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Synthesis of fluorinated glutamic acid derivatives via vinylalumination

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Abstract

A variety of structural types of fluorinated allylic acetates, prepared by vinylalumination of fluorinated aldehydes, were reacted with the benzophenone imine of glycine *tert*-butyl ester to provide 4-(fluorobenzylidenyl)- and 4-(fluoroalkylidenyl) glutamic acid derivatives in 61–96% yield. The 4-(4-fluorobenzylidenyl) glutamic acid derivative was hydrolyzed to give the 4-(4-fluorobenzylidenyl)pyroglutamate and then hydrogenated to the 4-(4-fluorobenzyl)pyroglutamate. The catalytic enantioselective conjugate addition-elimination of the benzophenone imine of glycine *tert*-butyl ester with the fluorinated allylic acetates prepared from fluoral, pentafluorobenzaldehyde, and 2,6-difluorobenzaldehyde provided the corresponding 4-(fluoroalkylidenyl)- and 4-(fluorobenzylidenyl) glutamic acid derivatives in 42, 45 and 80% ee, respectively.

Keywords: Fluorine-containing amino acids; Conjugate addition-elimination; Glutamates; Vinylalumination; Excitatory amino acids

1. Introduction

Due to the similarity in size, hydrogen has been replaced with fluorine in many biologically active organic molecules, including amino acids [1]. Naturally occurring amino acids play an important role in living systems, and therefore synthetic fluorine-containing amino acids have been of significant interest in a variety of biological applications [2]. Fluorinated amino acids can be used as tracers and mechanistic probes for investigations into the structure and properties of enzymes [3]. They are also useful in the control of blood pressure, tumour growth, and allergies [4] and find applications as key intermediates in the synthesis of bioactive natural products [5]. Moreover, fluorinated amino acids have recently emerged as valuable building blocks for the design of hyperstable protein folds as well as directing highly specific protein–protein interactions [6], aiding the remarkable progress in protein engineering involving fluorinated amino acids [7]. It has also been demonstrated that the presence of monofluorinated amino acid residues in peptides can influence enzyme inhibition [8].

Glutamic acid is the main excitatory amino acid in the mammalian central nervous system (CNS). 4-Substituted glutamate analogs, such as 4-substituted alkylidene glutamic acids, have been the targets of several synthetic and pharmacological studies [9]. Many 4-substituted glutamates are available in nature, and others with various substituents have been synthesized to study various structure–activity relationships in biological systems [10]. It was found that a critical size and structure of the alkylidene group gave potent and selective GluR5 receptor agonists [9a]. Although several classes of fluorinated amino acids have been synthesized, the preparation of 4-substituted alkylidene glutamates containing fluorine substitution on the alkylidene group is not known. Hence, new methods for the synthesis of such fluorinated glutamates are highly desirable. Herein we report a simple, general and new procedure for the synthesis of 4-(fluoroalkylidenyl)- and 4-(fluorobenzylidenyl) glutamic acid derivatives, which is based on the tandem conjugate addition-elimination of the Schiff base of glycine *tert*-butyl ester with fluorinated allylic acetates prepared by vinylalumination.

2. Results and discussion

Baylis–Hillman reaction of acrylates and aldehydes is normally used to prepare functionalized allylic acetates [11]; however, this reaction was not facile with fluorinated aldehydes. For example, it is known that the simplest fluorocarbonyl compound, fluoral, polymerize instantaneously

