Efficient stereoselective route to β-lactams and their application to the stereoselective synthesis of a key intermediate for carbapenem antibiotic (+)-PS-5[1]

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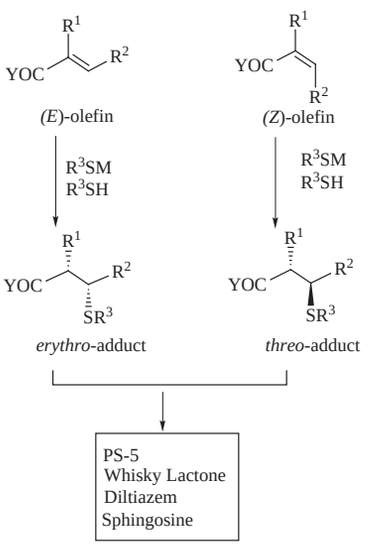
A combination of a stereoselective addition of benzenethiol to α,β-unsaturated carboxylic acid derivatives and a subsequent substitution reaction of the corresponding sulfonium group with *O*-alkylhydroxamate anion has provided a new practical and stereoselective method for the construction of 3,4-disubstituted *cis*- and *trans*-β-lactams. A successful application was demonstrated by the formal asymmetric synthesis of (+)-PS-5.

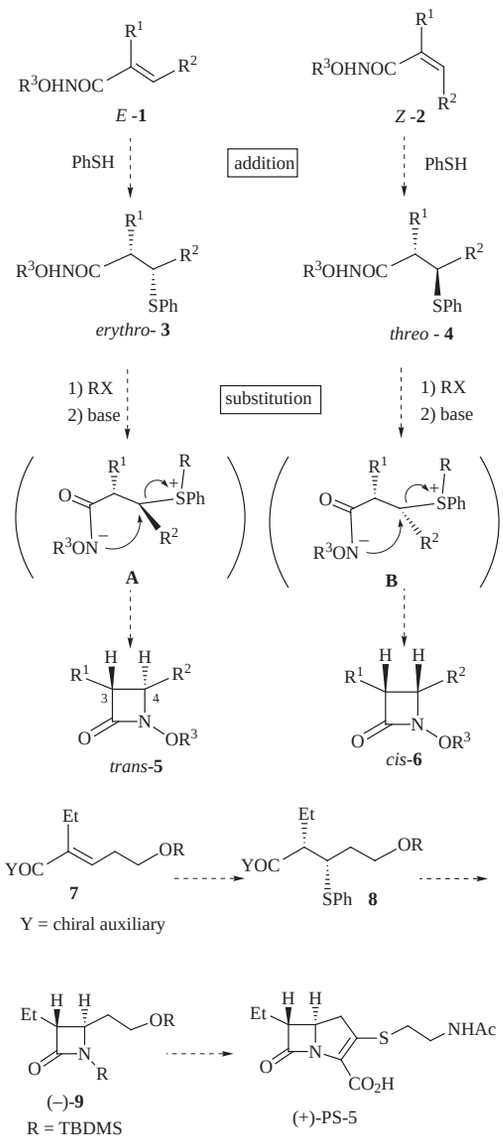
Introduction

The Michael-type addition of nucleophiles to α,β-unsaturated carbonyl compounds is one of the most widely used reactions known. Recently we found that nucleophilic addition of thiols to electron-deficient olefins proceeds stereospecifically and with high stereoselectivity in the presence of excess thiol as a proton source, thus forming two contiguous stereogenic centers with a phenylsulfanyl substituent which has high potential for further conversion to various types of structures[2] (Scheme 1). The



Scheme 1

addition is thought to proceed *via* the course of rapid protonation of the intermediary enolate formed by attack of the nucleophile (RSM). Thus the *erythro*-adduct was obtained stereoselectively from the (*E*)-olefin whilst the *threo*-adduct was obtained predominantly from the (*Z*)-isomer under the conditions employing an excessive amount of protic thiol. Furthermore, we have shown asymmetric total synthesis of (+)-diltiazem,[3] (+)-whisky lactone,[4] (+)-PS-5[1] and L-*erythro*-C18-sphingosine[5] on the basis of the successful expansion of this addition reaction to an asymmetric addition reaction.[2] In this paper, we describe full details of the stereoselective synthesis of substituted β-lactams and the asymmetric synthesis of a key intermediate for the synthesis of carbapenem antibiotic (+)-PS-5.[6] Our approach is shown in Scheme 2. The synthetic strategy consists of two key steps: (i) stereospecific nucleophilic



Scheme 2

addition of the thiols (**1** ⟶ **3** or **2** ⟶ **4**) and (ii) stereoselective displacement of the corresponding sulfonium group (**3** ⟶ **5** or **4** ⟶ **6**). *S*-Alkylation of the *erythro*-adduct **3**, generated from (*E*)-amide **1**, and subsequent intramolecular and stereoselective displacement of the resulting sulfonium

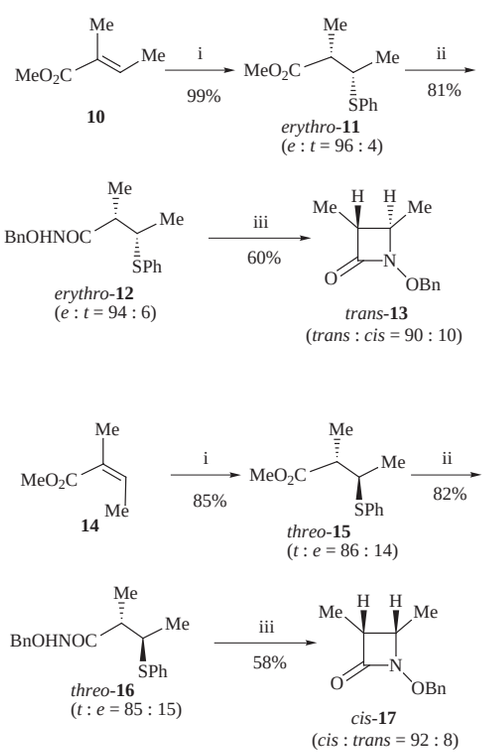
group with *O*-alkyl hydroxamate anion **A** would furnish the *trans*-β-lactam **5**. Since the pK_a (pK_a: 6–10) of the N–H in the hydroxamate moiety is lower[7] than that (pK_a: *ca.* 25) of the N–H in the amide group, the desired cyclization of the *O*-alkyl hydroxamate anion is expected to proceed smoothly in the presence of a weak base without both competitive β-elimination and epimerization to provide *trans*-β-lactam **5**.[8] In a similar manner, the *threo*-adduct **4**, prepared from (*Z*)-amide **2**, would be converted into *cis*-β-lactam **6**. Furthermore, the usefulness of this method can be demonstrated by the asymmetric synthesis of a key intermediate, (−)-**9**, for the synthesis of the carbapenem antibiotic (+)-PS-5 by using oxazolidinone as a chiral auxiliary.

Results and discussion

Stereoselective synthesis of *cis*- and *trans*-β-lactams

In the synthesis of carbapenem antibiotics, the difficulty in achieving control of the relative and absolute stereochemistries of the contiguous chiral centers and the construction of the β-lactam ring has remained unresolved. Particularly, the stereoselective and practical method for the construction of the *cis*-β-lactams has been unexploited compared with the many known[8] synthetic works on the *trans*-lactams. We now provide a potential method for the stereoselective synthesis of both *cis*- and *trans*-β-lactams.

