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Interconversion of (*R*) and (*S*)-α-hydroxy esters: precursors of (*S*) and (*R*)-O-benzyl-α-hydroxylamino acid esters of high optical purity.

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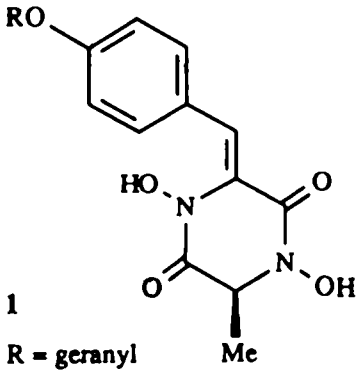
Summary: (*R*)- and (*S*)-α-hydroxy esters **5** are interconverted *via* their triflates **6** in high chemical as well as optical yields by reaction with dimethylformamide. The same triflates are efficiently converted into N-hydroxy-α-amino acid derivatives **7** of high optical purity.

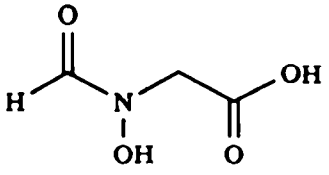
Introduction

N-hydroxy-α-amino acid derivatives have been found ubiquitously in nature as metabolites in primitive organisms, plants and even in man. For example, mycellanamide **1** has been isolated from *Penicillium griseofulvum*[1]. In this molecule derivatives of N-hydroxylated alanine and tyrosine are to be seen. In hadacidine **2**, isolated from *Penicillium frequentans*[2], N-hydroxy-glycine can be recognized.



1

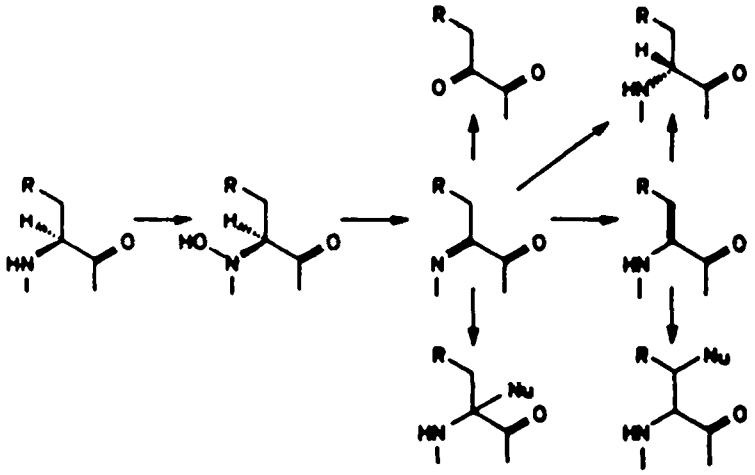
R = geranyl



2

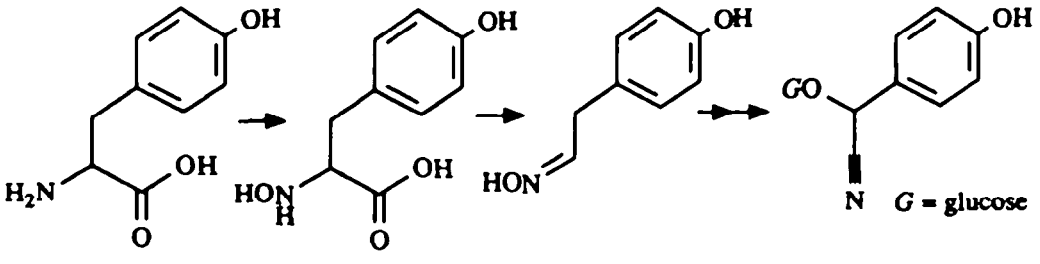
Peptides and other compounds containing N-hydroxy-amino acid residues are often physiologically active compounds. For example, the previously mentioned hadacidine is capable of

inhibiting the growth of malignant cells[2], while other N-hydroxy compounds show antibiotic activity[3]. Though the physiological meaning of this kind of metabolites is not fully understood, there is evidence that naturally occurring N-hydroxy-amino acids play a role in the metabolism of protein amino acids. It has been postulated[4] that they might form a central precursor for a variety of other non-protein amino acids as depicted in scheme 1. This scheme might have chemosynthetic as well as biosynthetic implications.



scheme 1

The process of N-hydroxylation - in particular of aromatic amines - has been amply documented[5]. Much effort has been taken to reveal *in vivo* processes in which endogenic amino acids are converted into their corresponding N-hydroxy amino acids[6]. Strong indications have been found that in the biosynthesis of the cyanogenic glucoside dhurrin[7] 4, N-hydroxytyrosine 3 is involved(scheme 2). However, research in this domain is hampered severely by the lability of free N-hydroxy amino acids[8] and the lack of adequate detection methods[4].



