ASYMMETRIC SYNTHESIS OF HETEROORGANIC ANALOGS OF NATURAL COMPOUNDS.

2. A CONVENIENT PREPARATIVE METHOD FOR THE SYNTHESIS OF ENANTIOMERICALLY PURE (S)-(−)-o-, m-, and p-FLUOROPHENYLALANINES AND THEIR 2-METHYL-SUBSTITUTED ANALOGS

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A convenient preparative method for the synthesis of the enantiomerically pure o-, m-, and p-fluorophenylalanines and their α-methyl-substituted analogs by means of the alkylation with the corresponding fluorine-containing benzyl chlorides of glycine and alanine in the Ni(II)-complexes of their Schiff bases with (S)-2-N(N'-benzylprolyl)aminobenzophenone is proposed.

The o-, m-, and p-fluorophenylalanines (I) possess a broad spectrum of biological activity [1]. Moreover, these compounds have recently been actively utilized in the synthesis of pharmacologically active peptides [2-5]. The application of the enantiomerically pure amino acids is required, as a rule, for this purpose. Therefore, the development of an effective method for the asymmetric synthesis of the fluorophenylalanines (I) is timely.

Known routes for the isolation of optically active fluorophenylalanines (I) are based on the possibility of performing the enantioselective hydrolysis of the ester or amide groupings in the corresponding derivatives of the amino acids (I) with the utilization of enzymes such as subtilisin [6], papain [7], or α-chymotrypsin [8]. Moreover, the possibility of the synthesis of optically active fluorophenylalanines (I) by the reductive amination of the fluorine-substituted phenylpyruvic acids in the presence of transaminases was indicated [9]. The asymmetric synthesis of the compounds (I) is described in the literature by the single example of the isolation of (S)-p-fluorphenylalanine by the reductive aminolysis of the azlactone of p-fluoro-α-acetaminocinnamic acid with the enantiomeric excess of 46% [10]. All the methods, enumerated above, for the isolation of optically active o-, m-, and p-fluorophenylalanines have certain disadvantages which limit their preparative importance: the formation of different amounts of the (S)- and (R)-isomers (the enzymatic cleavage of the racemates [6-8]), the low availability of the fluorine-containing α-ketoacids (the enzymatic reductive amination [9]), and the low optical yield of the object product (the reductive aminolysis in the presence of a chiral Pd-catalyst [10]).

A method which was previously proposed for the synthesis of the optically active α-methyl-o-, m-, and p-fluorophenylalanines consisted of the α-methylation of chiral heterocyclic derivatives of the fluorophenylalanines (I). The main disadvantage of this method, limiting its possibilities, is the necessity to utilize the enantiomerically pure fluorine-substituted phenylalanines (I) as the initial compounds [11].

In the present work, we communicate the asymmetric synthesis of o-, m-, and p-fluorophenylalanines and their α-methyl derivatives by means of the method, which has been widely approved in the series of unfluorinated amino acids, using the alkylation of glycine and alanine in their Ni(II)-complexes of the Schiff bases with (S)-2-N-(N-benzylprolyl)aminobenzophenone [(S)-PAP]. The initial complexes were obtained by the interaction of (S)-PAP in MeOH, in the presence of MeONa, with $Ni(NO_3)_2$ and the corresponding amino acid [12, 13].

