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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 1135–1145

Asymmetric synthesis of α-mercapto-β-amino acid derivatives: application to the synthesis of polysubstituted thiomorpholines

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Received 22 March 2006; accepted 10 April 2006
Available online 6 May 2006

Abstract—Tandem conjugate addition of homochiral lithium *N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amide to *tert*-butyl cinnamate and enolate trapping with Ts*S*^{t}Bu proceeds with high diastereoselectivity to give a homochiral *anti*-α-*tert*-butylthio-β-amino ester. Stepwise deprotection gives the corresponding free α-*tert*-butylthio-β-amino acid without epimerisation. Tandem conjugate addition of homochiral lithium *N*-allyl-*N*-(α-methylbenzyl)amide to *tert*-butyl cinnamate and enolate trapping with Ts*S*^{t}Bu followed by conversion of the *S*-*tert*-butyl group to a disulphide, and reduction with Lalancette's reagent generates polysubstituted thiomorpholine derivatives.

1. Introduction

The synthesis of β-amino acids and their derivatives has been an actively pursued area of research for many years.[1] Previous investigations from this laboratory have demonstrated that the conjugate addition of a homochiral lithium amide derived from α-methylbenzylamine to an α,β-unsaturated carbonyl compound is a highly versatile protocol for the synthesis of β-amino carbonyl compounds.[2] The preparation of *anti*-α-alkyl- and *anti*-α-hydroxy-β-amino esters is readily achieved upon treatment of the intermediate β-amino enolate with an alkyl halide[3] or (camphorsulphonyl)oxaziridine,[4] respectively. Recent studies by a number of groups have demonstrated that the α-mercapto-β-amino carbonyl motif displays potent biological activity: for instance, pseudotripeptides containing an α-mercapto-β-amino acid residue have been shown to be potent inhibitors of aminopeptidase A,[5] tetanus neurotoxin[6] and botulinum neurotoxin type B,[7] whilst azetidinones derived from α-mercapto-β-amino acids display potent inhibition of cholesterol absorption.[8] As a result of the biological activity associated with this motif, we proposed to extend our conjugate addition methodology to allow for the preparation of α-alkylthio-β-amino esters, through tandem conjugate addition of a homochiral lithium amide to an α,β-unsaturated ester and trapping of the resultant β-amino enolate with an electrophilic source of sulphur. The results of these investigations are delineated herein.

2. Results and discussion

2.1. Preparation of α-alkylthio-β-amino esters

Initial studies sought to develop a one-pot synthesis of α-alkylthio-β-amino esters and various electrophilic sulphur sources were examined viz. *N*-phenylthio-ε-caprolactam, TsSBn,[9] Ts*S*^{t}Bu,[10] TsSCPh$_3$[10] and S_8. Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to *tert*-butyl cinnamate at −78 °C was followed by treatment with 2 equiv of the electrophilic sulphur source for 1 h at −78 °C. Standard aqueous work-up gave the crude reaction product, which was analysed by ^{1}H NMR spectroscopy (Scheme 1). When *N*-phenylthio-ε-caprolactam was utilised as the electrophilic sulphur source, two diastereoisomeric products **2** and **3** were observed in a ratio of 94:6. Lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide has previously been shown to exhibit high diastereocontrol upon conjugate addition to *tert*-butyl cinnamate[11] and therefore **2** and **3** were assumed to be epimeric at C(2). The relative configuration of

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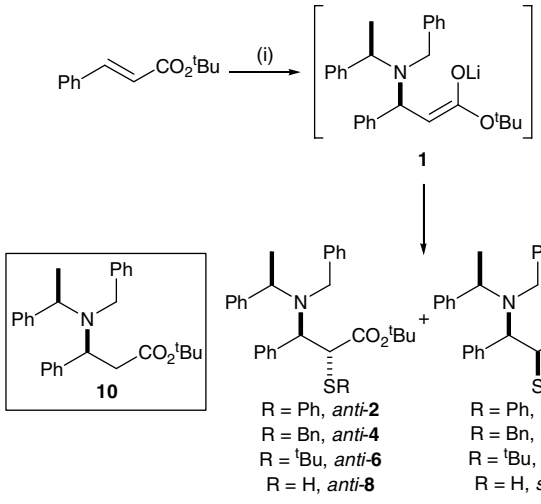
doi:10.1016/j.tetasy.2006.04.004

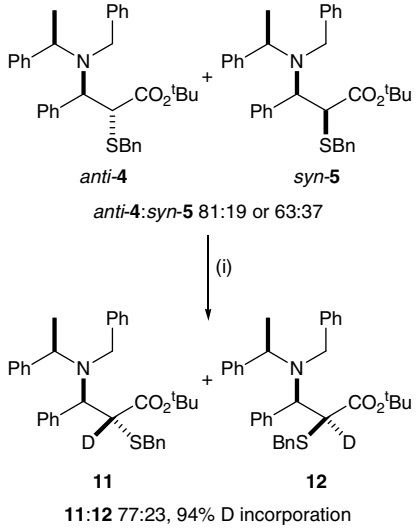


Sulphur source	R	*anti*:*syn* ratio[a]	Yield[b] *anti* (de) %	Yield[b] *syn* (de) %
N-phenylthio-ε-caprolactam	Ph	94:6	76 (>98)	-
TsSBn	Bn	85:15	80[c] (70)	-
TsS^{t}Bu	^{t}Bu	98:2	78 (>98)	-
$TsSCPh_3$	CPh_3	-	-	-
S_8	H[d]	85:15	51 (>98)	9 (>98)

Scheme 1. Reagents and conditions: (i) lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h, then electrophilic sulphur source, −78 °C, 1 h, then NH_4Cl (satd aq) [[a]crude; [b]purified; [c]*anti* and *syn* diastereoisomers inseparable; [d]after reduction with $NaBH_4$ in EtOH].

the major product **2** was then assigned as *anti* based upon the previously demonstrated preference for protonation or alkylation of β-amino enolates *anti* to the amino group.[12] Purification allowed isolation of *anti*-**2** in 76% yield and >98% de (Scheme 1). Analogous procedures with TsSBn and TsS^{t}Bu as the electrophilic sulphur sources gave an inseparable 85:15 mixture of *anti*-**4**:*syn*-**5** and a separable 98:2 mixture of *anti*-**6**:*syn*-**7**, respectively. When $TsSCPh_3$ was used as the electrophilic sulphur source, a complex mixture was obtained, of which *tert*-butyl cinnamate and β-amino ester **10** were the only identifiable components. Quenching β-amino enolate **1** with S_8, meanwhile, produced an intractable mixture containing several polysulphides. Reduction of the crude reaction mixture with $NaBH_4$ in EtOH, however, gave a separable 85:15 mixture of *anti*-**8**:*syn*-**9** (Scheme 1). From these results, reaction of enolate **1** with TsS^{t}Bu was the most diastereoselective, giving *anti*-**6** in 78% yield and >98% de after purification (Scheme 1).

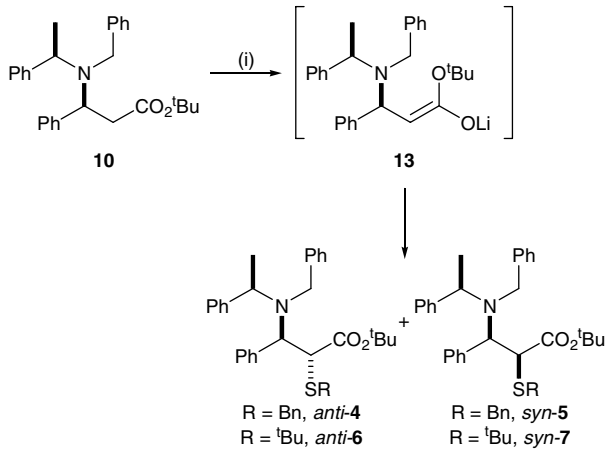
It was postulated that reduced selectivity of the reaction of enolate **1** with TsSBn when compared to TsS^{t}Bu could be due to epimerisation of the products by unreacted **1**. A reverse addition was therefore investigated: a THF solution of **1** was added dropwise to a solution of TsSBn in THF at −78 °C over 20 min, giving an 81:19 mixture of *anti*-**4**:*syn*-**5** (62% de). To discover if the low diastereoselectivity was due to post-reaction equilibration, the thermodynamic equilibrium ratio of *anti*-**4**:*syn*-**5** was determined. Equilibration of the 81:19 mixture of *anti*-**4**:*syn*-**5** (62% de) with KO^{t}Bu in CD_3OD allowed the incorporation of deuterium at the α-centre to be followed by ^{1}H NMR. This reached a plateau at 94% after 25 days, and a ratio of 72:28 for **11**:**12** was determined (44% de). Identical treatment of a 63:37 mixture of *anti*-**4**:*syn*-**5** (26% de)[13] gave the same result. These experiments suggest that the low diastereoselectivity of the reaction of enolate **1** with TsSBn is a kinetic phenomenon and is not due to a post-reaction equilibration (Scheme 2).



