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Asymmetric synthesis of both diastereomers of protected *S*-methyl-L-cysteine and *S*-*n*-propyl-L-cysteine sulphoxides

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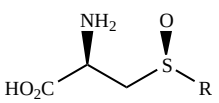
Abstract—The preparation of both isomers at sulphur of *N*-(benzyloxycarbonyl)-*S*-methyl (-propyl)-*S*-oxo-L-cysteine methyl ester has been carried out using L-cysteine and diacetone-D-glucose (DAG) as starting material and inductor of the chirality at sulphur, respectively.

1. Introduction

Sulphoxides of the amino acid *S*-alkyl-L-cysteine (alkyl = Me, **1** and ^{n}Pr, **2**, Scheme 1) possess a wide variety of biological properties. Among them, these sulphoxides are two of the aroma and flavour components of vegetables of the genus *Brassica* (cabbage, cauliflower, broccoli, turnip, etc.)[1] and *Allium* (garlic, onion, leek, etc.).[2] *S*-Methyl-L-cysteine sulphoxide **1** is also responsible for the anti-bacterial action of cabbage,[3] possesses the ability to lower serum cholesterol levels (by inhibition of cholesterol synthesis)[4] and has shown activity as an inhibitor of platelet aggregation.[5] Sulphoxide **1** and its enzymatically derived methyl methane thiolsulphinate, both naturally occurring in *Brassica* vegetables, have shown anti-carcinogenic activity in mice.[6] Additionally, **1** is the substrate for the enzyme cysteine–sulphoxide lyase, whose activity in old and damaged vegetable tissues leads to the volatile sulphur compounds responsible for the characteristic rotting vegetable smells.[7] The configuration of naturally occurring **1** and **2** has been assigned as (R_C,S_S).[8,9]



1 ; R= -CH_3
2 ; R=-CH_2-CH_2-CH_3

Scheme 1.

The synthesis of this type of amino acid sulphoxide has normally been carried out by chemical oxidation of *S*-alkyl-L-cysteine derivatives followed by separation of the 1:1 mixture of diastereomers by fractional crystallisation.[8] Recently, a diastereoselective enzyme-mediated oxidative method has been developed.[10] We report herein the asymmetric synthesis of the two isomers at sulphur of sulphoxides **1** and **2** as *N*-Cbz-protected methyl esters, using diacetone-D-glucose (DAG) and L-cysteine as starting materials. For the generation of the chiral sulphinyl group we have selected the DAG methodology developed previously by our research group,[11] since DAG has been shown to be a very efficient chiral auxiliary in this context, allowing the preparation of both enantiomers of a wide variety of sulphoxides (diaryl, alkyl–aryl and particularly dialkyl-sulphoxides) through the displacement reaction of their arene- or alkanesulphinates with Grignard reagents. These sulphinates are prepared by condensation between sulphinyl chlorides and DAG in the presence of an appropriate base. The combination of base and solvent determines the stereogenicity at sulphur and the diastereoselectivity of the reaction. For example, when *iso*-Pr_2EtN/toluene is used, sulphinates with (S_S) configuration were obtained as the major diastereomer, whereas using Py/THF gave mainly sulphinates with (R_S) configuration.

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Additionally, the methylsulphoxide (R_C,S_S)-**7a** has been used as a precursor for the preparation of the chiral fragment of (*R*)-(−)-Sparsomycin.[12]

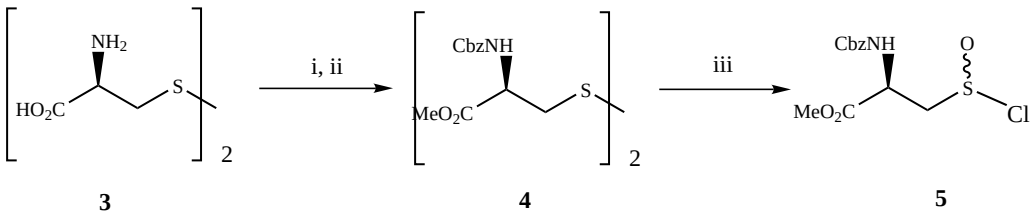
2. Results and discussion

As starting material for the synthesis of alkylsulphoxides using our DAG methodology, acid chloride **5** was prepared from commercially available L-cysteine **3** as indicated in Scheme 2. Standard protection of the two amino acid fragments of **3** gave *N*-benzyloxycarbonyl-L-cysteine methyl ester **4**,[13] which was oxidised with Cl_2SO_2 in acetic acid following the procedure developed by Herrmann[14] to afford sulphinyl chloride **5**[12a] in 77% overall yield.

