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OXIDATIVE PREPARATION OF OPTICALLY ACTIVE N-HYDROXY-α-AMINO ACID AMIDES

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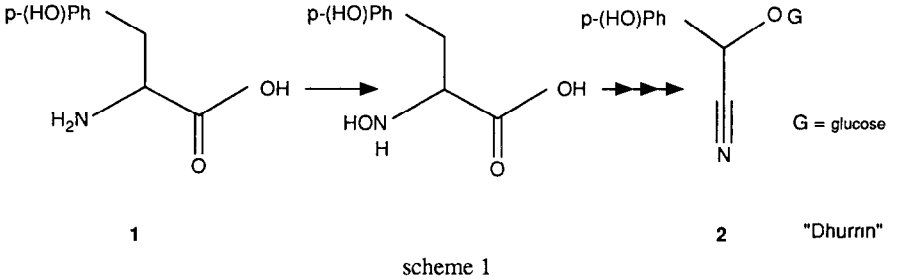
Summary Two routes are presented for the conversion of optically active α-amino acid amides into the title compounds One route(route A) features the formation of the Schiff's base **6** which is subsequently oxidized to the corresponding oxazindines **7** Route B is characterized by the formation of an imidazolin **11** which is hydroxylated to compound **12** Alcoholysis of **7** and **12** in the presence of hydroxylamine hydrochloride yields the title compounds in overall yields ranging from 65 to 85%(route A) and from 14 to 21%(route B)

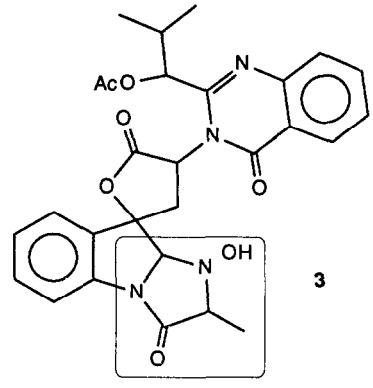
Introduction

N-hydroxy-α-amino acid derivatives are widely encountered in nature[1] They can be found amongst others as constituents of peptides, to which physiological properties can be attributed like antibiotic activity[2] for example Moreover, it has been postulated[3] that N-hydroxy amino acids play an important role in the metabolism of peptidogenic amino acids For example in the biosynthesis of dhurrin[4] **2**, the intermediate N-hydroxy tyrosin **1** has been proposed(scheme 1) Another natural product that contains an N-hydroxy amino acid as a structural feature is nortryptoquivaline **3**, a toxic metabolite[5a] isolated from a strain of *Aspergillus clavatus*



1 **2** "Dhurrin"

scheme 1



3

Most of the methods reported for the synthesis of N-hydroxy-α-aminoacids yield racemic mixtures[5b] Hence, there is a need for a general route to homochiral N-hydroxy-α-amino acids

Our contribution to the answer addressing this challenge has resulted in three approaches The first one features a substitution reaction involving triflates of α-hydroxy esters and hydroxylamine or derivatives thereof[6] The second approach is based on the enzymatic resolution of N-benzyloxy-amino acid ethyl esters[7] Here we report our third approach which is based on the selective N-oxidation of derivatives of optically active amino acids

Although oxidation of amino acids directly to the title compounds seems to be straight forward, a method for the *direct* oxidation of the amino function in amino acids has been unsuccessful[8]

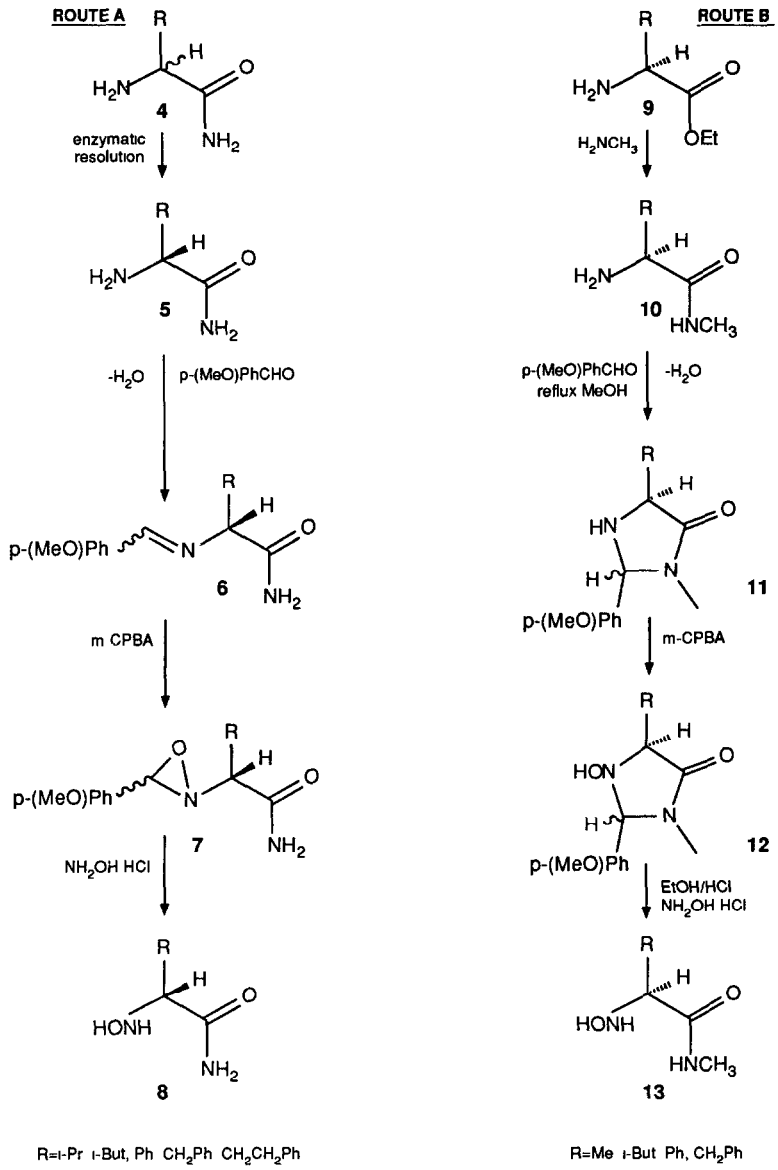
Indirect oxidation - of which two examples are discussed here - however offers a viable approach Połoński *et al*[9] demonstrated that conversion of the amino function of an α-amino acid ester into an imine renders this functionality susceptible to N-hydroxylation, a process involving an oxaziridine as intermediate (*cf* structure **7**, scheme 3) Despite later improvements to this method[10], this approach still suffers from variable yields that are - occasionally - unacceptably low We now report that this approach can be made more efficient and reliable by employing α-amino carboxy amides **5**(scheme 2, route A)

