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UNUSUAL AMINO ACIDS
III. ASYMMETRIC SYNTHESIS OF 3-ARYLALANINES

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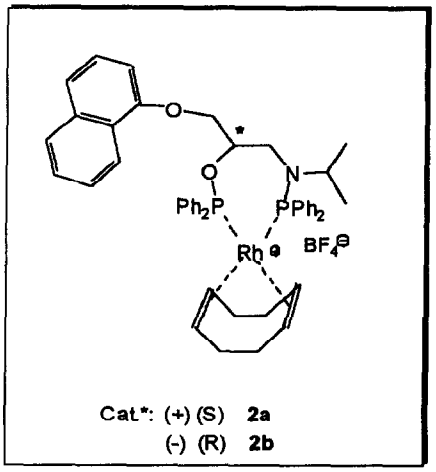
Abstract: 21 (Z)-α-N-benzoylamino-ß-arylacrylic acids and their esters were prepared by known procedures and hydrogenated to the corresponding optically active α-benzoyl-ß-arylalanine derivatives with optical yields in the range of 82-95% ee using the cationic rhodium complex of "PROPRAPHOS" as the chiral catalyst No electronical influences of the substituents at the aryl moiety on the enantioselectivity were observed but a sterical one, proved by X-ray crystallographic analysis and computer-aided modellings. Deacylation of the hydrogenated spezies produced the hydrochlorides of the 3-arylalanines attended by a partial racemisation. In this case the hydrogenation of urethane type protected dehydroaminoacid derivatives seems to be the alternative.

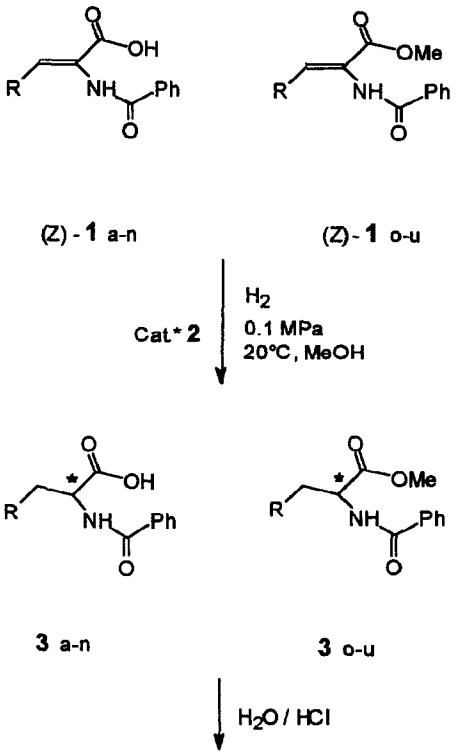
Introduction: Both 3-arylsubstituted alanines and fluorine-containing amino acids **1** are of considerable pharmacological interest. The (S)- and the (R)-enantiomers are used in biologically active peptides and often achieve important agonistic and antagonistic effects.

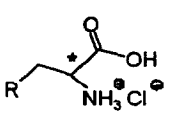
This applies particularly to the 3-(2-naphthyl)-alanine (in LHRH[2,3], oxytocin[4]) but also the 4-chlorophenylalanine[5] Optically active 3-arylalanines R-CH_2-CH(NH_2)-COOH have been obtained almost exclusively by separation of racemic compounds. This can be achieved both enzymatically (e.g. α-chymotrypsin, carboxypeptidase AII and other acylases; R= 4-Cl-C_6H_4, 4-CH_3O-C_6H_4, 2- and 4-CH_3-C_6H_4, 1- and 2-naphtyl)[6,7], and by using optically active auxiliars (e.g. (-)-α-phenylethylamine, L-(+)-threo-1-(p-nitrophenyl)-2-amino-1,3-propanediol; R= 4-Cl-C_6H_4)[8]. p-Nitrophenylalanine can be obtained by nitration of (S)-phenylalanine[9]

The homogeneous catalytic hydrogenation using rhodium-phosphane complexes has become a powerful tool in the field of asymmetric synthesis. It is extensively used and described (see [10] for reviews) and successfully applied e.g. to 2-acylamino-3-alkylacrylates[11], α-aminoketones[12], diketones[13] as well as to phenylalanine- and DOPA-precursors. In spite of this success the synthesis of 3-arylalanine derivatives by the pathway shown in scheme 1 is mentioned very rarely. Cativiela et al. could achieve only unsatisfactory enantioselectivities (75%ee, only one case of 85% ee) for the hydrogenation of dehydroaminoacid derivatives **1** (R= 4-CH_3-C_6H_4, 4-CH_3O-C_6H_4, 4-Cl-C_6H_4, 4-NO_2-C_6H_4, 4-NH_2-C_6H_4) with the DIOP-ligand[14]. Only Nagel et al. have attained enantiomeric excesses of 95-99% ee by the use of N-substituted 3,4-bis-(diphenylphosphano)-pyrrolidine ligands (e.g. for **1**; R= 4-HO-C_6H_4, 4-CH_3O-C_6H_4, 4-CH_3-C_6H_4, 3-indenyl)[15].