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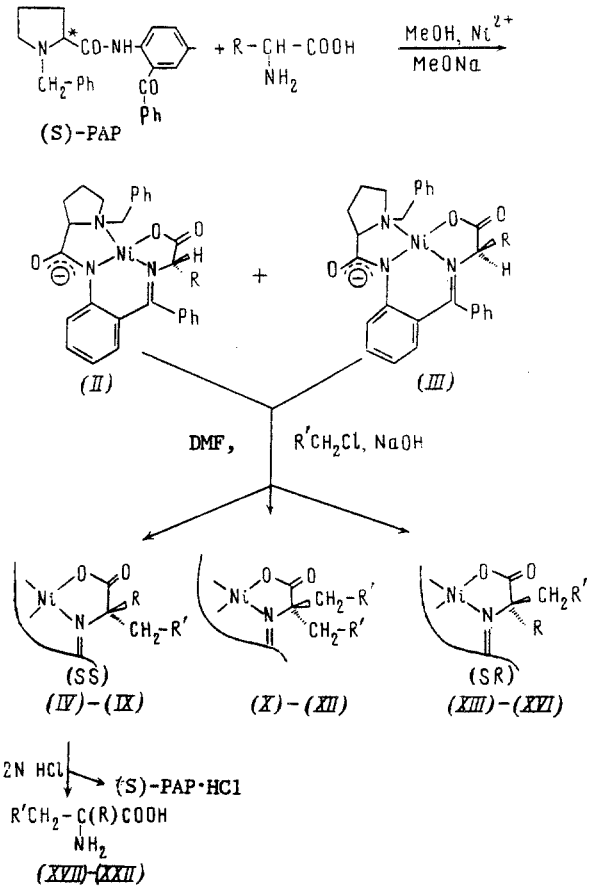
As was previously shown [13], the complex (III) is formed as the mixture of the (SS)- and (SR)-diastereomers, which were utilized without separation for the further conversions.

It was found that the complexes (II) and (III) react exothermically with o-, m-, and p-fluorobenzyl chlorides in DMF in the presence of solid NaOH at 20°C with the formation of the mixture of the alkylation products; the composition of the mixture depends on the fluorobenzyl chloride utilized and the initial complex (Scheme).

Scheme 1



R = H (II), Me (III).
R = H, R' = 2-F-C_6H_4 (IV), (XIII), (XVII), 3-F-C_6H_4 (V), (XVIII), 4-F-C_6H_4 (VI); (XIX); R = Me, R' = 2-F-C_6H_4 (VII), (XIV), 3-F-C_6H_4 (VIII), (XV), 4-F-C_6H_4 (IX), (XVI).
R' = 2-F-C_6H_4 (X), (XX); 3-F-C_6H_4 (XI), (XXI), 4-F-C_6H_4 (XII), (XXII).

Thus, in the alkylation of the complex (II), the reaction was complicated by the formation of the products of bis-alkylation (X)-(XII), the yield of which did not exceed 5% with the 1:1.2 ratio of (II):alkyl halide (Table 1). The compounds (XI) and (XII) were isolated in a discrete state. Their structure was confirmed by a complex of physicochemical methods and the data of the elemental analysis (Table 2). The PMR spectra of the products (XI) and (XII) contain three AB-quartets of the benzyl groups; their ^{19}F NMR spectra have two multiplets of the fluorine atoms with the 1:1 integral intensities. Moreover, the shape of the curves in the ORD spectra of the compounds (XI) and (XII), which contain the achiral aminoacid, should be determined by the influence of the (S)-proline fragment, and have the dependence characteristic of the ORD curve of the initial complex (II) [12], which we also observed in the ORD spectra of the compounds (XI) and (XII) (Fig. 1).

The formation of the complexes (XIII)-(XVI), which contain the (R)-aminoacid, in the process of the alkylation of (II) and (III) with fluorobenzyl chlorides is insignificant as for the products of the bis-alkylation (XI) and (XII), and does not exceed 5%. We isolated the complex (III) in the discrete state, and characterized it (Table 2, Fig. 1), and (XIV)-(XVI) were identified by their NMR spectra using the mixture with the corresponding (SS)-diastereomers.

