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UNUSUAL AMINO ACIDS

II*. Asymmetric Synthesis of Fluorine Containing Phenylalanines

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Abstracts: Few (Z)-α-N-benzoylamino-β-(fluorophenyl)-acrylic acids and their esters were prepared by known procedures and hydrogenated to the corresponding optically active α-benzoyl-β-(fluorophenyl)-alanine derivatives with optical yields up to 90% using the rhodium complexes of "PROPRAPHOS" and O,N-bis(diphenylphosphino)-2-exo-hydroxy,3-endo-methylamino-norbornane as chiral catalysts. The method proved to be apt for upscaling the preparation. Deacylation of the obtained amino acids gave the hydrochlorides of the fluorinated phenylalanines in very pure state.

Introduction

Fluorine-containing amino acids[1] attracted attention because of their potential pharmacological utility in drugs. The isomeric fluorophenylalanines have been prepared by several methods[2,3,4] accomplishing racemic compounds[5]. This holds also for the β-(2,3,4,5,6-pentafluorophenylalanine)[6,7]. Optically active compounds could be obtained by classical and enzymic resolution processes the latter applying acylases[4,5,7].
Trifluoromethyl substituted phenylalanines were reported by Filler et al. also as racemates[8]. Recently Ando et al. synthesized optically active fluorophenylalanines using a chiral enzyme mimic (pyridoxamine-type) with optical yields of 65 % and Belokon et al. used the alkylation of (S)-proline containing Schiff-bases-Ni(II)-complexes to achieve the chiral monofluoro-phenylalanines[10].

* 1st Communication: Chirality, accepted

In spite of the considerable progress made in the field of asymmetric hydrogenation[11] examples are lacking to use this methods for the preparation of this class.
Only the stereoselective hydrogenation of N-benzoyldehydrotrifluoronorleucine-methylester to the corresponding aliphatic amino acid in the presence of [Rh(NBD)DIPAMP]ClO_4 with 89 % ee (S) has been described by Ojima et al.[12]
Some disadvantages of enzymic resolution procedures especially concerning the L-Tryptophane process (toxic impurities by genetically manipulated microorganisms) prompted us to check the rhodium catalyzed asymmetric hydrogenation for fluoro-substituted aromatic dehydro amino acids also with respect to scale up the preparation since the precursors are easily and in good yields available.

