Asymmetric Syntheses via Heterocyclic Intermediates; XVII[1]. Enantioselective Synthesis of (*R*)-α-Methyl-*S*-benzylcysteine Methyl Ester and (*R*)-α-Methyl-*S*-*t*-butylcysteine Methyl Ester using L-Valine as Chiral Auxiliary Reagent

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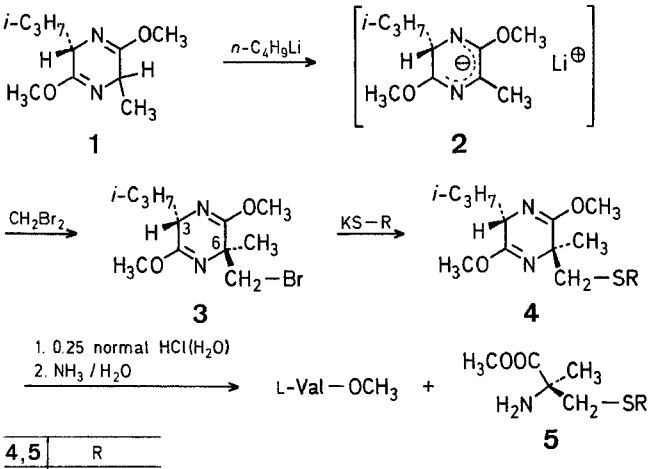
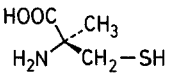
Optically pure (*R*)-α-methylcysteine **(6)** deserves attention as a potential enzyme inhibitor. We describe here a method for the synthesis of (*R*)-α-methyl-*S*-benzylcysteine methyl ester **(5a)** and (*R*)-α-methyl-*S*-*t*-butylcysteine methyl ester **(5b)**, suitable precursors of **6**[2], in practically optically pure form.

The lithio derivative **2** of the bis-lactim ether **1**[3] obtained from cyclo(L-Val-Ala) reacts with dibromomethane to give the bromomethyl compound **3** in satisfactory chemical yield (~80%) and with a d.e. (diastereoisomeric excess = asymmetric induction) of >95% (only one diastereomer is detectable in the ^{13}C-N.M.R. spectrum). As was proved in analogous cases[3] the alkylating agent enters *trans* to the isopropyl group at C-3, i.e. the (6*R*)-configuration is induced [with D-valine as chiral auxiliary reagent, the (6*S*)-diastereomer would be formed]. With potassium benzylmercaptide and potassium *t*-butylmercaptide the *S*-alkyl compounds **4** are formed[a] which on hydrolysis (0.25 normal hydrochloric acid, r.t., 5–12 d) are hydrolyzed to L-Val-OCH_3 and the (*R*)-α-methyl-*S*-alkylcysteine methyl esters **5**. The esters can be separated by distillation. With $Eu(hfc)_3$, only one enantiomer of **5** is detectable in the ^{1}H-N.M.R.-spectrum (i.e., e.e. > 95%).



1 **2** **3** **4** **5**

4,5	R
a	$-CH_2-C_6H_5$
b	*t*-C_4H_9



6

Recently, we reported on the enantioselective synthesis of (*R*)-α-methylserine[4] (OH instead of SH in **6**) starting from **2** and chloromethyl benzyl ether. Possibly, compounds **4a, b** can be alternatively obtained from **2** and benzyl chloromethyl sulfide or *t*-butyl chloromethyl sulfide.

Bis-lactim ether **1** is obtained from L-valine according to Ref.[3].

(3*S*,6*R*)-6-Bromomethyl-3-isopropyl-2,5-dimethoxy-6-methyl-3,6-dihydropyrazine (3):

To a stirred solution of the bis-lactim ether **1** (2.77 g, 14 mmol) in tetrahydrofuran (25 ml) at −70 °C, a 1.8 normal solution (8.3 ml, 15 mmol) of butyllithium in hexane is added by syringe and stirring is continued for 15 min. Then, a precooled solution of dibromomethane (26.1 g, 0.15 mol) in tetrahydrofuran (15 ml) is added and stirring is continued for 30 h at −70 °C. The cooling bath is removed, the solvent evaporated in vacuo, and the residue dissolved in ether (30–40 ml). The ether solution is shaken with water (30–40 ml), the water layer is extracted with ether (3 × 20 ml), and the combined ether phases are dried with magnesium sulfate. The solvent is evaporated in vacuo and

[a] Since the bromo derivative **3** is a halide of the neopentyl type, only highly reactive nucleophiles undergo the substitution reaction. Our experiments to displace the Br-atom using triphenylphosphine or sodium diethyl phosphite failed.

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the residual crude product purified by bulb-to-bulb distillation; yield: 3.2 g (79%); b.p. 70–80 °C/0.1 torr.

$C_{11}H_{19}BrN_2O_2$	calc.	C 45.37	H 6.58
(291.2)	found	45.44	6.56

M.S. (70 eV): $m/e = 292.290$ (M^+, 10%).

I.R. (film): $\nu = 1700$ cm^{-1} (C=N).