3 "Dhurrin" 4

scheme 2

For the synthesis of optically pure N-hydroxy peptides, optically pure N-hydroxy amino acid

derivatives are needed. Several approaches to optically active N-hydroxy-α-amino acid derivatives have been studied[4]. The most successful procedures are

a) substitution of optically active α-functionalized carboxylic esters by hydroxylamine derivatives[9],

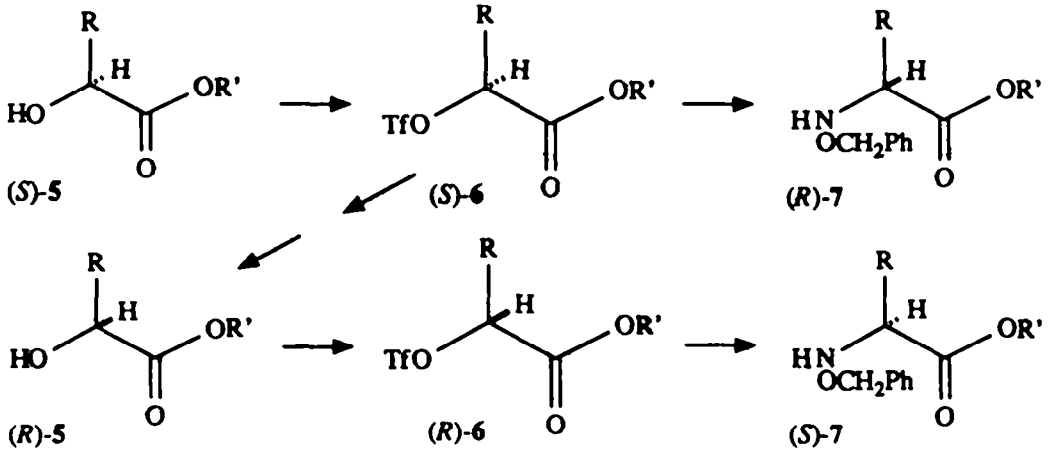
b) oxidation of amino acid derivatives[10],

c) enzymatic resolution[11] of racemic N-hydroxy amino acid derivatives.

This variety of methods is a consequence of the variety of amino acids displayed by nature. It is to be expected that e.g. N-hydroxy-cysteine and N-hydroxy-tryptophane are not accessible via method b) since oxidation of the sulfur atom(Cys) and the indole nucleus(Trp) will occur. For these amino acids one has to rely on method a) or c). In this report method a) is addressed.

Recently we observed that triflates of optically pure α-hydroxy acid esters 6(scheme 3) are successfully substituted by O-benzylhydroxylamine to yield O-benzyl-hydroxylamino acid esters 7 in high chemical and optical yields. Details of this observation are reported in ref. 9a.

Subsequently, we realized that most of the naturally occurring and commercially available, optically active α-hydroxy esters possess the (*S*)-configuration[12], so that only (*R*)-O-benzyl-hydroxylamino esters became accessible by this approach. We have solved this shortcoming and report in the second part a convenient method for the interconversion of (*R*) and (*S*)-α-hydroxy esters 5. It employs the previously mentioned triflates and enables the preparation of (*S*)- as well as (*R*)-O-benzyl-hydroxyl-α-amino acid esters 7. This procedure is summarized in scheme 3.



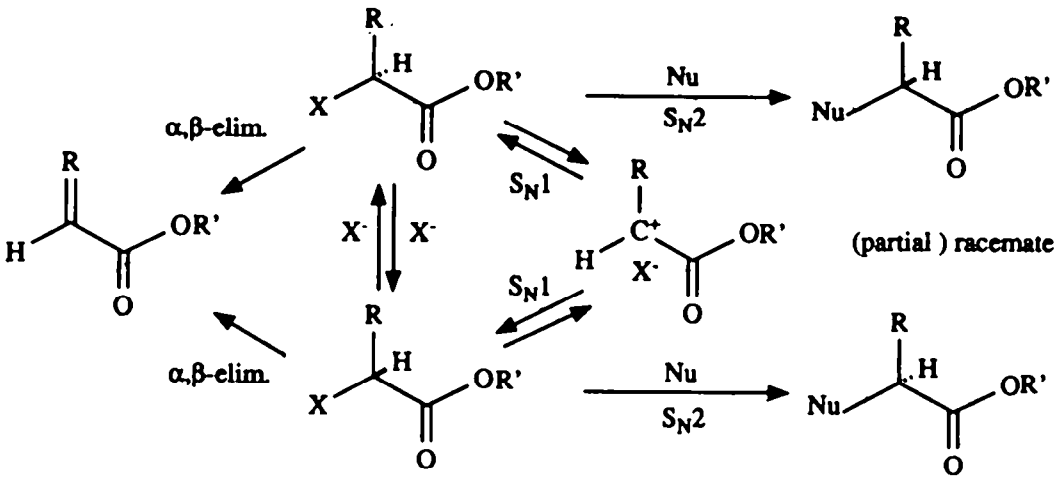
scheme 3

Results:

Conversion of 5 into 7 via 6.

A general problem in substitution reactions of α-functionalized carboxylic acids or esters is racemization and α,β-elimination, both of which can occur to a considerable extent(scheme 4).

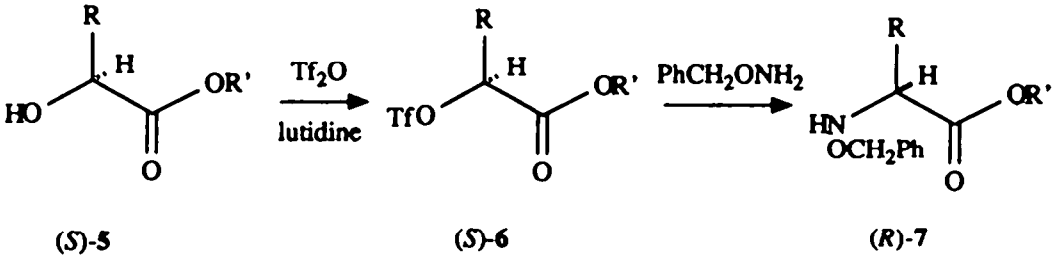
Most studies until now have been done with α-bromo carboxylic acids, and due to bromide exchange these compounds are prone to racemization[13]. An illustrative example of this



scheme 4

phenomenon is the reaction of (*S*)-α-bromosuccinic acid dimethyl ester with O-benzyl-hydroxylamine (scheme 4, R=CH_2COOMe, R'=Me, X=Br). The resulting O-benzyl-hydroxylamino acid ester can be isolated in an excellent chemical yield(93%) but the optical yield amounts to only 12 %[9a,14]. Therefore we abandoned α-bromo-acid esters and turned our attention to α-hydroxy esters(X=OH). It is clear that the hydroxyl group had to be activated, and from literature data it could be expected that activation as a mesylate or tosylate should not be sufficient to realize efficient substitutions by hydroxylamine derivatives[15]. The activation of choice appeared to be the formation of triflates[16]. The reaction sequence employed is depicted in scheme 5.

