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TETRAHEDRON

Asymmetric Synthesis of Novel Highly Sterically Constrained (2*S*,3*S*)-3-Methyl-3-Trifluoromethyl- and (2*S*,3*S*,4*R*)-3-Trifluoromethyl-4-Methylpyroglutamic Acids[1]

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Abstract: Asymmetric synthesis of the *novel* highly sterically constrained (2*S*,3*S*)-3-methyl-3-trifluoromethyl- and (2*S*,3*S*,4*R*)-3-trifluoromethyl-4-methylpyroglutamic acids has been developed *via* diastereoselective Michael addition reactions between a Ni(II) complex of the chiral non-racemic Schiff base of glycine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone (BPB) and the corresponding trifluoromethyl-containing crotonates. Of particular synthetic interest is the reaction of the glycine Ni-complex with ethyl 3-trifluoromethyl crotonate featuring excellent diastereoselectivity (>98% de) as a result of complete stereochemical discrimination between the methyl and trifluoromethyl groups. A mechanistic rationale for the observed kinetically controlled stereochemical outcome is discussed.

Key words: *amino acids and derivatives; asymmetric synthesis; addition reactions; mechamism*

INTRODUCTION

Over the past 10 years, unusual, tailor-made[2] amino acids have evolved from merely curious analogues of the natural molecules, to extraordinary useful biologically relevant compounds with a wide range of potential bio-medicinal and synthetic applications.[3-5] One of the most exciting current endeavors in life sciences is the development of insights into the chemical-physical basis for peptide-mediated biological information transfer. Tailor-made amino acids are of critical importance to explore the relationship of peptides' three-dimensional structure and biological functions.[4i,6] As a part of our efforts in this area, recently we have begun a research project on asymmetric synthesis of Chi(χ)-constrained[4i,7] pyroglutamic acids and related compounds.[1] Apart from their importance in *de novo* peptide design,[8] pyroglutamic acids can be transformed readily to afford the corresponding glutamic acids, glutamines and prolines,[9] which are of particular interest in the design of conformationally and topographically constrained peptides and peptide mimetics.[4i,8a,10] This project has additional importance due to the promising applications of pyroglutamic acid derivatives as chiral auxiliaries for general asymmetric synthesis.[11] In this paper, we report a preparatively convenient asymmetric synthesis of the hitherto unknown χ-constrained (2*S*,3*S*)-3-methyl-3-trifluoromethyl- and (2*S*,3*S*,4*R*)-3-trifluoromethyl-4-methylpyroglutamic acids *via* diastereoselective Michael addition reactions between a Ni(II) complex of the chiral non-racemic Schiff base of glycine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]-benzophenone [(*S*)-**BPB**], and the corresponding ethyl 3-trifluoromethyl- and 2-methyl-4,4,4-trifluorocrotonates. The ready availability of all starting compounds, combined with the simplicity of the experimental procedure should render this method synthetically attractive for preparing numerous target amino acids.

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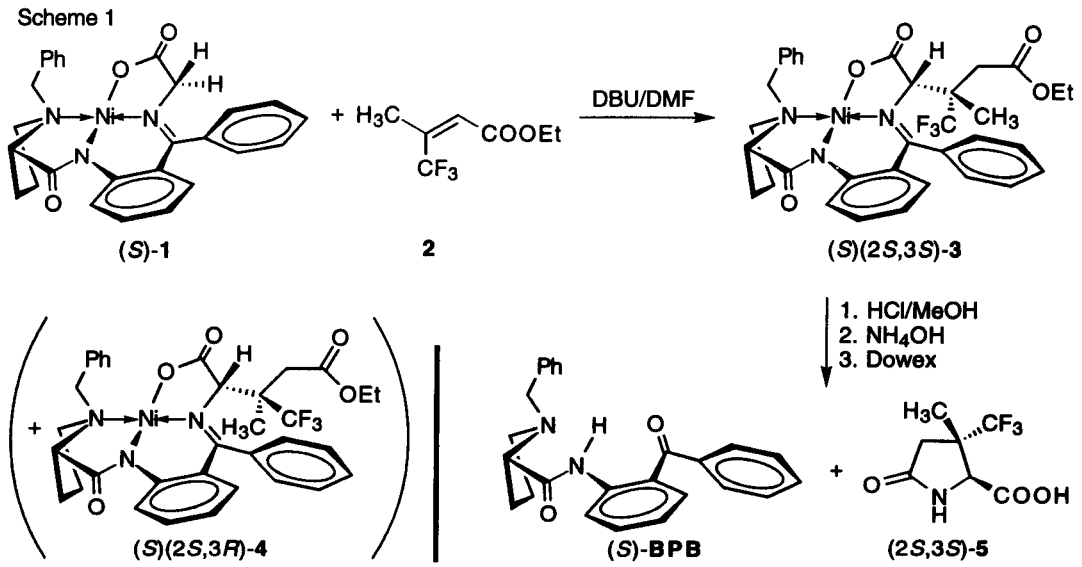
RESULTS AND DISCUSSION

Diastereoselective Michael addition reactions between chiral equivalents of a nucleophilic glycine and an α,β-unsaturated carboxylic acid derivative have been shown to provide a general approach to stereochemically defined 3-substituted glutamic/pyroglutamic acids.[4a-f,4i,5b,9,12] However, to our knowledge, unsymmetrically β,β- and α,β-disubstituted acrylic acid derivatives have never been used as electrophiles in asymmetric Michael additions. Therefore, apart from our need for the target amino acids, the present study was stimulated by a desire to know whether these types of substrates could be used in the addition reactions with a chiral equivalent of a nucleophilic glycine, and what would be the corresponding stereochemical outcome.

