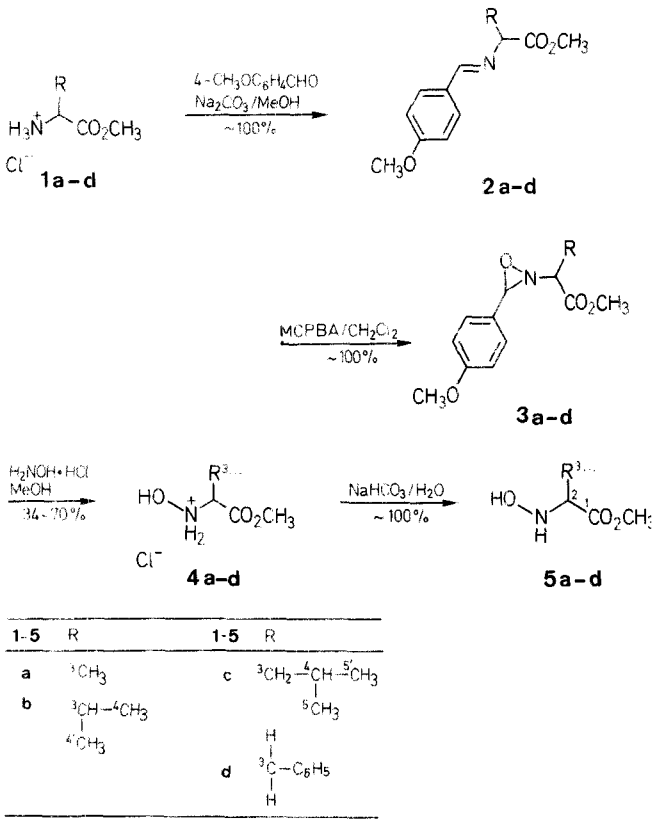

1–5	R	1–5	R
a	$^3CH_3$	c	$^3CH_2-{}^4CH(-{}^5CH_3)$
b	$^3CH(-{}^4CH_3)$	d	$^3C(H)-C_6H_5$

Optically Active *N*-Hydroxy-α-L-Amino Acid Methyl Esters: An Improved and Simplified Synthesis

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The preparation of optically active *N*-hydroxy-α-L-amino acid methyl esters from α-L-amino acid methyl esters is described. Readily available starting materials are used and the yields are good.

The availability of optically active *N*-hydroxyamino acids is of particular importance for the synthesis of *N*-hydroxypeptides which until now have almost exclusively been prepared from racemic *N*-hydroxyamino acids.[1]

We needed free *N*-hydroxy-α-L-amino acid esters for the reaction with α-(*tert*-butoxycarbonylamino)aldehydes[2] resulting in N^{α}-(*tert*-butoxycarbonyl) "nitrono" dipeptide esters.[3]

A synthesis which leads to the salts of *N*-hydroxy-α-L-amino acid esters has been described.[4] However, the yields based on the α-L-amino acid ester hydrochlorides used as starting material were relatively low. We now describe an improved synthesis of optically active *N*-hydroxy-α-L-amino acid methyl esters which uses readily available starting materials and affords good yields.

The schiff bases **2** are obtained in nearly quantitative yield by reaction of the α-L-amino acid methyl ester hydrochlorides **1** with 4-methoxybenzaldehyde in absolute methanol in the presence of dry sodium carbonate. The yield decreases to 60% when dichloromethane is used as solvent. Dry sodium carbonate as base and water-binding agent is advantageous because it is simply filtered off at the end of the reaction. The schiff base **2** is oxidized with 85% *m*-chloroperbenzoic acid (MCPBA) in dichloromethane at −15°C to give the oxaziridine **3** as a mixture of diastereoisomeres, both having the two substituents on the oxaziridine ring in a *cis* configuration. Cleavage of the oxaziridine C–O bond is carried out to give the *N*-hydroxy-α-L-amino acid methyl ester hydrochlorides **4** is achieved with the available hydroxylamine hydrochloride in methanol (use of hydroxylamine *p*-toluenesulfonate as described in the literature neither results in higher yields nor in better crystallizing salts). The *N*-hydroxy-α-L-amino acid methyl ester hydrochlorides **4** are treated with saturated sodium hydrogen carbonate solution to afford the *N*-hydroxy-α-L-amino acid methylesters **5** in 34–70% yields based on the α-L-amino acid methylester hydrochlorides **1**.