An advantage of the use of triflates **6** for the preparation of O-benzyl-hydroxylamino acid esters **7** is that high reaction temperatures which stimulate racemization can be avoided; substitutions performed between -78 and 0 °C lead to excellent chemical as well as optical yields(see table 1). The reaction time is reduced to about half an hour. It deserves attention that the yields strongly depend on the base used; other bases like pyridine give under the same conditions low yields. Another advantage of the triflates **6** is that they can be generated *in situ* and need not to be isolated. The overall chemical yields of conversions **5** → **7** and the corresponding optical yields are given in table 1.



(*S*)-**5** (*S*)-**6** (*R*)-**7**

scheme 5

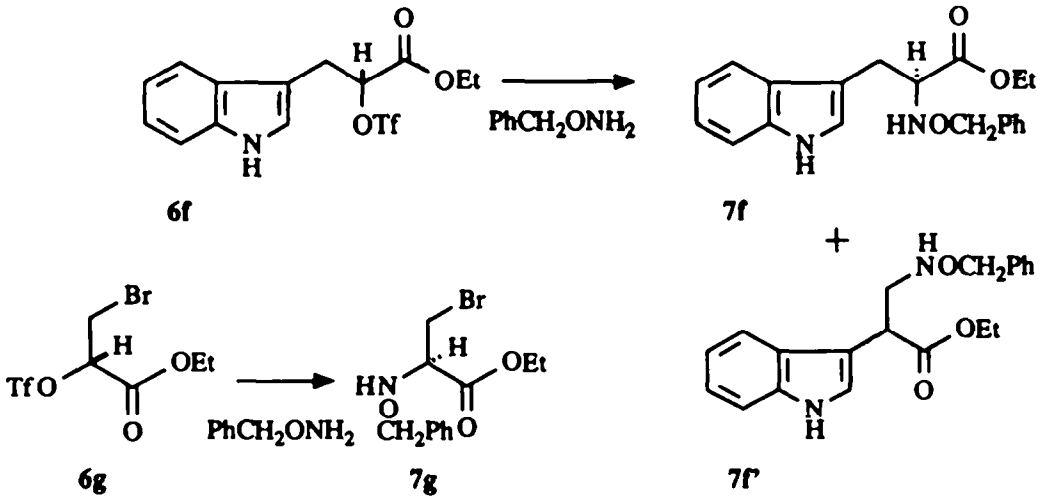
Table 1. Conversion of **5** to **7** *via* **6**

entry	product	R	yield(%) chemical	optical
i	(*R*)-**7a**	CH_3	89	100
ii	(*R*)-**7b**	CH_2Ph	84	100
iii	(*R*)-**7c**	$CH_2CH(CH_3)_2$	78	100
iv	(*R*)-**7d**	CH_2COOCH_3	88	95
v	(*S*)-**7e**[a]	Ph	88	76

7a: R'= Et, **7b-e**: R'= Me. [a]): (*R*)-**5e** was used as the starting compound.

In the substitution of the mandelic acid methyl ester **5e** the conversion to **7e** proceeds with only 50% optical yield when dichloromethane is used as the solvent. By addition of hexane to the reaction mixture the optical yield raises to 75%. Probably a more polar solvent induces S_N1 reactivity or causes the base-induced formation of an enolate structure[17]. In both these rationalizations stabilization can be furnished by the phenyl group. The influence of the phenyl group is also demonstrated by the fact that triflate **6e** decomposes at room temperature while triflate **6a** can be distilled though with slight racemization[18].

The reactions of the triflates **6f** and **6g**(scheme 6) with O-benzyl-hydroxylamine deserve further comment. The desired compounds **7f** and **7g** could only be isolated in low yields. We are inclined to ascribe these low yields by side reactions due to intramolecular nucleophilic displacements involving the indole nucleus of **7f** and the bromine substituent of **7g**. Indeed, the product **7f** was accompanied by a compound to which we tentatively assign the structure **7f'**.

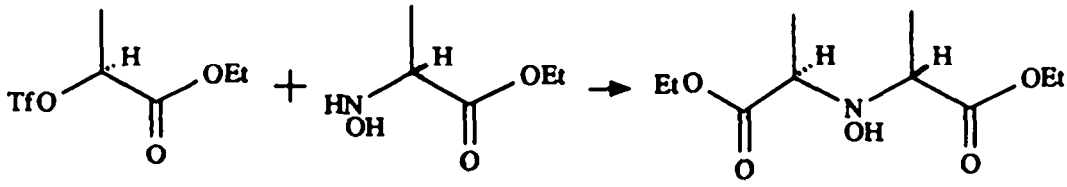


scheme 6

When **6a** is prepared *in situ* and without isolation is allowed to react with unprotected hydroxylamine, the N-hydroxy- alanine ethyl ester **8** is isolated in 80% chemical yield and 100% optical yield. However, when this reaction is carried out with **6a** which is isolated and purified by distillation, the optical yield amounts to 50% only[9a]. Apparently, distillation of **6a** causes a higher

degree of racemization than reported by Effenberger[18].

