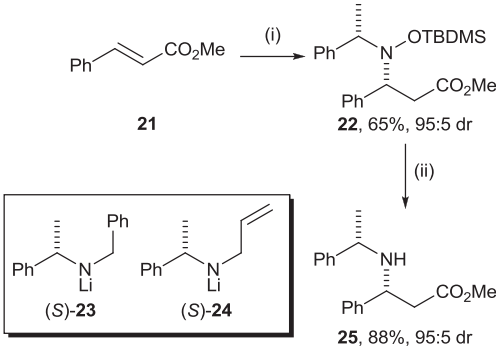
The conjugate addition of *O*-*tert*-butyl protected hydroxylamine **16**[12] to both *tert*-butyl and methyl cinnamate was initially investigated but returned only starting material under a range of conditions. *O*-Silyl protected hydroxylamine **20** was prepared from (*S*)-α-methylbenzylamine **17** in four steps following literature procedures.[12a,13] Alkylation of **17** with bromoacetonitrile gave **18**, which was oxidised with *m*CPBA to give nitrone **19**. Hydroxylaminolysis afforded (*S*)-*N*-(α-methylbenzyl)hydroxylamine **1** in 44% overall yield. Treatment of **1** with TBDMSCl furnished **20** in 85% yield and >99:1 er[14] (Scheme 1).

Treatment of **20** with BuLi in THF at −78 °C followed by addition of *tert*-butyl cinnamate returned only starting material under a range of conditions, although reaction with methyl cinnamate **21** under optimized conditions gave β-*N*-silyloxyamino ester **22** as the sole product in 95:5 dr. Attempted purification of the crude reaction mixture on silica led to substantial mass loss, giving **22** in only 40% isolated yield; chromatography on basic alumina, however, allowed the isolation of **22** in 65% yield and 95:5 dr. The ^{1}H NMR spectrum of **22** exhibited line broadening when the spectrum was recorded in a range of solvents. A range of hydroxylamines have been shown to exhibit this behaviour, which is attributable to either slow rotation about the N–O bond, or slow inversion at the nitrogen atom.[15] Heating the sample to 373 K in PhMe-d_8 provided a much sharper spectrum, although cooling to 213 K failed to effect



Scheme 1. Reagents and conditions: (i) $BrCH_2CN$, $^iPr_2NEt$, MeCN, rt, 16 h; (ii) *m*CPBA, CH_2Cl_2, 0 °C, 45 min, then rt, 15 min; (iii) NH_2OH, MeOH, 60 °C, 2 h; (iv) TBDMSCl, imidazole, DMF, rt, 16 h.

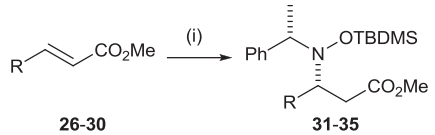
resolution into sharp distinct sets of peaks and therefore the origin of the broadness (restricted rotation about the N–O bond or slow inversion at nitrogen) in this system could not be determined. The absolute (3*R*,α*S*)-configuration within **22** was initially assigned by reference to our transition state mnemonic[16] to rationalize the high facial selectivity exerted by lithium *N*-benzyl-*N*-(α-methylbenzyl) amide **23**[10] and lithium *N*-allyl-*N*-(α-methylbenzyl)amide **24**[17] in their conjugate addition reactions. In confirmation of this assignment, treatment of **22** with Zn in AcOH gave the known *N*-α-methylbenzyl protected β-amino ester **25**[18] in 88% yield and 95:5 dr (Scheme 2).



Scheme 2. Reagents and conditions: (i) lithium (*S*)-*N*-*tert*-butyldimethylsilyloxy-*N*-(α-methylbenzyl)amide **36** (0.1 M in THF), −78 °C, 10 h; (iii) Zn, AcOH, •))), rt, 60 h.

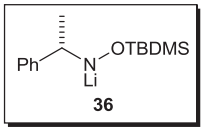
In order to explore the generality of this methodology, the conjugate addition of lithium (*S*)-*N*-*tert*-butyldimethylsilyloxy-*N*-(α-methylbenzyl)amide **36** to a range of α,β-unsaturated esters **26**–**30** was investigated, and proceeded with modest to good levels of diastereoselectivity. β-(*N*-Silyloxy)amino esters **31**–**35** proved somewhat unstable to purification on alumina and were isolated in modest yields. In each case, the absolute configuration within the major diastereoisomeric product of the conjugate addition reaction was assigned by reference to the transition state mnemonic for this class of lithium amides[16] (Scheme 3).

With a range of *N*-silyloxyamino esters **22** and **31**–**35** in hand, their conversion to the corresponding isoxazolidin-5-ones was investigated. Initial studies employing excess TBAF at rt to promote the desilylation and concomitant cyclisation of **22** proved unsuccessful, affording a complex mixture of products, with no starting material or isoxazolidin-5-one observed by ^{1}H NMR



26-30 31-35

	R	Product	dr [a]	Yield %
26	*p*-C_6H_4OMe	31	86:14	45
27	*p*-C_6H_4CN	32	88:12	46
28	Me	33	75:25	43
29	C_7H_{15}	34	78:22	29
30	^{i}Pr	35	>95:5	33



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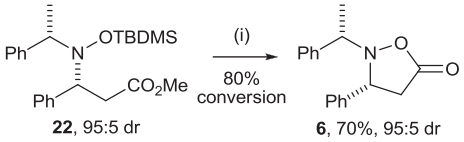
Scheme 3. Reagents and conditions: (i) lithium (*S*)-*N*-*tert*-butyldimethylsilyloxy-*N*-(α-methylbenzyl)amide **36** (0.1 M in THF), −78 °C, 10 h. [[a]Diastereoisomeric ratio refers to both crude reaction mixture and isolated product].

spectroscopic analysis. Upon treatment of **22** with 1.1 equiv of TBAF, however, 80% conversion to isoxazolidin-5-one **6** (95:5 dr) was observed. Purification allowed the isolation of **6** in 70% yield and 95:5 dr (Scheme 4).

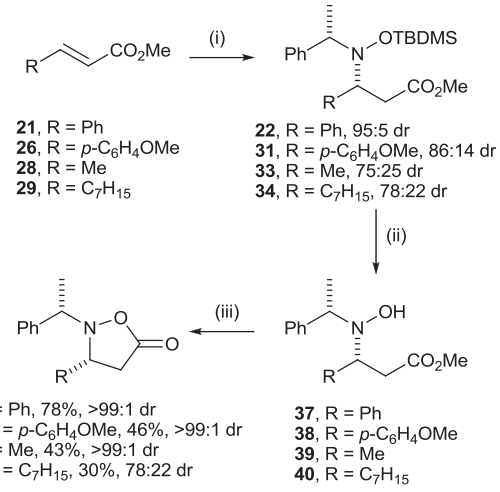


22, 95:5 dr **6**, 70%, 95:5 dr

Scheme 4. Reagents and conditions: (i) TBAF, THF, rt, 12 h.

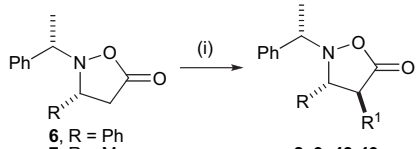
In order to obviate the difficulties associated with the purification of β-*N*-silyloxyamino ester **22**, direct cyclisation of the crude reaction product was next investigated. Unfortunately, conjugate addition of lithium (*S*)-*N*-*tert*-butyldimethylsilyloxy-*N*-(α-methylbenzyl)amide **36** to methyl cinnamate **21** followed by treatment of the crude reaction product with TBAF (1.1 equiv) gave a complex mixture of products. In light of this result, a range of conditions were screened for their efficacy in promoting the desilylation/cyclisation reaction sequence and although treatment with TBAF/AcOH,[19] TMSOTf,[20] LiCl/H_2O/DMF[21] and PPTS/EtOH[22] gave no trace of the desired isoxazolidin-5-one **6** in each case,[23] it was found that treatment of the crude reaction product **22** with HF·pyridine followed by LiHMDS afforded isoxazolidin-5-one **6** in 95:5 dr, and in 78% yield (over three steps from **21**) and >99:1 dr after chromatographic purification. Application of this sequential conjugate addition and cyclisation reaction sequence to α,β-unsaturated esters **26**, **28** and **29** (as representative examples) gave the corresponding isoxazolidin-5-ones **41**, **7** and **42** in modest yields over the three steps, and in >99:1 dr after purification, except for **42**, which was isolated as a 78:22 diastereoisomeric mixture (Scheme 5).

Studies were next directed towards the investigation of the alkylation reactions of isoxazolidin-5-ones **6** and **7**. Saito et al. have previously shown that treatment of diastereoisomerically pure isoxazolidin-5-one **6** with LiHMDS followed by MeI affords exclusively the *anti*-product **8** in 59% yield.[5a] Application of this protocol to ethylation of **6** gave predominantly the desired *anti*-product **45**, but was accompanied by the formation of ~10% of the dialkylated product **50**, which presumably arises through deprotonation of the product isoxazolidin-5-one by the excess base followed by further alkylation. In order to suppress this side reaction, use of the hindered base LiTMP was investigated.[24] Under these conditions, exclusive mono-alkylation of **6** was observed upon treatment with a range of electrophiles, giving the corresponding C(4)-substituted isoxazolidin-5-ones **8** and **43**–**46** as single diastereoisomers



Scheme 5. Reagents and conditions: (i) lithium (*S*)-*N*-*tert*-butyldimethylsilyloxy-*N*-(α-methylbenzyl)amide **36** (0.1 M in THF), −78 °C, 10 h ; (ii) HF·pyridine, THF, 0 °C, 20 min; (iii) LiHMDS, THF, −78 °C, 30 min.

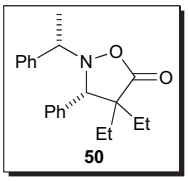
(>99:1 dr). Purification via flash column chromatography gave **8** and **43**–**46** in good isolated yield and >99:1 dr in each case. A further series of alkylations applied to isoxazolidin-5-one **7** gave alkylated products **9** and **47**–**49** in modest to good diastereoselectivity (Scheme 6). The relative configuration within **9** was unambiguously established via single crystal X-ray analysis, with the absolute (*S*,*S*,*S*)-configuration being assigned from the known configuration of the (*S*)-stereocentre within the α-methylbenzyl fragment (Fig. 3). This stereochemical outcome is consistent with the alkylation proceeding on the face of the enolate opposite to the C(3)-stereodirecting group. The relative and absolute configurations within **8** and **43**–**49** were assigned by analogy to that unambiguously proven for **9** (Scheme 6).



6, R = Ph
7, R = Me

8, **9**, **43**-**49**

	R	R^1X	product	dr [a]	yield %
6	Ph	MeI	8	>99:1	71
6	Ph	BnBr	43	>99:1	75
6	Ph	allyl iodide	44	>99:1	82
6	Ph	EtI	45	>99:1	75
6	Ph	$BrCH_2CO_2{}^tBu$	46	>99:1	81
7	Me	MeI	47	70:30	71
7	Me	BnBr	9	>99:1	70
7	Me	allyl iodide	48	92:8	64
7	Me	EtI	49	69:31	60



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Scheme 6. Reagents and conditions: (i) LiTMP (1.2 equiv), THF, −78 °C, 30 min, then R^1X (3 equiv), −78 °C to rt, 12 h. [[a]Diastereoisomeric ratio refers to both crude reaction mixture and isolated product].

The preparation of 3,4,4-trisubstituted-isoxazolidin-5-ones was next investigated. Deprotonation of 3-phenyl-4-methyl-isoxazolidin-5-one **8** with LiHMDS followed by quenching with benzyl bromide gave **53** in >99:1 dr, and in 76% isolated yield after chromatography (Scheme 7). The relative configuration within **53** was unambiguously established by single crystal X-ray analysis, with

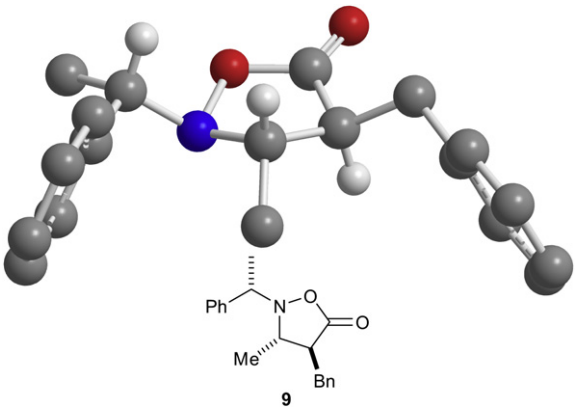
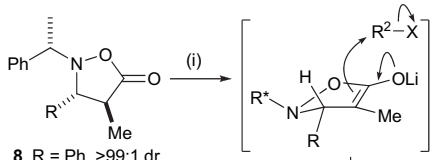


Figure 3. Chem3D representation of the single crystal X-ray structure of **9** (some H atoms omitted for clarity).



	R	R^2X	products	dr [a]	yield (dr) %[b]
8	Ph	CD_3I	**51**:**58**	68:32	48 (68:32)
8	Ph	allyl iodide	**52**:**59**	>99:1	74 (>99:1)
8	Ph	BnBr	**53**:**60**	>99:1	76 (>99:1)
47	Me	CD_3I	**54**:**61**	62:38	57 (62:38)
47	Me	allyl iodide	**55**:**62**	69:31	39 (>99:1)
47	Me	$H_2C{=}C(Me)CH_2Br$	**56**:**63**	97:3	56 (>99:1)
47	Me	BnBr	**57**:**64**	>99:1	88 (>99:1)

Scheme 7. Reagents and conditions: (i) LiHMDS (1.2 equiv), THF, −78 °C, 1 h, then R^2X (3 equiv), −78 °C to rt, 12 h. [R*=(*S*)-α-methylbenzyl; [a]crude; [b]isolated].

the absolute (*S*,*S*,*S*)-configuration being assigned from the known configuration of the (*S*)-stereocentre within the α-methylbenzyl fragment (Fig. 4). Allylation of **8** proceeded with similarly excellent levels of diastereoselectivity, furnishing **52** in 74% isolated yield and >99:1 dr. Meanwhile, alkylation with CD_3I gave a 68:32 mixture of the diastereoisomeric isoxazolidin-5-ones **51** and **58**, respectively, which were inseparable by chromatography. The configurations within **51** and **52** were assigned by analogy to that unambiguously proven for **53**, and in the case of **52** this assignment was supported by ^{1}H NMR NOE analysis.[25] These results are consistent with benzylation and allylation of the intermediate lithium enolate occurring exclusively on the sterically more accessible face, *anti* to the C(3)-phenyl group. In the case of alkylation with CD_3I, steric interactions between the C(3)-phenyl group and the electrophile are smaller, which is manifest in a concomitant decrease in the diastereoselectivity of the reaction. In order to probe this phenomenon further, alkylation of **47** (bearing a relatively small C(3)-methyl group) was investigated. Here, a trend towards increasing alkylation diastereoselectivity with increasing steric demand of the electrophile was noted, with benzylation of **47** (a 70:30 mixture of C(4)-epimers) resulting in the production of a single diastereoisomer **57**, thus confirming that the alkylation reaction is

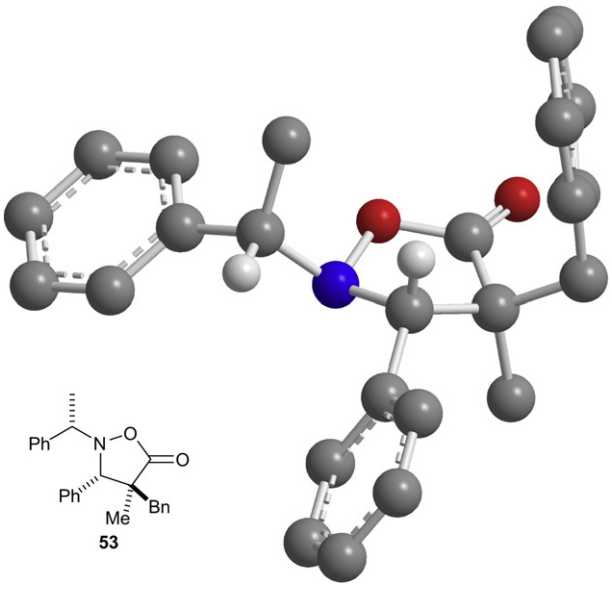


Figure 4. Chem3D representation of the single crystal X-ray structure of **53** (some H atoms omitted for clarity).

a stereoselective rather than stereospecific process, as expected. In each case (with the exception of **54** and **61**, resulting from alkylation with CD_3I) purification of the crude reaction mixtures gave diastereoisomerically pure (>99:1 dr) samples of the major diastereoisomers from the alkylation reactions (Scheme 7). The relative configuration within **57** was unambiguously established by single crystal X-ray analysis, with the absolute (*S*,*S*,*S*)-configuration being assigned from the known configuration of the (*S*)-stereocentre within the α-methylbenzyl fragment (Fig. 5). The C(3)–C(4) relative configurations within **55** and **56** were assigned by analogy to that proven for **57**; in each case this assignment was supported by ^{1}H NMR NOE analysis. These results are again consistent with the alkylation reaction occurring preferentially on the face of the intermediate enolate opposite to the C(3)-methyl group, albeit with reduced levels of diastereoselectivity as compared to the analogous alkylation reactions of **8**, bearing a C(3)-phenyl group (Scheme 7).