TABLE 1. Yield and Ratio of the Products Obtained in the Alkylation of the Complexes (II) and (III)

Initial complex	R	Ratio of products, %*		
		(SS)	(SR)	product of bis-alkylation
(II)	2-F-C_6H_4	95	4	1
(II)	3-F-C_6H_4	95	–	5
(II)	4-F-C_6H_4	96	–	4
(III)	2-F-C_6H_4	95	5	–
(III)	3-F-C_6H_4	97	3	–
(III)	4-F-C_6H_4	95	5	–

*The ratio of the integral intensities of the signals in the ^{19}F NMR spectra.

TABLE 2. Yield and Properties of the Complexes (IV)-(IX) and (XI)-(XIII)

Complex	Empirical formula	Found/Calculated, %				Mp, °C	λ_{max} (log ε) (MeOH)	$[\alpha]_D^{24}$ (g/100 ml) (MeOH)	Yield, %
		C	H	F	N				
(IV)	$C_{34}H_{30}FN_3O_3Ni$	67,34 / 67,35	4,85 / 4,99	3,12 / 3,13	6,85 / 6,93	260–264	262(4,25) 333(3,74) 410(3,53) 520(2,41)	+2589.2 (0,07)	72
(V)	$C_{34}H_{30}FN_3O_3Ni$	67,51 / 67,35	4,77 / 4,99	3,10 / 3,13	7,09 / 6,93	163–168	262(4,24) 333(3,72) 410(3,52) 520(2,35)	+2401.2 (0,08)	70
(VI)	$C_{34}H_{30}FN_3O_3Ni$	67,23 / 67,35	4,99 / 4,99	3,15 / 3,13	7,01 / 6,93	214–217	262(4,27) 333(3,74) 410(3,54) 520(2,37)	+2516.3 (0,09)	71
(VII)	$C_{35}H_{32}FN_3O_3Ni$	67,77 / 67,76	5,15 / 5,20	3,16 / 3,06	6,84 / 6,77	143–147	262(4,14) 333(3,62) 418(3,47) 520(2,32)	+1939.8 (0.13)	72
(VIII)	$C_{35}H_{32}FN_3O_3Ni$	67.71 / 67.76	5.17 / 5.20	3.08 / 3.06	6.65 / 6.77	130–133	261(4,05) 333(3.66) 418(3.46) 520(2,41)	+1925.7 (0,09)	70
(IX)	$C_{35}H_{32}FN_3O_3Ni$	67.84 / 67.76	5,24 / 5,20	3.12 / 3.06	6,58 / 6.77	95–100	261(4.17) 333(3.64) 417(3,44) 520(2,34)	+1976,9 (0,15)	63
(XI)	$C_{41}H_{35}F_2N_3O_3Ni$	68,89 / 68,93	4,95 / 4,94	5,13 / 5,32	5,91 / 5,88	125–129	267(4,13) 333(3,69) 425(3,50) 520(2,54)	+1932.9 (0.07)	3,7
(XII)	$C_{41}H_{35}F_2N_3O_3Ni$	68,98 / 68,93	4,81 / 4,94	5,47 / 5,32	5,71 / 5,88	204–210	263(4,18) 333(3,68) 423(3,47) 520(2,35)	+1880.0 (0,09)	3
(XIII)	$C_{34}H_{30}FN_3O_3Ni$	67,44 / 67,35	5,03 / 4,99	3,23 / 3,13	6,87 / 6,93	224–228	262(4,29) 330(3,75) 410(3,52) 525(2,32)	–1297.3 (0,11)	3

The main reaction products – the compounds (IV)-(IX) – were isolated by the crystallization of the mixture of isomers obtained after the alkylation, with the subsequent chromatography of the residue on SiO_2.