These surprising facts as well as the good results in the use of aminophosphanphosphinite complex **2**[1,16] prompted us to check this system for the hydrogenation of 3-arylsubstituted dehydroaminoacid derivatives **1**







Scheme 1

4 a-u

Abbr.	R	Abbr.	R	Abbr.	R
a	4-Cl-C_6H_4	h	2.4.6.$(CH_3)_3$-C_6H_2	o	4-Cl-C_6H_4
b	4-NO_2-C_6H_4	i	4-CH_3-C_6H_4	p	4-NO_2-C_6H_4
c	4-NC-C_6H_4	j	4-iC_3H_7-C_6H_4	q	4-CH_3O-C_6H_4
d	4-CH_3O-C_6H_4	k	1-naphtyl	r	4-$(CH_3)_2N$-C_6H_4
e	4-$(CH_3)_2N$-C_6H_4	l	2-naphthyl	s	2.4.$(CH_3)_2$-C_6H_3
f	2-CH_3-C_6H_4	m	9-anthracyl	t	4-iC_3H_7-C_6H_4
g	2.4.$(CH_3)_2$-C_6H_3	n	9-phenanthryl	u	2-naphthyl

Results and discussion: The substrates (Z)-**1** were synthesized from the (Z)-2-phenyl-4-arylmethylidene-Δ^2-oxazoline-(5)-ones (azlactones), available by the Erlenmeyer condensation[17]. The azlactones leading to **1**m,n were obtained by the reaction of 2-phenyl-Δ^2-oxazoline-(5)-one[18] with the corresponding aldehydes. The resulting mixture of (Z)- and (E)-isomers can be separated either before or after conversion to **1**m,n. The ring opening by known methods led to **1**a-n using diluted aqueous NaOH (method A[14]), NaOH in aqueous alcohols (method B[19]) or an aqueous solution of Na_2CO_3 (method C). The methyl esters **1**o-u were obtained by conversion of the corresponding azlactones with Na/CH_3OH (method D[20]), $NaHCO_3/CH_3OH$ (method E[21]) or H_2SO_4/CH_3OH (method F[22]). The results concerning the synthesis of **1**a-u are summarized in table 1

Table 1 (Z)-dehydroaminoacids **1**a-n and their esters **1**o-u from azlactones

	R	meth.[a]	yield [%][b]	m.p. [°C]	m.p.(lit.) [°C]	ref
1a	4-Cl-C_6H_4	A	68	210-212(Z)[c]	213-214[c]	[14]
1b	4-NO_2-C_6H_4	C	45	236-242(Z)[d]	243[d]	[23]
1c	4-NC-C_6H_4	B	[e]	203-208[f]	218-220[g]	[24]
1d	4-CH_3O-C_6H_4	A	80	224-228(Z)[f]	225[f]	[21]
1e	4-$(CH_3)_2N$-C_6H_4	B	30	211-213(Z)[c]	214-216[c]	[25]
1f	2-CH_3-C_6H_4	A	58	211-218[c]	225-228[f]	[26]
1g	2.4.$(CH_3)_2$-C_6H_3	A	36	215-216[c]	--	--
1h	2.4.6.$(CH_3)_3$-C_6H_2	B	60	211-213[c]	--	--
1i	4-CH_3-C_6H_4	A	82	221-222[c]	232[f]	[26]
1j	4-iC_3H_7-C_6H_4	A	82	194-196[f]	201[f]	[21]
1k	1-naphthyl	B	60	214-218(Z)[c]	221[f]	[27]
1l	2-naphthyl	A	57	226-230(Z)[h]	229-230[h]	[27]
1m	9-anthracyl	A	47[i]	218-220(Z)[c]	--	--
1n	9-phenanthryl	A	48	225-228[j]	--	--
1o	4-Cl-C_6H_4	E	55	137-138[g]	135-136[g]	[28]
1p	4-NO_2-C_6H_4	F	39	192-193[c]	193-194[g]	[28]
1q	4-CH_3O-C_6H_4	F	72	152-153[k]	158[l]	[21]
1r	4-$(CH_3)_2N$-C_6H_4	D	55	183-184[h]	180-181[g]	[28]
1s	2 4.$(CH_3)_2$-C_6H_3	D	65	144-145[h]	--	--
1t	4-iC_3H_7-C_6H_4	E	56	122-124[g]	128[g]	[21]
1u	2-naphthyl	D	56	139-142[g]	--	--

a see text **b** regarding the azlactone **c** from EtOH **d** from HOAc **e** by stirring a mixture of acid/ester in $CHCl_3$ and separating **f** from 75% $EtOH/H_2O$ **g** from MeOH **h** from 75% $MeOH/H_2O$ **i** from the pure(Z)-azlactone **j** 1xEtOH, 1x ac./H_2O **k** from benzene/MeOH **l** from benzene/ligroin

The asymmetric hydrogenations of the dehydroaminoacid derivatives 1a-u in the presence of **2** were performed by using 2 mmol of the substrate in 15 ml methanol at 25°C and 0,1 MPa (substrate : catalyst = 200 : 1) The results are summarized in tables 2 and 3.

