Tetrahedron Vol. 49, No. 10, pp. 2131-2138, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Enantioselective Synthesis of 2-Alkyl Substituted Cysteines.‡

Gerald Pattenden,* Stephen M. Thom and Martin F. Jones†

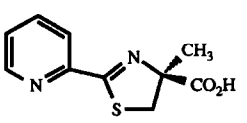
Department of Chemistry, The University, Nottingham NG7 2RD

†Glaxo Group Research Ltd., Greenford, Middlesex UB6 0HE

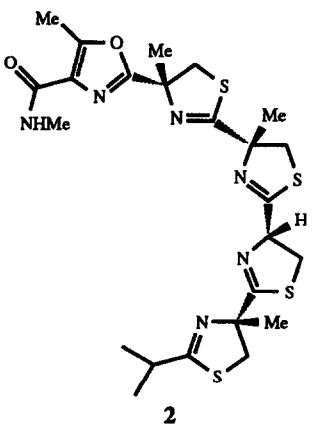
(*Received in UK* 23 *November* 1992)

Abstract: Treatment of the N-formyl derivative of the thiazolidine adduct derived from (*R*)-cysteine methyl ester hydrochloride and pivalaldehyde, with LDA-DMPU at -90°C, followed by reaction with iodomethane produces the corresponding methylated thiazolidine containing the methyl and t-butyl groups virtually exclusively *anti-* to one another. Hydrolysis in the presence of 5M HCl then affords (*R*)-2-methylcysteine hydrochloride in excellent yield and enantiomeric purity. A range of other 2-alkyl substituted cysteines of excellent optical purity are prepared by this modification of Seebach's "self-reproduction of chirality" protocol.

The applications of modified amino acids as building blocks for the preparation of peptide analogues are well documented, and these studies now complement a large part of contemporary medicinal chemistry, protein engineering and molecular biology. Secondary metabolites whose biosynthesis ostensibly uses 2-methylcysteine (**10**) as the amino acid starter unit are not common. Indeed, until 1990 the only known example of a 2-methylcysteine (*S*-enantiomer) derived secondary metabolite was the siderophore desferrithiocin (**1**), isolated from cultures of *Streptomyces antibioticus*.[1] Over the past two years however, a new and completely novel family of apparently (*R*)-2-methylcysteine derived metabolites has been isolated from blue green-algae *e.g.* tantazole A (**2**), mirabazole C (**3**);[2] and from the cell extract of *Polyangium sp.*, *e.g.* thiangazole (**4**).[3]



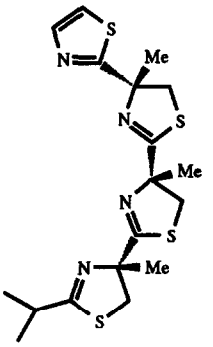
1



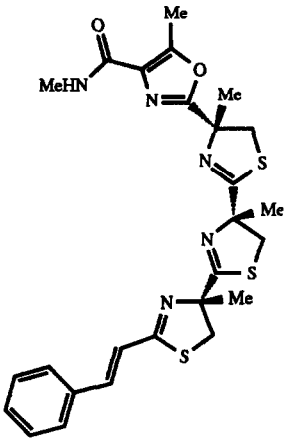
2

‡Dedicated to Professor Charles W. Rees on the occasion of his 65th birthday.

The compounds, which have structures based on the linear fusion of successive 2,4-disubstituted oxazole/thiazoline/thiazole rings terminating in a C-2-isopropyl or C-2-cinnamyl substituted thiazoline, also show a diverse range of biological activity which includes murine solid tumour selective cytotoxicity and the capacity to inhibit HIV-1 infection.