Our choice of a chiral equivalent for a nucleophilic glycine, a Ni(II) complex of the chiral non-racemic Schiff base of glycine with (*S*)-BPB (*S*)-**1** (Scheme 1), was based on the ready availability[13] of (*S*)-**1**, and the high reactivity (C-H acidity) of the glycine methylene group in this complex. As a result, the corresponding homologation reactions proceed under extraordinary mild conditions, allowing use of organic bases (instead of *n*-BuLi, for instance) to generate the enolate.[14]

Synthesis of (2S,3S)-3-methyl-3-trifluoromethylpyroglutamic acid. Michael addition reaction between the glycine complex (*S*)-**1** and ethyl 4,4,4-trifluorocrotonate readily occurred in DMF solution in the presence of a catalytic amount of DBU (5 mol %) to afford a kinetically controlled mixture of the (2*S*,3*S*)- and (2*S*,3*R*)-diastereomers in a ratio of 5.6/1, respectively.[1] Under these same reaction conditions, Michael addition of the complex (*S*)-**1** with ethyl 3-trifluoromethylcrotonate (**2**) was not observed, but application of equimolar amount of the base DBU allowed the reaction to proceed, albeit at a much slower rate and with incomplete conversion of the starting material (*S*)-**1**. After a series of experiments, we found that trifluoromethylcrotonate (**2**) is relatively unstable under the reaction condition used, necessitating the use of a substantial excess of **2** to achieve a reasonable conversion of the glycine complex (*S*)-**1**. The best synthetic result, an 85% conversion of (*S*)-**1**, was obtained using a 3 mol excess of **2** in the presence of 2 mol equivalents of DBU. The low reactivity of

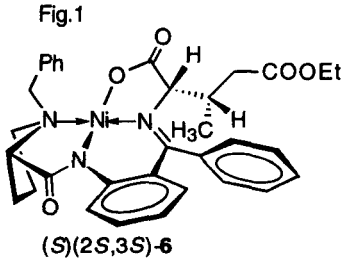
Scheme 1



trifluoromethylcrotonate **2** (5 hrs reaction time), as compared with that of ethyl 4,4,4-trifluorocrotonate in the Michael addition with complex (*S*)-**1** (almost instant reaction),[1] could be expected considering the unfavorable electronic and steric effects brought about by the additional methyl group in ester **2**. Nonetheless, a very favorable stereochemical outcome for the reaction was obtained. Thus, the Michael addition between complex (*S*)-**1** and ester **2** afforded the product **3** (Scheme 1), as the only detectable product by ^{1}H-NMR and HPLC analyses on the crude reaction mixture. Considering the 5.6/1 ratio of the (2*S*,3*S*)- and (2*S*,3*R*)-diastereomeric products, obtained in the reaction of ethyl 4,4,4-trifluorocrotonate with (*S*)-**1**, as a result of stereochemical discrimination between H and CF_3 groups, complete discrimination between methyl and trifluoromethyl in the reaction under study was a pleasant surprise. A plausible rationale for these results might involve *cis* and *trans* disposition of the trifluoromethyl and ester groups in the starting ethyl 4,4,4-trifluorocrotonate and 3-trifluoromethylcrotonate (**2**) (*vide infra*). Due to substantial differences in chromatographic behavior between the product **3** (R_f = 0.42, in $CHCl_3$/acetone 10/1) and the starting complex (*S*)-**1** (R_f = 0.21), isolation of the former could be easily achieved by routine column chromatography. However, with the aim of preparing 3-methyl-3-trifluoromethylpyroglutamic acid **5** as a final target, the separation step could be avoided, and the crude reaction mixture of **3** and (*S*)-**1** can be used as is for the further transformations (*vide infra*).

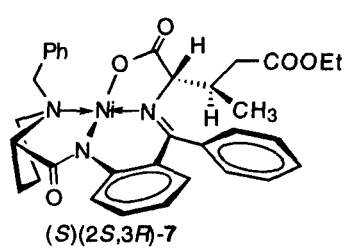
The absolute configuration of the α-stereogenic carbon of the glutamic acid residue in **3** was easily determined to be (*S*) on the basis of the chiroptical properties of Ni-complex **3**.[15] However, assignment of the stereochemistry at the β-carbon turned out to be far from straightforward. Unfortunately, all attempts to obtain crystals suitable for X-ray analysis of complex **3** have failed, thus far, leaving ^{1}H-NMR analysis as the only way to determine the stereochemistry of the 3-methyl-3-trifluoromethylglutamic acid in the product **3**. Previously we have shown that the relative stereochemistry of the (2*S*,3*S*)- and (2*S*,3*R*)-configured diastereomeric products **6**,**7**, (Fig. 1), respectively, obtained in the reaction of the ethyl crotonate with (*S*)-**1**, can be unambiguously assigned using the chemical shifts of the corresponding methyl groups at C-3.[1,16] Thus, while the resonance of the 3-methyl protons of the (2*S*,3*R*)-configured diastereomer **7** featured a normal chemical shift of 0.78 ppm, the signal of the methyl protons in (2*S*,3*S*)-**6** was found to be anomalously downfield (1.97 ppm), indicating that the methyl group is situated under the Ni(II) ion and exposed to its deshielding influence.[17] Unfortunately, these data could not be applied for unambiguous determination of the absolute configuration of complex **3** as the chemical shift of the methyl group of the glutamic acid residue in **3** is 1.43 ppm, that is just in the middle of the values reported for **6**,**7**. Considering the strong electron-withdrawing effect of a trifluoromethyl group, which usually causes a down-field shift of neighboring groups, the chemical shift of 1.43 ppm for the methyl in complex **3** support the (2*S*,3*S*) configuration with the methyl directed away from the Ni(II) ion. However, taking into account the highly sterically constrained nature of complex **3**, which possesses a quaternary β-stereogenic carbon atom, one could suggest that there might be

