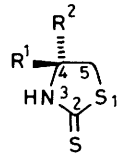
Investigation of New Chiral 1,3-Oxazolidine-2-thiones: Analytical Separation and Optical Resolution of Racemic Carboxylic Acids and Amino Acids†

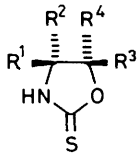
Yoshimitsu Nagao, Toshio Kumagai, Shozo Yamada, and Eiichi Fujita*
Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan
Yoshinori Inoue, Yunosuke Nagase, Sakae Aoyagi, and Takao Abe
Chemical and Formulation Laboratory, Lederle (Japan) Ltd., Kashiwacho, Shiki, Saitama 353, Japan

New chiral five-membered heterocycles, (4*S*)-(**4**) and (4*R*)-4-ethyl-1,3-oxazolidine-2-thione (**5**), (4*S*)-4-isopropyl-1,3-oxazolidine-2-thione (**6**), and (4*R*,5*S*)-4-methyl-5-phenyl-1,3-oxazolidine-2-thione [(4*R*,5*S*)-MPOT] (**7**) have been developed. Among these heterocycles, (4*R*,5*S*)-MPOT (**7**) proved to be an excellent chiral reagent for analytical and efficient separation of racemic products from transformations of chiral carboxylic acids and amino acids.

Our recent research interests have been focussed on the development of new reactions utilizing functional five-membered heterocycles, particularly 1,3-thiazolidine-2-thiones (**1**) and (**2**) and 1,3-oxazolidine-2-thiones (**3**).[1] In a series of studies, we have prepared the new chiral, 1,3-oxazolidine-2-thiones (**4**)—(**7**) and have investigated their potential as nucleofuges for asymmetric synthesis.



(1) $R^1 = R^2 = H$
(2) $R^1 = H, R^2 = CO_2Me$

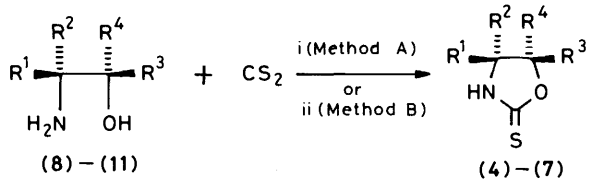


(3) $R^1 = R^3 = R^4 = H, R^2 = CO_2Me$
(4) $R^1 = Et, R^2 = R^3 = R^4 = H$
(5) $R^1 = R^3 = R^4 = H, R^2 = Et$
(6) $R^1 = Pr^i, R^2 = R^3 = R^4 = H$
(7) $R^1 = R^3 = H, R^2 = Me, R^4 = Ph$

Our choice of heterocycles such as (**4**)—(**7**) for chiral design was made for the following reasons. (*a*) Various β-amino alcohols which are commercially available and readily obtained by reduction of ordinary α-amino acids can be employed. (*b*) Because the heterocycles containing the thiocarbonyl group conjugated with hetero atoms exhibits a strong u.v. absorption ($\pi \rightarrow \pi^*$) with a high ε-value, it was expected that reactions utilizing reagents (**4**)—(**7**) could be monitored by h.p.l.c. equipped with a u.v. detector.‡ (*c*) There is no possibility of racemisation for compounds (**4**)—(**7**).

Thus, compounds (**4**)—(**7**) were prepared by treatment of the corresponding β-amino alcohols (**8**)—(**11**) with carbon disulphide in the presence of Et_3N (Method A)[2] or KOH (Method B) (Scheme 1).§ Characteristic physical data for the chiral 1,3-oxazolidine-2-thiones are shown in Table 1.

The enantiomeric purity of these chiral heterocycles (**4**)—(**7**) was checked by h.p.l.c. analysis[4] of their (α*R*)-α-methoxy-α-trifluoro-methylphenylacetyl (MTPA) derivatives which were obtained by Mosher's method.[5] While compounds (**4**), (**6**), and



(8)—(11) (4)—(7)

(4),(8) $R^1 = Et, R^2 = R^3 = R^4 = H$
(5),(9) $R^1 = R^3 = R^4 = H, R^2 = Et$
(6),(10) $R^1 = Pr^i, R^2 = R^3 = R^4 = H$
(7),(11) $R^1 = R^3 = H, R^2 = Me, R^4 = Ph$

Scheme 1. *Reagents:* i, Et_3N, CH_2Cl_2, room temp.; ii, KOH, aqueous EtOH, 70—80 °C

(**7**) showed high enantiomeric purity, compound (**5**) was enantiomerically impure. This was due to the low purity of the starting β-amino alcohol (**9**) which was purchased commercially. The h.p.l.c. analytical conditions and the retention time of each MTPA amide derivative (**12**)—(**17**) are listed in Table 2.

In order to realize the nucleofugacity of the chiral heterocycles (**4**) and (**7**), we tried conventional aminolysis[6] and sodium borohydride reduction[7] of some 3-acyl-1,3-oxazolidine-2-thiones (**18**)—(**21**) which were prepared by the usual acylation method. Both reactions, the aminolysis and the reduction, proceeded smoothly at room temperature to afford the amides (**22**)—(**24**) or benzyl alcohol (**25**) respectively, in high yields (Scheme 2).

Subsequently, we attempted an asymmetric Michael type addition of benzenethiol to 3-crotonoyl-1,3-oxazolidine-2-thiones (**26**) and (**27**). Although the Michael type reaction proceeded readily, the desired stereoselective introduction at C-3 for compounds (**28**) and (**29**) was unsuccessful (Scheme 3), each reaction affording a mixture (*ca.* 1:1) of the corresponding C-3-diastereoisomers (^1H n.m.r. analysis). This may be because the asymmetric centre of the chiral starting material is too far from the C-3 reaction centre.

Not only is a determination of the enantiomeric purity of optically active carboxylic acids and amino acids important for an evaluation of their asymmetric syntheses but optical resolution of racemic modifications of chiral carboxylic acid derivatives and chiral amino acids is industrially important. There are, however, few useful reagents for this purpose. Thus, we have attempted a separation on both an analytical and a preparative scale of the racemically modified and commercially available carboxylic acids (**30**)—(**33**) and amino acids (**34**)—(**36**) utilizing (4*R*,5*S*)-MPOT (**7**). The condensations between

† This paper forms Part 8 of the series 'Utilization of Sulphur-containing Leaving Groups.' Part 7, Y. Nagao, T. Ikeda, T. Inoue, M. Yagi, M. Shiro, and E. Fujita, *J. Org. Chem.*, in the press.

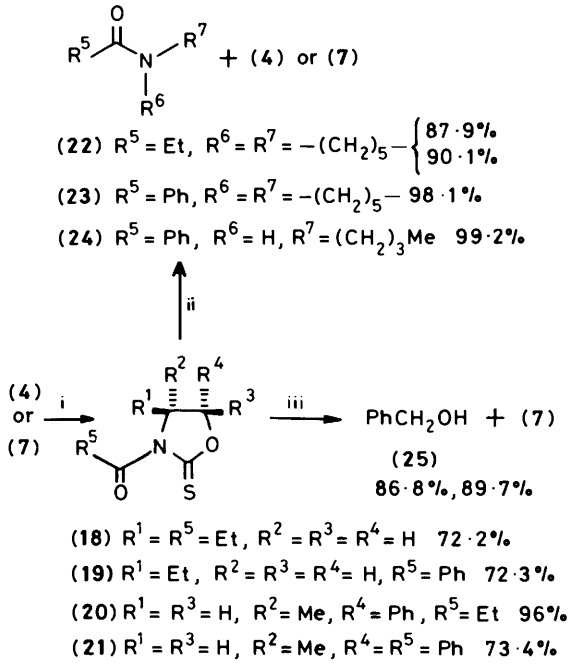
‡ 1,3-Oxazolidin-2-one derivatives are not readily available for h.p.l.c. analysis equipped only with a u.v. detector, because of their weak u.v. absorption.