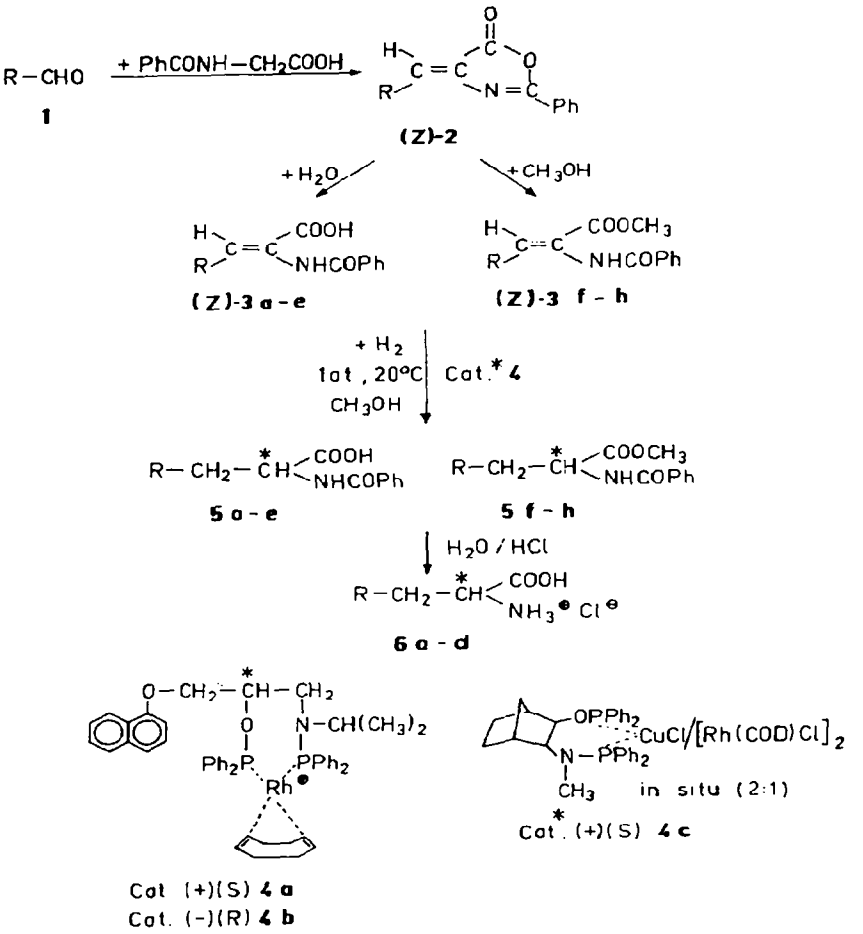
Results and Discussion

The substrates (Z)-3 used for the asymmetric hydrogenation were prepared as shown in Scheme 1. Starting from the fluorine containing benzaldehydes 1 the (Z)-2-phenyl-4-(fluorobenzylidene)-5-oxazolones (Z)-2, were available by the Erlenmeyer reaction. The ring opening described by Schiemann[2] and Siskin[6] leads to the dehydroamino acids (Z)-3a-e, whereas the esters (Z)-3f-h were obtained using the procedure reported by Nicolas et al.[13]. Yields and physical data are given in Table 1.

Table 1 Yields and Melting Points of 3

Compound No.	R	Yield [%][a]	m. p. [°C]	(Lit.) 2
3a	2-F-C_6H_4	60	206-211[b]	209.5-10
3b	3-F-C_6H_4	50	210-214[b]	203-203.5
3c	4-F-C_6H_4	65	219-222[b]	225
3d	4-CF_3-C_6H_4	80	218-221[b]	- -
3e	C_6F_5	42*	214-221[d]	230-32
3f	2-F-C_6H_4	70	116-117,5[c]	
3g	3-F-C_6H_4	90	139,5-140,5[c]	
3h	4-F-C_6H_5	80	133,5-134,5[c]	

* Ref. 6 [a] with respect to the azlactone, recrystallized
[b] from 75 % EtOH/H_2O [c] from 75 % MeOH/H_2O [d] from aceton/water



Compound 3, 5, 6

Abbr	R	Abbr	R
a	2-F-C_6H_4	f	2-F-C_6H_4
b	3-F-C_6H_4	g	3-F-C_6H_4
c	4-F-C_6H_4	h	4-F-C_6H_4
d	4-CF_3-C_6H_4		
e	C_6F_5		

Scheme 1

The results of the asymmetric hydrogenation, summarized in Table 2-4, demonstrate that the used chiral catalysts of the amino-phosphine-phosphinite-type are very efficient in activity and enantioselectivity, also. Catalyst 4c was generated in situ after transformation with CuCl because of a better handling and probably relates to the neutral complex.

Table 2 Catalytic Asymmetric Hydrogenation of 3 a-e

Entry	Substr.	Cat.	Substr. Cat.	Product (config.)[a]	t/2 [Min]	ee[f] [%]	after Recryst.
1	3a	4a	200	5a (R)	1.3	91	99
2	3a	4b	200	5a (S)	1.0	91	99
3	3b	4a	200	5b (R)	1.3	88	99
4	3b	4b	200	5b (S)	1.0	90	
5	3c	4a	200	5c (R)	1.0	88	99
6	3c	4b	200	5c (S)	1.0	88	89
7	3b	4b	1000	5b (S)	20.0	89	
8	3c[b]	4a	3000	5c (R)	160.0	86	
9	3c[b]	4a	2000	5c (R)	17.0	90	
10	3c[c]	4a	2000	5c (R)	30.0	90	
11	3d	4a	200	5d (R)	1.0	90	92
12	3e[d]	4b	100	5e (S)	10.0	86	
13	3a	4c	200	5a (R)	10.0	75	
14	3b	4c	200	5b (R)	13.0	71	
15	3c	4c	200	5c (R)	9.0	75	
16	3c[e]	4a	50	5c (R)	1.0	90	
17	3i[g]	4b	1000	5i (S)	43.0	79	