Table 1. *N*-Hydroxy-α-L-amino Acid Methyl Esters **5** prepared

Product	Yield (%)	m.p. (°C)	R_f (Et_2O)	$[\alpha]_D^{20}$ (solvent)	Molecular Formula[a] or m.p. (°C) reported	^{1}H-NMR (solvent/TMS) δ, *J* (Hz)
5a	42	16–17	0.5	−26.8° (*c* = 3, CH_2Cl_2)	$C_4H_9NO_3$ (119.1)	($CDCl_3$): 1.28 (d, 3H, $^3CH_3$, $J_{3,2}$ = 7); 3.69–3.83 (m, 4H, OCH_3 and ^2CH); 5.0–7.5 (br., 2H, NH and OH)
5b	60	63–64	0.76	−15.5° (*c* = 1, CH_2Cl_2)	$C_6H_{13}NO_3$ (147.2)	(DMSO-d_6): 0.83 (d, 3H, $^4CH_3$, $J_{4,3}$ = 7); 0.93 (d, 3H, $^4CH_3$, $J_{4',3}$ = 7); 1.66–1.84 (m, 1H, $^3CH_3$); 3.18 (dd, 1H, ^2CH, $J_{2,3}$ = 7.5, $J_{2,NH}$ = 10.5); 3.64 (s, 3H, OCH_3); 5.70 (dd, 1H, NH, $J_{NH,2}$ = 10.5, $J_{NH,OH}$ = 3); 7.53 (d, 1H, OH, $J_{OH,NH}$ = 3)
5c	70	32–33	0.75	−14.0° (*c* = 1, CH_2Cl_2)	$C_7H_{15}NO_3$ (161.2)	(DMSO-d_6): 0.88 (d, 3H, $^5CH_3$, $J_{5,4}$ = 7); 0.89 (d, 3H, $^5CH_3$, $J_{5',4}$ = 7); 1.27–1.36 (m, 2H, $^3CH_2$); 1.53–1.71 (m, 1H, ^4CH); 3.39–3.53 (m, 1H, ^2CH); 3.64 (s, 3H, OCH_3); 5.70 (br., 1H, NH); 5.72 (s, 1H, OH)
5d	34	68–69	0.71	+18.3°[b] (*c* = 2, C_6H_6)	63[4]	($CDCl_3$): 2.88 (dd, 1H, $^3CH^a$, $J_{3a,3b}$ = 13.5, $J_{3a,2}$ = 9); 3.01 (dd, 1H, $^3CH^b$, $J_{3b,3a}$ = 13.5, $J_{3b,2}$ = 6); 3.73 (s, 3H, OCH_3); 3.88 (dd, 1H, ^2CH, $J_{2,3a}$ = 9, $J_{2,3b}$ = 6); 4.90–6.10 (br., 2H, NH and OH); 7.31–7.36 (m, $5H_{arom}$)

[a] Satisfactory microanalyses obtained: C ±0.34, H ±0.31, N ±0.13. [b] Lit.[4] $[\alpha]_D^{20}$ +16.5 (*c* = 1, C_6H_6).

Table 2. Specific Rotations of α-L-Amino Acid Methyl Ester Hydrochlorides Obtained by Reduction of Compounds **5**

Starting Compound **1** (Fluka)	Reduction Product Obtained from **5**	Lit. Value
a + 7.5° ± 0.5° (*c* = 10, MeOH)	+ 7.3° (*c* = 10, MeOH)	+ 6.5° (MeOH)[5]
b + 23.0° ± 1.0° (*c* = 2, MeOH)	+ 23.6° (*c* = 2, MeOH)	
c + 20.0° ± 1.0° (*c* = 4.5, MeOH)	+ 19.6° (*c* = 4.5, MeOH)	
d + 38.0° ± 1.0° (*c* = 2, EtOH)	+ 37.5° (*c* = 2, EtOH)	+ 37° (EtOH)[6]

To establish the stereochemical identity of the *N*-hydroxy-α-L-amino acid methyl esters **5** these compounds were reduced with zinc powder in 2 normal hydrochloric acid; the specific rotations of the resultant α-L-amino acid methyl ester hydrochlorides **1** were in good agreement with those of the commercial starting compounds and with literature values.