We first investigated conversion of methyl tiglate [(*E*)-methyl 2-methylbut-2-enoate] into the *trans*-lactam as a model study (Scheme 3). Methyl tiglate **10** was treated with 10 equiv. of

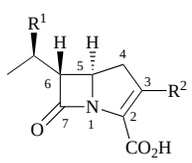


Scheme 3 *Reagents*: i, 0.1 equiv. PhSLi, 10 equiv. PhSH; ii, BnO-NH_2·HCl, Me_3Al; iii, 1) MeI, $AgClO_4$, 2) K_2CO_3

benzenethiol in the presence of 0.1 equiv. of lithium benzenethiolate to give an inseparable mixture of the *erythro*- and *threo*-adducts **11**[2] and **15**[2] in 99% yield with a ratio of 96:4 which was determined by ^{1}H NMR spectroscopy. Treatment of *erythro*-**11** (*erythro*:*threo* = 96:4) with benzyloxylamine hydrochloride and trimethylaluminium[9] afforded the *O*-benzyl hydroxamate **12** (*erythro*:*threo* = 94:6) in 81% yield. *S*-Alkylation of the sulfide **12** (*erythro*:*threo* = 94:6) with methyl iodide in the presence of silver perchlorate[4,10] followed by treatment of the resulting sulfonium salt with potassium carbonate caused it to undergo smooth lactamization by intramolecular substitution to give the *trans*-lactam **13** with high stereoselectivity (*trans*:*cis* = 90:10) in 60% yield. In a similar manner, the (*Z*)-ester **14** was transformed into the *cis*-β-lactam **17** *via* the *threo*-adduct **15**[2] and the *threo*-hydroxamate **16** with high stereoselectivity (*cis*:*trans* = 92:8) (Scheme 3). The stereostructures of **13** and **17** were confirmed by their spectral data. The *trans*-β-lactam **13** showed a molecular ion peak at *m*/*z* 205, an IR absorption at 1752 cm^{-1} (β-lactam) and ^{1}H NMR peaks at δ 2.46 (1H, qd, *J* 7.5, 2, 3-H) and 3.21 (1H, qd, *J* 6, 2, 4-H). Similarly, the *cis*-β-lactam **17** showed the following characteristic spectra [*m*/*z* 205 (M^+), ν_{max} 1754 cm^{-1} (β-lactam), δ 2.92 (1H, qd, *J* 7.5, 6, 3-H), 3.72 (1H, quint., *J* 6, 4-H)]. It has been established[11] that in the series of 3,4-disubstituted azetidinones, the coupling constants (*J* values) between the 3- and 4-hydrogens in the 3,4-*trans* series (2.2–2.8 Hz) are smaller than those in the *cis* series (5.0–5.9 Hz). Their observation in the present cases showed a $J_{3,4}$ value of 2 Hz for **13** and a $J_{3,4}$ value of 6 Hz for **17**. The result established that the β-lactam **13** is the *trans*-isomer and the β-lactam **17** is the *cis*-isomer. Thus, we have developed a new and simple synthetic method for making 3,4-disubstituted β-lactams.

Synthesis of a key intermediate for carbapenem antibiotic (+)-PS-5

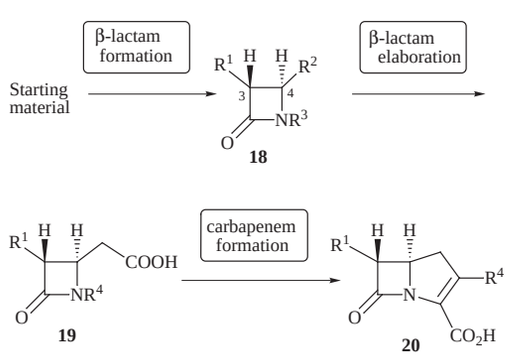
Carbapenem antibiotics PS-5, PS-6 and thienamycin comprise an interesting family of streptomycete metabolites characterized by the presence of the 7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid system.[8] The main strategies towards their



	R^1	R^2
PS-5	H	S-CH_2CH_2NHAc
thienamycin	HO	S-$CH_2CH_2NH_2$
PS-6	Me	S-CH_2CH_2NHAc

Carbapenem antibiotics

synthesis usually take place first with the preparation of an appropriately substituted monocyclic β-lactam **18** (a key intermediate) with the correct stereochemistry at the C_3- and C_4-positions of the β-lactam ring, followed by chemical manipulations (**18** ⟶ **19**) at the N_1- and C_4-positions and subsequent ring closure (**19** ⟶ **20**) to form the bicyclic carbapenem system in the last steps of the synthesis (Scheme 4).

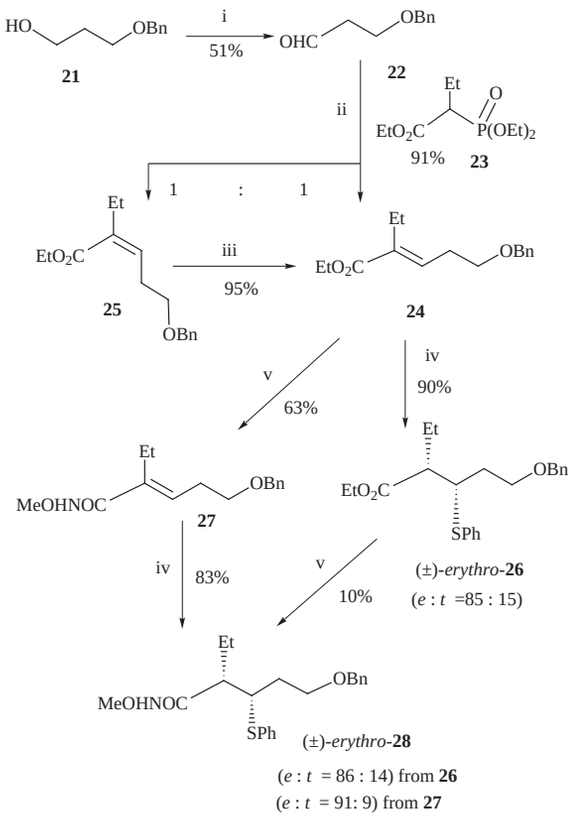


Scheme 4

Since in the asymmetric synthesis of PS-5, the first step of stereoselective β-lactam formation is a crucial step, we focused our attention on exploring a synthetic route to PS-5 applying our newly found strategy established above.

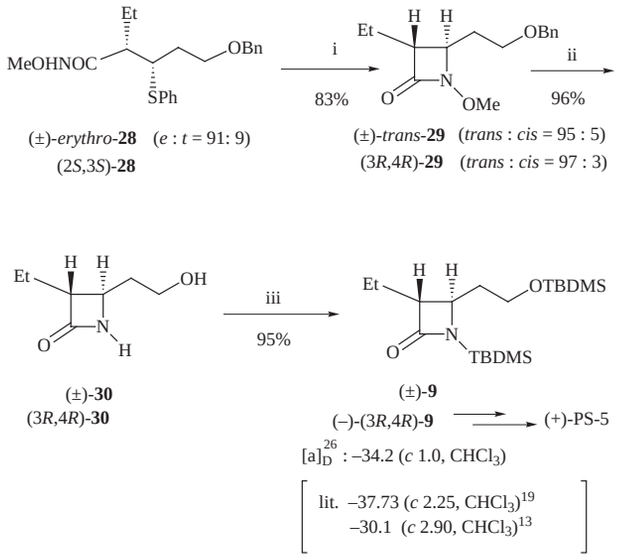
Before approaching its asymmetric synthesis, we examined

the synthesis of the key racemic intermediate **9** for (±)-PS-5. The requisite (*E*)-olefin **24** was prepared by the conventional method involving the Wittig–Horner reaction and subsequent olefin isomerization (Scheme 5). The Swern oxidation of 3-



Scheme 5 *Reagents*: i, $(COCl)_2$, DMSO; ii, NaH; iii, $(PhS)_2$; iv, 0.1 equiv. PhSLi, 10 equiv. PhSH; v, $MeONH_2$·HCl, Me_3Al

benzyloxypropanol **21** followed by the Wittig–Horner reaction of the resulting aldehyde **22**[12,13] with the phosphonate **23**[14] gave a 1 : 1 mixture of (*E*)-**24** and (*Z*)-**25** in 91% combined yield. The unstable (*Z*)-**25** was isomerized to the stable (*E*)-**24** upon heating at 100 °C in the presence of diphenyl disulfide.[15] (*E*)-Ester **24** and the corresponding hydroxamate **27**, which was readily prepared in 63% yield from the former by treatment with methoxylamine hydrochloride in the presence of trimethylaluminium, were subjected to the Michael-type addition of benzenethiol. (*E*)-**24** was treated with benzenethiol in the presence of lithium benzenethiolate at room temperature to give a mixture of two adducts, (±)-*erythro*-**26** and its (±)-*threo*-isomer, as an inseparable mixture in 90% yield with a ratio of 85 : 15. The addition reaction of benzenethiol to the hydroxamate **27** proceeded smoothly at 60 °C to give a mixture of two adducts, (±)-*erythro*-**28** and its (±)-*threo*-isomer, as an inseparable mixture in 83% yield with high stereoselectivity (*erythro* : *threo* = 91 : 9) (Scheme 5). Unfortunately, treatment of the (±)-*erythro*-ester **26** (*erythro* : *threo* = 85 : 15) with methoxylamine hydrochloride in the presence of trimethylaluminium gave the corresponding *O*-methyl (±)-hydroxamate **28** (*erythro* : *threo* = 86 : 14) in only 10% yield as an isolated product in addition to a complex mixture. The structure of the (±)-*erythro*-adduct **28** was determined by the facts that it showed a molecular ion peak at *m*/*z* 373 and ^{1}H NMR peaks at δ 2.18 (1H, m, 2-H) and 3.54 (1H, td, *J* 7.5, 4, 3-H). The relative configuration of the (±)-*erythro*-**28** was established by its chemical conversion into the (±)-*trans*-β-lactam **29** (*trans* : *cis* = 95 : 5) which was accomplished in 83% yield through *S*-alkylation of (±)-**28** (*erythro* : *threo* = 91 : 9) and subsequent treatment of the resulting sulfonium salt with potassium carbonate (Scheme 6). The (±)-*trans*-azetidinone **29** thus prepared showed a molecular ion