§ Optically inactive 4-methyl-5-phenyl-1,3-oxazolidine-2-thione has been reported.[3]

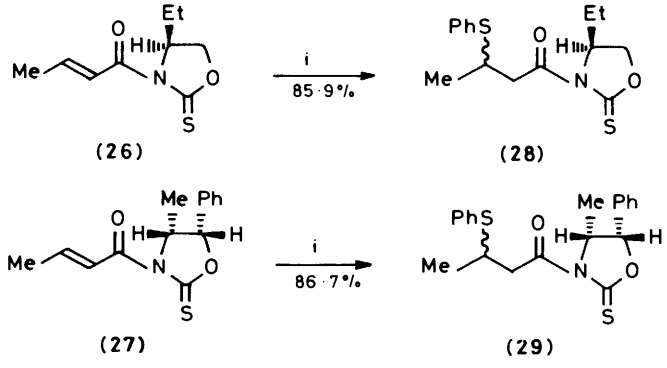
Table 1. Synthesis of chiral 1,3-oxazolidine-2-thione derivatives (**4**)—(**7**)

1,3-Oxazolidine -2-thiones	Yield (%)	M.p. (°C)	$\lambda_{max.}$/nm (EtOH) (ε)	$[\alpha]_D^{t°C}$[a] (c, t °C)	Enantiomeric purity[b] (%)
(**4**)	58.4[c]	oil	243 nm (1.61×10^4)	−22.2° (1.0, 20)	99.2
(**5**)	58.0[c]	oil	243 nm (1.61×10^4)	+17.8° (1.0, 20)	76.0
(**6**)	46.5[c]	45—46	244 nm (1.88×10^4)	−22.5° (0.4, 16)	99.7
(**7**)	73.1[c] 69.0[d]	81—82	246 nm (2.11×10^4)	+219.2° (0.4, 20)	100.0

[a] Determined in $CHCl_3$. [b] Determined by h.p.l.c. analysis of the corresponding MTPA derivative. [c] Prepared by Method A. [d] Prepared by Method B.

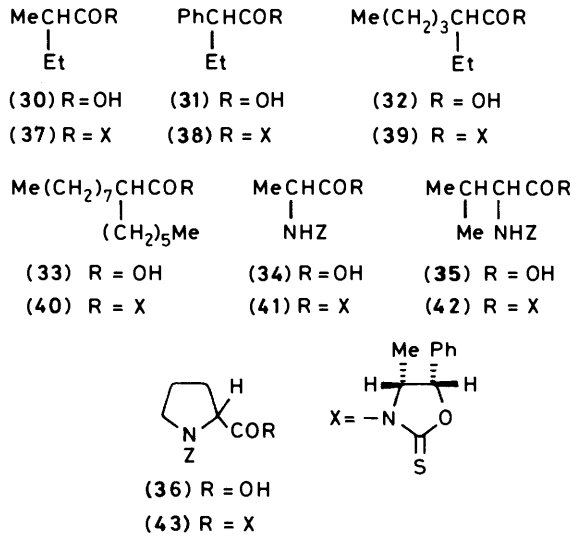


Scheme 2. *Reagents:* i, R^5COCl, pyridine, benzene; ii, piperidine or butylamine, CH_2Cl_2; iii, $NaBH_4$, aqueous THF.



Scheme 3. *Reagents:* i, PhSH, cat. Et_3N, EtOH, room temp.

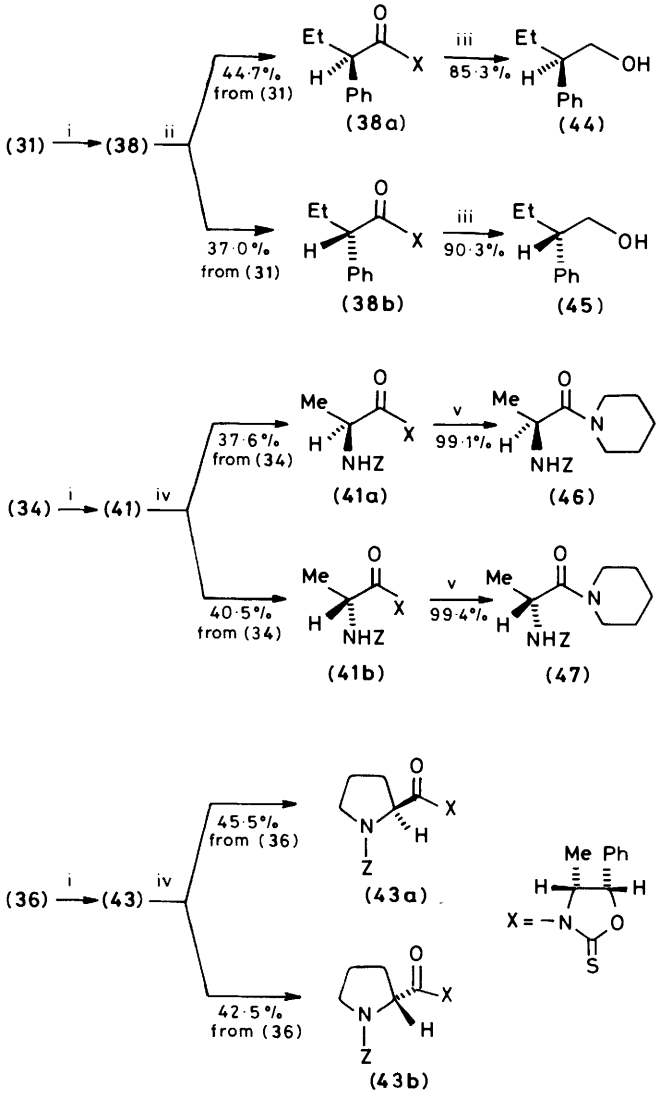
(**7**) and the carboxylic and amino acids (**30**)—(**36**) were carried out in the presence of dicyclohexylcarbodi-imide (DCC) (1.1 equiv.) and catalytic amounts of 4-*N*,*N*-dimethylaminopyridine (DMAP) in CH_2Cl_2 to afford the corresponding (4*R*,5*S*)-3-acyl-4,5-MPOT derivatives (**37**)—(**43**). Their analytical separation was readily achieved by the h.p.l.c. method as shown in Table 3. Of course, the ^1H n.m.r. techniques can also be useful for the analysis of the diastereoisomeric ratio of the amides (**37**)—(**43**). We have here demonstrated that (4*R*,5*S*)-MPOT (**7**) could be employed as a good reagent useful for the analysis of racemic carboxylic acids. Other similar reagents (**4**) and (**6**) also may be useful in the same sense.



Finally, we have performed the optical resolution of the racemates (**31**), (**34**), and (**36**) by chromatographic separation of their (4*R*,5*S*)-MPOT amide derivatives. The reaction sequence is shown in Scheme 4.

Separation of the diastereoisomeric mixture (**38**) was smoothly carried out on a silica gel column using 30% AcOEt in hexane to give the corresponding pure diastereoisomers (**38a**) (44.7%) and (**38b**) (37.0%). The diastereoisomers (**38a**) and (**38b**) were reduced with $NaBH_4$ (1.4 mol equiv.) in aqueous THF with ice cooling to give the corresponding alcohols (**44**) and (**45**) in good yields. The absolute stereochemistry of (**44**) and (**45**) was ascertained by comparison of the specific rotation of (**44**) with that of authentic material.[8]

The diastereoisomeric mixture (**41**) was also readily separated by silica gel column chromatography (10% AcOEt in hexane) to afford the pure diastereoisomers (**41a**) and (**41b**) in high yields (Scheme 4). The absolute stereochemistry of these was ascertained by comparison of the R_t and the R_f-value from the h.p.l.c. and t.l.c. analyses of (**41a**) with those of an authentic sample derived from L-alanine. Aminolysis of (**41a**) and (**41b**) with piperidine (1 mol equiv.) in CH_2Cl_2 gave the amide (**46**)



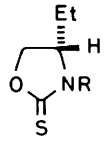
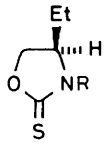
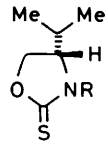
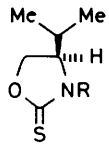
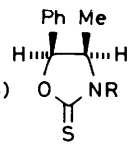
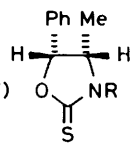
Scheme 4. *Reagents:* i, (4*R*, 5*S*)-MPOT (7), DCC or WSC[EtN=C=N(CH$_2$)$_3$NMe$_2$·HCl], DMAP, CH_2Cl_2; ii, silica gel column, 10% AcOEt in hexane; iii, $NaBH_4$ aqueous THF; iv, silica gel column, 30% AcOEt in hexane; v, piperidine, CH_2Cl_2.