Table 2 Catalytic asymmetric hydrogenations of 1a-n

Entry	Substr.	Cat.	Product (config.[a])	ee [%]	after re-crystall.
1	**1a**	**2a**	**3a** (R)	90	99[b]
2	**1b**	**2a**	**3b** (R)	91	
3		**2b**	**3b** (S)	90	
4	**1c**	**2a**	**3c** (R)	95	
5	**1d**	**2a**	**3d** (R)	90	97[c]
6		**2b**	**3d** (S)	92	
7	**1e**	**2b**	**3e** (S)	72d	
8	**1f**	**2a**	**3f** (R)	86	
9	**1g**	**2a**	**3g** (R)	79	92[b]
10	**1h**	**2a**	no reaction		
11	**1i**	**2a**	**3i** (R)	89	92[e]
12	**1j**	**2a**	**3j** (R)	92	
13	**1k**	**2a**	**3k** (R)	86	98[b]
14		**2b**	**3k** (S)	88	
15	**1l**	**2a**	**3l** (R)	87	97[f]
16		**2b**	**3l** (S)	92	97[f]
17	**1m**	**2a**	no reaction		
18	**1n**	**2a**	**3n** (R)	65[g]	
19		**2b**	**3n** (S)	63[h]	

a assumed configuration **b** from 70% MeOH/H_2O **c** from benzene/petrol-ether **d** 1:100, see text **e** from benzene/n-hexane **f** from benzene
g 1:100 **h** 1:50

Table 3 Catalytic asymmetric hydrogenations of **1**o-u

Entry	Substr.	Cat.	Product (config.[a])	ee [%]	after re-crystall.[b]
1	1o	2a	3o (R)	89	96
2	1p	2a	3p (R)	80[c]	
3	1q	2a	3q (R)	88	93
4		2b	3q (S)	91	92
5	1r	2b	3r (S)	85	
6	1s	2b	3s (S)	82	
7	1t	2b	3t (S)	89	99
8	1u	2a	3u (R)	89	
9		2b	3u (S)		89

a assumed configuration **b** from 70% MeOH/H_2O **c** small impurities in **1**p (TLC)

The results allow the following conclusions:

1. The catalyst **2** is capable to hydrogenate the used 3-aryl-substituted dehydroaminoacid derivatives **1**a-n with high enantioselectivities (85-95% ee, exceptions see text below). The corresponding methyl esters 1o-u gave some lower enantiomeric excesses (82-91% ee), they do not show any advantages in relation to the acids. The yields are quantitative. By realizing good stirring conditions the hydrogenations can be carried out in suspension too without any diminution of the enantioselectivity (i.e. **1**b). The t/2-time (for uptake of 50% of theoretical hydrogen volume) amounts to three minutes at most, the best less than one minute, but are not correct due to the diffusion controlled uptake of hydrogen.

2. In some cases the enantiomeric purities of **3** can be raised up by recrystallisation (see last column in the tab's 2 and 3).

3. The purity of the substrate 1 is essential for reaching high enantioselectivities. So the two-fold recrystallized acid 1j gave 92% ee (1 : 200, tab.2, entry 12), whereas the single recrystallized one showed an enantioselectivity of 72% ee only (1:100). This effect of small impurities in the substrate must be assumed as the reason for the low enantioselectivity of the hydrogenation of **1**e too (tab.2, entry 7) - especially as the methyl ester **1**r could be hydrogenated with 85% ee (tab.3, entry 5).

4. There do not exist any electronical influences of the substituents at the aryl moiety R on the enantioselectivity of the hydrogenation. No significant differences between the enantiomeric excesses of substrates with electronwithdrawing and electrondonating substituents were observed.

However, there seems to exist a steric influence by substitution ortho to the linking atom with the double bond If the aryl moiety is substituted only at one side (**1f,g,k,l,n** and **1s,u**), the hydrogenation could be carried out with satisfactory but reduced (**1g,n**) enantioselectivities. Substituition on both sides (**1h,m**) seems to reduce the accessibility of the double bond and prevent the formation of the catalyst-substrate adduct. The X-ray crystallographic analysis of **1h** (fig.1) suggests this conclusion.