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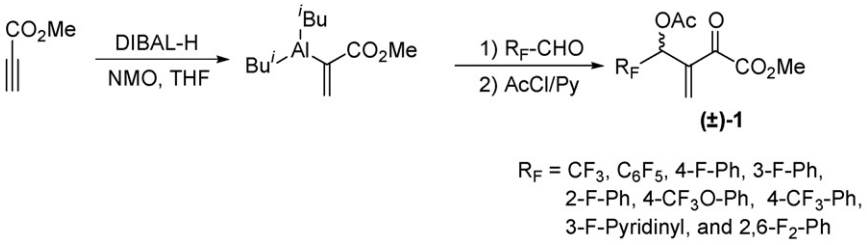
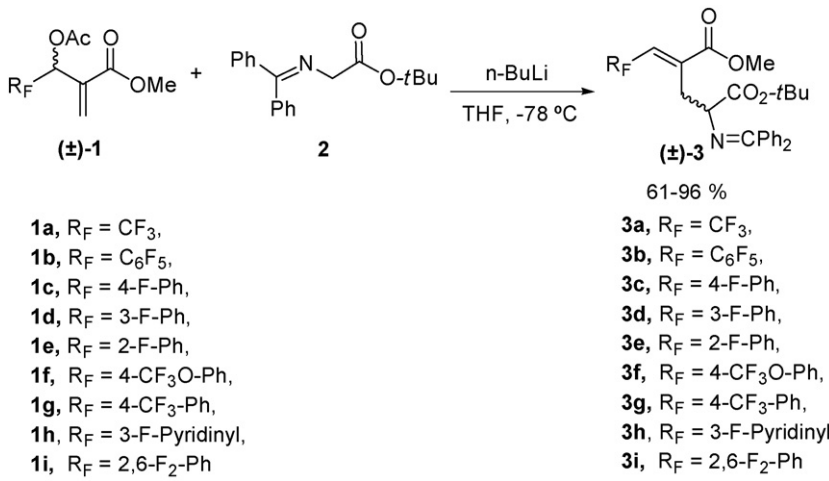


Scheme 1. Synthesis of the fluorinated allylic acetates (±)-**1**.



Scheme 2. Synthesis of the 4-(fluoroalkylidenyl)- and 4-(fluorobenzylidenyl) glutamic acid derivatives (±)-**3**.

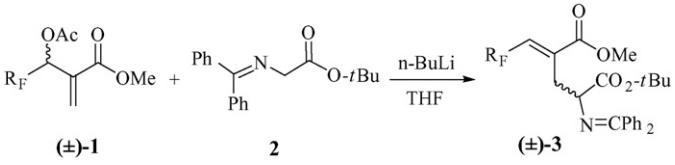
in the presence of amines [12]. Accordingly, a series of fluorinated allylic alcohols was recently prepared by vinylalumination (Scheme 1) [13]. These alcohols were then converted to the corresponding acetates **1**, which were used as starting materials for the conjugate addition-elimination reaction.

Initially we focused on standardizing the reaction conditions and determining the scope of the methodology by preparing the racemic 4-(fluoroalkylidenyl)- and 4-(fluorobenzylidenyl) glutamic acid derivatives **3**. Reaction of the lithium enolate of the benzophenone imine of glycine *tert*-butyl ester (**2**) [14,15] with fluorinated allylic acetate **1a**, synthesized from fluoral by the vinylalumination method gave the racemic 4-(trifluoroethylidenyl) glutamic acid derivative **3a** in 65% yield (Scheme 2) (Table 1, entry 1). THF was found to be the solvent of choice and best results were obtained at −78 °C [16].

This methodology was extended to a series of fluorosubstituted benzaldehydes, which gave products in high yields (61–96%) (Table 1, **3b**–**3g**, **3i**). Even a fluorosubstituted heteroaromatic allylic acetate (**1h**) underwent the conjugate addition-elimination to provide 82% yield of **3h** (Table 1, entry 8). It is noteworthy that, with allylic acetates that are not activated with an ester group at the 2-position, palladium catalysis is required in similar reactions [17].