Fig.1



(*S*)(2*S*,3*S*)-**6**

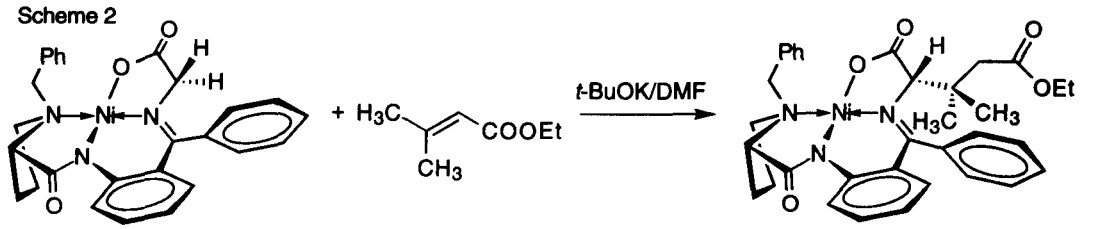
δ of the Me at C-3: 1.97 ppm



(*S*)(2*S*,3*R*)-**7**

δ of the Me at C-3: 0.78 ppm

Scheme 2



(*S*)-**1** (*S*)(2*S*)-**8**

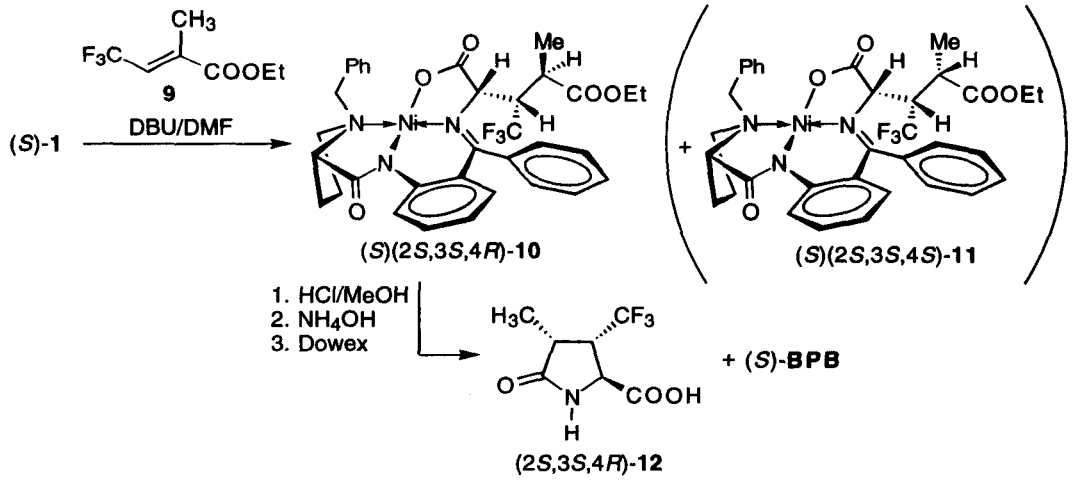
some other steric or electronic effects influencing the chemical shift of protons in compound **3**. To provide a more closely related model, we prepared the corresponding Ni-complex containing 3,3-dimethylglutamic acid residue *via* Michael addition between (*S*)-**1** and ethyl 3-methylcrotonate (Scheme 2). The much less electrophilic ethyl 3-methylcrotonate (as compared with trifluoromethyl-containing analog **2**), was found to be totally inactive toward complex (*S*)-**1** in the presence of DBU. However, use of potassium *tert*-butoxide as a base, led to an efficient addition reaction giving rise to complex **8** as the sole reaction product. The absolute configuration of the glutamic acid residue in **8** was assigned to be (*S*) on the basis of its spectral and chiroptical properties. As expected, the resonances of the methyl groups of the more sterically constrained 3,3-dimethylglutamic acid residue in **8** were found to be shifted downfield as compared with the resonances of the methyl groups in complexes **6** and **7**. Thus in the ^{1}H-NMR spectrum of **8**, the 3-methyl group located under the Ni(II) ion appeared at 1.98 ppm [1.97 ppm in (2*S*,3*S*)-**6**], while the chemical shift of the second methyl was found at 1.14 ppm [0.78 ppm in (2*S*,3*R*)-**7**]. Although these data provided valuable information, supporting the (2*S*,3*S*) stereochemistry of complex **3**, we still are uneasy claiming that the (2*S*,3*S*) stereochemistry is unambiguously proven. Since no chemical reactions occurs with 100% stereoselectivity, as a final effort to solve the problem, we decided to search for an α-(*S*)-configured diastereomer which might be formed in a minute amount in the reaction of complex (*S*)-**1** with trifluoromethylcrotonate **2**. Taking into account that all Ni-complexes of this type have a distinguishable red, yellow or orange color, we carefully examined all products from column chromatography of 19.6 g of the crude reaction mixture, obtained by the Michael addition of (*S*)-**1** with **2**. To our satisfaction, one of the fractions yielded 41 mg (0.2% yield!) of complex **4**, which had spectral and analytical data consistent with the α-(*S*)-configured diastereomer. The pattern of the ^{1}H-NMR spectrum of complex **4** was found to be very similar to that of **3** except for the chemical shift of 2.69 ppm for the methyl group. As discussed above, such an anomalously downfield chemical shift strongly indicates that the methyl group in complex **4** is located under the Ni(II) ion and thus exposed to the deshielding influence of the Ni(II) ion in its d^8 electronic configuration.[18] Accordingly, the absolute configurations of complexes **3** and **4** can be unambiguously assigned as (2*S*,3*S*) and (2*S*,3*R*), respectively.

Having determined the absolute configuration of (2*S*,3*S*)-**3**, we set about to prepare chemically and enantiomerically pure 3-methyl-3-trifluoromethylpyroglutamic acid (2*S*,3*S*)-**5**, avoiding a laborious chromatographic separation of the product (2*S*,3*S*)-**3** from the starting (*S*)-**1**. We reasoned that the decomposition of the mixture (*vide supra*) of (2*S*,3*S*)-**3** with the starting complex (*S*)-**1** by the action of 3 *N* HCl in MeOH solution, followed by the treatment of the resulting mixture with NH_4OH, would give rise, after recovery of the chiral ligand (*S*)-**BPB**, to a mixture of pyroglutamic acid (2*S*,3*S*)-**5** and glycine (coming from (*S*)-**1**) and Ni^{2+}

ions. Since in our standard procedure we employ a cation exchange column to separate the target pyroglutamic acid from the Ni^{2+} ions, one can expect that the glycine also might be trapped by the cation exchange resin and thus will not impose any problems for preparing pyroglutamic acid (2*S*,3*S*)-**5** directly from the reaction mixture of (2*S*,3*S*)-**3** with (*S*)-**1**. First, we decomposed the purified complex (2*S*,3*S*)-**3** under standard reaction conditions[1] to afford the target pyroglutamic acid (2*S*,3*S*)-**5** in 93.5% isolated yield, along with the recovered chiral ligand (*S*)-**BPB** in 93% yield. The decomposition of the mixture containing *ca.* 85% of complex (2*S*,3*S*)-**3** and 15% of starting (*S*)-**1**, clearly afforded pyroglutamic acid (2*S*,3*S*)-**5** in 92.8% isolated yield which showed the same spectral and chiroptical characteristics as that of (2*S*,3*S*)-**5** obtained from the purified (2*S*,3*S*)-**3**. Thus, the incomplete conversion of the glycine complex (*S*)-**1** in the reaction with trifluoromethylcrotonate **2** does not complicate workup, and makes this approach easy to scale up to multi-gram quantities of enantiomerically pure (2*S*,3*S*)-3-methyl-3-trifluoromethylpyroglutamic acid (**5**).