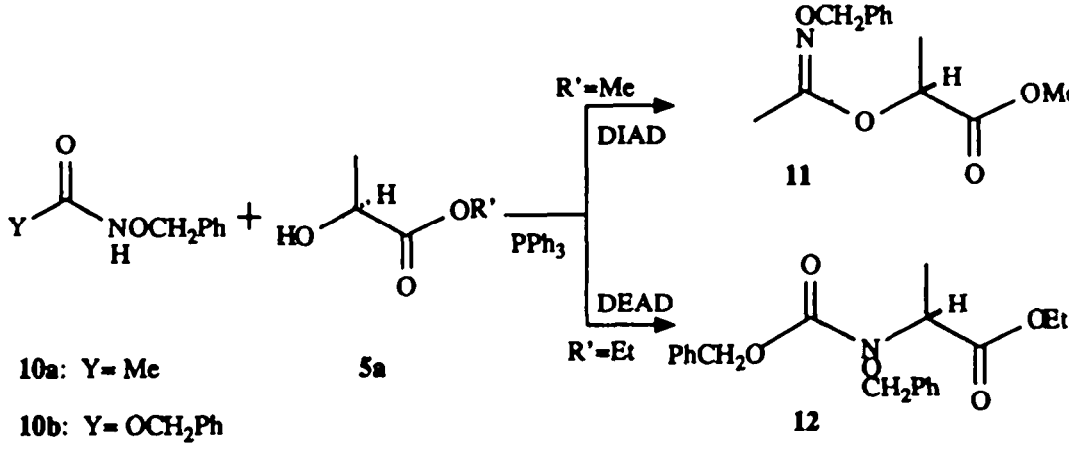
Reaction of **6a** with (*R*)-N-hydroxy-alanine ethyl ester **8** gave **9**(scheme 7) in good yield(88%); **9** is the di-ethyl ester and the optical antipode of the natural product amavidine[19].



(*S*)-**6a** (*R*)-**8** **9**

scheme 7

In addition to the preparation of **7a** by substitution as given in scheme 5 we made an attempt to obtain **12**, an N-protected derivative of **7a** by coupling of the N- and O-protected hydroxylamines **10** with α-hydroxy esters **5**(scheme 8). Reaction of **10b** with **5a** gave **12** in 37% yield only, whereas this variation of the Mitsunobu reaction did not give the desired product but **11** instead when **10a** was employed. A reaction related to the second one has been reported for primary alcohols[20].



10a: Y= Me **5a** **11**

10b: Y= OCH_2Ph **12**

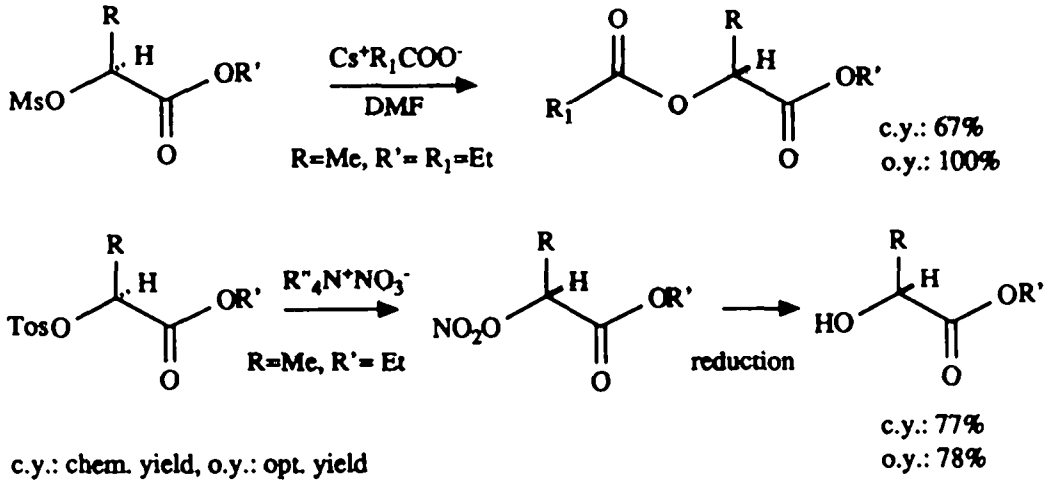
scheme 8

The stereochemistry of **12** has not been investigated. Because of the low chemical yields we abandoned this method[21].

Interconversion of (R)- and (S)-α-hydroxy esters 5.

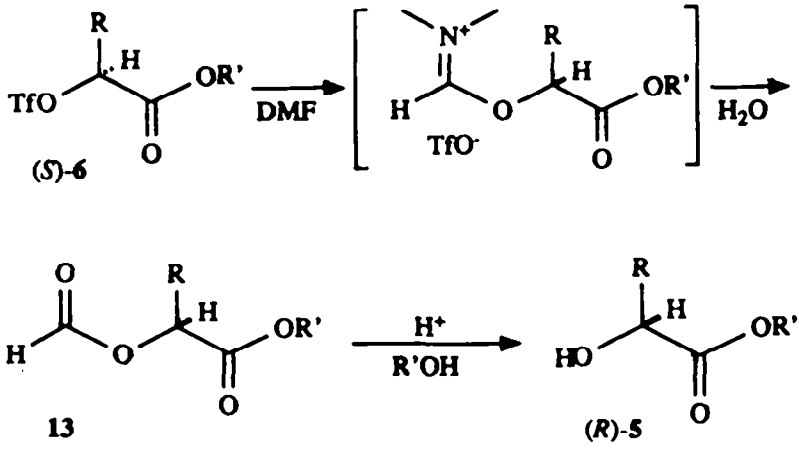
As stated in the introduction, most of the available optically active α-hydroxy esters possess the (*S*)-configuration. Consequently, the S_N2 substitution as depicted in scheme 5 yields N-hydroxy

