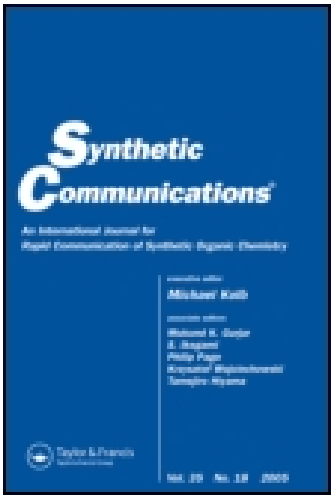

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A New Approach to the Efficient Method for the Asymmetric Synthesis of (S)-O-, M-, P-Fluorophenylalanines and Their 2-Methyl-substituted Analogs

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A NEW APPROACH TO THE EFFICIENT METHOD FOR THE ASYMMETRIC SYNTHESIS OF (*S*)-O-, M-, P-FLUOROPHENYLALANINES AND THEIR 2-METHYL-SUBSTITUTED ANALOGS

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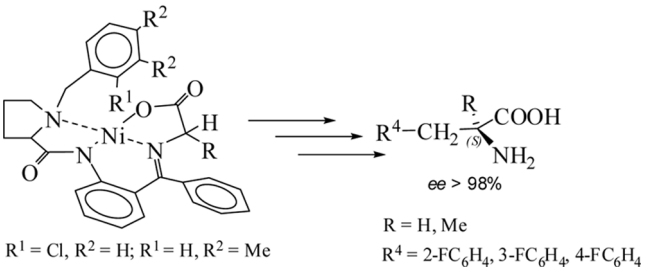
GRAPHICAL ABSTRACT



Abstract *The reactions of asymmetric C-alkylation of glycine and alanine in Ni^{II} complexes of their Schiff's bases with modified chiral auxiliaries (*S*)-2-N-[(N′-2-chlorobenzylprolyl)-amino]benzophenone and (*S*)-2-N-[N′-(3,4-dimethylbenzylprolyl)amino]benzophenone by fluorine-substituted benzyl halogenides have been studied. As a result, a highly stereoselective and relatively rapid method for the asymmetric synthesis of (*S*)-o-, m-, p-fluorophenylalanines and their 2-methyl substituted analogs has been developed.*

Keywords Asymmetric synthesis; c-alkylation; chiral Ni^{II} complex; fluorophenylalanine

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INTRODUCTION

In a series of nonproteinogenic α-amino acids, β-phenyl-α-alanine derivatives, especially o-, m-, p-fluorophenylalanines and their derivatives, which have a broad spectrum of biological activity,[1] are of particular interest. For example, p-fluorophenylalanine and its derivatives have antiviral and antitumor activities.[2,3]

It should be mentioned that individually pure optically active enantiomers of amino acids are physiologically and pharmacologically active, and as a rule, the optical antipode of a pharmacologically active compound has a negative pharmacological effect.[4] In this connection, the synthesis of new enantiomerically pure analogs of phenylalanine, including derivatives with halogen substituents in the aromatic ring, is an urgent task.