Synthesis of (2S,3S,4R)-3-trifluoromethyl-4-methylpyroglutamic acid. Simultaneous formation of α-,β- and γ-stereogenic centers (eight theoretically possible stereoisomers) in the reaction between Ni-complex (*S*)-**1** and ethyl 2-methyl-4,4,4-trifluorocrotonate (**9**) represents a challenging stereochemical problem. On the basis of literature on asymmetric Michael additions of β-monosubstituted α,β-unsaturated carboxylic acid derivatives,[4a-f,5b,9,12] one can assume that the absolute configuration of the α- and β-stereogenic carbons might be effectively controlled by the stereochemical preferences of starting chiral glycine equivalent and by the geometry (*cis/trans*) of the unsaturated acid. However, there are no examples reported in the literature on how to control the stereochemistry of the γ-stereogenic center. For instance, it was found that asymmetric Michael additions of several chiral glycine equivalents,[9,12m] including the Ni(II)-complex (*S*)-**1**,[12l] with derivatives of methylacrylic acid, give rise to a mixture of the corresponding γ-methylglutamic/pyroglutamic acids with a ratio of the diastereomers at γ-position, ranging from 1/1 to 1.5/1. Considering esters **2** and **9**, one can assume that while the electrophilicity of these crotonates might be the same, the C-2 methyl in **9** should render this ester less sterically hindered, allowing the reaction with (*S*)-**1** to proceed with a higher rate as compared with the Michael addition between ester **2** and complex (*S*)-**1**. Indeed, we found that the Michael addition of (*S*)-**1** with crotonate **9**

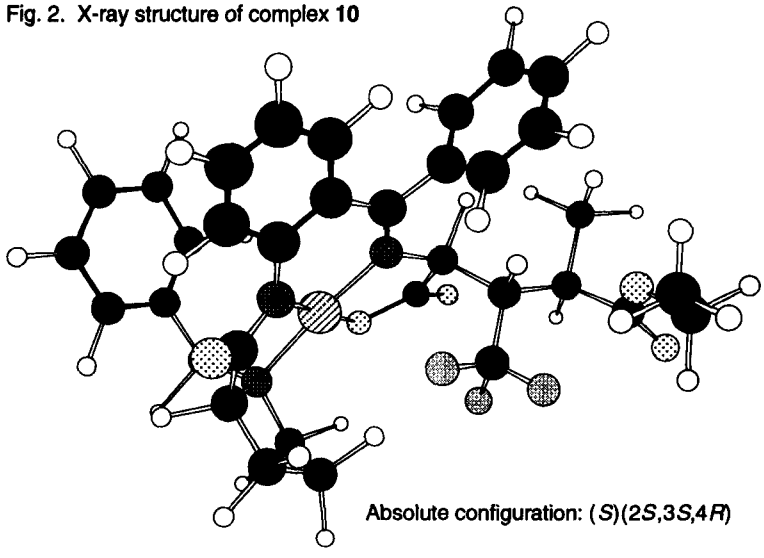
Scheme 3



(Scheme 3) readily occurred (1.5 hr reaction) in a DMF solution in the presence of 200 mol % of DBU to afford primarily a mixture of two diastereomeric complexes **10** and **11**, along with some by-products of unidentified structure. Analysis of the ^{1}H- and ^{19}F-NMR spectra of the by-products revealed that these compounds did not possess structural features of the expected products such as the methyl and trifluoromethyl groups bound to sp^3 C-4 and C-3, respectively. It is possible that the substantial amount of DBU (2 mol equivalent), the strong polar solvent (DMF), and the relatively long reaction time could cause dehydrofluorination of the products leading to further addition-dehydrofluorination reactions and thus formation of the by-products. The ratio of the diastereomers **10**, **11** and of by-products, determined by NMR of the crude reaction mixture, was found to be *ca.* 5/0.3/2. Treatment of the reaction mixture with diethyl ether allowed us to obtain the major product **10** in diastereo- and enantiomerically pure form in 45.5% isolated yield. Column chromatography of the ether extracts afforded the minor diastereomer **11** (3%), as a pure compound, along with an additional amount of the major product **10** (17%); (Total yield, 62-5%).

Analysis of the spectral and chiroptical data of pure complexes **10** and **11** revealed that both products were α-(*S*) configured 3-trifluoromethyl-4-methylglutamic acids. Compounds **10** and **11** showed similar patterns in the ^{1}H-NMR spectra, except for the chemical shift of the methyl groups of the pyroglutamic acid moieties. Thus, the methyl group in complex **10** was substantially shifted upfield (0.55 ppm) as compared with the "regular" position of the methyl in **11** at 1.03 ppm. The anomalous chemical shift of the methyl group in the major product **10** could be accounted for by placing this group in close proximity to the ketimine phenyl which now experiences its shielding influence. Determination of the absolute configuration of the β- and γ-stereogenic carbons in compounds **10** and **11** based on the NMR data was not possible, so we took advantage of the highly crystalline properties of the major product **10**, and solved its stereochemistry by X-ray analysis. As shown in Fig. 2, complex **10** was found to have (2*S*,3*S*,4*R*) absolute configuration. It is interesting to note, that, as we had postulated based on the NMR data of compound **10**, the methyl group in the structure in Fig. 2 is directed toward the plane of the ketimine phenyl, experiencing its shielding effect. Taking into account the close similarity between the patterns of the NMR spectra of complexes (2*S*,3*S*,4*R*)-**10** and **11**, the absolute configuration of the latter most likely is (2*S*,3*S*,4*S*).

Fig. 2. X-ray structure of complex **10**



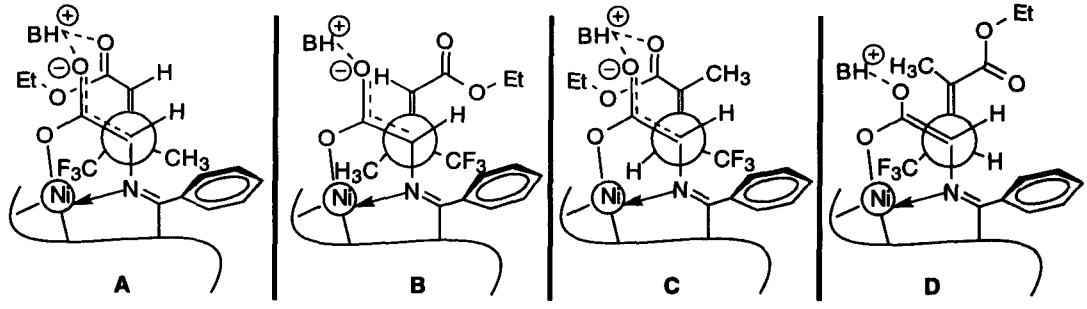
Absolute configuration: (*S*)(2*S*,3*S*,4*R*)

Decomposition of the diastereomerically pure complex (2*S*,3*S*,4*R*)-**10**, under standard reaction conditions, afforded the

target (2*S*,3*S*,4*R*)-3-trifluoromethyl-4-methylpyroglutamic acid (**12**) in 94.5% yield, along with a 95% recovery of the chiral ligand (*S*)-**BPB** (Scheme 3). It is worth noting that the methyl group in the ^{1}H-NMR spectrum of pyroglutamic acid (2*S*,3*S*,4*R*)-**12** appeared as a doublet of quartets, suggesting coupling with the fluorine atoms, and thus *cis*-disposition of the methyl and trifluoromethyl groups in the five-membered ring of **12**.

