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Synthesis of (*R*)-α-benzylmethionine: a novel rearrangement during alkylation of the Seebach (*R*)-methionine oxazolidinone

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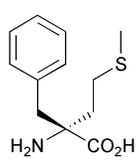
Alkylation of the enolate of the Seebach (*R*)-methionine oxazolidinone with benzyl bromide gave the expected benzylated product in low yield. The major product was a novel amine arising from oxazolidinone cleavage, decarboxylation, alkylation and finally hydrolysis. The rearrangement could be suppressed by using a more reactive electrophile or by using the *N*-Cbz instead of the *N*-benzoyl protecting group, and the required (*R*)-α-benzylmethionine was obtained in 78% yield and in an enantiomeric ratio of 90 : 10.

As a part of a research programme directed toward the design and synthesis of novel peptidomimetics, we required an efficient synthesis of (*R*)-α-benzylmethionine (**1**). There are no reports in the literature describing the preparation of **1** apart from a short communication outlining a chiral TLC method for resolving racemic α-dialkyl amino acids and reporting R_f values of the respective enantiomers.[1]



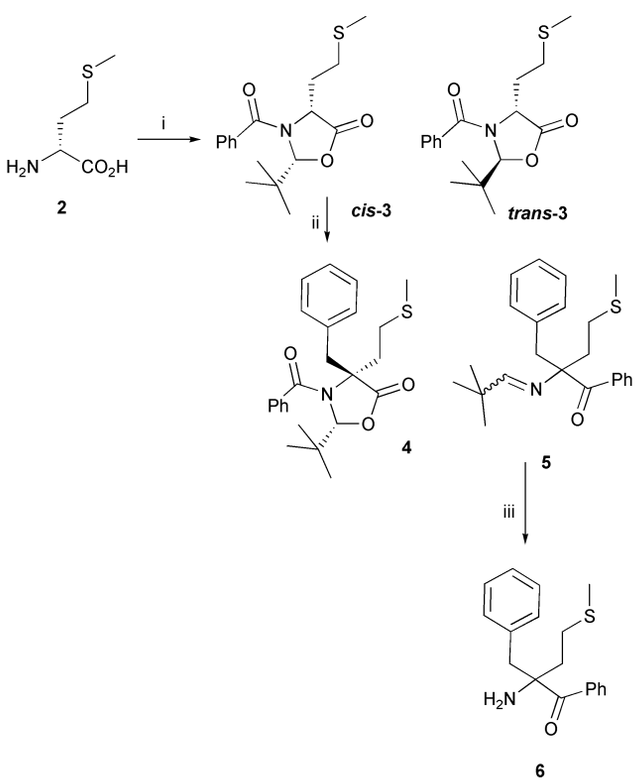
1

Methods for the asymmetric synthesis of homochiral α-substituted α-amino acids include Schöllkopf's bis-lactim ether,[2] Seebach's oxazolidinones,[3] Williams' diphenyloxazinones[4] and Corey's[5] and Lygo's[6] asymmetric alkylation of alanine Schiff's bases. The most commonly used method, at the time that this work was initiated, was Seebach's oxazolidinone methodology or one of its variants.[7]

The oxazolidinone **3** was prepared from (*R*)-methionine (**2**), pivalaldehyde and benzoyl chloride in 30% yield according to the Seebach protocol[3] (Scheme 1). The *trans* (2*S*,4*R*) isomer **3** was also obtained (6%). Enolisation of *cis*-**3** with lithium diethylamide in tetrahydrofuran at −70 °C and reaction with benzyl bromide gave only 7% of the expected alkylation product **4** and 6% recovered starting material **3**. Seebach recommended the use of lithium diethylamide as the base having previously examined a number of bases for the generation of the corresponding enolate. Fadel subsequently recommended the use of lithium diethylamide particularly for the enolisation of methionine and valine oxazolidinones.[8] The relationship between the low yield of the alkylation product **4** and the base used to form the enolate was not obvious to us and we therefore examined the enolisation of **3** using three more bases and the results of its alkylation with benzyl bromide are shown in Table 1. The yield of alkylated product **4** remained low (maximum 24%), and there was always recovered starting material. Interestingly the recovered starting material was not pure *cis*-**3** but a mixture of *cis* : *trans* isomers (87 : 13 in entry 3 and 72 : 28 in entry 4). This suggested that enolisation does occur with other bases and that alkylation is slow. The unreacted enolate was quenched on work-up to give **3** as a mixture of isomers based on the 2-H, *tert*-Bu and MeS signals in the ^{1}H NMR spectrum. More importantly an additional unexpected product (**5**), which was unstable to silica gel and aqueous acid, was observed in entries 3 and 4. This product was less polar than **4** and was probably present in entries 1 and 2, however, it was not distinguished from benzyl bromide by the TLC system used at the time. Careful chromatography of the unknown product **5** gave a new more polar product **6** (the most polar component in the reaction mixture). The polar decomposition product **6** was identified as the α-amino ketone as shown based on spectro-

Table 1 Variation of yield of **4** with base used for enolising **3**

Entry	Base	**4** (%)	**3** (%)
1	$LiNEt_2$	7	6
2	$LiN(TMS)_2$	24	19
3	$NaN(TMS)_2$	9	17 (87 : 13)
4	$KN(TMS)_2$	10	17 (72 : 28)



Scheme 1 *Reagents and conditions*: i) NaOH, *tert*-BuCHO, PhCOCl, CH_2Cl_2; ii) base, BnBr, THF; iii) silica gel chromatography or aqueous acid.