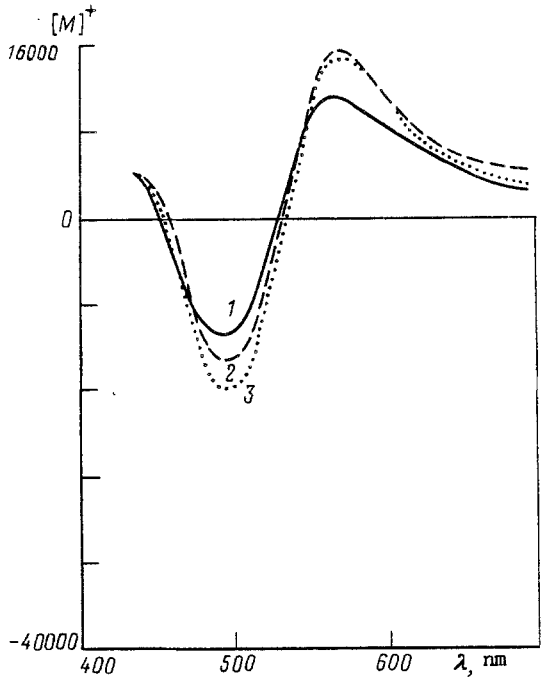


Fig. 1. ORD curve obtained in methanol at 25°C for the Ni(II) complexes of the Schiff bases formed by (S)-2-[N(N-benzylprolyl)amino]benzophenone and amino acids: 1) amino-acetic acid (II); 2) α-p-fluorobenzyl-p-fluorophenylalanine (XII); 3) α-m-fluorobenzyl-m-fluorophenylalanine (XI).

TABLE 3. Yield and Properties of the Amino acids (XVII)-(XXII) $RCH_2(R^1)C(NH_2)COOH$

Compound	R	R¹	Yield, %	$[\alpha]_D^{25}$ (H_2O) (c, g/100 ml)	Mp, °C	Found/Calculated, %		
						C	H	F
(XVII)	H	2-F-C_6H_4	94	−14,3(0,021)	208–210	59,21 / 59,01	5,64 / 5,50	10,31 / 10,37
(XVIII)	H	3-F-C_6H_4	95,5	−27,0(0,025)	240–245	59,17 / 59,01	5,47 / 5,50	10,28 / 10,37
(XIX)	H	4-F-C_6H_4	83	−26,9(0,028)	252–255	59,08 / 59,01	5,67 / 5,50	10,09 / 10,37
(XX)	CH_3	2-F-C_6H_4	91	−14,8(0,338)	289–292	60,84 / 60,90	6,00 / 6,14	9,54 / 9,63
(XXI)	CH_3	3-F-C_6H_4	80	−21,7(0,276)	298–300	60,99 / 60,90	6,08 / 6,14	9,61 / 9,63
(XXII)	CH_3	4-F-C_6H_4	85	−17,3(0,150)	300–303	61,12 / 60,90	5,96 / 6,14	9,81 / 9,63

The absolute configuration of the amino acids in the complexes (IV)-(IX) and (XIII) was determined on the basis of the data of their ORD spectra. It was previously shown [14] that, behind the positive Cotton effects at 520-580 nm in the ORD or CD spectra of the Ni(II) complexes of the Schiff bases of the (S)-β-amino acids including (S)-phenylalanine and (S)-α-methylphenylalanine, they are negative at 410-500 nm; on the other hand, they are positive for the (R)-α-amino acids following the negative Cotton effects. As can be seen from the data of the ORD spectra (Fig. 2), the complexes (IV)-(IX) contain fluorine-substituted phenylalanines of the (S)-configuration, and the complex (XIII) has (R)-o-fluorophenyl-alanine.