Furthermore, from Buchi's synthesis[5a] of nortryptoquivaline **3** we concluded that N-hydroxylation should also be feasible when a secundary amine is subjected to oxidation conditions Studies on the possibility whether the imidazolidinones **11** - masked derivatives of the corresponding L-amino acid amides **10** - could be oxidized to the 1-hydroxy-imidazolidinones **12** as potential precursors for **13**, have proved route B(scheme 2) to be viable indeed

Results and discussion

Route A

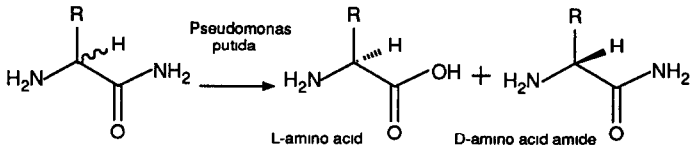
Optically active amino acid amides **5** are readily available on a large scale by applying enzymatic hydrolysis to D,L-amino acid amides[11] **4** Using an L-specific aminopeptidase from *Pseudomonas putida*, stereoselective hydrolysis of the L-amino acid amide into the L-α-amino acid is achieved while the D-amino acid amide **5** remains untouched, see scheme 3 Separation of the



scheme 2

ester and the amide is afforded by adding one equivalent(with respect to the D-α-amino acid amide) of an aromatic aldehyde, *e g* anysaldehyde, to the enzymatic hydrolysate[12] Since the Schiff's base **6** of the amino acid amide, which is formed quantitatively, is insoluble in water it can easily be isolated by filtration

The Schiff's base of the amino acid derivative having either the L or D chirality is the intermediate of choice for the oxidation procedure



4 **5**

scheme 3

The dry imine **6** when dissolved in dry dichloromethane at -15°C is nearly quantitatively converted into the oxaziridine **7** when a slight excess of *m*-CPBA is used Subsequent treatment with hydroxylamine gives the hydrochloride of the N-hydroxy α-D- or L-amino acid amide **8** Trituration with ether gives white crystals in good yields based on L- or D-α-amino acid amide **5**, see table 1

Table 1 Chemical yields of the conversion **5** → **8**(route A)

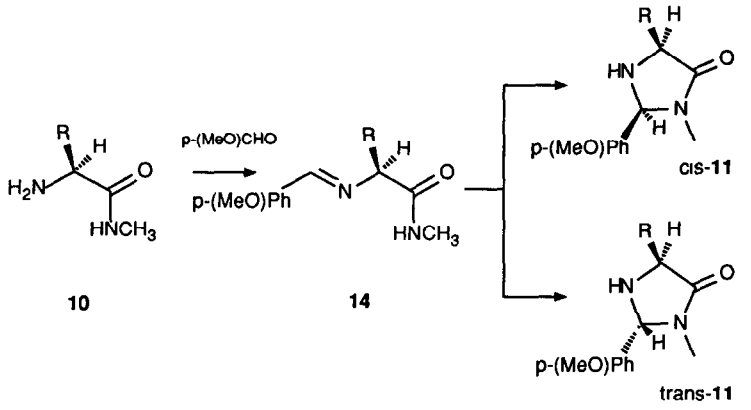
		chemical yield (%)	
entry	R	**5→6**	**6→8**
a	*i*-Pr	≥95	76
b	*i*-But	≥95	65
c	Ph	≥95	83
d	CH_2Ph	≥95	80
e	CH_2CH_2Ph	≥95	80

To establish the stereochemical identity, the N-hydroxy-α-amino acid amides **8** are reduced in a Parr-apparatus with Pd/C The specific rotations of the resulting α-amino acid amides **5** were in good agreement with those of the starting material **5**

Route B

Subsequently, we studied the oxidation of imidazolidinones **11** The latter compounds are easily obtained by refluxing a solution of the amide **10** and anysaldehyde in methanol For this cyclization reaction an aldehyde was selected and not a ketone as we observed that the aminals resulting from ketones, *e g* acetone, were very difficult to hydrolyse after the oxidation step From the reaction with *p*-methoxybenzaldehyde two diastereomers emerge, the ratio of which in some cases could be determined by isolation of the separate diastereomers, see scheme 4

The total yields of the two diastereomers of **11** together average 75% after purification by column chromatography, see table 2 It should be stressed here that reaction of **10** with the aldehyde yields the five membered ring only at elevated temperature, at room temperature the corresponding Schiff's base **14** is formed as discussed for route A Refluxing in MeOH probably causes the initially formed Schiff's base **14** to cyclize to give **11**



scheme 4

The principle of the conversion **14**→**11** has a precedent in literature[13]

The oxidation of **11** to **12** is performed as before with one equivalent of *m*-chloroperbenzoic acid in methanol Subsequently, the ring is cleaved by treatment with ethanolic HCl and an equimolar amount of H_2NOH HCl(see scheme 2)

The solvolysis of **12** by ethanolic HCl alone also takes place, but recondensation of the N-hydroxy amino acid amide **13** with the released aldehyde moiety to give the corresponding nitrone decreases the yield of **13** This problem is solved by the addition of H_2NOH HCl which binds the aldehyde diethyl acetal liberated from the solvolysis reaction