Scheme 2. Reagents and conditions: (i) KO^{t}Bu, CD_3OD, rt, 25 days.

The geometry of β-amino enolates such as **1** has been shown to play an important role in determining the level of diastereofacial selectivity of enolate alkylation reactions.[14] Enolate trapping studies have shown that whilst the (*Z*)-β-amino enolate is produced from conjugate addition of a lithium amide to an α,β-unsaturated ester, deprotonation of a β-amino ester with LDA proceeds via an Ireland transition state to generate the diastereoisomeric (*E*)-β-amino enolate.[14] In order to investigate the effect of

enolate geometry on the reaction selectivity, a stepwise protocol was performed. Deprotonation of **10**[15] with LDA gave (*E*)-enolate **13**, with subsequent addition of TsSBn at −78 °C giving almost a complete reversal in the diastereofacial selectivity: *syn*-**5** was obtained as the major diastereoisomer of an inseparable 21:79 mixture of *anti*-**4**:*syn*-**5** (58% de). Disappointingly, when TsS^tBu was used as the electrophilic sulphur source, no incorporation of sulphur was observed. To investigate this reaction further, TsS^tBu was added to enolate **13** and stirred for 1 h at −78 °C, followed by addition of TsSBn and stirring for a further hour at −78 °C. ^1H NMR spectroscopic analysis of the crude reaction product indicated that a mixture of *S*-benzyl products *anti*-**4** and *syn*-**5** was formed exclusively, with no trace of S^tBu incorporation detected. Interestingly, when the temperature of the quench was raised to 0 °C, addition of TsS^tBu to enolate **13** gave 35% conversion to a 98:2 mixture of *anti*-**6**:*syn*-**7** (96% de) (Scheme 3).



Sulphur source	R	Conditions	*anti*:*syn* ratio[a]	Yield *syn* (de) %
TsSBn	Bn	(i)	21:79	81[b] (58)
TsS^tBu	^tBu	(i)	-	-
TsS^tBu	^tBu	(ii)	98:2	35[c]

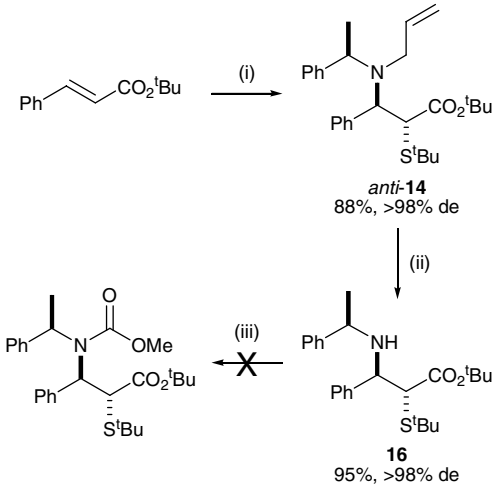
Scheme 3. Reagents and conditions: (i) LDA, THF, −78 °C, 30 min, then TsSR, −78 °C, 1 h, then NH_4Cl (satd aq); (ii) LDA, THF, −78 °C, 30 min, then TsSR, 0 °C, 1 h, then NH_4Cl (satd aq) [[a]crude; [b]*anti* and *syn* diastereoisomers inseparable; [c]conversion].

2.2. Preparation of 2-(*tert*-butylthio)-3-amino-3-phenylpropanoic acid

With a reliable protocol for the formation of α-*tert*-butylthio-β-amino ester *anti*-**6** in hand, attention next turned to deprotection to the corresponding β-amino acid. N-Debenzylation of β-amino esters is usually performed via hydrogenolysis mediated by a palladium catalyst, but it was predicted that this may be problematic in the case of *anti*-**6** due to poisoning of the catalyst by sulphur.[16] Nonetheless, it was of interest to determine whether the bulky *tert*-butyl protecting group on the sulphur atom would retard the rate of catalyst poisoning and therefore allow hydrogenolysis. A range of hydrogenolysis conditions were investigated for deprotection of *anti*-**6**, but no N-debenzylation was observed.

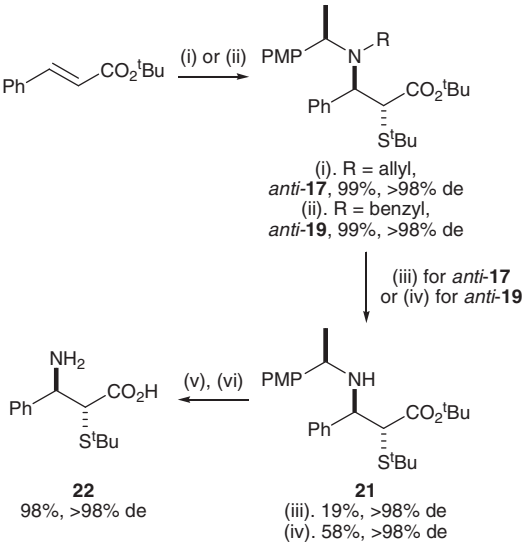
An alternative strategy to allow for the synthesis of α-mercapto-β-amino acid derivatives was therefore sought by altering the N-protecting groups of the lithium amide. A range of homochiral lithium amides have been developed within this laboratory, which allows for N-deprotection without recourse to hydrogenolysis. Lithium *N*-allyl-*N*-(α-methylbenzyl)amide enables stepwise deprotection via deallylation, carbamate formation and acid-promoted debenzylation,[17] whilst lithium *N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amide[18] and lithium *N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amide[19] allow for oxidative deprotection, and these were therefore evaluated for their utility in the synthesis of α-mercapto-β-amino acid derivatives.

The conjugate addition of lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amide to *tert*-butyl cinnamate and quenching with TsS^tBu gave a 97:3 mixture of *anti*-**14**:*syn*-**15**, which was purified to a single diastereoisomer *anti*-**14** in 88% isolated yield. Removal of the *N*-allyl group of *anti*-**14** with Wilkinson's catalyst[20] gave **16** in 65% yield, whilst deprotection with $Pd(PPh_3)_4$ and *N*,*N*-dimethylbarbituric acid (NNDMBA)[21] gave **16** in 95% yield. Subsequent attempts to reprotect the nitrogen of **16** with a carbamate group were unsuccessful under a variety of conditions and so the use of this lithium amide was abandoned (Scheme 4).



Scheme 4. Reagents and conditions: (i) lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h, then TsS^tBu, −78 °C, 1 h, then NH_4Cl (satd aq); (ii) $Pd(PPh_3)_4$, NNDMBA; (iii) MeOCOCl, Et_3N, DCM, rt, 12 h.