The decomposition of the diastereomerically pure complexes (IV)-(IX) in 2 N HCl gave fluorine-substituted (S)-phenylalanines (Table 3) with the enantiomeric purity >99%; we

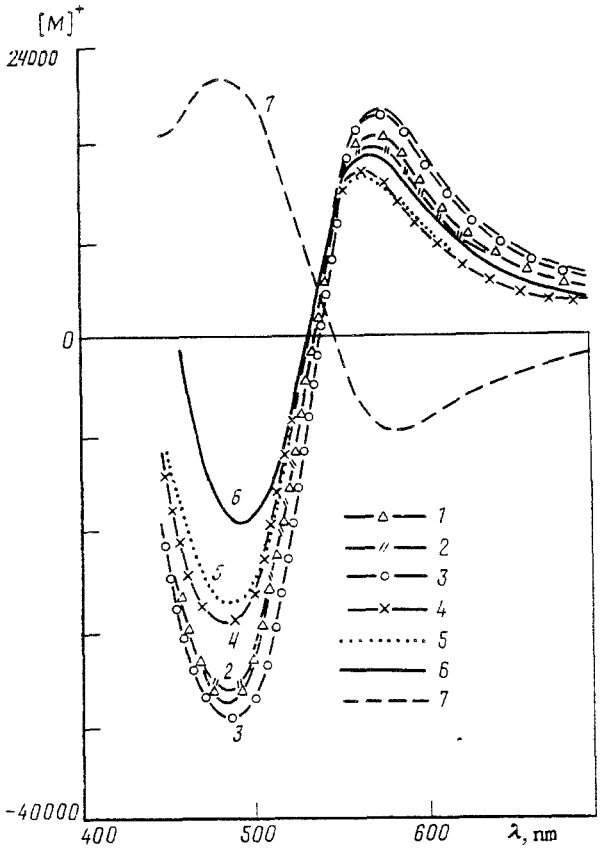


Fig. 2. ORD curves obtained in methanol at 25°C for the Ni(II) complexes of the Schiff bases formed by (S)-2-[N(N-benzylprolyl)-amino]benzophenone and amino acids: 1) (S)-o-fluorophenylalanine (IV); 2) (S)-m-fluorophenylalanine (V); 3) (S)-p-fluorophenylalanine (VI); 4) (S)-α-methyl-p-fluorophenylalanine (VII); 5) (S)-α-methyl-m-fluorophenylalanine (VIII); 6) (S)-α-methyl-o-fluorophenylalanine (IX); 7) (R)-o-fluorophenylalanine (XIII).

determined this by the method of GLC [14]. The chiral inducing reagent (S)-PAP from the decomposition of the complexes (IV)-(IX) was isolated with the yield of 97-99%.

EXPERIMENTAL

The work utilized o-, m-, and p-fluorobenzyl chlorides of "Reakhim" purity; the DMF was purified by the method of [15].

The NMR spectra were taken on a Bruker WP-200 instrument (200 MHz); the internal standard was HMDS (^1H), and the external standard was CF_3COOH (^{19}F). The electronic spectra were recorded on the M-40 spectrophotometer. The ORD spectra were recorded on a Jasko instrument. The optical rotation was measured on a Perkin-Elmer-241 polarimeter. The chiral reagent (S)-PAP and the complex (II) were obtained by the method of [12], and the complex (III) was obtained by the method of [13].

General Method for the Alkylation of the Complex (II) with o-, m-, and p-Fluorobenzyl Chlorides. To the solution of 14 mmoles of the complex (II) in 10 ml of DMF were added 16.8 mmoles of the corresponding fluorobenzyl chloride and 35 mmoles of finely ground NaOH; the mixture was stirred at 20°C in a stream of Ar for 30 min. The mixture was neutralized with a 2% solution of CH_3COOH. The resulting residue was filtered off, washed with water, dried in vacuo, and chromatographed on SiO_2 $L_{5/40}$ in the 4:1 system of $CHCl_3$–Me_2CO. The yield, constants, data of the elemental analysis, and UV spectra, as well as the values of the specific optical rotation of the complexes (IV)-(VI) and (XI)-(XIII), are presented in Table 2.