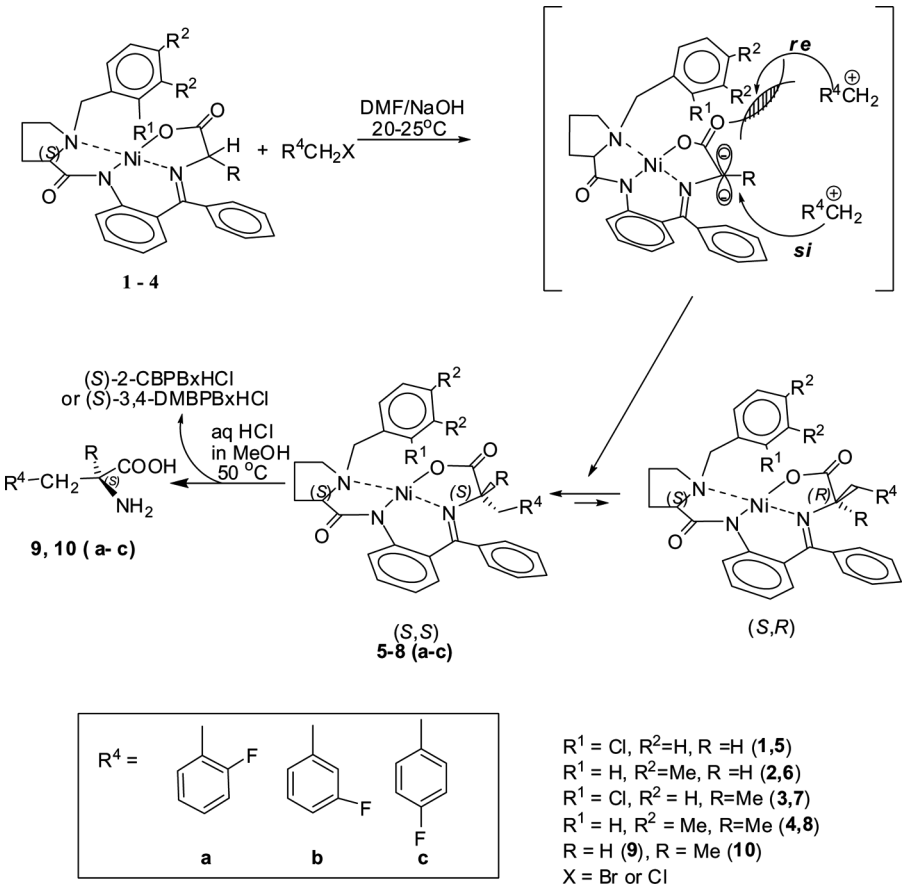
Among various approaches proposed for the syntheses of enantiomerically pure (*S*)-o-, m-, p-fluorophenylalanines and their 2-methyl-substituted derivatives, asymmetric C-alkylation of glycine and alanine moieties with the use of Ni^{II} complexes of their Schiff base and chiral auxiliary (*S*)-2-N-(N′-benzylprolyl)aminobenzophenone [(*S*)-BPB] as an amino acid synthon was the most efficient.[5] Stereoselectivities of the syntheses were reported as being 90% *de* on average, and the duration of asymmetric reactions was 2–3 h. These complexes were also used for the production of a wide spectrum of optically active, nonproteinogenic (*S*)-α-amino acids containing aliphatic, aromatic, and heterocyclic substituents in the side chain.[6]

Different modifications of the BPB auxiliary were recently introduced to increase the stereoselectivity and to reduce the duration of the asymmetric reactions.[7] Various electron-donating and acceptor substituents (Cl, Br, Me, $C_6H_5CH_2O$, NO_2, etc.) were introduced in the aromatic ring of the N-benzylprolyl moiety of BPB. For example, glycine and alanine Schiff base complexes with modified chiral auxiliaries, 2-chloro [(*S*)-2-N-[N′-(2-chlorobenzylprolyl)amino]-benzophenone [(*S*)-2-CBPB)] and 3,4-dimethyl [(*S*)-2-N-[N′-(3,4-dimethylbenzylprolyl)amino]benzophenone [(*S*)-3,4-DMBPB], were prepared. Their use in reactions of asymmetric C-alkylation of the amino acid moieties by alkyl halogenides ($C_6H_4Cl_2Br$, CH_2=CH-CH_2Cl) and carbonyl compounds [CH_2O, CH_3CHO, $(CH_3)_2CO$], resulted in relatively high stereoselectivities of the reactions [$de \geq 95\%$).[8,9]

We put ourselves to the task of developing efficient methods to asymmetrically synthesize enantiomerically enriched fluorine-substituted phenylalanines via Ni^{II} complexes of glycine and alanine Schiff bases with [(*S*)-2-CBPB)] and [(*S*)-3,4-DMBPB] auxiliaries.

RESULTS AND DISCUSSION

The initial complexes derived from (*S*)-2-CBPB and (*S*)-3,4-DMBPB, Ni^{II}-(*S*)-2-CBPB-Gly (**1**), Ni^{II}-(*S*)-3,4-DMBPB-Gly (**2**), Ni^{II}-(*S*)-2-CBPB-Ala (**3**), and Ni^{II}-(*S*)-3,4-DMBPB-Ala (**4**), have been obtained according the earlier method.[8d] 2-F-$C_6H_4CH_2Br$, 3-F-$C_6H_4CH_2Cl$, and 4-F-$C_6H_4CH_2Br$ were used as the alkylating agents. The alkylation was conducted in dimethylformamide (DMF) at room temperature with NaOH employed as a base (Scheme 1).



Scheme 1. Synthesis of complexes **5–8(a–c)**.

The reaction of alkylation was monitored by thin-layer chromatography (TLC) [SiO_2, $CHCl_3$–CH_3COCH_3 (3:1)] following the disappearance of traces of the initial complexes **1–4**.