For conjugate addition of lithium (*R*)-*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amide and lithium (*R*)-*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amide, the reaction protocol was modified to allow warming to room temperature over 12 h after the addition of TsS^tBu to effect efficient incorporation of the electrophile, giving exclusively *anti*-**17** and *anti*-**19** in excellent yield (Scheme 5). Attempted deallylation of *anti*-**17** using Wilkinson's catalyst returned only a complex mixture after 6 days; addition of magnesium chloride to the reaction mixture[22] did not prove fruitful. Use of $Pd(PPh_3)_4$ and NNDMBA was not effective even after extended reaction times: only 50% of the starting material was recovered after 24 h with no deallylation taking place. Alternative literature N-deallylation strategies mediated



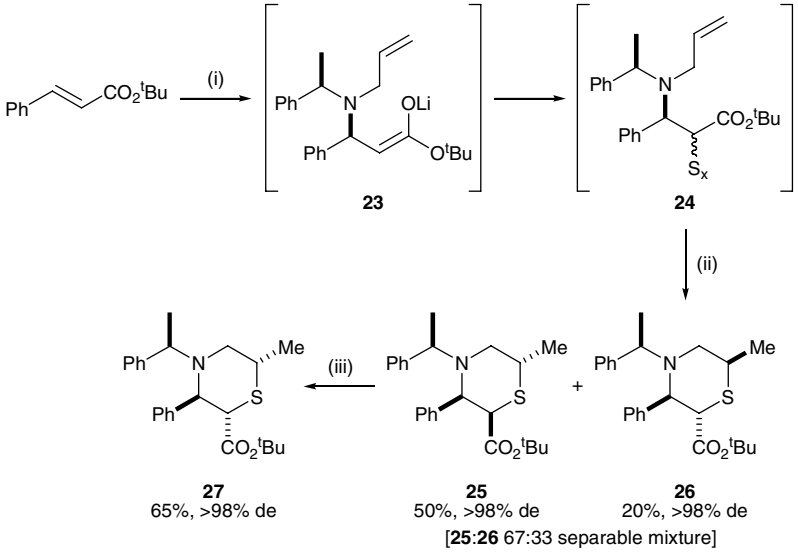
Scheme 5. Reagents and conditions: (i) lithium (*R*)-*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amide, THF, −78 °C, 2 h, then Ts*S*^{t}Bu, −78 °C to rt, 12 h, then NH_4Cl (satd aq); (ii) lithium (*R*)-*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amide, THF, −78 °C, 2 h, then Ts*S*^{t}Bu, −78 °C to rt, 12 h; (iii) TolSH, AIBN, benzene, reflux; (iv) CAN, MeCN–H_2O (v:v 5:1), −7 °C, 5 min; (v) TFA–DCM (v:v 1:1), 55 °C, 24 h; (vi) Dowex 50WX8-200 [PMP = *p*-methoxyphenyl].

by dibenzylidenediacetone palladium[23] or Grubbs' catalyst[24] similarly failed. Radical deallylation was next assayed:[25] this gave **21** in only 19% yield and recovered starting material in 32% yield (Scheme 5). Attempted bis-deprotection of *anti*-**19** with ceric ammonium nitrate (CAN)[19] was also unsuccessful, giving a complex mixture, while mono-debenzylation under the reported procedure[26] gave only 4% yield of **21**. However, extensive reaction optimisation showed that treatment of *anti*-**19** with CAN at −7 °C for 5 min allowed isolation of mono-debenzylated **21** in 58% yield and >98% de (Scheme 5). With **21** available in acceptable yield, it was anticipated that the removal of the *N*-(*p*-methoxybenzyl) group and *tert*-butyl ester functionality could be achieved in one-pot upon treatment with TFA. In the event, treatment of **21** at room temperature for 24 h cleaved only the *tert*-butyl ester but at 55 °C both protecting groups were removed, giving amino acid **22** in 98% yield and as a single diastereoisomer after ion exchange chromatography (Scheme 5).

2.3. Preparation of polysubstituted thiomorpholines

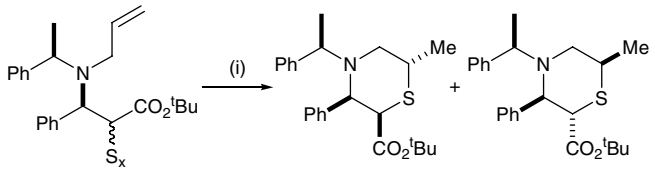
During the course of these studies concerned with the synthesis of α-alkylthio-β-amino esters, it was noted that whilst the tandem conjugate addition of lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amide to *tert*-butyl cinnamate and quenching with 2 equiv of S_8 gave the expected complex mixture of polysulphides **24**, subsequent reduction of crude mixture **24** with $NaBH_4$ gave a 67:33 ratio of thiomorpholines **25** and **26**. Chromatographic separation allowed isolation of **25** in 50% yield and **26** in 20% yield (Scheme 6). The thiomorpholine sub-unit is a commonly recurring sub-structure in several drugs and drug-like molecules that exhibit potent biological activity,[27] and it was therefore of interest to probe the formation of **25** and **26** in some detail. The relative configurations of both **25** and **26** were first established through ^3J coupling constant analysis between C(2)H and C(3)H, and between $C(5)H_2$ and C(6)H, in the ^{1}H NMR spectra. Additionally, epimerisation of **25** with KO^{t}Bu in MeOH gave the thermodynamically more stable isomer **27** whilst identical treatment of **26** did not produce any epimerisation of the C(2) centre, thus further serving to confirm the relative stereochemistry of **25** and **26**. The absolute stereochemistry of (2*R*,3*R*,6*S*,α*R*)-**25** and (2*S*,3*R*,6*R*,α*R*)-**26** was then assigned on the assumption that the C(3) stereocentre was formed in a highly diastereoselective manner from the conjugate addition of the lithium amide (Scheme 6).[11]

In order to optimise the cyclisation reaction of **24** to thiomorpholines **25** and **26**, some highly purified **24** was



Scheme 6. Reagents and conditions: (i) lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amide, THF, −78 °C, 2 h, then S_8, −78 °C, 1 h, then NH_4Cl (satd aq); (ii) $NaBH_4$, EtOH, 0 °C to rt, 12 h; (iii) KO^{t}Bu, MeOH, rt, 4 days.

prepared, removing by precipitation and chromatography any trace amounts of impurities, and especially unreacted sulphur. The reduction of **24** was then studied with various reducing agents (Scheme 7). The use of $NaBH_4$ gave only partial conversion to a 67:33 mixture of thiomorpholines **25** and **26**, which were isolated in 45% combined yield. A mixture of $NaBH_4$ and S_8 proved more efficient and no starting material could be detected in the ^1H NMR spectrum of the crude reaction mixture. The best result was achieved with a 1:3 mol ratio of $NaBH_4$–S_8; this corresponds to the Lalancette reagent, $NaBH_2S_3$, which has been shown to have reducing properties that are intermediate between $NaBH_4$ and $LiAlH_4$.[28] No difference in reaction efficiency was noted when either a 1:3 mol ratio of solid $NaBH_4$ and S_8 was added to a solution of **24** in EtOH, or when the Lalancette reagent was preformed in THF and added to a solution of **24** in EtOH. Thus, thiomorpholines **25** and **26** were produced as a 67:33 mixture and isolated in 85% combined yield from **24**.



24 **25** **26**

Reagents	Solvent	Yield 25+26 (%)[c]
S_8	EtOH	0
$NaBH_4$	EtOH	45
$NaBH_4$:S_8 (1:6)[a]	EtOH	80
$NaBH_4$:S_8 (1:3)[a]	EtOH	85
$NaBH_4$:S_8 (1:3)[a,b]	THF-EtOH	85

Scheme 7. Reagents and conditions: (i) reagents, solvent, 0 °C to rt, 12 h [[a]molar ratio; [b]preformed Lalancette reagent; [c]a separable 67:33 mixture of thiomorpholines **25** and **26** was produced; combined yields are reported].

The cyclisations of δ,ε- or ε,ζ-unsaturated thiols via radical chain processes involving homolytic fission of the S–H bond, 6-*exo* cyclisation of the resultant *S*-radical onto the double bond, and chain propagation by H-atom abstraction from the chain carrier are well documented[29] and have been shown to proceed readily even at room temperature.[30] The mechanism for the cyclisation was therefore postulated to involve reduction of the mixture of polysulphides **24** to the corresponding mixture of thiols **28**. Generation of a thiol radical **29** is then immediately followed by cyclisation onto the allyl group to generate the thiomorpholine skeleton **30**. Chain propagation results from H-atom abstraction (Fig. 1). The higher yield of thiomorpholines obtained with the Lalancette reagent therefore presumably arises because the reagent is more efficient in effecting the reduction of polysulphides **24** to thiols **28** than $NaBH_4$ alone. Further corroboration for this mechanism was obtained from labelling studies to determine the origin of the hydrogen atom that appears at the C(6) methyl group: these indicated that the hydrogen source is a proton from the solvent (Scheme 8), presumably as a result of exchange of the acidic S–H proton of **28** for deuterium in the solvent.