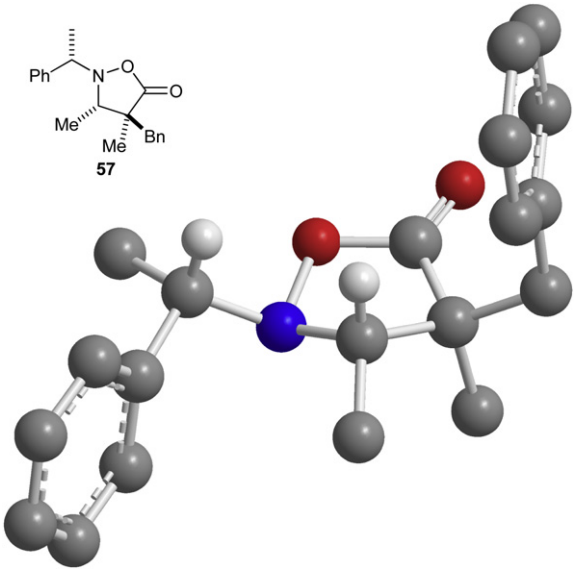
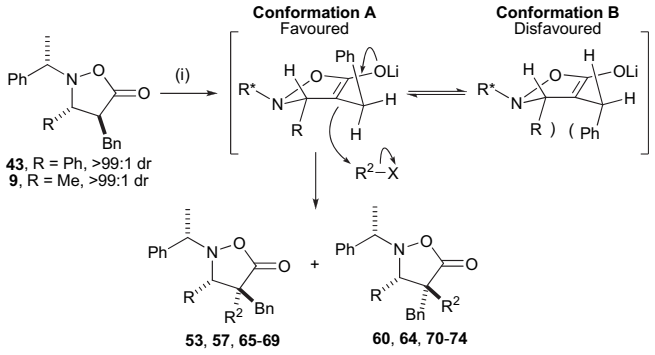


Figure 5. Chem3D representation of the single crystal X-ray structure of **57** (some H atoms omitted for clarity).

Saito et al. have previously reported that alkylation of the lithium anion of isoxazolidin-5-one **9** with methyl iodide gives (3*S*,4*R*,α*S*)-**10** exclusively. However, all the data reported for (3*S*,4*R*,α*S*)-**10** matches that obtained by us for (*S*,*S*,*S*)-**57**, suggesting that the stereochemical assignment of Saito et al. is in error.[5a] Furthermore, these observations imply that the facial selectivity of alkylation of the C(4)-benzyl substituted isoxazolidin-5-one **9** may not be ascribed simply to preferential reaction of the intermediate enolate on the face *anti* to the C(3)-stereodirecting group. In order to investigate this apparent discrepancy, the alkylations of 4-benzyl-isoxazolidin-5-ones **9** and **43** were examined. Methylation of 3-phenyl-4-benzyl-isoxazolidin-5-one **43** gave **53**:**60** in 97:3 dr, i.e., the *same* major diastereoisomeric product as benzylation of 3-phenyl-4-methyl-isoxazolidin-5-one **8**: in the former reaction methylation of **43** occurs preferentially *syn* to the C(3)-phenyl group, whereas in the latter reaction benzylation of **8** occurs preferentially on the face *anti* to the C(3)-phenyl group. A further series of alkylation reactions applied to both **9** and **43** gave the dialkylated products **57** and **64**–**74**, thus establishing that with increasing steric demand of the electrophile, the diastereoselectivity of the alkylation reaction decreased (Scheme 8). The relative configuration within **65** was unambiguously established via single crystal X-ray analysis, with the absolute (*S*,*S*,*S*)-configuration being assigned



	R	R^2X	products	dr %[a]	yield (dr) %[b]
43	Ph	MeI	**53**:**60**	97:3	72 (>99:1)
43	Ph	allyl iodide	**65**:**70**	73:27	54 (>99:1)
43	Ph	$H_2C{=}C(Me)CH_2Br$	**66**:**71**	56:44	30 (>99:1)
43	Ph	$ArCH_2Br$	**67**:**72**	54:46	65 (54:46)
9	Me	MeI	**57**:**64**	>99:1	83 (>99:1)
9	Me	allyl iodide	**68**:**73**	90:10	78 (>99:1)
9	Me	$ArCH_2Br$	**69**:**74**	61:39	18 (61:39)

Scheme 8. Reagents and conditions: (i) LiHMDS (1.2 equiv), THF, −78 °C, 1 h, then R^2X (3 equiv), −78 °C to rt, 12 h. [Ar=*p*-bromophenyl. R*=(*S*)-α-methylbenzyl; [a]crude; [b]isolated].

from the known configuration of the (*S*)-stereocentre within the α-methylbenzyl fragment, confirming that the alkylation reaction occurs preferentially on the face *syn* to the C(4)-phenyl group (Fig. 6). The stereochemical outcome resulting from the remaining alkylation reactions were assigned via ^{1}H NMR NOE analysis. Notably, methylation of **9** gave **57** as the only product, i.e., the *same* major diastereoisomeric product as benzylation of 3,4-dimethyl-isoxazolidin-5-one **47**. As predicted, therefore, these results clearly demonstrate that the selectivity of alkylation of the C(4)-benzyl substituted isoxazolidin-5-ones **9** and **43** is not simply a result of preferential reaction of the intermediate enolate on the face *anti* to the *C*(3)-substituent, but is dependent on the steric bulk of both the *C*(3)- and *C*(4)-substituents (Scheme 8). A similar phenomenon has been noted during the alkylation reactions of some lactone enolates,[26] and these observations may be rationalized by invoking a chiral relay effect.[27] In this scenario, it is expected that the lithium enolates derived from isoxazolidin-5-ones **9** and **43** adopt an envelope conformation within which the *C*(3)-substituent and the *N*-α-methylbenzyl group occupy pseudo-equatorial sites.

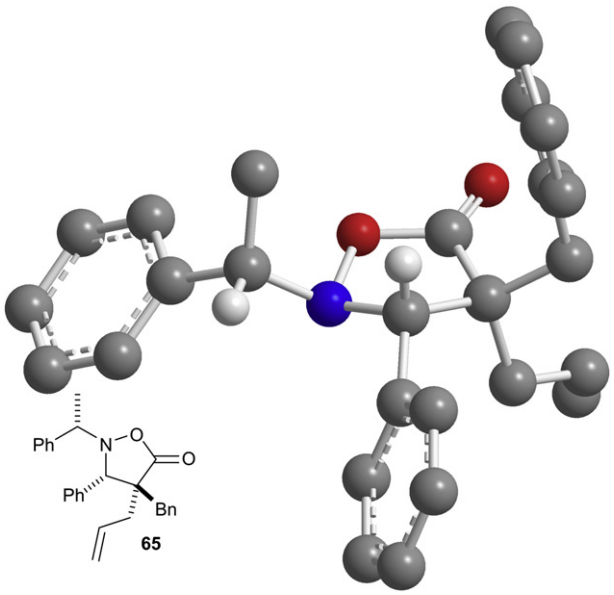
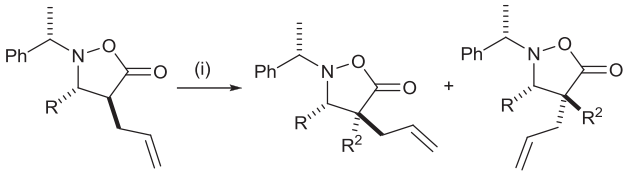


Figure 6. Chem3D representation of the single crystal X-ray structure of **65** (some H atoms omitted for clarity).

Minimization of A^{1,3} strain places one of the C(4)-benzylic hydrogen atoms *syn*-pentane to the enolate oxygen atom. The phenyl ring of the C(4)-benzyl group may then occupy one of two possible sites, with conformation **A** being expected to be favoured over conformation **B** due to minimization of steric repulsions with the *C*(3)-substituent. During alkylation of the lithium enolate derived from C(3)-methyl substituted **9**, the steric bulk of the phenyl ring of the C(4)-benzyl group is clearly dominant over that of the C(3)-methyl group, and therefore in all cases alkylation occurs preferentially through conformation **A**, on the face *syn* to the pseudo-equatorial C(3)-methyl group, although a decrease in diastereoselectivity with increased bulk of the electrophile is noted. In the case of alkylation of the lithium enolate derived from C(3)-phenyl substituted **43**, the steric bulk of the phenyl ring of the C(4)-benzyl group dominates over that of the C(3)-phenyl group, potentially due to the location of the latter in a pseudo-equatorial position somewhat remote from the site of alkylation. Enolate alkylation then occurs preferentially through conformation **A** on the face *syn* to the C(3)-phenyl group although a more pronounced decrease in selectivity with increased bulk of the electrophile is observed relative to the C(3)-methyl series. In the case of alkylation of the C(4)-methyl substituted isoxazolidin-5-ones **8** and **47**, the methyl group is unable to protrude over either face of the enolate and therefore the reaction diastereoselectivity is controlled by the relative steric bulk of the *C*(3)-substituent (vide supra).

A further series of alkylation reactions using isoxazolidin-5-one templates **44**, **45**, **48** and **49** were also conducted, which gave mixtures of the corresponding diastereoisomeric products. In each case the C(3)–C(4) relative stereochemistry of the major diastereoisomer was established by ^{1}H NMR NOE analysis. These results again illustrate that the diastereoselectivity observed in the second alkylation reaction is a function of the relative steric bulk of both the *C*(3)- and *C*(4)-substituents (Schemes 9 and 10).

Having prepared a range of 3,4,4-trisubstituted-isoxazolidin-5-ones, their conversion to the corresponding β^{2,2,3}-trisubstituted amino acids was investigated. Attempted hydrogenolysis of **53** using Pearlman's catalyst in EtOH gave a 59:41 mixture of β-amino acid **87** and β-amino ester **88**, indicating that competitive ring-opening of the isoxazolidin-5-one ring by the solvent, followed by hydrogenolysis, had occurred (Scheme 11). It was envisaged that replacing EtOH with a kinetically less nucleophilic alcohol as the solvent would prevent the formation of this unwanted side-

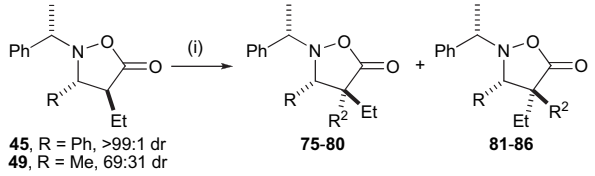


44, R = Ph, >99:1 dr
48, R = Me, 92:8 dr

52, **55**, **70**, **73** **59**, **62**, **65**, **68**

	R	R^2X	products	dr %[a]	yield (dr) %[b]
44	Ph	MeI	**52**:**59**	60:40	38 (>99:1)
44	Ph	BnBr	**70**:**65**	11:89	71 (>99:1)
48	Me	MeI	**55**:**62**	>99:1	89 (>99:1)
48	Me	BnBr	**73**:**68**	33:67	47 (>99:1)

Scheme 9. Reagents and conditions: (i) LiHMDS (1.2 equiv), THF, −78 °C, 1 h, then R^2X (3 equiv), −78 °C to rt, 12 h. [[a]crude; [b]isolated].

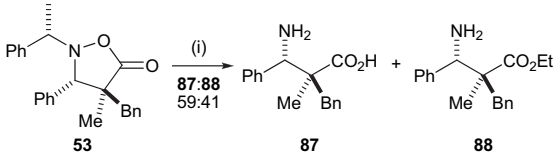


45, R = Ph, >99:1 dr
49, R = Me, 69:31 dr

75-80 **81-86**

	R	R^2X	products	dr %[a]	yield (dr) %[b]
45	Ph	MeI	**75**:**81**	42:58[c]	25 (>99:1)
45	Ph	allyl iodide	**76**:**82**	22:78	67 (93:7)
45	Ph	BnBr	**77**:**83**	21:79	55 (>99:1)
49	Me	MeI	**78**:**84**	64:36	38 (>99:1)
49	Me	allyl iodide	**79**:**85**	69:31	40 (92:8)
49	Me	BnBr	**80**:**86**	90:10	53 (90:10)

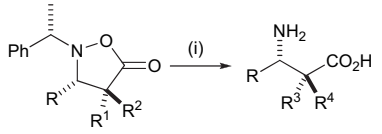
Scheme 10. Reagents and conditions: (i) LiHMDS (1.2 equiv), THF, −78 °C, 1 h, then R^2X (3 equiv), −78 °C to rt, 12 h. [[a]crude; [b]isolated; [c]reaction proceeded to 77% conversion].



53 **87** **88**

Scheme 11. Reagents and conditions: (i) H_2, $Pd(OH)_2$/C, EtOH, rt, 48 h.

product. Indeed, when the reaction was run in ^{t}BuOH, clean formation of **87** was noted. Ion-exchange chromatography gave **87** in 90% yield. Application to isoxazolidin-5-ones **52**, **57**, **65** and **67** gave the corresponding $\beta^{2,2,3}$-trisubstituted amino acids **89**–**92** in good yield and in >99:1 dr in all cases (Scheme 12).



52, **53**, **57**, **65**, **67** **87**, **89-92**

	R	R^1	R^2	product	R^3	R^4	yield %
53	Ph	Me	Bn	**87**	Me	Bn	90
65	Ph	allyl	Bn	**89**	C_3H_7	Bn	96
52	Ph	Me	allyl	**90**	Me	C_3H_7	78
57	Me	Me	Bn	**91**	Me	Bn	90
67	Me	allyl	Bn	**92**	C_3H_7	Bn	86

Scheme 12. Reagents and conditions: (i) H_2, $Pd(OH)_2$/C, ^{t}BuOH, 70 °C, 20 h. [All compounds were isolated diastereoisomerically pure (>99:1 dr)].

3. Conclusion

In conclusion, the conjugate addition of the homochiral ammonia equivalent lithium *N*-*tert*-butyldimethylsilyloxy-*N*-(α-methylbenzyl) amide to a range of α,β-unsaturated esters gives the corresponding β-amino esters in moderate to excellent levels of diastereoselectivity. O-Desilylation and subsequent cyclisation furnishes homochiral isoxazolidin-5-ones in >99:1 dr after purification. Alkylation of these isoxazolidin-5-one templates proceeds to give the corresponding 3,4-*anti*-disubstituted and 3,4,4-trisubstituted derivatives as single diastereoisomers after purification. The first alkylation occurs with high levels of diastereoselectivity on the face of the enolate *anti* to the *C*(3)-substituent, whereas the facial selectivity of the second alkylation is governed by a chiral relay effect, which depends upon the relative steric bulk of both the *C*(3)- and *C*(4)-substituents. Subsequent hydrogenolysis promotes cleavage of both the *N*-α-methylbenzyl group and the N–O bond within the isoxazolidin-5-one ring in one pot to give the corresponding $\beta^{2,2,3}$-trisubstituted amino acids directly.

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 et al.[28] Other solvents and reagents 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 on a glass column, or on a Biotage SP4 automated flash column chromatography platform.

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 as either a thin film on NaCl plates (film) or 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. Spectra were recorded at rt unless otherwise 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 m×0.25 mm) using amyl acetate as a lock mass.

4.2. General experimental procedures

4.2.1. General procedure 1: lithium amide conjugate addition. BuLi (solution in hexanes, 2 equiv) was added dropwise to a stirred solution of *N*-*tert*-butyldimethylsilyloxy-*N*-(α-methylbenzyl)amine **20** (2 equiv) in dry THF at −78 °C under N_2. After stirring for 30 min a solution of α,β-unsaturated ester (1 equiv) was added in dry THF via cannula. After stirring for a further 10 h at −78 °C the reaction mixture was quenched with satd aq NH_4Cl. After warming to rt over 15 min the mixture was extracted three times with Et_2O, then the organic phases were combined and washed with satd aq NaCl, before being dried and concentrated in vacuo to give the crude reaction mixture.

4.2.2. General procedure 2: isoxazolidin-5-one alkylation using LiTMP. Preparation of LiTMP: BuLi (solution in hexanes, 1 equiv) was

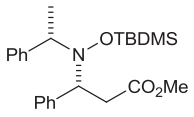
added to a stirred solution of 2,2,6,6-tetramethylpiperidine (1.1 equiv) in THF at −78 °C and left for 1 h.

Alkylation procedure: LiTMP (1.1 equiv) was added to a stirred solution of the requisite isoxazolidin-5-one (1 equiv) in THF at −78 °C and stirred for 2 h. The requisite alkyl halide (3 equiv) was then added and the reaction mixture allowed to slowly warm to rt over 16 h, after which time satd aq NH_4Cl was added and the two phases separated. The aqueous phase was then extracted three times with Et_2O, and the organic phases combined, washed with satd aq NaCl, dried and concentrated in vacuo to give the crude reaction mixture.

4.2.3. General procedure 3: isoxazolidin-5-one alkylation using LiHMDS. LiHMDS (1.2 equiv) was added to a stirred solution of the requisite isoxazolidin-5-one in THF at −78 °C and stirred for 2 h. The requisite alkyl halide (3 equiv) was then added and the reaction mixture allowed to slowly warm to rt over 16 h, after which time satd aq NH_4Cl was added and the two phases separated. The aqueous phase was then extracted three times with Et_2O, and the organic phases combined, washed with satd aq NaCl, dried and concentrated in vacuo to give the crude reaction mixture.