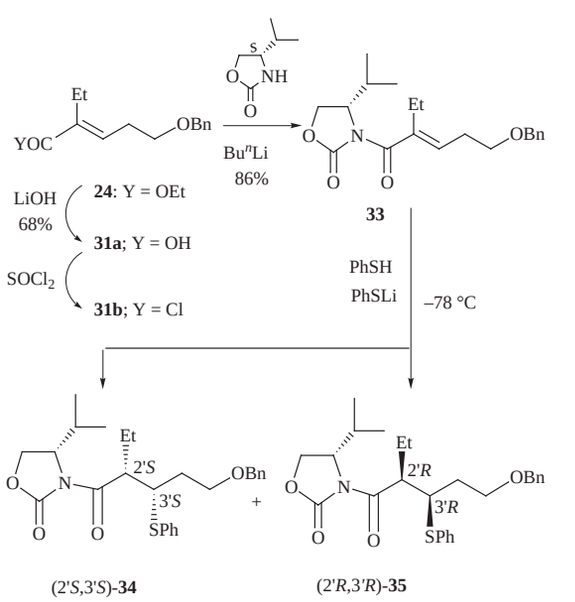


Scheme 6 *Reagents*: i, 1) MeI, $AgClO_4$, 2) K_2CO_3; ii, Ca, liq. NH_3; iii, TBDMSOTf, 2,6-lutidine

peak at *m*/*z* 263, an IR absorption at 1760 cm^{-1} (β-lactam) and ^{1}H NMR peaks at δ 2.57 (1H, ddd, *J* 8, 6, 2, 3-H) and 3.71 (1H, ddd, *J* 7.5, 6, 2, 4-H).

Next, (±)-**29** was converted into (±)-**9**, a known[13] key intermediate for the synthesis of (±)-PS-5. Reductive cleavage of both the N–O and O–CH_2Ph bonds of (±)-**29** by use of calcium[17,18] in liquid ammonia proceeded smoothly to give the desired product (±)-**30** in 96% yield whilst the conventional method,[13,16] using sodium metal (Na/liq. NH_3, −78 °C), was unsuccessful. Finally, treatment of (±)-**30** with TBDMSOTf in the presence of 2,6-lutidine afforded the disilylated (±)-β-lactam **9**, which was identical with an authentic specimen on comparison of their spectral data (Scheme 6).[13,19]

The above result established that a new synthetic route to PS-5 based on the racemic compound (±)-**9** was successful and was then applied to the asymmetric synthesis of (−)-β-lactam **9**. We first examined the addition of benzenethiol to the olefins having oxazolidinone[20] as a chiral auxiliary (Scheme 7, Table 1).



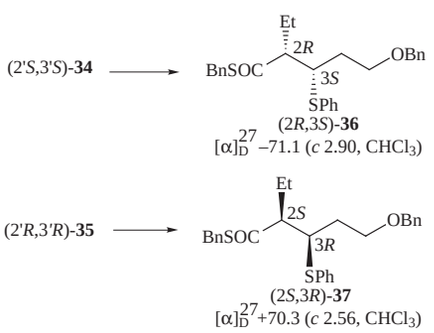
Scheme 7

Unsaturated chiral imide **33** was readily prepared by condensation of the acid chloride **31b** with the lithiated oxazolidinone. The imide (*E*)-**33** was treated with 10 equiv. of benzenethiol in the presence of 1 equiv. of lithium benzenethiolate in THF at −78 °C to give a mixture of two products (2′*S*,3′*S*)-**34** and

Table 1 Addition reaction of benzenethiol to the chiral imide **33**

Entry	PhSLi/PhSH (equiv.)	Time (h)	Solv.	Yield (%)	Ratio **34**:**35**
1	1/10	5	THF	33	74:26
2	1/10 [+LiI (1.3 equiv.)]	5	THF	74	75:25
3	5/10	5	THF	97	80:20
4	1/10	0.6	Et_2O	100	50:50

(2′*R*,3′*R*)-**35** in 33% yield with a ratio of 74:26 (entry 1). These diastereomers were separated by medium pressure column chromatography. In the presence of lithium iodide as an additive, a mixture of two adducts **34** and **35** was obtained in 74% yield with almost the same diastereoselectivity (entry 2). Employment of 5 equiv. of lithium benzenethiolate improved the yield and the ratio of a mixture of **34** and **35** to 97% yield and 80:20, respectively (entry 3). The addition reaction in diethyl ether proceeded very smoothly but the stereoselectivity was markedly diminished giving a 1:1 mixture of **34** and **35** (entry 4). The structures of the adducts **34** and **35** were determined based on the facts that these adducts showed a molecular ion peak at *m*/*z* 455 and ^{1}H NMR peaks due to the 2- and 3-hydrogens as shown in the Experimental section. The absolute configuration of (2′*S*,3′*S*)-**34** was established by its chemical conversion into the known[13,19] intermediate (−)-**9** for the synthesis of (+)-PS-5. The absolute configuration of the minor adduct (2′*R*,3′*R*)-**35** was determined as follows (Scheme 8). As

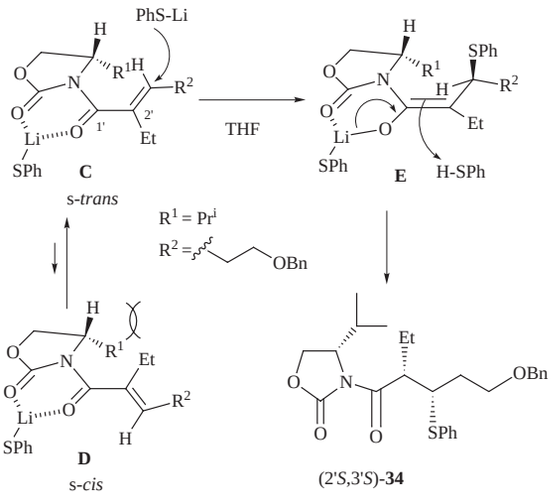


Scheme 8

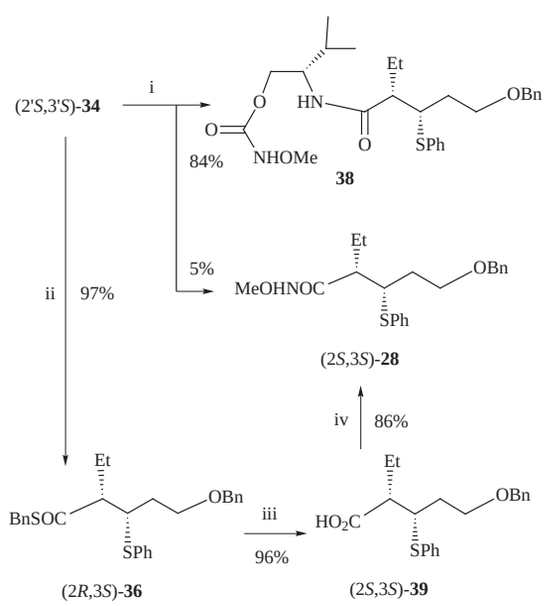
described later, (2′*S*,3′*S*)-**34** and (2′*R*,3′*R*)-**35** were converted into the enantiomeric thioesters (2*R*,3*S*)-**36** and (2*S*,3*R*)-**37**, respectively which showed identical IR and ^{1}H NMR spectra. Comparison of the optical rotation of (2*S*,3*R*)-**37** with that of (2*R*,3*S*)-**36** established unambiguously their absolute configurations.

We propose the possible reaction pathway for the addition of benzenethiol to **33** in THF as shown in Scheme 9.[2b,3b,21] It is presumed that both carbonyl groups of the α,β-unsaturated carboxylic acid moiety and the chiral auxiliary would be fixed by chelation with lithium benzenethiolate. The conformation of the chiral imide with respect to the rotamers arising from rotation about the C-1′–C-2′ axis would be in the s-*trans* form **C** due to steric hindrance between the ethyl and the isopropyl groups on the chiral auxiliary found in the corresponding s-*cis* conformation **D**. Addition of lithium benzenethiolate to the metal coordinated imide **C** would occur from the β-face, according to the 1,5-asymmetric induction by the isopropyl group on the oxazolidinone ring, to form the enolate **E**. The following protonation of **E** would occur from the α-face, due to the stereoelectronic effect[2b] of the newly introduced sulfur group in overcoming the steric hindrance of the isopropyl group, to give (2′*S*,3′*S*)-**34**.