Table 2 Chemical yields of the conversion **9** → **13**(route B)

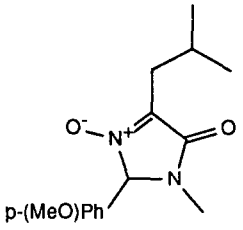
		chemical yield (%)			
entry	R	**9**→**10**	**10**→**11**[a]	**11**→**12**[a]	**12**→**13**
a	Me	99	36/36[b]	24[c]	78
b	*i*-But	93	38/38[d]	9/27[e]	78
c	Ph	99	50/26[#]	--/88	37[f]
d	CH_2Ph	99	46/33[#]	--/74	83

[a]) diast I/diast II [b]) ratio estimated from ^{1}H-NMR [c]) one diastereomer isolated [d]) ratio estimated from TLC [e]) a mixture of diastereomers of **11b** was oxydized, but the separate diastereomers of **12b** could be isolated [f]) yield not optimized [#]) diastereomers isolated in the ratio given

From table 2 it can be seen that the yield of the oxidation step **11**→**12** varies with the nature of the side chain and is highest when R = phenyl or benzyl(entries **c** and **d**) Another feature is that one of the diastereomers of **11a-d** is oxidized significantly faster than the other In the case of **11b** the reaction with the slow reacting diastereomer is accompanied by the formation of more side

products When the slower reacting diastereomers of **11c** and **11d** were treated with more than one molar equivalent of *m*-CPBA, the corresponding N-hydroxylated compound **12** could not be isolated

The formation of **12b** was also accompanied by a small amount of the corresponding, overoxidized product **15b**



15b

The optical purity(100%) of **13a** could be determined by comparison to a reference compound

Conclusions

Two routes for the synthesis of optically pure N-hydroxy-α-amino acid amides are described and in both routes the stereochemical identity of the starting material is retained

Route A starts with the optically pure amino acid amides **5** which are available in large quantities by methods developed at DSM[11] This route has proven to be very efficient (overall chemical yields ranging from 65 to 85%) and yields the chiral N-hydroxy-α-amino acid amides **8** Although the yield of the oxidation step **6** → **7** has not been determined separately it can be concluded that this reaction proceeds in high yield(>65%)

Route B starts with the amino acid amides **10** and follows the reaction sequence **10** → **11** → **12** → **13** which shows some noteworthy features In the conversion **10** → **11** diastereoselectivity is nearly absent In the conversion **11** → **12** only one diastereomer is oxidized cleanly, which drastically reduces the total yield of this oxidation step In route B the presence of an aromatic side chain increases the yield of the oxidation reaction In route A this reaction invariably proceeds in good yield regardless of the substituent present The alcoholysis of **7** and **12** carried out in the presence of H_2NOH HCl yields the desired title compounds in satisfactory yields

Acknowledgement

We wish to thank N K de Vries and H Linssen for recording the NMR spectroscopic data and P van Tilburg for recording the IR and melting point data J W Kortenoeven is greatfully acknowledged for typing part of the manuscript

Experimental part

^{1}H-NMR spectra were measured on a Bruker 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) For preparative column chromatography Merck silicagel type H60 was used

General procedure for the preparation of the Schiff's bases **6**
Solution of 5-10 % w/w of the amides **5** are made in water of 40 °C (5 % w/w for R= Ph, and 10 %w/w for R = *i*-Pr)
The pH of the solution is adjusted to 11 by adding 1 N KOH
Then in about 15 min 1 10 equivalents of *p*-methoxybenzaldehyde is added to the solution After 2 hours of stirring at roomtemperature the crystallized Schiff's bases are isolated by filtration, washed with water and dried *in vacuo* The products **6** are obtained in nearly quantitative yields

General procedure for the preparation of oxaziridines **7**
100 mmol of the Schiff's bases are dissolved in about 100-150 ml of dry dichloromethane This solution is cooled to 0-5 °C and 1,1 equivalent of *m*-CPBA (85 %) is added in portions Stirring is continued for 4 hours at room temperature after which the *m*-CBA is filtered off The filtrate is washed several times with dichloromethane The remaining solution is then evaporated *in vacuo* (T<30 °C)

General procedure for the preparation of N-hydroxyaminoacid amides **8**
The solid oxaziridines **7** were not purified due to their instability but directly dissolved in about 150 ml of methanol and 1 1 equivalents of H_2NOH HCl are added After stirring at room temperature for about 5-12 hours, the solution is triturated with about 1 L of dry ether The precipitate is isolated by filtration

General procedure for the preparation of the amides **10**
The hydrochlorides of **9**(20 mmol) are suspended in 150 ml $CHCl_3$, together with 1 equivalent(2 03 g, 20 mmol) of triethylamine After 15 minutes the solvent is removed, the residue extracted with diethylether(3x) The combined etherfractions are concentrated *in vacuo* yielding the free α-amino ester The yields are almost quantitative, except in the case of the hydrochloride of alanine ethyl ester **9a**(16%) which has been handled in another way(*vide infra*) The free α-amino ester is immediately dissolved(to prevent self aminolysis) in 140 ml 40% CH_3NH_2/H_2O After half an hour the reaction mixture is concentrated *in vacuo*, yielding amides **10** in almost quantitative yields(see table 2) In the case of **9a** the hydrochloride was dissolved immediately in 40% CH_3NH_2/H_2O After half an hour the reaction mixture was concentrated *in vacuo* yielding a residue containing equimolar amounts of **10a** and CH_3NH_2 HCl This residue is used without further purification for the preparation of **11a**

General procedure for the preparation of the isoxazolidinones **11**
Twenty mmol amide **10** and 20 mmol freshly distilled *p*-methoxybenzaldehyde are dissolved in 150 ml of MeOH This solution is refluxed over molecular sieves 3 Å during 18 hours after which the solvent is evaporated The residue is purified by column chromatography