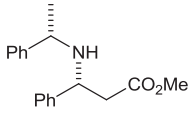
4.2.4. General procedure 4: hydrogenolysis of isoxazolidin-5-ones. Pearlman's catalyst (50% by weight) was added to a stirred, degassed solution of the requisite isoxazolidin-5-one in *tert*-butanol. The reaction mixture was then put under 1 atm of hydrogen, heated to 70 °C and stirred for 20 h. Water was added to the solution before filtering through Celite. The Celite was washed with warm water (~40 °C), then the combined water phases were washed with Et_2O, before being concentrated in vacuo to give the β-amino acid.

4.3. Methyl (3*R*,α*S*)-3-[*N*-*tert*-butyldimethylsilyloxy-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 22



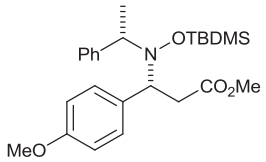
Following *general procedure* 1, BuLi (1.6 M in hexanes, 0.72 mL, 1.16 mmol), **20** (300 mg, 1.2 mmol) and **21** (121 mg, 0.75 mmol) in dry THF (15 mL) at −78 °C gave **22** in 95:5 dr. Purification via flash column chromatography (basic alumina, eluent 30–40 °C petrol/Et_2O, 80:1) gave **22** as a colourless oil (200 mg, 65%, 95:5 dr); $[\alpha]_D^{23}$ −9.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1745 (C=O); δ_H (500 MHz, PhMe-d_8, 373 K) −0.01 (3H, s, Si*Me*), 0.02 (3H, s, Si*Me*), 0.99 (9H, s, SiC*Me*$_3$), 1.28 (3H, d, *J* 6.8, C(α)*Me*), 2.67 (1H, dd, *J* 15.4, 9.5, C(2)H_A) 3.06 (1H, dd, *J* 15.4, 4.4, C(2)H_B), 3.26 (3H, s, O*Me*), 4.04 (1H, q, *J* 6.8, C(α)*H*), 4.72 (1H, dd, *J* 9.5, 4.4, C(3)*H*), 7.00–7.10 (4H, m, *Ph*), 7.15–7.18 (3H, m, *Ph*), 7.35–7.46 (3H, m, *Ph*); δ_C (125 MHz, PhMe-d_8) −4.1 (2×Si*Me*), 1.4 (SiCMe$_3$), 18.7 (C(α)*Me*), 26.7 (SiC*Me*$_3$), 36.0 (*C*(2)), 50.9 (O*Me*), 63.6 (*C*(α)), 65.7 (*C*(3)), 127.5, 127.8, 128.3, 128.4, 129.2, 137.3 (*o*-, *m*-, *p*-*Ph*), 141.1, 143.7 (*i*-*Ph*), 171.7 (*C*(1)); *m*/*z* (ESI$^+$) 414 ([M+H]$^+$, 100%), 310 (80%); HRMS (ESI$^+$) $C_{24}H_{35}NNaO_3Si^+$ ([M+Na]$^+$) requires 436.2278; found 436.2281.

4.4. Methyl (3*R*,α*S*)-3-(*N*-α-methylbenzylamino)-3-phenylpropanoate 25



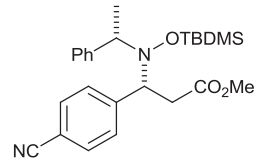
Zinc (500 mg, 7.5 mmol), was added to a stirred solution of **22** (50 mg, 0.12 mmol, 95:5 dr) in AcOH (2 mL) and the resultant mixture was sonicated for 60 h. The mixture was filtered and the remaining zinc was sonicated with EtOAc (3 mL) for a further 15 min before being filtered. The combined filtrates were washed with aq NaOH (2.0 M, 10 mL) and the aqueous layer was extracted with EtOAc (2×10 mL). The combined organic phases were washed with NaOH (2.0 M, 20 mL), dried and concentrated in vacuo to give **25** as a clear oil (30 mg, 88%, 95:5 dr);[18] $[\alpha]_D^{20}$ −16.3 (*c* 1.0 in $CHCl_3$); {lit.[18] $[\alpha]_D^{21}$ −14.9 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.40 (3H, d, *J* 6.5, C(α)*Me*), 1.95 (1H, br s, N*H*), 2.72 (1H, dd, *J* 15.4, 6.1, C(2)H_A), 2.80 (1H, dd, *J* 15.4, 7.5, C(2)H_B), 3.68 (3H, s, O*Me*), 3.72 (1H, q, *J* 6.5, C(α)*H*), 4.26 (1H, m, C(3)*H*), 7.25–7.39 (10H, m, *Ph*).

4.5. Methyl (3*R*,α*S*)-3-[*N*-*tert*-butyldimethylsilyloxy-*N*-(α-methylbenzyl)amino]-3-(*p*-methoxyphenyl)propanoate 31



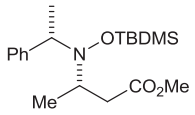
Following *general procedure* 1, BuLi (1.41 M in hexanes, 0.42 mL, 0.60 mmol), **20** (150 mg, 0.60 mmol) and **26** (58 mg, 0.30 mmol) in dry THF (8 mL) at −78 °C gave **31** in 86:14 dr. Purification via flash column chromatography (basic alumina, gradient elution, 30–40 °C petrol/Et_2O, 50:1; increased to 30–40 °C petrol/Et_2O, 20:1) gave **31** as a colourless oil (60 mg, 45%, 86:14 dr); ν_{max} (film) 1750 (C=O); δ_H (500 MHz, $CDCl_3$) −0.29 (3H, s, Si*Me*), −0.08 (3H, s, Si*Me*), 0.92 (9H, s, SiC*Me*$_3$), 1.29 (3H, d, *J* 6.5, C(α)*Me*), 2.45–2.65 (1H, m C(2)H_A), 2.94–3.03 (1H, m, C(2)H_B), 3.50 (3H, s, O*Me*), 3.81 (3H, s, O*Me*), 3.94 (1H, q, *J* 6.5, C(α)*H*), 4.40–4.48 (1H, m, C(3)*H*), 6.85 (2H, d, *J* 8.8, *Ar*), 7.13–7.34 (7H, m, *Ar*, *Ph*); δ_C (62.5 MHz, PhMe-d_8) −4.3 (Si*Me*), −4.2 (Si*Me*), −3.4 (SiCMe$_3$), 18.4 (C(α)*Me*), 26.4 (SiC*Me*$_3$), 37.2 (*C*(2)), 51.4 (O*Me*), 55.2 (O*Me*), 62.7 (*C*(α)), 64.4 (*C*(3)), 113.5, 127.1, 128.0, 128.5, 129.7 (*o*-, *m*-, *p*-*Ph*, *Ar*), 143.3, 146.8 (*i*-*Ph*, *Ar*), 172.5 (*C*(1)); *m*/*z* (ESI$^+$) 444 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{37}NNaO_4Si^+$ ([M+Na]$^+$) requires 466.2384; found 466.2392.

4.6. Methyl (3*R*,α*S*)-3-[*N*-*tert*-butyldimethylsilyloxy-*N*-(α-methylbenzyl)amino]-3-(*p*-cyanophenyl)propanoate 32



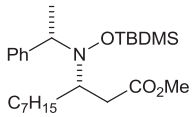
Following *general procedure* 1, BuLi (2.5 M in hexanes, 0.08 mL, 0.20 mmol), **20** (50 mg, 0.20 mmol) and **27** (18.7 mg, 0.10 mmol) in dry THF (3 mL) at −78 °C gave **32** in 88:12 dr. Purification via flash column chromatography (basic alumina, gradient elution, 30–40 °C petrol/Et_2O, 100:1; increased to 30–40 °C petrol/Et_2O, 40:1) gave **32** as a colourless oil (20 mg, 46%, 88:12 dr); ν_{max} (film) 2955 (C–H), 2230 (C≡N), 1740 (C=O); δ_H (250 MHz, PhMe-d_8, 363 K) −0.16 (3H, s, Si*Me*), 0.00 (3H, s, Si*Me*), 0.93 (9H, s, SiC*Me*$_3$), 1.18 (3H, d, *J* 6.7, C(α)*Me*), 2.48 (1H, dd, *J* 15.9, 9.5, C(2)H_A), 2.90 (1H, dd, *J* 15.9, 4.5, C(2)H_B), 3.23 (3H, s, O*Me*), 3.89 (1H, q, *J* 6.7, C(α)*H*), 4.54 (1H, dd, *J* 9.5, 4.5, C(3)*H*), 6.97–7.26 (9H, m, *Ph*); δ_C (62.5 MHz, PhMe-d_8) −4.1 (Si*Me*), −4.0 (Si*Me*), 1.2 (SiCMe$_3$), 18.0 (C(α)*Me*), 26.5 (SiC*Me*$_3$), 36.0 (*C*(2)), 50.8 (O*Me*), 64.9 (*C*(3), *C*(α)), 118.2 (*C*N), 127.8, 128.5, 128.6, 129.5, 131.7 (*o*-, *m*-, *p*-*Ph*, *Ar*), 142.8, 146.0 (*i*-*Ph*, *Ar*), 171.0 (*C*(1)); *m*/*z* (ESI$^+$) 439 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{34}N_2NaO_3Si^+$ ([M+Na]$^+$) requires 461.2231; found 461.2231.

4.7. Methyl (*S*,*S*)-3-[*N*-*tert*-butoxydimethylsilyloxy-*N*-(α-methylbenzyl)amino]butanoate 33



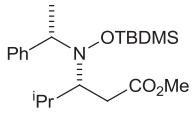
Following *general procedure* 1, BuLi (2.5 M in hexanes, 0.16 mL, 0.40 mmol), **20** (100 mg, 0.40 mmol) and **28** (20 mg, 0.20 mmol) in dry THF (5 mL) at −78 °C gave **33** in 75:25 dr. Purification via flash column chromatography (silica, gradient elution, 30–40 °C petrol/Et_2O, 100:1; increased to 30–40 °C petrol/Et_2O, 40:1) gave **33** as a colourless oil (30 mg, 43%, 75:25 dr); ν_{max} (film) 2955 (C–H), 1739 (C=O); δ_H (250 MHz, PhMe-d_8, 363 K) 0.11 (3H, s, Si*Me*), 0.14 (3H, s, Si*Me*), 0.89 (3H, d, *J* 6.7, C(4)H_3), 0.97 (9H, s, SiCMe_3), 1.36 (3H, d, *J* 6.7, C(α)*Me*), 2.19 (1H, dd, *J* 14.8, 8.2, C(2)H_A), 2.78 (1H, dd, *J* 14.8, 5.5, C(2)H_B), 3.37 (3H, s, O*Me*), 3.50–3.66 (1H, m, C(3)*H*), 3.92–4.02 (1H, m, C(α)*H*), 6.98–7.30 (5H, m, *Ph*); δ_C (62.5 MHz, PhMe-d_8, 363 K) −3.7 (SiMe_2), 1.2 (SiCMe$_3$), 18.6 (C(α)*Me*), 19.3 (*C*(4)), 26.6 (SiCMe_3), 39.1 (*C*(2)), 50.5 (O*Me*), 57.4 (*C*(3)), 64.8 (*C*(α)), 127.3, 128.5 (*o*-, *m*-, *p*-*Ph*), 144.2 (*i*-*Ph*), 171.9 (*C*(1)); *m*/*z* (ESI$^+$) 352 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{33}NNaO_3Si^+$ ([M+Na]$^+$) requires 374.2122; found 374.2122.

4.8. Methyl (*S*,*S*)-3-[*N*-*tert*-butoxydimethylsilyloxy-*N*-(α-methylbenzyl)amino]decanoate 34



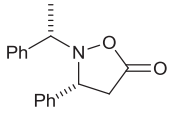
Following *general procedure* 1, BuLi (2.5 M in hexanes, 0.16 mL, 0.40 mmol), **20** (100 mg, 0.40 mmol) and **29** (33 mg, 0.20 mmol) in dry THF (5 mL) at −78 °C gave **34** in 78:22 dr. Purification via flash column chromatography (silica, gradient elution, 30–40 °C petrol/Et_2O, 100:1; increased to 30–40 °C petrol/Et_2O, 50:1) gave **34** as a colourless oil (25 mg, 29%, 78:22 dr); ν_{max} (film) 2960 (C–H), 1741 (C=O); δ_H (250 MHz, PhMe-d_8, 363 K) 0.02 (3H, s, Si*Me*), 0.10 (3H, s, Si*Me*), 0.83–0.89 (3H, m, C(10)H_3), 0.94 (9H, s, SiCMe_3), 1.16–1.26 (12H, m, C(4)H_2–C(9)H_2), 1.39 (3H, d, *J* 6.7, C(α)*Me*), 2.26 (1H, dd, *J* 15.2, 7.6, C(2)H_A), 2.92 (1H, dd, *J* 15.2, 4.9, C(2)H_B), 3.46 (3H, s, O*Me*), 3.90–3.97 (1H, m, C(3)*H*), 4.02–4.08 (1H, m, C(α)*H*), 6.85–7.17 (5H, m, *Ph*); δ_C (62.5 MHz, PhMe-d_8, 363 K) −5.2 (Si*Me*), −5.0 (Si*Me*), 1.5 (SiCMe$_3$) 14.4 (*C*(10)), 23.2, 26.7, 28.4, 29.6 (*C*(4)–*C*(9)), 18.3 (C(α)*Me*), 6.5 (SiCMe_3), 32.4 (*C*(2)), 50.8 (O*Me*), 58.2 (*C*(3)), 62.6 (*C*(α)), 127.7, 127.9, 128.5 (*o*-, *m*-, *p*-*Ph*), 142.4 (*i*-*Ph*), 173.1 (*C*(1)); *m*/*z* (ESI$^+$) 436 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{45}NNaO_3Si^+$ ([M+Na]$^+$) requires 458.3061; found 458.3062.

4.9. Methyl (3*R*,α*S*)-3-[*N*-*tert*-butoxydimethylsilyloxy-*N*-(α-methylbenzyl)amino]-4-methylbutanoate 35



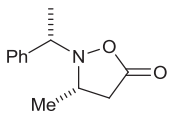
Following *general procedure* 1, BuLi (1.6 M in hexanes, 0.63 mL, 1.00 mmol), **20** (250 mg, 1.00 mmol) and **30** (64 mg, 0.50 mmol) in dry THF (15 mL) at −78 °C gave **35** in >95:5 dr. Purification via flash column chromatography (basic alumina, eluent 30–40 °C petrol/Et_2O, 40:1) gave **35** as a colourless oil (63 mg, 33%, >95:5 dr); $[\alpha]_D^{23}$ −8.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2957 (C–H), 1738 (C=O); δ_H (250 MHz, PhMe-d_8, 363 K) 0.07 (3H, s, Si*Me*), 0.12 (3H, s, Si*Me*), 0.75 (3H, d, *J* 6.6, C(4)Me_A), 0.85 (3H, d, *J* 6.6, C(4)Me_B), 0.94 (9H, s, SiCMe_3), 1.42 (3H, d, *J* 6.8, C(α)*Me*), 1.50–1.62 (1H, m, C(4)*H*), 2.24 (1H, dd, *J* 16.6, 7.0, C(2)H_A), 3.07 (1H, dd, *J* 16.6, 3.8, C(2)H_B), 3.27–3.34 (1H, m, C(3)*H*), 3.42 (3H, s, O*Me*), 4.06 (1H, q, *J* 6.8, C(α)*H*), 6.97–7.36 (5H, m, *Ph*); δ_C (62.5 MHz, PhMe-d_8, 363 K) −3.9 (Si*Me*), −3.8 (Si*Me*), 1.2 (SiCMe$_3$), 17.6 (C(α)*Me*), 18.6 (C(4)Me_A), 19.0 (C(4)Me_B), 26.5 (SiCMe_3), 31.8 (*C*(4)), 33.7 (*C*(2)), 50.7 (O*Me*), 63.9 (*C*(α)), 65.8 (*C*(3)), 127.4, 128.1, 129.0 (*o*-, *m*-, *p*-*Ph*), 143.8 (*i*-*Ph*), 173.5 (*C*(1)); *m*/*z* (ESI$^+$) 402 ([M+Na]$^+$, 42%), 380 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{37}NNaO_3Si^+$ ([M+Na]$^+$) requires 402.2435; found 402.2435.