Condensation of acid chloride **5** with DAG was carried out using different experimental conditions since, as stated above, diastereoselectivity in the formation of chiral sulphur atom in sulphinates strongly depends on the combination of solvent and base used.[11] The results are collected in Table 1.

As was anticipated, the best stereoselectivities were obtained using *iso*-Pr_2EtN/toluene, for the preparation of the (S_S) isomer (entry 1) and Py/CH_2Cl_2 for the synthesis of the (R_S) derivative (entry 7). From the former reaction mixture (entry 1), sulphinate (R_C,S_S)-**6** was obtained in enantiomerically pure form and in 75% yield by a single crystallisation from Et_2O:CH_2Cl_2:hexane (4:1:1). Its epimer at sulphur (R_C,R_S)-**6** was prepared in optically pure form in 93% chemical yield by column chromatography of the reaction crude obtained using Py/CH_2Cl_2 (entry 7). D.e.s were determined by integration of ^{1}H NMR spectra at 500 MHz of the reaction crude using signals for three different protons. Sugar H_1 resonates at 5.95 ppm (d, $J=3.4$ Hz) in the sulphinate (R_C,S_S)-**6** while it appears at 5.90 ppm (d, $J=3.5$ Hz) in the isomer (R_C,R_S)-**6**. Amide NH protons resonate at 5.86 ppm (d, $J=7.4$ Hz) and 6.05 ppm (d, $J=8.0$ Hz) for sulphinates (R_C,S_S)-**6** and (R_C,R_S)-**6**, respectively. Finally, one of the protons of the AB fragment CH_2-SO appears at 3.25 ppm (portion B of an ABX system, $J_{AB}=13.9$ Hz, $J_{AX}=7.6$ Hz) in the sulphinate (R_C,S_S)-**6** while it resonates at 3.38 ppm (portion B of an ABX system, $J_{AB}=13.9$ Hz, $J_{AX}=5.0$ Hz) in the (R_S) isomer.

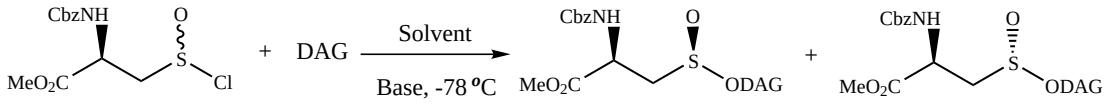
With sulphinates **6** in hand, methyl and *n*-propyl sulphoxides were prepared by Andersen type displacement reactions with MeMgI and *n*-PrMgCl, respectively. As in similar cases of Andersen's synthesis of sulphoxides using sulphinates with a nitrogen within their structure, the Grignard displacement reactions were carried out in the presence of Me_3Al.[15] Otherwise only elimination products were isolated from the reaction between sulphinates **6** and Grignard reagents. The results are shown in Scheme 3.



3 **4** **5**

Scheme 2. (i) Cl_2SO/MeOH, 100%; (ii) ClCbz/$NaHCO_3$, 83%; (iii) Cl_2SO_2/AcOH, 93%.

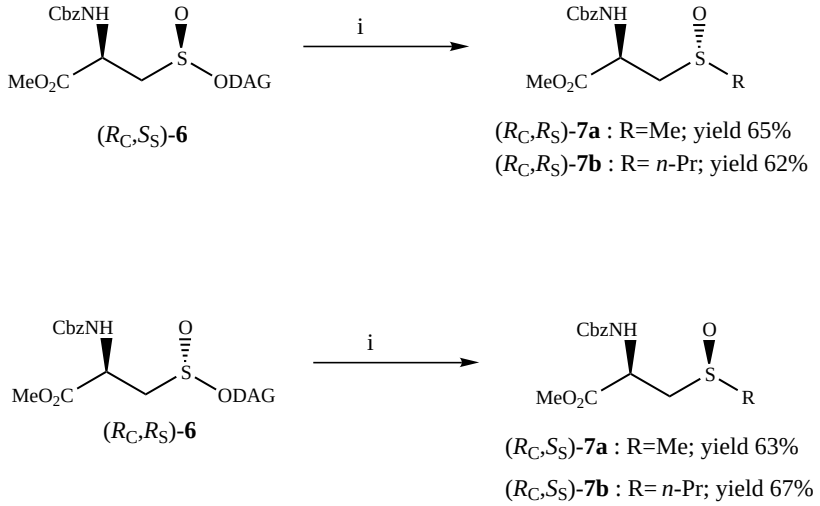
Table 1. Condensation of acid chloride **5** with diacetone-D-glucose (DAG)