Mechanistic considerations. To determine whether the stereochemical outcome of the Michael additions is kinetically or thermodynamically controlled, we exposed the diastereomerically pure minor products (2*S*,3*R*)-**4** and (2*S*,3*S*,4*S*)-**11**, obtained in the reactions of (*S*)-**1** with ethyl 3-trifluoromethylcrotonate (**2**) and 2-methyl-4,4,4-trifluorocrotonate (**9**), respectively, to the original reaction conditions. In both cases, except for some decomposition, no traces of the major diastereomers (2*S*,3*S*)-**3** and (2*S*,3*S*,4*R*)-**10**, respectively, or starting glycine complex (*S*)-**1**, were detected in the reaction mixture. Accordingly, the observed stereochemical outcome in these reactions is a result of stereochemical preferences in the transition state (TS) of the C,C-bond forming process. Considering the basic steric requirements[1] for the transition states in the Michael additions of glycine complex (*S*)-**1**, one can assume that the proposed transition state (TS-**A**, Fig. 3), which gives rise to the major diastereomer (2*S*,3*S*)-**3** in the reaction of (*S*)-**1** with ester **2**, might be substantially favorable relative to TS-**B** (Fig. 3), because in the latter case the bulky trifluoromethyl group experiences direct repulsive steric interactions with the ketimine phenyl. Moreover, the TS-**A** could be additionally stabilized by chelation of the ester carbonyl group, while in the TS-**B** this group in a quite remote position from the enolate oxygen to realize a cyclic TS. In contrast, for the reaction between glycine complex (*S*)-**1** and trifluorocrotonate **9**, the cyclic TS-**C** (Fig. 3) might be unfavorable relative to TS-**D**. Thus, the *trans*-disposition of the ester and trifluoromethyl groups in crotonate **9** is not compatible with the cyclic TS-**C** in which the trifluoromethyl is directed toward the ketimine phenyl. Taking into account that in the absence of strongly coordinating species (e.g. a Li cation) a thermodynamic preference between cyclic and acyclic transition states would play a secondary role, the position of the sterically demanding trifluoromethyl group might be of paramount importance.[19] The TS-**D** also could explain the high (*R*)-stereoselectivity observed at the C-4 stereogenic carbon. In this case, the intermolecular protonation at the C-4 position can occur simultaneously with formation of the C-C bond *via* preferential attack on the sterically unshielded side of the crotonate moiety. On the other hand, in the cyclic TS-**C**, the formation of the corresponding ω-enolate is likely, protonation of which is hardly expected to be a highly stereoselective process.

Fig. 3



CONCLUSION

In Michael addition reactions of the chiral glycine complex (*S*)-**1** with ethyl 3-trifluoromethylcrotonate and ethyl 2-methyl-4,4,4-trifluorocrotonate presented in this paper, the kinetically controlled stereochemical outcome was found to favor strongly the (2*S*,3*S*) and (2*S*,3*S*,4*R*) absolute configurations, respectively. The position of stereochemically demanding trifluoromethyl group in the corresponding transition states was shown to play a pivotal role in governing the stereochemical course of the reactions. The ready availability and low cost of the starting chiral glycine complex (*S*)-**1**, the simplicity of the experimental procedures, and the appreciable chemical and stereochemical yields of the reactions, makes the methods presented here synthetically attractive for preparing multi-gram quantities of enantiomerically pure β,β- and β,γ-disubstituted pyroglutamic acids.

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EXPERIMENTAL SECTION

General. ^{1}H, ^{13}C and ^{19}F NMR were performed on a Varian Unity-300 (299.94 MHz) and Gemini-200 (199.98 MHz) spectrometers using TMS, $CDCl_3$ and CCl_3F as internal standards. High Resolution Mass Spectra (HRMS) were recorded on a JEOL HX110A instrument. Optical rotations were measured on a JASCO P-1010 polarimeter. Melting points (mp) are uncorrected and were obtained in open capillaries. All reagents and solvents, unless otherwise stated, are commercially available and were used as received. Synthesis of the Ni(II)-complex of the Schiff base of (*S*)-BPB and glycine (*S*)-**1** was accomplished by the procedure given in ref. 13. Unless otherwise stated, yields refer to isolated yields of products of greater than 95% purity as estimated by ^{1}H, ^{19}F and ^{13}C NMR spectrometry. All new compounds were characterized by ^{1}H, ^{19}F, ^{13}C NMR and HRMS.

Crystals of compound **10** were grown from chloroform. Crystal data for **10**: $C_{34}H_{34}F_3N_3NiO_5$, monoclinic, space group $P2_1$. Radiation: Mo Kα λ = 0.71073 Å. Crystal size: 0.20 x 0.35 x 0.35 mm^3. Unit cell dimensions: a = 9.400(4), b = 12.031(3), c = 14.239(3) Å, β = 90.77°, V = 1610.2(9) $Å^3$, Z = 2, D_x = 1.403 $g.cm^{-3}$. Diffraction data were measured on a Siemens P4-PC diffractometer. 4776 reflections were collected and 3913 independent reflections used in the analysis. System used: Siemens SHELXTL PLUS (PC Version); solution: direct methods; refinement method: Full-Matrix Least-Squares on F^2, final R and wR_2 values 0.0533 and 0.1508, respectively. Full crystallographic data have been deposited with the Cambridge Crystallographic Data Center, and can be obtained on request from: The Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K.