4.10. (3*R*,α*S*)-*N*(2)-α-Methylbenzyl-3-phenylisoxazolidin-5-one 6



BuLi (2.5 M in hexanes, 0.40 mmol, 0.16 mL) was added to a stirred solution of **20** (100 mg, 0.40 mmol) in THF (4 mL) at −78 °C. After 30 min a solution of **21** (32 mg, 0.20 mmol) in THF (1 mL) was added and the reaction was stirred at −78 °C for a further 10 h. Satd aq NH_4Cl (5 mL) was added, the two phases were separated and the aqueous phase extracted with Et_2O (3×5 mL). The organic phases were combined and washed with satd aq NaCl (15 mL) before being dried and concentrated in vacuo to give **22** as an orange oil (130 mg, 95:5 dr). Hydrogen fluoride–pyridine complex (10 μL, 0.48 mmol) was added to a stirred solution of **22** (125 mg, 0.40 mmol) in dry THF (4 mL) at 0 °C. After stirring for 20 min the reaction mixture was diluted with Et_2O (25 mL) then quenched with satd aq $NaHCO_3$ (20 mL). The phases were then separated and the aqueous phase extracted with Et_2O (3×20 mL). The organic phases were combined, dried and concentrated in vacuo to give **37** (74 mg). This residue was dissolved in THF (3 mL) and cooled to −78 °C. LiHMDS (1.0 M in THF, 0.6 mmol, 0.6 mL) was added and the resultant mixture was left to stir for 30 min. The reaction was then quenched with satd aq NH_4Cl (2 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3×2 mL), then the organic phases were combined and washed with satd aq NaCl, before being dried and concentrated in vacuo. Purification via flash column chromatography (silica, eluent 40–60 °C petrol/Et_2O, 20:1) gave **6** as a pale yellow solid (37 mg, 78% over three steps, >99:1 dr);[5a] mp 101–102 °C (EtOH); $[\alpha]_D^{23}$ +120 (*c* 1.0 in $CHCl_3$); {lit.[5a] $[\alpha]_D^{22}$ +154 (*c* 2.05 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.60 (3H, d, *J* 6.5, C(α)*Me*), 2.91 (1H, dd, *J* 17.4, 8.9, C(4)H_A), 3.11 (1H, dd, *J* 17.4, 7.9, C(4)H_B), 4.19 (1H, d, *J* 6.5, C(α)*H*), 4.48–4.50 (1H, m, C(3)*H*), 7.24–7.31 (10H, m, *Ph*).

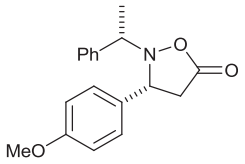
4.11. (*S*,*S*)-*N*(2)-α-Methylbenzyl-3-methylisoxazolidin-5-one 7



BuLi (1.41 M, 0.60 mmol, 0.43 mL) was added to a stirred solution of **20** (150 mg, 0.60 mmol) in THF (6 mL) at −78 °C. After 30 min a solution of **28** (30 mg, 0.30 mmol) in THF (2 mL) was added and the reaction was stirred at −78 °C for a further 10 h. Satd aq NH_4Cl (8 mL) was added, the two phases were separated and the aqueous phase was extracted with Et_2O (3×8 mL). The organic phases were

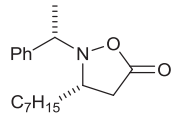
combined and washed with satd aq NaCl (20 mL) before being dried and concentrated in vacuo to give **33** as an orange oil (180 mg, 75:25 dr). Hydrogen fluoride–pyridine complex (30 μL, 0.72 mmol) was added to a stirred solution of **33** (180 mg, 0.60 mmol) in dry THF (6 mL) at 0 °C. After stirring for 20 min the reaction mixture was diluted with Et_2O (35 mL) then quenched with satd aq $NaHCO_3$ (30 mL). The layers were then separated and the aqueous phase was extracted with Et_2O (3×30 mL). The organic phases were combined, dried and concentrated in vacuo to give **39** (114 mg). This residue was dissolved in THF (4 mL) and cooled to −78 °C. LiHMDS (1.0 M, 0.90 mmol, 0.9 mL) was added and the mixture was left to stir for 30 min. The reaction was then quenched with satd aq NH_4Cl (4 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3×4 mL), then the organic phases were combined and washed with satd aq NaCl, before being dried and concentrated in vacuo. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 20:1; increased to 40–60 °C petrol/Et_2O, 5:1) gave **7** as a yellow oil (26 mg, 43% over three steps, >99:1 dr);[5a] $[\alpha]_D^{23}$ +76.3 (*c* 1.0 in $CHCl_3$); {lit.[5a] $[\alpha]_D^{19}$ +84.3 (*c* 2.9 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.00 (3H, d, *J* 6.1 C(3)*Me*), 1.55 (3H, d, *J* 6.5, C(α)*Me*), 2.38 (1H, dd, *J* 17.4, 6.5, C(4)H_A), 2.84 (1H, dd, *J* 17.4, 7.5, C(4)H_B), 3.40–3.60 (1H, m, C(3)*H*), 4.02 (1H, q, *J* 6.5, C(α)*H*), 7.30–7.36 (5H, m, *Ph*).

4.12. (3*R*,α*S*)-*N*(2)-α-Methylbenzyl-3-(*p*-methoxyphenyl) isoxazolidin-5-one 41



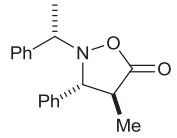
BuLi (1.41 M, 0.60 mmol, 0.42 ml) was added to a stirred solution of **20** (150 mg, 0.60 mmol) in THF (6 mL) at −78 °C. After 30 min a solution of **26** (58 mg, 0.3 mmol) in THF (2 mL) was added and the reaction was stirred at −78 °C for a further 10 h. Satd aq NH_4Cl (8 mL) was added, the two phases were separated and the aqueous phase extracted with Et_2O (3×8 mL). The organic phases were combined and washed with satd aq NaCl (20 mL) before being dried and concentrated in vacuo to give **31** as an orange oil (190 mg, 86:14 dr). Hydrogen fluoride–pyridine complex (2 μL, 0.72 mmol) was added to a stirred solution of **31** (190 mg, 0.60 mmol) in dry THF (6 mL) at 0 °C. After stirring for 20 min the reaction mixture was diluted with Et_2O (40 mL) then quenched with satd aq $NaHCO_3$ (30 mL). The phases were then separated and the aqueous phase was extracted with Et_2O (3×30 mL). The organic phases were combined, dried and concentrated in vacuo to give **38** (110 mg). This residue was dissolved in THF (3 mL) and cooled to −78 °C. LiHMDS (1.0 M, 0.90 mmol, 0.9 mL) was added and the mixture was left to stir for 30 min. The reaction was then quenched with satd aq NH_4Cl (3 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3×3 mL), then the organic phases were combined and washed with satd aq NaCl (10 mL), before being dried and concentrated in vacuo. Purification via flash column chromatography (silica, eluent 40–60 °C petrol/Et_2O, 20:1) gave **41** as a yellow oil (41 mg, 46% over three steps, >99:1 dr); $[\alpha]_D^{23}$ +78.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1778 (C=O); δ_H (400 MHz, $CDCl_3$) 1.54 (3H, d, *J* 6.6, C(α)*Me*), 2.85 (1H, dd, *J* 17.3, 9.1, C(4)H_A), 3.00 (1H, dd, *J* 17.3, 7.6, C(4)H_B), 3.79 (1H, s, O*Me*), 4.13 (1H, q, *J* 6.6, C(α)*H*), 4.41–4.44 (1H, m, C(3)*H*), 6.79 (2H, d, *J* 8.7, *Ar*), 7.16 (2H, d, *J* 8.7, *Ar*), 7.20–7.25 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.1 (C(α)*Me*), 39.2 (*C*(4)), 55.3 (O*Me*), 65.7 (*C*(α)), 65.9 (*C*(3)), 114.1, 127.8, 127.9, 128.3, 128.4 (*o*-, *m*-, *p*-*Ph*, *Ar*) 130.3, 140.4, 159.4 (*i*-*Ph*, *Ar*), 173.9 (*C*(5)); *m*/*z* (ESI$^+$) 617 ([2M+Na]$^+$, 100%), 320 ([M+Na]$^+$, 78%), 298 ([M+H]$^+$, 52%); HRMS (ESI$^+$) $C_{18}H_{19}NNaO_3^+$ ([M+Na]$^+$) requires 320.1257; found 320.1256.

4.13. (*S*,*S*)-*N*(2)-α-Methylbenzyl-3-heptylisoxazolidin-5-one 42



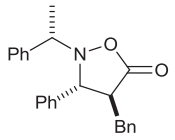
BuLi (1.22 M, 0.33 mmol, 0.27 ml) was added to a stirred solution of **20** (83 mg, 0.33 mmol) in THF (3 mL) at −78 °C. After 30 min a solution of **29** (30 mg, 0.16 mmol) in THF (1 mL) was added and the reaction was stirred at −78 °C for a further 10 h. Satd aq NH_4Cl (4 mL) was added, the two phases were separated and the aqueous phase was extracted with Et_2O (3×4 mL). The organic phases were combined and washed with satd aq NaCl (10 mL) before being dried and concentrated in vacuo to give **34** as an orange oil (105 mg, 78:22 dr). Hydrogen fluoride–pyridine complex (10 μL, 0.40 mmol) was added to a stirred solution of **34** (105 mg, 0.33 mmol) in dry THF (5 mL) at 0 °C. After stirring for 20 min the reaction mixture was diluted with Et_2O (35 mL) then quenched with satd aq $NaHCO_3$ (25 mL). The phases were then separated and the aqueous phase was extracted with Et_2O (3×25 mL). The organic phases were combined, dried and concentrated in vacuo to give **40** (75 mg). This residue was dissolved in THF (2 mL) and cooled to −78 °C. LiHMDS (1.0 M, 0.50 mmol, 0.50 mL) was added and the mixture was left to stir for 30 min. The reaction was then quenched with satd aq NH_4Cl (3 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3×3 mL), then the organic phases were combined and washed with satd aq NaCl (10 mL), before being dried, filtered, and concentrated in vacuo. Purification via flash column chromatography (silica, eluent 40–60 °C petrol/Et_2O, 30:1) gave **42** as a yellow oil (41 mg, 30% over three steps, 78:22 dr); ν_{max} (film) 1770 (C=O); δ_H (400 MHz, $CDCl_3$) 0.85–0.91 (3H, m, C(3)$(CH_2)_6CH_3$), 1.25–1.31 (12H, m, C(3)$(CH_2)_6CH_3$), 1.64 (3H, d, *J* 6.9, C(α)*Me*), 2.33–2.35 (1H, m, C(4)H_A), 2.86 (1H, dd, *j* 17.4, 7.7, C(4)H_B), 3.26 (1H, dd, *J* 7.7, 5.8, C(3)*H*), 4.08 (1H, q, *J* 6.9, C(α)*H*), 7.32–7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (C(3)$(CH_2)_6CH_3$), 20.4 (C(α)*Me*), 22.6, 25.5, 25.8, 29.0, 29.1, 29.4 (C(3)$(CH_2)_6CH_3$), 35.8 (*C*(4)), 60.9 (*C*(3)), 61.6 (*C*(α)), 126.0, 128.4, 129.2 (*o*-, *m*-, *p*-*Ph*), 136.5 (*i*-*Ph*), 175.0 (*C*(5)); *m*/*z* (ESI$^+$) 601 ([2M+Na]$^+$, 100%), 312 ([M+Na]$^+$, 62%), 290 ([M+H]$^+$, 34%); HRMS (ESI$^+$) $C_{18}H_{27}NNaO_2^+$ ([M+Na]$^+$) requires 312.1934; found 312.1945.

4.14. (3*R*,4*S*,α*S*)-*N*(2)-α-Methylbenzyl-3-phenyl-4-methylisoxazolidin-5-one 8



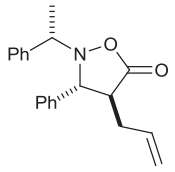
Following *general procedure* 2, LiTMP (0.2 M in THF, 0.55 mL, 0.11 mmol), **6** (26 mg, 0.10 mmol), MeI (20 μL, 0.30 mmol) and THF (1 mL) gave **8** in >99:1 dr. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 20:1; increased to 40–60 °C petrol/Et_2O, 5:1) gave **8** as a colourless oil (20 mg, 71%, >99:1 dr);[5a] $[\alpha]_D^{23}$ +102 (*c* 1.0 in $CHCl_3$); {lit.[5a] $[\alpha]_D^{25}$ +128 (*c* 1.3 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.8, C(4)*Me*), 1.58 (3H, d, *J* 6.6, C(α)*Me*), 2.98–3.02 (1H, m, C(4)*H*), 3.95 (1H, d, *J* 12.3, C(3)*H*), 4.11 (1H, q, *J* 6.6, C(α)*H*), 7.16–7.32 (10H, m, *Ph*).

4.15. (3*R*,4*S*,α*S*)-*N*(2)-α-Methylbenzyl-3-phenyl-4-benzylisoxazolidin-5-one 43



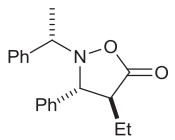
Following *general procedure* 2, LiTMP (0.2 M in THF, 1.45 mL, 0.29 mmol), **6** (70 mg, 0.26 mmol), BnBr (50 μL, 0.78 mmol) and THF (2 mL) gave **43** in >99:1 dr. Purification via flash column chromatography (silica, 40–60 °C petrol/Et_2O, 20:1; increased to 40–60 °C petrol/Et_2O, 5:1) gave **43** as a colourless oil (70 mg, 75%, >99:1 dr); $[\alpha]_D^{23}$ +69.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3031 (C–H), 1773 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.6, C(α)*Me*), 2.87 (1H, dd, *J* 14.5, 5.9, C(4)CH_A), 3.10 (1H, dd, *J* 14.5, 4.9, C(4)CH_B), 3.31–3.38 (1H, m, C(4)*H*), 3.89 (1H, q, *J* 6.6, C(α)*H*), 4.03 (1H, d, *J* 11.6, C(3)*H*), 7.10–7.32 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.5 (C(α)*Me*), 32.8 (*C*(4)CH_2), 52.8 (*C*(4)), 66.2 (*C*(α)), 71.9 (*C*(3)), 127.3, 128.1, 128.3, 128.4, 128.7, 128.8, 128.9, 129.8, 130.0 (*o*-, *m*-, *p*-*Ph*), 137.3, 137.9, 140.2 (*i*-*Ph*), 174.7 (*C*(5)); *m*/*z* (ESI^+) 358 ($[M+H]^+$, 90%), 254 (100%); HRMS (ESI^+) $C_{24}H_{24}NO_2^+$ ($[M+H]^+$) requires 358.1802; found 358.1802.

4.16. (3*R*,4*S*,α*S*)-*N*(2)-α-Methylbenzyl-3-phenyl-4-allylisoxazolidin-5-one 44



Following *general procedure* 2, LiTMP (0.2 M in THF, 1.45 mL, 0.29 mmol), **6** (70 mg, 0.26 mmol), allyl iodide (70 μL, 0.80 mmol) and THF (2 mL) gave **44** in >99:1 dr. Purification via flash column chromatography (silica, 40–60 °C petrol/Et_2O, 40:1; increased to 40–60 °C petrol/Et_2O, 20:1) gave **44** as a colourless oil (66 mg, 82%, >99:1 dr); $[\alpha]_D^{23}$ +100 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3032 (C–H), 1774 (C=O); δ_H (400 MHz, $CDCl_3$) 1.53 (3H, d, *J* 6.6, C(α)*Me*), 2.26–2.31 (1H, m, C(4)CH_A), 2.47–2.53 (1H, m, C(4)CH_B), 3.05–3.11 (1H, m, C(4)*H*), 4.07 (1H, q, *J* 6.6, C(α)*H*), 4.16 (1H, d, *J* 11.9, C(3)*H*), 5.07–5.11 (2H, m, C(4)CH_2CH=CH_2), 5.64–5.74 (1H, m, C(4)CH_2C*H*=CH_2), 7.13–7.24 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.5 (C(α)*Me*), 31.0 (C(4)CH_2), 51.2 (*C*(4)), 66.3 (*C*(α)), 72.4 (*C*(3)), 100.0 (C(4)CH_2CH=CH_2), 119.2 (C(4)CH_2CH=CH_2), 128.1, 128.3, 128.5, 128.6, 129.0, 133.6, (*o*-, *m*-, *p*-*Ph*), 137.9, 140.2 (*i*-*Ph*), 174.3 (*C*(5)); *m*/*z* (ESI^+) 308 ($[M+H]^+$, 40%); HRMS (ESI^+) $C_{20}H_{22}NO_2^+$ ($[M+H]^+$) requires 308.1645; found 308.1645.