We then investigated conversion of (2′*S*,3′*S*)-**34** into (2*S*,3*S*)-**28** *via* cleavage of the chiral auxiliary (Scheme 10). We first attempted transamination of **34** into hydroxamate (2*S*,3*S*)-**28** in one step by treatment with methoxylamine hydrochloride



Scheme 9



Scheme 10 *Reagents*: i, $MeONH_2$·HCl, Me_3Al; ii, Bu^{n}Li, BnSH, Me_3Al; iii, CF_3CO_2Ag, H_2O; iv, $MeONH_2$·HCl, WSC

and trimethylaluminium.[9,22] However, the desired hydroxamate (2*S*,3*S*)-**28** was obtained in only 5% yield, although the undesired amide **38** was obtained in 84% yield as a result of the attack of methoxylamine onto the oxazolidinone carbonyl group. Recently, we have found[4] that the aluminium thiobenzyloxy 'ate' complex is an excellent reagent for the cleavage of *N*-acyloxazolidinones and camphor sultams. Therefore, this method was applied to (2′*S*,3′*S*)-**34**. As expected, removal of the chiral auxiliary by treatment with the aluminium thiobenzyloxy 'ate' complex was smoothly achieved to give the thioester (2*R*,3*S*)-**36** in 97% yield, which was also obtained in 63% yield by a known[23] approach employing lithium phenylmethanethiolate as a nucleophile. Hydrolysis of the thioester (2*R*,3*S*)-**36** in the presence of silver trifluoroacetate proceeded smoothly to give the corresponding acid (2*S*,3*S*)-**39** in 96% yield which was also obtained, but in only 45% yield, in the presence of silver perchlorate.[4] (2*S*,3*S*)-**39** was then treated with methoxylamine hydrochloride in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC) to give the desired hydroxamate (2*S*,3*S*)-**28** in 86% yield. According to the procedure established with the racemic (±)-**9**, formation of the azetidinone (3*R*,4*R*)-**29**, cleavage of both the N–O and O–CH_2Ph bonds of (3*R*,4*R*)-**29** and subsequent disilylation afforded the disilylated β-lactam (3*R*,4*R*)-**9**, $[a]_D^{26}$ −34.2 (*c* 0.79, $CHCl_3$) {lit.,[19] $[a]_D$ −37.73 (*c* 2.25, $CHCl_3$); lit.,[13] $[a]_D$ −30.1 (*c* 2.9, $CHCl_3$)} in

42% overall yield from the carboxylic acid **31a** in a nine-step sequence (Scheme 6). Since (3*R*,4*R*)-**9** had previously been transformed into (+)-PS-5,[24–27] the present method provides a new highly efficient asymmetric synthesis of (+)-PS-5.

In conclusion, we have now developed a new strategy for the stereoselective construction of the β-lactam ring *via* stereospecific nucleophilic addition of thiols and the stereoselective displacement of the corresponding sulfonium group with *O*-alkyl hydroxamate anions. This method has been successfully applied to the asymmetric synthesis of a key intermediate for the synthesis of carbapenem antibiotic (+)-PS-5.

Experimental

^{1}H and ^{13}C NMR spectra were measured using Varian Gemini-200 (^{1}H, 200 MHz), Varian Gemini-300 (^{1}H, 300 MHz) and VXR-500 (^{1}H, 500 MHz; ^{13}C, 125 MHz) instruments for solutions in deuteriochloroform, unless otherwise stated (tetramethylsilane was used as the internal reference); *J* values are given in Hz. IR spectra were measured with a Perkin-Elmer 1600 FTIR machine for solutions in chloroform, unless otherwise stated and mass spectra were taken with an Hitachi M-4100 spectrometer. Mps were determined with a Kofler-type hot-stage apparatus and are uncorrected. All reactions were performed under nitrogen and extracts from the reaction mixtures were washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. TLC was performed on precoated silica gel $60F_{254}$ (0.25 mm thick, Merck) with UV detection at 254 and 300 nm. Medium-pressure column chromatography (MPCC) was undertaken on a 530-4-10V apparatus (Yamazen) with Lobar größe B (310-25, Lichroprep Si60, Merck) as column absorbent. For flash column chromatography (FCC), Merck Kieselgel 60 (230–400 mesh) was used. Short column chromatography (SCC) was undertaken on a short glass filter using Merck Kieselgel 60 (230–400 mesh) under reduced pressure. For inseparable mixtures, the ^{1}H NMR spectra of the major isomer is assigned.

***erythro*-2-Methyl-*N*-benzyloxy-3-(phenylsulfanyl)butanamide 12**

According to the method previously described,[2] the *erythro*-ester **11**[2] (*erythro*:*threo* = 96:4) was prepared by the addition of benzenethiol to (*E*)-methyl 2-methylbut-2-enoate. Trimethylaluminium (2 M solution in hexane; 1.2 cm^3, 2.4 mmol) was added with stirring at 0 °C to a suspension of *O*-benzylhydroxylamine hydrochloride (382 mg, 2.4 mmol) in toluene (2.4 cm^3). This resulting solution was added with stirring at room temperature to a solution of the *erythro*-ester **11** (269 mg, 1.2 mmol) in toluene (4 cm^3). After being stirred at 60 °C for 1 h, the mixture was acidified with 10% hydrochloric acid and extracted with CH_2Cl_2. The organic layer was washed, dried and concentrated to give a residue which was purified by MPCC (CH_2Cl_2) to give a mixture of the *erythro*-hydroxamate **12** and its *threo*-isomer (*erythro*:*threo* = 94:6) (306 mg, 81%) as a colorless oil. The ratio of *erythro*- to *threo*-adducts was determined by 200 MHz ^{1}H NMR spectroscopy. ν_{max}/cm^{-1} 3398 (NH) and 1690 (NCO) (Found: M$^+$, 315.1290. $C_{18}H_{21}NO_2S$ requires *M*, 315.1291). *erythro*-**12**; δ_H(200 MHz) 8.44 (1H, s, NH), 7.50–7.22 (10H, m, Ph × 2), 4.95 (2H, s, OCH_2Ph), 3.38 (1H, quint., *J* 7, 3-H), 2.19 (1H, m, 2-H) and 1.28 (6H, d, *J* 7, Me × 2).

***trans*-3,4-Dimethyl-1-(benzyloxy)azetidin-2-one 13**

Methyl iodide (2 cm^3, 31 mmol) was added with stirring at room temperature to a solution of the *erythro*-**12** (95 mg, 0.3 mmol) (*erythro*:*threo* = 94:6) and silver perchlorate (280 mg, 1.4 mmol) in MeCN (4 cm^3). After being stirred at room temperature for 15 h, the mixture was filtered to remove the resulting silver iodide. The filtrate was concentrated to give the sulfonium salt. To a stirred suspension of K_2CO_3 (360 mg, 2.6 mmol) in refluxing acetone (12 cm^3) was added a solution of the sulfonium salt in acetone (7 cm^3) and the mixture was refluxed for 2 h. After addition of water, the mixture was extracted with CH_2Cl_2. The extract was dried and concentrated to give the residue which was purified by MPCC (CH_2Cl_2–AcOEt 10:1) to give the *trans*-azetidinone **13** (*trans*:*cis* = 90:10) as a colorless oil (37 mg, 60%). The ratio of *trans*- to *cis*-products was determined by 200 MHz ^{1}H NMR spectroscopy. ν_{max}/cm^{-1} 1752 (NCO) (Found: M$^+$, 205.1105. $C_{12}H_{15}NO_2$ requires *M*, 205.1102). *trans*-**13**; δ_H(200 MHz) 7.46 (5H, m, Ph), 5.02 and 4.98 (2H, ABq, *J* 12, OCH_2Ph), 3.21 (1H, qd, *J* 6, 2, 4-H), 2.46 (1H, qd, *J* 7.5, 2, 3-H), 1.24 (3H, d, *J* 7.5, 3-Me) and 1.19 (3H, d, *J* 6, 4-Me).