5 (R_C,S_S)-**6** (R_C,R_S)-**6**

Entry	Base	Solvent	Yield (%)	(R_C,S_S)-**6**:(R_C,R_S)-**6**[a]
1	*iso*-Pr_2EtN	Toluene	98	4:1[b]
2	*iso*-Pr_2EtN	THF	86	6:4
3	*iso*-Pr_2EtN	CH_2Cl_2	84	68:32
4	*iso*-Pr_2EtN	CH_3CN[c]	95	79:21
5	Pyridine	Toluene	98	13:87
6	Pyridine	THF	93	15:85
7	Pyridine	CH_2Cl_2	98	8:92[d]
8	Pyridine	CH_3CN[c]	96	22:78

[a] D.e.s were determined by ^{1}H NMR at 500 MHz.
[b] (R_C,S_S)-**6** was purified by crystallisation from Et_2O:CH_2Cl_2:hexane (4:1:1).
[c] Reaction carried out at −20°C.
[d] (R_C,R_S)-**6** was purified by column chromatography.



Scheme 3. (i) (1) Me_3Al/THF/t.a.; (2) RMgX, −78°C.

The configuration at sulphur for sulphinates **6** was assigned taking into account that the use of $^{i}Pr_2EtN$ as the base in the condensation of DAG with any kind of sulphinyl chloride always gives the sulphinate with *S* configuration at sulphur in higher proportion, irrespective of the solvent used.[11] In contrast, when Py is used as base, the major isomer obtained always has (R_S) configuration. For sulphoxides **7a** and **7b**, configuration at sulphur was assigned assuming total inversion of the configuration as is always observed using this Andersen-type synthesis of sulphoxides.[11]

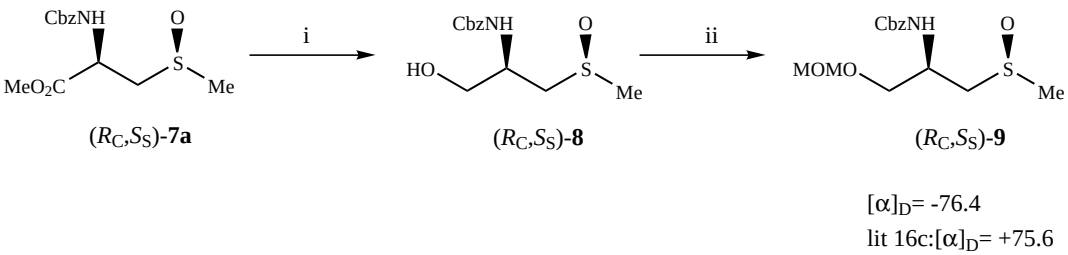
Additionally, the absolute configuration for sulphoxide (R_C,S_S)-**7a** was confirmed by chemical correlation with the chiral fragment of the antibiotic (*S*)-Sparsomycin,[16] as shown in Scheme 4. In this way, (R_C,S_S)-**7a** was treated with $LiBH_4$ and the free hydroxy group protected as MOM derivative to yield (R_C,S_S)-**9** in 70% overall yield. The enantiomer of this compound has been described in the literature in the context of Sparsomycin synthesis,[16c] being its melting point, ^1H and ^{13}C NMR spectra and absolute specific rotation essentially identical to those of **9**. The preparation of **9** can be considered as a formal synthesis of (*R*)-Sparsomycin.[12]

In order to prepare *S*-methyl-L-cysteine sulphoxide **1**, we attempted hydrolysis of the ester groups present in **7a** using different experimental conditions with any success. Unfortunately we were unable to isolate any identifiable reaction product.