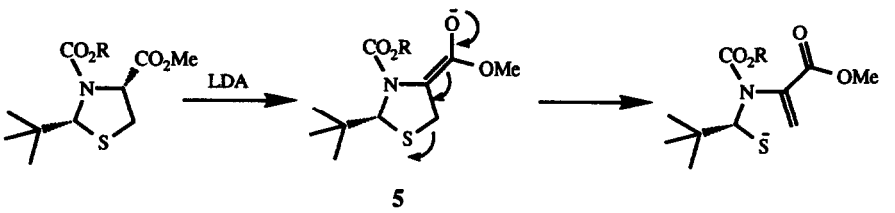
3



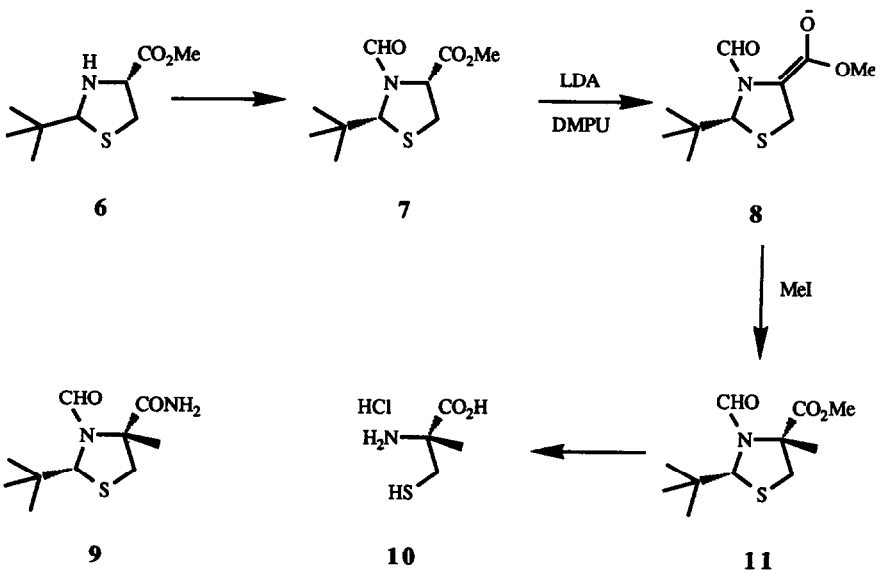
4

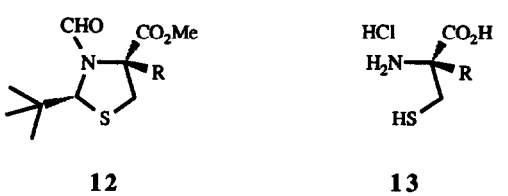
In connection with synthetic studies amongst the tantazole/mirabazole/ thiangazole family of 4-methylthiazoline based metabolites[4] we required a concise synthesis of (*R*)-2-methylcysteine. Procedures for the synthesis of chiral proteinogenic α-amino acids, their derivatives and their analogues have been well-reviewed.[5] Although Schöllkopf and his collaborators[6] have applied their method based on metallation and alkylation of *bis*-lactim ethers derived from (*S*)-valine to synthesise S-benzyl and S-butyl (*S*)-2-methylcysteine esters, the method of Seebach,[7] involving enolate alkylation of thiazolidines which works so well for oxazolidines (dubbed "self-reproduction of chirality") cannot be applied to the synthesis of chiral 2-substituted cysteines. Indeed, Seebach has indicated that cysteine has always taken a special role in this respect, owing to the fact that the sulphide group in the enolate intermediate (**5**) cannot be prevented from undergoing β-elimination (see Scheme 1). We were oblivious of this limitation when we began our studies of a synthesis of (*R*)-2-methylcysteine, and in one approach we indeed examined the methylation (and other alkylations) of the enolate (**8**) produced from the N-*formyl*thiazolidine (**7**) derived from (*R*)-cysteine and pivalaldehyde. To our pleasure and initial surprise this method, which is now detailed here, provided an excellent enantioselective synthesis of chiral 2-methylcysteine and other 2-substituted cysteine derivatives.