Catalyst 4a, 4b as crystallized cationic complex, 0.01 mmol; 4c as neutral complex, in situ formed; 15 ml MeOH, 25°C, 0.1 MPa H_2
[a] assumed configuration [b] recrystallized starting product, 30 ml MeOH [c] raw product from ring opening, 40 ml MeOH [d] recrystallized starting product, mp. 205-214 °C [e] deuteriation [f] t/2 time for uptake of 50 % of theoretical hydrogen volume. The value gives a rough indication since exact measurement of the rate and the diffusion control has not been performed. From experimental work we assume t/2 > 5-10 min (substrate 200: catalyst 1) should be more reliable. [g] 3i=(Z)-benzamidocinamic acid, 5i=N-benzoyl-Phe

Table 2 shows that the optical yields obtained are in the range of 90 % ee. Compared with α-benzoylamino acrylic acid they are slightly enhanced. Chemical yields are about 80-90 %. Suffice to say that both enantiomers are provided. Since the fluorine atom is small (Van der Waals radius 1.35 Å against 1.20 Å for hydrogen) no complications are to be expected and the chirality transfer works independent of the position of the fluorine substituent in the aromatic nucleus. Simple recrystallisation of the benzoyl amino acid in some cases enables the optical purity to become 99 % (see Table 2, entry 1,2,3,5).

The (S)-configurated catalyst 4a induces (R)-configurated phenylalanines, catalyst 4b shows the opposite behaviour. Because of the high activity and enantioselectivity of catalyst 4a and 4b we increased the substrate: catalyst ratio up to 3000 (see entry 7-10). In this cases the substrate is hydrogenated in suspension. After reaching approximately the half life the solution becomes clear and sometimes during the further hydrogenation unsaturated product precipitates.

The hydrogenation of N-benzoyl-pentafluoro cinnamic acid 3e can be inhibited by traces of an unknown impurity. As the TLC analysis indicated the by-product has a R_f value of 0.31, the main product of 0.55. After repeated recrystallisation the substrate was free of the inhibitor and could be hydrogenated with good rate and 86 % enantiomeric excess (see entry 12). The optical purity of the crude hydrogenation product [$[\alpha]_D^{23}$ - 55.7°(c 0.1, MeOH), mp 165 - 185 °C] can be increased by recrystallisation from toluene to give $[\alpha]_D^{23}$ - 56.1° (c 1, MeOH), mp 193-196 °C. The mass spectrum shows the mol peak (M^+ 359) and typical fragments (181, 178, 121, 105). The ^{13}CNMR spectrum is not easy to interpret. Because of the strong coupling with the fluorine atoms an assignment of the fluorine substituted carbon atoms is hampered.

Using the methylesters 3f-h the rate and selectivity remains unchanged in accordance with observations previously made for this typ of catalyst. Purification by recrystallisation, however, seems to be less efficient, thus the application of the esters excludes advantages.

The efficiency of our catalytic system, where the advantage of 4a, 4b is significant in both activity and enantioselectivity with respect to 4c, is demonstrated in Table 4 by comparison with well known ligands like DIOP, BPPM, $K\beta^+$ and DPPB. In this connection the extremly small selectivity of the latter is surprising (see entry 7). The results show also that catalyst 4a is comparable with BPPM.

Table 3 Catalytic Asymmetric Hydrogenation of 3 f-h

Entry	Substr.	Cat.	Substr. Cat.	Product (config.)	t/2 [Min.]	ee [%]	after Recryst.
1	3f(2-F-)	4b	100	5f (S)	1.1	90.4	-
2	3f	4a	100	5f (R)	1.5	86.4	-
3	3f	4a	200	5f (R)	1.3	88.0	89.0
4	3f	4b	200	5f (S)	1.1	89.0	95.0
5	3g(3-F-)	4a	200	5g (R)	1.7	89.0	99.0
6	3g	4b	200	5g (S)	1.6	88.0	91.0
7	3h(4-F-)	4a	200	5h (R)	2.6	89.0	88.0
8	3h	4b	200	5h (S)	2.3	90.0	89.0