3. Experimental

Melting points were determined in open capillary tubes on a Gallenkamp apparatus and are uncorrected. ^1H NMR spectra were registered on a Bruker AC-200 (200 MHz) or AMX-500 (500 MHz) and ^{13}C NMR on AC-200 (50.3 MHz) or AMX-500 (125.72 MHz). All spectra were obtained using $CDCl_3$ as solvent and TMS as internal standard. Chemical shifts are reported in ppm, and coupling constants in Hz. Optical rotations were taken on a Perkin–Elmer 241-MC polarimeter in a 1 dm tube; concentrations are given in g/100 mL. High resolutions mass measurements were performed on a Kratos MS-80-RFA spectrometer. HPLC analysis was carried out on a Waters, Millipore 600A model using a Chiral OD (Diacel) column or a reverse-phase column Lichrocart C-18. Routine monitoring of reactions was performed using Merck 60 F 254 silica gel, aluminium supported TLC plates. For flash chromatography,[17] silica gel 60 (230–400 mesh ASTM, Merck) was used.

Flasks, stirrings bars, and hypodermic needles used for the generation of organometallic compounds were dried for ca. 12 h at 120°C and allowed to cool in a dessicator over anhydrous calcium sulphate. Anhydrous solvents



Scheme 4. (i) $LiBH_4$/DME, 82%; (ii) ClMOM/*n*-BuLi/THF, 86%.

(ethers) were obtained by distillation from benzophenone ketyl.[18]

3.1. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranosyl) (R_C,S_S)-2-[(benzyloxycarbonyl)amino]-2-methoxycarbonyl ethanesulphinate (R_C,S_S)-6

To a solution of DAG (2.603 g, 10 mmol) in dry toluene (30 mL) at −78°C was added *iso*-Pr_2EtN (2.15 mL, 13 mmol) and the mixture was stirred for 0.5 h at this temperature and a solution of freshly prepared *N*-(benzyloxycarbonyl)-L-cysteine-*S*-chloro-*S*-oxo methyl ester **5** (5.436 g, 17 mmol) in dry toluene (25 mL) was added dropwise. After stirring for 0.5 h. the reaction was quenched with water (10 mL) and extracted with dichloromethane (4×50 mL). The organic phases were washed with 10% HCl solution (20 mL), saturated aqueous Na_2CO_3 solution (20 mL), brine (20 mL) and dried over sodium sulphate. Concentration under reduced pressure gave an orange residue (5.327 g, 98% yield) which was crystallised (ether–dichloromethane–hexane 4:1:1) to obtain (R_C,S_S)-**6** (4.077 g, 75%) as a white solid; mp 130–131°C; $[\alpha]_D$ = +2.8 (*c* 2, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (m, 5H, C_6H_5), 5.95 (d, J = 3.4 Hz, 1H, sugar H_1), 5.86 (d, J = 7.4 Hz, 1H, NH), 5.13 (s, 2H, CH_2Ph), 4.76 (d, J = 2.6 Hz, 1H, sugar H_3), 4.49 (m, portion X of an ABX system, 1H, $CHCO_2Me$), 4.70 (d, J = 3.4 Hz, 1H, sugar H_2), 4.25 (m, 2H, sugar H_4 and H_5), 4.05 (dd, J = 8.5 Hz, J = 5.9 Hz, 1H, sugar H_6), 4.0 (dd, J = 8.5 Hz, J = 4.7 Hz, 1H, sugar H6), 3.81 (s, 3H, CH_3O), 3.48 (portion A of an ABX system, J_{AB} = 13.9 Hz, J_{BX} = 4.2 Hz, 1H, CH_2S), 3.25 (portion B of an ABX system, J_{AB} = 13.9 Hz, J_{AX} = 7.6 Hz, 1H, CH_2S), 1.52 (s, 3H, CH_3CO), 1.43 (s, 3H, CH_3CO), 1.33 (s, 3H, CH_3CO), 1.32 (s, 3H, CH_3CO); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 155.6, 135.7, 128.5, 128.3, 128.1, 112.3, 109.3, 105.0, 83.1, 80.2, 79.7, 72.1, 67.3, 66.8, 59.0, 53.1, 49.0, 26.7, 26.6, 26.1, 25.0. Anal. calcd for $C_{24}H_{33}NO_{11}S$: C, 53.01; H, 6.12; N, 2.57. Found: C, 53.04; H, 6.12; N, 2.56%.