amino acid derivatives 7 possessing the unnatural (*R*) configuration. So the challenge we faced was the conversion of (*S*)-5 into (*R*)-5(scheme 3). Although the inversion of secondary alcohols has received much attention[22] only a few reports deal with the inversion of α-hydroxy esters. Methods reported so far are the nitrate-[22b], and cesium carboxylate-[17] mediated inversions of sulfonates(OTos, OMs) of α-hydroxy esters(scheme 9):



scheme 9

However, these methods do not fulfil our needs. The drawback of the nitrate- mediated inversion[22b] is the necessity of a reduction step after the inversion reaction, which lowers the chemical yield. Moreover, the overall optical yield does not exceed 78% for substrate **5a**. The "cesium carboxylate"[17] inversion yields no enantiomeric excess at all in the case of **5e**. In our hands the method of choice for the conversion of (*S*)-**5** into (*R*)-**5** is the reaction of the triflate (*S*)-**6** with dimethylformamide as depicted in scheme 10.

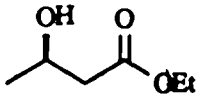


scheme 10

The use of dimethylformamide as a nucleophile deserves some comment. The reaction proceeds at roomtemperature and yields the formate **13** of the inverted ester. Transesterification conditions give the inverted alcohol (*R*)-**5**. The mechanism of the nucleophilic displacement reaction involving dimethylformamide must be similar to that reported for the solvolysis of sulphonylates by the same nucleophile[23].

Two procedures were studied. In one of them(method A) the formates **13** were isolated prior to alcoholysis to (*R*)-**5**. The overall chemical yields were acceptable(65%-85%) and the optical yields excellent(91%-100%)(table 2). When the formate was not isolated(method B) the chemical yields increased significantly but in most cases a slight drop in the optical yield was observed. We were particularly pleased to observe that the inversion of the triflate (*R*)-**6e** to yield (*S*)-**5e** proceeds with 95%(method B) optical yield[24].

Table 2. Interconversion of (*R*) and (*S*)-**5** *via* **13**

entry	product	R	yield(%) chemical *meth.A/B*[a]	yield(%) optical *meth.A/B*[a]	**13**
i	(*R*)-**5a**	CH_3	47/92	96/95	67
ii	(*R*)-**5b**	CH_2Ph	71/94	99/93(99)[b]	81
iii	(*R*)-**5c**	$CH_2CH(CH_3)_2$	49/85	96/94	65
iv	(*R*)-**5d**	CH_2COOCH_3	65/93	100/98	85
v	(*S*)-**5e**[c]	Ph	66/95	91/95	80
vi	 (*R*)-**5h**		--/35	--/94[d]	--

5a: R'= CH_2Ph, **5b-e**: R'= Me. Temperature at which triflates **6** were generated: **5a,c,d**: T = 0°C, **5b,e,h**: T = -78°C. [a]): *meth.A/B*: *A*: with isolation formate, *B*: without isolation formate. [b]): after crystallization from CH_2Cl_2/hexane. [c]): (*R*)-**5e** was used as the starting compound. [d]): inversion yield, the starting compound was not optically pure.

Though not being an α-hydroxy ester, (*S*)-β-hydroxy butyric acid ethyl ester **5h** was also subjected to this method B for inversion. The inverted β-hydroxy ester was isolated with a high(94%) inversion yield but in a low chemical yield(35%). We consider this result noteworthy as O-sulphonylated β-hydroxy esters are prone to α,β-elimination[22b]. We anticipate that the chemical yield may be improved considerably when the corresponding benzyl ester of **5h** is inverted; the high volatility of the ethyl ester **5h** causes problems of practical nature during the work-up.

p-nitrobenzylesters of α-hydroxy carboxylic acids can not be used; with (*S*)-lactic acid *p*-nitrobenzyl ester complete racemization took place, probably due to the nucleophilic nature of the nitro group which is expected to be capable of displacing the triflate moiety.

Finally, we have studied whether the triflates **6** in scheme 10 can be replaced by other

preferably cheaper - O-activated α-hydroxy esters[25]. The results of these investigations are summarized in table 3. Using tosylates or mesylates, the reaction temperature had to be increased to ca. 100°C, but under these circumstances the optical- or chemical yields, or both, were low.

Table 3. Inversion reaction of mesylates and tosylates of (*S*)-5 with DMF

entry	acti-vation	R	t(days)	yield(%) chem.(13)	opt.((*R*)-5)
i	Ms	CH_2COOR'	1	14	89
ii	Ms	CH_2COOR'	2	20	92
iii	Ms	Ph	1	69	18[a]
iv	Tos	Me	6	21	4
v	Tos	CH_2COOR'	2	0[b]	42

T = 100°C. R' = Me(*i,ii,iii,v*), Et(*iv*). [a]) (*S*)-5e, the mesylate of (*R*)-5e was used. [b]): 13 could not be isolated; spontaneous transesterification occurs to (*R*)-5 in 13% yield.