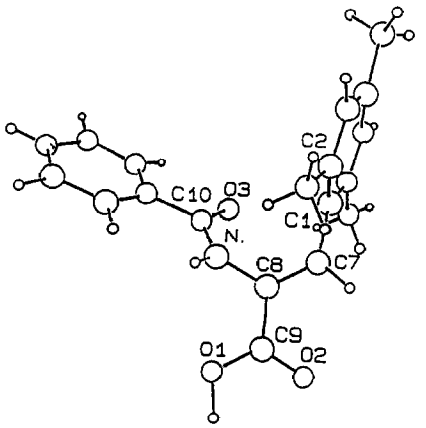


Fig.1. **1h** (one of six conformations with minimal free energy)

The deacylation of **3** to the aminoacid hydrochlorides **4** succeeds by using concentrated hydrochloric acid, attended by partial racemisation depending on the duration of hydrolysis and the moiety R (see table 4) This suggests the hydrogenation of dehydroaminoacid derivatives with milder decomposing protective groups (urethane type, available by a Wittig-Horner reaction[29]). So the (Z)-methyl-2-benzyloxycarboxyamino-3-(2-naphthyl)-acrylate could be hydrogenated by **2a** (1:100, 15 ml CH_3OH, 25°C, 0,1 MPa) to the corresponding optically active protected aminoacid methyl ester with 89 % ee (R).

Table 4 Deacylation of **3** to the α-aminoacid hydrochlorides **4**

compound	ee [3] [%]	ee [4][a] [%]	t[b] [h]	chem.yield[c] [%]
(R)-3a	99	90	5	50
(R)-3b	91	82	7	70
(R)-3g	92	85	7	80
(R)-3j	91	85	5	75
(R)-3k	98	90	7	85

a not recrystallized product **b** duration of hydrolysis **c** regarding **3**

Experimental: Apparatus ^{1}HNMR spectra were recorded on a 100 MHz spectrometer (KRH 100), ^{13}CNMR. spectra on a 80 MHz spectrometer (TESLA BS 587 A) with TMS as internal standard. Optical rotation was measured on a Polamat A polarimeter (Carl Zeiss Jena) The enantiomeric excess (%ee) were determined by GLC on a Hewlett-Packard chromatograph 5880 A fitted with a 4,3 m capillary column XE-60 (N-L-valine-tert.-butylamide, FID, split 1:60, 175°C for the acylated amino acid derivatives **3**o-u, for **3**a-n after esterification with diazomethane. HPLC measurements were carried out on a Knauer chromatograph (pump 64) equiped with a CHIRALPAK WH column (J.T. Baker B.V.) and connected with an EPSON PC AX 2e Melting points were determined by a BÜCHI 535 apparatus (Thiele type).

Hydrogenation, general procedure:

Hydrogenations were performed under normal pressure and 25°C principally as described by Kagan[30] 1 ml of the hydrogenated solution was esterified by a freshly prepared solution of diazomethane (**3**a-n) in order to determine the ee by GLC. The other part was freed from the solvent and recrystallized

Deacylation, general procedure:

The recrystallized optically active compounds were refluxed in concentrated hydrochloric acid for several hours. The formed benzoic acid was filtered off, the filtrate extracted three times with ether and the acidic aqueous layer carefully concentrated under reduced pressure at 30-35°C. The colorless crystals were collected and recrystallized from concentrated hydrochloric acid (results see table 4).

Chemicals:

All solvents were purified and dried by usual methods and stored, if necessary under argon. Catalysts were prepared according to published methods.[16,31]

(R)-4-Chloro-N-benzoyl-phenylalanine **3a**:

m.p. 159-161°C (MeOH/H_2O), $[\alpha]_D^{20}$ = +31.6 (c1,MeOH), 99% ee (HPLC)

^{1}HNMR ($CDCl_3$): 3.20 (m, 2H, CH_2), 5.05 (dt, 1H, CH, ^{3}J=7.5 Hz), 6.60 (d, 1H, NH, ^{3}J=7.5 Hz), 7 00 (d, 2H, 3',5', ^{3}J=8 Hz), 7.25 (d, 2H, 2',6', ^{3}J=8 Hz), 7 35-7 50 (m, 3H, m,p-PhCO), 7.70 (dd, 2H, o-PhCO, ^{3}J=8 Hz, ^{4}J=2 Hz)

^{13}CNMR ($CDCl_3$): 37.7 (CH_2), 53.5 (CH), 127.0 (m-PhCO), 128.7 (o-PhCO), 128.7 (3',5'), 130 7 (2',6'), 132 0 (p-PhCO), 133 2 (4'), 133.7 (C-CO), 134.5 (1'), 167.8 (C=O), 175.0 (COOH)

(R)-4-Nitro-N-benzoyl-phenylalanine **3b**:

m.p 196-198°C (dec.) (MeOH/H_2O). $[\alpha]_D^{20}$ = +58.4 (c1,MeOH), 91% ee (HPLC)