Reaction of glycine complex (S)-1 with ethyl 3-trifluoromethylcrotonate (2). To a suspension of complex (*S*)-**1** (15 g, 0.03 mol) in DMF (60 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU) (9.17 g, 0.06 mol) was added under stirring. The mixture was stirred at rt for 10-15 min to get a homogeneous solution, and then ethyl crotonate (**2**) (16.45 g, 0.09 mol) was added dropwise. The course of reaction was

monitored by TLC (SiO_2). Each sample was quenched with 5% aqueous acetic acid and the products were extracted with chloroform before being applied to the plate. When the ratio of the product (R_f = 0.42, in $CHCl_3$/acetone 10/1) and the starting complex (*S*)-**1** (R_f = 0.21) ceased to change, the reaction mixture was poured into an icy 5% aqueous acetic acid (600 mL) and extracted with $CHCl_3$. The chloroform solution was washed with water, dried over $MgSO_4$ and evaporated *in vacuo*. The crude residue was subjected to column chromatography on SiO_2 ($CHCl_3$/acetone 10/1) to afford 16.59 g (81%) of diastereomerically pure complex **3**. After the target product **3** was collected, the column was eluted with a 1 to 1 mixture of $CHCl_3$/acetone to recover 1.65 g (11%) of the starting complex (*S*)-**1**.

To isolate small amounts of the minor product **4**, the crude reaction mixture (19.6 g) was subjected to column chromatography on silica using a mixture of acetone and *n*-hexane (1 to 1) as an eluent to afford 41 mg (0.2%) of compound **4** (R_f= 0.16, complex **3**: R_f= 0.25).

Ni(II) complex of Schiff base of (*S*)-BPB with ω-ethyl (2*S*,3*S*)-3-methyl-3-trifluoromethylglutamate (3). m.p. 200.0-200.5°C, $[\alpha]_D^{25}$ +1755, (*c* 0.20, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.01 (3H, t, *J*=7.5 Hz), 1.43 (3H, s), 2.07-2.19 (2H, m), 2.51-2.62 (1H, m), 2.81, 3.11 (2H, AB, *J*=15.6 Hz), 2.96-3.04 (1H, m), 3.45, 4.31 (2H, AB, *J*=12.6 Hz), 3.33-3.54 (3H, m), 3.81, 3.95 (2H, ABX, *J*=10.8 Hz, *J*=7.5 Hz), 4.60 (1H, s), 6.61-6.75 (2H, m), 6.97-7.02 (2H, m), 7.06-7.12 (1H, m), 7.19-7.24 (2H, m), 7.33-7.35 (1H, m), 7.44-7.61 (3H, m), 8.09 (2H, part of AB, *J*=6.9 Hz), 8.44 (1H, part of AB, *J*=8.7 Hz). ^{19}F-NMR ($CDCl_3$) δ -72.57 (s). ^{13}C-NMR ($CDCl_3$) δ 13.8 (s), 17.2 (s), 22.7 (s), 30.4 (s), 36.0 (s), 47.7 (q, *J*=24.0 Hz), 57.5 (s), 60.7 (s), 64.1 (s), 70.8 (s), 71.5 (s), 120.09 (s), 121.9 (s), 127.9 (s), 128.3 (s), 128.7 (s), 129.3 (s), 130.2 (s), 130.7 (s), 131.1 (s), 133.4 (s), 133.9 (s), 134.1 (s), 134.7 (s), 143.5 (s), 169.2 (s), 175.3 (s), 175.4 (s), 179.8 (s); The resonance of the CF_3 carbon is obscured due to its low intensity. HRMS(FAB) $[M+H]^+$ calcd. for $C_{34}H_{34}F_3N_3NiO_5$: 680.1882, found 680.1897.

Ni(II) complex of Schiff base of (*S*)-BPB with ω-ethyl (2*S*,3*R*)-3-methyl-3-trifluoromethylglutamate (4). m.p. 228.0-229.0°C, $[\alpha]_D^{25}$ +1736, (*c* 0.24, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.17 (3H, t, *J*=7.2 Hz), 2.12-2.23 (2H, m), 2.56-2.67 (1H, m), 2.70 (3H, s), 2.63, 2.96 (2H, AB, *J*=15.0 Hz), 2.91-3.07 (1H, m), 3.12-3.26 (1H, m), 3.34, 4.32 (2H, AB, *J*=12.6 Hz), 3.44-3.52 (2H, m), 4.03 (2H, q, *J*=7.2 Hz), 4.41 (1H, s), 6.63-6.70 (1H, m), 6.73-6.77 (1H, m), 6.93-7.01 (2H, m), 7.07-7.13 (1H, m), 7.18-7.23 (2H, m), 7.35-7.37 (1H, m), 7.41-7.45 (1H, m), 7.51-7.60 (2H, m), 8.08 (2H, part of AB, *J*=7.2 Hz), 8.48 (1H, part of AB, *J*=8.7 Hz). ^{19}F-NMR ($CDCl_3$) δ -71.38 (s). ^{13}C-NMR ($CDCl_3$) δ 13.9 (s), 17.7 (s), 22.9 (s), 30.8 (s), 37.6 (s), 46.9 (q, *J*=24.0 Hz), 57.4 (s), 60.7 (s), 64.2 (s), 71.5 (s), 72.0 (s), 120.2 (s), 121.6 (s), 126.1 (s), 127.8 (s), 128.2 (s), 128.3 (s), 128.8 (s), 130.2 (s), 131.0 (s), 133.5 (s), 133.6 (s), 133.8 (s), 134.7 (s), 143.2 (s), 169.0 (s), 174.6 (s), 175.6 (s), 179.7 (s); The resonance of the CF_3 carbon is obscured due to its low intensity. HRMS(FAB) $[M+H]^+$ calcd. for $C_{34}H_{34}F_3N_3NiO_5$: 680.1882, found 680.1893.

Decomposition of complex (2*S*,3*S*)-(3); Isolation of (2*S*,3*S*)-3-methyl-3-trifluoromethylpyroglutamic acid (5). A solution of the diastereo- and enantiomerically pure complex (2*S*,3*S*)-(**5**) (4.48 g) in MeOH (80 mL) was slowly added with stirring to a mixture of aqueous 3 *N* HCl and MeOH (100 mL, ratio 1/1) at 70-75 °C. Upon disappearance of the red color of the starting complex, the reaction mixture was

evaporated *in vacuo* to dryness. Water (23 mL) was added to the crystalline residue and insoluble material was filtered off and washed with water (3 x 5 mL) to give 2.3 g (83.3 %) of the hydrochloric salt of (*S*)-**BPB**. The aqueous solution was neutralized with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried over $MgSO_4$ and evaporated *in vacuo* to afford 0.4 g (15.8%) of free (*S*)-**BPB**. The aqueous solution was evaporated *in vacuo*, dissolved in a minimum amount of water and subjected to the cation exchange resin Dowex 50X2 100. The column was washed with water and the acidic fraction was collected to give, after evaporation *in vacuo*, 1.29 g (93.5%) of (2*S*,3*S*)-3-methyl-3-trifluoromethylpyroglutamic acid (**5**). An analytically pure sample of (2*S*,3*S*)-**5** was obtained by crystallization of the compound from THF/*n*-hexane.