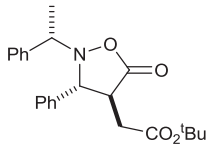
4.17. (3*R*,4*S*,α*S*)-*N*(2)-α-Methylbenzyl-3-phenyl-4-ethylisoxazolidin-5-one 45



Method A: LiHMDS (1 M in THF, 0.41 mL, 0.41 mmol) was added to a stirred solution **6** (100 mg, 0.37 mmol) in THF (2 mL) at −78 °C and left for 2 h. Ethyl iodide (90 μL, 1.12 mmol) was then added and the reaction mixture allowed to slowly warm to rt over 16 h, after which time satd aq NH_4Cl (0.5 mL) was added and the two phases were separated. The aqueous phase was then extracted with Et_2O (3×2 mL), and the organic phases were combined, washed with satd aq NaCl (5 mL), dried and concentrated in vacuo to give a 89:11 mixture of **45**:**50**. Purification via flash column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 20:1) gave **45** as a colourless oil (68 mg, 63%, >99:1 dr); $[\alpha]_D^{24}$ +49.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1773 (C=O); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.3, C(4)CH_2CH_3), 1.53 (3H, d, *J* 6.5, C(α)*Me*), 1.64–1.71 (2H, m, C(4)CH_2), 2.92 (1H, dt, *J* 12.0, 6.0, C(4)*H*), 4.03–4.08 (2H, m, C(3)*H*, C(α)*H*), 7.12–7.31 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 10.8 (C(4)CH_2CH_3), 17.2 (C(α)*Me*), 20.0 (C(4)CH_2), 52.2 (*C*(4)), 65.8 (*C*(α)), 73.0 (*C*(3)), 127.7, 127.8, 127.8, 128.1, 128.2, 128.6 (*o*-, *m*-, *p*-*Ph*), 137.9, 139.9 (*i*-*Ph*), 174.6 (*C*(5)); *m*/*z* (ESI^+) 613 ($[2M+Na]^+$, 78%), 591 ($[2M+H]^+$, 88%), 318 ($[M+Na]^+$, 18%), 296 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{21}NNaO_2^+$ ($[M+Na]^+$) requires 318.1470; found 318.1458. Further elution gave **50** as a colourless oil (8 mg, 7%, >99:1 dr); $[\alpha]_D^{24}$ +54.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1770 (C=O); δ_H (400 MHz, $CDCl_3$) 0.80 (3H, t, *J* 7.5, C(4)CH_2CH_3), 1.04 (3H, t, *J* 7.5, C(4)CH_2CH_3), 1.33–1.43 (1H, m, C(4)CH_AH_BCH$_3$), 1.48 (3H, d, *J* 6.8, C(α)Me), 1.61–1.70 (1H, m, C(4)CH_AH_BCH$_3$), 1.82–1.98 (2H, m, C(4)CH_2CH_3), 4.15 (1H, q, J 6.8, C(α)H), 4.63 (1H, s, C(3)H), 7.21–7.36 (10H, m, Ph); δ_C (100 MHz, $CDCl_3$) 7.9 (C(4)CH_2CH_3), 8.9 (C(4)CH_2CH_3), 14.0 (C(α)*Me*), 23.9 (C(4)CH_2), 25.1 (C(4)CH_2), 53.3 (*C*(4)), 62.8 (*C*(α)), 71.3 (*C*(3)), 127.4, 127.8, 128.0, 128.2, 128.4 (*o*-, *m*-, *p*-*Ph*), 134.6, 141.1 (*i*-*Ph*), 176.2 (*C*(5)); *m*/*z* (ESI^+) 669 ($[2M+Na]^+$, 100 %), 346 ($[M+Na]^+$, 90%), 324 ($[M+H]^+$, 55%); HRMS (ESI^+) $C_{21}H_{25}NNaO_2^+$ ($[M+Na]^+$) requires 346.1778; found 346.1786.

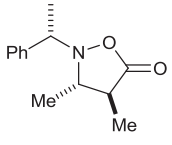
Method B: following *general procedure* 2, LiTMP (0.2 M in THF, 2.05 mL, 0.41 mmol), **6** (100 mg, 0.37 mmol), ethyl iodide (90 μL, 1.12 mmol) and THF (3 mL) gave **45** in >99:1 dr. Purification via flash column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 20:1) gave **45** as a colourless oil (82 mg, 75%, >99:1 dr).

4.18. (3*R*,4*S*,α*S*)-*N*(2)-α-Methylbenzyl-3-phenyl-4-(*tert*-butoxycarbonylmethyl)isoxazolidin-5-one 46



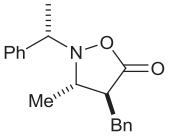
Following *general procedure* 2, LiTMP (0.23 M in THF, 2.00 mL, 0.45 mmol), **6** (100 mg, 0.37 mmol), *tert*-butyl bromoacetate (0.16 mL, 1.11 mmol) and THF (2 mL) gave **46** in >99:1 dr. Purification via flash column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 20:1) gave **46** as a colourless oil (116 mg, 81%, >99:1 dr); $[\alpha]_D^{24}$ +69.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2979 (C–H), 1778 (C=O), 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 1.35 (9H, s, C*Me*$_3$), 1.56 (3H, d, *J* 6.6, C(α)*Me*), 2.53 (2H, d, *J* 5.6, C(4)CH_2), 3.31 (1H, ddd, *J* 11.9, 5.8, 5.6, C(4)*H*), 4.10 (1H, q, *J* 6.6, C(α)*H*), 4.26 (1H, d, *J* 11.9, C(3)*H*), 7.10–7.32 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.2 (C(α)*Me*), 27.9 (C*Me*$_3$), 32.3 (C(4)CH_2), 48.3 (*C*(4)), 65.9 (*C*(α)), 73.1 (*C*(3)), 81.6 (CMe_3), 127.7, 127.8, 128.1, 128.2, 128.4, 128.7 (*o*-, *m*-, *p*-*Ph*), 137.0, 139.9 (*i*-*Ph*), 169.2 (*C*(5)), 169.2 (CO_2^tBu); *m*/*z* (ESI^+) 404 ($[M+Na]^+$, 75%), 382 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{23}H_{27}NNaO_4^+$ ($[M+Na]^+$) requires 404.1833; found 404.1817.

4.19. (*S*,*S*,*S*)-*N*(2)-α-Methylbenzyl-3,4-dimethylisoxazolidin-5-one 47



Following *general procedure* 2, LiTMP (0.23 M in THF, 3.20 mL, 0.73 mmol), **7** (125 mg, 0.61 mmol), methyl iodide (0.11 mL, 1.83 mmol) and THF (3 mL) gave **47** in 70:30 dr. Purification via flash column chromatography (silica, eluent 30–40 °C petrol/Et_2O, 20:1) gave **47** as a white solid (80 mg, 71%, 70:30 dr); mp 155–157 °C (dec); ν_{max} (film) 1768 (C=O); δ_H (400 MHz, $CDCl_3$) 0.75 (3H, d, *J* 5.8, C(3)*Me*), 1.20 (3H, d, *J* 6.8, C(4)*Me*), 1.58 (3H, d, *J* 6.4, C(α)*Me*), 2.51–2.59 (1H, m, C(4)*H*), 2.97–3.08 (1H, m, C(3)*H*), 3.97 (1H, q, *J* 6.4, C(α)*H*), 7.31–7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.7 (C(4)*Me*), 17.8 (*C*(3)*Me*), 19.3 (C(α)*Me*), 44.4 (*C*(4)), 67.4 (*C*(α)), 68.1 (*C*(3)), 127.1, 127.9, 128.6 (*o*-, *m*-, *p*-*Ph*), 140.6 (*i*-*Ph*), 175.7 (*C*(5)); *m*/*z* (ESI^+) 461 ($[2M+Na]^+$, 100%), 242 ($[M+Na]^+$, 68%), 220 ($[M+H]^+$, 27%); HRMS (ESI^+) $C_{13}H_{17}NNaO_2^+$ ($[M+Na]^+$) requires 242.1151; found 242.1162.

4.20. (*S*,*S*,*S*)-*N*(2)-α-Methylbenzyl-3-methyl-4-benzylisoxazolidin-5-one 9



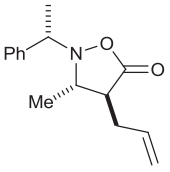
Following *general procedure* 2, LiTMP (0.36 M in THF, 14.9 mL, 5.37 mmol), **7** (1.00 g, 4.88 mmol), benzyl bromide (1.74 mL, 14.6 mmol) and THF (20 mL) gave **9** in >99:1 dr. Purification via flash column chromatography (silica, gradient elution, 30–40 °C petrol/Et_2O, 20:1; increased to 30–40 °C petrol/Et_2O, 5:1) gave **9** as a white solid (1.01 g, 70%, >99:1 dr);[5a] mp 79–81 °C (EtOH); $[\alpha]_D^{24}$ +85.3 (*c* 1.0 in $CHCl_3$); {lit.[5a] +89.6 (*c* 2.4 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.67 (3H, d, *J* 5.6, C(3)*Me*), 1.48 (3H, d, *J* 6.5, C(α)*Me*), 2.83–2.88 (1H, m, C(4)*H*), 2.94–2.99 (1H, m, C(4)CH_A), 3.09–3.16 (2H, m, C(3)*H*, C(4)CH_B), 3.85 (1H, q, *J* 6.5, C(α)*H*), 7.19–7.36 (10H, m, *Ph*).

4.20.1. X-ray crystal structure determination for ***9****.* Data were collected using an Enraf–Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[29]

X-ray crystal structure data for **9** [$C_{19}H_{21}NO_2$]: *M*=295.38, orthorhombic, space group *P* 2_1 2_1 2_1, *a*=5.8643(2) Å, *b*=9.9505(4) Å, *c*=27.5990(12) Å, *V*=1610.48(11) $Å^3$, *Z*=4, *μ*=0.079 mm^{-1}, colourless plate, crystal dimensions=0.10×0.10×0.20 mm^3. A total of 2106 unique reflections were measured for $5<\theta<27$ and 1210 reflections were used in the refinement. The final parameters were wR_2=0.058 and R_1=0.087 [$I>1.0\sigma(I)$].

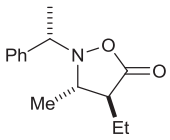
Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 747489. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.21. (*S*,*S*,*S*)-*N*(2)-α-Methylbenzyl-3-methyl-4-allylisoxazolidin-5-one 48



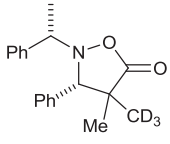
Following *general procedure* 2, LiTMP (0.43 M in THF, 5 mL, 2.15 mmol), **7** (400 mg, 1.95 mmol), allyl iodide (0.54 mL, 5.85 mmol) and dry THF (10 mL) gave **48** in 92:8 dr. Purification via flash column chromatography (silica, gradient elution, 30–40 °C petrol/Et_2O, 20:1; increased to 30–40 °C petrol/Et_2O, 5:1) gave **48** as a colourless oil, (307 mg, 64%, 92:8 dr); $[\alpha]_D^{18}$ +42.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2935 (C–H), 1771 (C=O); δ_H (400 MHz, $CDCl_3$) 0.80 (3H, d, *J* 5.9, C(3)*Me*), 1.57 (3H, d, *J* 6.5, C(α)*Me*), 2.44 (2H, app t, *J* 6.3, C(4)CH_2), 2.63 (1H, app dt, *J* 11.4, 5.7, C(4)*H*), 3.19 (1H, dq, *J* 11.4, 5.9, C(3)*H*), 3.98 (1H, q, *J* 6.5, C(α)*H*), 5.11–5.15 (2H, m, C(4)CHCH=CH_2), 5.73–5.83 (1H, m, C(4)CHC*H*=CH_2), 7.30–7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.4 (C(3)*Me*), 19.3 (C(α)*Me*), 31.6 (C(4)CH_2), 48.8 (*C*(4)), 64.7 (*C*(3)), 67.3 (*C*(α)), 118.4, 133.6, 134.5 (*o*-, *m*-, *p*-*Ph*), 140.8 (*i*-*Ph*), 174.8 (*C*(5)); *m*/*z* (ESI^+) 246 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{15}H_{19}NNaO_2^+$ $([M+Na])^+$ requires 268.1308; found 268.1303.

4.22. (*S*,*S*,*S*)-*N*(2)-α-Methylbenzyl-3-methyl-4-ethylisoxazolidin-5-one 49



Following *general procedure* 2, LiTMP (0.25 M in THF, 9.40 mL, 2.34 mmol), **7** (400 mg, 1.95 mmol), ethyl iodide (0.47 mL, 5.85 mmol) and THF (6 mL) gave **49** in 69:31 dr. Purification via flash column chromatography (silica, gradient elution, 30–40 °C petrol/Et_2O, 20:1; increased to 30–40 °C petrol/Et_2O, 5:1) gave **49** as a colourless oil (273 mg, 60%, 69:31 dr); ν_{max} (film) 1762 (C=O); δ_H (400 MHz, $CDCl_3$) 0.80 (3H, d, *J* 6.0, C(3)*Me*), 1.03 (3H, t, *J* 7.6, C(4)CH_2CH_3), 1.57 (3H, d, *J* 6.6, C(α)*Me*), 1.65–1.73 (2H, m, C(4)CH_2), 2.47 (1H, dt, *J* 11.2, 6.0, C(4)*H*), 3.13–3.20 (1H, m, C(3)*H*), 3.98 (1H, q, *J* 6.6, C(α)*H*), 7.28–7.39 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 10.9 (C(4)CH_2CH_3), 18.7 (C(3)*Me*), 19.5 (C(α)*Me*), 20.5 (C(4)CH_2), 50.3 (*C*(4)), 64.8 (*C*(3)), 67.5 (*C*(α)), 128.0, 128.2, 128.7 (*o*-, *m*-, *p*-*Ph*), 140.8 (*i*-*Ph*), 175.5 (*C*(5)); *m*/*z* (ESI^+) 489 ($[2M+Na]^+$, 100%), 256 ($[M+Na]^+$, 74%); HRMS (ESI^+) $C_{14}H_{19}NNaO_2^+$ ($[M+Na]^+$) requires 256.1308; found 256.1306.

4.23. (3*S*,4*R*,α*S*)- and (*S*,*S*,*S*)-*N*(2)-α-Methylbenzyl-3-phenyl-4-methyl-4-trideuteriomethylisoxazolidin-5-one 51 and 58

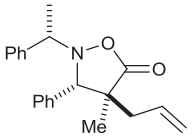


Following *general procedure* 3, LiHMDS (1.0 M in THF, 0.21 mL, 0.21 mmol), **8** (50 mg, 0.18 mmol), trideuteriomethyl iodide (30 μL, 0.54 mmol) and THF (1 mL) gave a 68:32 mixture of **51**:**58**. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 20:1; increased to 40–60 °C petrol/Et_2O, 5:1) gave **51**:**58** in 68:32 dr as a colourless oil (26 mg, 48%); ν_{max} (film) 1774 (C=O); *m*/*z* (ESI^+) 619 ($[2M+Na]^+$, 100%), 321 ($[M+Na]^+$, 32%), 299 ($[M+H]^+$, 20%); HRMS (ESI^+) $C_{19}H_{18}D_3NNaO_2^+$ ($[M+Na]^+$) requires 321.1653; found 321.1645.

Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 0.99 (3H, s, C(4)*Me*), 1.50 (3H, d, *J* 6.8, C(α)*Me*), 4.14 (1H, q, *J* 6.8, C(α)*H*), 4.23 (1H, s, C(3)*H*), 7.21–7.34 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 14.2 (C(α)*Me*), 19.8 (C(4)CH_3), 46.1 (*C*(4)), 63.1 (*C*(α)), 76.3 (*C*(3)), 127.5, 127.9, 128.2, 128.3, 128.3, 128.4 (*o*-, *m*-, *p*-*Ph*), 134.2, 141.0 (*i*-*Ph*) 178.5 (*C*(5)).

Data for minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.23 (3H, s, C(4)CH_3), 1.50 (3H, d, *J* 6.8, C(α)*Me*), 4.14 (1H, q, *J* 6.8, C(α)*H*), 4.23 (1H, s, C(3)*H*), 7.21–7.34 (10H, m, *Ph*).

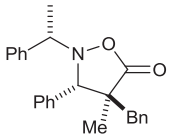
4.24. (*S*,*S*,*S*)-*N*(2)-α-Methylbenzyl-3-phenyl-4-allyl-4-methylisoxazolidin-5-one 52



Method A: following *general procedure* 3, LiHMDS (1.0 M in THF, 0.16 mL, 0.16 mmol), **8** (30 mg, 0.11 mmol), allyl iodide (20 μL, 0.22 mmol) and THF (1 mL) gave **52**:**59** in >99:1 dr. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 50:1; increased to 40–60 °C petrol/Et_2O, 10:1) gave **52** as a colourless oil (26 mg, 74%, >99:1 dr); $[\alpha]_D^{24}$ +50.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2927 (C–H), 1773 (C=O); δ_H (400 MHz, $CDCl_3$) 1.01 (3H, s, C(4)*Me*), 1.47 (3H, d, *J* 6.7, C(α)*Me*), 2.12 (1H, dd, *J* 14.3, 9.5, C(4)CH_A), 2.52 (1H, dd, *J* 14.3, 5.1, C(4)CH_B), 4.13 (1H, q, *J* 6.7, C(α)*H*), 4.55 (1H, s, C(3)*H*), 5.22–5.27 (2H, m, C(4)CH_2CH=CH_2), 5.77–5.87 (1H, m, C(4)CH_2C*H*=CH_2), 7.20–7.34 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.1 (C(α)*Me*), 19.8 (C(4)*Me*), 39.4 (C(4)*C*H_2), 49.8 (*C*(4)), 63.4 (*C*(α)), 71.3 (*C*(3)), 119.9 (C(4)CH_2CH=*C*H_2), 127.6, 127.9, 128.2, 128.3, 128.4, 128.5 (*o*-, *m*-, *p*-*Ph*), 133.2 (C(4)CH_2*C*H=CH_2), 134.6, 140.9 (*i*-*Ph*), 177.3 (*C*(5)); *m*/*z* (ESI$^+$) 643 ([2M+H]$^+$, 17%), 344 ([M+Na]$^+$, 38%), 322 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{23}NNaO_2^+$ ([M+Na]$^+$) requires 344.1621; found 344.1621.

Method B: following *general procedure* 3, LiHMDS (1.0 M in THF, 0.35 mL, 0.35 mmol), **44** (90 mg, 0.29 mmol), methyl iodide (0.06 mL, 0.87 mmol) and THF (2 mL) gave **52**:**59** in a 60:40 dr. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 50:1; increased to 40–60 °C petrol/Et_2O, 10:1) gave **52** as a colourless oil (35 mg, 38%, >99:1 dr).