As expected, a mixture of two (*S*,*S*)- and (*S*,*R*)-diastereoisomeric complexes were obtained in all the cases. The major diastereomers of the alkylation products were separated by preparative chromatography [SiO_2, 20×20 cm, $CHCl_3$–CH_3COCH_3 (3:1)], and their absolute configuration was determined by the sign of optical rotation at 589 nm wavelength. It was established earlier that the complexes of (*S*)-α-amino acids based on the BPB chiral auxiliaries and their modified analogs had a positive sign of rotation and the complexes of (*R*)-α-amino acids had a negative one.[10] The signs of the optical rotation of the major diastereomeric complexes **5–8** had positive values, which reflected their (*S*,*S*)-absolute configuration.

The ratio of (*S*,*S*)- and (*S*,*R*)-diastereomers of alkylation products was determined by chiral high-performence liquid chromatographic (HPLC) analysis of the amino acid mixture recovered after decomposition of the mixture of diastereomeric complexes (before chromatography) and ion-exchange demineralization. The data

Table 1. Results of alkylation of glycine complexes (**1, 2**) by fluorine-substituted benzyl halogenides in DMF/NaOH at 20–25 °C

Run[a]	Initial complex	Alkylating agent	Chemical yield (%)[b]	Duration (min)	Ratio of products (%)[c]		
					(*S*,*S*)	(*S*,*R*)	Product of bis-alkylation
1	1	2-F-BnBr	70	15	76.8	9.32	13.88
2	1	3-F-BnCl	82	5	96.74	2.71	0.55
3	1	4-F-BnBr	81	8	86.47	10.43	3.10
4	2	2-F-BnBr	62	20	60.99	5.03	33.98
5	2	3-F-BnCl	72	12	82.36	2.16	15.48
6	2	4-F-BnBr	85	20	50.62	4.00	45.38
7	Ni^{II}-(*S*)-BPB-Gly	2-F-BnBr	72	30	80.24	5.01	14.74
8	Ni^{II}-(*S*)-BPB-Gly	3-F-BnCl	70	30	95.08	4.36	0.55
9	Ni^{II}-(*S*)-BPB-Gly	4-F-BnBr	71	30	77.44	7.20	15.36

[a]Reaction conditions: the reactions were run in DMF, concentration of initial complex was 1.4 M, ratio of the initial complex–alkylating agent–NaOH = 1:1.2:2.5, at 20–25 °C, under Ar.
[b]Chemical yield on the stage of alkylation (mixture of diastereomeric complexes).
[c]Data obtained by chiral HPLC analysis.

are presented in Tables 1 and 2. In addition, in the case of unmodified BPB, the determination of the ratio of diastereomeric complexes of the alkylation products was also carried out by ^{1}H NMR. The HPLC analyses of the same amino acids are also presented in the tables.

As seen from the data of Table 1, the best results were registered in the case of alkylation of the chiral auxiliary complex (*S*)-2-CBPB (**1**) by 3-F-benzyl chloride (run 2); stereoselectivity of the syntheses was 94%. The chiral auxiliary (*S*)-3,4-DMBPB (2) was less effective (runs 4, 5, and 6). A significant shortening of asymmetric reaction (~5–15 min) was also observed in the case of complex **1** (runs 1, 2, and 3).

Table 2. The results of alkylation of alanine complexes (**3**, **4**) by fluorine-substituted benzyl halogenides in DMF/NaOH at 20–25 °C

Run[a]	Initial complex	Alkylating agent	Chemical yield (%)[b]	Duration (min)	Ratio of products (%)[c]	
					(*S*,*S*)	(*S*,*R*)
1	3	2-F-BnBr	70	120	94.57	5.43
2	3	3-F-BnCl	82	70	96.07	3.93
3	3	4-F-BnBr	74	90	93.65	6.35
4	4	2-F-BnBr	62	120	94.03	5.97
5	4	3-F-BnCl	78	90	95.23	4.77
6	4	4-F-BnBr	65	110	93.48	6.52
7	Ni^{II}-(*S*)-BPB-(*S*)-Ala	2-F-BnBr	72	120	86.90	13.10
8	Ni^{II}-(*S*)-BPB-(*S*)-Ala	3-F-BnCl	70	120	87.41	12.59
9	Ni^{II}-(*S*)-BPB-(*S*)-Ala	4-F-BnBr	63	120	84.72	15.28