***threo*-2-Methyl-*N*-benzyloxy-3-(phenylsulfanyl)butanamide 16**

According to the method previously described,[2] the *threo*-ester **15**[2] (*threo*:*erythro* = 86:14) was prepared by the addition of benzenethiol to (*Z*)-methyl 2-methylbut-2-enoate. According to the procedure described for the preparation of *erythro*-hydroxamate **12**, a solution of *threo*-**15** (*threo*:*erythro* = 86:14) (134 mg, 0.6 mmol), *O*-benzylhydroxylamine hydrochloride and trimethylaluminium in toluene was stirred at 60 °C for 3 h. The crude product was purified by MPCC (CH_2Cl_2) to give a mixture of the *threo*-hydroxamate **16** and the *erythro*-isomer (*threo*:*erythro* = 85:15) (155 mg, 82%) as a colorless oil. The ratio of *erythro*- to *threo*-adducts was determined by 200 MHz ^{1}H NMR spectroscopy. ν_{max}/cm^{-1} 3398 (NH) and 1692 (NCO) (Found: M$^+$, 315.1277. $C_{18}H_{21}NO_2S$ requires *M*, 315.1291). *threo*-**16**; δ_H(200 MHz) 8.84 (1H, s, NH), 7.50–7.20 (10H, m, Ph × 2), 4.91 (2H, s, OCH_2Ph), 3.46 (1H, m, 3-H), 2.16 (1H, m, 2-H), 1.24 and 1.12 (each 3H, d, *J* 7, Me × 2).

***cis*-3,4-Dimethyl-1-(benzyloxy)azetidin-2-one 17**

According to the procedure described for the preparation of *trans*-**13**, the *threo*-**16** (*threo*:*erythro* = 85:15) (190 mg, 0.6 mmol) was alkylated with methyl iodide in the presence of silver perchlorate and the resulting sulfonium salt was treated with K_2CO_3. The crude product was purified by MPCC (CH_2Cl_2) to give the *cis*-azetidinone **17** (*cis*:*trans* = 92:8) as a colorless oil (71 mg, 58%). The ratio of *trans*- to *cis*-products was determined by 200 MHz ^{1}H NMR spectroscopy. ν_{max}/cm^{-1} 1754 (NCO) (Found: M$^+$, 205.1092. $C_{12}H_{15}NO_2$ requires *M*, 205.1102). *cis*-**17**; δ_H(200 MHz) 7.44 (5H, m, Ph), 4.98 (2H, s, OCH_2Ph), 3.72 (1H, quint., *J* 6, 4-H), 2.92 (1H, qd, *J* 7.5, 6, 3-H), 1.10 (3H, d, *J* 7.5, 3-Me) and 1.03 (3H, d, *J* 6, 4-Me).

(*E*)-Ethyl 2-ethyl-5-(benzyloxy)pent-2-enoate 24

According to the literature procedure,[12,13] aldehyde **22**[12,13] was prepared from alcohol **21**. A solution of triethyl α-phosphonopropionate **23**[14] in THF (50 cm^3) was added at 0 °C to a stirred suspension of NaH (60% dispersion in mineral oil; 0.8 g, 20 mmol) in THF (10 cm^3). After being stirred at room temperature for 0.5 h, a solution of the aldehyde **22** (3.28 g, 20 mmol) in THF (50 cm^3) was added dropwise at 0 °C and the whole was stirred at the same temperature for 1 h. The resulting solution was poured into ice-cooled water (20 cm^3) and then extracted with Et_2O. The extract was washed with saturated aqueous NaCl, dried and concentrated to give a mixture of (*E*)-ester **24** and (*Z*)-ester **25** (**24**:**25** = 1:1) as a colorless oil (4.8 g, 91%). The ratio of (*E*)- to (*Z*)-esters was determined by 200 MHz ^{1}H NMR spectroscopy. δ_H(200 MHz) 7.40 (5H, m, Ph), 6.79 [0.5H, t, *J* 7, (*E*)-3-H], 6.00 [0.5H, t, *J* 7, (*Z*)-3-H], 4.59 and 4.58 (each 1H, s, OCH_2Ph), 4.24 (2H, m, OCH_2Me), 3.60 [1H, t, *J* 7, (*E*)-5-H_2], 3.58 [1H, t, *J* 7, (*Z*)-5-H_2], 2.80 (1H), 2.56 (1H) and 2.36 (2H) (each q, *J* 7, 4-H_2 and 2-CH_2) and 1.40–0.96 (6H, m, *Me* × 2). A solution of a mixture of (*E*)- and (*Z*)-esters **24** and **25** (3.6 g, 14 mmol) and diphenyl disulfide[15] (914 mg, 4.2 mmol) in THF (170 cm^3) was refluxed for 3 h. The mixture was then cooled and the solvent was removed under reduced pressure. The residue was purified by MPCC (*n*-hexane–AcOEt 15:1) to give the (*E*)-ester **24** as a colorless oil (3.5 g, 95%).

ν_{max}/cm^{-1} 1702 (COOEt); *m*/*z* (CI) 263 (MH^+); δ_H(200 MHz) 7.40 (5H, s, Ph), 6.79 (1H, t, *J* 7, 3-H), 4.58 (2H, s, OC*H*$_2$Ph), 4.24 (2H, q, *J* 7, OC*H*$_2$Me), 3.60 (2H, t, *J* 7, 5-H$_2$), 2.56 and 2.36 (each 2H, q, *J* 7, 4-H$_2$ and 2-CH$_2$), 1.32 (3H, t, *J* 7, OCH$_2$*Me*) and 1.02 (3H, t, *J* 7, CH$_2$*Me*).

(±)-Ethyl *erythro*-2-ethyl-5-benzyloxy-3-(phenylsulfanyl)pentanoate 26

Benzenethiol (0.38 cm^3, 3.7 mmol) was added with stirring at 0 °C to a solution of *n*-butyllithium (1.63 M solution in hexane; 0.02 cm^3, 0.037 mmol) in THF (2.5 cm^3) to give a solution of a 10 : 0.1 mixture of benzenethiol and lithium benzenethiolate. To the resulting solution was added a solution of **24** (97 mg, 0.37 mmol) in THF (2.5 cm^3) at room temperature. After being stirred at room temperature for 2 h, the mixture was made alkaline by adding 5% aqueous NaOH and extracted with CH_2Cl_2. The extract was washed, dried and concentrated to give the residue which was purified by MPCC (*n*-hexane–CH_2Cl_2 1 : 1) to give a mixture of (±)-*erythro*-**26** and the *threo*-isomer (*erythro* : *threo* = 85 : 15) (124 mg, 90%) as a colorless oil. The ratio of *erythro*- to *threo*-adducts was determined by 200 MHz ^{1}H NMR spectroscopy. ν_{max}/cm^{-1} 1724 (CO_2Et) (Found: M^+, 372.1758. $C_{22}H_{28}O_3S$ requires *M*, 372.1758). *erythro*-**26**; δ_H(200 MHz) 7.50–7.20 (10H, m, Ph × 2), 4.48 (2H, s, OC*H*$_2$Ph), 4.10 (2H, m, OC*H*$_2$Me), 3.82–3.60 (2H, m, 5-H$_2$), 3.51 (1H, ddd, *J* 11.5, 8, 4.5, 3-H), 2.50 (1H, ddd, *J* 10, 8, 4.5, 2-H), 2.16–1.66 (4H, m, 2-H$_2$ and 4-H$_2$), 1.22 (3H, t, *J* 7, OCH$_2$*Me*) and 0.88 (3H, t, *J* 7, CH$_2$*Me*).

(±)-*erythro*-2-Ethyl-*N*-methoxy-5-benzyloxy-3-(phenylsulfanyl)pentanamide 28

According to the procedure described for the preparation of the *erythro*-hydroxamate **12**, a solution of (±)-*erythro*-**26** (*erythro* : *threo* = 85 : 15) (74 mg, 0.2 mmol), methoxylamine hydrochloride and trimethylaluminium in toluene (1.5 cm^3) was stirred under reflux for 3 h. The crude product was purified by MPCC (CH_2Cl_2–*n*-hexane 1 : 1) to give a mixture of the (±)-*erythro*-hydroxamate **28** and the *threo*-isomer (*erythro* : *threo* = 86 : 14) (7 mg, 10%) as a colorless oil. The ratio of *erythro*- to *threo*-adducts was determined by 200 MHz ^{1}H NMR spectroscopy. ν_{max}/cm^{-1} 3400 (NH), 1694 (NCO) (Found: M^+, 373.1703. $C_{21}H_{27}NO_3S$ requires *M*, 373.1701). **28**; δ_H(200 MHz) 8.70 (1H, br s, NH), 7.44–7.30 (10H, m, Ph × 2), 4.52 and 4.46 (2H, ABq, *J* 11, OC*H*$_2$Ph), 3.90 (1H, m, 5-H), 3.66 (1H, m, 5-H), 3.64 (3H, s, OMe), 3.54 (1H, td, *J* 7.5, 4, 3-H), 2.18 (1H, m, 2-H), 1.99 (1H, m, 4-H), 1.91–1.76 (3H, m, 2-CH$_2$ and 4-H) and 0.86 (3H, t, *J* 7, CH$_2$*Me*).