11a The residue containing equimolar quantities of amide **10a** and CH_3NH_2 HCl(see general procedure for amides **10**) are refluxed in methanol with *p*-methoxybenzaldehyde as described above The residue is purified chromatographically(eluent 2% MeOH/CH_2Cl_2) The product **11a** is a mixture of two diastereomers(R_f 0 50, 3% MeOH/CH_2Cl_2)

11b: According to TLC, the diastereomers are formed in a ratio of about 1/1(1% MeOH/$CHCl_3$) The residue is subjected to flash column chromatography(eluent 1% MeOH/CH_2Cl_2) The eluate is divided in three fractions, the first yielding pure diastereomer II(R_f 0 52, 3% MeOH/$CHCl_3$)(crystals from CH_2Cl_2/hexane), the last one yielding pure diastereomer I(R_f 0 45, 3% MeOH/$CHCl_3$) The fraction in between was a mixture of both diastereomers

11c Chromatography of the residue(eluent EtOAc/hexane 40/60) gives two fractions, one

containing diastereomer I(R_f 0 34, EtOAc/hexane 1/1)(crystals from Et_2O/hexane), another containing diastereomer II(R_f 0 11, EtOAc/hexane 1/1)(crystals from CH_2Cl_2/hexane)

11d Chromatography of the residue(eluent 1% MeOH/CH_2Cl_2) gives two fractions, one containing diastereomer I(R_f 0 21, 1% MeOH/$CHCl_3$)(crystals from CH_2Cl_2/hexane), another containing diastereomer II(R_f 0 11, 1% MeOH/$CHCl_3$)(crystals from Et_2O/hexane)

General procedure for the preparation of the 1-hydroxy-isoxazolidinones **12**

A solution of 1 014 g(5 mmol) of 85% *m*-CPBA in 10 ml CH_2Cl_2 is added dropwise to a cooled solution(ice/water) of **11** (5 mmol) in 100 ml CH_2Cl_2 After 3 hours(unless otherwise stated, see below) the solvent is evaporated and the residue is chromatographed

12a A mixture of diastereomers of **11a**(see preparation of **11a**) is oxidized with *m*-CPBA The reaction period has to be extended to 2 days(0°C) TLC showed two iodine positive spots(R_f 0.57 and 0 51, toluene/ethylformiate/formic acid 10/7/3) After chromatography of the residue(eluent toluene/ethylformiate/formic acid 90/7/3), only one of the diastereomers of **12a** is isolated(24%, R_f 0 51 toluene/ethylformiate/formic acid 10/7/3)(crystals from CH_2Cl_2/hexane)

12b A mixture of diastereomers of **11b**(see preparation of **11b**) is oxidized with *m*-CPBA The reaction period had to be extended to 2 days(0°C) After chromatography(eluent toluene/-ethylformiate/formic acid 90/7/3) two fractions were collected each containing one of the diastereomers of **12b** Diastereomer I(14%) R_f 0 49 EtOAc/hexane 1/1(crystals from CH_2Cl_2/hexane) Diastereomer II(2 5%) R_f 0 32 EtOAc/hexane 1/1(crystals from CH_2Cl_2/hexane) Another impure fraction containing diastereomer I together with the concentrated filtrates of the previous crystallizations were chromatographed again(eluent EtOAc/hexane 20/80 changing to 50/50) Again two fractions were collected each containing one of the diastereomers After crystallizations(from CH_2Cl_2/hexane) 13% of diastereomer I and 6 5% of diastereomer II could be isolated Another impure fraction was chromatographed again(eluent EtOAc/hexane 1/1) and afforded in 7% yield the cyclic nitrone **15b**(R_f 0 22, EtOAc/hexane 1/1)

12c Diastereomer II of **11c** was oxidized The residue was chromatographed(eluent toluene/-ethylformiate/formic acid 90/7/3), 88% of diastereomer II of **12c** could be isolated(R_f 0 63 toluene/ethylformiate/formic acid 10/7/3)(crystals from CH_2Cl_2/hexane)

12d Diastereomer II of **11d** was oxidized The residue was chromatographed(eluent toluene/ethylformiate/formic acid 90/7/3) 74% of diastereomer II of **12d** could be isolated(R_f 0 53 3% MeOH/$CHCl_3$)(crystals from CH_2Cl_2/hexane)

General procedure for the preparation of the N-hydroxyamides **13**

2 mmol of compound **12** is dissolved in 7 N HCl/EtOH together with 139 mg(2 mmol) of H_2NOH HCl After 3 hours of *gently* refluxing, the solvent is evaporated The residue is stripped three times with EtOH Subsequently the residue is subjected to flash column chromatography

13a Diastereomer I of **12a** is used for the hydrolysis using hydroxylamine hydrochloride Eluent 3% MeOH/CH_2Cl_2 changing to 7% MeOH/CH_2Cl_2 Crystals from MeOH/CH_2Cl_2/hexane in the ratio 1/25/25 To check the optical purity of this compound, the compound was synthesized also from optically pure N-hydroxy-alanine ethyl ester[6a](3 mmol) and 40% H_2NCH_3/H_2O(1 5 ml) at 0°C After 1 hour the reaction mixture was concentrated *in vacuo* and stripped with MeOH three times The residue was crystallized from MeOH/CH_2Cl_2/hexane 1/25/25 Yield 25% The latter method yielded **13a** with $[\alpha]_D^{20}$ +45 8(c 2, MeOH) **13a** obtained by the oxidative method showed $[\alpha]_D^{20}$ -45 7(c 2, MeOH), so the optical purity is 100%

13b Diastereomer I of **12b** is used for the hydroxylaminolyse Eluent 2% MeOH/CH_2Cl_2 changing to 5% MeOH/CH_2Cl_2 Crystals from EtOAc/hexane

