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Stereochemically Defined *C*-Substituted Glutamic Acids and their Derivatives. 1. An Efficient Asymmetric Synthesis of (2*S*,3*S*)-3-Methyl- and -3-Trifluoromethylpyroglutamic Acids

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Abstract: An efficient asymmetric synthesis of biologically important (2*S*,3*S*)-3-methyl- and (2*S*,3*S*)-3-trifluoromethylpyroglutamic acid has been developed. The method consists of diastereoselective Michael addition reaction between ethyl crotonate or ethyl 4,4,4-trifluorocrotonate and a Ni(II) complex of the chiral non-racemic Schiff base of glycine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone (BPB) followed by decomposition of the addition products by aq. HCl and treatment of the resultant glutamic acid derivatives with NH_4OH to afford the target pyroglutamic acids along with recovery of the chiral auxiliary BPB. The stereochemical outcome of the addition reactions was found to be subjected to kinetic control. A mechanistic rationale for the observed stereochemical preferences is discussed.

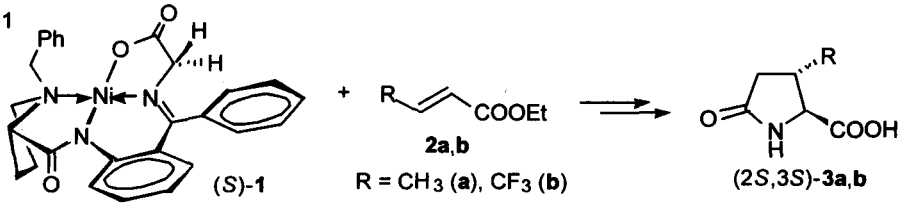
Keywords: amino acids and derivatives, asymmetric synthesis, addition reactions, nickel, mechanism

INTRODUCTION

The recent upsurge of interest in the peptide-based drug molecules has been accompanied by a great deal of attention to the synthesis of stereochemically defined non-proteinogenic amino acids.[1,2] It has been clearly demonstrated that the incorporation of stereochemically constrained amino acids into peptides can effectively reduce the populations of possible peptide chain conformations allowing for rational design of receptor-specific peptides with pre-supposed pattern of biological activity and enhanced stability to metabolic degradation.[3] Of particular current interest is a family of β-substituted-α-amino acids featuring, by virtue of steric constraints, a substantially limited number of possible side-chain rotamers.[4]

Since glutamic acid and its derivatives such as pyroglutamic acid and glutamine are critically important for biological activity of numerous peptides, we have begun a project to develop reliable and convenient synthetic approaches to the stereochemically defined *C*-substituted glutamic acids and their derivatives and to employ these compounds in the *de novo* peptide design. In this paper, we report a simple, multi-gram asymmetric synthesis of (2*S*,3*S*)-3-methyl and (2*S*,3*S*)-3-trifluoromethyl-substituted pyroglutamic acids **3a,b** (Fig. 1) *via* diastereoselective Michael addition reactions between a Ni(II) complex of the chiral non-racemic Schiff base of glycine **1** and the corresponding ethyl crotonates **2a,b**.

Fig. 1



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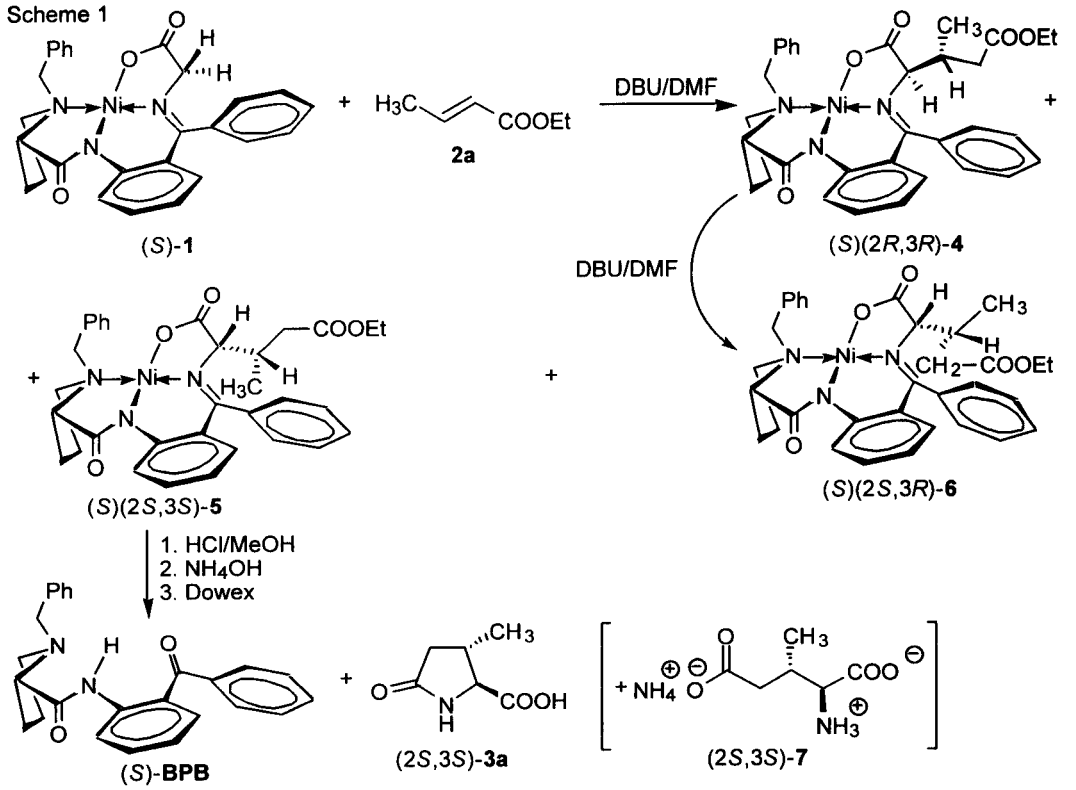
RESULTS AND DISCUSSION