(SS)-(IV). The PMR spectrum ($CDCl_3$, δ, ppm, J, Hz) is as follows: 1.66-3.32 m [7H, PrO), 2.95, 3.19 (ABX, 2H, CH_2(Phe), J_{AB} = 13.0, J_{AX} = 4.5, J_{BX} = 5.5], 3.50, 4.29 (AB, 2H, CH_2-Bzl, J_{AB} = 12.0), 4.25 m [1H, α-H (Phe)], and 6.65-8.29 m (18H, ArH). The ^{19}F NMR spectrum ($CDCl_3$, δ, ppm) is characterized at −37.62 m (ArF).

(SS)-(V). The PMR spectrum ($CDCl_3$, δ, ppm, J, Hz) is as follows: 1.70-3.33 mm (7H, PrO), 2.85, 3.08 [ABX, 2H, CH_2(Phe), J_{AB} = 13.5, J_{AX} = 6.0, J_{BX} = 4.5), 3.50, 4.30 (AB, 2H, CH_2-Bzl, J_{AB} = 12.0), 4.25 m [1H, α-H, (Phe)], and 6.69-8.25 m (18H, ArH). The ^{19}F NMR spectrum ($CDCl_3$, δ, ppm) is characterized at −34.82 m (ArF).

(SS)-(VI). The PMR spectrum ($CDCl_3$, δ, ppm, J, Hz) is as follows: 1.75-3.36 m (7H, Pro), 2.83, 3.05 [ABX, 2H, CH_2(Phe), J_{AB} = 13.2, J_{AX} = 5.4, J_{BX} = 4.2], 3.48, 4.30 (AB, 2H, CH_2-Brl, J = 12.2), 4.25 m [1H, α-H (Phe)], and 6.67-8.23 m (18H, ArH). The ^{19}F NMR spectrum ($CDCl_3$, δ, ppm) is characterized at −37.66 m (ArF).

(SS)-(XI). The PMR spectrum ($CDCl_3$, δ, ppm, J, Hz) is as follows: 2.25-3.25 m (7H, Pro), 2.78, 3.30 (AB, 2H, CH_2-Bzl, J = 16.5), 3.02, 3.13 (AB, 2H, CH_2-Bzl, J = 14.0), 3.32, 4.33 (AB, 2H, CH_2-Bzl, J = 12.0), and 6.56-8.08 m (22H, ArH). The ^{19}F NMR spectrum ($CDCl_3$, δ, ppm) is as follows: −34.27 m (1F, ArF) and −34.89 m (1F, ArF).

(SS)-(XII). The PMR spectrum ($CDCl_3$, δ, ppm, J, Hz) is as follows: 2.02-3.20 m (7H, Pro), 2.75, 3.26 (AB, 2H, CH_2-Bzl, J = 16.5), 2.98, 3.13 (AB, 2H, CH_2Bzl, J = 14.0), 3.26, 4.26 (AB, 2H, CH_2-Bzl, J = 12.0), and 6.55-8.07 m (22H, ArH). The ^{19}F NMR spectrum ($CDCl_3$, δ, ppm) is as follows: −37.42 (1F, ArF) and −38.58 m (1F, ArF).

(SR)-(XIII). The spectrum ($CDCl_3$, δ, ppm, J, Hz) is as follows: 1.60-3.85 m (7H, Pro), 2.88, 3.21 [ABX, 2H, CH_2(Phe), J_{AB} = 13.5, J_{AX} = 3.0, J_{BX} = 6.0), 3.45, 3.92 (AB, 2H, CH_2-Bzl, J = 13.3), 4.26 d.d [1H, α-H (Phe), J = 3.0 6.0), and 6.80-8.52 m (18H, ArH). The ^{19}F NMR spectrum ($CDCl_3$, δ, ppm) is characterized at −37.34 m (ArF).