13c Diastereomer II of **12c** is used for the hydroxylaminolyse Eluent 2% MeOH/CH_2Cl_2 changing to 5% MeOH/CH_2Cl_2 Crystals from $CHCl_3$/hexane

13d Diastereomer II of **12d** is used for the hydroxylaminolyse Eluent 5% MeOH/CH_2Cl_2 Crystals from $CHCl_3$/hexane

Spectroscopic data and elemental analyses

6a: (*R*)-isomer

m p 115-115 5 °C ^{1}H-NMR($CDCl_3$) δ 0 92(dd, 6H, $CHCH(C\underline{H}_3)_2$), 2 28(m, 1H, $CHC\underline{H}(CH_3)_2$), 3.54(d, 1H, $C\underline{H}CH(CH_3)_2$), 3 81(s, 3H, $PhOC\underline{H}_3$), 5 86 and 6 67(2H, $CONH_2$), 6 91 and 7 68(d 2x, 4H, C_6H_4), 8 05(s, 1H, $N{=}C\underline{H}PhOCH_3$) IR(KBr, cm^{-1}) 3320(m), 3180(m), 1650(s), 1605(s) ^{13}C-NMR($CDCl_3$) δ 17 5 and 19 5($CHCH(\underline{C}H_3)_2$), 32 8($C\underline{C}H(CH_3)_2$), 55 4(OCH_3), 79 2($\underline{C}HCH(CH_3)_2$), 114 0, 128 8 and 162 0(C_6H_4), 161 5($N{=}\underline{C}HPhOCH_3$), 175 7($CONH_2$) $[\alpha]_{20}^{D}$

-8 7(c 2, MeOH)

6b: (*S*)-enantiomer
m p 126-128 °C ^{1}H-NMR($CDCl_3$) δ 0 90(d, 6H, $CHCH_2CH(CH_3)_2$), 1 52(m, 1H, $CHCH_2CH(CH_3)_2$), 1 76(t, 2H, $CHCH_2CH(CH_3)_2$), 3 92(4H, $CHCH_2CH(CH_3)_2$ and $PhOCH_3$), 5 43 and 6 66(2H, $CONH_2$), 6 93 and 7 68(d 2x, 4H, C_6H_4), 8 12(s, 1H, $N=CHPhOCH_3$) IR(KBr, cm^{-1}) 3340(m), 3150(m), 1650(s), 1608(s) ^{13}C-NMR($CDCl_3$) δ 21 2, 23 4 and 24 2($CHCH_2CH(CH_3)_2$), 43 6($CHCH_2CH(CH_3)_2$), 55 4($PhOCH_3$), 72 2($CHCH_2CH(CH_3)_2$), 114 3, 128 5, 130 0 and 162 2(C_6H_4), 116 3($N=CHPhOCH_3$), 176 5($CONH_2$) $[\alpha]_D^{19.5}$ -32 5(c 2, MeOH)

6c: (*R*)-enantiomer
m p 124-5°C ^{1}H-NMR($CDCl_3$) δ 3 82(s, 3H, OCH_3), 4 90(s, 1H, CHPh), 6 02 and 7 04(2H, NH_2), 6 90-7 75(9H, CHPh, $N=CHPhOCH_3$), 8 21(s, 1H, $NCHPhOCH_3$) IR(KBr, cm^{-1}) 3300(m), 1665(s), 1605(s) ^{13}C-NMR($CDCl_3$) δ 55 4($N=CHPhOCH_3$), 76 8(CHPh), 114 1, 128 6, 130 0 and 162 2(N=CHPhOMe), 127 2, 127 8, 128 4 and 139 5(CHPh), 162 4($N=CHPhOCH_3$), 174 4($CONH_2$) $[\alpha]_D^{20}$ +30 0(c 2, MeOH)

6d: (*R*)-enantiomer
m p 130-2 °C ^{1}H-NMR($CDCl_3$) δ 2 9-3 38(m, 2H, CH_2Ph), 3 80(s, 3H, N=CHPhOMe), 4 87(m, 1H, $CHCONH_2$), 5 84(1H, $CHCONH_2$(1H)), 6 90-7 6(11H, CH_2Ph, N=CHPhOMe and NH_2(1H) IR(KBr, cm^{-1}) 3350(m), 3160(m), 1660(s), 1605(s) ^{13}C-NMR($CDCl_3$) δ 41 1($CHCH_2Ph$), 55 3(N=CHPhOMe), 74 9($CHCONH_2$), 114 0, 128 2 and 130 0(N=CHPhOMe), 126 4, 128 1, 129 8 and 137 6($CHCH_2Ph$), 162 0($CHCONH_2$), 175 0(N=CHPhOMe) $[\alpha]_D^{21}$ -262 5(c 2, MeOH)

6e: racemic modification
m p 136-8°C ^{1}H-NMR($CDCl_3$) δ 1 24 and 1 43(m 2x, 2H, $CHCH_2CH_2Ph$), 1 77(m, 2H, $CHCH_2CH_2Ph$), 2 92(m, 1H, $CHCH_2CH_2Ph$), 3 00(s, 3H, N=CHPhOMe), 4 66 and 5 86(2H, $CHCONH_2$), 6 1-6 9(m, 9H, N=CHPhOMe and $CHCH_2CH_2Ph$), 7 23(s, 1H, NCHPhOMe) IR(KBr, cm^{-1}) 3310(m), 3150(m), 1650(s), 1605(s) ^{13}C-NMR($CDCl_3$) δ 31 8 and 36 2($CHCH_2CH_2Ph$), 55 4(N=CHPhOMe), 114 2, 130 0 and 162 3(N=CHPhOMe), 125 9, 128 4 and 141 1($CHCH_2CH_2Ph$), 162 1(N=CHPhOMe), 175 8($CHCONH_2$)