3.2. (1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranosyl) (R_C,R_S)-2-[(benzyloxycarbonyl)amino]-2-methoxycarbonyl ethanesulphinate (R_C,R_S)-6

To a solution of DAG (1.7 g, 6.53 mmol) in dry methylene chloride (15 mL) at −78°C was added pyridine (0.6 mL, 8.49 mmol) and the mixture was stirred for 0.5 h at this temperature and a solution of freshly prepared *N*-(benzyloxycarbonyl)-L-cysteine-*S*-chloro-*S*-oxo methyl ester **5** (3.55 g, 11.10 mmol) in dry methylene chloride (25 mL) was added dropwise. After stirring for 0.5 h. the reaction was quenched with water (10 mL) and extracted with dichloromethane (4×50 mL). The organic phases were washed with 10% HCl solution (20 mL), saturated aqueous Na_2CO_3 solution (20 mL), brine (20 mL) and dried over sodium sulphate. Concentration under reduced pressure gave an orange residue (3.48 g, 98% yield) which was purified by column chromatography (ether–hexane 3:2) to obtain (R_C,R_S)-**6** as an oil (3.301 g, 93%); $[\alpha]_D$ = −41 (*c* 6.7, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (m, 5H, C_6H_5), 6.05 (d, J = 8.0 Hz, 1H, NH), 5.90 (d, J = 3.5 Hz, 1H, sugar H_1), 5.14 (AB system, 2H, CH_2Ph), 4.82 (m, portion X of an ABX system, 1H, $CHCO_2Me$), 4.76 (d, J = 3.5 Hz, 1H, sugar H_2), 4.70 (s, 1H, sugar H_3), 4.14 (m, 2H, sugar H_4 and H_5), 4.10 (dd, J = 8.7 Hz, J = 3.2 Hz, 1H, sugar H_6), 4.0 (dd, J = 8.7 Hz, J = 2.0 Hz, 1H, sugar H6), 3.80 (s, 3H, CH_3O), 3.49 (portion A of an ABX system, J_{AB} = 13.9 Hz, J_{BX} = 6.3 Hz, 1H, CH_2S), 3.38 (portion B of an ABX system, J_{AB} = 13.9 Hz, J_{AX} = 5.0 Hz, 1H, CH_2S), 1.50 (s, 3H, CH_3CO), 1.37 (s, 3H, CH_3CO), 1.31 (s, 3H, CH_3CO), 1.30 (s, 3H, CH_3CO); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 155.6, 135.8, 128.5, 128.2, 128.1, 112.4, 109.5, 105.2, 83.8, 83.7, 80.7, 72.0, 67.6, 67.3, 58.3, 53.0, 49.3, 26.7, 26.6, 26.1, 24.9. Anal. calcd for $C_{24}H_{33}NO_{11}S$: C, 53.01; H, 6.12; N, 2.57. Found: C, 53.14; H, 6.21; N, 2.44%.

3.3. General procedure for the preparation of alkyl L-cysteine sulphoxides

To a solution of sulphinate **6** (1 mmol) in dry THF (15 mL) was added a solution of $AlMe_3$ (2 M, 1.2 mmol) in hexanes and the mixture was stirred at rt for 1 h. The reaction mixture was cooled at −78°C and a freshly prepared solution of the corresponding Grignard reagent (3 mmol) in diethyl ether (5 mL) was added dropwise and the stirring continued for 1.5 h. Then aqueous H_2SO_4 (1 N, 25 mL) was added and the reaction mixture was extracted with methylene chloride (3×25 mL). The combined organic layers were washed with a saturated $NaHCO_3$ aqueous solution (25 mL) and brine (25 mL) and dried over sodium sulphate. Concentration under reduced pressure and purification by flash chromatography gave the corresponding sulphoxide.

3.3.1. (R_C,R_S)-*N*-(Benzyloxycarbonyl)-*S*-methyl-*S*-oxo-L-cysteine methyl ester (R_C,R_S)-7a. The general procedure was followed for the alkylation of sulphinate (R_C,S_S)-**6** (2.0 g, 3.68 mmol) with a freshly prepared solution of methyl magnesium bromide (11 mmol). Column chromatography (ethyl acetate:methanol 4:1) of the reaction mixture gave *N*-(benzyloxycarbonyl)-(*R*)-*S*-methyl-*S*-oxo-L-cysteine methyl ester (R_C,R_S)-**7a** as a white solid (717 mg, 65%); mp 149–150°C; $[\alpha]_D$ = +196 (*c* 2.1, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (s, 5H, C_6H_5), 6.36 (br, 1H, NH), 5.08 (s, 2H, CH_2O), 4.70 (m, 1H, CH), 3.73 (s, 3H, CH_3O), 3.15 (m, 2H, CH_2S), 2.57 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 155.9, 135.9, 128.4, 128.1, 128.0, 67.1, 55.8, 52.9, 50.3, 39.1. HRMS calcd m/z for $C_{13}H_{17}NO_5S$: 299.0827. Found: 299.0832. Anal. calcd for $C_{13}H_{17}NO_5S$: C, 52.17; H, 5.72; N, 4.68. Found: C, 52.35; H, 5.79; N, 4.43%.