4.25. (*S*,*S*,*S*)-*N*(2)-α-Methylbenzyl-3-phenyl-4-benzyl-4-methylisoxazolidin-5-one 53



Method A: following *general procedure* 3, LiHMDS (1.0 M in THF, 0.13 mL, 0.13 mmol), **8** (30 mg, 0.11 mmol), benzyl bromide (40 μL, 0.39 mmol) and THF (1 mL) gave **53**:**60** in >99:1 dr. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 20:1; increased to 40–60 °C petrol/Et_2O, 5:1) gave **53** as a white solid (31 mg, 76%, >99:1 dr); mp 145–147 °C; $[\alpha]_D^{20}$ +27.0 (*c* 0.4 in $CHCl_3$); ν_{max} (film) 3033 (C–H), 1762 (C=O); δ_H (400 MHz, $CDCl_3$) 1.11 (3H, s, C(4)*Me*), 1.15 (3H, d, *J* 6.6, C(α)*Me*), 2.53 (1H, d, *J* 14.3, C(4)CH_A), 3.35 (1H, d, *J* 14.3, C(4)CH_B), 3.82 (1H, q, *J* 6.6, C(α)*H*), 4.41 (1H, s, C(3)*H*), 7.18–7.41 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.2 (C(α)*Me*), 21.5 (C(4)*Me*), 41.2 (C(4)CH_2), 51.8 (*C*(4)), 63.6 (*C*(α)), 69.9 (*C*(3)), 127.2, 127.5, 127.8, 128.1, 128.2, 128.4, 128.6, 128.8, 130.5 (*o*-, *m*-, *p*-*Ph*), 135.2, 136.6, 140.9 (*i*-*Ph*), 177.9 (*C*(5)); *m*/*z* (ESI$^+$) 430 ([M+59]$^+$, 100%); HRMS (ESI$^+$) $C_{25}H_{25}NNaO_2^+$ ([M+Na]$^+$) requires 394.1778; found 394.1763.

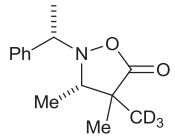
Method B: following *general procedure* 3, LiHMDS (1.0 M in THF, 0.92 mL, 0.92 mmol), **43** (275 mg, 0.77 mmol), methyl iodide (0.17 mL, 2.76 mmol) and THF (10 mL) gave **53**:**60** in 97:3 dr. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 20:1; increased to 40–60 °C petrol/Et_2O, 5:1) gave **53** as a white solid (206 mg, 72%, >99:1 dr).

*4.25.1. X-ray crystal structure determination for **53**.* Data were collected using an Enraf–Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[29]

X-ray crystal structure data for **53** [$C_{25}H_{25}NO_2$]: *M*=371.48, orthorhombic, space group *P* 2_1 2_1 2_1, *a*=7.43100(10) Å, *b*=12.1146(2) Å, *c*=22.5635(4) Å, *V*=2031.25(6) Å^3, *Z*=4, μ=0.076 mm^{-1}, colourless plate, crystal dimensions=0.05×0.05×0.20 mm^3. A total of 2639 unique reflections were measured for $5<\theta<27$ and 2639 reflections were used in the refinement. The final parameters were wR_2=0.100 and R_1=0.058 [$I>-3.0\sigma(I)$].

Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 747490. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.26. (3*S*,4*R*,α*S*)- and (*S*,*S*,*S*)-*N*(2)-α-Methylbenzyl-3,4-dimethyl-4-trideuteriomethylisoxazolidin-5-one 54 and 61

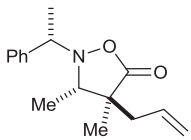


Following *general procedure* 3, LiHMDS (1.0 M in THF, 0.21 mL, 0.21 mmol), **47** (50 mg, 0.23 mmol), trideuteriomethyl iodide (30 μL, 0.68 mmol) and THF (1 mL) gave **54**:**61** in 62:38 dr. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 20:1; increased to 40–60 °C petrol/Et_2O, 5:1) gave **54**:**61** in 62:38 dr as a colourless oil (28 mg, 57%); ν_{max} (film) 1772 (C=O); *m*/*z* (ESI$^+$) 259 ([M+Na]$^+$, 100%), 237 ([M+H]$^+$, 58%); HRMS (ESI$^+$) $C_{14}H_{16}D_3NNaO_2^+$ ([M+Na]$^+$) requires 259.1496; found 259.1500.

Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 0.62 (3H, d, *J* 6.3, C(3)*Me*), 1.15 (3H, s, C(4)*Me*), 1.58 (3H, d, *J* 6.6, C(α)Me), 3.07 (1H, q, *J* 6.3, C(3)*H*), 3.97 (1H, q, *J* 6.6, C(α)H), 7.30–7.39 (5H, m, Ph); δ_C (125 MHz, $CDCl_3$) 13.0 (C(3)*Me*), 17.2 (quin, *J* 20.0, C(3)CD_3) 19.3 (C(α)*Me*), 21.3 (C(4)CH_3), 45.3 (*C*(4)), 67.0 (*C*(3)) 69.7 (*C*(α)), 127.8, 128.0, 128.5 (*o*-, *m*-, *p*-*Ph*), 141.4 (*i*-*Ph*), 179.0 (*C*(5)).

Data for minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) 0.62 (3H, d, *J* 6.3, C(3)*Me*), 1.17 (3H, s, C(4)*Me*), 1.58 (3H, d, *J* 6.6, C(α)*Me*), 3.07 (1H, q, *J* 6.3, C(3)*H*), 3.97 (1H, q, *J* 6.6, C(α)*H*), 7.30–7.39 (5H, m, Ph).

4.27. (*S*,*S*,*S*)-*N*(2)-α-Methylbenzyl-3,4-dimethyl-4-allylisoxazolidin-5-one 55

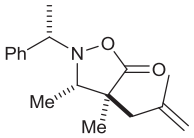


Method A: following *general procedure* 3, LiHMDS (1.0 M in THF, 0.27 mL, 0.27 mmol), **47** (50 mg, 0.23 mmol), allyl iodide (0.06 mL, 0.69 mmol) and THF (1 mL) gave a 69:31 mixture of **55**:**62**. Purification via flash column chromatography (silica, gradient

elution, 40–60 °C petrol/Et_2O, 20:1; increased to 40–60 °C petrol/Et_2O, 5:1) gave **55** as a colourless oil (23 mg, 39%, >99:1 dr); $[\alpha]_D^{22}$ +49.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2937 (C–H), 1770 (C=O); δ_H (400 MHz, $CDCl_3$) 0.65 (3H, d, *J* 6.0, C(3)*Me*), 1.19 (3H, s, C(4)*Me*), 1.54 (3H, d, *J* 6.6, C(α)*Me*), 2.13 (1H, dd, *J* 14.2, 8.5, C(4)CH_A), 2.45 (1H, dd, *J* 14.2, 6.1, C(4)CH_B), 3.31 (1H, q, *J* 6.0, C(3)*H*), 3.97 (1H, q, *J* 6.6, C(α)*H*), 5.08–5.16 (2H, m, C(4)CH_2CH=CH_2), 5.71–5.82 (1H, m, C(4)CH_2C*H*=CH_2), 7.28–7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.0 (*C*(3)*Me*), 17.3 (C(4)*Me*), 19.0 (C(α)*Me*), 39.4 (C(4)CH_2), 48.7 (*C*(4)), 65.7 (*C*(3)), 66.6 (*C*(α)), 119.4 (C(4)CH_2CH=CH_2), 127.8, 127.9, 128.5 (*o*-, *m*-, *p*-*Ph*), 132.7 (C(4)CH_2CH=CH_2), 141.4 (*i*-*Ph*), 177.9 (*C*(5)); *m*/*z* (ESI^+) 541 ($[2M+Na]^+$, 100%), 282 ($[M+Na]^+$, 29%), 260 ($[M+H]^+$, 16%); HRMS (ESI^+) $C_{16}H_{21}NNaO_2^+$ ($[M+Na]^+$) requires 282.1465; found 282.1459.

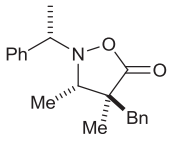
Method B: following *general procedure* 3, LiHMDS (1.0 M in THF, 0.2 mL, 0.2 mmol), **48** (40 mg, 0.16 mmol), methyl iodide (0.03 mL, 0.48 mmol) and THF (1 mL) gave **55**:**62** in >99:1 dr. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 20:1; increased to 40–60 °C petrol/Et_2O, 5:1) gave **55** as a colourless oil (37 mg, 89%, >99:1 dr).

4.28. (*S*,*S*,*S*)-*N*(2)-α-Methylbenzyl-3,4-dimethyl-4-methallylisoxazolidin-5-one 56



Following *general procedure* 3, LiHMDS (1.0 M in THF, 0.2 mL, 0.22 mmol), **47** (36 mg, 0.17 mmol), methallyl bromide (67 mg, 0.5 mmol) and THF (1 mL) gave **56**:**63** in 97:3 *dr*. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 25:1; increased to 40–60 °C petrol/Et_2O, 15:1) gave **56** as a colourless oil (25 mg, 56%, >99:1 dr); $[\alpha]_D^{23}$ +71.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2975 (C–H), 1769 (C=O); δ_H (400 MHz, $CDCl_3$) 0.66 (3H, d, *J* 5.9, C(3)*Me*), 1.20 (3H, s, C(4)*Me*), 1.55 (3H, d, *J* 6.7, C(α)*Me*), 1.7 (3H, s, C(2′)*Me*), 2.04 (1H, d, *J* 14.2, C(1′)H_A), 2.60 (1H, d, *J* 14.2, C(1′)H_B), 3.31 (1H, q, *J* 5.9, C(3)*H*), 3.99 (1H, q, *J* 6.7, C(α)*H*), 4.72 (1H, app s, C(3′)H_A), 4.88 (1H, app s, C(3′)H_B), 7.30–7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.0 (*C*(3)*Me*), 18.7 (C(α)*Me*), 19.4 (C(4)*Me*), 23.5 (C(2′)*Me*), 42.7 (*C*(1′)), 48.3 (*C*(4)), 64.3 (*C*(3)), 66.4 (*C*(α)), 115.9 (*C*(3′)), 127.9, 127.9, 128.5 (*o*-, *m*-, *p*-*Ph*), 141.2, 141.4 (*C*(2′), *i*-*Ph*), 178.4 (*C*(5)); *m*/*z* (ESI^+) 569 ($[2M+Na]^+$, 100%), 296 ($[M+Na]^+$, 28%), 274 ($[M+H]^+$, 18%); HRMS (ESI^+) $C_{17}H_{23}NNaO_2^+$ ($[M+Na]^+$) requires 296.1621; found 296.1616.

4.29. (*S*,*S*,*S*)-*N*(2)-α-Methylbenzyl-3,4-dimethyl-4-benzylisoxazolidin-5-one 57



Method A: following *general procedure* 3, LiHMDS (1.0 M in THF, 0.16 mL, 0.16 mmol), **47** (30 mg, 0.14 mmol), benzyl bromide (20 μL, 0.42 mmol) and THF (1 mL) gave **57**:**64** in >99:1 dr. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 20:1; increased to 40–60 °C petrol/Et_2O, 5:1) gave **57** as a colourless oil (38 mg, 88%, >99:1 dr). Recrystallisation of an aliquot (EtOH/hexane) gave an analytical sample; mp 71–73 °C; $[\alpha]_D^{25}$ +58.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1768 (C=O); δ_H (400 MHz, $CDCl_3$) 0.62 (3H, d, *J* 6.5, C(3)*Me*), 1.29 (3H, s, C(4)*Me*), 1.35 (3H, d, *J* 6.5, C(α)*Me*), 2.59 (1H, d, *J* 14.0, C(4)CH_A), 3.13–3.18 (1H, m, C(3)*H*), 3.20 (1H, d, *J* 14.0, C(4)CH_B), 3.73 (1H, q, *J* 6.5, C(α)*H*), 7.15–7.32 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.0 (*C*(3)*Me*), 18.3 (C(α)*Me*), 29.7 (C(4)*Me*), 40.9 (C(4)CH_2), 50.4 (*C*(4)), 64.5 (*C*(3)), 66.2 (*C*(α)), 127.0, 127.8, 127.9, 128.5, 129.1, 130.2 (*o*-, *m*-, *p*-*Ph*), 136.3, 141.4 (*i*-*Ph*), 178.1 (*C*(5)); *m*/*z* (ESI^+) 641 ($[2M+Na]^+$, 100%), 332 ($[M+Na]^+$, 78%), 310 ($[M+H]^+$, 23%); HRMS (ESI^+) $C_{20}H_{23}NNaO_2^+$ ($[M+Na]^+$) requires 332.1621; found 332.1621.

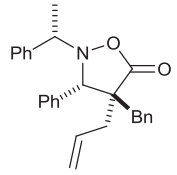
Method B: following *general procedure* 3, LiHMDS (1.0 M in THF, 0.40 mL, 0.40 mmol), **9** (100 mg, 0.34 mmol), methyl iodide (60 μL, 1.02 mmol) and THF (2.5 mL) gave **57**:**64** in >99:1 dr. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 20:1; increased to 40–60 °C petrol/Et_2O, 5:1) gave **57** as a colourless oil (87 mg, 83%, >99:1 dr).

*4.29.1. X-ray crystal structure determination for **57**.* Data were collected using an Enraf–Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[29]

X-ray crystal structure data for **57** [$C_{20}H_{23}NO_2$]: *M*=309.41, orthorhombic, space group *P* 2_1 2_1 2_1, *a*=10.6697(2) Å, *b*=7.2058(2) Å, *c*=22.4278(5) Å, *V*=1724.33(7) $Å^3$, *Z*=4, μ=0.076 mm^{-1}, colourless plate, crystal dimensions=0.09×0.13×0.26 mm^3. A total of 2256 unique reflections were measured for $5<\theta<27$ and 1853 reflections were used in the refinement. The final parameters were wR_2=0.074 and R_1=0.042 [$I>-3.0\sigma(I)$].

Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 753400. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.30. (*S*,*S*,*S*)-*N*(2)-α-Methylbenzyl-3-phenyl-4-allyl-4-benzylisoxazolidin-5-one 65



Method A: following *general procedure* 3, LiHMDS (1.0 M in THF, 0.18 mL, 0.18 mmol), **44** (50 mg, 0.16 mmol), benzyl bromide (50 μL, 0.42 mmol) and THF (1.5 mL) gave **65**:**70** in 89:11 dr. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 50:1; increased to 40–60 °C petrol/Et_2O, 10:1) gave **65** as a white solid (47 mg, 71%, >99:1 dr); $C_{27}H_{27}NO_2$ requires C, 81.6; H, 6.85; N, 3.5%; found C, 81.5; H, 6.7; N, 3.5%; mp 84–86 °C; $[\alpha]_D^{24}$ +73.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2921 (C–H) 1771 (C=O); δ_H (400 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.8, C(α)*Me*), 1.88 (1H, dd, *J* 14.2, 8.5, C(4)CH_AH$_B$CH=CH_2), 2.44 (1H, d, *J* 14.4, C(4)CH_AH$_B$Ph), 2.64 (1H, dd, *J* 14.2, 6.1, C(4)CH_AH$_B$CH=CH_2), 3.47 (1H, d, *J* 14.4, C(4)CH_AH$_B$Ph), 3.83 (1H, q, *J* 6.8, C(α)*H*), 4.52 (1H, s, C(3)*H*), 5.00 (1H, app d, *J* 17.0, C(4)CH_2CH=CH_AH$_B$), 5.10 (1H, app d, *J* 10.1, C(4)CH_2CH=CH_AH$_B$), 5.69–5.77 (1H, m, C(4)CH_2C*H*=CH_2), 7.17–7.42 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.5 (C(α)*Me*), 38.7 (C(4)CH_2CH=

CH_2), 38.7 (C(4)CH_2Ph), 54.6 (*C*(4)), 63.1 (*C*(α)), 69.5 (*C*(3)), 119.3 (C(4)CH_2CH=CH_2), 127.2, 127.5, 127.7, 128.2, 128.4, 128.6, 128.6, 128.9, 130.6 (*o*-, *m*-, *p*-*Ph*), 132.2 (C(4)CH_2CH=CH_2), 134.6, 136.9, 141.1 (*i*-*Ph*), 173.9 (C(5)); *m*/*z* (ESI$^+$) 420 ([M+Na]$^+$, 50%), 398 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{27}NNaO_2^+$ ([M+Na]$^+$) requires 420.1934; found 420.1922.

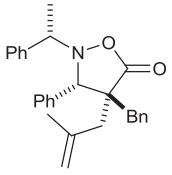
Method B: following *general procedure* 3, LiHMDS (1.0 M in THF, 0.20 mL, 0.20 mmol), **43** (60 mg, 0.17 mmol), allyl iodide (47 μL, 0.51 mmol) and THF (1 mL) gave **65**:**70** in 73:27 dr. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 50:1; increased to 40–60 °C petrol/Et_2O, 10:1) gave **65** as a white solid (36 mg, 54%, >99:1 dr).

*4.30.1. X-ray crystal structure determination for **65**.* Data were collected using an Enraf–Nonius κ-CCD diffractometer with graphite monochromated Mo Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[29]

X-ray crystal structure data for **65** [$C_{27}H_{27}NO_2$]: M=795.03, orthorhombic, space group $P2_12_12_1$, a=9.98060(10) Å, b=12.3492(2) Å, c=35.5508(6) Å, V=4381.72(11) Å^3, Z=8, μ=0.075 mm^{-1}, colourless plate, crystal dimensions=0.20×0.20×0.40 mm^3. A total of 5516 unique reflections were measured for $5<\theta<27$ and 3517 reflections were used in the refinement. The final parameters were wR_2=0.055 and R_1=0.060 [$I>1.5\sigma(I)$].