8a: (*R*)-enantiomer hydrogenchloride
Yield 76 % m p 108-9 °C ^{1}H-NMR(DMSO) δ 0 94(d, 6H, $CH(CH_3)_2$), 1 74(d, 1H, $CH(CH_3)_2$, NHOH not detected IR(KBr, cm^{-1}) 3360(m), 3060(m), 1690(s), 1605(m), 1400(s) $[\alpha]_D^{20}$ -73(c 1, H_2O)

8b: (*S*)-enantiomer, hydrogenchloride
Yield 65 % m p 114-5°C ^{1}H NMR($CDCl_3$) δ 0 94(d, 6H, $CH_2CH(CH_3)_2$), 1 29-1 84(m, 3H, $CH_2CH(CH_3)_2$), 3 50(4 lines, X-part of ABX, $CHCH_2CH(CH_3)_2$), 3 8-5 1(s, broad, 2H, NHOH), 7 00-7 54(2H ,$CONH_2$) IR(KBr, cm^{-1}) 3350(m), 3150(m), 1680(s), 1600(s)

8c: racemic modification
Yield 83 % m p 162-3 °C ^{1}H-NMR(DMSO) δ 4 32(d, 1H, CHPh, $J(H_\alpha,NH)$=8 Hz), 6 10(d, CHNHOH), 7 45(d, 1H, NHOH, J(NH,OH)=2 Hz), 7 14-7 42(2H, $CONH_2$), 7 24-7 4(5H, Ph) IR(KBr, cm^{-1}) 3350(m), 3140(m), 1650(s), 1600(m)

8c: (*R*)-enantiomer hydrogenchloride $[\alpha]_D^{20}$ -107 5(c 1, MeOH)

8c: (*S*)-enantiomer hydrogenchloride $[\alpha]_D^{20}$ +107 5(c 1, MeOH)

8c: (*R*)-enantiomer $[\alpha]_D^{20}$ -57 6(c 1, MeOH)

8c: (*S*)-enantiomer $[\alpha]_D^{20}$ +57 3(c 1, MeOH) m p 137 4-137 8 °C

8d: racemic modification
Yield 80 % m p 145-6°C ^{1}H-NMR(DMSO) δ 2 62 - 2 77(2H, $CHCH_2Ph$, J_{ax}= 8 Hz, J_{ab} = 14 Hz, J_{bx}=5 5 Hz), 3 45(m, 1H, $CHCH_2Ph$, J_{ax}= 8 5 Hz, J_{bx}= 5 5 Hz), 5 59(1H, NH, J_{NHOH}= 3 Hz), 7 41(1H, OH, J= 3 Hz), 7 01 and 7 15(2H, $CONH_2$), 7 1-7 3(5H ,Ph) IR(KBr, cm^{-1}) 3345(m), 3170(m), 1645(s), 1610(s)

8d: (*R*)-enantiomer $[\alpha]_D^{20}$ +4 3(c 1, MeOH)

8d: (*S*)-enantiomer $[\alpha]_D^{20}$ -4 3(c 1, MeOH)

8e: racemic modification, hydrogenchloride m p 128-30 °C IR(KBr, cm^{-1}) 3300(m), 3150(m), 1675(s), 1620(m), 1600(?)

11a (two diastereomers)
^{1}H-NMR($CDCl_3$) δ 1 35(d, 3H, $CHCH_3$), 1 44(d, 3H, $CHCH_3$), 1 77(s, 1H, NH), 2 62(s, 3H, NCH_3), 2 67(s, 3H, NCH_3), 3 60(q, 1H, $CHCH_3$), 3 83(s, 3H, PhOMe), 3 84(q, 1H, $CHCH_3$), 5 18(s, 1H, CHPhOMe), 5 28(s, 1H, CHPhOMe), 6 69 and 7 02(AB, 4H, CHPhOMe, J_{ab}=8 5 Hz), 6 73 and 7 02(AB, 4H, CHPhOMe, J_{ab}=8 6 Hz) IR(neat, cm^{-1}) 3450(w), 3330(m), 1690(s), 1615(s), 1590(m) MS(EI, m/z) 220(M^+, 34), 219(66), 163(53), 162(53), 148(100), 113(55)

11b (diast I)
^{1}H-NMR($CDCl_3$) δ 0 99(d, 6H, $CH_2CH(CH_3)_2$), 1 23-2 14(m, 4H, $CH(NH)CH_2CH(CH_3)_2$), 2 64(s, 3H, NCH_3), 3 55(4 lines, X-part of ABX, 1H, NH_2CHCH_2, J_{ax}+ J_{bx}=12 9 Hz), 3 86(s, 3H, CHPhOMe), 5 18(d, 1H, CHPhOMe, J=1 1 Hz due to coupling with the C_α-proton), 6 97 and 7 29(AB, 4H, CHPhOMe, J_{ab}=8 7 Hz) MS(EI, m/z) 262(M^+, 11), 261(36), 206(63), 205(73), 177(14), 162(100), 149(73), 148(93), 135(30)

11b (diast II)
m p 118 5-119 5 °C ^{1}H-NMR($CDCl_3$) δ 0 91 and 0 98(2x d, 6H, $CHCH_2CH(CH_3)_2$), 1 22-2 03(m, 3H, $CHCH_2CH(CH_3)_2$), 1 85(s, 1H, NH), 2 66(s, 3H, NCH_3), 3 73(m, 1H, $CHCH_2CH(CH_3)_2$, 3 83(s, 3H, CHPhOMe), 5 24(d, 1H, CHPhOMe, J=1 2 Hz due to coupling with C_α proton), 6 97 and 7 29(AB, 4H, CHPhOMe, J_{ab}=8 7 Hz) IR(KBr, cm^{-1}) 3310(m), 1685(s), 1615(m), 1590(w) MS(EI, m/z) 262(M^+, 18), 261(39), 206(60), 205(100), 177(10), 162(49), 149(51), 148(56), 135(11) Elem anal calc C 68 67, H 8 45, N 10 68, found C 68 65, H 8 47, N 10 56