3.3.2. (R_C,S_S)-*N*-(Benzyolycarbonyl)-*S*-methyl-*S*-oxo-L-cysteine methyl ester (R_C,S_S)-7a. The general procedure was followed for the alkylation of sulphinate (R_C,R_S)-**6** (1.4 g, 2.57 mmol) with a freshly prepared solution of methyl magnesium bromide (7.72 mmol). Purification of the mixture by flash chromatography (AcOEt–methanol 4:1), afforded *N*-(benzyloxycarbonyl)-(*S*)-*S*-methyl-*S*-oxo-L-cysteine methyl ester (R_C,S_S)-**7a** (485

mg, 63%) as a white solid; mp 86–88°C; $[\alpha]_D = +10.3$ (*c* 2.7, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (s, 5H, C_6H_5), 6.26 (br, 1H, NH), 5.07 (s, 2H, CH_2O), 4.66 (m, 1H, CH), 3.73 (s, 3H, CH_3O), 3.24 (m, 2H, CH_2S), 2.57 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 155.7, 135.9, 128.4, 128.2, 128.0, 67.1, 55.8, 53.0, 49.9, 38.8. HRMS calcd *m*/*z* for $C_{13}H_{17}NO_5S$: 299.0827. Found: 299.0873. Anal. calcd for $C_{13}H_{17}NO_5S$: C, 52.17; H, 5.72; N, 4.68. Found: C, 51.91; H, 5.74; N, 4.45%.

3.3.3. (R_C,R_S)-*N*-(Benzyloxycarbonyl)-*S*-oxo-*S*-propyl-L-cysteine methyl ester (R_C,R_S)-7b. The reaction of sulphinate (R_C,S_S)-**6** (0.5 g, 0.92 mmol) with a solution of *n*-propyl magnesium chloride (2.76 mmol) following the general procedure gave, after purification by column chromatography (AcOEt–methanol 20:1), *N*-(benzyloxycarbonyl)-(*R*)-*S*-oxo-*S*-propyl-L-cysteine methyl ester (R_C,R_S)-**7b** as a white solid (187 mg, 62%); mp 96–97°C; $[\alpha]_D = -27$ (*c* 1.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (s, 5H, C_6H_5), 6.20 (br, 1H, NH), 5.12 (s, 2H, CH_2O), 4.79 (m, 1H, CH), 3.78 (s, 3H, CH_3O), 3.20 (m, 2H, CH_2), 2.73 (m, 2H, $SOCH_2$), 1.82 (m, 2H, CH_2), 1.07 (t, $J = 7.3$ Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 155.9, 136.0, 128.3, 128.0, 127.9 67.2, 54.7, 53.8. 52.5, 50.4, 16.1, 13.2. HRMS calcd *m*/*z* for $C_{15}H_{21}NO_5S$: 327.1151. Found: 327.1140. Anal. calcd for $C_{15}H_{21}NO_5S$: C, 55.03; H, 6.47; N, 4.28. Found: C, 54.98; H, 6.67; N, 4.18%.

3.3.4. (R_C,S_S)-*N*-(Benzyloxycarbonyl)-*S*-oxo-*S*-propyl-L-cysteine methyl ester (R_C,S_S)-7b. The general procedure was followed for the alkylation of sulphinate (R_C,R_S)-**6** (0.5 g, 0.92 mmol) with a solution of propyl magnesium chloride (2.76 mmol). Purification of the reaction mixture by flash chromatography (AcOEt–methanol 20:1), gave *N*-(benzyloxycarbonyl)-(*R*)-*S*-oxo-*S*-propyl-L-cysteine methyl ester (R_C,S_S)-**7b** (202 mg, 67%) as a white solid; mp 124–125°C; $[\alpha]_D = +36$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (s, 5H, C_6H_5), 6.03 (br, 1H, NH), 5.10 (s, 2H, CH_2O), 4.69 (m, 1H, CH), 3.76 (s, 3H, CH_3O), 3.20 (m, 2H, CH_2), 2.27 (m, 2H, $SOCH_2$), 1.72 (m, 2H, CH_2), 1.11 (t, $J = 7.3$ Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 155.7, 135.9, 128.5, 128.2, 128.0, 67.2, 54.7, 53.8, 53.1, 50.1, 16.2, 13.5. HRMS calcd *m*/*z* for $C_{15}H_{21}NO_5S$: 327.1151. Found: 327.1129. Anal. calcd for $C_{15}H_{21}NO_5S$: C, 55.25; H, 6.61; N, 4.06. Found: C, 54.98; H, 6.67; N, 4.18%.