For construction of the carbon skeleton of *C*-substituted glutamic acids a Michael addition reaction between a nucleophilic glycine and the correspondingly substituted acrylic acid derivative represents the most straightforward and general solution, and methodologically it cannot be rivaled by alternative approaches such as, for instance, homologation of aspartic acid derivatives.[5] The issue of stereochemical outcome of the addition reaction can be effectively addressed by use of a chiral equivalent of a nucleophilic glycine. For example, Schöllkopf *et al.* reported the Michael addition reaction between lithio-*c*-(*S*)-Val-Gly *bis*-lactim ether and methyl crotonate to afford a mixture (65% yield) of the corresponding (2*R*,3*S*)- and (2*R*,3*R*)-3-methylglutamic acid derivatives in a ratio of 74/26, respectively.[6] Latter, Gani *et al.* studied the same reaction and found that addition of the lithium derivative of *c*-(*R*)-Val-Gly *bis*-lactim ether and methyl crotonate occurred with high diastereoselectivity (>80% de) giving rise to the corresponding (2*S*,3*S*)-3-methylglutamic acid derivative.[5] Whatever the diastereoselectivity of the reaction and the relative stereochemistry of the products, the synthetic value of this method is limited by a tricky separation of the target amino acids from the valine, used as a chiral auxiliary.[7] In contrast, application of the chiral glycine equivalents developed by Seebach could lead to a potentially practical and generalized approach to stereochemically defined *C*-substituted glutamic acids. It was shown that use of sterically hindered 2,6-di-*tert*-butyl-4-methoxyphenyl esters of α,β-unsaturated carboxylic acids, instead of the "normal" methyl or ethyl esters,[8] provides excellent stereocontrol in Michael addition reactions.[2b,9] Thus, the reaction between lithium derivative (*S*)-2-*tert*-butyl-3-methyl-4-oxo-1-imidazolidinecarboxylate[9] or *rac*-*tert*-butyl 2-*tert*-butyl-methoxy-2,5-dihydroimidazole-1-carboxylate[2b] and 2,6-di-*tert*-butyl-4-methoxyphenylbut-2-enecarboxylate afforded (80-95% yield) two diastereomeric 3-methylglutamic acid derivatives in a ratio of >94/6.[10] While the application of "sterically protected but electronically activating"[9] 2,6-di-*tert*-butyl-4-methoxyphenyl esters of α,β-unsaturated carboxylic acids could be eventually justified by achieving an excellent stereochemical outcome,[11] this methodology still has a significant synthetic drawback concerned with the high cost of the non-recyclable starting chiral glycine derivatives available through laborious resolutions of racemic mixtures. One other method reported in the literature should be mentioned in this short overview as it has been applied for asymmetric synthesis of both our target 3-methyl- and 3-trifluoromethylglutamic acids. Viallefont *et al.* reported the asymmetric Michael addition reaction between ethyl crotonate and a chiral Schiff base derived from enantiomerically pure (1*R*,2*R*,5*R*)-2-hydroxy-3-pinanone and methyl glycinate.[12] The reaction was shown to proceed with low diastereoselectivity giving rise (74% yield) to all four possible stereoisomers in a ratio of 55/18/27.[13] The absolute configuration of the 3-methylglutamic acid fragment in the major diastereomer was assigned to be (2*S*,3*R*). Recently, Laurent *et al.* have applied the same method for the synthesis of 3-trifluoromethylglutamic acid using ethyl 4,4,4-trifluorocrotonate as a Michael acceptor.[14] The stereochemical outcome of the reaction was found to be very similar to that of the fluorine free ethyl crotonate addition affording four possible diastereoisomers (63% yield) in a ratio of 52:13 (*cis*):31:4 (*trans*). Alternatively, Prati *et al.* developed a chemo-enzymatic approach to the enantiomers of *trans*-3-trifluoromethylpyroglutamic acid involving diastereoselective preparation of ethyl *trans*-3-trifluoromethylpyroglutamate followed by its biocatalytic resolution to the enantiomerically pure compounds.[15]

From a synthetic point of view, the above methods suffer drawbacks, in particular when considering multi-gram scale preparations of the target compounds. In our experience, a Ni(II) complex of the chiral non-racemic Schiff base of glycine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]-benzophenone [(*S*)-BPB] (*S*)-**1**, introduced by Belokon' *et al.*,[16] possesses significant advantages over other chiral equivalents of a nucleophilic glycine, in terms of its low cost and ready availability, even on a kilogram scale,[16] and the simplicity of experimental procedures and isolation of products. The synthetic value of complex (*S*)-**1** for preparing natural and unnatural amino acids *via* alkylation and aldol reactions of (*S*)-**1** has been well documented.[17] Michael additions of complex (*S*)-**1** are less well known, and have been studied previously nearly exclusively on the reactions of (*S*)-**1** with α,β-unsaturated aldehydes and ketones.[18] In particular, only a few examples of the reactions of acrylic acid derivatives with complex (*S*)-**1** have been reported. It was shown that the additions of (*S*)-**1** with the methyl methacrylate and the methyl *trans*-cinnamate occur in the presence of strong bases such as NaOMe in MeOH to afford, regardless of the nature of the electrophile, a thermodynamic mixture of two α-(*S*) configured diastereomeric products in a ratio of about 2:1.[18a]

Synthesis of (2S,3S)-3-methylpyroglutamic acid. Under the similar reaction conditions (NaOEt in EtOH), the Michael addition between (*S*)-**1** and ethyl crotonate gave a complex mixture of products unsuitable for separation and/or characterization.[19] We reasoned that ethyl crotonate might be unstable under these strongly basic reaction conditions and so we started to search for a milder alternative using organic bases and aprotic solvents. After a series of experiments we have found that DMF is the solvent of choice (*vide infra*).

Scheme 1



Regarding the base, triethylamine and DABCO were found to be ineffective in catalyzing the reaction, while in the presence of DBU (50 mol %) the addition between (*S*)-**1** and ethyl crotonate occurred (in DMF) at rt with a reasonable reaction rate affording a mixture (78% chemical yield) of three diastereomeric products **4-6** in a ratio 19.0/76.2/4.8 (Scheme 1). Since both DMF and DBU are miscible with water, and the resultant Ni-complexes are not soluble in water, isolation of the reaction products was easily accomplished by pouring the reaction mixture into ice-water followed by filtration of the crystalline precipitate. Next, to avoid laborious and costly chromatographic separations, we set out to search for the best solvent to isolate the major product simply by crystallization of the reaction mixture. Having tried a series of solvents we found that the minor products **4** and **6** are highly soluble in diethyl ether while the major diastereomer **5** is not. Thus, washing the diastereomeric mixture **4-6** with diethyl ether afforded the target product **5** in diastereo- and enantiomerically pure form in 53% overall yield. The ether solution was subjected to column chromatography to give an additional amount of **5** (5.5%) along with diastereomerically pure complexes **4** (15.1%) and **6** (3.3%). Decomposition of complex **5** under the standard reaction conditions (HCl/MeOH), with further treatment of the resultant mixture with NH_4OH gave the target 3-methylpyroglutamic acids **3a** in 88% yield along with chiral auxiliary (*S*)-**BPB**, recycled in 96.6% yield. Pyroglutamic acid **3a** was isolated from the aqueous solution using ion-exchange resin while (*S*)-**BPB**, was extracted with $CHCl_3$. Washing the ion-exchange resin with NH_4OH gave 3-methylglutamic acid **7** in 7% yield, as its ammonium salt.