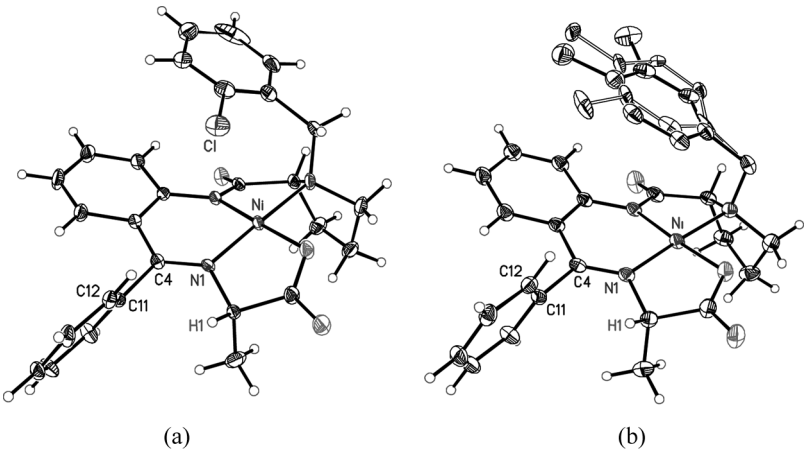
[a]Reaction conditions: the reactions were run in DMF, was concentration of initial complex 0.3 M, ratio of the initial complex–alkylating agent–NaOH = 1:3.5:5, at 20–25 °C, under Ar.
[b]Chemical yield on the stage of alkylation (mixture of diastereomeric complexes).
[c]Data obtained by chiral HPLC analysis.

Kinetic stereoselectivity of the synthesis was controlled by the relative rate of the alkylating agent attack on the *re*- or *si*- sides of the sp^2-carbanion of alanine moieties of the complexes. The relative thermodynamic stability of the formed diastereomeric complexes (thermodynamic stereoselectivity) was established in case of glycine alkylation via the base induced equilibration of the diastereoisomers.

Table 2 summarizes the data of alanine complex (**3,4**) alkylation. As can be seen from the data collected in Table 2, the increase of the stereoselectivities of the alkylations was observed in the modified complexes **3** and **4**, as compared with the unsubstituted complex Ni^{II}-(*S*)-BPB-(*S*)-Ala [runs 1–6 and 7–9].

The results on C-alkylation of modified complexes **1–4** with fluorine-substituted benzyl halogenides were in full agreement with the previously obtained data on the alkylation by other alkylating agents of the same complexes obtained earlier.[8] As was suggested earlier, the increase in the stereoselectivity in the case of alkylation of the modified complexes based on 2-CBPB and 3,4-DMBPB was caused by the change in the sizes of the torsion angle C4–C11–C12–N formed by the phenyl substituent at the -C=N- bond. The torsion angle for these complexes was 81.7° for Ni^{II}-(*S*)-3,4-DMBPB-(*S*)-Ala (**4**) and 70° for Ni^{II}-(*S*)-2-CBPB-(*S*)-Ala (**3**) (see Fig. 1) (In the case of the unmodified Ni^{II}-(*S*)-BPB-(*S*)-Ala complex, this angle was 90°.)

The decrease of the angle from a 90° value was accompanied with the inevitable increase in the shielding of the *re*- side of the flat carbanion formed in the initial stage of the reaction. This leads to greater kinetic diastereoselectivity of alkylation in the case of complexes **3** and **4** (and to greater thermodynamic diastereoselectivity in the case of complexes **1** and **2** also). Hence, the ratio of (*S*,*S*)/(*S*,*R*) becomes greater. The most significant deviation of the C4–C11–C12–N torsion angle from a 90° value is observed in the case of amino acid complexes based on a modified chiral auxiliary (*S*)-2-CBPB. As a result, high efficiency of the asymmetric reaction is registered exactly in the case of these complexes. This can also be facilitated by a decrease in the distance between the Cl and Ni atoms in the case of complex **3** (see Fig. 1).



(a) (b)

Figure 1. Structures of **3(a)** and *exo*- and *endo*-conformers of **4(b)** based on PCA data.

After decomposition of the complexes **5–8(a–c)** with 2*N* HCl solution, the target amino acids were isolated from the solution by a routine cation-exchange procedure followed by crystallization of the raw amino acids from aqueous alcohols.[8] The initial chiral auxiliaries (*S*)-2CBPB and (*S*)-3,4-DMBPB were recovered with >95% yield with full retention of the initial enantiomeric purity and could be reused repeatedly without any further purification.

Optically active o-, m-, p-fluorine-substituted derivatives of phenylalanine **9(a–c)** and (*S*)-β-phenyl-2-methyl-α-alanine **10(a–c)** have been obtained in >75% yields and >99.5% enantiomeric purity.

CONCLUSION

A relatively fast and highly selective asymmetric synthesis of (*S*)-o-, m-, p-fluorine-substituted phenylalanines and their 2-methyl-substituted analogs has been elaborated.