3.4. (R_C,S_S)-*N*-(Benzyloxycarbonyl)-(*S*)-*S*-methyl-*S*-oxo-L-cysteinol (R_C,S_S)-8

To a solution of *N*-(benzyloxycarbonyl)-(*S*)-*S*-methyl-*S*-oxo-L-cysteine methyl ester (R_C,S_S)-**7a** (233 mg, 0.78 mmol) in dimethoxyethane (15 mL) cooled at 0°C was added dropwise a solution of $LiBH_4$ in THF (2 M, 2.32 mL, 1.16 mmol) and the resulting mixture was stirred for 1 at rt. Aqueous H_2SO_4 (3 N, 5 mL) was added and the reaction mixture was stirred for 10 min. and extracted with ether (4×50 mL). The organic extracts were washed with a saturated aqueous solution of NaCl (25 mL) and concentrated under reduced pressure. Column chromatography (ethyl acetate:methanol 4:1) of the reaction crude afforded *N*-(benzyloxycarbonyl)-(*R*)-*S*-methyl-*S*-oxo-L-cysteinol (R_C,R_S)-**8** as a white solid (174 mg, 82%), mp 129–130°C; $[\alpha]_D = +66$ (*c* 2.12, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (s, 5H, C_6H_5), 5.79 (br, 1H, NH), 5.07 (s, 2H, CH_2O), 4.12 (m, 1H, CH), 3.81 (m, 2H, CH_2OH), 3.28 (br, 1H, OH), 3.00 (m, 2H, CH_2S), 2.60 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.0, 136.1, 128.5, 128.2, 128.1 67.0, 63.6, 55.4, 50.0, 39.0. HRMS calcd *m*/*z* for $C_{12}H_{17}NO_4S$: 271.0878. Found: 271.0834. Anal. calcd for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.31; N, 5.16. Found: C, 52.94; H, 6.29; N, 4.93%.

3.5. (R_C,S_S)-*N*-(Benzyloxycarbonyl)-*O*-methoxymethyl-*S*-methyl-*S*-oxo-L-cysteinol (R_C,S_S)-9

To a solution of *N*-(benzyloxycarbonyl)-*S*-methyl-*S*-oxo-L-cysteinol (R_C,S_S)-**8** (80 mg, 0.295 mmol) in dry THF (20 mL) cooled at 0°C, was added dropwise a solution of *n*-BuLi in hexanes (1.4 M, 630 μL, 0.88 mmol) and methoxymethyl chloride (340 μL, 0.44 mmol) and the reaction mixture was allowed to warm to rt. After 3 days the reaction was quenched with a saturated aqueous solution of NH_4Cl (15 mL), extracted with dichloromethane (4×25 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (AcOEt–MeOH 95%) to afford *N*-(benzyolycarbonyl)-*O*-methoxymethyl-(*S*)-*S*-methyl-*S*-oxo-L-cysteinol (R_C,S_S)-**9**. (80 mg, 86% yield) as a white solid, mp 112–113°C; $[\alpha]_D = -76.4$ (*c* 1.1, acetone); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (s, 5H, C_6H_5), 5.77 (br, 1H, NH), 5.11 (s, 2H, CH_2O), 4.64 (s, 2H, OCH_2O), 4.34 (m, 1H, CH), 3.77 (m, 2H, CH_2O), 3.35 (s, 3H, CH_3O), 3.04 (d, $J = 6.1$ Hz, 2H, CH_2S), 2.64 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.7, 136.2, 128.5, 128.5 128.1, 96.8, 68.4, 66.9, 56.1, 55.6 47.9, 39.4. HRMS calcd *m*/*z* for $C_{14}H_{21}NO_5S$: 315.1664. Found: 315.1654. Anal. calcd for $C_{14}H_{21}NO_5S$: C, 53.31; H, 6.71; N, 4.44. Found: C, 53.36; H, 6.73; N, 4.41%.

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