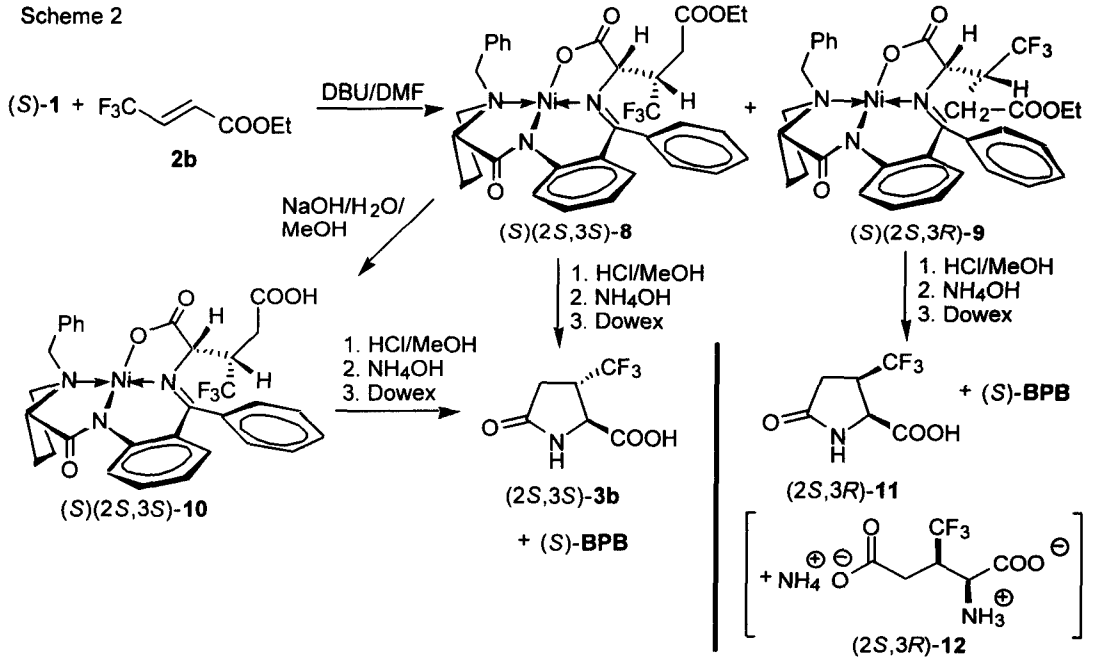
Due to the complex structure of the Ni-complexes, composed of two rigid five- and one six-membered rings, the absolute configuration of the α-stereogenic center of a newly formed amino acids could be easily and unambiguously deduced from the spectral data of a given Ni-complex.[20] Analysis of spectral and chiroptical data (see Experiment) of compounds **4-6** revealed that the 3-methylglutamic acid moiety in diastereomers **5,6** had an (*S*) absolute configuration at the α-carbon, while the glutamic acid in complex **4** had an α-(*R*) configuration. The ^{1}H-NMR spectra of α-(*S*)-**5** and α-(*S*)-**6** are very similar to each other, except for the chemical shifts of the 3-methyl and methylene protons of the glutamic acid moieties. Thus, the 3-methyl protons of the major diastereomer **5** are significantly down-fielded (d, 1.97 ppm) as compared with that of minor isomer **6** (d, 0.78 ppm). On the other hand, the ABX system of the methylene protons of **5** appears at a "normal" region of 2.2 ppm, while one of the methylene protons of **6** shows an anomalous chemical shift of 4.67 ppm, testifying to its strong deshielding. As shown earlier for Ni-complexes containing β-methyl substituted amino acid side chains,[18b,21] such down-fielded chemical shifts are observed for alkyl groups located above or under the Ni(II) coordination plane and thus exposed to the deshielding influence of the Ni(II) ions in their d^8 electronic configuration.[22] The structures of complexes **5** and **6**, have the methyl and methylene protons located under the Ni(II), and thus, the absolute configuration of the 3-methylglutamic acid moiety in **5** might be assigned as (2*S*,3*S*) and that of **6** as (2*S*,3*R*). Accordingly, the absolute configuration of the pyroglutamic acid **3a**, obtained from the major (2*S*,3*S*)-**5** diastereomer is (2*S*,3*S*). The assigned stereochemistry is also supported by the ^{1}H-NMR data of **3a** which are in full agreement with the spectral characteristics reported for methyl (2*S*,3*S*)-methyl pyroglutamate[5] and substantially differ from that of its (2*S*,3*R*) diastereomer.[2b,5] Finally, the absolute configuration of diastereomer **4** was determined to be (2*R*,3*R*) by epimerization of this compound at the α-(*R*) stereogenic center to give (2*S*,3*R*)-**6** (Scheme 1) (*vide infra*).

Synthesis of (2S,3S)-3-trifluoromethylpyroglutamic acid. Due to the strong electron-withdrawing effect of trifluoromethyl group, ethyl 4,4,4-trifluorocrotonate (**2b**) was expected to be much more reactive as a