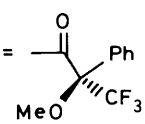
and its enantiomer (**47**) respectively, in excellent yields. Z-DL-Pro-OH (**36**) was resolved in a similar manner *via* column chromatography of the diastereoisomeric mixture (**43**). Here, (4*R*,5*S*)-MPOT (**7**) proved to be a satisfactory chiral reagent which was also a good leaving group. Therefore, compound (**7**) can be considered to be a dual purpose reagent.

We applied this racemate separation method to the synthesis of the β-lactam (**54**) starting from the commercially available Z-DL-Ser-OH (**48**) (Scheme 5).

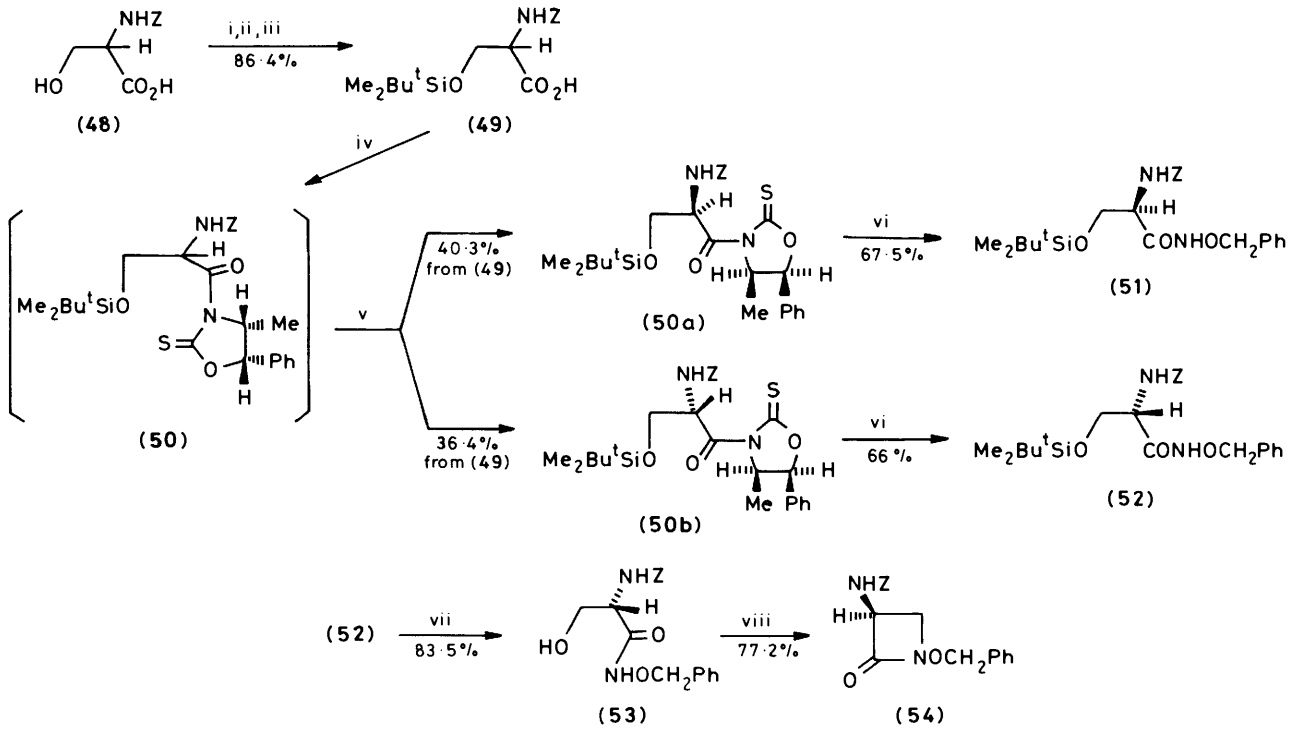
The racemic compound (**48**) was treated with dimethyl-t-butylsilyl chloride (DMTBSC) (4 mol equiv.) in imidazole (8 mol equiv.)—DMF, followed by alkaline hydrolysis with 10% aqueous K_2CO_3 to give the silyl ether (**49**) in 86.4% yield after acidification (pH 3) with 1M-$KHSO_4$. Compound (**49**) was then subjected to the usual condensation reaction with (4*R*,5*S*)-MPOT (**7**) (1 mol equiv.) in the presence of water-soluble carbodi-imide (1.1 mol equiv.)—DMAP (0.1 mol equiv.). The crude product (**50**) was chromatographed on a silica gel column with 10% AcOEt in hexane to give the pure diastereoisomers (**50a**) (40.3%) and (**50b**) (36.4%), respectively. The active amides

Table 2. H.p.l.c. analysis of the MTPA amides (**12**)—(**17**)[a]

MTPA Amide[b,c]	Eluant (hexane–AcOEt)	U.v. detection (λ/nm)	R_t (min)
(**12**) 	75:25	262	4.9
(**13**) 	75:25	262	4.0
(**14**) 	80:20	268	5.3
(**15**) 	80:20	268	4.1
(**16**) 	90:10	254	4.5
(**17**) 	90:10	254	5.7

[a] L.c. machine: JASCO TRI ROTAR SR; column: Partisil-10 (Whatman); flow rate: 2 ml min^{-1}. [b] Preparation of MTPA amide sample: see Experimental section. [c] R = 

(**50a**) and (**50b**) were allowed to react with *O*-benzylhydroxylamine hydrochloride (1 mol equiv.) in the presence of Et_3N (1 mol equiv.) to afford the corresponding optically pure amides (**51**) and (**52**) in good yields. Treatment of (**52**) with tetrabutylammonium fluoride (1.8 mol equiv.) in THF containing a catalytic amount of AcOH gave the known compound (**53**) (83.5%), which was subjected to the conventional Mitsunobu method employing diethyl azodicarboxylate (DEAD) and triphenylphosphine to afford the known β-lactam (**54**)[9] in 77.2% yield. The physical data (m.p. and specific rotation) of both optically pure compounds (**53**) and (**51**) agreed with those of previously reported compounds.[9]



Scheme 5. *Reagents:* i, Me_2Bu^tSiCl, imidazole, DMF; ii, 10% aqueous K_2CO_3, THF–MeOH (1:3); iii, 1M-$KHSO_4$; iv, (4*R*,5*S*)-MPOT(**7**), WSC, DMAP, CH_2Cl_2; v, silica gel column, 10% AcOEt in hexane; vi, $PhCH_2ONH_2$·HCl, Et_3N, CH_2Cl_2; vii, Bu_4NF, AcOH, THF; viii, $EtO_2CN{=}NCO_2Et$, Ph_3P, THF

Table 3. H.p.l.c. analysis of the (4*R*,5*S*)-MPOT amides (**37**)—(**43**)[a]

(4*R*,5*S*)-MPOT amide	Eluant (hexane–AcOEt)	R_t for the two diastereoisomers (min)
(**37**)	97:3	11.4, 13.3
(**38**)	90:10	3.5, 4.3
(**39**)	97:3	7.4, 9.6
(**40**)	97:3	4.9, 5.2
(**41**)	70:30	3.9, 5.0
(**42**)	80:20	5.8, 6.1
(**43**)	70:30	9.4, 16.1

[a] L.c. machine: JASCO TRI ROTAR SR; column: Finepak SIL(JASCO); detection: u.v. (267 nm); flow rate: 2 ml $min.^{-1}$

These chiral functional five-membered heterocycles, *i.e.* (4*R*,5*S*)-MPOT (**7**), (4*S*)-EOT (**4**), and (**6**) promise to be useful chiral reagents for asymmetric synthesis, *e.g.*, the diastereo-controlled aldol condensation reaction.[10]

Experimental

M.p.s were determined with Yamato MP-21 and Yanagimoto micro-apparatuses. I.r. spectra were run on Hitachi 260-50 and JASCO A-202 spectrophotometers. U.v. spectra were recorded on a JASCO UVIDEC-610 spectrophotometer. Optical rotations were measured on a JASCO DIP-181 polarimeter. ^1H N.m.r. spectra were recorded on JEOL JNM-FX100, Hitachi R-900, and Varian EM-360 instruments in $CDCl_3$ solutions with $SiMe_4$ as an internal standard. E.i. (electron impact) mass spectra were determined with a JEOL JMS-DX300 mass spectrometer. H.p.l.c. analyses were carried out on a JASCO TRI ROTAR SR (UV-100) instrument equipped with a JASCO DP-L220 LC data processor. Extracts were dried over anhydrous Na_2SO_4. Wako silica gel C-100 and C-200 were used for column chromatography.