Conclusion:

Triflates of α-hydroxy esters are good substrates for the preparation of O-benzyl-α-hydroxylamino esters and for the interconversion of (*R*) and (*S*)-hydroxy esters. These reactions proceed in high chemical and optical yields. When O-unprotected hydroxylamine derivatives are used in combination with 6, N-alkylation takes place. The smooth reaction of triflates 6 with the weak nucleophile DMF demonstrates the extreme reactivity of 6, which sometimes causes nucleophilic parts of the substrate itself, when present, to react intramolecularly.

Experimental part:

^{1}H-NMR spectra were measured on a Brüker WH-90 spectrometer. Infra red spectra were measured on a Perkin Elmer 298 spectrometer. Mass spectra were obtained with a double focussing VG 7070E spectrometer. Optical rotations were taken on a Perkin Elmer 241 polarimeter. Thin-layer chromatography(TLC) was carried out by using Merck precoated silicagel F-254 plates(thickness 0.25 mm).

General procedure for the preparation of the triflates 6
Trifluoromethanesulphonic acid anhydride(3.3 mmol) is added at once to a stirred solution of 5 (3 mmol) in dry CH_2Cl_2 (10 ml) which is kept at either -78°C(acetone/CO_2) or 0°C (ice/water)(see table 2 for the temperature of the inversion reactions and ref. 9a for the substitution reactions depicted in scheme 5) and under an argon atmosphere. After five minutes, lutidine(369 mg, 3.45 mmol) is added in one portion to the reaction mixture which is stirred for another five minutes. Then the hydroxycompound is added(*vide infra*).

General procedure for the preparation of the O-benzyl-α-hydroxylamino-acid esters 7
To the freshly prepared triflate 6, a solution of O-benzylhydroxylamine(738 mg, 6 mmol)(ref. 9a) in dry CH_2Cl_2(5 ml) is added dropwise, under stirring. Subsequently, the cooling bath is removed. When the mixture has reached room temperature, stirring is continued for 25 minutes. The reaction mixture is concentrated *in vacuo* and the residual oil is subjected to flash column chromatography(silicagel, Merck H60).

The experimental data concerning the compounds **7a-7e** have been given in the preliminary report(ref. 9a).

7f/7f':
The preparation of **7f** was carried out at -78°C on 1 mmol scale (**5f**). Following the general procedure, the residual oil obtained after evaporation of the solvent is subjected to flash column chromatography(silicagel, Merck H60, eluent ether/hexane 1/4), yielding two fractions which are not completely homogenous by TLC.
Fraction 1 contains **7f**: R_f=0.26(1% MeOH/CH_2Cl_2), yield about 20%.
Fraction 2 contains presumably **7f'**: R_f=0.15(1% MeOH/CH_2Cl_2), yield about 15%.

7g:
The preparation of **7g** was carried out at -78°C on 1 mmol scale (**5g**). Following the general procedure, the residual oil obtained after evaporation of the solvent is subjected to flash column chromatography(silicagel, Merck H60, EtOAc/hexane 1/9). **7g** was isolated in 20 % yield, R_f=0.29(EtOAc/hexane 1/9).

(*R*)-N-hydroxy-alanine ethyl ester **8**
230 mg(10 mmol) of Na is reacted with 20 ml dry of MeOH. After the sodium has dissolved completely, 695 mg(10 mmol) of $NH_2OH.HCl$ is added, and the mixture is stirred until neutral pH(addition of more $NH_2OH.HCl$ may be necessary). The solution is filtered and cooled to -78°C(acetone/dry ice). Under an argon atmosphere, freshly prepared **6a**(2 mmol) in 8 ml of dry CH_2Cl_2 is added dropwise to the cooled solution. After the reaction mixture has reached room temperature, the solvent is evaporated and the residue subjected to flash column chromatography(silicagel Merck H60, 3% MeOH/CH_2Cl_2) to yield **8** in 80% yield. **8** was acetylated to the hydroxamate **8'** having $[\alpha]_D^{20}$ -55.9(c 1, $CHCl_3$) which corresponds to an optical purity of 100%. The *reference* compound **8'** was prepared from optically pure **7a** and acetylchloride yielding the O-benzyl derivative of **8'**. The latter is reduced by H_2/Pd-C/MeOH, giving optically pure **8'** having $[\alpha]^{20}_D$ -55.0(c 1, $CHCl_3$).

N-hydroxy-α,α'-iminodipropionic acid diethyl ester **9**
To a cooled(-78°C, acetone/dry ice) solution of 532 mg(4 mmol) of (*R*)-N-hydroxy alanine ethyl ester **8** in 6 ml of dry CH_2Cl_2 under an argon atmosphere, 2 mmol of freshly prepared **6a** in CH_2Cl_2 is added dropwise. After the reaction mixture has reached room temperature, the solvent is evaporated and the residue subjected to flash column chromatography(silicagel Merck H60, 2% MeOH/CH_2Cl_2). Compound **9** is isolated in 88% yield; only one diastereomer could be detected by ^{1}H-NMR. $[\alpha]^{20}_D$ -7.6(c 2, $CHCl_3$).

α-(α'-benzyloximino ethoxy)-propionic acid methyl ester **11**
To a cooled(ice/water) solution of 1.05 g(4 mmol) of triphenylphosphine in 10 ml of dry tetrahydrofuran, 808 mg(4 mmol) of diisopropylazodicarboxylate (DIAD) is added under an argon atmosphere. After stirring for 30 minutes a solution of 660 mg(4 mmol) of N-acetyl-O-benzyl-hydroxylamine **10a** and 208 mg(2 mmol)[30] of (*S*)-methyl lactate in 5 ml of dry tetrahydrofuran is added dropwise to the cooled solution. After the reaction mixture has reached room temperature the solvent is evaporated, and the residue subjected to flash column chromatography (silicagel Merck H60, EtOAc/hexane 15/85). Yield: 24%.