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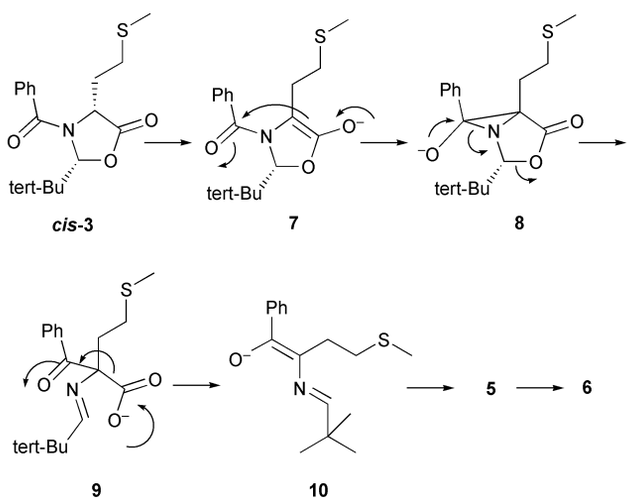
scopic evidence and microanalytical data of its hydrochloride salt.

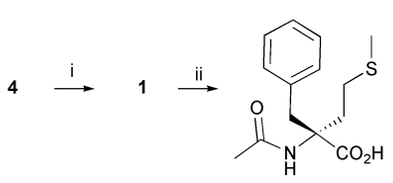
Compound **5** was the second least polar component in the reaction mixture (after benzyl bromide) on TLC. Although **5** was the major component in the reaction mixture (TLC) before work-up only a small amount of **5** could be isolated, following quenching of the reaction mixture with 2.5% aqueous ammonium chloride solution (pH 6) and flash chromatography. The structure of **5** was deduced from the ^{1}H NMR spectrum. The presence of two AB quartets due to the benzylic protons was consistent with two geometrical isomers of the imine **5**. The Seebach group reported the X-ray diffraction structure of oxazolidinone **3** which showed the five-membered ring to be essentially planar with the *tert*-butyl and acyl groups occupying opposite sides of the ring plane which was effected by pyramidalisation of the amide N-atom.[9] The amide carbonyl O-atom occupied an s-*cis*-position with the *tert*-butyl-substituted acetal C-atom. The enolate of **3** would be expected to retain the five-membered ring planar, and the carbonyl of the amide group *anti* to the C4 double bond (Scheme 2).



Scheme 2 Proposed mechanism for the rearrangement of enolate **7** to **5** and **6**.

As alkylation with benzyl bromide was slow, the enolate **7** could attack intramolecularly the amide carbonyl to produce the strained bicyclic intermediate **8**, which would rapidly rearrange to the β-ketoacid **9**. This in turn would readily decarboxylate to form the new enolate **10**, which on reaction with benzyl bromide would produce imine **5**. As the geometry of the enolate **10** is not known, the configuration of **5** is not known either and was assumed to be racemic. Hydrolysis of **5** would produce amine **6**. One way of minimising the degradation of the enolate of **3** and increasing the formation of the alkylation product **4** would be to use a more reactive electrophile. Thus, treatment of **3** with lithium bis(trimethylsilyl)amide at −65 °C, followed by benzyl iodide gave after crystallisation the expected product **4** in 80% yield. Deprotection of **4** by heating to reflux in hydrobromic acid gave **1** in 96% yield (Scheme 3).

The amino acid **1** was finally converted to the *N*-acetyl derivative **11** for further characterisation and enantiomeric purity determination. The enantiomeric ratio was obtained by



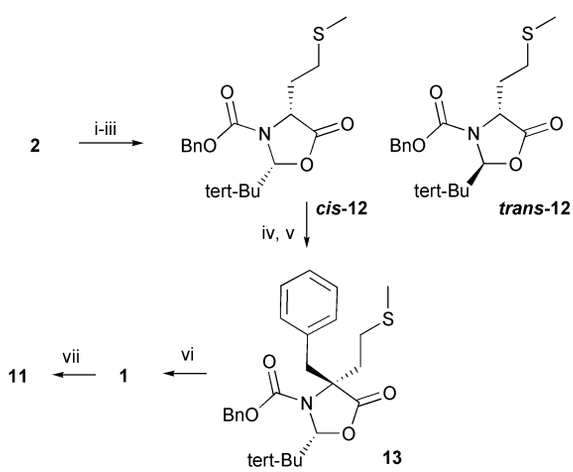
Scheme 3 *Reagents and conditions*: i) conc. HBr, reflux; ii) AcCl, Et_3N, CH_2Cl_2.

^{1}H NMR using chiral solvating agent (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol and also by chiral HPLC and found to be 90 : 10.

A search of the literature for any reports of oxazolidinones giving unexpected by-products revealed the following: Seebach[10] described the enolates of oxazolidinones as less stable and poorer nucleophiles than the corresponding enolates of imidazolidinones, reacting only with more reactive electrophiles. No decomposition products were reported however, and only the alkylation of (2*S*,4*S*)-**3** with the least hindered and very reactive methyl iodide was described. Kemp[11] reported that the above enolate failed to react with 2-phthalimidoethyl bromide or tosylate, however, it reacted with bromoacetonitrile to give the expected alkylation product in 42% yield.

Mutter,[12] using alanine *trans*-oxazolidinone and ethyl iodide as the electrophile, reported unsuccessful alkylation possibly because of "ring-opening to an *N*-acyliminium species and lability of the configuration at C2", however, no degradation products were isolated. Abell,[13] using phenylalanine and valine *trans*-oxazolidinones and benzhydryl or ethyl bromoacetate as the electrophile, observed "self-addition by-products".