^{1}HNMR ($CDCl_3$): 3.25 (m,2H,CH_2), 4.70 (m, 1H, CH), 7 30-7.50 (m, 3H, m,p-PhCO), 7.50 (d, 2H, 2',6', ^{3}J=9 Hz), 7.70 (dd, 2H, o-PhCO, ^{3}J=8 Hz, ^{4}J=2 Hz), 8.05 (d, 2H, 3',5', ^{3}J=9 Hz), 8.70 (d, 1H, NH), 12 80 (br, 1H, COOH)

^{13}CNMR ($CDCl_3$): 37.9 (CH_2), 53.5 (CH), 127.0 (m-PhCO), 127.7 (3',5'), 128.7 (o-PhCO), 130.3 (2',6'), 132 0 (p-PhCO), 133.7 (C-CO), 143.9 (1'), 147.3 (4'), 167.8 (C=O), 175.0 (COOH)

4-Methoxy-N-benzoyl-phenylalanine **3d**:

m.p. 128-130°C (benzene/ligroin), **(R)** $[\alpha]_D^{20}$ = +33.4 (c1,MeOH), 97% ee (HPLC), **(S)** $[\alpha]_D^{20}$ = -29 7 (c1,MeOH), 96% ee (HPLC)

^{1}HNMR ($CDCl_3$):3.20 (m, 2H, CH_2), 3.70 (s, 3H, CH_3O), 5.00 (m, 1H, CH), 6.75 (d, 2H, 3',5', ^{3}J=8 Hz), 7 05 (d, 2H, 2',6', ^{3}J=8 Hz), 7.30-7.50 (m, 3H, m,p-PhCO), 7.60 (dd, 2H, o-PhCO), 7.60 (br, 1H, NH)

^{13}CNMR ($CDCl_3$): 36.3 (CH_2), 53 5 (CH), 55.2 (CH_3O), 114.2 (3',5'), 127.0 (m-PhCO), 127.7 (1'), 128 7 (o-PhCO), 130.4 (2',6'), 132.0 (p-PhCO), 133.7 (C-CO), 158.9 (4'), 167.8 (C=O), 175.0 (COOH)

(R)-2,4. Dimethyl-N-benzoyl-phenylalanine **3g**:

m.p. 164-166°C (MeOH/H_2O), $[\alpha]_D^{20}$ = +69.7 (c1,MeOH), 92% ee (HPLC)

^{1}HNMR (Aceton-d_6): 2.15 (s, 3H, 2-CH_3), 2.30 (s, 3H, 4-CH_3), 3.00 (CH), 3.24 (CH', $^2J_{HH'}$=14 Hz, $^3J_{HH\alpha}$=9 Hz, $^3J_{H'H\alpha}$=5.5 Hz), 4.82 (H_α, $^3J_{H\alpha\text{-}NH}$=9 Hz), 6.80 (d, 1H, 5', $^3J_{HH}$=7 Hz), 6.85 (s, 1H, 3'), 7.10 (d, 1H, 6'), 7.25-7.40 (m,p-PhCO), 7.70 (dd, 2H, o-PhCO, $^3J_{HH}$=8 Hz, $^4J_{HH}$=2 Hz), 7.70 (d, 1H, NH, $^3J_{NH\text{-}H\alpha}$=9 Hz)

^{13}CNMR (Aceton-d_6): 19.3 (2-CH_3), 20.9 (4-CH_3),35.4 (CH_2), 53.5 (CH), 126.7 (5'), 127 0 (m-PhCO), 128.7 (o-PhCO), 129.8 (6'), 131.2 (1'), 131.5 (3'), 132.0 (p-PhCO), 133.7 (C-CO), 136.6 (2'), 136.8 (4'), 167 8 (C=O), 175.0, (COOH)

(R)-4-Methyl-N-benzoyl-phenylalanine **3i**:

m.p. 133-136°C (benzene/n-hexane), $[\alpha]_D^{20}$ = +35,8 (c1,MeOH), 92% ee (HPLC)

^{1}HNMR ($CDCl_3$): 2.25 (s, 3H, 4-CH_3), 3 25 (m, 2H, CH_2), 5.05 (dt, 1H, CH), 6.70 (d, 1H, NH), 7 00 (s, 4H, 2',3',5',6'), 7.30-7.45 (m,p-PhCO), 7.65 (dd, 2H, o-PhCO), 9.00 (br, 1H, COOH)

^{13}CNMR ($CDCl_3$): 21.0 (4-CH_3), 36.9 (CH_2), 53.2 (CH), 127.0 (m-PhCO), 128.7 (o-PhCO), 129 3 (2',6'), 129 4 (3',5'), 132.0 (p-PhCO), 132.5 (4'), 133.7 (C-CO), 136.9 (1'), 167.8 (C=O), 175.0 (COOH)