For preparation of (2*S*,3*S*)-**5** directly from the reaction mixture of (*S*)-**1** and (2*S*,3*S*)-**3** the same procedure was followed. (2*S*,3*S*)-**5** was isolated in 92.8% yield, recovery of (*S*)-**BPB**, as a hydrochloric salt and a free base, 95%. m.p. 190.0-191.0°C, $[\alpha]_D^{25}$ 13.87, (*c* 1.34, MeOH); ^{1}H-NMR (CD_3COCD_3) δ 1.39 (3H, s), 2.34, 2.60 (2H, AB *J*=17.4 Hz), 4.41 (1H, s), 7.32 (1H, br.s). ^{19}F-NMR (CD_3COCD_3) δ -79.93 (s). ^{13}C-NMR (CD_3COCD_3) δ 17.5 (q, *J*=3.0 Hz), 38.4 (s), 46.7 (q, *J*=26.9 Hz), 59.7 (s), 128.9 (q, *J*=280.3 Hz), 171.2 (s), 173.8 (s). HRMS(FAB) $[M+H]^+$ calcd. for $C_7H_9F_3NO_3$: 212.0535, found 212.0531.

***Reaction of glycine complex (S)-1 with ethyl* 3-methylcrotonate.** The procedure described for the reaction of 3-trifluoromethylcrotonate **2** with (*S*)-**1** was followed, except that potassium *tert*-butoxide was used as a base. Starting from 0.5 g (1 mmol) of complex (*S*)-**1** and 0.257 g (2 mmol) of ethyl 3-methylcrotonate the addition reaction afforded 0.399 g (63.5%) of complex (2*S*)-**8**, isolated by column chromatography (SiO_2, $CHCl_3$/acetone 7/1) of the reaction mixture.

Ni(II) complex of Schiff base of (*S*)-BPB and ω-ethyl (2*S*)-3,3-dimethylglutamate (8). m.p. 207.0-208.5°C, R_f 0.26 ($CHCl_3$/acetone, 7/1), $[\alpha]_D^{25}$ +2181, (*c* 0.24, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.14 (3H, s), 1.17 (3H, d, *J*=7.2 Hz), 1.98 (3H, s), 2.05-2.20 (2H, m), 2.47, 2.93 (2H, AB, *J*=14.1 Hz), 2.54-2.66 (1H, m), 2.90-2.99 (1H, m), 3.11-3.61 (1H, m), 3.40, 4.37 (2H, AB, *J*=12.6 Hz), 3.44-3.52 (2H, m), 3.95, 4.03 (2H, ABX, *J*=7.2 Hz, *J*=10.8 Hz), 4.05 (1H, s), 6.62-6.72 (2H, m), 6.92-6.94 (1H, m), 6.98-7.03 (1H, m), 7.06-7.12 (1H, m), 7.19-7.25 (2H, m), 7.32-7.35 (1H, m), 7.40-7.46 (1H, m), 7.50-7.58 (2H, m), 8.08 (2H, part of AB, *J*=7.2 Hz), 8.43 (1H, part of AB, *J*=8.4 Hz). ^{13}C-NMR ($CDCl_3$) δ 14.2 (s), 22.8 (s), 24.9 (s), 25.8 (s), 30.8 (s), 38.3 (s), 43.6 (s), 57.1 (s), 60.1 (s), 64.0 (s), 71.3 (s), 77.9 (s), 120.3 (s), 121.8 (s), 126.1 (s), 128.2 (s), 128.4 (s), 128.8 (s), 129.1 (s), 129.9 (s), 130.8 (s), 131.1 (s), 132.9 (s), 133.7 (s), 134.4 (s), 142.1 (s), 171.0 (s), 173.2 (s), 176.7 (s), 179.8 (s). HRMS(FAB) $[M+H]^+$ calcd. for $C_{34}H_{38}N_3O_5Ni$ 626.2165, found 626.2160.

Reaction of glycine complex (S)-1 with ethyl 2-methyl-4,4,4-trifluorocrotonate (9). The procedure described above for the reaction of crotonate **2** with (*S*)-**1** was followed, except that a 1.5 mol excess of ethyl 2-methyl-4,4,4-trifluorocrotonate (**9**) was used in the presence of 2 mol equivalents of DBU. Starting from (15 g, 0.03 mol) of complex (*S*)-**1** and 11 g (0.06 mol) of 4,4,4-trifluorocrotonate **9**, the addition reaction afforded 19 g of a crude mixture of products, which was treated with diethyl ether to give 9.32 g (45.5%) of crystalline (2*S*,3*S*,4*R*)-**10** in diastereo- and enantiomerically pure form. Chromatographic separation (eluent:

$CHCl_3$/acetone as 10/1) of the ethereal fraction afforded 3.48 g (17%) more of the major complex (2*S*,3*S*,4*R*)-**10**, and 0.615 g (3%) of the minor diastereomer (2*S*,3*S*,4*S*)-**11**.

Ni(II) complex of Schiff base of (*S*)-BPB with ω-ethyl (2*S*,3*S*,4*R*)-3-trifluoromethyl-4-methylglutamate (10). m.p. 287.0-288.0°C, R_f 0.30 ($CHCl_3$/acetone, 10/1), $[\alpha]_D^{25}$ +2582, (*c* 0.30, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 0.55 (3H, d, *J*=6.3 Hz), 1.20 (3H, t, *J*=7.2 Hz), 2.05-2.22 (2H, m), 2.47-2.61 (1H, m), 2.77-2.93 (3H, m), 3.33-3.47 (2H, m), 3.48-3.57 (1H, m), 3.58, 4.39 (2H, AB, *J*=12.3 Hz), 3.96-4.12 (2H, m), 4.27 (1H, d, *J*=3.3 Hz), 6.64-6.69 (2H, m), 7.08-7.21 (3H, m), 7.24-7.27 (1H, m), 7.32-7.37 (2H, m), 7.57-7.66 (3H, m), 8.05 (2H, part of AB, *J*=8.4 Hz), 8.31 (1H, part of AB, *J*=9.0 Hz). ^{19}F-NMR ($CDCl_3$) δ -62.92 (d, *J*=6.2 Hz). ^{13}C-NMR ($CDCl_3$) δ 13.9 (s), 15.5 (s), 22.4 (s), 30.6 (s), 36.6 (s), 48.5 (q, *J*=24.0 Hz), 57.0 (s), 60.8 (s), 63.3 (s), 64.6 (s), 70.7 (s), 120.6 (s), 123.5 (s), 126.6 (s), 128.3 (s), 128.8 (s), 128.8 (s), 129.2 (s), 129.8 (s), 130.1 (s), 131.5 (s), 132.8 (s), 133.3 (s), 133.5 (s), 133.9 (s), 143.2 (s), 172.4 (s), 174.6 (s), 175.7 (s), 180.4 (s); The resonance of the CF_3 carbon is obscured due to its low intensity. HRMS(FAB) $[M+H]^+$ calcd. for $C_{34}H_{34}F_3N_3NiO_5$: 680.1882, found 680.1862.