[Cat] 0.01 mmol, 15 ml MeOH, 25 °C, 0.1 MPa H_2:

Table 4 Catalytic Asymmetric Hydrogenation of 3c
(Comparison with some known Catalysts)
(15 ml MeOH, 25 °C, 0.1 MPa H_2, 0.01 mmol Catalyst)

Entry	Catalyst	Substr. Cat.	Product (config.)	t/2 [Min.]	ee [%]
1	(-)-DIOP*	200	R	1.6	51
2	(-)-BPPM*	200	R	2.5	85
3	(+)-4a	200	R	2.0	88
4	(-)-4c	200	R	4.0	75
5	Kβ$^+$	200	S	40.0	87
6	Kβ$^+$-OH	200	S	40.0	87
7	(+)-DPPB*	200	R	5.0	6

Catalyst-Abbreviation.: (-)-DIOP: (4R,5R)-(-)-4,5-Bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane, (-)-BPPM: (2S,4S)-N-tert-Butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphino-methylpyrrolidine, Kβ$^+$: Rhodium(I)-[phenyl-4,6-O-(R)-benzylidene-2,3-bis(O-diphenylphosphino)-β-D-glucopyranoside]-(cis,cis-cycloocta-1,5-diene)-tetrafluoroborate, Kβ$^+$-OH: Rhodium(I)-[phenyl (2,3-bis(O-diphenylphosphino)-β-D-glucopyranoside]-(cis,cis-cycloocta-1,5-diene)-tetrafluoroborate.
DPPB: 2,3-Diphenyl-1,4-bis(diphenylphosphino)butane
* in situ prepared using $[Rh(COD)_2]^+BF_4^-$
4a and 4c see scheme 1

The deacylation of the hydrogenation products has been investigated in concentrated hydrochloric acid with the results summarized in Table 5. The values obtained for the optical purity based upon GLC or HPLC analysis show that in some cases racemisation in considerable range accured. To avoid this disadvantage other easier to remove protecting groups should be checked.

Table 5 Hydrochlorides 6a-d (isolated after deacylation)

Compound No.	Purity [% ee]	Reaction time [hours]	$[\alpha]_D^{26}$ [b]	Hydrochl. No.	Purity[a] [% ee]	m. p. [°C]	Yield [%]
5a	99 (R)	9		6a	95[c]		
5a	99 (R)	8	-13,8[e]	6a	98[d]	200- 6	56
5a	99 (S)	7		6a	82[c]/85[d]	201- 3	
5b	93 (R)	12		6b	73[c]	206- 8	
5b	93 (R)	6	+ 4.2[f]	6b	92[d]	205- 7	61
5b	82 (S)	9		6b	69[c]/68[d]	204- 5	
5b	99 (S)	9		6b	85[c]/82[d]	200- 2	
5c	96 (R)	6		6c	87[c]	208-11	
5c	96 (R)	4	+ 3.8[g]	6c	86[d]	215-20	59
5c	91 (R)	8		6c	82[c]	200-11	
5c	89 (S)	3		6c	86[c]	211-15	
5d	90 (R)	12		6d	89	195- 7	

[a] Elemental analysis gave exact results
[b] After recrystallisation from iso-propanol
[c] Determined by GLC after trifluoroacetylation and esterification with iso-propanol
[d] Determined by HPLC
[e] (c 2.30, MeOH)
[f] (c 5.20, 1 n HCl)
[g] (c 5.67, 1 n HCl)

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 excesses (% ee) were determined by glc on a Hewlett-Packard chromatograph 5880 A fitted with a 4,3 m capillary column XE-60 (N-stearoyl-L-valine-tert.-butylamide, FID, split 1:60, 175 °C for the acylated amino acid derivatives 5f-h, for 5a-e after esterifica-

tion 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 are uncorrected and were determined on a Boetius microscope.

Hydrogenation, general procedure

Hydrogenations were performed under normal pressure and 25°C principially as described by Kagan[16].
1 ml of the hydrogenated solution was esterified by a freshly prepared solution of diazomethane (5a-e) in order to determine the ee by glc. The other part was freed from the solvent and recrysatallized.