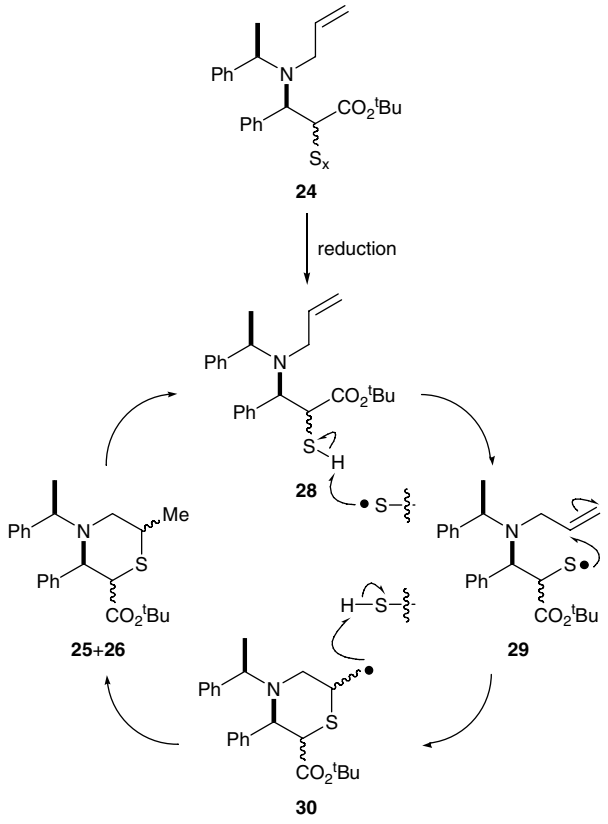
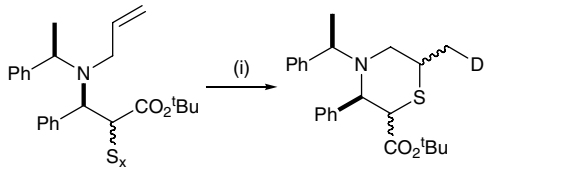


Figure 1. Postulated mechanism for the cyclisation of **24** to thiomorpholines **25** and **26**.

The observation that thiomorpholine **25** is the major product suggests that the cyclisation reaction proceeds without epimerisation of the C(2)-stereocentre, since no trace of the thermodynamically more stable thiomorpholine **27** was observed. It was therefore hypothesised that the 67:33 mixture of thiomorpholines **25** and **26** was a result of poor stereocontrol upon reaction of β-amino enolate **23** with S_8 giving **24** with an *anti*:*syn* ratio of 67:33, rather than stereochemical drift during the cyclisation to thiomorpholines **25** and **26**. To investigate the stereoselectivity of the cyclisation reaction, *anti*-**14** (of known 94% de) was treated with 2-nitrobenzenesulphenyl chloride to give disulphide **32** in 60% yield and 88% de.[31] Reduction of **32** with Lalancette's reagent in EtOH gave thiomorpholine **25** in 88% de, consistent with cyclisation of **32** to thiomorpholine **25** being stereospecific (Scheme 9). Therefore, assuming that both reactions proceed via the corresponding thiol intermediate, this result supports the hypothesis that the 67:33 mixture of thiomorpholines **25** and **26** arises because of low diastereoselectivity of the reaction of enolate **23** with S_8, giving polysulphides **24** with an overall *anti*:*syn* ratio of 67:33 (Scheme 6).

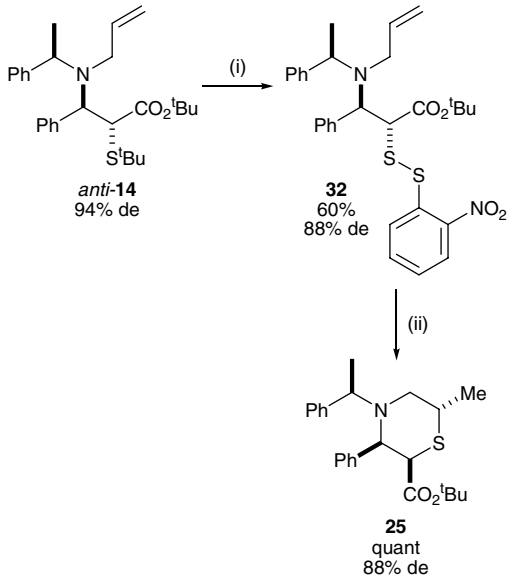
The following transition states for the stereospecific cyclisations of the intermediate thiols *anti*-**33** and *syn*-**34** to the corresponding thiomorpholines **25** and **26**, respectively, are proposed. In the case of *anti*-**33**, cyclisation presumably proceeds via the chair-like transition state **35**: this places only the C(2)-*tert*-butyl ester substituent in an axial position. For *syn*-**34**, however, a boat-like transition state **36**



24 31

Solvent	Reducing agent	D incorporation (%)
CD_3OD	$NaBH_4$:S_8 (1:3)	75
CH_3OD	$NaBH_4$:S_8 (1:3)	75
CH_3OH	$NaBD_4$:S_8 (1:3)	0

Scheme 8. Reagents and conditions: (i) reducing agent, solvent, 0 °C to rt, 12 h.



Scheme 9. Reagents and conditions: (i) 2-nitrobenzenesulphenyl chloride, AcOH, rt, 2 h; (ii) $NaBH_2S_3$, EtOH, 0 °C to rt, 12 h.

is preferred because of the large $A_{1,2}$ strain or $A_{1,3}$ strain that would be present in either of the possible chair transition states (assuming that the *N*-α-methylbenzyl group preferentially lies equatorial). Cyclisation gives the observed stereochemical arrangement of thiomorpholines **25** and **26**, respectively (Fig. 2).

3. Conclusion

The tandem conjugate addition of a range of homochiral lithium amides to *tert*-butyl cinnamate and enolate trapping with a variety of electrophilic sulphur sources proceeds with generally high selectivity to generate the corresponding *anti*-α-alkylthio-β-amino ester. TsS^{t}Bu proved to be the most selective electrophilic sulphur source, giving *anti*-α-*tert*-butylthio-β-amino esters typically in >95% de, which could be purified chromatographically to single diastereoisomers. In the case of conjugate addition of lithium *N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amide and quenching with TsS^{t}Bu, the resultant homochiral N-protected *anti*-α-*tert*-butylthio-β-amino ester can be deprotected in a stepwise manner to give the corresponding α-*tert*-butylthio-β-amino acid. Meanwhile, conjugate addition of homochiral lithium *N*-allyl-*N*-(α-methylbenzyl)amide to *tert*-butyl cinnamate followed by addition of TsS^{t}Bu, conversion of the *S*-*tert*-butyl group to a disulphide, and reduction with Lalancette's reagent offers an efficient entry to differentially protected, polysubstituted thiomorpholine derivatives.

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. The solvents were dried according to the procedure outlined by Grubbs and co-workers.[32] Water was purified by an Elix® UV-10 system. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with $60F_{254}$ silica. The plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$ or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Elemental analyses were recorded by the microanalysis service of the Inorganic Chemistry Laboratory, University of

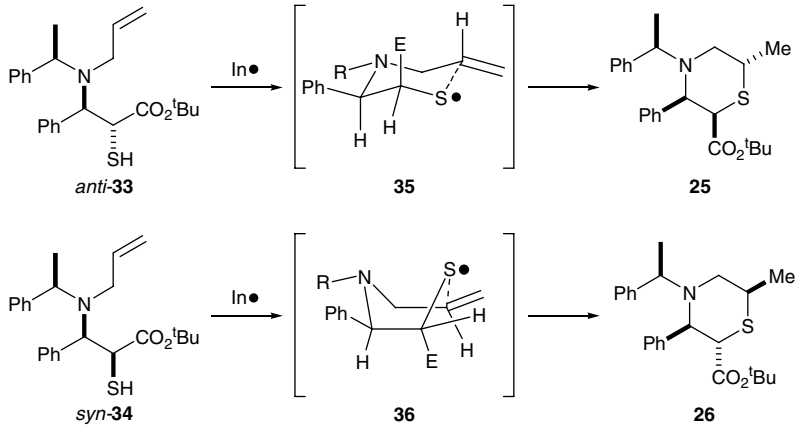


Figure 2. Postulated transition states for cyclisation [R = α-methylbenzyl, E = *tert*-butoxycarbonyl].