EXPERIMENTAL

The amino acids were purchased from Reanal (Hungary); silica gel L-40/100 from Chemapol (Praha, Czech Republic); $CHCl_3$, CH_3CN, CH_3OH, NaOH, and ROH, from Reakhim (Russia); and 2-fluorobenzylbromide, 3-fluorobenzylchloride, and 4-fluorobenzylbromide from Aldrich. All used solvents were freshly distilled. Enantiomeric purity of amino acids was determined by HPLC on the chiral phase Diaspher-110-Chirasel-E-PA 6.0 mkm 4.0×250 mm with 20% MeOH–80% 0.1 M $NaH_2PO_4 \times 2H_2O$ used as an eluent. A 254-nm ultraviolet (UV) detector was used. The ^1H NMR and ^{13}C NMR spectra were recorded on a Mercury-300 Varian (300-MHz)instrument in $CDCl_3$ (unless otherwise indicated). The optical rotations were measured on Perkin-Elmer-341 polarimeter in a 5-cm thermostated cell with an accuracy of 0.1%.

Alkylations of the initial complexes (1–4) were conducted as previously described.[5]

Upon completion of the reaction, the mixture was neutralized with AcOH and diluted with H_2O. The precipitate of the mixture of diastereomer complexes was filtered and washed with water. A small part of the mixture (~0.5 g) was separated by preparative chromatography [20×20 cm, SiO_2, $CHCl_3$–CH_3COCH_3 (3:1)], and the structure and absolute configuration of the pure major diastereomer of complexes **5–8(a–c)** were established by spectral methods. The ratio of the diastereomers was determined with chiral HPLC analysis of the amino acid mixture isolated after the decomposition of the mixture of diastereomeric complexes (without chromatographic purification).

Rating of signals in NMR ^1H spectra to hydrogen atoms of methylene groups CH_2-aryl does not present any difficulties, whereas rating of signals of proline protons and aromatic rings is significantly complicated because of the overlapping multiplet signals from several nuclei of hydrogen atoms. This requires application of modern methods of two-dimensional correlation spectroscopy (COSY). The same methods are also necessary for rating carbon atoms in ^{13}C NMR. Rating of signals presented in Tables 3 and 4 is based on COSY, heteronuclear multiple quantum

Table 3. Characteristics of ^{1}H NMR spectra

Compound	Parameter	**5a**	**5b**	**5c**	**7a**	**7b**	**7c**
Proline							
	α-CH	3.38, dd	3.37, dd	3.38, dd	3.30, t	3.31, dd	3.31, dd
	^3J	9.9, 6.8	10.3, 6.6	10.0, 6.8	8.7	9.4, 7.8	9.3, 6.4
β-CH_2							
	H_a	2.38, m	2.48, m	2.43, m	2.30, m	2.36, m	2.35, m
	H_b	2.44, m	2.50, m	2.48, m	2.33, m	2.38, m	2.37, m
γ-CH_2							
	H_a	1.83, m	1.83, m	1.82, m	1.66, m	1.73, m	1.71, m
	H_b	2.35, m	2.55, m	2.43, m	2.16, m	2.20, m	2.13, m
δ-CH_2							
	H_a	1.92, td	1.91, td	1.92, td	1.82, td	1.82, td	1.83, td
	^2J, ^3J	10.1, 6.5	10.1, 6.5	10.0, 6.4	10.4, 6.5	10.3, 6.5	10.3, 6.4
	H_b	3.15, m	3.18, m	3.15, m	3.16, ddd	3.18, ddd	3.14, ddd
	^3J				6.4, 2.4	7.0, 2.3	6.7, 2.5
$\underline{CH_2}C_6H_4Cl$							
	H_a	3.75, d	3.76, d	3.75, d	3.85, d	3.85, d	3.82, d
	H_b	4.37, d	4.36, d	4.36, d	4.40, d	4.42, d	4.40, d
	^2J	12.9	12.9	12.9	12.8	12.9	12.9
β-H, Phe							
	H_a	2.79, dd	2.82, dd	2.79, dd	2.97, d	3.08, s	3.06, d
	H_b	3.04, dd	3.05, dd	3.03, dd	3.41, d	3.08, s	3.09, d
	^2J	13.9	4.22, dd	13.9	13.8	—	13.8
α-H, Phe		4.22, dd	13.8	4.22, dd	—	—	—
	^3J	5.5, 4.5	5.9, 4.5	5.6, 4.5	—	—	—
	α-Me	—	—	—	1.09, s	1.19, s	1.15, s
C_6H_4							
	6-CH	8.18, dd	8.17, dd	8.17, dd	8.16, dd	8.10, dd	8.08, dd
	^3J, ^4J	8.7, 1.0	8.6, 1.0	8.7, 1.0	8.6, 1.3	8.6, 1.1	8.6, 1.2
	5-CH	7.13	7.15	7.14	7.09, ddd	7.10 m	7.10, ddd
	^3J, ^4J				8.6, 5.8, 2.5		8.6, 6.5, 2.0