Deacylation, general procedure

The recrystallized optically active fluorine 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 solution carefully concentrated under reduced pressure at 30-35 °C. The colorless crystals were collected and sometimes recrystallized from concentrated hydrochloric acid (Results see in Table 5.)

Chemicals

All solvents were purified and dried by usual methods and stored, if necessary, under argon.
Catalysts[14,15] and substrates 3a-h were prepared according to published methods[2,6,13].

(R)-2-Fluoro-N-benzoyl-phenylalanine (5a):

m. p. 147-149 °C (MeOH/H_2O), $[\alpha]_D^{20}$ + 61.1 (c 1, MeOH), 99 % ee (GLC).
^{1}HMNR ($CDCl_3$): 3.4(m, 2H, CH_2); 5.05(dt, 1H, CH); 6.8(d, 1H, NH); 6.95-7.3(m, 4H, 3'-6'); 7.35-7.5(m, 3H, m,p-PhCO); 7.7(dd, 2H, o-PhCO).
^{13}CNMR ($CDCl_3$): 31.0(CH_2, ^3J=1.2Hz); 53.4(CH); 115.5(3', ^2J= 22.0Hz); 123.0(1', ^2J=15.9Hz); 124.5(5', ^4J=3.7Hz); 127.1(m-PhCO); 128.7(o-PhCO); 129.3(4', ^3J=8.5Hz); 131.8(6', ^3J=4.9Hz); 132.1(p-PhCO); 133.5(C-C=O); 161.5(2', ^1J=244.2Hz); 168.0(C=O); 164.5(COOH).
$C_{16}H_{14}FNO_3$(287.3), calcd. C 66.89 H 4.91 N 4.88
found C 67.01 H 4.91 N 4.89

(R)-3-Fluoro-N-benzoyl-phenylalanine (5b):

m. p. 135-137 °C (MeOH/H_2O), $[\alpha]_D^{20}$ + 43.0 (c 1, MeOH), 99 % ee (GLC).
^{1}HNMR ($CDCl_3$): 3.3(m, 2H, CH_2); 5.05(dt, 1H, CH); 6.8-7.2(m, 4H, 2',4'-6'); 7.3-7.5(m, 3H, m,p-PhCO); 7.7(dd, 2H, o-PhCO); 8.65 (br, 1H, NH).
^{13}CNMR($CDCl_3$): 37.1(CH_2, ^4J=1.2Hz); 53.2(CH); 114.3(4', ^2J=20.8Hz); 116.4(2', ^2J=21.4Hz); 125.1(6', ^4J=2.5Hz); 127.1(m-PhCO); 128.8 (o-PhCO); 130.2(1', ^3J=7.9Hz); 132.2(p-PhCO); 138.2(5', ^3J=7.3Hz); 163.0(3', ^1J=246.6Hz); 167.8(C=O); 175.5(COOH).

$C_{16}H_{14}FNO_3$(287.3),	calcd	C 66.89	H	4.91	N	4.88
	found	C 67.08	H	4.86	N	5.01

(R)-4-Fluoro-N-benzoylphenylalanine (5c):

m. p. 158-161 °C (MeOH/H_2O), $[\alpha]_D^{20}$ + 38.1 (c 1, MeOH), 99 % ee (GLC).
^{1}HNMR($CDCl_3$): 3.2(m, 2H, CH_2); 4.95(dt, 1H, CH); 6.6(d, 1H, NH); 6.8(dd, 2H, 3'); 6.95(dd, 2H, 2'); 7.25-7.4(m, 3H, m,p-PhCO); 7.6 (dd, 2H, o-PhCO).

^{13}CNMR($CDCl_3$): 36.6(CH_2); 53.8(CH, ^6J=1.9Hz); 115.6(3', ^2J=21.9Hz); 127.1(m-PhCO); 128.8(o-PhCO); 130.9(2', ^3J=8.6Hz); 131.4(1', ^4J= 3.1Hz); 132.2(p-PhCO); 133.4(C-C=O); 162.2(4', ^1J=245.9Hz); 167.8 (C=O); 174.7(COOH).