Thin-layer chromatography was carried out on Riedel-de Haen DC-Micro-Cards SiF (254 nm). Melting points were determined on a Büchi apparatus according to Dr. Tottoli and are uncorrected. Microanalyses were performed using a Carlo Erba Mod. 1106 Element Analyser. Optical rotations were obtained using a Perkin Elmer 241 polarimeter in 10 cm cell. ^{1}H-NMR spectra were recorded on a Bruker WH 270 MHz spectrometer.

MCPBA (85%) and hydroxylamine hydrochloride (99%) were purchased from Fluka AG.

N-Hydroxy-α-L-amino Acid Methyl Esters (5); General Procedure:

To a solution of the α-L-amino acid methyl ester hydrochloride (**1**; 0.1 mol) in MeOH (120 mL) is added 4-methoxybenzaldehyde (13.6 g, 0.1 mol) and dry Na_2CO_3 (16.2 g, 0.15 mol). The mixture is stirred for 12 h at room temperature, filtered, and evaporated. The residue is dissolved in Et_2O (80 mL) and this solution is filtered and evaporated to give the schiff base **2**; yield: ~ 100%.

The schiff base (80 mmol) is dissolved in dry CH_2Cl_2 (60 mL), this solution is cooled to −15 °C, and a solution of 3-chloroperoxybenzoic acid (MCPBA, 85%; 16.24 g, 80 mmol) in dry CH_2Cl_2 (200 mL) is added dropwise. Stirring is continued for 14 h at room temperature. The precipitated 3-chlorobenzoic acid is filtered off and the filtrate is washed with saturated $NaHCO_3$ solution (80 mL) and with water (80 mL), dried ($MgSO_4$), and evaporated to give the crude oxaziridine **3**; yield: ~ 100%.

The oxaziridine (80 mmol) is dissolved in MeOH (100 mL), hydroxylamine hydrochloride (5.56 g, 80 mmol) is added, and the mixture is stirred for 12 h at room temperature. The solvent is then evaporated, water (75 mL) is added, and the oily 4-methoxybenzaldoxime is filtered off. The filtrate is extracted with Et_2O (2 × 100 mL), this Et_2O extract being discarded. The aqueous phase is saturated with $NaHCO_3$ (*Caution:* vigorous foam evolution) and the free *N*-hydroxyamino acid methyl ester is extracted with Et_2O (3 × 100 mL). The organic layer is dried ($MgSO_4$) and the product is isolated by evaporation.

N-Hydroxy-L-alanine methyl ester **(5a)** is soluble in water. For isolation of **5a**, the water phase is evaporated in vacuum and the residue is taken up in CH_2Cl_2 (50 mL). This solution is dried ($MgSO_4$) and evaporated.

Reduction of the N-Hydroxy-α-L-amino Acid Methyl Esters (5); General Procedure:

The *N*-hydroxy-α-L-amino acid methyl ester (**5**; 2 mmol) is dissolved in 2 N aqueous HCl (10 mL), and zinc powder (2 g, 30 mmol) is added. Reduction is complete within 4–8 h (TLC). Excess zinc powder is filtered off and the solution made alkaline to pH ≃ 11. The α-L-amino acid methyl ester is extracted with EtOAc (3 × 30 mL). The organic extract is dried ($MgSO_4$) and the solvent is removed. The residue is dissolved in 3 N HCl in MeOH (2 mL) and the amino acid methyl ester hydrochloride is precipitated by the addition of ether. The product is isolated by suction and the specific rotation is measured.

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