(*Continued*)

Table 3. Continued

Compound	Parameter	**5a**	**5b**	**5c**	**7a**	**7b**	**7c**
	4-CH	6.68, m	6.68, m	6.68, m	6.60, ddd	6.62, ddd	6.61, ddd
	^3J, ^4J				8.5, 5.8, 1.3	8.5, 6.5, 1.2	8.5, 6.5, 1.2
	3-CH	6.67, m	6.67, m	6.67, m	6.57, dd	6.57, dd	6.57, dd
	^3J, ^4J				8.5, 2.5	8.5, 2.0	8.5, 2.0
C_6H_4-F							
	2-CH	—	6.86	7.14, m	—	7.17, m	7.31, m
	3-CH	7.18, m	—	7.10, m	7.19, m	—	7.15, m
	4-CH	7.42, m	7.07, td	—	7.42, m	7.14, m	—
	^3J, ^4J		8.5, 2.6				
	5-CH	7.20, m	7.26, m	7.10, m	7.26, m	7.36, m	7.15, m
	6-CH	7.26, m	6.90, m	7.14, m	7.52	7.14, m	7.31, m
C_6H_4-Cl							
	3-CH	7.27, m	7.27, m	7.29, m	7.32, m	7.31, m	7.33, m
	4,5-CH,	7.18, 7.26, m	7.15, 7.25, m	7.13, 7.25, m	7.19, 7.25, m	7.15, 7.26, m	7.15, 7.26, m
	6-CH	8.18, dd	8.14, dd	8.17, dd	8.13, dd	8.10, dd	8.11, dd
	^3J, ^4J	7.6, 1.6	7.6, 1.6	7.6, 1.7	7.6, 1.7	7.6, 1.8	7.6, 1.8
C_6H_5							
	2-CH,	7.01, m	6.90, m	6.90, m	7.23, m	7.00, m	7.00, m
	2′-CH	7.29, m	7.33, m	7.31, m	7.33, m	7.36, m	7.37, m
	3-CH,	7.40, m	7.46, m	7.47, m	7.46, m	7.42, m	7.40, m
	3′-CH,	7.46, m	7.56, m	7.54, m	7.43, m	7.50, m	7.49, m
	4-CH	7.56, m	7.58, m	7.58, m	7.50, m	7.50, m	7.50, m

Table 4. Characteristics of ^{13}C NMR spectra

Compound	Parameter	**5a**	**5b**	**5c**	**7a**	**7b**	**7c**
Proline							
	α-CH	70.83	70.76	70.71	70.63	70.54	70.41
	β-CH_2	30.78	30.72	30.74	30.51	30.39	30.38
	γ-CH_2	23.18	23.22	23.20	22.98	22.86	22.88
	δ-CH_2	57.34	57.43	57.50	57.20	57.26	57.31
	CH_2-Ar	60.01	60.01	60.09	60.30	60.30	60.28
	$\underline{C}H_2$-CR	33.39	39.71	39.11	41.15	46.01	45.73
	CH_2-$\underline{C}$R	71.03	71.34	71.61	79.02	78.75	79.11
	α-Me	—	—	—	29.76	30.01	29.84
C_6H_4-F							
	1-C, d	123.38	138.54	131.78	124.13	139.43	132.68
		$^2J_{C,F}$ 16.0	$^3J_{C,F}$ 7.3	$^4J_{C,F}$ 3.2	$^2J_{C,F}$ 15.2	$^3J_{C,F}$ 7.3	$^4J_{C,F} \sim 3.5$
	2-C, d	162.69	117.64	132.27	162.55	118.08	133.00
		$^1J_{C,F}$ 246.8	$^2J_{C,F}$ 21.1	$^3J_{C,F}$ 8.0	$^1J_{C,F}$ 246.8	$^2J_{C,F}$ 21.0	$^3J_{C,F}$ 7.9
	3-C, d	115.82	163.33	115.90	115.89	163.31	115.82
		$^2J_{C,F}$ 22.5	$^1J_{C,F}$ 247.5	$^2J_{C,F}$ 21.2	$^2J_{C,F}$ 23.0	$^1J_{C,F}$ 247.0	$^2J_{C,F}$ 21.1
	4-C, d	129.45	114.52	162.80	129.53	114.51	162.80
		$^3J_{C,F}$ 8.3	$^2J_{C,F}$ 20.9	$^1J_{C,F}$ 245.5	$^3J_{C,F}$ ~8.0	$^2J_{C,F}$ 21.0	$^1J_{C,F}$ 246.6
	5-C, d	124.97	130.29	115.90	125.01	130.24	115.82
		$^4J_{C,F}$ 3.4	$^3J_{C,F}$ 8.1	$^2J_{C,F}$ 21.2	$^4J_{C,F}$ 3.3	$^3J_{C,F}$ 8.2	$^2J_{C,F}$ 21.1
	6-C, d	133.24	126.40	132.27	133.79	126.56	133.00
		$^3J_{C,F}$ 4.5	$^4J_{C,F} \sim 2.5$	$^3J_{C,F}$ 8.0	$^3J_{C,F}$ 4.7	$^4J_{C,F}$ 2.7	$^3J_{C,F}$ 7.9
C_6H_4							
	6-CH	123.43	123.60	123.61	123.21	123.59	123.56
	5-CH	132.53	132.69	132.70	132.12	132.21	132.20
	4-CH	120.62	120.72	120.76	120.42	120.62	120.61
	3-CH	133.70	133.66	133.69	134.14	133.98	134.01
C_6H_4-Cl							
	3-CH	130.54	130.56	130.58	130.52	130.56	130.55