N-benzyloxy-N-benzyloxycarbonyl-alanine ethyl ester **12**
The same procedure is followed as for the preparation of **11**, except for the use of diethyl azodicarboxylate(DEAD) instead of DIAD and that (*S*)-ethyl lactate was used. Flash column chromatography was done with silicagel Merck H60, elution with EtOAc/hexane 1/9. Yield: 37%.

General procedure for the conversion of (*S*)-**5** into (*R*)-**5** via (*R*)-**13**

To a fresly prepared solution of triflate **6**, N,N-dimethylformamide (1 ml) is added dropwise. Subsequently, the cooling bath is removed. When the reaction mixture has reached room temperature, stirring is continued for another 15 minutes. The reaction mixture is concentrated *in vacuo* to remove the excess DMF.

Method A(with isolation of formate **13***)*
The residual oil which is obtained after evaporation of the solvents is subjected to flash column chromatography (silicagel Merck H60, CH_2Cl_2) to yield (*R*)-**13** as an oily product. Formate (*R*)-**13** (1.5 mmol) is solved in MeOH (10 ml) which contains about 20 mg of *p*-toluenesulphonic acid. This solution is stirred at room temperature for one hour(10 minutes in the case of (*R*)-**13a**, to avoid

transesterification of the benzyl ester). The solution is concentrated *in vacuo*, and the residue subjected to column chromatography(silicagel Merck H60, eluent: 5a,h: EtOAc/hexane 1/3; 5b,c,d: 1% MeOH/CH_2Cl_2; 5e: CH_2Cl_2). The product is distilled *in vacuo*(Kugelrohr) to yield (*R*)-5 as an oily product.

$[\alpha]^{20}_D$ (c 2, $CHCl_3$) values of the *starting* compounds 5:

(*S*)-5a	(*S*)-5b	(*S*)-5c	(*S*)-5d	(*R*)-5e	(*S*)-5h
-13.5	-7.2	+42.4[a]	+20.4[a]	-171	+31.5

[a]): measured at 365 nm(Hg)

$[\alpha]^{20}_D$ (c 2, $CHCl_3$) values of the compounds 5 *after* the inversion reaction:

(R)-5a	(R)-5b	(R)-5c	(R)-5d	(S)-5e	(R)-5h
+13.0	+7.1	-40.7[a]	-21.4[a]	+156	--

[a]): measured at 365 nm(Hg).

Method B(without isolation of formate 13):

The residual oil is dissolved in MeOH (20 ml) containing about 40 mg of *p*-toluenesulphonic acid. Stirring is continued at room temperature for one hour (10 minutes in the case of (*R*)-13a, to avoid transesterification of the benzyl ester). The reaction mixture is concentrated *in vacuo*, and the resulting oil is subjected to flash column chromatography(silicagel, Merck H60, eluent see method A). The product is distilled (Kugelrohr) to yield (*R*)-5 as an oily product. Compound 5b can be crystallized from CH_2Cl_2/hexane, what increases the optical purity from 93% to 99%.

$[\alpha]^{20}_D$ (c 2, $CHCl_3$) values of the compounds 5 *after* the inversion reaction:

(R)-5a	(R)-5b	(R)-5c	(R)-5d	(S)-5e	(R)-5h
+12.8	+6.7(7.1)[a]	-39.8[b]	-20.0[b]	+162	-29.6

[a]): crystallized from CH_2Cl_2/hexane. [b]): measured at 365 nm(Hg)

Inversion reactions with mesylates and tosylates derived from 5

A tosylate or mesylate(4 mmol) of 5 is dissolved in 2 ml of N,N-dimethylformamide (DMF). The solution is kept at 100°C for the time given in table 3. The work up of the reaction mixture is identical to method A(*vide supra*).

Spectroscopic data and elemental analyses

The spectroscopic data and elemental analyses of compounds 7a-7e can be found in the preliminary report(ref. 9a).

7f: ^{1}H-NMR($CDCl_3$): see reference 31.

7f': ^{1}H-NMR($CDCl_3$): δ 1.20(t, 2H, $OCH_2\underline{CH_3}$); 3.34 and 3.65(8 lines, ABX, 2H, J_{ax}= 6.8 Hz, J_{bx}= 8.3 Hz, J_{ab}= 30.5 Hz, indole C(3)$\underline{CH_2}$), 4.15(q, 2H, $O\underline{CH_2}CH_3$), 4.36(4 lines, ABX, 1H, J_{ax}+ J_{bx}= 14.8 Hz, indole C(3)$\underline{CH}CH_2$), 4.71(s, 1H, $O\underline{CH_2}Ph$), 5.4-6.1(broad s, 1H, NH), 7.10(d, 1H, indole C(2)H), 7.30(s, 5H, $O\underline{CH_2Ph}$, 7.0-7.8(m, 4H, indole C(4)-C(7) H), 8.13(broad s, 1H, indole NH)

MS(CI, m/z): 339(M^++1, 70), 232(12), 216(35), 203(100), 174(23), 130(41), 91(62).