Ni(II) complex of Schiff base of (*S*)-BPB with ω-ethyl (2*S*,3*S*,4*S*)-3-trifluoromethyl-4-methylglutamate (11). m.p. 220.0-221.0°C, R_f 0.32 ($CHCl_3$/acetone, 10/1), $[\alpha]_D^{25}$ +2618, (*c* 1.22, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.03 (3H, d, *J*=6.6 Hz), 1.21 (3H, t, *J*=7.2 Hz), 2.04-2.18 (2H, m), 2.45-2.63 (2H, m), 2.78-2.93 (1H, m), 3.28 (1H, qdd, *J*=9.3 Hz, *J*=5.7 Hz, *J*=4.5 Hz), 3.40-3.51 (3H, m), 3.54, 4.39 (2H, AB, *J*=12.6 Hz), 3.99-4.11 (2H, m), 4.36 (1H, d, *J*=5.7 Hz), 6.59-6.70 (2H, m), 6.94-7.01 (1H, m), 7.11-7.19 (2H, m), 7.30-7.35 (3H, m), 7.47-7.61 (3H, m), 8.06 (2H, part of AB, *J*=7.2 Hz), 8.23 (1H, part of AB, *J*=8.4 Hz). ^{19}F-NMR ($CDCl_3$) δ -59.93 (d, *J*=9.3 Hz). ^{13}C-NMR ($CDCl_3$) δ 13.9 (s), 14.2 (s), 22.6 (s), 30.6 (s), 37.7 (s), 48.0 (q, *J*=24.0 Hz), 57.0 (s), 60.9 (s), 63.3 (s), 67.3 (s), 70.6 (s), 120.4 (s), 123.2 (s), 126.1 (s), 127.0 (s), 128.1 (s), 128.7 (s), 129.2 (s), 129.2 (s), 129.9 (s), 131.4 (s), 132.7 (s), 133.2 (s), 133.6 (s), 133.6 (s), 143.0 (s), 172.2 (s), 173.0 (s), 176.0 (s), 180.2 (s); The resonance of the CF_3 carbon is obscured due to its low intensity. HRMS(FAB) $[M+H]^+$ calcd. for $C_{34}H_{34}F_3N_3NiO_5$: 680.1882, found 680.1873.

Decomposition of complex (2*S*,3*S*,4*R*)-10; Isolation of (2*S*,3*S*,4*R*)-3-trifluoromethyl-4-methylpyroglutamic acid (12). The procedure described for preparing (2*S*,3*S*)-3-methyl-3-trifluoromethylpyroglutamic acid (**5**) was followed. Starting from 4 g of complex (2*S*,3*S*,4*R*)-**10**, 1.15 g (93%) of diastereo- and enantiomerically pure (2*S*,3*S*,4*R*)-**12** was obtained, along with 94.3% recovery of (*S*)-**BPB**, as a hydrochloric salt and a free base. m.p. 171.0-171.5°C, $[\alpha]_D^{25}$ +15.92, (*c* 1.51, MeOH); ^{1}H-NMR (CD_3COCD_3) δ 1.19 (3H, dq, *J*=7.8 Hz, *J*=2.4 Hz), 2.86 (1H, q, *J*=7.5 Hz), 3.56 (1H, qdd *J*=9.0 Hz, *J*=7.5 Hz, *J*=1.8 Hz), 4.34 (1H, d, *J*=1.8 Hz), 7.41 (1H, br.s). ^{19}F-NMR (CD_3COCD_3) δ -68.65 (d, *J*=9.0 Hz). ^{13}C-NMR (CD_3COCD_3) δ 10.7 (q, *J*=2.0 Hz), 35.8 (s), 46.4 (q, *J*=27.0 Hz), 54.2 (q, *J*=3.0 Hz), 127.6 (q, *J*=278.4 Hz), 172.1 (s), 176.8 (s). HRMS(FAB) $[M+H]^+$ calcd. for $C_7H_9F_3NO_3$: 212.0535, found 212.0525.

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1 Part 2 of series: Stereochemically Defined *C*-Substituted Glutamic Acids and their Derivatives. For part 1 see: Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Meervelt, L. V.; Mischenko, N. *Tetrahedron*, **1999**, *55*, 12031.

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15 As has been demonstrated (see ref. 14), the CD and ORD spectra of Ni(II)-complexes of this type in neutral solutions exhibit two maxima in the region of metal d-d transition (*Cotton* effects at 450 and 550 nm). In the ORD spectra, the sign of *Cotton* effects in this region strictly depends upon a conformation of the polycyclic system of chelate rings. Thus, in the case of complexes containing α-monosubstituted α-amino acid, the pseudoaxial orientation of the amino acid side chain, corresponding to an α-(*L*) configuration of α-amino acid, causes a *Cotton* effect with a positive sign at the 500-700 nm region and negative sign at 400-450 nm. On the other hand, a pseudoequatorial orientation of the amino acid side chain brings about opposite signs of

the *Cotton* effects at 400-450 (positive) and at the 500-700 nm (negative) region. As was established in numerous studies, this general trend is not influenced by the structure and nature of the α-amino acid side chain, and the configuration of stereogenic centers within it. ^{1}H-NMR spectra of the complexes containing α-(*L*)- and α-(*D*)-amino acids also are very characteristic, featuring substantial differences in chemical shifts of aromatic and methylene protons of the (*N*-benzyl)proline moiety.

16 The absolute configuration deduced from the ^{1}H-NMR data was also confirmed by X-ray analysis of the (2*S*,3*S*)-configured diastereomer; see ref. 1.

17 As shown earlier for the Ni-complexes containing β-methyl substituted amino acid side chains, such downfield chemical shifts are usually observed for alkyl groups located above or under the Ni(II) coordination plane, and are thus exposed to the deshielding influence of the Ni(II) ions in their d^8 electronic configuration; for more details see refs. 18.

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