Typical Preparation of Chiral 1,3-*Oxazolidine*-2-*thiones* (**4**)—(**7**) *from* β-*Amino Alcohols* (**8**)—(**11**).—*Method A.* To a solution of (2*S*)-aminobutan-1-ol (**8**) (8.9 g, 0.1 mol) and CS_2 (9.1 g, 0.12 mol) in CH_2Cl_2 (140 ml) was added Et_3N (12.1 g, 0.12 mol) with ice cooling. The reaction mixture was stirred at room temperature for 4 h, after which it was washed with brine, dried, and evaporated under reduced pressure to give an oily residue. Purification of the residue on a silica gel column using $CHCl_3$ as the eluant gave (4*S*)-ethyl-1,3-oxazolidine-2-thione (**4**) (7.65 g, 58.4%) as a colourless oil.

Method B. A solution of KOH (26.35 g, 0.4 mol) in water (30 ml) and EtOH (50 ml) was added dropwise to a solution of (+)-norephedrine hydrochloride (**11**) (25 g, 0.13 mol) and CS_2 (20.3 g, 0.26 mol) in water (10 ml) and EtOH (50 ml) with stirring and ice cooling. The mixture was stirred at 70—80 °C for 6 h and the excess of EtOH was removed under reduced pressure to give an aqueous solution. After acidification with concentrated HCl (30 ml) and water (120 ml), the water solution was extracted with Et_2O. The ethereal extract was washed with brine, dried, and evaporated under reduced pressure to yield an oily residue. The residue was purified on a silica gel column with CH_2Cl_2 as the eluant to afford (4*R*,5*S*)-4-methyl-5-phenyl-1,3-oxazolidine-2-thione (**7**) (17.8 g, 69%).

Physical Data for the 1,3-*Oxazolidine*-2-*thione Derivatives* (**4**)—(**7**).—(4*S*)-4-*Ethyl*-1,3-*oxazolidine*-2-*thione*[(4S)-*EOT*](**4**). Colourless oil; 99.2% e.e; $[\alpha]_D^{20}$ −22.2° (*c* 1.0, $CHCl_3$); $\nu_{max.}$(neat) 3 180 and 1 520 cm^{-1}; $\lambda_{max.}$(EtOH) (ε) 243 nm (1.61×10^4); δ (90 MHz) 0.98 (3 H, t, *J* 7 Hz), 1.50—1.85 (2 H, m), 3.90—4.25 (1 H, m), 4.33 (1 H, dd, *J* 9 and 7 Hz), 4.76 (1 H, t,

J 9 Hz), and 8.93 (1 H, br s) (Found: M^+, 131.041. C_5H_9NOS requires *M*, 131.040).

(4R)-4-*Ethyl*-1,3-*oxazolidine*-2-*thione* [(4R)-*EOT*] (**5**). Colourless oil; 76% e.e.; $[\alpha]_D^{20}$ +17.8° (*c* 1.0, $CHCl_3$).

(4S)-4-*Isopropyl*-1,3-*oxazolidine*-2-*thione* [(4S)-*IPOT*] (**6**). Colourless needles, m.p. 45—46 °C (from AcOEt–hexane); 99.7% e.e.; $[\alpha]_D^{16}$ −22.5° (*c* 0.41, $CHCl_3$); $\nu_{max.}$(KBr) 3 160 and 1 515 cm^{-1}; $\lambda_{max.}$(EtOH) (ε) 244 nm (1.88 × 10^4); δ (90 MHz) 0.90 (3 H, d, *J* 6.5 Hz), 0.93 (3 H, d, *J* 6.5 Hz), 1.60—2.05 (1 H, m), 3.80—4.10 (1 H, m), 4.40 (1 H, dd, *J* 9 and 7 Hz), 4.73 (1 H, t, *J* 9 Hz), and 8.93 (1 H, br s) (Found: C, 49.45; H, 7.6; N, 9.7%; M^+, 145. $C_6H_{11}NOS$ requires C, 49.65; H, 7.65; N, 9.65%; *M*, 145).

(4R,5S)-4-*Methyl*-5-*phenyl*-1,3-*oxazolidine*-2-*thione* [(4R,5S)-*MPOT*] (**7**). Colourless prisms, m.p. 81—82 °C (from AcOEt–hexane); 100% e.e.; $[\alpha]_D^{20}$ +219.2° (*c* 0.44, $CHCl_3$); $\nu_{max.}$(KBr) 3 175 and 1 500 cm^{-1}; $\lambda_{max.}$(EtOH) (ε) 246 nm (2.11 × 10^4); δ (90 MHz) 0.85 (3 H, d, *J* 7 Hz), 4.30—4.65 (1 H, m), 5.93 (1 H, d, *J* 8.5 Hz), 7.20—7.50 (5 H, m), and 8.60 (1 H, br s) (Found: C, 62.1; H, 5.6; N, 7.25%; M^+, 193. $C_{10}H_{11}NOS$ requires C, 62.15; H, 5.75; N, 7.25%; *M*, 193).

Typical Preparation of the MTPA Amides (**12**)—(**17**) *for H.p.l.c. Analyses.*—A dry test tube covered with a rubber cap was charged with a solution of (4*S*)-EOT (**4**) (13.1 mg, 0.10 mmol) in CCl_4 (300 ml) *via* syringe. To this was added (α*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride (35 mg, 0.14 mmol) and dry pyridine (300 μl) *via* a syringe. The mixture was shaken and allowed to stand at room temperature for 15 h. Et_2O (5 ml) was added to the reaction mixture and the ethereal solution was washed with cold 10% HCl, cold saturated aqueous Na_2CO_3, and brine. The dried solution was evaporated under reduced pressure to give an oily residue which was used for h.p.l.c. analysis. Other analytical samples were prepared similarly. All h.p.l.c. analytical results of the MTPA amides (**12**)—(**17**) are shown in Table 2.

A Typical Example of the Preparation of 3-*Acyl*-1,3-*oxazolidine*-2-*thiones* (**18**)—(**21**), (**26**), *and* (**27**).—A solution of benzoyl chloride (1.55 g, 11 mmol) in benzene (10 ml) was added dropwise with stirring to a solution of (4*S*)-EOT (**4**) (1.31 g, 10 mmol) and pyridine (0.89 ml, 11 mmol) in benzene (20 ml) at room temperature. After 2 h, the reaction mixture was worked up as usual[7] to give compound (**19**) (1.7 g, 72.3%).

Physical Data for the 3-*Acyl*-1,3-*oxazolidine*-2-*thiones* (**18**)—(**21**), (**26**), *and* (**27**).—(4S)-3-*Propanoyl*-4-*ethyl*-1,3-*oxazolidine*-2-*thione* (**18**). 72.2% Yield; pale yellow oil; $[\alpha]_D^{20}$ +108.1° (*c* 1.0, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 702 cm^{-1}; $\lambda_{max.}$(EtOH) (ε) 267 nm (1.39 × 10^4); δ (60 MHz) 0.97 (3 H, t, *J* 7.5 Hz), 1.20 (3 H, t, *J* 7.5 Hz), 1.60—2.10 (2 H, m), 3.10—3.60 (2 H, m), and 4.23—4.97 (3 H, m) (Found: M^+, 187.067. $C_8H_{13}NO_2S$ requires *M*, 187.067).