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 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. 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 and were internally calibrated with polyanaline in positive and negative modes, 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 procedures (a) and (b) for lithium amide conjugate addition/electrophilic sulphur quench

BuLi (2.5 M in hexanes, 1.55 equiv) was added dropwise via a syringe to a stirred solution of the requisite amine (1.6 equiv) in THF at −78 °C. After stirring for 30 min, a solution of *tert*-butyl cinnamate (1 equiv) in THF at −78 °C was added dropwise via a cannula. After stirring for a further 2 h at −78 °C, the reaction mixture was quenched with the requisite electrophilic sulphur source (2 equiv) and *either* (a) stirred at rt for 1 h; *or* (b) allowed to warm to rt over 12 h. Satd aq NH_4Cl was added and the reaction mixture was concentrated in vacuo. The residue was partitioned between DCM and H_2O. The organic phase was separated and the aqueous phase was extracted twice with DCM. The combined organic extracts were washed with brine, dried and concentrated in vacuo to give the crude reaction mixture.

4.3. *tert*-Butyl (2*R*,3*R*,α*R*)- and (2*S*,3*R*,α*R*)-2-phenylthio-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate (2*R*,3*R*,α*R*)-*anti*-2 and (2*S*,3*R*,α*R*)-*syn*-3

BuLi (2.5 M in hexanes, 0.61 mL, 1.52 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (331 mg, 1.57 mmol) in THF (2 mL), *tert*-butyl cinnamate (200 mg, 0.98 mmol) in THF (2 mL) and *N*-phenylthio-ε-caprolactam (433 mg, 1.96 mmol) were reacted according to *general procedure (a)* and gave a 94:6 mixture of *anti*-**2**:*syn*-**3**. Purification via flash column chromatography (eluent pentane–Et_2O 4:1) gave *anti*-**2** as a colourless oil (388 mg, 76%, >98% de); $C_{34}H_{37}NO_2S$ requires C, 78.0; H, 7.1; N, 2.7; S, 6.1; found C, 78.0; H, 7.0; N, 2.3; S, 5.5; $[\alpha]_D^{25} = +31.6$ (*c* 1.0, $CHCl_3$); ν_{max} (film) 1727; δ_H (500 MHz, $CDCl_3$) 1.19 (3H, d, *J* 6.9, C(α)*Me*), 1.44 (9H, s, C*Me*$_3$), 3.67 (1H, d, *J* 14.4, NCH_A), 3.80 (1H, d, *J* 14.4, NCH_B), 4.18 (1H, q, *J* 6.9, C(α)*H*), 4.19 (1H, d, *J* 11.7, C(2)*H*), 4.52 (1H, d, *J* 11.7, C(3)*H*), 7.07–7.65 (20H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 17.6, 27.8, 50.8, 54.1, 59.2, 63.5, 81.2, 126.6, 126.7, 127.4, 127.5, 127.7, 127.8, 127.9, 128.1, 128.4, 129.9, 132.8, 133.8, 136.4, 140.5, 144.2, 170.6; *m*/*z* (CI^+) 524 ([M+H$^+$], 58%), 300 (72), 212 (100), 196 (77), 91 (32).

Data for *syn*-**3**: δ_H (500 MHz, $CDCl_3$) 0.83 (9H, s, C*Me*$_3$), 1.11 (3H, d, *J* 6.9, C(α)*Me*), 3.79 (1H, d, *J* 13.8, NCH_A), 4.10 (1H, d, *J* 13.8, NCH_B), 4.24 (1H, q, *J* 6.9, C(α)*H*), 4.31 (1H, d, *J* 11.7, C(2)*H*), 4.45 (1H, *J* 11.7, C(3)*H*), 7.07–7.65 (20H, m, *Ph*).

4.4. *tert*-Butyl (2*R*,3*R*,α*R*)- and (2*S*,3*R*,α*R*)-2-benzylthio-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate (2*R*,3*R*,α*R*)-*anti*-4 and (2*S*,3*R*,α*R*)-*syn*-5

BuLi (2.5 M in hexanes, 0.61 mL, 1.52 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (331 mg, 1.57 mmol) in THF (2 mL), *tert*-butyl cinnamate (200 mg, 0.98 mmol) in THF (2 mL) and TsSBn (545 mg, 1.96 mmol) were reacted according to *general procedure (a)* and gave an 85:15 mixture of *anti*-**4**:*syn*-**5**. Purification via flash column chromatography (eluent pentane–Et_2O 4:1) gave an 85:15 mixture of *anti*-**4**:*syn*-**5** as a colourless oil (421 mg, 80%); $C_{35}H_{39}NO_2S$ requires C, 78.2; H, 7.3; N, 2.6; S, 6.0; found C, 78.2; H, 7.6; N, 2.45; S, 5.7; ν_{max} (film) 1719; *m*/*z* (CI^+) 538 ([M+H$^+$], 48%), 300 (100), 196 (50), 105 (28), 91 (50).

Data for *anti*-**6**: δ_H (500 MHz, $CDCl_3$) 0.94 (3H, d, *J* 6.8, C(α)*Me*), 1.06 (9H, s, C*Me*$_3$), 3.61 (1H, d, *J* 13.8, SCH_A), 3.66 (2H, AB system, *J* 13.1, NCH_2), 3.80 (1H, d, *J* 13.8, SCH_B), 3.89 (1H, d, *J* 11.7, C(2)*H*), 4.08 (1H, q, *J* 6.9, C(α)*H*), 4.15 (1H, d, *J* 11.7, C(3)*H*), 7.18–7.54 (20H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 14.4, 27.4, 35.4, 50.2, 51.4, 55.8, 60.7, 80.9, 126.7, 126.9, 127.2, 127.4, 127.7, 127.9, 128.0, 128.1, 128.3, 128.8, 129.1, 129.2, 129.8, 137.9, 139.2, 140.0, 143.8, 170.0.

Data for *syn*-**7**: δ_H (500 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6.9, C(α)*Me*), 1.60 (9H, s, C*Me*$_3$), 3.48 (1H, d, *J* 13.0, SCH_A), 3.59 (1H, d, *J* 13.0, SCH_B), 3.60 (2H, s, NCH_2), 3.61 (1H, d, *J* 12.0, C(2)*H*), 4.10 (1H, q, *J* 6.9, C(α)*H*), 4.45 (1H, d, *J* 12.0, C(3)*H*), 6.88–7.52 (20H, m, *Ph*).

4.5. *tert*-Butyl (2*R*,3*R*,α*R*)- and (2*S*,3*R*,α*R*)-2-*tert*-butylthio-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate (2*R*,3*R*,α*R*)-*anti*-6 and (2*S*,3*R*,α*R*)-*syn*-7

BuLi (2.5 M in hexanes, 0.61 mL, 1.52 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (331 mg, 1.57 mmol) in THF (2 mL), *tert*-butyl cinnamate (200 mg, 0.98 mmol) in THF (2 mL), and TsS^{t}Bu (479 mg, 1.96 mmol) were reacted according to *general procedure (a)* and gave a 98:2 mixture of *anti*-**6**:*syn*-**7**. Purification via flash column chromatography (eluent pentane–Et_2O 4:1) gave *anti*-**6** as a white solid (384 mg, 78%, >98% de); $C_{32}H_{41}NO_2S$ requires C, 76.3; H, 8.2; N, 2.8; S, 6.4; found C, 76.3; H, 8.5; N, 2.6; S, 6.7; mp 69–70 °C; $[\alpha]_D^{25} = -8.5$ (*c* 1.0, $CHCl_3$); ν_{max} (film) 1718; δ_H (500 MHz, $CDCl_3$) 1.12 (3H, d, *J* 6.8, C(α)*Me*), 1.13 (9H, s, C*Me*$_3$), 1.56 (9H, s, C*Me*$_3$), 3.77 (2H, app br d, *J* 12.0, C(2)*H*, NCH_A), 4.09 (1H, d, *J* 14.3, NCH_B), 4.15 (1H, q, *J* 6.8, C(α)*H*), 4.27 (1H, *J* 11.8, C(3)*H*), 7.13–7.42 (15H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 16.8, 28.0, 31.2, 44.1, 49.7, 51.0, 58.7, 63.9, 80.9, 126.6, 127.1, 127.5, 127.7, 127.8, 127.9,

128.3, 128.9, 130.0, 137.8, 140.6, 143.7, 172.8; *m/z* (CI^+) 504 ([M+H^+], 60%), 300 (100), 196 (60).

Data for *syn*-**5**: δ_H (500 MHz, $CDCl_3$) 1.10 (9H, s, CMe_3), 1.11 (3H, d, *J* 7.0, C(α)*Me*), 1.64 (9H, s, CMe_3), 3.65 (1H, d, *J* 14.9, NCH_A), 3.72 (1H, d, *J* 11.7, C(2)*H*), 3.91 (1H, q, *J* 7.0, C(α)*H*), 4.31 (1H, d, *J* 11.7, C(3)*H*), 4.39 (1H, d, *J* 14.9, NCH_B), 7.12–7.45 (15H, m, *Ph*).