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): $\delta = 0.73$, 1.13 [2d, 6H, $J = 7$ Hz, $CH(CH_3)_2$]; 1.50 (s, 3H, 6-CH_3); 2.34 (d sept, 1H, $J = 3$ and 7 Hz; $CH(CH_3)_2$]; 3.42, 3.80 (AB-signal, 2H, $J_{AB} = 9$ Hz, CH_2); 3.72, 3.75 (2s, 6H, OCH_3); 4.06 ppm (d, 1H, $J = 3$ Hz, 3-H).

^{13}C-N.M.R. ($CDCl_3$/TMS_{int}): $\delta = 16.82$, 19.37 [$CH(CH_3)_2$]; 26.59 (6-CH_3); 30.86 [$CH(CH_3)_2$]; 43.02 (CH_2Br); 52.46, 52.52 (OCH_3); 58.89 (C-3); 61.27 (C-6); 162.46, 163.82 ppm (C=N).

(3*S*,6*R*)-6-Alkylthiomethyl-3-isopropyl-2,5-dimethoxy-6-methyl-3,6-dihydropyrazines (4a, b):

To a stirred solution of the alkylmercaptan (3.5 mmol: 0.44 g of benzylmercaptan, 0.32 g of *t*-butylmercaptan) in dimethyl sulfoxide (10 ml), potassium *t*-butoxide (0.37 g, 3.3 mmol) is added and stirring is continued for 5 min. Then, a solution of compound **3** (0.87 g, 3 mmol) in dimethyl sulfoxide (2 ml) is added and stirring is continued for 5 h at 70 °C. The solution is mixed with petroleum ether (30 ml) and shaken with water (10 ml), the water layer is extracted with petroleum ether (3 × 20 ml), and the combined organic phases are dried with magnesium sulfate. The solvent is removed and the residual product **4** bulb-to-bulb distilled in vacuo.

6-Benzylthiomethyl Derivative **4a**; yield: 88%; b.p. 100–110 °C (bath)/0.1 torr; d.e. > 95%.

$C_{18}H_{26}N_2O_2S$	calc.	C 64.64	H 7.84
(334.5)	found	64.49	7.77

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): $\delta = 0.76$, 1.17 (2d); 1.44 (s); 2.38 (d sept); 2.72, 2.98 (AB signal); 3.70, 3.76 (2s); 3.73, 3.75 (2s); 4.15 (d); 7.28–7.37 ppm (m).

6-t-Butylthiomethyl Derivative **4b**; yield: 93%; b.p. 80–90 °C (bath)/0.1 torr; d.e. > 95%.

$C_{15}H_{28}N_2O_2S$	calc.	C 59.96	H 9.39
(300.5)	found	60.38	9.42

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): $\delta = 0.72$, 1.13 (2d); 1.32 (s); 1.48 (s); 2.32 (d sept); 2.81, 3.01 (AB signal); 3.71 (s); 4.05 ppm (d).

(*R*)-*S*-Alkyl-α-methylcysteine Methyl Esters (5a, b):

A suspension of compound **4a** (0.84 g, 2.5 mmol) or **4b** (0.75 g, 2.5 mmol) in 0.25 normal hydrochloric acid (20 ml, 5 mmol) is stirred at room temperature for 12 days **(4a)** or 5 days **(4b)**. The solution is extracted with ether (5 ml) to remove unreacted **4** and is then evaporated to dryness. The residue (**5** · HCl and L-Val-OCH_3 · HCl) is dissolved in the minimum amount of water, ether (20 ml) is added, and concentrated aqueous ammonia is added with shaking to adjust the mixture to pH 8–10. The ether layer is separated and the aqueous layer extracted with ether (3 × 10 ml). The combined ether layers are dried with magnesium sulfate, the solvent is evaporated in vacuo, and the residue is bulb-to-bulb distilled whereby L-Val-OCH_3 is obtained as the forerun.

(R)-S-*Benzyl-α-methylcysteine Methyl Ester* **(5a)**; yield: 0.38 g (64%); b.p. 100–110 °C (bath)/0.1 torr; $[\alpha]_D^{20}$: −32.7° (*c* 1.1, ethanol); e.e. > 95%.

$C_{12}H_{17}NO_2S$	calc.	C 60.22	H 7.16
(239.3)	found	60.38	7.33

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): $\delta = 1.37$ (s); 1.81 (s); 2.62, 2.95 (AB signal); 3.73 (s); 3.76 (s); 7.31–7.36 ppm (m).

(R)-S-t-*Butyl-α-methylcysteine Methyl Ester* **(5b)**; yield: 0.37 g (72%); b.p. 60–70 °C (bath)/0.1 torr; $[\alpha]_D^{20}$: −16.3° (*c* 1.0, ethanol); e.e. > 95%.

$C_9H_{19}NO_2S$	calc.	C 52.65	H 9.33
(205.3)	found	52.75	9.45

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): $\delta = 1.35$ (s); 1.45 (s); 2.19 (s); 2.74, 3.02 (AB signal); 3.75 ppm (s).

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