(4S)-3-*Benzoyl*-4-*ethyl*-1,3-*oxazolidine*-2-*thione* (**19**). 72.3% Yield; colourless needles, m.p. 82—84 °C (from AcOEt–hexane); $[\alpha]_D^{18}$ +239.0° (*c* 1.0, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 690 cm^{-1}; δ (90 MHz) 1.00 (3 H, t, *J* 7.5 Hz), 1.63—2.10 (2 H, m), 4.20—4.50 (1 H, m), 4.57—4.90 (2 H, m), 7.30—7.60 (3 H, m), and 7.63—7.80 (2 H, m) (Found: C, 61.4; H, 5.6; N, 5.95%; M^+, 235. $C_{12}H_{13}NO_2S$ requires C, 61.25; H, 5.55; N, 5.95%; *M*, 235).

(4R,5S)-3-*Propanoyl*-4-*methyl*-5-*phenyl*-1,3-*oxazolidine*-2-*thione* (**20**). 96% Yield; colourless needles, m.p. 61—62 °C (from Et_2O–hexane); $[\alpha]_D^{25}$ +107.4° (*c* 1.0, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 702 cm^{-1}; $\lambda_{max.}$(EtOH) (ε) 267 nm (1.4 × 10^4); δ (60 MHz) 0.93 (3 H, d, *J* 6.5 Hz), 1.16 (3 H, t, *J* 7 Hz), 3.00—3.33 (2 H, m), 4.80 (1 H, m), 5.66 (1 H, d, *J* 6.5 Hz), and 7.23 (5 H, s) (Found: C, 62.8; H, 6.15; N, 5.55. $C_{13}H_{15}NO_2S$ requires C, 62.6; H, 6.05; N, 5.6%).

(4R,5S)-3-*Benzoyl*-4-*methyl*-5-*phenyl*-1,3-*oxazolidine*-2-*thione* (**21**). 73.4% Yield; pale yellow needles, m.p. 119—121 °C (from Et_2O–hexane); $[\alpha]_D^{20}$ +155.4° (*c* 1.0, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 685 cm^{-1}; δ (60 MHz) 1.10 (3 H, d, *J* 7 Hz), 4.90—5.27 (1 H, m), 5.93 (1 H, d, *J* 7.5 Hz), and 7.33—7.90 (10 H, m) (Found: C, 68.65; H, 5.15; N, 4.8%; M^+, 297. $C_{17}H_{15}NO_2S$ requires C, 68.65; H, 5.1; N, 4.7%; *M*, 297).

(4S)-3-*Crotonoyl*-4-*ethyl*-1,3-*oxazolidine*-2-*thione* (**26**). 49% Yield; pale yellow oil; $[\alpha]_D^{20}$ +93.9° (*c* 0.49, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 680 cm^{-1}; δ (60 MHz) 0.95 (3 H, t, *J* 7 Hz), 1.60—2.10 (5 H, m), 4.10—4.90 (3 H, m), 6.80—7.27 (1 H, m), and 7.60—7.90 (1 H, m) (Found: M^+, 199.066. $C_9H_{13}NO_2S$ requires *M*, 199.067).

(4R,5S)-3-*Crotonoyl*-4-*methyl*-5-*phenyl*-1,3-*oxazolidine*-2-*thione* (**27**). 61.4% Yield; pale yellow oil; $[\alpha]_D^{18}$ +92.2° (*c* 0.96, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 680 cm^{-1}; δ (60 MHz) 1.00 (3 H, d, *J* 7 Hz), 2.00 (3 H, dd, *J* 7 and 1 Hz), 4.76—5.20 (1 H, m), 5.73 (1 H, d, *J* 7 Hz), 6.95—7.30 (1 H, m), and 7.50 (5 H, s) (Found: M^+, 261.081. $C_{14}H_{15}NO_2S$ requires *M*, 261.082).

A Typical Example of the Aminolysis of 3-*Acyl*-1,3-*oxazolidine*-2-*thiones.*—A solution of piperidine (93.5 mg, 1.1 mmol) in CH_2Cl_2 (1 ml) was added to a solution of (4*S*)-3-benzoyl-EOT (**19**) (235 mg, 1 mmol) in CH_2Cl_2 (4 ml). After being stirred at room temperature for 10 min, the reaction mixture was concentrated under reduced pressure to give an oily residue, which was dissolved in a minimum amount of $CHCl_3$. The solution was passed through a short silica gel column impregnated with 5% $AgNO_3$ by elution with $CHCl_3$ to afford *N*-benzoylpiperidine (**23**) (185.4 mg, 98.1%).

Physical Data for the Amides (**22**)—(**24**). N-*Propanoylpiperidine* (**22**). Reaction time 90 min [from compound (**19**)] or 25 min [from compound (**20**)]; 87.9% yield [from compound (**19**)] or 90.1% [from compound (**20**)]; colourless oil; $\nu_{max.}$($CHCl_3$) 1 615 cm^{-1}; δ (60 MHz) 1.17 (3 H, t, *J* 7 Hz), 1.60 (6 H, br s), 2.40 (2 H, q, *J* 7 Hz), and 3.50 (4 H, br s) (Found: M^+, 141.116. $C_8H_{15}NO$ requires *M*, 141.115).

N-*Benzoylpiperidine* (**23**). Colourless prisms, m.p. 45—46 °C (from CH_2Cl_2–hexane); i.r. and n.m.r. spectral data of (**23**) were identified with those of an authentic sample.[6]

N-*Butylbenzamide* (**24**). Reaction time 65 min [from compound (**21**)]; 99.2% yield; colourless oil; $\nu_{max.}$($CHCl_3$) 3 450, 1 655, and 1 530 cm^{-1}; δ (60 MHz) 0.90 (3 H, t, *J* 6 Hz), 1.10—1.80 (4 H, m), 3.37 (2 H, q, *J* 6 Hz), and 7.00—7.90 (6 H, m) (Found: M^+, 177.117. $C_{11}H_{15}NO$ requires *M*, 177.115).

Reduction of 3-*Acyl*-1,3-*oxazolidine*-2-*thione* (**19**) *and* (**21**) *with* $NaBH_4$.—A solution of $NaBH_4$ (38.2 mg, 1 mmol) in THF (4 ml)–water (5 drops) was added to a solution of compound (**19**) (77.6 mg, 0.33 mmol) in THF (4 ml). After being stirred at room temperature for 45 min, the reaction mixture was treated with 10% aqueous HCl and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with brine, dried, and evaporated under reduced pressure to give an oily residue. The residue was purified on a silica gel column impregnated with 5% $AgNO_3$, by elution with $CHCl_3$ to give benzyl alcohol (32.0 mg, 89.7%). The reduction of (**21**) with $NaBH_4$ was done similarly to give benzyl alcohol (86.6%, reaction time 30 min).