4.6. *tert*-Butyl (2*R*,3*R*,α*R*)- and (2*S*,3*R*,α*R*)-2-mercapto-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate (2*R*,3*R*,α*R*)-*anti*-8 and (2*S*,3*R*,α*R*)-*syn*-9

BuLi (2.5 M in hexanes, 0.61 mL, 1.52 mmol), (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (331 mg, 1.57 mmol) in THF (2 mL), *tert*-butyl cinnamate (200 mg, 0.98 mmol) in THF (2 mL) and S_8 (502 mg, 1.96 mmol) were reacted according to *general procedure (a)* and gave a complex mixture of polysulphides. The crude reaction mixture was suspended twice in Et_2O (2 × 5 mL), and the insoluble sulphur was filtered off. The resultant yellow oil was redissolved in EtOH (10 mL), cooled to 0 °C and $NaBH_4$ (74 mg, 1.96 mmol) was added portionwise. After 30 min, the resultant orange suspension was allowed to warm to rt over 12 h. The solvent was evaporated in vacuo and the residue diluted with H_2O (5 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash chromatography (eluent pentane–Et_2O 9:1) gave *anti*-**8** as colourless crystals (first to elute, 225 mg, 51%, >98% de) and *syn*-**9** as a colourless oil (second to elute, 39 mg, 9%, >98% de).

Data for *anti*-**8**: $C_{28}H_{33}NO_2S$ requires C, 75.1; H, 7.4; N, 3.1; found C, 75.0; H, 7.3; N, 3.6; mp 193–194 °C, $[\alpha]_D^{22} = -749.2$ (*c* 0.6, $CHCl_3$), ν_{max} (film) 1730; δ_H (300 MHz, $CDCl_3$) 0.73 (3H, d, *J* 6.8, C(α)*Me*), 1.15 (9H, s, CMe_3), 3.35 (1H, d, *J* 13.7, NCH_A), 3.80 (1H, d, *J* 13.7, NCH_B), 3.92 (1H, q, *J* 6.8, C(α)*H*), 4.16 (1H, d, *J* 11.9 C(2)*H*), 4.54 (1H, d, *J* 11.9, C(3)*H*), 7.08–7.71 (15H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 12.2, 27.5, 49.8, 54.7, 56.0, 60.7, 81.4, 127.0, 127.2, 127.9, 128.1, 128.2, 128.6, 128.7, 129.5, 129.6, 138.8, 139.6, 142.6, 169.1; *m/z* (CI^+) 448 ([M+H^+], 12%), 236 (100).

Data for *syn*-**9**: δ_H (300 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.8, C(α)*Me*), 1.51 (9H, s, CMe_3), 3.50 (1H, d, *J* 14.4, NCH_A), 3.69 (1H, d, *J* 14.4, NCH_B), 3.70 (1H, d, *J* 11.5, C(2)*H*), 4.04 (1H, q, *J* 6.8, C(α)*H*), 4.42 (1H, d, *J* 11.5, C(3)*H*), 7.05–7.49 (15H, m, *Ph*).

4.7. *tert*-Butyl (2*R*,3*R*,α*R*)-2-*tert*-butylthio-3-[*N*-allyl-*N*-(α-methylbenzyl)amino]-3-phenylpropanoate *anti*-14

BuLi (2.5 M in hexanes, 3.0 mL, 7.6 mmol), (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amine (1.3 g, 7.8 mmol) in THF (10 mL), *tert*-butyl cinnamate (1.0 g, 4.9 mmol) in THF (10 mL) and Ts*S*^{t}Bu (2.4 g, 9.8 mmol) were reacted according to *general procedure (a)* and gave a 97:3 mixture of *anti*-**14**:*syn*-**15**. Purification via flash column chromatography (eluent pentane–Et_2O 4:1) gave *anti*-**15** as a colourless oil (1.95 g, 88%, >98% de); $C_{28}H_{39}NO_2S$ requires C, 74.1; H, 8.7; N, 3.1; S, 7.1; found C, 74.3; H, 8.7; N, 2.9; S, 6.9; $[\alpha]_D^{25} = -10.0$ (*c* 0.9, $CHCl_3$); ν_{max} (film) 1725; δ_H (500 MHz, $CDCl_3$) 1.06 (3H, d, *J* 6.8, C(α)*Me*), 1.24 (9H, s, CMe_3), 1.56 (9H, s, CMe_3), 3.18 (1H, dd, *J* 14.8, 7.2, NCH_A), 3.37 (1H, dd, *J* 14.8, 5.8, NCH_B), 3.95 (1H, d, *J* 12.2, C(2)*H*), 4.08 (1H, q, *J* 6.8, C(α)*H*), 4.27 (1H, d, *J* 12.2, C(3)*H*), 5.03–5.09 (2H, m, CH=CH_2), 5.83–5.91 (1H, m, C*H*=CH_2), 7.19–7.36 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 17.9, 28.0, 31.3, 44.1, 49.2, 50.3, 58.7, 63.1, 80.8, 116.0, 126.7, 127.4, 127.6, 127.7, 128.0, 128.1, 128.2, 129.8, 137.2, 139.0, 145.2, 173.3; *m/z* (CI^+) 454 ([M+H^+], 83%), 250 (100), 146 (38), 105 (16).

4.8. *tert*-Butyl (2*R*,3*R*,α*R*)-2-*tert*-butylthio-3-[*N*-(α-methylbenzyl)amino]-3-phenylpropanoate 16

A solution of *anti*-**14** (1.0 g, 2.3 mmol) in DCM (15 mL) was added to a solution of *N*,*N*-dimethyl barbituric acid (1.3 g, 8.3 mmol) and $Pd(PPh_3)_4$ (100 mg, 0.09 mmol) in DCM (15 mL), and refluxed for 2 h. After cooling to rt, the solvent was removed in vacuo, Et_2O (50 mL) was added and the precipitate filtered off. The organic extract was washed twice with a satd aq $NaHCO_3$ and the aqueous layers were extracted with Et_2O. The combined Et_2O extracts were washed with brine, dried, filtered and concentrated in vacuo. Purification via flash column chromatography (eluent pentane–Et_2O 19:1) gave **16** as a colourless oil which crystallised slowly (900 mg, 95%, >98% de); $C_{25}H_{35}NO_2S$ requires C, 72.6; H, 8.5; N, 3.4; S, 7.75; found C, 72.6; H, 8.8; N, 3.7; S, 7.1; mp 66–67 °C; $[\alpha]_D^{25} = +11.2$ (*c* 1.0, $CHCl_3$); ν_{max} (film) 1724; δ_H (500 MHz, $CDCl_3$) 1.12 (9H, s, CMe_3), 1.29 (3H, d, *J* 6.4, C(α)*Me*), 1.50 (9H, s, CMe_3), 2.1 (1H, br s, N*H*), 3.32 (1H, d, *J* 9.3, C(2)*H*), 3.64 (1H, q, *J* 6.4, C(α)*H*), 3.98 (1H, d, *J* 9.3, C(3)*H*), 7.18–7.31 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 22.0, 27.9, 30.9, 43.6, 52.8, 55.1, 62.0, 80.8, 126.6, 126.8, 127.2, 127.9, 128.2, 140.6, 146.2, 172.6; *m/z* (CI^+) 414 ([M+H^+], 100%).