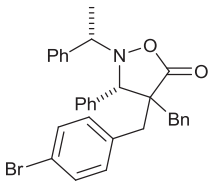
Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 747491. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.31. (*S*,*S*,*S*)-*N*(2)-α-Methylbenzyl-3-phenyl-4-benzyl-4-methallylisoxazolidin-5-one 66



Following *general procedure* 3, LiHMDS (1.0 M in THF, 0.41 mL, 0.41 mmol), **43** (100 mg, 0.34 mmol), methallyl bromide (136 mg, 1.01 mmol) and THF (3 mL) gave **66**:**71** in 56:44 dr. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 25:1; increased to 40–60 °C petrol/Et_2O, 15:1) gave **66** as a colourless oil (42 mg, 30%, >99:1); $[\alpha]_D^{23}$ +88.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 1771 (C=O); δ_H (400 MHz, $CDCl_3$) 1.10 (3H, d, *J* 6.8, C(α)*Me*), 1.72 (1H, d, *J* 13.7, C(1′)H_A), 1.78 (3H, s, C(2′)*Me*), 2.44 (1H, d, *J* 14.2, C(4)C$H_A$$H_B$Ph), 2.70 (1H, d, *J* 13.7, C(1′)H_B), 3.65 (1H, d, *J* 14.2, C(4)C$H_A$$H_B$Ph), 3.84 (1H, q, *J* 6.8, C(α)*H*), 4.51 (1H, s, C(3)*H*), 4.68 (1H, app s, C(3′)H_A), 4.95 (1H, app s, C(3′)H_B), 7.19–7.39 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 14.0 (C(α)*Me*), 23.0 (C(2′)*Me*), 40.0 (*C*(1′)), 40.7 (C(4)*C*H_2Ph), 51.8 (*C*(4)), 62.9 (*C*(α)), 70.2 (*C*(3)), 117.2 (*C*(3′)), 127.0, 127.6, 127.7, 128.1, 128.3, 128.5, 128.6, 128.9, 130.8 (*o*-, *m*-, *p*-*Ph*), 135.0 (*C*(2′)), 140.8, 141.2, 142.3 (*i*-*Ph*) 175.0 (*C*(5)); *m*/*z* (ESI$^+$) 434 ([M+Na]$^+$, 100%), 412 ([M+H]$^+$, 23%); HRMS (ESI$^+$) $C_{28}H_{29}NNaO_2^+$ ([M+Na]$^+$) requires 434.2091; found 434.2098.

4.32. (3*S*,4*R*,α*S*)- and (*S*,*S*,*S*)-*N*(2)-α-Methylbenzyl-3-phenyl-4-benzyl-4-(*p*-bromobenzyl)isoxazolidin-5-one 67 and 72

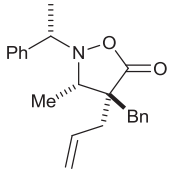


Following *general procedure* 3, LiHMDS (1.0 M in THF, 0.18 mL, 0.18 mmol), **43** (50 mg, 0.14 mmol), *p*-bromobenzyl bromide (80 mg, 0.42 mmol) and THF (2 mL) gave **67**:**72** in 54:46 dr. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 20:1; increased to 40–60 °C petrol/Et_2O, 5:1) gave **67**:**72** in 54:46 dr as a colourless oil (48 mg, 65%); ν_{max} (film) 1770 (C=O); δ_C (125 MHz, $CDCl_3$) 13.4, 14.1, 37.4, 38.2, 39.7, 40.3, 54.8, 54.9, 63.0, 63.2, 69.8, 69.9, 121.1, 121.2, 127.1, 127.2, 127.5, 127.6, 127.8, 127.9, 128.0, 128.2, 128.6, 128.6, 128.6, 128.7, 129.0, 130.5, 130.9, 131.0, 131.8, 132.2, 132.6, 134.1, 134.1, 134.3, 134.9, 135.7, 136.4, 140.2, 141.0, 174.8, 175.0; *m*/*z* (ESI$^+$) 548 ([M+Na]$^+$, ^{79}Br, 100%); HRMS (ESI$^+$) $C_{31}H_{28}{}^{79}BrNNaO_2^+$ ([M+Na]$^+$) requires 548.1196; found 548.1175.

Data for major diastereoisomer: δ_H (400 MHz, $CDCl_3$) 1.13 (3H, d, *J* 6.6, C(α)*Me*), 2.19–2.26 (2H, m, 2×C(4)CH_A), 3.19–3.30 (2H, m, 2×C(4)CH_B), 3.86 (1H, q, *J* 6.6, C(α)*H*), 4.60 (1H, s, C(3)*H*), 6.90–7.44 (19H, m, *Ph*).

Data for minor diastereoisomer: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.17 (3H, d, *J* 6.7, C(α)*Me*), 2.42–2.47 (2H, m, 2×C(4)CH_A), 3.30–3.38 (2H, m, 2×C(4)CH_B), 4.02 (1H, q, *J* 6.7, C(α)*H*), 4.46 (1H, s, C(3)*H*).

4.33. (*S*,*S*,*S*)-*N*(2)-α-Methylbenzyl-3-methyl-4-allyl-4-benzylisoxazolidin-5-one 68

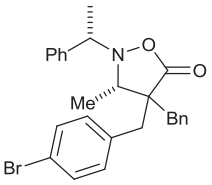


Method A: following *general procedure* 3, LiHMDS (1.0 M in THF, 0.81 mL, 0.81 mmol), **9** (200 mg, 0.68 mmol), allyl iodide (0.19 mL, 2.04 mmol) and THF (5 mL) gave **68**:**73** in 90:10 dr. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 20:1; increased to 40–60 °C petrol/Et_2O, 5:1) gave **68** as a colourless oil (178 mg, 78%, >99:1 dr); $[\alpha]_D^{18}$ +96.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2979 (C–H), 1767 (C=O); δ_H (400 MHz, $CDCl_3$) 0.68 (3H, d, *J* 6.1, C(3)*Me*), 1.33 (3H, d, *J* 6.5, C(α)*Me*), 2.27 (1H, dd, *J* 14.1, 8.6, C(4)C$H_A$$H_B$CH=$CH_2$), 2.53 (1H, d, *J* 14.3, C(4)C$H_A$$H_B$Ph), 2.72 (1H, dd, *J* 14.1, 6.1, C(4)C$H_A$$H_B$CH=$CH_2$), 3.21 (1H, q, *J* 6.1, C(3)*H*), 3.28 (1H, d, *J* 14.3, C(4)C$H_A$$H_B$Ph), 3.72 (1H, q, *J* 6.5, C(α)*H*), 5.18–5.23 (2H, m, C(4)CH_2CH=CH_2), 5.95–6.06 (1H, m, C(4)CH_2CH=CH_2), 7.26–7.31 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.5 (C(3)*Me*), 18.1 (C(α)*Me*), 36.5 (C(4)CH_2), 38.6 (C(4)*C*H_2Ph), 53.5 (*C*(4)), 64.5 (*C*(3)), 66.1 (*C*(α)), 107.8 (C(4)CH_2CH=CH_2), 120.0 (C(4)CH_2CH=CH_2), 127.6, 127.7, 128.4, 128.5, 130.1, 132.6 (*o*-, *m*-, *p*-*Ph*), 136.3, 141.4 (*i*-Ph), 176.0 (*C*(5)); *m*/*z* (ESI$^+$) 394 ([M+59]$^+$, 100%); HRMS (ESI$^+$) $C_{22}H_{25}NNaO_2^+$ ([M+Na]$^+$) requires 358.1778; found 358.1773.

Method B: following *general procedure* 3, LiHMDS (1.0 M in THF, 0.2 mL, 0.2 mmol), **48** (40 mg, 0.16 mmol), benzyl bromide (0.06 mL, 0.48 mmol) and THF (1 mL) gave **68**:**73** in 67:33 dr. Purification via

flash column chromatography on silica gel (silica, gradient elution, 40–60 °C petrol/Et_2O, 20:1; increased to 40–60 °C petrol/Et_2O, 5:1) gave **68** as a colourless oil (25 mg, 47%, >99:1 dr).

4.34. (3*S*,4*R*,α*S*)- and (*S*,*S*,*S*)-*N*(2)-α-Methylbenzyl-3-methyl-4-benzyl-4-(*p*-bromobenzyl)isoxazolidin-5-one 69 and 74

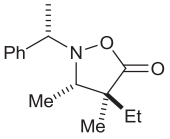


Following *general procedure* 3, LiHMDS (1.0 M in THF, 0.28 mL, 0.28 mmol), **9** (70 mg, 0.24 mmol), *p*-bromobenzyl bromide (176 mg, 0.72 mmol) and THF (2 mL) gave **69**:**74** in 61:39 dr. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 20:1; increased to 40–60 °C petrol/Et_2O, 5:1) gave **69**:**74** in 61:39 dr as a colourless oil (20 mg, 18%); ν_{max} (film) 2980 (C–H), 1771 (C=O); δ_C (125 MHz, $CDCl_3$) 12.2, 12.3, 18.1, 18.8, 37.0, 37.3, 37.7, 37.9, 54.5, 54.6, 64.5, 64.7, 65.9, 66.2, 121.0, 121.2, 127.0, 127.1, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.5, 128.6, 130.2, 130.7, 131.2, 131.6, 131.9, 131.9, 132.4, 134.5, 135.2, 136.0, 141.1, 141.4, 174.7, 174.9; *m*/*z* (ESI^+) 486 ($[M+Na]^+$, ^{79}Br, 100%), 464 ($[M+H]^+$, ^{79}Br, 38%); HRMS (ESI^+) $C_{26}H_{26}{}^{79}BrNNaO_2^+$ ($[M+Na]^+$) requires 486.1039; found 486.1042.

Data for major diastereoisomer: δ_H (500 MHz, $CDCl_3$) 0.81 (3H, d, *J* 6.3, C(3)*Me*), 1.32 (3H, d, *J* 6.5, C(α)*Me*), 2.52 (1H, d, *J* 14.2, C(4)CH_A), 2.70 (1H, d, *J* 13.6, C(4)CH_C), 3.17–3.19 (1H, m, C(3)*H*), 3.20 (1H, d, *J* 14.2, C(4)CH_B), 3.30 (1H, d, *J* 13.6, C(4)CH_D), 3.72 (1H, q, *J* 6.5, C(α)*H*), 7.10 (2H, d, *J* 8.2, *Ar*), 7.18–7.34 (10H, m, *Ph*), 7.44–7.45 (2H, d, *J* 8.2, *Ar*).

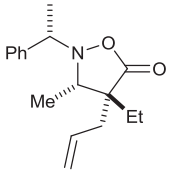
Data for minor diastereoisomer: δ_H (500 MHz, $CDCl_3$) [selected peaks] 1.39 (3H, d, *J* 6.6, C(α)*Me*), 2.47 (1H, d, *J* 14.2, C(4)CH_A), 2.72 (1H, d, *J* 13.8, C(4)CH_C), 3.09–3.12 (1H, m, C(3)*H*), 3.16 (1H, d, *J* 14.2, C(4)CH_B), 3.38 (1H, d, *J* 13.8, C(4)CH_D), 3.79 (1H, q, *J* 6.6, C(α)*H*), 6.95 (2H, d, *J*, 8.2, *Ar*), 7.37 (2H, d, *J* 8.2, *Ar*).

4.35. (*S*,*S*,*S*)-*N*(2)-α-Methylbenzyl-3,4-dimethyl-4-ethylisoxazolidin-5-one 78



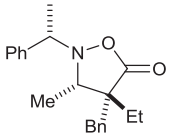
Following *general procedure* 3, LiHMDS (1.0 M in THF, 0.13 mL, 0.13 mmol), **49** (25 mg, 0.11 mmol), methyl iodide (0.02 mL, 0.33 mmol) and THF (0.5 mL) gave **78**:**84** in 64:36 dr. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 20:1; increased to 40–60 °C petrol/Et_2O, 5:1) gave **78** as a colourless oil (10 mg, 38%, >99:1 dr); $[\alpha]_D^{23}$ +48.9 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 2918 (C–H), 1763 (C=O); δ_H (400 MHz, $CDCl_3$) 0.64 (3H, d, *J* 5.7, C(3)*Me*), 0.95 (3H, t, *J* 7.4, C(4)CH_2CH_3), 1.17 (3H, s, C(4)*Me*), 1.44–1.51 (1H, m, C(4)CH_A), 1.56 (3H, d, *J* 6.6, C(α)*Me*), 1.69 (1H, dq, *J* 14.5, 7.4, C(4)CH_B), 3.28 (1H, q, *J* 5.7, C(3)*H*), 3.98 (1H, q, *J* 6.6, C(α)*H*), 7.28–7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 8.6 (C(4)CH_2CH_3), 13.2 (C(3)*Me*), 17.3 (C(4)*Me*), 19.2 (C(α)*Me*), 27.6 (C(4)CH_2), 53.0 (*C*(4)), 65.6 (*C*(3)), 70.7 (*C*(α)), 127.9, 128.0, 128.6 (*o*-, *m*-, *p*-*Ph*), 136.0 (*i*-*Ph*), 174.5 (*C*(5)); *m*/*z* (ESI^+) 517 ($[2M+Na]^+$, 100%), 270 ($[M+Na]^+$, 54%), 248 ($[M+H]^+$, 21%); HRMS (ESI^+) $C_{15}H_{21}NNaO_2^+$ ($[M+Na]^+$) requires 270.1454; found 270.1464.

4.36. (3*S*,4*R*,α*S*)-*N*(2)-α-Methylbenzyl-3-methyl-4-allyl-4-ethylisoxazolidin-5-one 79



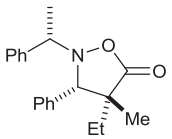
Following *general procedure* 3, LiHMDS (1.0 M in THF, 0.13 mL, 0.13 mmol), **49** (23 mg, 0.11 mmol), allyl iodide (0.03 mL, 0.33 mmol) and THF (0.5 mL) gave **79**:**85** in 69:31 dr. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 20:1; increased to 40–60 °C petrol/Et_2O, 5:1) gave **79** as a colourless oil (12 mg, 40%, 92:8 dr); ν_{max} (film) 2935 (C–H), 1766 (C=O); δ_H (400 MHz, $CDCl_3$) 0.71 (3H, d, *J* 5.5, C(3)*Me*), 0.92 (3H, t, *J* 7.5, C(4)CH_2CH_3), 1.34–1.47 (1H, m, C(4)C$H_AH_BCH_3$), 1.56 (3H, d, *J* 6.5, C(α)*Me*), 1.81 (1H, dq, *J* 14.8, 7.5, C(4)C$H_AH_BCH_3$), 2.15 (1H, dd, *J* 14.2, 8.5, C(4)C$H_AH_BCH{=}CH_2$), 2.63 (1H, dd, *J* 14.2, 6.3, C(4)C$H_AH_BCH{=}CH_2$), 3.40 (1H, q, *J* 5.5, C(3)*H*), 3.98 (1H, q, *J* 6.5, C(α)*H*), 5.09–5.14 (2H, m, C(4)$CH_2CH{=}CH_2$), 5.83–5.92 (1H, m, C(4)$CH_2CH{=}CH_2$), 7.30–7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 8.5 (C(4)CH_2CH_3), 13.0 (C(3)CH_2CH_3), 19.2 (C(α)*Me*), 25.1 (CH_3CH_2), 35.5 ($CH_2{=}CHCH_2$), 52.5 (*C*(4)), 65.6 (*C*(3)), 66.8 (*C*(α)), 118.5 ($CH_2{=}CH$), 127.8, 127.9, 128.5 (*o*-, *m*-, *p*-*Ph*), 132.8 ($CH_2{=}CH$), (*i*-*Ph*), 176.3 (C(5)); *m*/*z* (ESI^+) 569 ($[2M+Na]^+$, 100%), 296 ($[M+Na]^+$, 52%), 274 ($[M+H]^+$, 30%); HRMS (ESI^+) $C_{17}H_{23}NNaO_2^+$ ($[M+Na]^+$) requires 296.1621; found 296.1622.