(*Continued*)

Table 4. Continued

Compound	Parameter	**5a**	**5b**	**5c**	**7a**	**7b**	**7c**
	4,5-CH	127.18, 130.48	127.19, 130.48	127.22, 130.50	127.13, 130.48	127.17, 130.45	127.18, 130.46
	6-CH	134.22	134.18	134.21	134.15	134.09	134.12
C_6H_5							
	2-CH,	128.53	128.03	128.05	127.78	127.59	127.56
	2′-CH	127.41	127.43	127.47	131.11	131.10	131.22
	3-CH,	129.14	129.08	129.10	127.16	127.31	127.32
	3′-CH,	129.14	129.39	129.42	128.55	128.28	128.29
	4-CH	129.86	130.02	130.01	129.48	129.68	129.66
C (quarter.)							
		126.58	126.38	126.41	128.13	128.01	128.00
		131.47	131.43	131.49	131.62	131.53	131.56
		134.53	134.48	134.60	136.06	136.01	136.03
		135.98	135.96	135.98	137.53	137.12	137.22
		143.15	143.19	143.37	142.63	142.52	142.56
		172.15	171.40	171.37	173.21	172.38	172.25
		178.21	177.93	178.07	179.38	179.50	179.53
		179.50	179.56	179.63	180.66	180.70	180.67

correlation (HMQC), and nuclear Overhauser effect spectrosleaopy (NOESY) experiments.

As can be seen from Table 3, one of hydrogen atoms of the NCH_2 proline group is noticeably shielded and developed in the range of 1.80–1.90 ppm. Values of J constants show that the given hydrogen atom has an axial configuration. The other hydrogen atom of this group is developed in the range of 3.15–3.20 ppm, which is more typical of protons of the NCH_2 group. In ^{13}C NMR spectrum this group is developed in the range of ≈57 ppm. The hydrogen atom of proline in the α-position also occupies the axial position and shows a strong nuclear Overhauser effect (NOE) with proton in position 6 of the chloro-substituted aromatic ring.

Both ^{1}H and ^{13}C NMR spectra show that positions 2 and 2′ as well as 3 and 3′ in the phenyl ring are not equivalent, which proves the absence of free rotation of the whole phenyl group about an axis passing through C–C1–C4. Moreover, as is evident from the NOESY spectra, hydrogen atoms in positions 2 and 2′ have different-intensity NOE with proton 3-H of the neighboring aromatic ring. NOE, closer in intensity, are observed in compound **5a**, in which fluorine atom is in the ortho-position. The torsion angle C4–C11–C12–N is closer to 90°. Substitution of hydrogen atom by a methyl group turns the phenyl ring in such a way that the torsion angle C4–C11–C12–N decreases thus reducing the distance, between 2′-H and 3-H while the distance between 2-H and 3-H increases. In spectra, this is reflected by the growth and decrease of intensities of the corresponding NOE signals. In compounds **5b** and **5c**, where the fluorine atom is in meta- or para-positions, the phenyl ring is turned in such a way that the distance between 2′-H and 3-H is shorter than the distance between 2-H and 3-H, and introduction of the methyl group (compounds **7b** and **7c**) strengthens this tendency, resulting in a decrease of the torsion angle C4–C11–C12–N.