Thus, N-formylation of the thiazolidine (**6**) derived from (*R*)-cysteine methyl ester hydrochloride and pivalaldehyde, using sodium formate in the presence of formic acid first led to a single *syn*-diastereoisomer of the crystalline formate (**7**) in 82% yield. Treatment of a solution of (**7**) in tetrahydrofuran at -90°C with lithium diisopropylamide in the presence of DMPU followed by quenching the resulting enolate (**8**) with iodomethane at -90°C next produced the corresponding 4-methylthiazolidine (**11**) as white needles in 56% yield. The excellent diastereoselectivity in the methylation of (**8**), *i.e.* methylation occurred exclusively *anti*- to the bulky t-butyl



Scheme 1





a, R = CH_2Ph; *b*, R = $CH_2CH{=}CH_2$; *c*, R = CH_2CO_2Me; *d*, R = CH_2CH_3

group, was firmly established by carrying out an X-ray examination of the crystalline amide (**9**) produced from treatment of (**11**) with ethanolic ammonia.[8] At this moment in time we have no rational explanation why α-methylation of the thiazoline enolate (**8**) was so facile, whereas earlier attempts to achieve this objective were unsuccessful.[9] The hydrochloride salt (**10**) of (*R*)-2-methylcysteine was then released from the thiazolidine (**11**) following treatment with 5M hydrochloric acid.[10] In a similar manner using identical experimental conditions, (*S*)-2-methylcysteine hydrochloride was elaborated from (*S*)-cysteine.[11]

As a corollary we also examined the alkylation of the enolate (**8**) with a range of alternative electrophiles. Thus alkylations of (**8**) with benzyl bromide, allyl bromide and methyl bromoacetate led to the corresponding alkylated thiazolidines (**12*a***), (**12*b***) and (**12*c***) respectively in 74~86% yields. In addition, alkylation of (**8**) with iodoethane produced the 4-ethylthiazolidine (**12*d***) in an acceptable 44% yield. Perhaps not surprisingly, treatment of the 4-allyl and 4-methylacetate substituted thiazolidines (**12*b***) and (**12*c***) with 5M hydrochloric resulted in extensive degradation and neither of the corresponding 2-alkylcysteines (**13*b***) and (**13*c***) could be recovered from these reactions. However, the hydrolyses of the 4-benzyl and 4-ethyl substituted compounds (**12*a***) and (**12*d***) proceeded smoothly, and led to the corresponding 4-benzyl (**13*a***) and 4-ethyl cysteines (**13*d***) in good yields.

In conclusion, a useful and general method for the enantioselective synthesis of a range of 2-alkyl substituted cysteines has been established.

Experimental

2*R*,4*R*-Methyl 2-tert-butyl-1,3-thiazolidine-3-formyl-4-carboxylate (**7**). - Acetic anhydride (5.7 ml, 60.4 mmol) was added dropwise, over 1h, to a stirred solution of formic acid (30 ml), (4*R*) methyl 2-tert-butyl-1,3-thiazolidine-4-carboxylate (4.0 g, 19.7 mmol)[7] and sodium formate (1.50 g, 22.0 mmol) at 0-5°C. The solution was warmed to room temperature and then stirred overnight. The solvents were removed *in vacuo* and the residue was then carefully neutralised with $NaHCO_3$ solution and extracted with ether (3x30 ml). The combined ether extracts were dried, and evaporated *in vacuo* to leave a white solid. Recrystallisation from petrol-ether gave the thiazolidine (3.78 g, 82%) as white crystals, m.p. 77-78°C (8:1 mixture of conformers); $[\alpha]_D$ -130.4 (c 1.08 in $CHCl_3$); (Found : C, 52.2; H, 7.6; N, 6.2. $C_{10}H_{17}NO_3S$ requires C, 51.9; H, 7.4; N, 6.1%); $\nu_{max}(CHBr_3)$ 2956, 1753, 1670 and 1364 cm^{-1}; δ_H (250MHz; $CDCl_3$) major conformer, 8.36 (1H, s, CHO), 4.90 (1H, t, *J* 8.6 Hz, $CH(CO_2CH_3)$), 4.75 (1H, s, $CHC(CH_3)_3$), 3.78 (3H, s, CO_2CH_3), 3.31 (1H, d, *J* 8.4 Hz, CH_2), 3.29 (1H, d, *J* 8.9 Hz, CH_2), 1.04 (9H, s, $C(CH_3)_3$); δ_C (67.8MHz; $CDCl_3$) 169.97 (s, CO), 162.62 (d, CHO), 75.06 (d, $CHC(CH_3)_3$), 61.40 (d, $CH(CO_2CH_3)$), 52.60 (q, OCH_3), 38.54 (s, $C(CH_3)_3$), 32.81 (t, CH_2), 26.27 (q, $C(CH_3)_3$); m/z (CI) 232 (MH^+, 100%), 204 (10), 164 (24).