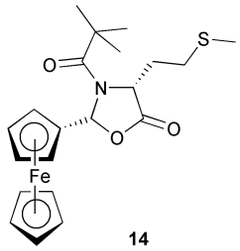
Although in the current study the formation of **5** and **6** was suppressed by using a more reactive electrophile, nevertheless, the enantiomeric ratio of the resulting dialkyl amino acid was 90 : 10. It was therefore of interest to compare some other oxazolidinone variants for the stability of the corresponding enolates and for the enantiomeric ratio of the resulting amino acid. The carbamate carbonyl of *N*-Cbz oxazolidinones is less electrophilic than the benzamide carbonyl of *N*-COPh oxazolidinones and hence not expected to give rise to rearrangement products. The oxazolidinone **12**, prepared by the method of Duffy,[14] was treated with lithium bis(trimethylsilyl)amide and benzyl bromide in tetrahydrofuran and gave the oxazolidinone **13** in 43% yield (Scheme 4).



Scheme 4 *Reagents and conditions*: i) NaOH, H_2O; ii) *tert*-BuCHO, CH_2Cl_2, 4 Å MS; iii) BnOCOCl; iv) $LiN(TMS)_2$, THF, −78 °C; v) BnBr; vi) $KOSiMe_3$, THF, 80 °C; vii) AcCl, Et_3N, CH_2Cl_2.

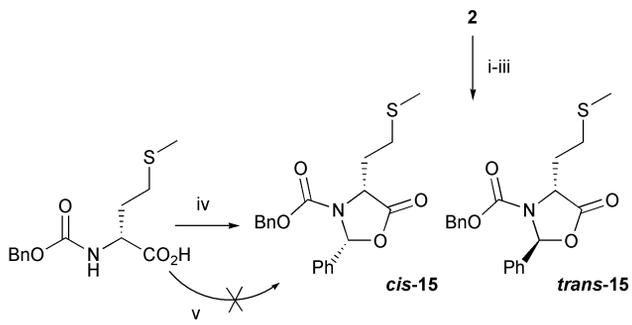
The ^{1}H NMR spectrum of **13** as in the case of **4** was very broad, however, when the ^{1}H NMR spectrum of **13** was run in DMSO-d_6 at 80 °C the broadening was eliminated, indicating the presence of rotamers. The broadness of the NMR spectra of alkylated oxazolidinones was also reported by Karady.[7] Attempted cleavage of the oxazolidinone with sodium hydroxide in refluxing methanol over a period of three days was unsuccessful, however, treatment of **13** with potassium trimethylsilanolate in refluxing tetrahydrofuran over 2 h completely de-protected **13** and provided **1** in 98% yield.[15] The enantiomeric ratio was determined on the crude acetyl derivative **11** and found to be 91 : 9.

The (*R*)-methionine derivative **14**, prepared by the method of Davies,[16] was found to be very unstable and therefore the alkylation was not attempted.



14

The oxazolidinone **15** was prepared from **2** using the method of Karady[7] and also from *N*-Cbz-(*R*)-methionine using the modification of Marlowe[17] and Jones.[18] The *cis* isomer predominated (4 : 1), however, the isomers could not be separated by crystallisation, chromatography or preparative HPLC and this was not pursued further (Scheme 5). Kapadia[19] reported yet another modification for the preparation of Karady oxazolidinones, which we had successfully utilised for the preparation of other amino acids.[15] This method, however, was incompatible with **2** as a multitude of decomposition products were formed.



Scheme 5 *Reagents and conditions*: i) NaOH, H_2O, EtOH; ii) PhCHO, cyclohexane, Dean and Stark apparatus; iii) BnOCOCl, CH_2Cl_2; iv) $PhCH(OMe)_2$, Et_2O, $BF_3{\cdot}OEt_2$, −78 °C; v) $PhCH(OMe)_2$, $SOCl_2$, $ZnCl_2$, THF, 0 °C.

In summary, we have examined a variety of methods for the formation of *cis*-oxazolidinones of (*R*)-methionine. Of the four different oxazolidinone variants examined the ferrocenecarboxaldehyde analogue **14** was unstable, the benzaldehyde analogue **15** was obtained as an inseparable mixture of *cis* and *trans* isomers, the oxazolidinone **12** was obtained in pure form as an oil after chromatography, and finally the oxazolidinone **3** was obtained in pure form after crystallisation. Oxazolidinone **3** on enolisation and reaction with benzyl bromide gave novel rearrangement products **5** and **6**. The rearrangement was suppressed by reacting the derived enolate with benzyl iodide. Alkylation of **12** with benzyl bromide did not give the rearrangement product. Both alkylation products **4** and **13** gave very broad ^{1}H NMR spectra due to restricted rotation. Alkylation was stereoselective but the minor isomer could not be completely removed. The alkylated oxazolidinone **4** was cleaved to the amino acid **1** by heating in concentrated hydrobromic acid whereas the oxazolidinone **13** was cleaved by potassium trimethylsilanolate. Both methods gave the amino acid **1** in an enantiomeric ratio of 90 : 10.

Experimental

Organic solutions were dried over anhydrous $MgSO_4$. TLC was performed on Merck 0.25 mm Kieselgel 60 F_{254} plates. Products were visualised under UV light and/or by staining with aqueous $KMnO_4$ solution. LCMS analysis was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm × 4.6 mm) eluting with 0.1% formic acid and 0.01 M ammonium acetate in water (solvent A), and 0.05% formic acid and 5% water in acetonitrile (solvent B), using the following elution gradient: 0–0.7 min 0% B, 0.7–4.2 min 100% B, 4.2–5.3 min 100% B, 5.3–5.5 min 0% B at a flow rate of 3 ml min^{-1}. The mass spectra were recorded on a Fisons VG Platform spectrometer using electrospray positive and negative mode (ES+ve and ES−ve). Analytical HPLC was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm × 4.6 mm) eluting with 0.1% formic acid and 0.01 M ammonium acetate in water (solvent A), and 0.05% formic acid and 5% water in acetonitrile (solvent B), using the following elution gradient: 0–2.00 min 0% B, 2.00–22.00 min 100% B, 22.00–27.00 min 100% B, 27.00–29.00 min 0% B, 29.00–30.00 min 0% B, at a flow rate of 1 ml min^{-1}, injecting 5 µl of solution and detecting between 215 and 330 nm. Column chromatography was performed on Merck Kieselgel 60 (art. 9385), or Biotage pre-packed silica gel cartridges containing KP-Sil run on a flash 12i chromatography module. Optical rotations were measured with an Optical Activity AA100 digital Polarimeter at 20 °C and are given in units of 10^{-1} deg cm^2 g^{-1}. ^{1}H NMR spectra were recorded at 400, 250 or 200 MHz and ^{13}C NMR at 100, 75, 62 or 25 MHz. The chemical shifts are expressed in ppm relative to tetramethylsilane.