Complex 5a

Yield: 70%. Calcd. for $C_{34}H_{29}ClFN_3NiO_3$ (640.76): C, 63.73; H, 4.56; N, 6.56. Found: C, 63.69; H, 4.62; N, 6.59. Mp 238–240 °C. $[\alpha]_D^{20} + 1951.67°$ (c 0.06, MeOH).

Complex 5b

Yield: 82%. Calcd. for $C_{34}H_{29}ClFN_3NiO_3$ (640.76): C, 63.73; H, 4.56; N, 6.56. Found: C, 63.78; H, 4.52; N, 6.60. Mp 192–195 °C. $[\alpha]_D^{20} + 936.25°$ (c 0.08, MeOH).

Complex 5c

Yield: 81%. Calcd. for $C_{34}H_{29}ClFN_3NiO_3$ (640.76): C, 63.73; H, 4.56; N, 6.56. Found: C, 63.69; H, 4.59; N, 6.59. Mp 207–209 °C. $[\alpha]_D^{20} + 1618.00°$ (c 0.03, MeOH).

Complex 6a

Yield: 62%. Calcd. for $C_{36}H_{34}FN_3NiO_3$ (634.37): C, 68.16; H, 5.40; N, 6.62. Found: C, 68.07; H, 5.48; N, 6.55. Mp 258–260 °C. $[\alpha]_D^{20} + 2056.68°$ (c 0.09, MeOH).

Complex 6b

Yield: 72%. Calcd. for $C_{36}H_{34}FN_3NiO_3$ (634.37): C, 68.16; H, 5.40; N, 6.62. Found: C, 68.22; H, 5.34; N, 6.67. Mp 205–207 °C. $[\alpha]_D^{20} + 1025.14°$ (*c* 0.08, MeOH).

Complex 6c

Yield: 85%. Calcd. for $C_{36}H_{34}FN_3NiO_3$ (634.37): C, 68.16; H, 5.40; N, 6.62. Found: C, 68.11; H, 5.38; N, 6.57. Mp 196–198 °C. $[\alpha]_D^{20} + 1802.02°$ (*c* 0.03, MeOH).

Complex 7a

Yield: 70%. Calcd. for $C_{35}H_{31}ClFN_3NiO_3$ (654.78): C, 64.20; H, 4.77; N, 6.42. Found: C, 64.27; H, 4.69; N, 6.48. Mp 200–202 °C. $[\alpha]_D^{20} + 1711.25°$ (*c* 0.08, MeOH).

Complex 7b

Yield: 82%. Calcd. for $C_{35}H_{31}ClFN_3NiO_3$ (654.78): C, 64.20; H, 4.77; N, 6.42. Found: C, 64.13; H, 4.65; N, 6.46. Mp 177–179 °C. $[\alpha]_D^{20} + 1190.0°$ (*c* 0.09, MeOH).

Complex 7c

Yield: 74%. Calcd. for $C_{35}H_{31}ClFN_3NiO_3$ (654.78): C, 64.20; H, 4.77; N, 6.42. Found: C, 64.29; H, 4.82; N, 6.37. Mp 122–124 °C. $[\alpha]_D^{20} + 2181.25°$ (*c* 0.08, MeOH).

Complex 8a

Yield: 62%. Calcd. for $C_{37}H_{36}FN_3NiO_3$ (648.39): C, 68.54; H, 5.60; N, 6.48. Found: C, 68.47; H, 5.53; N, 6.55. Mp 162–164 °C. $[\alpha]_D^{20} + 1450.0°$ (*c* 0.08, MeOH).

Complex 8b

Yield: 75%. Calcd. for $C_{37}H_{36}FN_3NiO_3$ (648.39): C, 68.54; H, 5.60; N, 6.48. Found: C, 68.59; H, 5.67; N, 6.41. Mp 218–220 °C. $[\alpha]_D^{20} + 1395.56°$ (*c* 0.08, MeOH).

Complex 8c

Yield: 65%. Calcd. for $C_{37}H_{36}FN_3NiO_3$ (648.39): C, 68.54; H, 5.60; N, 6.48. Found: C, 68.43; H, 5.56; N, 6.59. Mp 129–131 °C. $[\alpha]_D^{20} + 2020.05°$ (*c* 0.03, MeOH).

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