2*R*,4*R*-Methyl 2-tert-butyl-1,3-thiazolidine-3-formyl-4-methyl-4-carboxylate (**11**). - A solution of butyl lithium (1.6M) in hexanes (28.4 ml, 45.4 mmol) was added dropwise over 5 min to a stirred solution of diisopropylamine (9.1 ml, 64.8 mmol) in dry THF (200 ml) at -78°C under a nitrogen atmosphere. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (30 ml) was added in one portion, and the mixture was then stirred at -78°C for 1h. A solution of 2*R*,4*R*-methyl 2-tert-butyl-1,3-thiazolidine-3-formyl-4-carboxylate (10.0

g, 43.23 mmol) in THF (5 ml) was added over 10 min, keeping the internal temperature at -90°C. The resulting solution was stirred for 0.75 h at -90°C, and then iodomethane (3.23 ml, 51.9 mmol) was added dropwise over 5 min. The mixture was stirred for 2h at -90°C, and then warmed to room temperature. The solvents were evaporated *in vacuo* to leave an oily residue which was partitioned between brine (200 ml) and ether (100 ml). The separated aqueous layer was extracted with ether (3x300 ml), and the combined ether extracts were then dried and evaporated *in vacuo* to leave an oil. The oil was purified by chromatography on silica gel, using 10% ethyl acetate-light petroleum as eluant, to give the thiazolidine (5.94 g, 56%) which recrystallised from ether-light petroleum as white crystals, m.p. 49-50°C (2.3:1 mixture of conformers); $[\alpha]_D$ -100.2 (c 1.39 in $CHCl_3$); (Found: C, 53.8; H, 8.0; N, 5.9. $C_{11}H_{19}NO_3S$ requires C, 53.8; H, 7.8; N, 5.7%); $\nu_{max}(CHCl_3)$ 2954, 1739, 1668, 1353 and 1313 cm^{-1}; δ_H (250MHz; $CDCl_3$) major conformer, 8.29 (1H, s, CHO), 4.67 (1H, s, CH), 3.78 (3H, s, OCH_3), 3.33 (1H, d, *J* 11.6 Hz, CH_2), 2.74 (1H, d, *J* 11.6 Hz, CH_2), 1.77 (3H, s, CH_3), 1.08 (9H, s, $C(CH_3)_3$); minor conformer, 8.42 (1H, s, CHO), 5.31 (1H, s, CH), 3.83 (3H, s, OCH_3), 3.65 (1H, d, *J* 12.6 Hz, CH_2), 2.87 (1H, d, *J* 12.3 Hz, CH_2), 1.80 (3H, s, CH_3), 0.97 (9H, s, $C(CH_3)_3$); δ_C (67.8MHz; $CDCl_3$) major conformer 172.05 (s, CO), 161.13 (d, CHO), 74.30 (d, CH), 70.01 (s, CCO_2CH_3), 52.76 (q, OCH_3), 41.49 (t, CH_2), 39.44 (s, $C(CH_3)_3$), 26.67 (q, $C(CH_3)_3$), 20.61 (q, CH_3); minor conformer, 173.10 (s), 162.84 (d), 71.79 (d), 69.87 (s), 53.22 (q), 42.14 (t), 40.27 (s), 28.18 (q), 27.08 (q); m/z (FAB) 246 (MH^+, 100%), 188 (59), 176 (36), 160 (97).