(2*R*,4*R*)-3-Benzoyl-2-*tert*-butyl-4-[2-(methylthio)ethyl]-1,3-oxazolidin-5-one (*cis*-3)

Was prepared according to the Seebach[3] method: white crystals, mp 126–127 °C (from methanol), lit.[3] mp 126.2–126.6 °C; $[a]_D^{20}$ −61 (*c* 1.181 in $CHCl_3$), lit.[3] $[a]_D^{20}$ + 62.2 (*c* 1 in $CHCl_3$) (*ent*-**3**). [Found: C, 63.7; H, 7.3; N, 4.4; S, 9.8. $C_{17}H_{23}NO_3S$ requires C, 63.5; H, 7.2; N, 4.4; S, 10.0%]; ν_{max} ($CHBr_3$)/cm^{-1} 1787, 1665 and 750; δ_H ($CDCl_3$; 250 MHz) 7.55–7.35 (5H, m, Ph), 6.08 (1H, s, 2-H), 4.18 (1H, dd, *J* 10 and 3 Hz, 4-H), 2.62–1.95 (4H, m, CH_2CH_2S), 1.88 (3H, s, SCH_3) and 1.04 (9H, s, $C(CH_3)_3$).

(2*S*,4*R*)-3-Benzoyl-2-*tert*-butyl-4-[2-(methylthio)ethyl]-1,3-oxazolidin-5-one (*trans*-3)

White needles, mp 154–156 °C (from methanol), $[a]_D^{20}$ −129 (*c* 1.027 in $CHCl_3$). [Found: C, 63.45; H, 7.2; N, 4.4; S, 10.0. $C_{17}H_{23}NO_3S$ requires C, 63.5; H, 7.2; N, 4.4; S, 10.0%]; ν_{max} ($CHBr_3$)/cm^{-1} 1783, 1648, 1380, 1232 and 1010; δ_H ($CDCl_3$; 250 MHz) 7.70–7.45 (5H, m, Ph), 6.20 (1H, s, 2-H), 4.50 (1H, dd, *J* 5 and 1 Hz, 4-H), 2.30 (2H, t, *J* 7 Hz, CH_2S), 2.10–1.50 (2H, m, SCH_2CH_2), 1.85 (3H, s, SCH_3) and 1.02 (9H, s, $C(CH_3)_3$).

Alkylation of *cis*-3 using sodium bis(trimethylsilyl)amide and benzyl bromide

A solution of *cis*-**3** (964 mg, 3 mmol) in tetrahydrofuran (6 ml) was added dropwise at −70 °C to a solution of sodium bis-(trimethylsilyl)amide in tetrahydrofuran (1 M, 3 ml) under nitrogen. An orange colouration was obtained immediately on addition to the base, and the solution was stirred at −70 °C for 40 min before benzyl bromide (0.36 ml, 3 mmol) was added. The mixture was allowed to warm to 20 °C and stirred for 5 h whereupon the orange colour turned yellow. TLC [silica, ethyl acetate–hexane (1 : 19)] indicated the presence of a major product (**5**) slightly more polar than benzyl bromide, the alkylation product **4**, and a trace of starting material **3**. The reaction mixture was quenched by addition of 5% aqueous ammonium chloride solution (25 ml) and extracted into diethyl ether. The organic solution was dried, filtered and concentrated to give the crude mixture: ν_{max} (Nujol)/cm^{-1} 3350, 1790, 1680, 1655, 1600, 1580, 1500, 1258, 1230, 1180, 1050, 930, 840 and 700. The crude product was dissolved in dichloromethane (10 ml) and stirred with hydrochloric acid (2 M, 15 ml) until all of the major component **5** hydrolysed. The phases were separated and the organic phase was extracted with water (× 4). The combined aqueous extracts were basified with 2 M sodium hydroxide solution and extracted with diethyl ether. The ether layer was dried and concentrated to give 2-amino-2-benzyl-4-(methylthio)-1-phenylbutan-1-one (**6**) (289 mg, 32%) as a yellow oil: $[a]_{589}^{20}$ 0;