Michael Type Reaction of 3-*Crotonoyl*-1,3-*oxazolidine*-2-*thiones* (**26**) *and* (**27**) *with Benzenethiol.*—A solution of (4*S*)-3-crotonoyl-EOT (**26**) (199 mg, 1 mmol) in EtOH (3 ml) was added to a solution of benzenethiol (110 mg, 1 mmol) and a catalytic amount of Et_3N in EtOH (3 ml) at room temperature. After being stirred at room temperature for 1 h, the reaction mixture was evaporated under reduced pressure to give an oily residue. Purification of the residue on a silica gel column using $CHCl_3$ as the eluant gave the thiol adduct (**28**) (265.4 mg, 85.9%) as a pale yellow oil; $[\alpha]_D^{20}$ +58.3° (*c* 0.71, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 695 cm^{-1}; δ (100 MHz) 0.92 (3 H, t, *J* 7.3 Hz),

1.37 [1.5 H, d, *J* 6.3 Hz, *Me*CH(SPh)], 1.39 [1.5 H, d, *J* 6.3 Hz, *Me*CH(SPh)], 1.50—2.10 (2 H, m), 3.10—3.90 (3 H, m), 4.10—4.80 (3 H, m), and 7.20—7.70 (5 H, m) (Found: M^+, 309.087. $C_{15}H_{19}NO_2S_2$ requires *M*, 309.086). Similar treatment of (4*R*,5*S*)-3- crotonoyl-MPOT (**27**) with benzenethiol in the presence of Et_3N readily afforded the thiol adduct (**29**) (86.7%) as a pale yellow oil; $[\alpha]_D^{20}$ +50.1° (*c* 0.61, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 695 cm^{-1}; δ (60 MHz) 0.93 (3 H, d, *J* 7 Hz), 1.38 [1.5 H, d, *J* 7 Hz, *Me*CH(SPh)], 1.40 [1.5 H, d, *J* 7 Hz, *Me*CH(SPh)], 3.50—3.90 (3 H, m), 4.63—5.17 (1 H, m), 5.67 (0.5 H, d, *J* 7 Hz), 5.78 (0.5 H, d, *J* 7 Hz), and 7.20—7.60 (10 H, m) (Found: M^+, 371.102. $C_{20}H_{21}NO_2S_2$ requires *M*, 371.101).

A Typical Example of the Preparation of (4*R*,5*S*)-*MPOT Amides* (**37**)—(**43**) *for H.p.l.c. Analysis.* (4R,5S)-3-(N-*Benzyloxycarbonyl*-DL-*valinyl*)-4-*methyl*-5-*phenyl*-1,3-*oxazolidine*-2-*thione* (**42**). DCC (22.7 mg, 0.11 mmol) was added to a stirred solution of Z-DL-Val-OH (25.1 mg, 0.1 mmol) (4*R*,5*S*)-MPOT (**7**) (19.3 mg, 0.1 mmol) and DMAP (1.2 mg, 0.01 mmol) in CH_2Cl_2 (1 ml). The mixture was stirred at room temperature for 15 h and AcOEt was added. The resulting precipitate (dicyclohexylurea) was filtered off and the filtrate was evaporated under reduced pressure to give an oily residue, which was subjected to h.p.l.c. analysis (see Table 3). Other h.p.l.c. samples of the (4*R*,5*S*)-MPOT amides (**37**)—(**41**) and (**43**) were prepared in a similar manner.

A Typical Example of the Optical Resolution of the (4R,5S)-*MPOT Amides* (**38**), (**41**), *and* (**43**).—DCC (227 mg, 1.1 mmol) was added to a stirred solution of Z-DL-Ala-OH (223.2 mg, 1 mmol), (4*R*,5*S*)-MPOT (**7**) (193 mg, 1 mmol), and DMAP (12 mg, 0.1 mmol) in CH_2Cl_2 (10 ml). After being stirred at room temperature for 15 h, the solvent was removed under reduced pressure and AcOEt was added. The resulting precipitate (dicyclohexylurea) was filtered off and the filtrate was evaporated under reduced pressure to leave an oily residue. The residue was chromatographed on a column of silica gel (Wakogel C-200, 24 g) using AcOEt–hexane (3:7) as the eluant to give (4*R*,5*S*)-3-(*N*-benzyloxycarbonyl-L-alanyl)-4-methyl-5-phenyl-1,3-oxazolidine-2-thione (**41a**) (149.6 mg, 37.6%) and its diastereoisomer (**41b**) (161.2 mg, 40.5%), respectively. Other racemic modifications of (**38**) and (**43**) were resolved in a similar fashion.

Physical Data of Pure (4R,5S)-*MPOT Amides* (4R,5S)-3-(2R)-*Phenylbutanoyl*]-4-*methyl*-5-*phenyl*-1,3-*oxazolidine*-2-*thione* (**38a**). 44.7% Yield from (**31**); colourless oil; $[\alpha]_D^{20}$ +110.1° (*c* 0.92, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 690 cm^{-1}; δ (100 MHz) 0.92 (3 H, t, *J* 7.3 Hz), 0.99 (3 H, d, *J* 6.8 Hz), 1.70—2.40 (2 H, m), 4.72—5.00 (1 H, m), 5.55 (1 H, d, *J* 7.3 Hz), 6.02 (1 H, t, *J* 7.3 Hz), and 7.20—7.50 (10 H, m) (Found: M^+, 339.129. $C_{20}H_{21}NO_2S$ requires *M*, 339.129).

(4R,5S)-3-[(2S)-*Phenylbutanoyl*]-4-*methyl*-5-*phenyl*-1,3-*oxazolidine*-2-*thione* (**38b**). 37.0% Yield from (**31**); colourless oil; $[\alpha]_D^{17}$ +18.5° (*c* 1.53, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 690 cm^{-1}; δ (100 MHz) 0.74 (3 H, d, *J* 6.3 Hz), 0.94 (3 H, t, *J* 7.3 Hz), 1.70—2.40 (2 H, m), 4.88—5.16 (1 H, m), 5.72 (1 H, d, *J* 7.3 Hz), 5.92 (1 H, t, *J* 7.3 Hz), and 7.10—7.48 (10 H, m) (Found: M^+, 339.129. $C_{20}H_{21}NO_2S$ requires *M*, 339.129).

(4R,5S)-3-(N-*Benzyloxycarbonyl*-L-*alanyl*)-4-*methyl*-5-*phenyl*-1,3-*oxazolidine*-2-*thione* (**41a**). 37.6% Yield from (**34**); colourless amorphous solid; $[\alpha]_D^{18}$ +3.32° (*c* 11.53, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 715 cm^{-1}; δ (100 MHz) 0.89 (3 H, d, *J* 6.4 Hz), 1.50 (3 H, d, *J* 6.8 Hz), 4.95—5.24 (3 H, m), 5.55 (1 H, br d, *J* 8.3 Hz), 5.76 (1 H, br d, *J* 6.8 Hz), 6.00—6.32 (1 H, m), and 7.10—7.50 (10 H, m) (Found: M^+, 398.131. $C_{21}H_{22}N_2O_4S$ requires *M*, 398.130).

(4R5S)-3-(N-*Benzyloxycarbonyl*-D-*alanyl*)-4-*methyl*-5-*phenyl*-1,3-*oxazolidine*-2-*thione* (**41b**). 40.5% Yield from (**34**); colourless amorphous solid; $[\alpha]_D^{18}$ +60.9° (*c* 4.45, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 715 cm^{-1}; δ (100 MHz) 0.93 (3 H, d, *J* 6.4 Hz), 1.49 (3 H, d, *J* 6.8 Hz), 4.78—5.04 (1 H, m), 5.11 (2 H, s), 5.60 (1 H, br d, *J* 7.3 Hz), 5.76 (1 H, d, *J* 6.8 Hz), 6.30—6.58 (1 H, m), and 7.24—7.48 (10 H, m) (Found: C, 63.3; H, 5.55; N, 6.9. $C_{21}H_{22}N_2O_4S$ requires C, 63.3; H, 5.55; N, 7.05%).

(4R,5S)-3-(N-*Benzyloxycarbonyl*-L-*prolinyl*)-4-*methyl*-5-*phenyl*-1,3-*oxazolidine*-2-*thione* (**43a**). 45.5% Yield from (**36**); colourless viscous oil; $[\alpha]_D^{27}$ −73.6° (*c* 0.8, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 700 cm^{-1}; δ (100 MHz) 0.84 (1.5 H, d, *J* 6.0 Hz), 0.96 (1.5 H, d, *J* 6.6 Hz), 1.84—2.20 (3 H, m), 2.30—2.50 (1 H, m), 3.50—3.80 (2 H, m), 4.66—5.34 (3 H, m), 5.84—6.40 (1 H, m), and 7.34 (10 H, s) (Found: M^+, 424.147. $C_{23}H_{24}N_2O_4S$ requires *M*, 424.146).