Michael acceptor then its fluorine-free analog. Indeed, the reaction between trifluorocrotonate **2b** and glycine complex (*S*)-**1** in DMF (rt) in the presence of 50 mole % of DBU occurred almost instantly to afford a mixture of two diastereomeric products **8** and **9** in excellent chemical yield and in a ratio of 5/1 (Scheme 2). Application of 5 mol % of the base substantially slowed down the reaction rate (1 hr). However, this allowed us to improve the diastereomeric ratio to 5.6/1 (^{1}H-NMR). The reaction mixture was poured into water and the resultant precipitate of the products **8** and **9** was filtered. In this case, washing a mixture of diastereomers **8** and **9** with diethyl ether afforded diastereomerically pure **8** in 65% overall yield. Chromatography of the ethereal solution gave 5% more of the major diastereomer along with the minor product **9** in 11% yield. Analysis of the spectral and chiroptical properties of complexes **8** and **9** revealed that both products contained the α-(*S*) configured 3-trifluoromethylglutamic acids. In the ^{1}H-NMR spectra of the diastereomers the methylene protons of the glutamic acid moiety in **8** appear as a regular doublet at 2.58 ppm, while these protons of the minor diastereomer **9** have a definite ABX pattern with one of the protons anomalously downshifted to 4.35 ppm, thus indicating a location of this group under the Ni(II) ion. Accordingly, the absolute configuration of the diastereomers **8** and **9** should be (2*S*,3*S*) and (2*S*,3*R*), respectively. However, being aware of stereochemical tricks provided by fluorine and a trifluoromethyl group in particular, and taking advantage of well-formed crystals of the major diastereomer **8**, we performed X-ray analysis of this compound which proved the assigned (2*S*,3*S*) absolute configuration. Finally, the spectral and chiroptical data of the (2*S*,3*S*)-3-trifluoromethylpyroglutamic acid (2*S*,3*S*)-**3b**, obtained from (2*S*,3*S*)-**8** (*vide infra*), were found in good agreement with those reported in the literature for the (2*S*,3*S*) enantiomer.[15]

Decomposition of the diastereomerically pure complexes (2*S*,3*S*)-**8** and (2*S*,3*R*)-**9**, under the standard reaction conditions (Scheme 2), afforded the target 3-trifluoromethylpyroglutamic acids (2*S*,3*S*)-**3b** and

Scheme 2

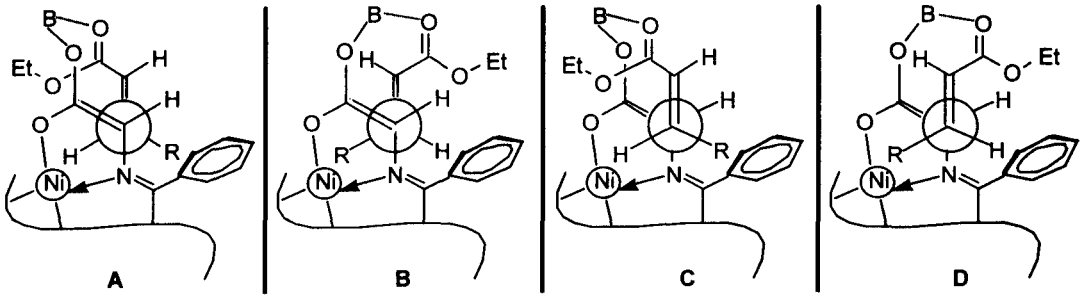


(2*S*,3*R*)-**11**, in 85% and 87% yield, respectively, along with 93-95% recovery of the chiral ligand (*S*)-**BPB**. In the case of the (2*S*,3*R*)-**9** diastereomer decomposition, we also obtained the salt of (2*S*,3*R*)-3-trifluoromethylglutamic acid **12** in 7% yield. Decomposition of the complexes using 2 *N* HCl in MeOH at 70-80 °C for 25-30 min, might afford the corresponding ω-ethyl 3-trifluoromethylglutamate which, upon treatment with NH_4OH, would give the target pyroglutamic acids. However, formation of small amounts of glutamic acids **7** (Scheme 1) and **12** (Scheme 2) could be accounted for by a partial hydrolysis of the ω-ester group during the decomposition of the complex to give fully deprotected glutamic acids which would undergo cyclization to pyroglutamic acids with greater difficulty than would cyclization of the corresponding ω-ethyl 3-trifluoromethylglutamates. To check this assumption, we hydrolyzed complex (2*S*,3*S*)-**8** to afford derivative (2*S*,3*S*)-**10** bearing the free ω-carboxylic function. To our surprise, decomposition of the compound (2*S*,3*S*)-**10** under standard condition gave (2*S*,3*S*)-3-trifluoromethylpyroglutamic acid (**3b**) in 86% chemical yield. These results clearly indicate that under the decomposition conditions, the ω-ester group of the complexes is being completely hydrolyzed and formation of the corresponding pyroglutamic acids proceeds through cyclization of the free glutamic acids under the basic (2 *N* NH_4OH) reaction conditions.

A mechanistic rationale for the observed stereochemical outcome of the Michael *addition reactions.* First we investigated the reversibility of the Michael additions to determine whether the stereochemical outcome of the reactions is kinetically or thermodynamically controlled. To this end, the diastereomerically pure minor diastereomer **4**, obtained in the reaction of (*S*)-**1** with ethyl crotonate (**2a**), was exposed to the original reaction conditions (Scheme 1) for 48 hr. This resulted in 85% conversion of complex **4** to the (2*S*,3*R*)-**6** diastereomer. No traces of the major diastereomer (2*S*,3*S*)-**5** or starting glycine complex (*S*)-**1** were detected in the reaction mixture (^{1}H-NMR). The observed transformation could be explained by assuming that DBU is capable of abstracting the α-proton of the glutamic acid moiety that might eventually lead to domination of the thermodynamically more favorable α-(*S*) configuration over the initial α-(*R*) stereochemistry of compound **4**.[17] A pleasant bonus from this unexpected α-epimerization was unambiguous assignment of the absolute configuration of complex **4**. A similar experiment was performed with the minor product (2*S*,3*R*)-**9**, obtained in the reaction of (*S*)-**1** with ethyl trifluorocrotonate **2b** (Scheme 2). After exposure of compound (2*S*,3*R*)-**9** to the exact reaction conditions for more than 2 days it was found to be chemically and diastereomerically intact. These results clearly indicate that the addition reaction is an irreversible process and thus its stereochemical outcome is kinetically controlled. Accordingly, the observed stereochemical outcome is a result of stereochemical preferences in the transition state of the C,C-bond forming process.