$[\alpha]_{546}^{20}$ −5.6 (*c* 0.948 in methanol); λ_{max} (EtOH) 243.2 nm (ε 9000), inflexion at 261.6 nm (3000); ν_{max} (Nujol)/cm^{-1} 3370, 1673, 1595, 1495, 1450, 750 and 700; δ_H ($CDCl_3$; 250 MHz) 7.80 (2H, d, *J* 8 Hz, *ortho*-PhCO), 7.55–7.35 (3H, m, Ph), 7.30–7.20 (3H, m, Ph), 7.17–7.05 (2H, m, Ph), 3.44 (1H, d, *J* 13 Hz, CH_2Ph), 2.97 (1H, d, *J* 13 Hz, CH_2Ph), 2.65–2.30 (3H, m), 2.12–1.90 (1H, m), 2.02 (3H, s, SCH_3) and 1.53 (2H, m, NH_2); δ_C ($CDCl_3$; 62 MHz) 206.0 (CO), aromatic C [137.4, 135.6, 131.6, 130.3, 128.5, 128.2, 128.0, 126.8], 66.6 (*C*NH_2), 46.7 (*C*H_2Ph), 40.4 (*C*H_2CH_2S), 28.7 (*C*H_2S) and 15.2 (S*C*H_3); FAB+ve *m*/*z* 300 (M + H)$^+$. The original dichloromethane solution was dried, concentrated and purified by chromatography on silica gel (37 g) eluting with ethyl acetate–hexane (1 : 19, 1 : 9, 1 : 6, 1 : 4) to give (2*R*,4*R*)-3-benzoyl-4-benzyl-2-*tert*-butyl-4-[2-(methylthio)ethyl]-1,3-oxazolidin-5-one (**4**) (113 mg, 9%) as a colourless gum: $[\alpha]_D^{20}$ +23.4 (*c* 1.047 in $CHCl_3$); ν_{max} ($CHBr_3$)/cm^{-1} 1783, 1640, 1376 and 715; δ_H ($CDCl_3$; 250 MHz) 7.45–7.15 (8H, m, Ph), 7.0–6.5 (2H, br, Ph), 5.42 (1H, s, 2-H), 4.1–3.65 (1H, m), 3.45–3.2 (1H, m), 3.2–2.7 (3H, m), 2.5–2.25 (1H, m), 2.20 (3H, s, SCH_3), 0.67 (9H, s, C(CH_3)$_3$); δ_C($CDCl_3$; 25 MHz) 173.9 (CO), 171.0 (CO), aromatic C [136.0, 134.6, 130.5, 130.1, 128.6, 127.9, 127.8, 127.3], 95.2 (2-C), 67.7 (4-C), 39.6 (PhCH_2), 38.6 (CHCH_2), 38.1 [*C*(CH_3)$_3$], 28.8 (*C*H_2SCH_3), 25.4 [C(*C*H_3)$_3$], 15.3 (S*C*H_3); the starting material **3** (160 mg, 17%) as a mixture of *cis* and *trans* isomers (87 : 13): δ_H ($CDCl_3$; 250 MHz) 7.70–7.35 (5H, m), 6.2 (0.13H, s), 6.08 (0.87H, s), 4.50 (0.13H, dd, *J* 5 and 1 Hz), 4.18 (0.87H, dd, *J* 10 and 3 Hz), 2.62–1.95 (4H, m), 1.88 (2.61H, s), 1.84 (0.39H, s) and 1.04 (9H, s), and finally the amine **6** (33 mg, 4%), same data as above.

2-Amino-2-benzyl-4-(methylthio)-1-phenylbutan-1-one hydrochloride (6·HCl)

The amine **6** (75 mg, 0.25 mmol) in diethyl ether (3 ml) was treated with hydrogen chloride solution in dioxane (4 M, 62 μl). The solid was collected by filtration to give the hydrochloride salt (69 mg, 82%) as a white solid: mp 217–220 °C (decomp) (from ethanol–diethyl ether). [Found: C, 64.25; H, 6.8; N, 4.1; S, 9.3; Cl, 10.5. $C_{18}H_{21}NOS$·HCl requires C, 64.4; H, 6.6; N, 4.2; S, 9.55; Cl, 10.6%]; ν_{max} (Nujol)/cm^{-1} 3290, 2700–2250, 1670, 1593,1500, 1455, 753 and 700; δ_H (DMSO-d_6; 250 MHz) 8.8–8.4 (3H, br, NH_3), 8.17 (2H, d, *J* 8 Hz, *ortho*-PhCO), 7.78 (1H, t, *J* 8 Hz, *para*-PhCO), 7.65 (2H, t, *J* 8 Hz, *meta*-PhCO), 7.34–7.15 (5H, m, Ph), 3.65 (1H, d, *J* 14 Hz, CH_2Ph), 3.56 (1H, d, *J* 14 Hz, CH_2Ph), 2.92–2.66 (2H, m), 2.5–2.0 (2H, m), 1.9 (3H, s, SCH_3).

Alkylation of *cis*-3 using lithium bis(trimethylsilyl)amide and benzyl iodide

A solution of **3** (940 mg, 2.92 mmol) in tetrahydrofuran (5 ml) was added dropwise at −65 °C to a solution of lithium bis-(trimethylsilyl)amide in tetrahydrofuran (1 M, 3 ml) under nitrogen. An orange colouration was obtained immediately on addition to the base, and the solution was stirred at −60 °C for 30 min before benzyl iodide (654 mg, 3 mmol) was added. The colour of the reaction mixture turned slowly yellow and after 5 h at 20 °C TLC [silica, ethyl acetate–hexane (1 : 19)] indicated complete disappearance of the starting material, a trace of the unstable intermediate **5**, and mainly the alkylation product **4**. The reaction mixture was quenched by addition of 2.5% aqueous ammonium chloride solution and extracted into diethyl ether. The organic solution was dried, filtered, concentrated and purified by chromatography on silica gel (35 g) eluting with ethyl acetate–hexane (1 : 10) to give the unstable intermediate 2-benzyl-2-{[(1*E*/*Z*)-2,2-dimethylpropylidene]amino}-4-(methylthio)-1-phenylbutan-1-one (**5**) as a colourless gum (16 mg, 1%): ν_{max}($CHBr_3$)/cm^{-1} 1675, 1655, 1500 and 1450; δ_H($CDCl_3$; 200 MHz) 7.90 (2H, d, *J* 8 Hz, *ortho*-PhCO), 7.55–7.20 (7H, m, Ph, N=C*H*), 7.20–7.00 (2H, m, Ph), 3.40 (1H, d, *J* 14 Hz, PhCH_2), 3.25 (1H, d, *J* 14 Hz, PhCH_2), 2.6–2.3 (3H, m), 2.2–1.9 (1H, m), 2.02 (3H, s, CH_3S) and 1.0 [9H, s, C(CH_3)$_3$]. The minor isomer had signals in the NMR spectrum at 3.48 and 3.06 (two d, 1 H each, *J* 14 Hz). A trace amount of pivalaldehyde, 1725 cm^{-1} and 9.5 ppm, was present in the IR and NMR spectra of **5** respectively, suggesting facile hydrolysis. Further elution of the column gave **4** (1.053 g, 88%) as a colourless gum, which was crystallised twice from methanol to give **4** as a white solid: mp 82–83 °C. [Found: C, 70.0; H, 7.1; N, 3.5; S, 7.7. $C_{24}H_{29}NO_3S$ requires C, 70.0; H, 7.1; N, 3.4; S, 7.8%]. Other data as reported above. The aqueous phase was acidified with 2 M hydrochloric acid to pH 1 and extracted with dichloromethane. The aqueous phase was then basified with 2 M sodium hydroxide to pH 13 and extracted with diethyl ether. The organic solution was dried, filtered and evaporated to give **6** as a yellow gum (8 mg, 1%). Characterising data as above.