4.37. (3*S*,4*R*,α*S*)-*N*(2)-α-Methylbenzyl-3-methyl-4-benzyl-4-ethylisoxazolidin-5-one 80



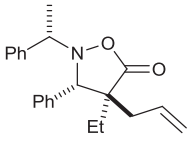
Following *general procedure* 3, LiHMDS (1.0 M in THF, 0.13 mL, 0.13 mmol), **49** (25 mg, 0.11 mmol), benzyl bromide (0.04 mL, 0.33 mmol) and THF (0.5 mL) gave **80**:**86** in 90:10 dr. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 20:1; increased to 40–60 °C petrol/Et_2O, 5:1) gave **80** as a colourless oil (19 mg, 53%, 90:10 dr); ν_{max} (film) 2928 (C–H), 1765 (C=O); δ_H (400 MHz, $CDCl_3$) 0.62 (3H, d, *J* 6.3, C(3)*Me*), 1.09–1.13 (3H, m, C(4)CH_2CH_3), 1.31 (3H, d, *J* 6.5, C(α)*Me*), 1.54–1.63 (1H, m, C(4)C$H_AH_BCH_3$), 1.95 (1H, dq, *J* 14.3, 7.4, C(4)C$H_AH_BCH_3$), 2.52 (1H, d, *J* 13.9, C(4)CH_AH_BPh), 3.16–3.21 (1H, d, *J* 6.3, C(3)*H*), 3.28 (1H, d, *J* 13.9, C(4)CH_AH_BPh), 3.67 (1H, q, *J* 6.5, C(α)*H*), 7.13–7.30 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 8.5 (C(4)CH_2CH_3), 13.3 (C(3)*Me*), 19.0 (C(α)*Me*), 27.7 (C(4)CH_2CH_3), 38.7 (C(4)CH_2Ph), 53.7 (*C*(4)), 64.5 (*C*(3)), 69.1 (*C*(α)), 127.2, 127.7, 128.1, 128.3, 128.8, 130.3 (*o*-, *m*-, *p*-*Ph*), 136.9, 140.7 (*i*-*Ph*), 175.6 (*C*(5)); *m*/*z* (ESI^+) 669 ($[2M+Na]^+$, 100%), 346 ($[M+Na]^+$, 70%), 324 ($[M+H]^+$, 38%); HRMS (ESI^+) $C_{21}H_{25}NNaO_2^+$ ($[M+Na]^+$) requires 346.1778; found 346.1780.

4.38. (3*S*,4*R*,α*S*)-*N*(2)-α-Methylbenzyl-3-phenyl-4-ethyl-4-methylisoxazolidin-5-one 81



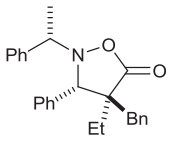
Following *general procedure* 3, LHMDS (1.0 M in THF, 0.08 mL, 0.08 mmol), **45** (23 mg, 0.08 mmol), methyl iodide (20 μL, 0.21 mmol) and THF (0.5 mL) gave **75**:**81** in 42:58 dr. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 20:1; increased to 40–60 °C petrol/Et_2O, 5:1) gave **81** as a colourless oil (6 mg, 25%, >99:1 dr); $[\alpha]_D^{24}$ +69.1 (*c* 0.4 in $CHCl_3$); ν_{max} (film) 2977 (C–H), 1767 (C=O); δ_H (400 MHz, $CDCl_3$) 0.81 (3H, t, *J* 7.5, C(4)CH_2CH_3), 1.25 (3H, s, C(4)*Me*), 1.49 (3H, d, *J* 6.6, C(α)*Me*), 0.92–1.00 (1H, m, C(4)CH_A), 1.86–1.95 (1H, m, C(4)CH_B), 4.13 (1H, q, *J* 6.6, C(α)*H*), 4.32 (3H, s, C(3)*H*), 7.11–7.36 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 8.0 (C(4)CH_2CH_3), 17.1 (C(α)*Me*), 18.7 (C(4)*Me*), 25.4 (C(4)CH_2), 49.3 (*C*(4)), 62.7 (*C*(α)), 73.0 (*C*(3)), 127.5, 127.8, 128.1, 128.2, 128.4, 128.6 (*o*-, *m*-, *p*-*Ph*), 134.0, 141.2 (*i*-*Ph*), 177.1 (*C*(5)); *m*/*z* (ESI^+) 332 ($[M+Na]^+$, 42%), 310 ($[M+H]^+$, 15%); HRMS (ESI^+) $C_{20}H_{23}NNaO_2^+$ ($[M+Na]^+$) requires 332.1621; found 332.1626.

4.39. (*S*,*S*,*S*)-*N*(2)-α-Methylbenzyl-3-phenyl-4-allyl-4-ethylisoxazolidin-5-one 82



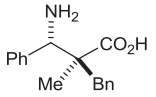
Following *general procedure* 3, LiHMDS (1.0 M in THF, 0.08 mL, 0.08 mmol), **45** (23 mg, 0.07 mmol), allyl iodide (30 μL, 0.21 mmol) and THF (0.5 mL) gave 77% conversion to **76**:**82** in 22:78 dr. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 20:1; increased to 40–60 °C petrol/Et_2O, 5:1) gave **82** as a colourless oil (13 mg, 67%, 93:7 dr); $[\alpha]_D^{24}$ +44.3 (*c* 0.5 in $CHCl_3$); ν_{max} (film) 2975 (C–H), 1768 (C=O); δ_H (400 MHz, $CDCl_3$) 0.83 (3H, t, *J* 7.5, C(4)CH_2CH_3), 1.00–1.09 (1H, m, C(4)$CH_AH_BCH_3$), 1.46 (3H, d, *J* 6.7, C(α)*Me*), 1.83–1.92 (1H, m, C(4)$CH_AH_BCH_3$), 2.04 (1H, dd, *J* 14.0, 10.7, C(4)$CH_AH_BCH{=}CH_2$), 2.74 (1H, dd, *J* 14.0, 4.6, C(4)$CH_AH_BCH{=}CH_2$), 4.12 (1H, q, *J* 6.7, C(α)*H*), 4.69 (1H, s, C(3)*H*), 5.29 (2H, app d, *J* 13.4, C(4)$CH_2CH{=}CH_2$), 5.74–5.84 (1H, m, C(4)$CH_2CH{=}CH_2$), 7.21–7.34 (10H, m, *Ph*); δ_C (100 MHz) 8.0 (C(4)CH_2CH_3), 13.9 (C(α)*Me*), 25.3 (C(4)CH_2CH_3), 36.0 (C(4)$CH_2CH{=}CH_2$) 52.9 (*C*(4)), 62.9 (*C*(α)), 71.3 (*C*(3)), 119.9 (C(4)$CH_2CH{=}CH_2$), 127.5, 127.9, 128.3, 128.4, 133.7, 134.5 (*o*-, *m*-, *p*-*Ph*), 133.7 (C(4)$CH_2CH{=}CH_2$), 141.2, 143.4 (*i*-*Ph*), 175.9 (*C*(5)); *m*/*z* (ESI^+) 693 ($[2M+Na]^+$, 100%), 358 ($[M+Na]^+$, 33%), 336 ($[M+H]^+$, 21%); HRMS (ESI^+) $C_{22}H_{25}NNaO_2^+$ ($[M+Na]^+$) requires 358.1778; found 358.1776.

4.40. (*S*,*S*,*S*)-*N*(2)-α-Methylbenzyl-3-phenyl-4-benzyl-4-ethylisoxazolidin-5-one 83



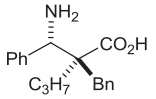
Following *general procedure* 3, LiHMDS (1.0 M in THF, 0.08 mL, 0.08 mmol), **45** (23 mg, 0.07 mmol), benzyl bromide (40 μL, 0.21 mmol) and THF (0.5 mL) gave **77**:**83** in 21:79 dr. Purification via flash column chromatography (silica, gradient elution, 40–60 °C petrol/Et_2O, 20:1; increased to 40–60 °C petrol/Et_2O, 5:1) gave **83** as a colourless oil (20 mg, 55%, >99:1 dr); $[\alpha]_D^{24}$ +55.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2950 (C–H), 1770 (C=O); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, t, J 7.6, C(4)CH_2CH_3), 1.10 (3H, d, J 6.7, C(α)*Me*), 1.17–1.25 (1H, m, C(4)$CH_AH_BCH_3$), 1.83–1.89 (1H, m, C(4)$CH_AH_BCH_3$), 2.45 (1H, d, *J* 14.2, C(4)CH_AH_BPh), 3.54 (1H, d, *J* 14.2, C(4)CH_AH_BPh), 3.80 (1H, q, J 6.7, C(α)*H*), 4.50 (1H, s, C(3)*H*), 7.16–7.41 (15H, m, Ph); δ_C (100 MHz, $CDCl_3$) 8.2 (C(4)CH_2CH_3), 18.1 (C(α)*Me*), 27.4 (C(4)CH_2CH_3), 38.3 (C(4)CH_2Ph), 54.8 (*C*(4)), 63.1 (*C*(α)), 69.8 (*C*(3)), 127.1, 127.3, 127.7, 128.1, 128.4, 128.5, 128.8, 130.5 (*o*-, *m*-, *p*-*Ph*), 134.9, 137.0, 141.2 (*i*-Ph), 176.5 (C(5)); *m*/*z* (ESI^+) 408 ($[M+Na]^+$, 100%), 386 ($[M+H]^+$, 52%); HRMS (ESI^+) $C_{26}H_{27}NNaO_2^+$ ($[M+Na]^+$) requires 408.1934; found 408.1929.

4.41. (*S*,*S*)-2-Benzyl-2-methyl-3-amino-3-phenylpropanoic acid 87



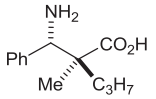
Following *general procedure* 4, **53** (45 mg, 0.12 mmol), Pearlman's catalyst (23 mg) and *tert*-butanol (1 mL) gave **87** as a white powder (29 mg, 90%, >99:1 dr); mp 168–170 °C; $[\alpha]_D^{25}$ −26.9 (*c* 1.0 in MeOH); ν_{max} (KBr) 3320 (NH_3^+ st), 1646 (COO^- as st), 1454 (NH_2^+ δ); δ_H (400 MHz, CD_3OD) 0.83 (3H, s, C(2)*Me*), 2.35 (1H, d, *J* 12.9, C(2)CH_AH_BPh), 3.31 (1H, d, *J* 12.9, C(2)CH_AH_BPh), 4.20 (1H, s, C(3)*H*), 7.10–7.40 (10H, m, Ph); δ_C (100 MHz, CD_3OD) 17.0 (C(2)*Me*), 44.6 (C(2)CH_2Ph), 52.4 (*C*(2)), 63.2 (*C*(3)), 126.2, 127.8, 127.9, 128.2, 128.7, 130.5 (*o*-, *m*-, *p*-Ph), 138.8, 140.8 (*i*-Ph), 182.8 (C(1)); *m*/*z* (ESI^+) 292 ($[M+Na]^+$, 73%), 270 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{17}H_{20}NO_2^+$ ($[M+H]^+$) requires 270.1489; found 270.1487.

4.42. (*S*,*S*)-2-Benzyl-2-propyl-3-amino-3-phenylpropanoic acid 89



Following *general procedure* 4, **65** (50 mg, 0.14 mmol), Pearlman's catalyst (25 mg) and *tert*-butanol (3 mL) gave **89** as a white powder (35 mg, 96%, >99:1 dr); mp 150–152 °C; $[\alpha]_D^{25}$ −25.3 (*c* 1.0 in MeOH); ν_{max} (KBr) 3418 (NH_3^+ st), 1644 (COO^- as st); δ_H (400 MHz, D_2O) 0.59 (3H, t, *J* 7.2, C(2)$CH_2CH_2CH_3$), 0.77–0.85 (1H, m, C(2)$CH_AH_BCH_2CH_3$), 1.00–1.08 (1H, m, C(2)$CH_AH_BCH_2CH_3$), 1.28–1.41 (2H, m, C(2)$CH_2CH_2CH_3$), 2.79 (1H, d, *J* 13.4, C(2)CH_AH_BPh), 3.18 (1H, d, *J* 13.4, C(2)CH_AH_BPh), 4.22 (1H, s, C(3)*H*), 7.15–7.28 (10H, m, *Ph*); δ_C (100 MHz, D_2O) 14.0 (C(2)$CH_2CH_2CH_3$), 16.3 (C(2)$CH_2CH_2CH_3$), 33.2 (C(2)$CH_2CH_2CH_3$), 39.4 (C(2)CH_2Ph), 54.3 (*C*(2)), 59.4 (*C*(3)), 126.9, 128.0, 128.7, 128.8, 129.0, 130.2 (*o*-, *m*-, *p*-*Ph*), 138.2, 147.4 (*i*-*Ph*), 182.2 (*C*(1)); *m*/*z* (ESI^-) 296 ($[M-H]^-$, 100%); HRMS (ESI^-) $C_{19}H_{22}NO_2^-$ ($[M-H]^-$) requires 296.1656; found 296.1656.

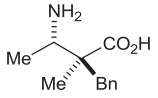
4.43. (*S*,*S*)-2-Methyl-2-propyl-3-amino-3-phenylpropanoic acid 90



Following *general procedure* 4, **52** (80 mg, 0.25 mmol), Pearlman's catalyst (40 mg) and *tert*-butanol (3 mL) gave **90** as a white powder (43 mg, 78%, >99:1 dr); mp 144–146 °C; $[\alpha]_D^{25}$ −29.0 (*c* 1.0 in MeOH); ν_{max} (KBr) 3385 (NH_2^+ st), 1644 (COO^- as st), 1456 (NH_3^+ δ); δ_H (500 MHz, CD_3OD) 0.94 (3H, s, C(2)*Me*), 0.94 (3H, t, *J* 6.9, C(2)$CH_2CH_2CH_3$), 1.35–1.41 (1H, m, CH_2), 1.43–1.53 (2H, m, CH_2), 1.65–1.71 (1H, m, CH_2), 4.21 (1H, s, C(3)*H*), 7.40–7.44 (5H, m, Ph); δ_C

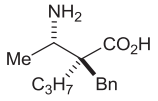
(125 MHz, CD_3OD) 14.9 (C(2)$CH_2CH_2CH_3$), 19.0 (C(2)$CH_2CH_2CH_3$), 20.3 (C(2)*Me*), 41.9 (C(2)$CH_2CH_2CH_3$), 49.5 (*C*(2)), 62.2 (*C*(3)), 129.4, 129.9, 130.0 (*o*-, *m*-, *p*-*Ph*), 137.6 (*i*-*Ph*), 182.0 (C(1)); *m*/*z* (ESI^+) 465 ($[2M+Na]^+$, 100%), 244 ($[M+Na]^+$, 58%), 222 ($[M+H]^+$, 41%); HRMS (ESI^+) $C_{13}H_{19}NNaO_2^+$ ($[M+Na]^+$) requires 244.1308; found 244.1305.

4.44. (*S*,*S*)-2-Benzyl-2-methyl-3-aminobutanoic acid 91



Following *general procedure* 4, **57** (22 mg, 0.07 mmol), Pearlman's catalyst (11 mg) and *tert*-butanol (1 mL) gave **91** as a white powder (13 mg, 90%, >99:1 dr); mp 184–186 °C; $[\alpha]_D^{25}$ −17.6 (*c* 0.5 in MeOH); ν_{max} (KBr) 3443 (NH_3^+ st), 1643 (COO^- as st); δ_H (400 MHz, D_2O) 1.11 (3H, d, *J* 6.8, C(4)H_3), 1.81 (3H, s, C(2)*Me*), 2.58 (1H, d, *J* 13.1, C(2)CH_AH_BPh), 2.87 (1H, d, *J* 13.1, C(2)CH_AH_BPh), 3.12 (1H, q, *J* 6.8, C(3)H), 7.09–7.23 (5H, m, *Ph*); δ_C (100 MHz, D_2O) 15.4 (C(2)*Me*), 16.7 (C(2)), 44.4 (C(2)CH_2*Ph*), 51.9 (*C*(2)), 59.3 (*C*(3)), 128.6, 130.3, 131.2 (*o*-, *m*-, *p*-*Ph*), 138.3 (*i*-*Ph*), 183.2 (C(1)); *m*/*z* (ESI^+) 230 ($[M+Na]^+$, 100%), 208 ($[M+H]^+$, 41%); HRMS (ESI^+) $C_{12}H_{17}NNaO_2^+$ ($[M+Na]^+$) requires 230.1151; found 230.1152.

4.45. (*S*,*S*)-2-Benzyl-2-propyl-3-aminobutanoic acid 92



Following *general procedure* 4, **67** (20 mg, 0.05 mmol), Pearlman's catalyst (10 mg) and *tert*-butanol (1 mL) gave **92** as a white powder (10 mg, 86%, >99:1 dr); mp 156–158 °C; $[\alpha]_D^{25}$ −23.4 (*c* 0.5 in MeOH); ν_{max} (KBr) 3424 (NH_3^+ st), 1643 (COO^- as st); δ_H (400 MHz, D_2O) 0.75 (3H, t, *J* 6.8, C(2)$CH_2CH_2CH_3$), 1.13 (3H, d, *J* 6.8, C(4)H_3), 1.16–1.21 (2H, m, CH_2), 1.26–1.39 (2H, m, CH_2), 2.77 (1H, d, *J* 13.4, C(2)CH_AH_BPh), 2.88 (1H, d, *J* 13.4, C(2)CH_AH_BPh), 3.30 (1H, q, *J* 6.8, C(3)*H*), 7.08–7.24 (5H, m, Ph); δ_C (100 MHz, D_2O) 14.3 (C(2)$CH_2CH_2CH_3$), 15.1 (C(2)$CH_2CH_2CH_3$), 16.4 (C(4)), 33.3 (C(2)$CH_2CH_2CH_3$), 39.3 (C(2)CH_2Ph), 51.3 (*C*(2)), 53.1 (*C*(3)), 127.1, 128.8, 130.1 (*o*-, *m*-, *p*-*Ph*), 138.0 (*i*-*Ph*), 182.3 (C(1)); *m*/*z* (ESI^-) 234 ($[M-H]^-$, 100%); HRMS (ESI^-) $C_{14}H_{20}NO_2^-$ ($[M-H]^-$) requires 234.1500; found 234.1499.

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