Taking into account, as generally assumed,[9,24] that Michael addition reactions of this type occur in such a way that the cationic species involved are transferred directly from the enolate oxygen to the carbonyl group of the α,β-unsaturated ester with minimum charge separation, four approach geometries **A-D** (Fig. 2), leading to the four theoretically possible diastereomeric products, should be considered. As was shown earlier,[17] the chiral puckering of the complex (*S*)-**1** chelate rings results in a steric shielding of the *re*-face of the corresponding enolate by the ketimine phenyl, that, in turn, favors electrophilic attack on the opposite *si*-face (**A,B** *vs.* **C,D**). This effect is much more pronounced under conditions of thermodynamic control [ratio α-(*S*)/α-(*R*) 95/5],[17] while the kinetically controlled *re*/*si*-face selectivity varies depending on the nature of the incoming electrophile. An example of this is the observed startling difference between the stereochemical outcomes of the ethyl crotonate (**2a**) and ethyl trifluorocrotonate **2b** reactions. The former was found to

Fig. 2



proceed with roughly 4/1 *si/re*-face preference, while the latter featured complete *si*-face selectivity. Considering transition states **C** and **D**, leading to the α-(*R*) configured products, one can conclude that approach **D** might be substantially more satirically favorable relative to **C**, for in the latter case the substituent R, methyl or trifluoromethyl, experiences direct steric interaction with the ketimine phenyl. The same mode of stereochemical preferences applied to the transition states **A** and **B**, renders geometry **B** favored relative to **A**. In good agreement with the experimental results, these models provide a reasonable rationale for the stereochemical outcome of the ethyl crotonate (**2a**) reaction with glycine complex (*S*)-**1**. On the other hand, the complete α-(*S*) stereoselectivity and substantially greater amount of the less favorable (2*S*,3*R*)-diastereomer, observed in the reaction of ethyl trifluorocrotonate **2b** is difficult to explain. The different stereochemical outcomes of these reactions likely are a result of steric demands of the methyl and trifluoromethyl groups.[25] Thus, transition state **C**, realized in the reaction of fluorine-free crotonate **2a** (R = CH_3), could be additionally destabilized when the substituent R is a trifluoromethyl group, by unfavorable steric interactions between the trifluoromethyl and the proline *N*-benzyl group, which usually tends to be located over the Ni(II) coordination plane. Considering transition states **A** and **B**, the substantial preference for the latter (16/1), observed in the reaction of crotonate **2a** (R = CH_3), could be diminished in the case of trifluorocrotonate **2b** (R = CF_3) addition by repulsive steric interactions in the structure **B** between the trifluoromethyl and methylene groups of the proline moiety occupying the space under the Ni(II). Indirect support for the plausibility of these sterically unfavorable interactions involving the trifluoromethyl group comes from a failure to react complex (*S*)-**1** with ethyl *trans*-3-*tert*-butylacrylate. The reaction did not proceed, even under forced conditions, indicating that the steric bulk of the *tert*-butyl group is not compatible with the steric requirements of the geometries **A-D**.

CONCLUSION

In the Michael addition reactions of the chiral glycine complex (*S*)-**1** with ethyl crotonate and ethyl trifluorocrotonate studied in this paper, the kinetically controlled stereochemical outcome was found to favor strongly the (2*S*,3*S*) absolute configuration of the major products, while the number, ratio and stereochemistry of the minor diastereomers were shown to be influenced by steric requirements of the methyl and trifluoromethyl groups of the starting crotonates. The ready availability and low cost of the starting compounds, the simplicity of the experimental procedures and the appreciable chemical and stereochemical

yields make this approach an attractive alternative to existing methods to provide convenient access to multi-gram quantities of enantiomerically pure 3-substituted 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. 16. 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 **8** were grown from chloroform. Crystal data for **8**: $C_{33}H_{32}F_3N_3NiO_5$, orthorhombic, space group $P2_12_12_1$. Radiation: Mo Kα λ = 0.71073 Å. Crystal size: 0.4 x 0.3 x 0.3 mm^3. Unit cell dimensions: a = 10.324(5), b = 13.570(2), c = 22.233(3) Å, V = 3115(2) Å^3, Z = 4, D_X = 1.421 g.cm^{-3}. Diffraction data were measured on a Siemens P4-PC diffractometer. 2503 Reflections were collected and 2342 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 0.0466 and 0.1304, respectively. Full crystallographic data[26] have been deposited with the Cambridge Crystallographic Data Centre, and can be obtained on request from: The Director, Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

Reaction of glycine complex (S)-1 with ethyl crotonate (2a). To a suspension of complex (*S*)-**1** (25 g, 0.05 mol) in DMF (100 mL), DBU (3.82 g, 0.025 mol) was added under stirring. The mixture was stirred at rt for 10-15 min to get a homogeneous solution, and then ethyl crotonate (**2a**) (6.28 g, 0.055 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. Upon disappearance of the starting (*S*)-**1**, the reaction mixture was poured into icy 5% aqueous acetic acid (1 L) and stirred with a glass bar to initiate crystallization of the product. The crystalline product was filtered off, thoroughly washed with water and dried *in vacuo* to afford 23.97 g (78%) of the three diastereomeric complexes in a ratio of 4/1/0.24 (by ^{1}H-NMR). The crude mixture was vigorously stirred with 200 mL of diethyl ether for 5 hr at rt and the insoluble material was filtered away, washed with ether and dried in air to give 16.28 g (53%) of diastereomerically pure complex **5**. The ethereal solution was evaporated and the residue was subjected to column chromatography on SiO_2 using a mixture of acetone and chloroform, in a ratio of 1/10, respectively, as an eluent, to afford 1.7 g (5.5%) of the major product **5** (emerges second) and a

mixture of complexes **4** and **6**. The latter was dissolved in a minimum amount of acetone and treated (dropwise) with *n*-hexane to initiate a precipitation of the complex **4**. The precipitate of diastereomerically pure **4** (3.93 g, 12.8%) was filtered off and washed with a mixture of acetone and *n*-hexane in a ratio of 1 to 2. The mother liquor was evaporated and the residue was subjected to column chromatography on SiO_2 using a mixture of acetone and *n*-hexane, in a ratio of 1/1, as an eluent, to afford 0.7 g (2.3%) of **4** and 1.02 g (3.3%) of **6**.