(*R*)-α-Benzylmethionine (1) by hydrolysis of 4

The oxazolidinone **4** (8 g, 19 mmol) was suspended in concentrated hydrobromic acid (9 M, 100 ml) and the mixture was heated to reflux for 3 h. On cooling to 20 °C long white needles crystallised. Water was added and the mixture was extracted with dichloromethane. The organic solution was discarded and the aqueous solution was evaporated to dryness. The residue was redissolved in water and applied to Dowex 50X8-200 ion-exchange resin (240 g). The resin was washed with water until the pH was neutral. The product was eluted with aqueous 1 M ammonium hydroxide solution and appropriate fractions were combined and evaporated to dryness under reduced pressure. The residue was dissolved in water (250 ml) and freeze-dried to give **1** (4.28 g, 94%) as a white solid: $[\alpha]_D^{20}$ +15 (*c* 0.63 in water). [Found: C, 60.6; H, 7.1; N, 6.2. $C_{12}H_{17}NO_2S$ requires C, 60.2; H, 7.2; N, 5.85%]; ν_{max} (Nujol)/cm^{-1} 3580–2100, 1590, 1450, 1375, 735 and 695; δ_H (D_2O; 250 MHz) 7.45–7.23 (5H, m, Ph), 3.35 (1H, d, *J* 14 Hz, CH_2Ph), 3.02 (1H, d, *J* 14 Hz, CH_2Ph), 2.7–2.44 (2H, m), 2.4–2.25 (1H, m) and 2.12 (3H, s, SCH_3); FAB+ve *m*/*z* 240 (M + H)$^+$; FAB−ve *m*/*z* 238 (M − H)$^-$.

N-Acetyl-(*R*)-α-benzylmethionine (11)

A suspension of the amino acid **1** (2.39 g, 10 mmol) in dichloromethane (40 ml) was treated with triethylamine (3.1 ml, 22 mmol) with ice cooling. Acetyl chloride (1.5 ml, 21 mmol) was added and the mixture was stirred at 20 °C for 3 h. The mixture was evaporated to dryness and the residue was dissolved in ethyl acetate. The organic solution was washed with 2 M hydrochloric acid, and sodium bicarbonate solution. The basic solution was acidified with 6 M hydrochloric acid and extracted with ethyl acetate. The organic solution was washed with brine, dried, and concentrated to give **11** (2.37 g, 84%) as a white solid: mp 187–188 °C; $[\alpha]_D^{20}$ +16.7 (*c* 1.348 in methanol). [Found: C, 59.7; H, 6.8; N, 4.9. $C_{14}H_{19}NO_3S$ requires C, 59.8; H, 6.8; N, 5.0%]; ν_{max} (Nujol)/cm^{-1} 3380, 3350, 3500–2100, 1700, 1610, 1525, 1445, 1210, 745 and 705; δ_H (DMSO-d_6, 250 MHz) 7.54 (1H, s, N*H*), 7.33–7.18 (3H, m, Ph), 7.10–7.05 (2H, m, Ph), 7.0–6.0 (1H, br, OH), 3.19 (2H, s, PhCH_2), 2.39 (2H, m, SCH_2CH_2), 2.15–1.8 (2H, m, SCH_2CH_2), 2.02 (3H, s, CH_3CO), and 1.88 (3H, s, CH_3S). The enantiomeric ratio was obtained by integration of the signal at 2 ppm using the chiral solvating agent (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol (25 mg) and **11** (5 mg) in $CDCl_3$ and found to be 89 : 11. The enantiomeric ratio was confirmed by chiral HPLC on a Chiralpak AD-RH column (15 cm × 0.46 cm) eluting with 50% *iso*-propanol–0.1% aqueous phosphoric acid, flow rate 0.5 ml min^{-1}, detecting at 215 nm, t_r 11.2 min, 11% (*S*-enantiomer), and t_r 17.8 min, 89% (*R*-enantiomer).