$C_{16}H_{14}FNO_3$(287.3)	calcd.	C 66.89	H	4.91	N	4.88
	found	C 66.95	H	4.84	N	4.95

(R)-4-Trifluoromethyl-N-benzoylphenylalanine (5d):

m. p. 167-168 °C (MeOH), $[\alpha]_D^{20}$ + 41.8 (c 1, MeOH), 92 % ee (GLC).
^{1}HNMR($CDCl_3$): 3.3(m, 2H, CH_2); 4.9(dt, 1H, CH); 7.3-7.45(m, 3H, m,p-PhCO); 7.5(s, 4H, 2',3'); 7.75(dd, 2H, o-PhCO).
^{13}CNMR($CDCl_3$): 37.6(CH_2); 54.4(CH); 125.5(CF_3, ^1J=271.1Hz); 125.9(3', ^3J=3.8Hz); 128.1(m-PhCO); 129.1(4', ^2J=32.0Hz); 129.2 (o-PhCO); 130.9(2'); 132.3(p-PhCO); 135.2(C-C=O); 172.9(COOH).

$C_{17}H_{14}F_3NO_3$(336.3)	calcd.	C 60.72	H	3.89	N	4.16
	found	C 60.53	H	4.18	N	4.15

(S)-β-(2.3.4.5.6)-Pentafluoro-N-benzoylphenylalanine (5e):

m. p. 193-196 °C (toluene), $[\alpha]_D^{20}$ -56.1 (c 1, MeOH), 86 % ee (GLC).
^{13}CNMR($CDCl_3$): 24.33(CH_2); 51.41(CH); 127.16(2'); 128.28(3'); 131.43(4'); 133.66(1'); 166.27(CONH); 171.61(COOH).
The aromatic fluorine bearing carbon atoms cannot be assigned because of strong coupling with the fluorine atoms.

(R)-2-Fluoro-N-benzoylphenylalanine methylester (5f):

m. p. 111-112 °C (MeOH/H_2O), $[\alpha]_D^{20}$ + 64.6 (c 1, MeOH), 89 % ee (GLC).
^{1}HNMR($CDCl_3$): 3.2(d, 2H, CH_2); 3.65(s, 3H, OCH_3); 4.95(dt, 1H, CH); 6.6(d, 1H, NH); 6.8-7.15(m, 4H, 3',6'); 7.25-7.4(m, 3H, m, p-PhCO); 7.6(dd, 2H, o-PhCO).
^{13}CNMR($CDCl_3$): 31.6(CH_2, ^3J=1.2Hz); 52.5(OCH_3); 53.0(CH); 115.4 (3', ^2J=22.6Hz); 123.1(1', ^2J=15.9Hz); 124.3(5', ^4J=3.7Hz); 127.0(m-PhCO); 128.6(o-PhCO); 129.1(4', ^3J=8.5Hz); 131.5(6', ^3J=4.3Hz); 131.7(p-PhCO); 134.0(C-C=O); 161.5(2', ^1J=244.8Hz); 167.0(C=O); 172.0($COOCH_3$).

$C_{17}H_{16}FNO_3$(301.3)	calcd.	C 67.76	H 5.35	N 4.65
	found	C 67.40	H 5.21	N 4.44

(R)-3-Fluoro-N-benzoylphenylalanine methylester (5g):

m. p. 79-80 °C (MeOH/H_2O), $[\alpha]_D^{20}$ + 56.5 (c 1, MeOH), 99 % ee (GLC).
^{1}HNMR($CDCl_3$): 3.25(dd, 2H, CH_2); 3.75(s, 3H, CH); 6.7(d, 1H, NH); 6.75-7.0(m, 2H, 4',6'); 7.1-7.25(m, 2H, 2',5'); 7.3-7.45(m, 3H, m,p-PhCO); 7.7(dd, 2H, o-PhCO);
^{13}CNMR($CDCl_3$): 37.7(CH_2, ^4J=1.8Hz); 52.5(OCH_3); 53.5(CH); 114.1 (4', ^2J=20.7Hz); 116.3(2', ^2J=21.4Hz); 125.1(6', ^4J=3.0Hz); 127.0(m-PhCO); 128.7(o-PhCO); 130.1(1', ^3J=8.0Hz); 131.9(p-PhCO); 133.9(C-C=O); 138.5(5', ^3J=7.3Hz); 162.9(3', ^1J=246.9Hz); 166.9 (C=O); 171.8($COOCH_3$).