Ni(II) complex of Schiff base of (*S*)-BPB and ω-ethyl (2*R*,3*R*)-3-methylglutamate (4). mp. 189-90 °C, $[\alpha]_D^{25}$ -1323, (*c* 0.12, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.19 (3H, t, *J*=7.2 Hz), 1.73-1.95 (3H, m), 1.81 (3H, d, *J*=6.3 Hz), 2.14-2.36 (3H, m), 2.50-2.64 (3H, m), 3.59, 3.63 (1H, AB, *J*=3.9 Hz), 3.87 (1H, d, *J*=2.7 Hz), 3.91-4.07 (3H, m), 4.11, 4.90 (2H, AB, *J*=13.2 Hz), 6.73-6.84 (2H, m), 7.17-7.68 (11H, m), 8.54 (1H, part of AB, *J*=8.7 Hz). ^{13}C-NMR ($CDCl_3$) δ 14.1 (s), 15.3 (s), 23.6 (s), 30.9 (s), 36.2 (s), 38.4 (s), 56.3 (s), 60.2 (s), 61.2 (s), 68.4 (s), 74.2 (s), 120.8 (s), 123.8 (s), 125.9 (s), 126.6 (s), 128.5 (s), 128.6 (s), 128.9 (s), 129.6 (s), 131.8 (s), 132.0 (s), 132.6 (s), 133.8 (s), 134.2 (s), 142.8 (s), 171.8 (s), 172.4 (s), 177.9 (s), 182.3 (s). HRMS(FAB) $[M+H]^+$ calcd. for $C_{33}H_{36}N_3O_5Ni$ 612.2008, found 612.2012.

Ni(II) complex of Schiff base of (*S*)-BPB and ω-ethyl (2*S*,3*S*)-3-methylglutamate (5). mp. 229-30 °C, $[\alpha]_D^{25}$ +2912, (*c* 0.12, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.17 (3H, t, *J*=7.2 Hz), 1.93, 2.29 (2H, ABX, *J*=14.5 Hz, *J*=10.2 Hz, *J*=2.7 Hz), 1.97 (3H, d, *J*=6.3 Hz), 2.02-2.12 (2H, m), 2.18-2.56 (1H, m), 2.45-2.57 (1H, m), 2.78-2.86 (1H, m), 3.33-3.44 (1H, m), 3.45-3.53 (2H, m), 3.62, 4.46 (2H, AB, *J*=12.8 Hz), 3.89 (1H, d, *J*=3.9 Hz), 3.94, 4.03 (2H, ABX, *J*=7.2 Hz, *J*=6.7 Hz), 6.65-6.70 (2H, m), 6.99-7.51 (9H, m), 8.02 (2H, part of AB, *J*=7.2 Hz), 8.26 (1H, part of AB, *J*=8.7 Hz). ^{13}C-NMR ($CDCl_3$) δ 14.1 (s), 15.7 (s), 23.0 (s), 30.7 (s), 35.0 (s), 38.3 (s), 56.6 (s), 60.2 (s), 63.2 (s), 70.3 (s), 73.9 (s), 120.6 (s), 123.3 (s), 126.2 (s), 126.9 (s), 128.0 (s), 128.8 (s), 128.9 (s), 129.7 (s), 131.5 (s), 132.4 (s), 133.1 (s), 133.6 (s), 133.8 (s), 142.5 (s), 171.5 (s), 171.7 (s), 177.5 (s), 180.3 (s). HRMS(FAB) $[M+H]^+$ calcd. for $C_{33}H_{36}N_3O_5Ni$ 612.2008, found 612.2034.

Ni(II) complex of Schiff base of (*S*)-BPB and ω-ethyl (2*S*,3*R*)-3-methylglutamate (6). mp. 95-6 °C, $[\alpha]_D^{25}$ +2520, (*c* 0.11, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 0.78 (3H, d, *J*=6.9 Hz), 1.25 (3H, t, *J*=7.2 Hz), 2.07-2.17 (2H, m), 2.25-2.53 (1H, m), 2.46-2.58 (1H, m), 2.57, 4.67 (2H, ABX, *J*=15.6 Hz, *J*=10.5 Hz, *J*=3.6 Hz), 2.75-2.86 (1H, m), 3.30-3.43 (1H, m), 3.46-3.57 (2H, m), 3.61, 4.47 (2H, AB, *J*=12.6 Hz), 3.83 (1H, d, *J*=3.9 Hz), 4.12, 4.19 (2H, ABX, *J*=7.2 Hz, *J*=2.1 Hz), 6.65-6.67 (2H, m), 7.03-7.56 (9H, m), 8.03 (2H, part of AB, *J*=7.2 Hz), 8.26 (1H, part of AB, *J*=8.7 Hz). ^{13}C-NMR ($CDCl_3$) δ 14.2 (s), 17.0 (s), 23.1 (s), 30.6 (s), 35.3 (s), 36.9 (s), 56.8 (s), 60.7 (s), 63.3 (s), 70.2 (s), 73.8 (s), 120.6 (s), 123.2 (s), 126.1 (s), 126.9 (s), 128.0 (s), 128.8 (s), 128.9 (s), 129.6 (s), 131.5 (s), 132.4 (s), 133.1 (s), 133.6 (s), 133.9 (s), 142.4 (s), 171.7 (s), 172.1 (s), 177.3 (s), 180.3 (s). HRMS(FAB) $[M+H]^+$ calcd. for $C_{33}H_{36}N_3O_5Ni$ 612.2008, found 612.1997.

Decomposition of complex (2*S*,3*S*)-(5); Isolation of (2*S*,3*S*)-3-methylpyroglutamic acid (3a) and (2*S*,3*S*)-3-methylglutamic acid (7). A solution of diastereo- and enantiomerically pure complex (2*S*,3*S*)-(**5**) (15 g) in MeOH (100 mL) was slowly added with stirring to a mixture of aqueous 3 *N* HCl and MeOH (120 mL, ratio 1/1) at 70 °C. Upon disappearance of the red color of the starting complex, the reaction mixture was evaporated *in vacuo* to dryness. Water (25 mL) was added to the crystalline residue and insoluble material was filtered off and washed with water (3 x 10 mL) to give 13.12 g (76.6 %) 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 3.14 g (20%) of free (*S*)-**BPB**. The aqueous solution was evaporated *in vacuo*, dissolved in a minimum amount of water and subjected to cation exchange resin Dowex 50X2 100. The column was washed with water and the acidic fraction was collected to give, after evaporation *in vacuo*, 5.14 g (88%) of (2*S*,3*S*)-3-methylpyroglutamic acid (**3a**). Analytically pure sample of (2*S*,3*S*)-**3a** was obtained by crystallization of the compound from THF/*n*-hexane. Elution of the column with 2 *N* NH_4OH and subsequent removal of water gave 460 mg (7%) of (2*S*,3*S*)-3-methylglutamic acid **7**, as an ammonium salt.