Benzyl (2*R*,4*R*)-2-*tert*-butyl-4-[2-(methylthio)ethyl]-5-oxo-1,3-oxazolidine-3-carboxylate (12)

Aqueous sodium hydroxide (1 M, 11.2 ml) was added to (*R*)-methionine (1.67 g, 11.2 mmol) and the mixture was stirred

for 5 min. The solution was evaporated to dryness under reduced pressure and the white solid was dried *in vacuo* at 60 °C for 40 min, before it was suspended in dichloromethane (50 ml). Molecular sieves (4 Å, 4 g) were added, followed by pivalaldehyde (1.83 ml, 16.8 mmol) and the mixture was stirred at 20 °C for 2 h. The molecular sieves were removed by filtration and washed with methanol. The filtrate and washings were concentrated under reduced pressure to give another white solid a portion of which (1.37 g, 5.7 mmol) was suspended in dichloromethane (80 ml) and cooled to −18 °C. A solution of benzyl chloroformate (1.23 ml, 8.6 mmol) in dichloromethane (10 ml) was added dropwise and the mixture was stirred vigorously for 10 h and then allowed to warm to 20 °C. The reaction mixture was washed with water, sodium bicarbonate solution, water and dried. The solution was filtered, concentrated under reduced pressure and the residue was purified by chromatography on silica gel eluting with ethyl acetate–hexane (0 : 1, to 1 : 19) to give **12**[14](1.07 g, 27%) as a colourless oil: ν_{max} (film)/cm^{-1} 1788, 1713, 1400 and 700; δ_H ($CDCl_3$, 250 MHz) 7.43–7.30 (5H, m, Ph), 5.57 (1H, s, 2-H), 5.18 (2H, s, CH_2Ph), 4.53 (1H, t, *J* 7 Hz, 4-H), 2.82–2.64 (2H, m), 2.30–2.00 (2H, m), 2.03 (3H, s, SCH_3) and 0.96 (9H, s, C(CH_3)$_3$); δ_C ($CDCl_3$, 75 MHz) 172.4 (CO), 156.0 (CO), aromatic C [135.1, 128.8, 128.7], 96.4 (2-C), 68.5 (*C*H$_2$Ph), 55.8 (4-C), 37.0 [*C*(CH$_3$)$_3$], 32.3 (CH*C*H$_2$), 30.6 (*C*H$_2$SCH$_3$), 24.9 [C(*C*H$_3$)$_3$], 15.1 (S*C*H$_3$); NOE was observed from 2-H to 4-H.

Benzyl (2*R*,4*R*)-4-benzyl-2-*tert*-butyl-4-[2-(methylthio)ethyl]-5-oxo-1,3-oxazolidine-3-carboxylate (13)

A solution of **12** (0.4 g, 1.1 mmol) in tetrahydrofuran (10 ml) was added to lithium bis(trimethylsilyl)amide solution in tetrahydrofuran (1 M, 1.14 ml) at −78 °C under nitrogen. The solution turned immediately to orange coloured and was stirred for 30 min before benzyl bromide (0.18 ml, 1.5 mmol) was added and the resulting mixture was allowed to warm to 20 °C. After stirring for 16 h 5% aqueous ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The organic solution was dried, concentrated and purified by chromatography on silica gel eluting with ethyl acetate–hexane (1 : 49 to 1 : 2) to give **13** (210 mg, 43%) as a colourless gum: analytical HPLC (30 min run) t_r 17.2 min, 100%; $[\alpha]_D^{22}$ +37 (*c* 0.65 in $CHCl_3$). [Found: C, 68.1; H, 7.0; N, 3.2. $C_{25}H_{31}NO_4S$ requires C, 68.0; H, 7.1; N, 3.2%]; ν_{max} (film)/cm^{-1} 1788, 1713, 1397, 1314, 1180, 1044, 754 and 700; δ_H (DMSO-d_6, 250 MHz at 80 °C) 7.50–7.15 (8H, m, Ph), 7.00–6.90 (2H, m), 5.30 (1H, d, *J* 12 Hz, OCH_2Ph), 5.17 (1H, d, *J* 12 Hz, OCH_2Ph), 4.65 (1H, s, 2-H), 3.59 (1H, d, *J* 14 Hz, CCH_2Ph), 3.01 (1H, d, *J* 14 Hz, CCH_2Ph), 2.80 (1H, m), 2.64 (1H, m), 2.46–2.41 (2H, m), 2.06 (3H, s, SCH_3) and 0.82 [9H, s, C(CH_3)$_3$] (at ambient temperature the NMR spectrum was very broad); δ_C ($CDCl_3$, 100 MHz at 30 °C) 173.7 (CO), 154.1 (CO), aromatic C [134.9, 134.0, 129.8, 129.1, 128.8, 128.7, 128.6, 128.2, 128.1, 127.5, 127.4], 95.0 (2-C), 67.9 (O*C*H$_2$Ph), 67.9 (4-C), 40.0 (very broad Ph*C*H$_2$), 38.0 [*C*(CH$_3$)$_3$], 37.9 (*C*H$_2$CH$_2$S), 29.0 (*C*H$_2$S), 25.7 [C(*C*H$_3$)$_3$], 15.4 (S*C*H$_3$); ES+ve *m*/*z* 442 (M + H)$^+$, 459 (M + NH$_4$)$^+$, 901 (2M + NH$_4$)$^+$.