(4R,5S)-3-(N-*Benzyloxycarbonyl*-D-*prolinyl*)-4-*methyl*-5-*phenyl*-1,3-*oxazolidine*-2-*thione* (**43b**). 42.5% Yield from (**36**); colourless viscous oil; $[\alpha]_D^{27}$ +106.5° (*c* 1.22, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 700 cm^{-1}; δ (100 MHz) 0.56 (1.5 H, d, *J* 6.0 Hz), 1.00 (1.5 H, d, *J* 6.6 Hz), 1.86—2.20 (3 H, m), 2.30—2.60 (1 H, m), 3.42—3.80 (2 H, m), 4.76—5.26 (3 H, m), 5.68 (0.5 H, d, *J* 7.1 Hz), 5.76 (0.5 H, d, *J* 7.1 Hz), 6.22—6.52 (1 H, m), and 7.24—7.40 (10 H, m) (Found M^+, 424.144. $C_{23}H_{24}N_2O_4S$ requires *M*, 424.146).

(2R)-2-*Phenylbutanol* (**44**) *and Its Enantiomer* (**45**).—A solution of $NaBH_4$ (52.6 mg, 1.4 mmol) in THF (5 ml)–water (0.2 ml) was added to a solution of (4*R*,5*S*)-3-[(2*R*)-phenylbutanoyl)-4-methyl-5-phenyl-1,3-oxazolidine-2-thione (**38a**) (169.5 mg, 0.5 mmol) in THF (7 ml) with stirring. After 30 min at room temperature, the reaction mixture was worked up to give the alcohol (**44**) (64.1 mg, 85.3%) as a colourless oil; $[\alpha]_D^{22}$ −21.0° (*c* 1.01, EtOH) {lit.,[8] $[\alpha]_D^{18}$ −20.4° (*c* 9.1, EtOH)}; $\nu_{max.}$(neat) 3 330 and 1 595 cm^{-1}; δ (100 MHz) 0.84 (3 H, t, *J* 7.4 Hz), 1.40—1.90 (3 H, m), 2.54—2.82 (1 H, m), 7.74 (2 H, d, *J* 7.1 Hz), and 7.14—7.40 (5 H, m) (Found: M^+, 150.104. $C_{10}H_{14}O$ requires *M*, 150.104). (2*S*)-2-Phenylbutan-1-ol (**45**) was prepared similarly from the amide (**38b**); 90.3% yield; colourless oil; $[\alpha]_D^{22}$ +21.9 (*c* 0.62, EtOH); i.r. and ^1H n.m.r. spectral data of (**45**) were identified by comparison with those of (2*R*)-2-phenylbutan-1-ol (**44**).

N-(N-*Benzyloxycarbonyl*-L-*alanyl*)*piperidine* (**46**) *and Its Enantiomer* (**47**).—A solution of piperidine (8.5 mg, 0.1 mmol) in CH_2Cl_2 (0.1 ml) was added to a stirred solution of (4*R*,5*S*)-3-(*N*-benzyloxycarbonyl-L-alanyl)-4-methyl-5-phenyl-1,3-oxazolidine-2-thione (**41a**) (39.8 mg, 0.1 mmol) in CH_2Cl_2 (0.4 ml). After being stirred at room temperature for 10 min the reaction mixture was worked up to give the amide (**46**) (28.7 mg, 99.1%) as a colourless oil; $[\alpha]_D^{17}$ +19.5° (*c* 0.99, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 1 710 and 1 630 cm^{-1}; δ (100 MHz) 1.32 (3 H, d, *J* 6.8 Hz), 1.62 (6 H, br s), 3.30—3.70 (4 H, m), 4.50—4.78 (1 H, m), 5.10 (2 H, s), 5.92 (1 H, br d, *J* 6.8 Hz), and 7.34 (5 H, br s) (Found: M^+, 290.161. $C_{16}H_{22}N_2O_3$ requires *M*, 290.163). *N*-(*N*-Benzyloxycarbonyl-D-alanyl)piperidine (**47**) was prepared similarly from the amide (**41b**); 99.4% yield; colourless oil; $[\alpha]_D^{17}$ −19.7° (*c* 0.99, $CHCl_3$); i.r. and ^1H n.m.r. spectral data were identified by comparison with those of *N*-L-alanylpiperidine (**46**).

N-*Benzyloxycarbonyl*-O-*dimethyl*-*butylsilyl*-DL-*serine* (**49**).—To a solution of Z-DL-Ser-OH (**48**) (2.39 g, 10 mmol) in DMF (10 ml) was added dimethyl-t-butylsilyl chloride (6.03 g, 40 mmol) and imidazole (5.44 g, 80 mmol). The mixture was stirred at room temperature under N_2 for 16 h, after which brine (420 ml) was added. The mixture was then extracted with AcOEt and the AcOEt extract washed successively with 1M-HCl and brine and then dried, and evaporated under reduced pressure to give an oily residue. The residue was dissolved in MeOH (130 ml)—THF (42 ml) and 10% aqueous K_2CO_3 was added. The mixture

was stirred at room temperature for 1 h and concentrated under reduced pressure to *ca.* a quarter of the original volume. To this was added 1M-$KHSO_4$ to adjust the acidity of the solution to pH 4—5. The acidic solution was extracted with AcOEt and the extract was washed with brine, and then dried, and evaporated under reduced pressure to afford a crude crystalline product. Recrystallization of the crude product from hexane gave compound (**49**) (3.05 g, 86.4%) as colourless plates, m.p. 65—66 °C (from hexane); $\nu_{max.}$($CHCl_3$) 3 440 and 1 720 cm^{-1}; δ (100 MHz) 0.04 (6 H, s), 0.86 (9 H, s), 3.84 (1 H, dd, *J* 10.0 and 3.7 Hz), 4.12 (1 H, dd, *J* 10.0 and 2.6 Hz), 4.32—4.56 (1 H, m), 5.12 (2 H, s), 5.58 (1 H, d, *J* 8.6 Hz), 7.32 (5 H, s), and 8.54 (1 H, br s) (Found: C, 57.9; H, 7.6; N, 3.9. $C_{17}H_{27}NO_5Si$ requires C, 57.75; H, 7.6; N, 3.95%).

(4R,5S)-3-(N-*Benzyloxycarbonyl*-O-*dimethyl*-*t*-*butylsilyl*-D-*serinyl*)-4-*methyl*-5-*phenyl*-1,3-*oxazolidine*-2-*thione* (**50a**) *and Its Diastereoisomer* (**50b**).—Compound (**49**) (2.824 g, 8 mmol), (4*R*,5*S*)-MPOT (**7**) (1.544 g, 8 mmol), water-soluble carbodiimide (WSC) (1.687 g, 8.8 mmol), and DMAP (96 mg, 0.8 mmol) were added to CH_2Cl_2 (60 ml) with stirring. After being stirred at room temperature for 5 h, the reaction mixture was washed successively with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, and evaporated under reduced pressure to give an oily residue. The residue was chromatographed on a silica gel column (Wakogel C-200, 400 g) with AcOEt–hexane (1:9). The first eluate gave (4*R*,5*S*)-3-(*N*-benzyloxycarbonyl-*O*-dimethyl-butylsilyl-D-serinyl)-4-methyl-5-phenyl-1,3-oxazolidine-2-thione (**50a**) (1.70 g, 40.3%) as a colourless viscous oil; $[\alpha]_D^{28}$ +28.3° (*c* 0.84, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 440, 1 720, and 1 710 cm^{-1}; δ (100 MHz) 0.04 (6 H, s), 0.87—1.00 (12 H, m), 3.92 (1 H, dd, *J* 11.4 and 3.4 Hz), 4.25 (1 H, dd, *J* 11.4 and 2.9 Hz), 5.12 (2 H, s), 5.68 (1 H, d, *J* 7.1 Hz), 5.74 (1 H, d, *J* 7.1 Hz), 6.48—6.70 (1 H, m), and 7.24—7.40 (10 H, m) (Found: M^+, 528.212. $C_{27}H_{36}N_2O_5SSi$ requires *M*, 528.211). The second eluate gave compound (**50b**) (1.54 g, 36.4%) as colourless needles, m.p. 105—106 °C (from AcOEt–hexane); $[\alpha]_D^{28}$ +10.8° (*c* 0.73, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 440, 1 720, and 1 710 cm^{-1}; δ (100 MHz) 0.04 (6 H, s), 0.80—0.98 (12 H, m), 3.98 (1 H, dd, *J* 11.4 and 3.4 Hz), 5.00—5.20 (3 H, m), 5.78 (2 H, d, *J* 7.1 Hz), 6.28—6.48 (1 H, m), and 7.28—7.48 (10 H, m) (Found: C, 61.4; H, 6.8; N, 5.2%; M^+, 528. $C_{27}H_{36}N_2O_5SSi$ requires C, 61.35; H, 6.85; N, 5.3%; *M*, 528).