General Method for the Alkylation of the Complex (III) with o-, m-, and p-Fluorobenzyl Chlorides. To the solution of 1 mmole of the complex (III) in 3 ml of DMF were added 3.5 mmoles of the corresponding fluorine-containing benzyl chloride and 5 mmoles of finely ground NaOH; the mixture was stirred at 20°C in a stream of Ar for 2 h. The mixture was neutralized with 0.1 N HCl; the precipitated residue was filtered off, washed with water, dried in vacuo, and chromatographed on SiO_2 $L_{5/40}$ in the 4:1 system of $CHCl_3$–Me_2CO. The yield, constants, the data of the elemental analysis, and the UV spectra, as well as the values of the specific optical rotation of the complexes (VII)-(IX), are presented in Table 2.

(SS)-(VII). The PMR spectrum ($CDCl_3$, δ, ppm, J, Hz) is as follows: 1.10 s (3H, CH_3), 1.63-3.30 m (7H, Pro), 3.03, 3.50 [AB, 2H, CH_2(Phe), J = 13.5], 3.60, 4.30 (AB, 2H, CH_2-Bzl, J = 12.5), and 6.51-8.23 (18H, ArH). The ^{19}F NMR spectrum ($CDCl_3$, δ, ppm) is characterized at −36.05 m (ArF).

(SS)-(VIII). The PMR spectrum ($CDCl_3$, δ, ppm, J, Hz) is as follows: 1.18 s (3H, CH_3), 1.65-3.20 m (7H, Pro), 3.11 m (2H, CH_2-Phe), 3.60, 4.31 (AB, 2H, CH_2-Bzl, J = 12.0), and 6.60-8.20 m (18H, ArH). The ^{19}F NMR spectrum ($CDCl_3$, δ, ppm) is characterized at −34.56 m (ArF).

(SS)-(IX). The PMR spectrum ($CDCl_3$, δ, ppm, J, Hz) is as follows: 1.15 s (3H, CH_3), 1.68-3.25 m (7H, Pro), 3.10 m (2H, CH_2-Phe), 3.55, 4.30 (AB, 2H, CH_2Bzl, J = 12.0), and 6.60-8.13 m (18H, ArH). The ^{19}F NMR spectrum ($CDCl_3$, δ, ppm) is characterized at −37.51 m (ArF).

Isolation of (S)-PAP and the Amino Acids (XVII)-(XXII) from the Corresponding Complexes (IV)-(VI) and (VII)-(IX). The complexes were decomposed according to a general method. To 20 ml of the boiling solution of 2 N HCl were added 6 mmoles of the corresponding complex in 10 ml of MeOH. After the disappearance of the coloration (2-5 min), the reaction mixture was neutralized with 20% NH_4OH until a neutral pH was reached. The precipitated residue of the (S)-PAP hydrochloride was filtered off. The yield of the reagent (in the form of the hydrochloride) comprised 97-99% in different experiments. The amino acid was separated from the aqueous solution on Dowex-50 (H^+-form) resin. The yield and physicochemical characteristics, as well as the data of the elemental analysis, of the amino acids (XVII)-(XXII) are presented in Table 3.

(XX). The PMR spectrum (D_2O, δ, ppm) is as follows: 1.25 s (3H, CH_3), 3.0 br. s (2H, CH_2-Phe), and 7.0-7.1 m (4H, ArH). The ^{19}F NMR spectrum (in D_2O, δ, ppm) is characterized at −38.9 m (ArF).

(XXI). The PMR spectrum (D_2O, δ, ppm, J, Hz) is as follows: 1.55 s (3H, CH_3), 3.05, 3.31 (AB, 2H, CH_2Phe, J = 13.5), and 7.0-7.3 m (4H, ArH). The ^{19}F NMR spectrum (D_2O, δ, ppm) is characterized at −35.2 m (ArF).

(XXII). The PMR spectrum (D_2O, δ, ppm, J, Hz) is as follows: 1.31 s (3H, CH_3), 2.85, 3.08 (AB, 2H, CH_2-Phe, J = 12.0), and 6.9-7.1 m (4H, ArH). The ^{19}F NMR spectrum (in D_2O, δ, ppm) is characterized at −37.3 m (ArF).

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