11c (diast I)
m p 87 5-88 5 °C ^{1}H-NMR($CDCl_3$) δ 1 80(s, 1H, NH), 2 67(s, 3H, NCH_3), 3 84(s, 3H, CHPhOMe), 4 88(d, 1H, NHCHPh), 5 44(d, 1H, CHPhOMe, J=1 5 Hz, due to coupling with C_α-proton), 6 96 and 7 30(AB, 4H, CHPhOMe, J_{ab}=8 7 Hz), 7 26-7 62(m, 5H, CHPh) IR(KBr, cm^{-1}) 3365(w), 3335(w), 1685(s), 1610(m), 1590(w) MS(EI, m/z) 282(M^+, 21), 225(100), 210(10), 175(7), 148(37), 106(15) Elem anal calc C 72 32, H 6 43, N 9 92, found C 72 35, H 6 43, N 9 85

11c (diast II)
m p 119 5-120 5 °C ^{1}H-NMR($CDCl_3$) δ 1 92(s broad, 1H, NH), 2 68(s, 3H, NCH_3), 3 84(s, 3H, CHPhOMe), 4 69(d, 1H, NHCHPh), 5 35(d, 1H, CHPhOMe, J=1 5 Hz, due to coupling with the C_α-proton), 6 97 and 7 37(AB, 4H, CHPhOMe, J_{ab}=8 8 Hz) IR(KBr, cm^{-1}) 3360(s), 1690(s), 1610(s), 1590(m) MS(EI, m/z) 282(M^+, 32), 225(100), 210(16), 196(7), 175(7), 148(54), 106(17) Elem anal calc C 72 32, H 6 43, N 9 92, found C 72 40, H 6 44, N 9 84

11d (diast I)
^{1}H-NMR($CDCl_3$) δ 1 85(s, 1H, NH), 2 55(s, 3H, NCH_3), 2 93 and 3 10(8 lines, AB-part of ABX, 2H, $CHCH_2Ph$, J_{ax}=7 7 Hz, J_{bx}=3 7 Hz, J_{ab}=13 6 Hz), 3 78(s, 3H, CHPhOMe), 4 05(X-part of ABX, 1H, $CHCH_2Ph$, J_{ax}+ J_{bx}=11 1 Hz), 4 80(d, 1H, CHPhOMe, J=1 4 Hz, due to coupling with the C_α-proton), 6 86 and 7 12(AB, 4H, CHPhOMe, J_{ab}=8 5 Hz), 7 26(s, 5H, $CHCH_2Ph$) IR(KBr, cm^{-1}) 3320(w), 1690(s), 1610(m) MS(EI, m/z) 296(M^+, 6), 205(100), 150(17), 91(10) Elem anal calc C 72 95, H 6 80, N 9 45, found C 72 81, H 6 68, N 9 37

11d (diast II)
^{1}H-NMR($CDCl_3$) δ 1 82(s, 1H, NH), 2 53(s, 3H, NCH_3), 3 12 and 3 23(8 lines, AB-part of ABX, 2H, J_{ax}=4 8 Hz, J_{bx}=5 1 Hz, J_{ab}=14 0 Hz, $CHCH_2Ph$), 3 78(s, 3H, CHPhOMe), 3 84(X-part of ABX, J_{ax}+ J_{bx}=9 6 Hz, 1H, $CHCH_2Ph$), 5 06(d, 1H, CHPhOMe, J=1 0 Hz, due to coupling with the C_α-proton), 6 73(s, 4H, CHPhOMe), 7 24(s, 5H, $CHCH_2Ph$) IR(KBr, cm^{-1}) 3320(m), 1680(s), 1610(m) MS(EI, m/z) 296(M^+, 6), 205(100), 150(16), 91(10) Elem anal calc C 72 95, H 6 80, N 9 45, found C 72 86, H 6 82, N 9 43

12a (one diastereomer isolated)
m p 179 5-180 5 °C ^{1}H-NMR($CDCl_3$) δ 1 42(d, 3H, $CHCH_3$), 2 54(s, 3H, NCH_3), 3 53(q, 1H, $CHCH_3$), 3 82(s, 3H, CHPhOMe, 4 87(s, 1H, CHPhOMe), 5 07(s, broad, 1H, NOH), 6 94 and 7 32(AB, 4H, CHPhOMe, J_{ab}=8 8 Hz) IR(KBr, cm^{-1}) 3330(s), 1675(s), 1610(m), 1590(w) MS(EI, m/z) 236(M^+, 8), 218(8), 162(15), 149(100), 148(100), 128(100) Elem anal calc C 61 00, H 6 83, N 11 86, found C 60 96, H 6 83, N 11 66

12b (diast I)
^{1}H-NMR($CDCl_3$) δ 0 96 and 0 99(d 2x, 6H, $CH(CH_3)_2$), 1 48-2 17(m, 3H, $CHCH_2CH(CH_3)_2$), 2 55(s, 3H, NCH_3), 3 58(t, 1H, $CHCH_2CH(CH_3)_2$), 3 84(s, 3H, CHPhOMe), 4 88(s, 1H, CHPhOMe), 5 02(s, 1H, NOH), 6 93 and 7 30(AB, 4H, CHPhOMe, J_{ab}8 8 Hz) IR(KBr, cm^{-1}) 3350(s), 1680(s), 1610(m), 1590(w) MS(EI, m/z) 278(M^+, 5), 221(22), 205(15), 170(50), 149(90), 114(100) Elem anal calc C 64 73, H 7 97, N 10 06, found C 64 75, H 7 97, N 10 00