(*R*)-2-Methylcysteine hydrochloride (**10**). - 5M Hydrochloric acid (500 ml) was added to 2*R*,4*R*-methyl-2-tert-butyl-1,3-thiazolidine-3-formyl-4-methyl carboxylate (32.6 g, 133 mmol) and the solution was then heated under reflux in an atmosphere of nitrogen for 3 days. The solution was washed with ethyl acetate (3x300 ml), and then the aqueous layer was evaporated *in vacuo* to leave the hydrochloride salt (21.21 g, 93%) as a white solid, m.p. 157-159°C (decomp.); $[\alpha]_D$ 8.13 (c 1.58 in H_2O); δ_H (270MHz; D_2O) 3.25 (1H, d, *J* 14.8 Hz, CH_2), 2.97 (1H, d, *J* 14.8 Hz, CH_2), 1.67 (3H, s, CH_3); δ_C (67.8MHz; D_20) 173.79 (s, CO), 62.31 (s, $C(CO_2H)$), 31.10 (t, CH_2), 22.08 (q, CH_3); m/z (FAB) 136 (MH^+-HCl, 100%).

Methyl (*R*)-2-methylcysteine hydrochloride. - Acetyl chloride (30 ml, 422 mmol) was added dropwise to a stirred solution of methanol (300 ml) at 0-5°C under a nitrogen atmosphere. The solution was stirred at room temperature for 0.5h then (*R*)-2-methylcysteine hydrochloride (18.0 g, 105 mmol) added in one portion. The solution was then refluxed for 6h after which the solvents were removed *in vacuo* to give the methyl ester as a viscous oil in a quantitative yield; $[\alpha]_D$ 2.1 (c 1.15 in H_2O); δ_H (250MHz; D_2O) 3.87 (3H, s, OCH_3), 3.22 (1H, d, *J* 15.1 Hz, CH_2), 2.96 (1H, d, *J* 15.1 Hz, CH_2), 1.63 (3H, s, CH_3); δ_C (67.8MHz; D_20) 172.14 (s, CO), 62.46 (s, $C(CO_2CH_3)$), 55.04 (q, OCH_3), 31.12 (t, CH_2), 21.97 (q, CH_3); m/z (FAB) 150 (MH^+-HCl, 100%)

2*R*, 4*R* 2-tert-Butyl-1,3-thiazolidine 3-formyl-4-methyl-4-carboxamide (**9**). -Aq. ammonia (20 ml) was added to a stirred solution of the ester (3.0 g, 12.2 mmol) in ethanol (20 ml). The solution was stirred for 48h then the ethanol evaporated *in vacuo* and the aqueous layer extracted with ethyl acetate (2x20 ml). The combined organics were dried and concentrated *in vacuo* to give a solid residue which was purified by column chromatography on

silica gel using 20% then 50% ethyl acetate-light petroleum as eluant. The amide was obtained as a white solid (614 mg, 22%) which was recrystallised from ether-light petroleum, m.p. 128-129°C; $[\alpha]_D$ -182 (c 0.27 in $CHCl_3$); (Found: C, 52.1; H, 8.2; N, 12.1. $C_{10}H_{18}N_2O_2S$ requires C, 52.1; H, 7.9; N, 12.2 %); $\nu_{max}(CHCl_3)$ 3467, 1680, 1663, 1588, 1364 and 1306 cm^{-1}; δ_H (250MHz; $CDCl_3$) 8.38 (1H, s, CHO), 7.85 and 5.69 (2H, 2xbrd, NH_2), 4.68 (1H, s, CH), 3.94 (1H, d, *J* 12.5 Hz, CH_2), 2.84 (1H, d, *J* 12.5 Hz, CH_2), 1.84 (3H, s, CH_3), 1.00 (9H, s, $C(CH_3)_3$); δ_C (67.8MHz; $CDCl_3$) 175.10 (s, CO), 163.82 (d, CHO), 77.32 (d, CH), 72.35 (s, $CCONH_2$), 42.50 (t, CH_2), 39.24 (s, $C(CH_3)_3$), 26.76 (q, $C(CH_3)_3$), 22.42 (q, CH_3); m/z (FAB) 231 (MH^+, 100%), 186 (58), 145 (89).