Cleavage of 13 with potassium trimethylsilanolate

A solution of **13** (180 mg, 0.4 mmol) in tetrahydrofuran (3 ml) was treated with potassium trimethylsilanolate (90% pure, 180 mg, 1.26 mmol) and the mixture was heated to 80 °C for 2 h. The mixture was diluted with methanol, and concentrated under reduced pressure. The concentrate was applied to an SCX-2 cartridge eluting with methanol and then with 0.2 M ammonia in methanol. Evaporation of the ammoniacal fractions gave **1** (94 mg, 98%) as a white solid: LCMS t_r 1.99 min, 100%; ES+ve *m*/*z* 240 (M + H)$^+$ and ES−ve *m*/*z* 238 (M − H)$^-$; δ_H (D_2O, 400 MHz) 7.45–7.36 (3H, m, Ph), 7.29 (2H, m, Ph), 3.35 (1H, d, *J* 14 Hz, CH_2Ph), 3.03 (1H, d, *J* 14 Hz, CH_2Ph), 2.67–2.48 (2H, m), 2.38–2.28 (1H, m), 2.14 (3H, s, SCH_3) and 2.11–2.03 (1H, m). The amino acid **1** was converted as before to the *N*-acetyl derivative **11**: LCMS t_r 2.58 min, 100%; ES+ve *m*/*z* 282 (M + H)$^+$ and ES−ve *m*/*z* 280 (M − H)$^-$; $[\alpha]_D^{20}$ +17 (*c* 1.1 in methanol); δ_H (DMSO-d_6, 400 MHz) 12.9 (1H, br, O*H*), 7.54 (1H, s, N*H*), 7.31–7.17 (3H, m, Ph), 7.10–7.00 (2H, m, Ph), 3.18 (2H, br s, CH_2Ph), 2.42–2.30 (2H, m, CH_2CH$_2$S), 2.1–1.8 (2H, m, SCH_2CH$_2$), 2.02 (3H, s, CH_3CO), 1.86 (3H, s, SCH_3); δ_C (DMSO-d_6, 100 MHz) 173.5 (CO), 169.1 (CO), aromatic C [136.5, 130.0, 127.9, 126.5], 62.4 (NH*C*CO$_2$H), 38.2 (*C*H$_2$Ph), 33.8 (SCH$_2$*C*H$_2$), 27.7 (CH$_3$S*C*H$_2$), 22.9 (*C*H$_3$CO), 14.7 (S*C*H$_3$). The enantiomeric ratio was determined by chiral HPLC (Chiralpak AD-RH) t_r 11.2 min, 10% (*S*-enantiomer) and 18.1 min, 90% (*R*-enantiomer).

(2*R*,4*R*)-2-Ferrocenyl-4-[2-(methylthio)ethyl]-3-pivaloyl-1,3-oxazolidin-5-one (14)

Was prepared according to the Davies[16] method: unstable orange solid (2.28 g, 97%): ν_{max} (KBr)/cm^{-1} 1785 and 1650; δ_H ($CDCl_3$, 400 MHz) 7.09 (1H, s, 2-H), 4.72 (1H, dd, *J* 5, 10 Hz, 4-H), 4.55–4.17 (4H, m, Cp), 4.25 (5H, m, Cp′), 2.75–2.68 (2H, m, CH_2CH$_2$S), 2.12–2.00 (2H, m, CH_2S), 2.08 (3H, s, SCH_3), 1.29 [9H, s, C(CH_3)$_3$]; δ_C ($CDCl_3$, 100 MHz) 176.5 (CO), 171.5 (CO), 87.6 (2-C), 83.5 (quaternary C in Cp), 69.8 (5 × CH in Cp′), 68.3, 67.1, 66.7, 64.7 (4 × CH in Cp), 53.4 (4-C), 39.8 [*C*(CH$_3$)$_3$], 32.3 (*C*H$_2$CH$_2$S), 28.7 (*C*H$_2$S), 26.9 [C(*C*H$_3$)$_3$], 14.7 (*C*H$_3$S).

Benzyl (2*R*,4*R*)-4-[2-(methylthio)ethyl]-5-oxo-2-phenyl-1,3-oxazolidine-3-carboxylate (15)

a) From (*R*)-methionine. Was prepared according to the Karady[7] method: colourless oil (220 mg, 6%); LCMS t_r 3.48 min, 18% and 3.54 min, 82%; ES+ve *m*/*z* 372 (M + H)$^+$, 389 (M + NH$_4$)$^+$; ν_{max} (KBr)/cm^{-1} 1792, 1712, 1595, 1455, 1404, 1350, 1321, 1239, 1017, 731 and 695; δ_H ($CDCl_3$, 400 MHz) 7.47–7.23 (10H, m, Ph), 6.74 (0.86H, s, 2-H), 6.47 (0.14H, s, 2-H), 5.20 (2H, s, PhCH_2O), 4.64 (1H, t, *J* 7 Hz, 4-H), 2.70–2.50 (2H, m, CH_2CH$_2$S), 2.17–1.92 (2H, m, CH$_2$CH_2S) and 1.97 (3H, s, CH_3S); δ_C ($CDCl_3$, 100 MHz) 171.7 (CO), 154.0 (CO), aromatic C [136.9, 135.1, 130.1, 129.6, 128.8, 128.7, 128.3, 126.4, 125.9], 89.9 (2-C, minor), 88.8 (2-C, major), 68.3 (*C*H$_2$Ph), 54.8 (4-C), 31.8 (*C*H$_2$CH$_2$S), 29.7 (CH$_2$*C*H$_2$S), 15.0 (S*C*H$_3$).

b) From *N*-Cbz-(*R*)-methionine. *N*-Cbz-(*R*)-Methionine (566 mg, 2 mmol) and benzaldehyde dimethyl acetal (304 mg, 2 mmol) in diethyl ether (10 ml) was cooled to −78 °C. Boron trifluoride etherate (1.23 ml, 10 mmol) was added and the mixture was allowed to warm to 20 °C and stirred for 4 days. The reaction mixture was then treated with aqueous sodium bicarbonate solution until the pH was neutral, and then extracted with ethyl acetate. The organic layer was dried, concentrated and purified by chromatography on Biotage (90 g cartridge) eluting with ethyl acetate–petroleum ether (0 : 1, 1 : 19, 1 : 9) to give **15** (485 mg, 65%) as an oil: LCMS t_r 3.49 min, 15% and 3.53 min, 85%; ES+ve *m*/*z* 372 (M + H)$^+$; ^{1}H NMR data as above.

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