12b (diast II)
^{1}H-NMR($CDCl_3$) δ 0 90 and 0 94(d 2x, 6H, $CHCH_2CH(CH_3)_2$), 1 47-2 05(m, 3H, $CHCH_2CH(CH_3)_2$), 2 78(s, 3H, NCH_3), 3 61(t, 1H, $CHCH_2CH(CH_3)_2$), 3 82(s, 3H, CHPhOMe), 4 8-5 5(s broad, 1H, NOH), 5 36(s, 1H, CHPhOMe), 6 92 and 7 20(AB, 4H, CHPhOMe, J_{ab}=8 7 Hz) IR(KBr, cm^{-1}) 3260(m), 1675(s), 1610(m), 1585(w) MS(EI, m/z) 278(M^+, 2), 221(20), 205(15), 170(44), 149(84), 114(100) Elem anal calc C 64 73, H 7 97, N 10 06, found C 64 67, H 8 00, N 9 85

12c (diast II)
m p 176-177°C(dec) ^{1}H-NMR($CDCl_3$) δ 2 62(s, 3H, NCH_3), 3 85(s, 3H, CHPhOMe), 4 54(s, 1H, CHPh), 5 02(s, 1H, NOH), 5 06(s, 1H, CHPhOMe), 6 98 and 7 54(AB, 4H, CHPhOMe, J_{ab}=8 7 Hz), 7 31-7 54(m, 5H, CHPh) IR(KBr, cm^{-1}) 3410(s, broad), 1695(s), 1610(m), 1585(w) MS(EI, m/z) 298(M^+, 6), 280(31), 224(18), 190(100), 149(84), 148(82) Elem anal calc C 68 44, H 6 08, N 9 39, found C 68 32, H 6 04, N 9 36

12d (diast II)
m p 160-161 °C ^{1}H-NMR($CDCl_3$) δ 2 51(s, 3H, NCH_3), 3 04 and 3 28(8 lines, AB-part of ABX, 2H, J_{ax}=7 0 Hz, J_{bx}=4 4 Hz, J_{ab}=13 9 Hz, $CHCH_2Ph$), 3 80(s, 3H, CHPhOMe), 3 84(X-part of ABX, 1H, $CHCH_2Ph$), 4 71(s, 1H, NOH), 4 86(s, 1H, CHPhOMe), 6 88 and 7 11(AB, 4H, CHPhOMe, J_{ab}=8 7 Hz), 7 26(s, 5H, $CHCH_2Ph$) IR(KBr, cm^{-1}) 3300(s, broad), 1680(s), 1610(m), 1585(w) MS(EI, m/z) 312(M^+, 2), 294(6), 221(100), 204(19), 148(30), 91(16), 85(54) Elem anal calc C 69 21, H 6 45 N 8 97, found C 69 17, H 6 49, N 8 81

13a
m p 131-132 °C ^{1}H-NMR($CDCl_3$) δ 1 25(d, 3H, $CHCH_3$), 2 85(d, 3H, $NHCH_3$), 3 60(q, 1H, $CHCH_3$), 4 8-5 3(s broad, 2H, NHOH), 6 5-6 9(s broad), 1H, $NHCH_3$) IR(KBr, cm^{-1}) 3100-3500(s, broad), 1650(s), 1550(s) MS(CI, m/z) 119(M^++1, 77), 103(8), 87(11), 74(17), 60(100) Elem anal calc C 40 67, H 8 53, N 23 71, found C 40 97, H 8 56, N 23 27 $[\alpha]_D^{20}$-45 7(c 2, MeOH)

13b
m p 85-86°C ^{1}H-NMR($CDCl_3$) δ 0 94(d, 6H, $CH_2CH(CH_3)_2$), 1 29-1 84(m, 3H, $CH_2CH(CH_3)_2$), 2 86(d, 3H, $NHCH_3$), 3 50(4 lines, X-part of ABX, $CHCH_2CH(CH_3)_2$, J_{ax}+ J_{bx}=14 4 Hz), 3 8-5 1(s broad, 2H, NHOH), 6 1-6 6(broad, 1H, $NHCH_3$) IR(KBr, cm^{-1}) 3340(s), 3250(s), 3130(s), 1660(s), 1560(s) MS(CI, m/z) 161(M^++1, 100), 141(21), 102(82), 86(14) $[\alpha]_D^{20}$ -28 0(c 2, $CHCl_3$)

13c
^{1}H-NMR($CDCl_3$) δ 2 83(d, 3H, $NHCH_3$), 4 2-5 0(broad, 2H, NHOH), 4 62(s, 1H, CHPh), 6 4-6 7(broad, 1H, $NHCH_3$), 7 35(s, 5H, CHPh)

13d
m p 151-152 5 °C ^{1}H-NMR($CDCl_3$) δ 2 36-3 93(s broad, 2H, NHOH), 2 81 and 3 12(8 lines, AB-part of ABX, 2H, J_{ax}=9 7 Hz, J_{bx}=4 9 Hz, J_{ab}=13 9 Hz, $CHCH_2Ph$), 2 84(d, 3H, $NHCH_3$), 3 67(4 lines, X-part of ABX, 1H, J_{ax}+ J_{bx}=14 5 Hz, $CHCH_2Ph$), 6 2-6 6(s broad, 1H, $NHCH_3$), 7 27(s, 5H, $CHCH_2Ph$) IR(KBr, cm^{-1}) 3390(s), 3220(s), 1645(s), 1550(s) MS(CI, m/z) 195(M^++1, 52), 120(100), 118(45), 91(51), 58(32) Elem anal calc C 61 84, H 7 27, N 14 42,

found C 61 78, H 7 27, N 14 35 $[\alpha]_D^{20}$ +6 6(c 2, MeOH), $[\alpha]_{Hg365}^{20}$+30 6(c 2, MeOH)

15b
^{1}H-NMR($CDCl_3$) δ 0 96 and 0 98(d 2x, 6H, $CH_2CH(CH_3)_2$), 2 00-2 71(m, 3H, $CH_2CH(CH_3)_2$), 2 91(s, 3H, NCH_3), 3 83(s, 3H, CHPhOMe), 5 70(s, 1H, CHPhOMe), 6 97 and 7 24(AB, 4H, CHPhOMe, J_{ab}=8 6 Hz) MS(EI, m/z) 276(14, M^+), 259(88), 148(100), 135(84), 121(17)

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