2*R*,4*R*-Methyl 2-tert-butyl-1,3-thiazolidine-3-formyl-4-benzyl-4-carboxylate (**12***a*). - The anion (**8**) derived from the thiazolidine (**7**) was alkylated with benzyl bromide, using the procedure described for the synthesis of (**11**), and gave the thiazolidine (2.05 g, 74%) as a white solid which recrystallised from ether-light petroleum as white crystals, m.p. 94-95°C (1.6:1 mixture of conformers); $[\alpha]_D$ -37.2 (c 2.44 in $CHCl_3$); (Found: C, 63.4; H, 7.4; N, 4.3. $C_{17}H_{23}NO_3S$ requires C, 63.5; H, 7.2; N, 4.4%); $\nu_{max}(CHCl_3)$ 2954, 1740, 1669, 1363, 1346 and 1312 cm^{-1}; δ_H (270MHz; $CDCl_3$) 8.68 and 8.45 (1H, s, CHO), 7.33-7.09 (5H, m, ArH), 5.37 and 4.50 (1H, s, $CH(CH_3)_3$), 3.80 and 3.78 (3H, s, CO_2CH_3), 3.67-2.96 (4H, m, 2xCH_2), 1.04 and 0.95 (9H, s, $C(CH_3)_3$); δ_C (67.8MHz; $CDCl_3$) 171.81 and 171.70 (s, CO), 163.43 and 161.58 (d, CHO), 136.50 and 134.59 (q, Ar), 130.76 (d, ArH), 130.06 (d, ArH), 128.64 (d, ArH), 128.05 (d, ArH), 127.71 (d, ArH), 126.79 (d, ArH), 74.90 and 71.82 (d, $CHC(CH_3)_3$), 73.62 and 73.12 (s, CCO_2CH_3), 52.92 and 52.71 (q, CO_2CH_3), 45.91 (t), 40.29 and 39.43 (s, $C(CH_3)_3$), 38.13 (t), 38.01 (t), 37.56 (t), 27.19 and 26.69 (q, $C(CH_3)_3$); m/z (FAB) 322 (MH^+, 80%), 294 (21), 264 (23), 236 (100), 91 (71).

2*R*,4*R*-Methyl 2-tert-butyl-1,3-thiazolidine-3-formyl-4-allyl-4-carboxylate (**12***b*). - The anion (**8**) derived from the thiazolidine (**7**) was alkylated with allyl bromide, using the procedure described for the synthesis of (**11**) and gave the thiazolidine (1.82 g, 77%) as a colourless oil (1:1 mixture of conformers); $[\alpha]_D$ -46.2 (c 1.29 in $CHCl_3$); ν_{max}(film) 2957, 1742, 1676, 1362, 1312, 1248, 1146 and 1041 cm^{-1}; δ_H (270MHz; $CDCl_3$) 8.53 and 8.34 (1H, s, CHO), 6.13-5.95 and 5.85-5.69 (1H, m, C*H*:CH_2), 5.37 and 4.66 (1H, s, C*H*C$(CH_3)_3$), 5.24-5.07 (2H, m, CH:C*H*$_2$), 3.83 and 3.78 (3H, s, CO_2CH_3), 3.70 and 3.28 (1H, d *J* 12.9 Hz and 11.9 Hz, CH_2S), 3.11-2.82 (3H, m, C*H*$_2$CH: and CH_2S), 1.07 and 0.95 (9H, s, $C(CH_3)_3$); δ_C (67.8MHz; $CDCl_3$) 172.27 and 171.64 (s), 162.73 and 161.18 (d), 133.64 and 130.40 (d, *C*H:CH_2), 120.94 and 118.92 (t, CH:CH_2), 74.77 and 71.81 (d, C*H*C$(CH_3)_3$), 72.60 and 72.06 (s, CCO_2CH_3), 53.14 and 52.62 (q, CO_2CH_3), 44.64 (t), 40.07 and 39.39 (s, $C(CH_3)_3$), 38.74 (t), 38.30 (t), 37.90 (t), 26.99 and 26.60 (q, $C(CH_3)_3$); m/z (FAB) 272 (MH^+, 63%), 214 (40), 186 (100), 126 (35).