(R)-4-Isopropyl-N-benzoyl-phenylalanine **3j**:

m.p. 192-194°C (MeOH/H_2O), $[\alpha]_D^{20}$ = +35,2 (c1,MeOH), 92% ee (HPLC)

^{1}HNMR ($CDCl_3$): 1.15 (d, 6H, $(CH_3)_2$, ^{3}J=7 Hz), 2.85 (qq, 1H, CH, ^{3}J=7 Hz), 3.25 (m, 2H, CH_2), 5 05 (m, 1H, CH_α), 6 60 (d, 1H, NH, ^{3}J=7 5 Hz), 7.10 (s, 4H, 2',3',5',6'), 7.30-7.50 (m, 3H, m,p-PhCO), 7 65 (o-PhCO), 9.90 (br, 1H, COOH)

^{13}CNMR ($CDCl_3$): 24.0 (CH_3), 33.8 (CH), 36.8 (CH_2), 53.5 (CH_α), 126.9 (3',5'), 127 0 (m-PhCO), 128 7 (o-PhCO), 129.4 (2',6'), 132.0 (p-PhCO), 132.9 (1'), 133.7 (C-CO), 148.0(4'), 167.8 (C=O), 175 0 (COOH)

N-Benzoyl-3-(1-naphthyl)-alanine **3k**:

m.p.155-157°C (MeOH/H_2O), **(R)** $[\alpha]_D^{20}$ = +140.6 (c1,MeOH), 98% ee (HPLC), **(S)** $[\alpha]_D^{20}$ = -144 2 (c1, MeOH), 91% ee (HPLC)

^{1}HNMR ($CDCl_3$): 3.74 (m, 2H, CH_2), 5.18 (dt, 1H, CH), 6.70 (d, 1H, NH, $^3J_{HH}$=8 Hz), 6.95-8.25 (m, 7H, 2'-8'), 7.40 (m, 3H, m,p-PhCO), 7.80 (m, 2H, o-PhCO)

^{13}CNMR ($CDCl_3$): 37.4 (CH_2), 53.9 (CH), 123.5 (8'), 125.4 (6'), 125.9 (7'), 126.6 (2'), 127 1 (m-PhCO), 127.7 (3'), 128.3 (4'), 128.6 (o-PhCO), 129.0 (5'), 132 0 (p-PhCO), 132.1/132 3 (9',10'), 133.3 (C-CO), 134 0 (1'), 168 1 (C=O), 174.7 (COOH)

N-Benzoyl-3-(2-naphthyl)-alanine **3l**:

m p.153-155°C (Benzene), **(R)** $[\alpha]_D^{20}$ = +32.0 (c1,MeOH), 97% ee (HPLC), **(S)** $[\alpha]_D^{20}$ = -28.4 (c1, MeOH), 97% ee (HPLC)

^{1}HNMR ($CDCl_3$): 3.40 (m, 2H, CH_2), 5.15 (dt, 1H, CH), 6.80 (d, 1H, NH, ^{3}J=8 Hz), 7.15-7.45 (m, 6H, 3',6',7', m,p-PhCO), 7.50-7.75 (m, 6H, 1',4',5',8'; o-PhCO), 8.45 (s, 1H, COOH)

^{13}CNMR ($CDCl_3$): 37.5 (CH_2), 53.8 (CH), 125.9 (6'), 126.3 (7'), 127.1 (m-PhCO), 127.4 (1'), 127.6-127 7 (3',4'), 128.3-128.4 (5',8'), 128.7 (o-PhCO), 132.0 (p-PhCO), 132.6 (10'), 133.2 (9'), 133.5 (2'), 133.5 (C-CO), 167.9 (C=O), 174.8 (COOH)

(R)-N-Benzoyl-3-(9-phenanthryl)-alanine **3n**:

m.p. 225-227°C ($MeOH/H_2O$), $[\alpha]_D^{20}$ = +56,3 (c1,MeOH), 72% ee (HPLC)

^{1}HNMR ($CDCl_3$): 3.70 (m, 2H, CH_2), 4.95 (m, 1H, CH), 7.50 (m, 3H, m,p-PhCO), 7.50-7.90 (m, 6H, 1',2',3',6',7',8'), 7.80 (m, 2H, o-PhCO), 8.70-8.90 (m, 2H, 4',5')

(R)-4-Chloro-N-benzoyl-phenylalanine-methylester **3o**:

m.p. 98-99°C ($MeOH/H_2O$), $[\alpha]_D^{20}$ = +51.9 (c1,MeOH), 96% ee (HPLC)