4.9. *tert*-Butyl (2*R*,3*R*,α*R*)-2-*tert*-butylthio-3-[*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-3-phenylpropanoate *anti*-17

BuLi (2.5 M in hexanes, 1.5 mL, 3.79 mmol), (*R*)-*N*-allyl-*N*-(α-methyl-*p*-methoxybenzyl)amine (749 mg, 3.92 mmol) in THF (5 mL), *tert*-butyl cinnamate (500 mg, 2.45 mmol) in THF (5 mL) and Ts*S*^{t}Bu (718 mg, 2.94 mmol) were reacted according to *general procedure (b)* and gave a 99:1 mixture of *anti*-**17**:*syn*-**18**. Purification via flash column chromatography (eluent pentane–Et_2O 25:1) gave *anti*-**17** as a yellow oil (1.18 g, 99%, >98% de); $[\alpha]_D^{23} = -6.4$ (*c* 1.7, $CHCl_3$); ν_{max} (film) 2975, 1724, 1512, 1367; δ_H (400 MHz, $CDCl_3$) 1.49 (3H, d, *J* 6.7, C(α)*Me*), 1.70 (9H, s, CMe_3), 2.04 (9H, s, CMe_3), 3.63 (1H, dd, *J* 14.7, 7.4, NCH_A), 3.85 (1H, dd, *J* 14.7, 5.6, NCH_B), 4.28 (3H, s, O*Me*), 4.42 (1H, d, *J* 12.2, C(2)*H*), 4.50 (1H, q, *J* 6.7, C(α)*H*), 4.72 (1H, d, *J* 12.2, C(3)*H*), 5.47–5.55 (2H, m, CH=CH_2), 6.26–6.37 (1H, m, C*H*=CH_2), 7.28 (2H, d, *J* 8.8, *Ar*), 7.66–7.84 (7H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.7, 28.1, 31.2, 44.1, 49.3, 50.2, 55.2, 57.1, 63.0, 80.7, 113.2, 115.6, 127.1, 127.8, 129.0, 129.5, 136.9, 137.2, 138.5, 158.2, 173.0; *m/z* (ESI^+) 484 ([M+H]$^+$, 100%); HRMS (ESI^+) $C_{29}H_{41}NNaO_3S^+$ ([M+Na]$^+$) requires 506.2699; found 506.2711.

4.10. *tert*-Butyl (2*R*,3*R*,α*R*)-2-*tert*-butylthio-3-[*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amino]-3-phenylpropanoate *anti*-19

BuLi (2.5 M in hexanes, 1.5 mL, 3.79 mmol), (*R*)-*N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amine (945 mg, 3.92 mmol) in THF (5 mL), *tert*-butyl cinnamate (500 mg, 2.45 mmol) in THF (5 mL) and TsS^{t}Bu (718 mg, 2.94 mmol) were reacted according to *general procedure (b)* and gave a 99:1 mixture of *anti*-**19**:*syn*-**20**. Purification via flash column chromatography (eluent pentane–Et_2O 25:1) gave *anti*-**19** as a yellow oil (1.30 g, 99%, >98% de); $[\alpha]_D^{23} = -13.5$ (*c* 0.5, $CHCl_3$); ν_{max} (film) 2975, 1717, 1512, 1367; δ_H (400 MHz, $CDCl_3$) 1.08 (3H, d, *J* 6.8, C(α)*Me*), 1.14 (9H, s, C*Me*$_3$), 1.58 (9H, s, C*Me*$_3$), 3.73 (1H, d, *J* 14.1, NCH_A), 3.78 (1H, d, *J* 11.8, C(2)*H*), 3.80 (3H, s, O*Me*), 4.07 (1H, q, *J* 6.8, C(α)*H*), 4.12 (1H, d, *J* 14.1, NCH_B), 4.26 (1H, d, *J* 11.8, C(3)*H*), 6.80 (2H, d, *J* 8.4, *Ar*), 7.14–7.38 (12H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.7, 28.1, 31.3, 44.1, 49.8, 51.0, 55.2, 58.1, 63.8, 81.0, 113.2, 126.6, 127.1, 127.6, 127.9, 128.9, 129.5, 130.0, 135.8, 138.1, 140.8, 158.3, 172.9; *m*/*z* (ESI^+) 534 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{33}H_{44}NO_3S^+$ ($[M+H]^+$) requires 534.3036; found 534.3032.

4.11. *tert*-Butyl (2*R*,3*R*,α*R*)-2-*tert*-butylthio-3-[*N*-(α-methyl-*p*-methoxybenzyl)amino]-3-phenylpropanoate 21

CAN (1.24 g, 2.27 mmol) was added portionwise (four portions of 311 mg, waiting between each addition until the orange colour of the solution had disappeared) to a −7 °C chilled and stirred solution of *anti*-**19** (807 mg, 1.51 mmol) in MeCN–H_2O (v:v 5:1, 15 mL). Stirring was continued at −7 °C for a further 5 min after the last CAN addition. The reaction was quenched by the addition of satd aq $NaHCO_3$ (20 mL) and stirred vigorously for 10 min before extracting with Et_2O (3 × 50 mL). The combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent pentane–Et_2O 15:1) gave **21** as a colourless oil (434 mg, 58%, >98% de); $[\alpha]_D^{23} = +24.0$ (*c* 1.6, $CHCl_3$); ν_{max} (film) 3320, 2973, 1724, 1513, 1367; δ_H (400 MHz, $CDCl_3$) 1.12 (9H, s, C*Me*$_3$), 1.27 (3H, d, *J* 6.3, C(α)*Me*), 1.49 (9H, s, C*Me*$_3$), 1.85–2.05 (1H, br s, N*H*), 3.32 (1H, d, *J* 9.2, C(2)*H*), 3.59 (1H, q, *J* 6.3, C(α)*H*), 3.78 (3H, s, O*Me*), 3.97 (1H, d, *J* 9.2, C(3)*H*), 6.79 (2H, d, *J* 8.6, *Ar*), 7.14 (2H, d, *J* 8.6, *Ar*), 7.23–7.34 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 22.0, 28.0, 30.8, 43.7, 52.8, 54.4, 55.2, 62.1, 80.8, 113.6, 127.2, 127.6, 127.9, 128.0, 138.5, 140.7, 158.4, 172.6; *m*/*z* (ESI^+) 444 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{38}NO_3S^+$ ($[M+H]^+$) requires 444.2567; found 444.2559.

4.12. (2*R*,3*R*)-2-*tert*-Butylthio-3-amino-3-phenylpropanoic acid 22

TFA (10 mL) was added dropwise to a solution of **21** (175 mg, 39.4 mmol) in DCM (10 mL) at 0 °C. After TFA addition was completed, the reaction mixture was heated at 55 °C for 24 h. The volatiles were removed in vacuo and the residue was dissolved in methanol (10 mL) and 6 M aq HCl (5 mL), and re-concentrated in vacuo. The residue was partitioned between Et_2O (3 mL) and H_2O (3 mL) and the aqueous mixture was purified via ion exchange chromatography (eluent 1 M aq NH_3) to give **22** as a white solid (97 mg, 98%); mp 142–144 °C; $[\alpha]_D^{23} = +23.7$ (*c* 0.4, MeOH); ν_{max} (film) 3441, 1641, 1364; δ_H (400 MHz, D_2O) 1.20 (9H, s, C*Me*$_3$), 3.50 (1H, d, *J* 5.2, C(2)*H*), 4.52 (1H, d, *J* 5.2, C(3)*H*), 7.26–7.30 (2H, m, *Ph*), 7.32–7.37 (3H, m, *Ph*); δ_C (100 MHz, D_2O) 30.5, 45.3, 50.9, 57.9, 127.0, 129.7, 130.0, 134.8, 177.5; *m*/*z* (ESI^-) 252 ($[M-H]^-$, 100%); HRMS (ESI^+) $C_{13}H_{19}NNaO_2S^+$ ($[M+Na]^+$) requires 276.1029; found 276.1027.

4.13. *tert*-Butyl (2*R*,3*R*,6*S*,α*R*)- and (2*S*,3*R*,6*R*,α*R*)-3-phenyl-4-(α-methylbenzyl)-6-methylthiomorpholine-2-carboxylate (2*R*,3*R*,6*S*,α*R*)-25 and (2*S*,3*R*,6*R*,α*R*)-26

BuLi (2.5 M in hexanes, 18.2 mL, 45.5 mmol), (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amine (7.58 g, 47.0 mmol) in THF (60 mL), *tert*-butyl cinnamate (6.0 g, 29.4 mmol) in THF (60 mL) and S_8 (15.1 g, 58.7 mmol) were reacted according to *general procedure (a)* and gave a complex mixture of polysulphides. The crude reaction mixture was suspended twice in Et_2O (2 × 150 mL) and the insoluble sulphur was filtered off. The resultant yellow oil was redissolved in EtOH (300 mL), cooled to 0 °C and $NaBH_4$ (2.2 g, 58.7 mmol) was added portionwise. After 30 min, the resultant orange suspension was allowed to warm to rt over 12 h. The solvent was evaporated in vacuo and the residue diluted with H_2O (150 mL) and extracted with DCM (3 × 300 mL). The combined organic extracts were dried and concentrated in vacuo to give a mixture of **25** and **26** plus other acyclic adducts. The crude product was dissolved in pentane–Et_2O (v:v 95:5) and the minor diastereoisomer **26** precipitated out. The concentrated mother-liquor was subjected to flash chromatography (eluent pentane–Et_2O 19:1) to give **25** as a viscous oil, which crystallised very slowly into a waxy solid (5.8 g, 50%, >98% de). Recrystallisation from ethanol gave **26** as colourless needles (2.3 g, 20%, >98% de).