N-(N-*Benzyloxycarbonyl*-O-*dimethyl*-*t*-*butylsilyl*-L-*serinyl*)-O-*benzylhydroxylamine* (**52**) *and Its Enantiomer* (**51**).—*O*-Benzylhydroxylamine hydrochloride (319.2 mg, 2 mmol) was added with stirring to a solution of (4*R*,5*S*)-MPOT amide (**50b**) (1.056 g, 2 mmol) and Et_3N (202 mg, 2 mmol) in CH_2Cl_2 (20 ml). After being stirred at room temperature for 72 h, the reaction mixture was washed successively with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried, and evaporated under reduced pressure to give an oily residue. Purification of the residue on a silica gel column with AcOEt–hexane (3:7) as the eluant gave compound (**52**) (605 mg, 66.0%) as colourless needles, m.p. 97—98 °C (from AcOEt–hexane); $[\alpha]_D^{28}$ +42.5° (*c* 0.65, $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 420, 1 720, and 1 700 cm^{-1}; δ (100 MHz) 0.04 (6 H, s), 0.83 (9 H, s), 3.56 (1 H, dd, *J* 10.0 and 8.6 Hz), 3.96 (1 H, dd, *J* 10.0 and 4.3 Hz), 4.08—4.26 (1 H, m), 4.82 (1 H, d, *J* 11.4 Hz), 4.96 (1 H, d, *J* 11.4 Hz), 5.09 (2 H, s), 5.60 (1 H, d, *J* 6.0 Hz), 7.32 (5 H, s), 7.34 (5 H, s), and 8.90 (1 H, br s) (Found: C, 63.0; H, 7.35, N, 6.2%; M^+, 458. $C_{24}H_{34}N_2O_5Si$ requires C, 62.85; H, 7.45; N, 6.1%; *M*, 458). The enantiomer (**51**) of (**52**) was also prepared in a similar manner; 67.5% yield; colourless needles, m.p. 97—98 °C (from AcOEt–hexane); $[\alpha]_D^{28}$ −42.5° (*c* 1.07, $CHCl_3$); i.r. and ^1H n.m.r. spectral data were identified by comparison with those of compound (**52**). (Found: C, 62.85; H, 7.35; N, 6.15%; M^+, 458).

O-*Benzyl*-N-(N-*benzyloxycarbonyl*-L-*serinyl*)*hydroxylamine* (**53**).—A 1.0M solution of Bu_4NF in THF (1.8 ml, 1.8 mmol) was added to a solution of compound (**52**) (458 mg, 1 mmol) and AcOH (60 mg, 0.1 mmol) in THF (12 ml) with stirring. After being stirred at room temperature for 5 min, the reaction mixture was poured into AcOEt (20 ml) and the organic portion was washed successively with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, and then dried, and evaporated under reduced pressure to give an oily residue. Purification of the residue on a silica gel column using $CHCl_3$–acetone (9:1) as the eluant gave the alcohol (**53**) (287.2 mg, 83.5%) as colourless flakes, m.p. 126—127 °C (from AcOEt–hexane) (lit.,[9] 125—127 °C); $[\alpha]_D^{28}$ −25.1° (*c* 1, 23, MeOH) {lit.,[9] $[\alpha]_D^{20}$ −25.9° (*c* 3.2, MeOH)}; $\nu_{max.}$($CHCl_3$) 3 425, 1 720, and 1 700 cm^{-1}; δ (100 MHz) 3.54 (1 H, dd, *J* 11.4 and 5.7 Hz), 3.84 (1 H, dd *J* 11.4 and 4.3 Hz), 4.00—4.20 (1 H, m), 4.80 (2 H, s), 5.00 (2 H, s), 5.94 (1 H, d, *J* 7.7 Hz), 7.28 (5 H, s), 7.30 (5 H, s), and 9.58 (1 H, br s) (Found: C, 62.95; H, 5.9; N, 8.2%; M^+, 344. $C_{18}H_{20}N_2O_5$ requires C, 62.8; H, 5.85; N, 8.15%; *M*, 344).

(3S)-1-*Benzyloxy*-3-*benzyloxycarbonylaminoazetidin*-2-*one* (**54**).—Compound (**53**) (172 mg, 0.5 mmol), triphenylphosphine (131.2 mg, 0.5 mmol), and diethyl azodicarboxylate (87.1 mg, 0.5 mmol) in THF (6 ml) were stirred at room temperature for 20 h. The solvent was then evaporated off under reduced pressure to give an oily residue, which was chromatographed on a silica gel column with $CHCl_3$–acetone (9:1) as eluant to afford the azetidinone (**54**) (125.8 mg, 77.2%) as colourless needles, m.p. 91—92 °C (from $CHCl_3$–hexane) (lit.,[9] m.p. 89.5—91 °C); $[\alpha]_D^{28}$ −10.6° (*c* 1.0, MeOH) {lit.,[9] $[\alpha]_D^{20}$ −9 ± 3° (*c* 2, MeOH)}; $\nu_{max.}$($CHCl_3$) 3 430, 1 775, and 1 720 cm^{-1}; δ (100 MHz) 3.24 (1 H, dd, *J* 5.1 and 2.3 Hz), 3.52 (1 H, t, *J* 5.1 Hz), 4.44—4.64 (1 H, m), 4.94 (2 H, s), 5.08 (2 H, s), 5.38 (1 H, d, *J* 6.6 Hz), 7.30 (5 H, s), and 7.34 (5 H, s) (Found: C, 66.5; H, 5.65; N, 8.55%; M^+, 326. $C_{18}H_{18}N_2O_4$ requires C, 66.25; H, 5.55; N, 8.6%; *M*, 326).

Acknowledgements

We thank Mrs. K. Ohmine (for n.m.r. spectra), Mrs. T. Terada (for mass spectra), and Miss T. Kishimoto (for elemental analysis) of this institute.

References

1 Y. Nagao and E. Fujita, *Heterocycles*, 1982, **17**, 537; Y. Nagao, T. Ikeda, M. Yagi, E. Fujita, and M. Shiro, *J. Am. Chem. Soc.*, 1982, **104**, 2079; Y. Nagao, T. Miyasaka, Y. Hagiwara, and E. Fujita, *J. Chem. Soc., Perkin Trans. 1*, 1984, 183; Y. Nagao, T. Miyasaka, K. Seno, E. Fujita, D. Shibata, and E. Doi, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2439.
2 A. I. Meyers and M. E. Ford, *J. Org. Chem.*, 1976, **41**, 1735; M. G. Ettlinger, *J. Am. Chem. Soc.*, 1950, **72**, 4792.
3 R. Santoro, R. Warren, and G. Roberts, *J. Chromatogr.*, 1976, **117**, 383.
4 Y. Nagao, *Farumashia*, 1983, **19**, 179.
5 J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543.
6 Y. Nagao, K. Seno, K. Kawabata, T. Miyasaka, S. Takao, and E. Fujita, *Chem. Pharm. Bull.*, 1984, **32**, 2687.
7 Y. Nagao, K. Kawabata, K. Seno, and E. Fujita, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2470.
8 S. Mitsui and S. Imaizumi, *Nippon Kagaku Zasshi*, 1965, **86**, 219.
9 P. G. Mattingly, J. F. Kerwin, Jr., and M. J. Miller, *J. Am. Chem. Soc.*, 1979, **101**, 3983.
10 '26th Symposium on the Chemistry of Natural Products,' Kyoto, Japan, October 14, 1983, and the 103rd Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, Japan, April 6, 1983.

Received 18*th February* 1985; *Paper* 5/270