^{1}HNMR ($CDCl_3$): 3.20 (m, 2H, CH_2), 3.70 (s, 3H, OCH_3), 5.05 (dt, 1H, CH, $^3J_{H\alpha\text{-}NH}$=7.5 Hz), 6.60 (d, 1H, NH, $^3J_{NH\text{-}H\alpha}$=7.5 Hz), 7.00 (d, 2H, 3'5', $^3J_{HH}$=8 Hz), 7.25 (d, 2H, 2',6', $^3J_{HH}$=8 Hz), 7 35-7 50 (m, 3H, m,p-PhCO), 7.70 (dd, 2H, o-PhCO, $^3J_{HH}$=8 Hz, $^4J_{HH}$=2 Hz)

^{13}CNMR ($CDCl_3$): 37.7 (CH_2), 52.5 (OCH_3), 53 5 (CH), 127.0 (m-PhCO), 128.7 (o-PhCO), 128.7 (3',5'), 130.7 (2',6'), 132.0 (p-PhCO), 133.2 (4'), 133.7 (C-CO), 134.5 (1'), 166.9 (C=O), 172.2 ($\underline{C}OOCH_3$)

(R)-4-Nitro-N-benzoyl-phenylalanine-methylester **3p**:

m.p 154-155°C ($MeOH/H_2O$), $[\alpha]_D^{20}$ = +73.2 (c1,MeOH), 91% ee (HPLC)

^{1}HNMR ($CDCl_3$): 3.4 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 5.10 (m, 1H, CH), 6.65 (d, 1H, NH), 7 25 (d, 2H, 2',6', $^3J_{HH}$=8 Hz), 7.35-7.50 (m, 3H, m,p-PhCO), 7.70 (dd, 2H, o-PhCO, $^3J_{HH}$=8 Hz, $^4J_{HH}$=2 Hz), 8.10 (d, 2H, 3',5', $^3J_{HH}$=8 Hz)

^{13}CNMR ($CDCl_3$): 37.9 (CH_2), 52.5 (OCH_3), 53.5 (CH), 127.0 (m-PhCO), 127.7 (3',5'), 128.7 (o-PhCO), 130.3 (2',6'), 132 0 (p-PhCO), 133.7 (C-CO), 143.9 (1'), 147 3 (4'), 166.9 (C=O), 172.3 (COOCH3)

4-Methoxy-N-benzoyl-phenylalanine-methylester **3q**:

m.p. 82-84°C ($MeOH/H_2O$), **(R)** $[\alpha]_D^{20}$ = +37.3 (c1,MeOH), 93% ee (HPLC), **(S)** $[\alpha]_D^{20}$ = -41 8 (c1,MeOH), 92% ee (HPLC)

^{1}HNMR ($CDCl_3$): 3.20 (m, 2H, CH_2), 3.75 (s, 3H, $COOCH_3$), 3.75 (s, 3H, OCH_3), 5.05 (dt, 1H, CH), 6 60 (d, 1H, NH, $^3J_{NH\text{-}H\alpha}$=7 Hz), 6.80 (d, 2H, 3',5', $^3J_{HH}$=8 Hz), 7.00 (d, 2H, 2',6', $^3J_{HH}$=8 Hz), 7.30-7 50 (m, 3H, m,p-PhCO), 7.70 (dd, 2H, o-PhCO)

^{13}CNMR ($CDCl_3$): 37.2 (CH_2), 52.5 ($COO\underline{C}H_3$), 55.3 (OCH_3), 114.1 (3',5'), 127.0 (m-PhCO), 127.9 (1'), 128.7 (o-PhCO), 130.4 (2',6'), 132.0 (p-PhCO), 133.7 (C-CO), 158.9 (4'), 166.9 (C=O), 172.3 (COOCH3)

(S)-2,4,Dimethyl-N-benzoyl-phenylalanine-methylester **3s**:

m p. 94-96°C (MeOH/H_2O), $[\alpha]_D^{20}$ = -58.1 (c1,MeOH), 82% ee (HPLC)

^{1}HNMR ($CDCl_3$): 2.30 (s, 3H, 2-CH_3), 2.35 (s, 3H, 4-CH_3), 3.20 (m, 2H, CH_2), 3.70 (s, 3H, OCH_3), 5 05 (dt, 1H, CH, $^3J_{H\text{-}NH}$=8 Hz), 6.80 (d, 1H, NH, $^3J_{NH\text{-}H}$=8 Hz), 7.0 (m, 3H, 3',5',6'), 7.30-7.50 (m, 3H, m,p-PhCO), 7.75 (dd, 2H, o-PhCO, $^3J_{HH}$=8 Hz, $^4J_{HH}$=2 Hz)

^{13}CNMR ($CDCl_3$): 19.3 (2-CH_3), 20.9 (4-CH_3), 35.4 (CH_2), 52.5 (OCH_3), 53.5 (CH), 126.7 (5'), 127 0 (m-PhCO), 128.7 (o-PhCO), 129.8 (6'), 131.2 (1'), 131.5 (3'), 132.0 (p-PhCO), 133.7 (C-CO), 136.6 (2'), 136 8 (4'), 166.9 (C=O), 172.3 (COOCH$_3$)