Data for **25**: $C_{24}H_{31}NO_2S$ requires C, 72.5; H, 7.9; N, 3.5; S, 8.1; found C, 72.45; H, 8.1; N, 3.5; S, 8.1; mp 70–72 °C; $[\alpha]_D^{25} = -70.3$ (*c* 1.0, $CHCl_3$); ν_{max} (KBr) 1729; δ_H (500 MHz, $CDCl_3$) 1.07 (3H, d, *J* 6.9, C(6)*Me*), 1.19 (3H, d, *J* 6.8, C(α)*Me*), 1.38 (9H, s, C*Me*$_3$), 2.32 (1H, dd, *J* 12.0, 10.6, C(5)H_A), 2.90 (1H, dd, *J* 12.0, 2.7, C(5)H_B), 3.39 (1H, d, *J* 3.9, C(2)*H*), 3.67 (1H, m, C(6)*H*), 4.11 (1H, d, *J* 3.9, C(3)*H*), 4.16 (1H, q, *J* 6.8, C(α)*H*), 7.21–7.70 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 8.5, 18.6, 27.9, 32.5, 47.5, 54.9, 55.1, 66.6, 80.6, 126.2, 127.2, 127.8, 128.1, 128.4, 128.5, 139.9, 144.1, 169.9; *m*/*z* (CI^+) 398 ($[M+H^+]$, 100%), 105 (42).

Data for **26**: $C_{24}H_{31}NO_2S$ requires C, 72.5; H, 7.9; N, 3.5; S, 8.1; found C, 72.5; H, 7.8; N, 3.35; S, 7.9; mp 171–172 °C; $[\alpha]_D^{25} = +106.4$ (*c* 1.0, $CHCl_3$); ν_{max} (KBr) 1727; δ_H (500 MHz, $CDCl_3$) 1.15 (9H, s, C*Me*$_3$), 1.22 (3H, d, *J* 6.8, C(α)*Me*), 1.46 (3H, d, *J* 6.9, C(6)*Me*), 2.68 (1H, dd, *J* 11.2, 3.4, C(5)H_A), 2.88 (1H, m, C(6)*H*), 2.99 (1H, dd, *J* 11.2, 2.8, C(5)H_B), 3.88 (1H, q, *J* 6.8, C(α)*H*), 4.05 (1H, d, *J* 9.5, C(2)*H*), 4.13 (1H, d, *J* 9.5, C(3)*H*), 7.21–7.68 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 9.0, 19.8, 27.9,

34.5, 48.2, 52.5, 55.6, 69.3, 81.7, 126.9, 128.0, 128.2, 128.4, 128.9, 129.3, 140.1, 144.2, 169.7; *m*/*z* (CI^+) 398 ([M+H^+], 100%), 105 (53).

4.14. *tert*-Butyl (2*S*,3*R*,6*S*,α*R*)-3-phenyl-4-(α-methylbenzyl)-6-methylthiomorpholine-2-carboxylate 27

KO^tBu (0.32 g, 2.8 mmol) was added to a solution of **25** (1.77 g, 4.45 mmol) in EtOH (50 mL). The resultant yellow mixture was stirred for 3 days at rt. The solvent was removed in vacuo, and the residue was suspended in H_2O (20 mL) and extracted with DCM (3 × 50 mL). The organic layer was dried and concentrated in vacuo. The resultant yellow oil crystallised rapidly and recrystallisation from ethanol gave **27** as colourless needles (1.15 g, 65%, >98% de); $C_{24}H_{31}NO_2S$ requires C, 72.5; H, 7.9; N, 3.5; S, 8.1; found C, 72.7; H, 7.55; N, 3.3; S, 7.9; mp 129–130 °C; $[\alpha]_D^{25} = +92.0$ (*c* 1.0, $CHCl_3$); ν_{max} (KBr) 1724; δ_H (500 MHz, $CDCl_3$) 1.10 (3H, d, *J* 6.8, C(α)*Me*), 1.14 (9H, s, C*Me*$_3$), 1.24 (3H, d, *J* 6.8, C(6)*Me*), 2.42 (1H, dd, *J* 12.4, 11.4, C(5)H_A), 2.81 (1H, dd, *J* 12.4, 2.5, C(5)H_B), 3.00 (1H, m, C(6)*H*), 3.85 (1H, q, *J* 6.8, C(α)*H*), 3.93 (1H, d, *J* 9.6, C(2)*H*), 3.96 (1H, d, *J* 9.6, C(3)*H*), 7.21–7.59 (10H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 8.5, 18.3, 27.4, 36.3, 53.5, 54.6, 55.2, 68.1, 81.3, 126.6, 127.6, 128.2, 128.6, 128.8, 129.1, 139.6, 143.9, 169.1; *m*/*z* (CI^+) 398 ([M+H^+], 100%), 105 (32).

4.15. *tert*-Butyl (2*R*,3*R*)-3-(*N*-allyl-*N*-α-methylbenzyl)-amino-2-(*o*-nitrophenyldithio)-3-phenylpropanoate 32

2-Nitrobenzenesulphenyl chloride (0.4 g, 2.1 mmol) was added to a solution of *anti*-**14** (1.0 g, 2.1 mmol) in AcOH (10 mL). The resultant yellow solution was stirred at rt for 2 h and the solvent was removed in vacuo. Purification via flash chromatography (eluent pentane–Et_2O 19:1) gave **32** as a yellow oil (700 mg, 60%, 88% de); ν_{max} (film) 1724; δ_H (300 MHz, $CDCl_3$) 0.96 (3H, d, *J* 6.7, C(α)*Me*), 1.43 (9H, s, C*Me*$_3$), 3.11 (1H, dd, *J* 14.8, 7.3, NCH_A), 3.19 (1H, dd, *J* 14.8, 5.7, NCH_B), 4.06 (1H, q, *J* 6.7, C(α)*H*), 4.13 (1H, d, *J* 12.0, C(2)*H*), 4.55 (1H, d, *J* 12.0, C(3)*H*), 5.06–5.13 (2H, m, CH=CH_2), 5.70–5.85 (1H, m, C*H*=CH_2), 7.20–8.25 (22H, m, *Ph*); δ_C (50 MHz, $CDCl_3$) 17.6, 28.0, 50.1, 56.3, 57.2, 62.4, 82.1, 116.6, 125.7, 126.1, 126.5, 127.5, 127.9, 128.3, 129.4, 130.6, 133.6, 134.2, 135.6, 137.3, 138.0, 144.7, 145.4, 169.4; *m*/*z* (CI^+) 551 ([M+H^+], 10%), 126 (100).

4.16. Alternative preparation of *tert*-butyl (2*R*,3*R*,6*S*,α*R*)- and (2*S*,3*R*,6*R*,α*R*)-3-phenyl-4-(α-methylbenzyl)-6-methylthiomorpholine-2-carboxylate (2*R*,3*R*,6*S*,α*R*)-25 and (2*S*,3*R*,6*R*,α*R*)-26

A mixture of $NaBH_4$ (68.7 mg, 1.81 mmol) and S_8 (1.4 g, 5.44 mmol) was added portionwise to a solution of **32** (500 mg, 0.91 mmol) in EtOH (15 mL) at 0 °C. After 30 min, the reaction mixture was allowed to warm to rt over 12 h. The solvent was removed in vacuo and the residue diluted with H_2O (15 mL) and extracted with DCM (3 × 20 mL). The combined organic extracts were dried and concentrated in vacuo. Unreacted sulphur was removed by dissolving the crude reaction mixture in DCM (15 mL) and filtering off the insoluble sulphur. The residue was then purified as previously described to give **25** and **26** (360 mg combined yield, quant).

Acknowledgements

The authors wish to thank Barbara Odell, for the acquisition of NMR spectra, and Robin Procter and Joanna Kirkpatrick, for the acquisition of mass spectra.

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