(*E*)-2-Ethyl-*N*-methoxy-5-(benzyloxy)pent-2-enamide 27

According to the procedure described for the preparation of the hydroxamate **12**, a solution of the ester **24** (286 mg, 1.1 mmol), methoxylamine hydrochloride and trimethylaluminium in toluene was stirred at 60 °C for 5 h. The crude product was purified by MPCC (CH_2Cl_2–AcOEt 5 : 1) to give the (*E*)-hydroxamate **27** (182 mg, 63%) as a colorless oil; ν_{max}/cm^{-1} 3404 (NH), 1680 (NCO) (Found: M^+, 263.1507. $C_{15}H_{21}NO_3$ requires *M*, 263.2519); δ_H(200 MHz) 8.59 (1H, br s, NH), 7.44–7.30 (5H, m, Ph), 6.12 (1H, t, *J* 7, 3-H), 4.54 (2H, s, OC*H*$_2$Ph), 3.79 (3H, s, OMe), 3.56 (2H, t, *J* 7, 5-H$_2$), 2.46 and 2.32 (each 2H, q, *J* 7, 4-H$_2$ and 2-CH$_2$) and 1.00 (3H, t, *J* 7, CH$_2$*Me*).

Addition of benzenethiol to hydroxamate 27

According to the procedure described for the preparation of (±)-*erythro*-**26**, a solution of **27** (145 mg, 0.55 mmol), PhSH (5.5 mmol) and PhSLi (0.055 mmol) in THF (3 cm^3) was stirred under reflux for 2 h. The crude product was purified by MPCC (*n*-hexane–CH_2Cl_2 1 : 1) to give a mixture of (±)-*erythro*-**28** and its *threo*-isomer (*erythro* : *threo* = 91 : 9) (170 mg, 82%) as a colorless oil. The ratio of *erythro*- to *threo*-adducts was determined by 200 MHz ^{1}H NMR spectroscopy. The (±)-*erythro*-**28** was identical with the authentic sample, prepared from (±)-*erythro*-**26** based on a comparison of their spectral data.

(±)-*trans*-3-Ethyl-1-methoxy-4-[2-(benzyloxy)ethyl]azetidin-2-one 29

According to the procedure described for the preparation of the *trans*-**13**, (±)-*erythro*-**28** (*erythro* : *threo* = 91 : 9) (116 mg, 0.3 mmol) was alkylated with methyl iodide in the presence of silver perchlorate and then the resulting sulfonium salt was treated with K_2CO_3. The crude product was purified by MPCC (AcOEt–CH_2Cl_2 1 : 10) to give the (±)-*trans*-azetidinone **29** (*trans* : *cis* 95 : 5) as a colorless oil (66 mg, 83%). The ratio of *trans*- to *cis*-products was determined by 200 MHz ^{1}H NMR spectroscopy. ν_{max}/cm^{-1} 1760 (NCO) (Found: M^+, 263.1549. $C_{15}H_{21}NO_3$ requires *M*, 263.1521) (Found: C, 66.8; H, 7.9; N, 5.1. $C_{15}H_{21}NO_3 \cdot \frac{1}{3}H_2O$ requires C, 66.9; H, 8.1; N, 5.2%). (±)-*trans*-**29**; δ_H(200 MHz) 7.40–7.26 (5H, m, Ph), 4.50 (2H, s, OC*H*$_2$Ph), 3.75 (3H, s, OMe), 3.71 (1H, ddd, *J* 7.5, 6, 2, 4-H), 3.60 (2H, m, OCH$_2$), 2.57 (1H, ddd, *J* 8, 6, 2, 3-H), 2.14 (1H, dq, *J* 14, 6, 4-CH), 1.91 (1H, dtd, *J* 14, 7.5, 6, 4-CH), 1.80–1.50 (2H, m, 3-CH$_2$) and 1.00 (3H, t, *J* 7.5, Me); δ_C 166.2 (s), 138.0 (s), 128.4 (d), 127.8 (d), 127.7 (d), 73.3 (t), 66.9 (t), 63.6 (q), 60.7 (d), 52.6 (d), 32.9 (t), 21.3 (t), 11.4 (q).

(±)-*trans*-3-Ethyl-1-[(1,1-dimethylethyl)dimethylsilyl]-4-{2-[(1,1-dimethylethyl)dimethylsilyloxy]ethyl}azetidin-2-one 9

Metallic calcium (58 mg, 1.45 mmol) was added to liquid ammmonia (10 cm^3) at −78 °C with stirring. A solution of (±)-**29** (*trans* : *cis* = 95 : 5) (50 mg, 0.19 mmol) in THF (0.3 cm^3) was added to the above solution and the resulting blue-colored solution was stirred for 2 h. Ammonium chloride was added until the blue color disappeared, then the liquid ammonia was evaporated to give a residue, to which water was added. The resulting mixture was extracted with CH_2Cl_2. The extract was washed, dried and concentrated to give the (±)-alcohol **30**. ν_{max}/cm^{-1} 3500–3400 (NH, OH) and 1760 (NCO); δ_H(200 MHz) 3.90–3.64 (2H, m, OCH$_2$), 3.48 (1H, ddd, *J* 8, 5.5, 2, 4-H), 2.78 (1H, br t, *J* 8, 3-H), 2.00–1.50 (4H, m, 4-CH$_2$ and 3-CH$_2$) and 1.02 (3H, t, *J* 8, Me).

According to the literature,[13,19] a solution of the (±)-alcohol **30** (15 mg, 0.1 mmol), 2,6-lutidine (0.12 cm^3, 1.1 mmol) and TBDMSOTf (0.09 cm^3, 0.4 mmol) in CH_2Cl_2 (5 cm^3) was stirred at 0 °C for 1 h. After addition of MeOH (0.25 cm^3), the mixture was concentrated to give the residue which was purified by FCC (*n*-hexane–AcOEt 92 : 8) to give the disilylated (±)-lactam **9** as a colorless oil (35 mg, 95%). ν_{max}/cm^{-1} 1720 (NCO) [Found (CI): $M^+ + 1$, 372.2752. $C_{19}H_{41}NO_2Si_2 + H$ requires $M + 1$, 263.1521]; δ_H(500 MHz) 3.64 (2H, m, OCH$_2$), 3.37 (1H, dt, *J* 10.5, 2.5, 4-H), 2.79 (1H, ddd, *J* 7.5, 5.5, 2.5, 3-H), 2.15–1.54 (4H, m, 4-CH$_2$ and 3-CH$_2$), 1.01 (3H, t, *J* 7, Me), 0.96 and 0.86 (each 9H, s, Bu^t × 2), 0.24 (3H, s, SiMe), 0.21 (3H, s, SiMe) and 0.04 (6H, s, SiMe$_2$). The ^{1}H NMR and IR spectra were identical with those of an authentic sample.[13,19]

(*E*,*S*)-4-(1-Methylethyl)-3-[2-ethyl-1-oxo-5-(benzyloxy)pent-2-enyl]oxazolidin-2-one 33

A solution of the ester **24** (553 mg, 2.1 mmol) and LiOH (170 mg, 7 mmol) in THF–H_2O–MeOH (1 : 1 : 2) (4 cm^3) was stirred at room temperature for 3.5 h. The mixture was acidified with 10% hydrochloric acid at 0 °C and extracted with CH_2Cl_2. The organic layer was washed, dried and concentrated to give the residue which was purified by SCC (AcOEt–CH_2Cl_2 1 : 1) and recrystallized from *n*-hexane to give the corresponding carboxylic acid **31a** (335 mg, 68%) as colorless crystals mp 47–48 °C. ν_{max}/cm^{-1} 3100–2500 and 1686 (COOH) (Found: C, 71.77; H, 7.74. $C_4H_{18}O_3$ requires C, 71.49; H, 7.76%); δ_H(200 MHz) 10.71 (1H, br s, OH), 7.24 (5H, m, Ph), 6.50 (1H, t, *J* 7, 3-H), 4.48 (2H, s, OC*H*$_2$Ph), 3.53 (2H, t, *J* 7, 5-H$_2$), 2.50 (2H, q, *J* 7, 4-H$_2$), 2.26 (2H, q, *J* 7, 2-CH$_2$) and 1.01 (3H, t, *J* 7, Me).