7g: ^{1}H-NMR($CDCl_3$): δ 1.29(t, 3H, $OCH_2\underline{CH_3}$), 3.66(3 lines, AB part of ABX, 2H, $CH\underline{CH_2}$), 3.89(4 lines, X part of ABX, J_{ax}+ J_{bx}= 10.8 Hz, 1H, $C\underline{H}CH_2$), 4.24(q, 2H, $O\underline{CH_2}CH_3$), 4.73(s, 2H, $O\underline{CH_2}Ph$), 6.2(broad s, 1H, NH), 7.33(s, 5H, $OCH_2\underline{Ph}$)

MS(CI, m/z): 304(M^++1, 10), 302(M^++1, 10), 222(17), 176(19), 119(14), 91(100)

8: ^{1}H-NMR($CDCl_3$): δ 1.26(d, 3H, $CHC\underline{H_3}$), 1.31(t, 3H, $OCH_2\underline{CH_3}$), 3.71(q, 1H, $C\underline{H}CH_3$, 4.23(q, 2H, $O\underline{CH_2}CH_3$), 4.7-5.5(broad, 2H, $N\underline{HOH}$). IR(neat, cm^{-1}): 3430(s), 3270(s), 1730(s). MS(CI, m/z): 134(M^++1, 18), 88(5), 60(74), 41(100). Elem. anal.: $C_5H_{11}NO_3$(%): calc.: C 45.10, H 8.33, N 10.52. Found: C 45.20, H 8.31, N 10.44.

9: ^{1}H-NMR($CDCl_3$): δ 1.29(t, 6H, $OCH_2\underline{CH_3}$(2x)), 1.36(d, 6H, $CHC\underline{H_3}$(2x)), 3.73(q, 2H, $C\underline{H}CH_3$(2x)), 4.22(q, 4H, $O\underline{CH_2}CH_3$(2x)), 5.80(s, 1H, NOH). IR(neat, cm^{-1}): 3455(s), 1725(s). MS(CI, m/z): 234(M^++1, 100), 216(3), 188(3), 160(37). Elem. anal.: $C_{10}H_{19}NO_5$: calc.: C 51.49, H 8.21, N 6.00. Found: C 51.24, H 8.35, N 5.94.

11: ^{1}H-NMR($CDCl_3$): δ 1.48(d, 3H, $CHC\underline{H_3}$), 1.88(s, 3H, $NCCH_3$), 3.61(s, 3H, OCH_3), 4.87(s, 2H,

$PhCH_2$), 5.14(q, 1H, $CHCH_3$), 7.25(s, 5H, Ph). IR(neat, cm^{-1}): 1750(s), 1650(s). MS(CI, m/z): 252(M^++1, 58), 119(8), 105(9), 91(100).

12: ^{1}H-NMR($CDCl_3$): δ 1.19(t, 3H, OCH_2CH_3), 1.44(d, 2H, $CHCH_3$), 4.13(q, 2H, OCH_2CH_3), 4.69(q, 1H, $CHCH_3$), 4.92(d, 2H, $COOCH_2Ph$), 5.23(d, 2H, $NOCH_2Ph$), 7.32 and 7.38(2 s, Ph(2x)). IR(neat, cm^{-1}): 1700-1750(s), 1655(m). MS(CI, m/z): 358(M^++1, 11), 314(42), 181(21), 91(100).

(*R*)-**13a**: ^{1}H-NMR($CDCl_3$): δ 1.53(d, 3H, CH_3CH), 5.18(s, 2H, CH_2Ph), 5.27(q, 1H, CH_3CH), 7.33(s, 5H, CH_2Ph), 8.08(s, 1H, HC=O). IR(neat, cm^{-1}): 1760(s), 1730(s).

(*R*)-**13b**: ^{1}H-NMR($CDCl_3$): δ 3.13 and 3.23(8 lines, ABX, 2H, J_{ax}= 9.3 Hz, J_{bx}= 3.5 Hz, J_{ab}= 14.1 Hz, $CHCH_2Ph$), 3.74(s, 3H, $COOCH_3$), 5.35(8 lines, X-part of ABX, 1H, J_{ax}+ J_{bx}=12.9 Hz), $CHCH_2Ph$, J= 0.9 Hz, due to coupling with HC=O proton), 7.23(s, 5H, $CHCH_2Ph$), 8.13(d, 1H, HC=O, J=0.9 Hz). IR(neat, cm^{-1}): 1750(s), 1725(s). MS(CI, m/z): 209(M^++1, 26), 177(9), 163(100), 149(9), 131(33), 121(79), 91(15).

(*R*)-**13c**: ^{1}H-NMR($CDCl_3$): δ 0.96(2d, 6H, $CH_2CH(CH_3)_2$), 1.50-1.99(m, 3H,$CH_2CH(CH_3)_2$), 3.76(s, 3H, $COOCH_3$), 5.18(m, 1H, $CHCOOCH_3$), 8.10(s, 1H, HC=O). IR(neat, cm^{-1}): 1760(s), 1735(s). MS(CI, m/z): 175(M^++1, 78), 143(28), 129(16), 115(11), 97(17), 87(32), 69(100).

(*R*)-**13d**: ^{1}H-NMR($CDCl_3$): δ 2.94(d, 2H, CH_2CH), 3.72 and 3.79(2 x s, 6H, $COOCH_3$(2x)), 5.61((t, 1H, CH_2CH), 8.09(s, 1H, HC=O). IR(neat, cm^{-1}): 1740(s).

(*R*)-**13e**: ^{1}H-NMR($CDCl_3$): δ 3.74(s, 3H, $COOCH_3$), 6.07(s, 1H, CHPh), 7.42(s, 5H, CHPh), 8.18(d, 1H, J= 0.9 Hz, HC=O). IR(neat, cm^{-1}): 1755(s), 1725(s).

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