(2*S*,3*S*)-3-methylpyroglutamic acid (3a). mp. 110-1.5 °C, $[\alpha]_D^{25}$ +41.0, (*c* 1.16, MeOH). ^{1}H-NMR (CD_3COCD_3) δ 1.28 (3H, d, *J*=6.6 Hz), 1.93, 2.48 (2H, ABX, *J*=15.9 Hz, *J*=8.5 Hz, *J*=5.7 Hz), 2.53 (1H, dqdd, *J*=8.5 Hz, *J*=6.6 Hz, *J*=5.7 Hz, *J*=5.1 Hz), 3.86 (1H, d, *J*=5.1 Hz), 7.19 (1H, br.s). ^{13}C-NMR (CD_3COCD_3) δ 20.1 (s), 34.8 (s), 38.4 (s), 63.1 (s), 174.0 (s), 178.3 (s). HRMS(FAB) $[M+H]^+$ calcd. for $C_6H_{10}NO_3$ 144.0661, found 144.0660.

(2*S*,3*S*)-3-methylglutamic acid (7). mp. 169.5-70 °C, $[\alpha]_D^{25}$ +42.8, (*c* 0.97, 6 *N* HCl). ^{1}H-NMR (D_2O) δ 0.86 (3H, d, *J*=6.6 Hz), 2.24, 2.45 (2H, ABX, *J*=15.0 Hz, *J*=7.2 Hz, *J*=5.1 Hz), 2.33 (1H, dqdd, *J*=7.2 Hz, *J*=6.6 Hz, *J*=5.1 Hz, *J*=3.4 Hz), 3.62 (1H, d, *J*=3.4 Hz). ^{13}C-NMR (D_2O) δ 14.3 (s), 37.7 (s), 58.1 (s), 66.5 (s), 172.8 (s), 176.8 (s). HRMS(FAB) $[M+H]^+$ calcd. for $C_6H_{12}NO_4$ 162.0766, found 162.0770.

Reaction of glycine complex (S)-1 with ethyl 4,4,4-trifluorocrotonate (2a). The procedure described above for the reaction of crotonate **2a** with (*S*)-**1** was followed, except that 0.025 mol (0.764 g) of DBU was used as a base. Starting from 20 g (0.04 mol) of complex (*S*)-**1** and 7.40 g (0.044 mol) of ethyl trifluorocrotonate **2b** the addition reaction afforded 24.34 g (91%) of two diastereomeric complexes in a ratio of 5.6 to 1 (by ^{1}H-NMR). After washing the crude mixture with diethyl ether and chromatographic separation (eluent: $CHCl_3$/acetone as 15/1) of the ethereal fraction, the major complex **8** 70% (18.73 g), emerges first, and 11% (2.94 g) of **9** were obtained in diastereomerically pure form.

Ni(II) complex of Schiff base of (*S*)-BPB and ω-ethyl (2*S*,3*S*)-3-trifluoromethylglutamate (8). mp. 247-48 °C, $[\alpha]_D^{25}$ +2702, (*c* 0.11, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.16 (3H, t, *J*=7.1 Hz), 2.02-2.17 (2H, m), 2.44-2.60 (1H, m), 2.58 (2H, d, *J*=6.4 Hz), 2.80-2.98 (2H, m), 3.31-3.54 (3H, m), 3.58, 4.42 (2H, AB, *J*=12.7 Hz), 3.98 (2H, q, *J*=7.1 Hz), 4.19 (1H, d, *J*=4.9 Hz), 6.61-6.68 (2H, m), 6.99-7.03 (1H, m), 7.13-7.37 (6H, m), 7.54-7.58 (3H, m), 8.04 (2H, part of AB, *J*=7.1 Hz), 8.27 (1H, part of AB, *J*=8.3 Hz). ^{19}F-NMR ($CDCl_3$) δ -63.7 (d, *J*=8.8 Hz). ^{13}C-NMR ($CDCl_3$) δ 14.0 (s), 22.5 (s), 30.6 (s), 31.3 (q, *J*=3.0 Hz), 42.2 (q, *J*=26.2 Hz), 57.0 (s), 60.8 (s), 63.4 (s), 67.4 (s), 70.6 (s), 76.6 (s), 120.6 (s), 123.4 (s), 126.1 (s), 126.5 (s), 127.9 (s), 128.8 (s), 129.3 (s), 129.5 (s), 130.0 (s), 131.5 (s), 132.8 (s), 133.2 (s), 133.7 (s), 143.1 (s), 169.7 (s), 172.8 (s), 176.0 (s), 180.4 (s), resonance of the CF_3 carbon is obscured due to its low intensity. HRMS(FAB) $[M+H]^+$ calcd. for $C_{33}H_{32}F_3N_3NiO_5$: 666.1726, found 666.1728. Anal. calcd for $C_{33}H_{32}F_3N_3NiO_5$: C, 59.48; H, 4.85; N, 6.31. Found: C, 59.53; H, 4.91; N, 6.27.

Ni(II) complex of Schiff base of (*S*)-BPB and ω-ethyl (2*S*,3*R*)-3-trifluoromethylglutamate (9). mp. 81-2 °C, $[\alpha]_D^{25}$ +2307 (*c* 0.23, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.21 (3H, t, *J*=7.1 Hz), 2.10-2.20 (2H, m), 2.45-2.58 (1H, m), 2.72-2.81 (1H, m), 2.91, 4.37 (2H, ABX, *J*=17.6 Hz, *J*=5.4 Hz, *J*=4.4 Hz), 3.25-3.42 (2H, m), 3.51 (1H, dd, *J*=10.7 Hz, *J*=6.1 Hz), 3.54-3.62 (1H, m), 3.56, 4.45 (2H, AB, *J*=12.7 Hz), 4.12 (2H, m), 4.28

(1H, d, *J*=4.6 Hz), 6.63-6.68 (2H, m), 7.12-7.21 (3H, m), 7.27-7.34 (3H, m), 7.49-7.60 (3H, m), 8.04 (2H, part of AB, *J*=7.3 Hz), 8.28 (1H, part of AB, *J*=8.8 Hz). ^{19}F-NMR ($CDCl_3$) δ -67.9 (d, *J*=9.2 Hz). ^{13}C-NMR ($CDCl_3$) δ 14.0 (s), 23.3 (s), 30.0 (s), 30.4 (b.s), 42.8 (q, *J*=26.6 Hz), 57.2 (s), 61.9 (s), 63.6 (s), 67.0 (s), 70.3 (s), 76.6 (s), 120.6 (s), 122.9 (s), 125.5 (s), 126.9 (s), 127.9 (s), 128.8 (s), 129.0 (s), 129.1 (s), 130.1 (s), 131.3 (s), 132.9 (s), 133.3 (s), 133.4 (s), 133.9 (s), 142.8 (s), 170.4 (s), 173.5 (s), 175.1 (s), 180.3 (s), resonance of the CF_3 carbon is obscured due to its low intensity. HRMS(FAB) $[M+H]^+$ calcd. for $C_{33}H_{32}F_3N_3NiO_5$: 666.1726, found 666.1713. Anal. calcd for $C_{33}H_{32}F_3N_3NiO_5$: C, 59.48; H, 4.85; N, 6.31. Found: C, 59.51; H, 4.89; N, 6.29.