(S)-4-Isopropyl-N-benzoyl-phenylalanine-methylester **3t**:

m.p. 104°C (MeOH/H_2O), $[\alpha]_D^{20}$ = -49.2 (c1,MeOH), 99% ee (HPLC)

^{1}HNMR ($CDCl_3$): 1.15 (d, 6H, $(CH_3)_2$, $^3J_{HH}$=7 Hz), 2.90 (qq, 1H, CH, $^3J_{HH}$=7 Hz), 3.20 (d, 2H, CH_2, $^3J_{HH}$=6 Hz), 3.75 (s, 3H, OCH_3), 5.10 (dt, 1H, CH), 6,70 (d, 1H, NH, $^3J_{NH\text{-}H\alpha}$=8 Hz), 7.05 (d, 2H, 2',6', $^3J_{HH}$=8 Hz), 7.15 (d, 2H, 3',5', $^3J_{HH}$=8 Hz), 7.35-7.50 (m, 3H, m,p-PhCO), 7.75 (dd, 2H, o-PhCO, $^3J_{HH}$=8 Hz, $^4J_{HH}$=2 Hz)

^{13}CNMR ($CDCl_3$): 23.9 ($(CH_3)_2$), 33.7 (CH), 37.5 (CH_2), 52.5 (OCH_3), 53.5 (CH), 126.7 (3',5'), 127.0 (m-PhCO), 128.7 (o-PhCO), 129.3 (2',6'), 132.0 (p-PhCO), 133.1 (1'), 133.7 (C-CO), 147.8 (4'), 166.9 (C=O), 172.3 (COOCH3)

N-Benzoyl-3-(2-naphthyl)-alanine-methylester **3u**:

m.p. 102-103°C (MeOH/H_2O), **(R)** $[\alpha]_D^{20}$ = +44 2 (c1,MeOH), 87% ee (HPLC), **(S)** $[\alpha]_D^{20}$ = -40 6 (c1,MeOH), 87% ee (HPLC)

^{1}HNMR ($CDCl_3$): 3.40 (d, 2H, CH_2, $^3J_{HH}$=6 Hz), 3.70 (s, 3H, OCH_3), 5.15 (dt, 1H, CH), 6.60 (d, 1H, NH, $^3J_{NH\text{-}H\alpha}$=8 Hz), 7.15-7.45 (m, 3H, 3',6',7'), 7.30-7 45 (m, 3H, m,p-PhCO), 7.50-7.80 (m, 4H, 1',4',5',8'), 7 70 (dd, 2H, o-PhCO)

^{13}CNMR ($CDCl_3$): 38.1 (CH_2), 52.4 (OCH_3), 53.7 (CH), 125.8 (6'), 126.2 (7'), 127.0 (m-PhCO), 127.4 (1'), 127.6-127.7 (3',4'), 128.1-128.3 (5',8'), 128.7 (o-PhCO), 132.0 (p-PhCO), 132.6 (10'), 133.5 (2'), 133 7 (C-CO), 134.0 (9'), 166.9 (C=O), 172.3 (COOCH$_3$)

(R)-4-Chlorphenyl-alanine-hydrochloride **4a**:

m.p. 210-212°C (HCl conc.), $[\alpha]_D^{20}$ = +10 2 (c1,H_2O), 90% ee (HPLC)

^{1}HNMR (D_2O): 3.15 (d, 2H, CH_2), 4.05 (t, 1H, CH), 7.30 (s, 4H, 2',3',5',6'), 8.60 (br, NH_3^+)

(R)-4-Nitrophenyl-alanine-hydrochloride **4b**:

m,p 200-205°C (dec.) (HCl conc.), $[\alpha]_D^{20}$ = +0.1 (c1,H_2O), 82% ee (HPLC)

^{1}HNMR (D_2O): 3.60-3.80 (m, 2H, CH_2), 4.65 (t, 1H, CH), 7.80 (d, 2H, 2',6', $^3J_{HH}$=8 Hz), 8.50 (d, 2H, 3',5', $^3J_{HH}$=8 Hz)

^{13}CNMR (D_2O): 40.2 (CH_2), 58 8 (CH), 128.8 (3',5'), 135.2 (2',6'), 147.1 (1'), 151.9 (4'), 176.2 (COOH)

(R)-3-(1-Naphthyl)-alanine-hydrochloride **4k**:

m.p. 210-220°C (dec.) (HCl conc.), $[\alpha]_D^{20}$ = +2.0 (c1,3m HCl), 90% ee (HPLC)

^{1}HNMR (CD_3OD): 3.40-4.00 (m, 2H, CH_2), 4.30 (m, 1H, CH), 7.40-8.25 (m, 7H, 2'-8')

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