$C_{17}H_{16}FNO_3$(301.3),	calcd.	C 67.76	H 5.35	N 4.65
	found	C 67.51	H 5.17	N 4.50

(R)-4-Fluoro-N-benzoylphenylalanine methylester (5h):

m. p. 96-97 °C (MeOH/H_2O), $[\alpha]_D^{20}$ + 50.1 (c 1, MeOH), 88 % ee (GLC).

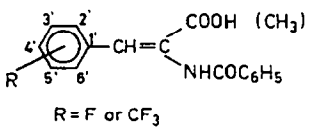
^{1}HNMR($CDCl_3$): 3.25(dd, 2H, CH_2); 3.75(s, 3H, OCH_3); 5.05(dt, 1H, CH); 6.6(d, 1H, NH); 6.9(dd, 2H, 2'); 7.05(dd, 2H, 3'); 7.35-7.5 (m, 3H, m,p-PhCO); 7.7(dd, 2H, o-PhCO);

^{13}CNMR($CDCl_3$): 37.2(CH_2), 52.4(OCH_3); 53.6(CH, ^6J=1.2Hz); 115.5 (3', ^2J=21.4Hz); 127.0(m-PhCO); 128.7(o-PhCO); 130.9(2', ^3J=7.9Hz); 131.7(1', ^4J=3.7Hz); 131.8(p-PhCO); 133.9(C-C=O); 162.2(4', ^1J= 245.3Hz); 166.8(C=O); 172.0($COOCH_3$).

$C_{17}H_{16}FNO_3$(301.3), calcd. C 67.76 H 5.35 N 4.65
found C 67.46 H 5.29 N 4.47

NMR spectra

^{1}HNMR(acetone-d_6), δ(ppm), compounds 3a-h



R = F or CF_3

3a: 7.05(m,1H;3') 7.1-7.4(m,3H;5',6',CH=) 7.35-7.5(m,3H;m,p-PhCO) 7.6(m,1H;4') 7.9(dd,2H;O-PhCO) 9.0(s,1H;NH)

3f: 3.75(s,3H;OCH_3) 6.95(m,1H;3') 7.0(m,1H;5') 7.3-7.4(m,6H;4',6', m,p-PhCO,CH=) 7.7(dd,2H;o-PhCO) 8.0(s,1H;NH)

3b: 7.0(m,1H;4') 7.25-7.55(m,7H;2',5',6',m,p-PhCO,CH=) 7.95(dd,2H; o-PhCO)

3g: 3.75(s,3H;OCH_3) 6.9(m,1H;4') 7.0-7.3(m,4H;2',5',6',CH=) 7.3-7.45(m,3H;m,p-PhCO) 7.75(dd,2H;o-PhCO) 7.9(s,1H,NH)

3c: 7.05(t,2H;3';$^3J_{HH}$=9Hz;$^3J_{HF}$=9Hz) 7.45(s,1H;CH=) 7.4-7.5(m,3H;m, p-PhCO) 7.65(dd,2H;2';$^4J_{HF}$=5.5Hz) 7.95(dd,2H;o-PhCO;$^3J_{HH}$=1.5Hz) 9.0(s,1H;NH)

3h: 3.75(s,3H;OCH_3) 6.9(dd,2H;2') 7.25-7.5(m,6H;3',m,p-PhCO;CH=) 7.75(dd,2H;o-PhCO) 7.8(s,1H;NH)

3d: 7.4-7.6(m,4H;m,p-PhCO,CH=) 7.7(d,2H;2',$^3J_{HH}$=8.5Hz) 7.85(d,2H 3',$^3J_{HH}$=8.5Hz) 8.0(dd,2H;o-PhCO $^3J_{HH}$=1.5Hz) 8.4(br,1H;COOH) 9.2(s,1H;NH)

3e: 6.6(br, 1H;COOH) 6.9(CH=) 7.69-7.3(C_{arom}) 8.91(s,1H;NH)

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