A solution of $SOCl_2$ (0.5 cm^3, 6.8 mmol) and **31a** (110 mg,

0.47 mmol) in benzene (16 cm^3) was stirred under reflux for 1 h. The solvent was removed under reduced pressure to give the acid chloride **31b** (110 mg) as a pale yellow oil. According to the literature,[20] (*S*)-4-(1-methylethyl)oxazolidin-2-one (58 mg, 0.45 mmol) was lithiated with *n*-butyllithium in THF at −78 °C and successively acylated with the acid chloride **31b** (110 mg, 0.47 mmol). The crude product was purified by MPCC (CH_2Cl_2) to give the imide **33** (140 mg, 86%) as a pale yellow oil; $[\alpha]_D^{28}$ +33.7 (*c* 3.09, $CHCl_3$); ν_{max}/cm^{-1} 1778 and 1682 (CONHCOO) (Found: M^+, 345.1942. $C_{20}H_{27}NO_4$ requires *M*, 345.1939); δ_H(200 MHz) 7.25 (5H, m, Ph), 6.00 (1H, t, *J* 6, 3′-H), 4.55 (2H, s, OCH_2Ph), 4.54 (1H, m, 4-H), 4.32 (1H, t, *J* 8, 5-H), 4.19 (1H, dd, *J* 8, 6, 5-H), 3.56 (2H, t, *J* 7, 5′-H_2), 2.60–2.24 (5H, m, 4′-H_2 , 2′-CH_2 and 4-CH), 1.03 (3H, t, *J* 8, CH_2*Me*) and 0.90 (6H, d, *J* 8, CHMe_2).

Addition of benzenethiol to chiral imide 33 (Table 1, entry 3)

Benzenethiol (1 cm^3, 10.8 mmol) was added with stirring at 0 °C to a solution of *n*-butyllithium (1.63 M solution in hexane; 2.3 cm^3, 3.6 mmol) in THF (5 cm^3) to give a solution of a 2:1 mixture of benzenethiol and lithium benzenethiolate. To the resulting solution was added a solution of **33** (250 mg, 0.72 mmol) in THF (5 cm^3) at −78 °C. After being stirred at −78 °C for 5 h, the mixture was made alkaline by adding 5% aqueous NaOH and extracted with CH_2Cl_2. The extract was dried and concentrated to give the residue which was purified by MPCC (*n*-hexane–AcOEt 3:1) to give (2′*S*,3′*S*,4*S*)-4-(1-methylethyl)-3-[2′-ethyl-1′-oxo-5′-benzyloxy-3′-(phenylsulfanyl)pentyl]oxazolidin-2-one **34** as a colorless oil (257 mg, 78%) and (2′*R*,3′*R*,4*S*)-4-(1-methylethyl)-3-[2′-ethyl-1′-oxo-5′-benzyloxy-3′-(phenylsulfanyl)pentyl]oxazolidin-2-one **35** as a colorless oil (64 mg, 19%). **34**: $[\alpha]_D^{26}$ −2.5 (*c* 2.77, $CHCl_3$); ν_{max}/cm^{-1} 1778 and 1692 (CONCOO) (Found: M^+, 455.2110. $C_{26}H_{33}NO_4S$ requires *M*, 455.2128) (Found: C, 67.7; H, 7.3; N, 3.0. $C_{26}H_{33}NO_4S\cdot\frac{1}{4}H_2O$ requires C, 67.9; H, 7.3; N, 3.0%); δ_H(500 MHz) 7.39–7.21 (10H, m, Ph × 2), 4.49 (1H, m, 4-H), 4.48 and 4.45 (2H, ABq, *J* 12, OCH_2Ph), 4.24 (1H, t, *J* 9, 5-H), 4.18 (2H, m, 3′- and 5-H), 3.79 (1H, dt, *J* 10, 5.5, 5′-H), 3.70 (1H, ddd, *J* 10, 7, 5, 5′-H), 3.61 (1H, ddd, *J* 10, 6, 4, 2-H), 2.27 (1H, m, C*H*Me_2), 2.13 (1H, m, 4′-H), 1.95–1.78 (3H, m, 4′-H and CH_2*Me*), 0.89 (3H, d, *J* 7, CH*Me*), 0.87 (3H, t, *J* 7, CH_2*Me*) and 0.80 (3H, d, *J* 7, CH*Me*); δ_C 174.3 (s), 153.7 (s), 138.6 (s), 135.6 (s), 131.6 (d), 128.9 (d), 128.3 (d), 127.6 (d), 127.4 (d), 126.8 (d), 72.8 (t), 67.6 (t), 63.0 (t), 58.6 (d), 48.9 (d), 48.6 (d), 33.2 (t), 28.4 (d), 22.6 (t), 18.1 (q), 14.6 (q), 11.6 (q). **35**: $[\alpha]_D^{26}$ +77.2 (*c* 2.63, $CHCl_3$); ν_{max}/cm^{-1} 1777 and 1695 (CONCOO) (Found: M^+, 455.2110. $C_{26}H_{33}NO_4S$ requires *M*, 455.2128) (Found: C, 66.8; H, 7.4; N, 3.0. $C_{26}H_{33}NO_4S\cdot\frac{2}{3}H_2O$ requires C, 66.8; H, 7.2; N, 3.0%); δ_H(500 MHz) 7.40–7.18 (10H, m, Ph × 2), 4.50 and 4.44 (2H, ABq, *J* 12, OCH_2Ph), 4.24 (1H, ddd, *J* 9, 4, 3, 4-H), 4.15 (1H, ddd, *J* 9, 7.5, 5, 3′-H), 4.08 (1H, dd, *J* 9, 3, 5-H), 3.96 (1H, t, *J* 9, 5-H), 3.78–3.69 (2H, m, 5′-H_2), 3.59 (1H, br ddd, *J* 10, 7, 3.5, 2′-H), 2.33 (1H, m, 4-CH), 2.08–1.96 (2H, m, 2′-CH_2), 1.92–1.82 (2H, m, 4′-H_2), 0.91 and 0.84 (each 3H, d, *J* 7, CHMe_2) and 0.89 (3H, t, *J* 7, CH_2*Me*); δ_C 174.3 (s), 153.6 (s), 138.5 (s), 135.7 (s), 131.9 (d), 128.9 (d), 128.3 (d), 127.6 (d), 127.5 (d), 126.9 (d), 72.9 (t), 67.6 (t), 63.0 (t), 58.7 (d), 48.6 (d), 48.2 (d), 32.7 (t), 28.5 (d), 23.1 (t), 18.0 (q), 14.6 (q), 10.9 (q).

Conversion of (2′*S*,3′*S*)-34 into (2*S*,3*S*)-28

Trimethylaluminium (2 M solution in hexane; 0.23 cm^3, 0.45 mmol) was added with stirring at 0 °C to a suspension of methoxylamine hydrochloride (38 mg, 0.45 mmol) in THF (0.3 cm^3). The resulting solution was added at 0 °C to a solution of (2′*S*,3′*S*)-**34** (25 mg, 0.05 mmol) in THF (5 cm^3). After being stirred at 0 °C for 7 h, the mixture was acidified with 10% hydrochloric acid and extracted with CH_2Cl_2. The organic layer was washed, dried and concentrated to give the residue which was purified by MPCC (AcOEt–CH_2Cl_2 5:1) to give (2*S*,3*S*)-2-ethyl-*N*-methoxy-5-(benzyloxy)-3-(phenylsulfanyl)pentanamide **28** (1 mg, 5%) as a colorless oil and (1′*S*,2*S*,3*S*)-2-ethyl-*N*-[2′-(methoxyaminocarbonyloxy)-1′-(1-methylethyl)ethyl]-5-benzyloxy-3-(phenylsulfanyl)pentanamide **38** (21 mg, 84%) as a colorless oil. The ^{1}H NMR and IR spectra of (2*S*,3*S*)-**28** were identical with those of (±)-**28**. **28**: $[\alpha]_D^{26}$ +3.4 (*c* 2.54, $CHCl_3$).

38: ν_{max}/cm^{-1} 3436 (NH), 1742, 1670 (NCO) (Found: M^+, 502.2491. $C_{27}H_{38}N_2O_5S$ requires *M*, 502.2499); δ_H(500 MHz) 8.30 (1H, br s, CON*H*OMe), 7.38–7.20 (10H, m, Ph × 2), 5.64 (1H, br d, *J* 9, CONH), 4.50 and 4.47 (2H, ABq, *J* 12, OCH_2Ph), 4.29 (1H, dd, *J* 11, 3.5, 2′-H), 4.12 (1H, m, 1′-H), 3.92 (1H, dd, *J* 11, 9, 2′-H), 3.83 (1H, ddd, *J* 9, 7, 6, 5-H), 3.64 (1H, dt, *J* 9, 7, 5-H), 3.35 (1H, td, *J* 9, 3.5, 3-H), 2.13–1.96 (3H, m, 2-CH_2 and 4-H), 1.76–1.65 (3H, m, 2-H, 4-H and 1′-CH), 0.92 and 0.85 (each 3H, d, *J* 7, CHMe_2) and 0.88 (3H, t, *J* 7.5, CH_2*Me*); $[\alpha]_D^{24}$ −5.3 (*c* 0.94, $CHCl_3$).