2*R*,4*R*-Methyl 2-tert-butyl-1,3-thiazolidine-3-formyl-4-methyl acetate-4-carboxylate (**12***c*). - The anion (**8**) derived from the thiazolidine (**7**) was alkylated with methyl bromoacetate, using the procedure described for the synthesis of (**11**) and gave the thiazolidine (2.26 g, 86%) as a colourless oil (5:1 mixture of conformers); $[\alpha]_D$ -31.8 (c 1.68 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 2957, 1738, 1674, 1437, 1348, 1308, 1252 and 1203 cm^{-1}; δ_H

(270MHz; $CDCl_3$) major conformer 8.34 (1H, s, CHO), 4.63 (1H, s, $CH(CH_3)_3$), 3.78 (3H, s, CO_2CH_3), 3.69 (3H, s, CO_2CH_3), 3.61 (1H, d, *J* 12.2 Hz, CH_2S), 3.34 (1H, d, *J* 11.9 Hz, CH_2S), 3.15 (2H, m, $CH_2CO_2CH_3$), 1.08 (9H, s, $C(CH_3)_3$); δ_C (67.8MHz; $CDCl_3$) major conformer 170.58 (s), 170.44 (s), 161.58 (d, CHO), 74.09 (d, $CHC(CH_3)_3$), 71.00 (s, CCO_2CH_3), 52.87 (q, CO_2CH_3), 51.72 (q, CO_2CH_3), 39.14 (t), 37.95 (s, $C(CH_3)_3$), 35.15 (t), 26.45 (q, $C(CH_3)_3$); m/z (FAB) 304 (MH^+, 67%), 276 (50), 218 (100).

2R,4R-Methyl 2-tert-butyl-1,3-thiazolidine-3-formyl-4-ethyl-4-carboxylate (**12*d***). - The anion (**8**) derived from the thiazolidine (**7**) was alkylated with iodoethane using the procedure described for the synthesis of (**11**) and gave the thiazolidine (990 mg, 44%) as a colourless oil (3.2:1 mixture of conformers); $[\alpha]_D$ -70.98 (c 1.08 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 2958, 1739, 1673, 1462, 1363, 1250, 1138, 1009 and 884 cm^{-1}; δ_H (270MHz; $CDCl_3$) major conformer 8.47 (1H, s, CHO), 5.42 (1H, s, $CH(CH_3)_3$), 3.82 (3H, s, CO_2CH_3), 3.74 (1H, d, *J* 12.8 Hz, CH_2), 3.00 (1H, d, *J* 12.5 Hz, CH_2), 2.12 (2H, m, CH_2CH_3), 1.01 (3H, t, *J* 7.2 Hz, CH_2CH_3), 0.94 (9H, s, $C(CH_3)_3$); δ_C (67.8MHz; $CDCl_3$) major conformer 173.05 (s), 162.71 (d, CHO), 72.98 (s, CCO_2CH_3), 71.75 (d, $CHC(CH_3)_3$), 53.07 (q, CO_2CH_3), 40.02 (s, $C(CH_3)_3$), 38.60 (t), 33.34 (t), 26.94 (q, $C(CH_3)_3$), 8.16 (q, CH_2CH_3); m/z (FAB) 260 (MH^+, 77%), 202 (45), 190 (31), 174 (100), 114 (40).