Ni(II) complex of Schiff base of (*S*)-BPB and (2*S*,3*S*)-3-trifluoromethylglutamic acid (10). To a solution of complex (2*S*,3*S*)-**8** (5.658 g) in 150 mL of EtOH and 50 mL of water, 50 mL of 1 *N* NaOH were added with stirring. 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. Upon completion, a complete transformation of (2*S*,3*S*)-**8** to the product with lower R_f, the reaction mixture was poured into an icy 5% aqueous acetic acid and extracted with $CHCl_3$. The extract was evaporated *in vacuo* and the oily residue was treated with water to give crystalline product which was filtered off, thoroughly washed with water and dried *in vacuo* to afford 5.39 g (99.5%) of complex (2*S*,3*S*)-**10**. Mp. 260-1 °C, $[\alpha]_D^{25}$ +3040, (*c* 0.19, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 2.05-2.18 (2H, m), 2.48-2.60 (2H, m), 2.71-2.89 (3H, m), 3.25-3.39 (1H, m), 3.42-3.49 (2H, m), 3.62, 4.38 (2H, AB, *J*=12.7 Hz), 4.32 (1H, d, *J*=4.9 Hz), 6.61-6.69 (2H, m), 6.94-6.96 (1H, m), 7.15-7.39 (6H, m), 7.49-7.58 (3H, m), 8.05 (2H, part of AB, *J*=7.1 Hz), 8.25 (1H, part of AB, *J*=8.8 Hz). ^{13}C-NMR ($CDCl_3$) δ 22.5 (s), 30.6 (s), 31.1 (s), 41.8 (q, *J*=23.3 Hz), 57.0 (s), 63.58 (s), 66.6 (s), 70.7 (s), 120.8 (s), 123.5 (s), 126.0 (s), 126.3 (s), 127.6 (s), 128.9 (s), 128.9 (s), 129.5 (s), 129.6 (s), 130.4 (s), 131.5 (s), 133.0 (s), 133.2 (s), 133.3 (s), 133.8 (s), 143.0 (s), 172.5 (s), 173.2 (s), 177.0 (s), 180.4 (s), resonance of the CF_3 carbon is obscured due to its low intensity. HRMS(FAB) $[M+H]^+$ calcd. for $C_{31}H_{29}F_3N_3NiO_5$: 638.1413, found 638.1441.

Decomposition of complexes (2*S*,3*S*)-(8), (2*S*,3*S*)-(10) and (2*S*,3*R*)-(9); Isolation of (2*S*,3*S*)-(3b) and (2*S*,3*R*)-3-trifluoromethylpyroglutamic acids (11) and (2*S*,3*R*)-3-trifluoromethylglutamic acid (12). The procedure described for preparing (2*S*,3*S*)-3-methylpyroglutamic acid (**3a**) was followed.

(2*S*,3*S*)-3-trifluoromethylpyroglutamic acid (3b). Yield 85% from ester (2*S*,3*S*)-(**8**); (2.1 g) 86% from acid (2*S*,3*S*)-(**10**); mp. 129-30 °C, $[\alpha]_D^{25}$ +28.8, (*c* 1.27, MeOH); lit:[15] $[\alpha]_D$ = +25.3 (*c*, 1.2, MeOH). ^{1}H-NMR (CD_3COCD_3) δ 2.36, 2.75 (2H, ABX, *J*=17.6 Hz, *J*=10.3 Hz, *J*=4.2 Hz), 3.59 (1H, dqdd, *J*=10.3 Hz, *J*=7.2 Hz, *J*=4.2 Hz, *J*=2.9 Hz), 4.40 (1H, d, *J*=2.9 Hz), 7.50 (1H, br.s). ^{19}F-NMR (CD_3COCD_3) δ -75.14 (d, *J*=9.1 Hz). ^{13}C-NMR (CD_3COCD_3) δ 41.9 (q, *J*=27.1 Hz), 55.4 (s), 55.4 (s), 127.9 (q, *J*=157.1 Hz), 172.0 (s), 174.2 (s). HRMS(FAB) $[M+H]^+$ calcd. for $C_6H_7F_3NO_3$: 198.0378, found 198.0374.

(2*S*,3*R*)-3-trifluoromethylpyroglutamic acid (11). Yield 87% from ester (2*S*,3*R*)-(**9**); mp. 192-3 °C, $[\alpha]_D^{25}$ +59.7, (*c* 0.95, MeOH). ^{1}H-NMR (CD_3COCD_3) δ 2.48, 2.55 (2H, ABX, *J*=16.4 Hz, *J*=9.8 Hz, *J*=9.0 Hz), 3.80 (1H, br.sep, *J*=8.7 Hz), 4.51 (1H, d, *J*=8.1 Hz), 7.31 (1H, br.s). ^{19}F-NMR (CD_3COCD_3) δ -70.06 (d,

J=9.1 Hz). ^{13}C-NMR (CD_3COCD_3) δ 43.0 (q, J=30.3 Hz), 55.3 (s), 55.4 (s), 126.6 (q, J=157.1 Hz), 171.5 (s), 174.6 (s). HRMS(FAB) $[M+H]^+$ calcd. for $C_6H_7F_3NO_3$: 198.0378, found 198.0365.

(2*S*,3*R*)-3-trifluoromethylglutamic acid (12). Yield 7% from ester (2*S*,3*R*)-(**9**); mp. 156-7 °C, ^{1}H-NMR (D_2O) δ 2.45, 2.55 (2H, ABX, J=16.5 Hz, J=7.5 Hz, J=5.7 Hz), 3.25 (1H, m), 3.88 (1H, d, J=2.4 Hz). HRMS(FAB) $[M+H]^+$ calcd. for $C_6H_9F_3NO_4$: 216.0484, found 216.0482.

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19 At least six partially separable products could be detected by TLC ($CHCl_3$/acetone or acetone/*n*-hexane).

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