(2*R*,3*S*)-S-Benzyl 2-ethyl-5-benzyloxy-3-(phenylsulfanyl)-pentanethioate 36

(A) Using aluminium thiobenzyloxy 'ate' complex. Phenylmethanethiol (0.08 cm^3, 0.7 mmol) and trimethylaluminium (2 M solution in hexane; 0.45 cm^3, 0.9 mmol) were added dropwise with stirring at 0 °C to a solution of *n*-butyllithium (1.63 M solution in hexane; 0.45 cm^3, 0.7 mmol) in THF (6 cm^3). After being stirred at 0 °C for 0.5 h, the resulting solution was added at 0 °C to a solution of (2′*S*,3′*S*)-**34** (159 mg, 0.35 mmol) in THF (10 cm^3). After being stirred at 0 °C for 1.5 h, the mixture was acidified with 10% hydrochloric acid and extracted with CH_2Cl_2. The organic layer was washed with 5% aqueous NaOH, dried and concentrated to give the residue which was purified by MPCC (*n*-hexane–CH_2Cl_2 4:1) to give (2*R*,3*S*)-**36** (153 mg, 97%) as a colorless oil; ν_{max}/cm^{-1} 1676 (COS) (Found: M^+, 450.1701. $C_{27}H_{30}O_2S_2$ requires *M*, 450.1686); δ_H(500 MHz) 7.27 (15H, m, Ph × 3), 4.44 and 4.41 (2H, ABq, *J* 12, OCH_2Ph), 4.15 and 4.11 (2H, ABq, *J* 14, SCH_2Ph), 3.75 (1H, td, *J* 9, 5, 5-H), 3.65 (1H, ddd, *J* 9, 6, 4, 5-H), 3.50 (1H, ddd, *J* 10, 6.5, 5, 3-H), 2.70 (1H, ddd, *J* 10, 7, 5, 2-H), 2.06–2.13 (1H, m, 4-H), 1.79–1.90 (2H, m, 2-CH_2), 1.72 (1H, m, 4-H) and 0.86 (3H, t, *J* 7.5, Me); $[\alpha]_D^{27}$ −71.1 (*c* 2.90, $CHCl_3$).

(B) Using lithium benzylthiolate. Phenylmethanethiol (0.028 cm^3, 0.24 mmol) was added dropwise with stirring at 0 °C to a solution of *n*-butyllithium (1.63 M solution in hexane; 0.1 cm^3, 0.18 mmol) in THF (3 cm^3). After being stirred at 0 °C for 0.5 h, the resulting solution was added at 0 °C to a solution of (2′*S*,3′*S*)-**34** (56 mg, 0.12 mmol) in THF (3 cm^3). After being stirred at 0 °C for 1.5 h, the mixture was made alkaline by addition of 5% aqueous NaOH and extracted with CH_2Cl_2. The organic layer was washed, dried and concentrated to give the residue which was purified by MPCC (*n*-hexane–CH_2Cl_2 4:1) to give (2*R*,3*S*)-**36** (34 mg, 63%) as a colorless oil. The ^{1}H NMR spectra and IR spectra of (2*R*,3*S*)-**36** were identical with those of the sample prepared in (A).

(2*S*,3*R*)-S-Benzyl 2-ethyl-5-benzyloxy-3-(phenylsulfanyl)-pentanethioate 37

According to the procedure described for preparation of (2*R*,3*S*)-**36**, a solution of (2′*R*,3′*R*)-**35** (75 mg, 0.16 mmol) and aluminium thiobenzyloxy 'ate' complex in THF was stirred at 0 °C for 1.5 h. The crude product was purified by MPCC (*n*-hexane–CH_2Cl_2 4:1) to give (2*S*,3*R*)-**37** (68 mg, 95%). The ^{1}H NMR and IR spectra of **37** were identical with those of **36**. $[\alpha]_D^{27}$ +70.3 (*c* 2.56, $CHCl_3$).

(2*S*,3*S*)-2-Ethyl-5-benzyloxy-3-(phenylsulfanyl)pentanoic acid 39

(A) Using silver trifluoroacetate. Silver trifluoroacetate (260 mg, 1.2 mmol) was added with stirring to a solution of the thioester **36** (41 mg, 0.09 mmol) in THF–H_2O (3:1) (2 cm^3). After being stirred under reflux for 5 h, the mixture was acidified with 10% hydrochloric acid and extracted with CH_2Cl_2.

The organic layer was washed, dried and concentrated to give the residue which was purified by SCC (CH_2Cl_2–MeOH 10:1) to give the carboxylic acid **39** (30 mg, 96%) as a colorless amorphous solid; ν_{max}/cm^{-1} 3000–2600, 1692 (COOH) (Found: M^+, 344.1449. $C_{20}H_{24}O_3S$ requires *M*, 344.1445); δ_H(500 MHz) 7.50–7.22 (10H, m, Ph × 2), 4.50 (2H, s, O*CH*$_2$Ph), 3.92–3.60 (2H, m, 5-CH_2), 3.60–3.46 (1H, m, 3-H), 2.60–2.48 (1H, m, 2-H), 2.20–1.64 (4H, m, 4-H_2 and 2-CH_2) and 0.94 (3H, t, *J* 8, Me).

(B) Using silver perchlorate. According to method A, a solution of the thioester **36** (20 mg, 0.04 mmol) and silver perchlorate (130 mg, 0.63 mmol) in THF–H_2O (3:1) (0.8 cm^3) was stirred under reflux for 5 h. The crude product was purified by SCC (CH_2Cl_2–MeOH 10:1) to give the carboxylic acid **39** (6 mg, 45%) as a colorless amorphous solid. The ^{1}H NMR and IR spectra of **39** were identical with those of the sample prepared in (A).

(2*S*,3*S*)-2-Ethyl-*N*-methoxy-5-benzyloxy-3-(phenylsulfanyl)-pentanamide 28

A solution of methoxylamine hydrochloride (44 mg, 0.5 mmol) in H_2O (0.25 cm^3) was added under stirring at room temperature to a solution of the carboxylic acid **39** (90 mg, 0.26 mmol) in THF–H_2O (6:1) (0.5 cm^3). Then a solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC) (96 mg, 0.5 mmol) in H_2O (0.25 cm^3) was added under stirring at room temperature to the resulting mixture. After being stirred for 5 h, the mixture was acidified with 10% hydrochloric acid and extracted with CH_2Cl_2. The organic layer was washed, dried and concentrated to give the residue which was purified by SCC (CH_2Cl_2–MeOH 10:1) to give the (2*S*,3*S*)-hydroxamate **28** (83 mg, 86%). **28** was identical with the product **28** formed from **34** based on comparison of their spectra and optical rotation.

(3*R*, *trans*)-3-Ethyl-1-methoxy-4-[2-(benzyloxy)ethyl]azetidin-2-one 29

According to the procedure described for the preparation of the *trans*-**13**, the (2*S*,3*S*)-**28** (112 mg, 0.3 mmol) was alkylated with methyl iodide in the presence of silver perchlorate and then the resulting sulfonium salt was treated with K_2CO_3. The crude product was purified by MPCC (AcOEt–CH_2Cl_2 1:10) to give (3*R*,4*R*)-**29** (*trans*:*cis* = 97:3) as a colorless oil (65 mg, 83%). The ratio of *trans*- to *cis*-products was determined by 200 MHz ^{1}H NMR spectroscopy. The ^{1}H NMR and IR spectra of (3*R*,4*R*)-**29** were identical with those of (±)-**29**; $[\alpha]_D^{26}$ +1.32 (*c* 2.27, $CHCl_3$).

(3*R*, *trans*)-3-Ethyl-1-[(1,1-dimethylethyl)dimethylsilyl]-4-{2-[(1,1-dimethylethyl)dimethylsilyloxy]ethyl}azetidin-2-one 9

According to the procedure described for the preparation of (±)-**9**, (3*R*,4*R*)-**29** (*trans*:*cis* = 97:3) (59 mg, 0.2 mmol) was converted into the disilylated (3*R*, *trans*)-β-lactam **9** (70 mg, 91%) as a colorless oil. The ^{1}H NMR and IR spectra of (3*R*, *trans*)-β-lactam **9** were identical with those of (±)-**9**; $[\alpha]_D^{26}$ −34.2 (*c* 0.79, $CHCl_3$) {lit. $[\alpha]_D$ −37.73 (*c* 2.25, $CHCl_3$),[19] −30.1 (*c* 2.9, $CHCl_3$)[13]}.

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