(*R*)-2-Ethylcysteine hydrochloride (**13*d***). - The 4-ethyl carboxylate (**12*d***) was hydrolysed with 5M hydrochloric acid, as described for the corresponding 4-methyl derivative (**11**) to give 2-ethylcysteine hydrochloride (94%) as a solid, m.p. 220-224 °C (decomp.); $[\alpha]_D$ 2.24 (c 0.8 in H_2O); δ_H (270MHz; D_2O) 3.03 (1H, d, *J* 15.2 Hz, CH_2SH), 2.72 (1H, d, *J* 15.2 Hz, CH_2SH), 1.87-1.55 (2H, m, CH_2CH_3), 0.80 (3H, t, *J* 7.2 Hz, CH_2CH_3); δ_C (67.8MHz; D_20) 174.16 (s), 67.46 (s), 30.76 (t), 30.19 (t), 9.00 (q); m/z (FAB) 150 (MH^+-HCl, 100%), 136 (20).

(*R*)-2-Benzylcysteine hydrochloride (**13*a***). - The 4-benzyl carboxylate (**12*a***) was hydrolysed with 5M hydrochloric acid, as described for the corresponding 4-methyl derivative (**11**) to give 2-benzylcysteine hydrochloride (91%) as a gummy solid; $[\alpha]_D$ 7.07 (c 1.07 in H_2O); δ_H (270MHz; D_2O) 7.32-7.17 (5H, m, ArCH), 3.30 (1H, d, *J* 14.5 Hz, CH_2), 3.24 (1H, d, *J* 16.2 Hz, CH_2), 3.07 (1H, d, *J* 14.5 Hz, CH_2), 2.84 (1H, d, *J* 14.8 Hz, CH_2); δ_C (67.8MHz; D_20) 172.61 (s), 133.34 (s), 131.06 (d), 130.15 (d), 129.32 (d), 66.75 (s), 41.67 (t), 30.02 (t); m/z (FAB) 212 (MH^+-HCl, 100%), 166 (22), 91 (28).

Acknowledgements

We thank Glaxo Group Research Ltd., for a Scholarship (to S.M.T.) and for generous financial support.

References

1. Naegeli, H.U.; Zähner, H. *Helv. Chim. Acta*, **1980**, *63*, 1400.
2. Carmeli, S.; Moore, R.E.; Patterson, G.M.L.; Corbett, T.H.; Valeriote, F.A. *J. Am. Chem. Soc.*, **1990**,

112, 8195; Carmeli, S.; Moore, R.E.; Patterson, G.M.L. *Tetrahedron Lett.*, **1991**, *32*, 2593.

3. Jansen, R.; Kunze, B.; Reichenbach, H.; Jurkiewicz, E.; Hunsmann, G.; Höfle, G. *Liebigs Ann. Chem.*, **1992**, 357.
4. see: Pattenden, G.; Thom, S.M. *Synlett*, **1992**, 533.
5. see: Synthesis of Optically Active α-Amino Acids, Williams, R.M. Pergamon Press, **1989**, and leading references therein.
6. Groth, U.; Schöllkopf, U. *Synthesis*, **1983**, 37.
7. see: Jeanguenat, A.; Seebach, D. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 2291 and references cited therein.
8. We thank Dr. R.B. Lamont of Glaxo Group Research for this information which will be published separately.
9. Seebach *et al.*[7] had demonstrated that the N-*ester* derivative (**5**) undergoes facile β-elimination, whereas the corresponding N-*formyl* thiazolidine derived from cysteine and benzaldehyde failed to undergo alkylation following deprotonation and reaction of the resulting enolate with electrophiles, Seebach, D.; Weber, T. *Helv. Chim. Acta.*, **1984**, *67*, 1650. An explanation for our results, based on increased delocalisation of the nitrogen lone pair in the formate (**7**), over the case with the corresponding urethane (**5**), leading to a more stabilised carbanion intermediate, *viz* (**8**), is feasible, but may also be too simplistic.
10. For an alternative synthesis of an *N*- and *S*-protected (R)-2-methylcysteine, published recently, see: Walker, M.A.; Heathcock, C.H. *J. Org. Chem.*, **1992**, *57*, 5566.
11. Mulqueen, G.; Pattenden, G. unpublished results.