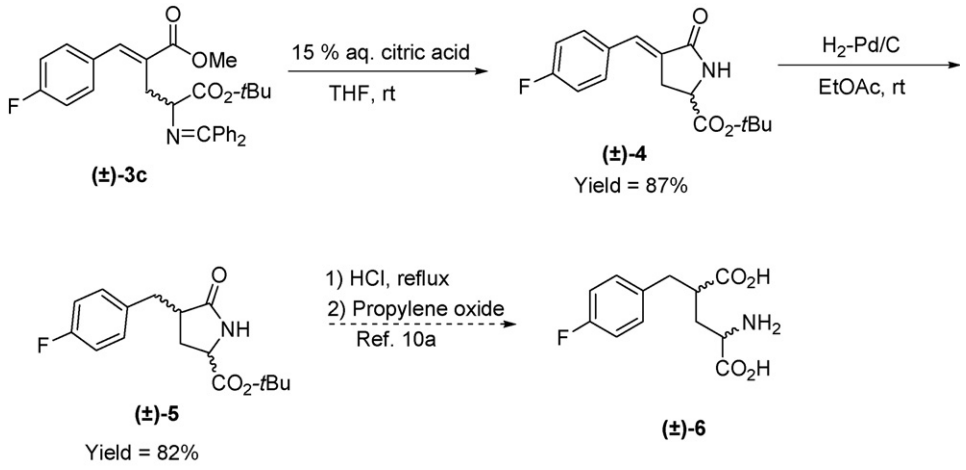
To further demonstrate the utility of this procedure, the 4-(4-fluorobenzylidenyl) glutamic acid (**3c**) derivative was converted to the corresponding 4-(4-fluorobenzylidenyl) pyroglutamate (**4**) in 87% by treatment with 15% aqueous citric acid in THF at ambient temperature. Hydrogenation with catalytic Pd/C gave the 4-(4-fluorobenzyl) pyroglutamate (**5**) in 82% isolated yield (Scheme 3). This pyroglutamate can be converted to the 4-(4-fluorobenzyl) glutamic acid (**6**) by known procedures [10a].

Table 1
Synthesis of the 4-(fluoroalkylidenyl)- and 4-(fluorobenzylidenyl) glutamic acid derivatives[a]

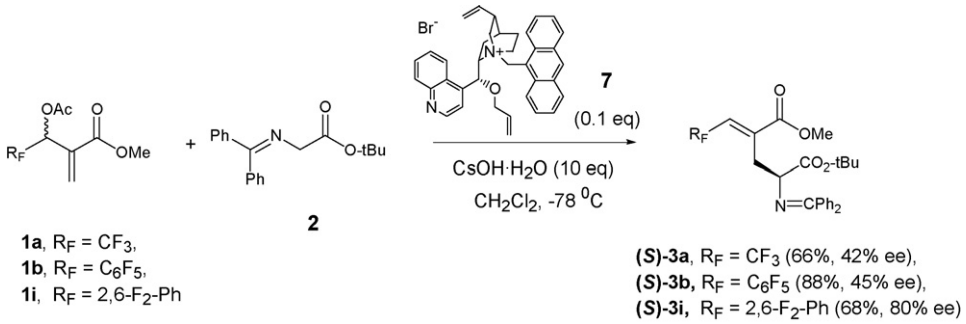


Entry	Allylic acetate (**1**)	R_F	Reaction time (h)	Glutamate (**3**)	Yield (%)[b]
1	(±)-**1a**	CF_3	6	(±)-**3a**	65
2	(±)-**1b**	C_6F_5	3.5	(±)-**3b**	84
3	(±)-**1c**	4-F–Ph	4	(±)-**3c**	96
4	(±)-**1d**	3-F–Ph	4	(±)-**3d**	92
5	(±)-**1e**	2-F–Ph	5	(±)-**3e**	95
6	(±)-**1f**	4-CF_3O–Ph	5	(±)-**3f**	88
7	(±)-**1g**	4-CF_3–Ph	4.5	(±)-**3g**	95
8	(±)-**1h**	3-F–Pyridinyl	6	(±)-**3h**	82
9	(±)-**1i**	2,6-F_2–Ph	4.5	(±)-**3i**	61[c]

[a] The benzophenone imine of glycine *tert*-butyl ester **2** (1 mmol), fluorinated allylic acetate **1** (1 mmol) and *n*-BuLi (1.2 equiv.) in THF were stirred at −78 °C for the indicated time.
[b] Isolated yield.
[c] Ref. [16].



Scheme 3. Synthesis of 4-(4-fluorobenzyl) pyroglutamate.



Scheme 4. Enantioselective synthesis of 4-(fluoroalkylidenyl)- and 4-(fluorobenzylidenyl) glutamic acid derivatives by catalytic enantioselective PTC.

With these encouraging results, the catalytic asymmetric version of the conjugate addition-elimination reaction of fluorinated allylic acetates under PTC conditions was then investigated. *O*-Allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide (**7**) was chosen as the PTC for alkylation reactions, since it provided the best enantioselectivity in our earlier studies [16]. Thus, the conjugate addition-elimination of **2** with **1b** using 0.1 equiv. of **7** and 10 equiv. of $CsOH{\cdot}H_2O$ in CH_2Cl_2 at $-78\ ^\circ C$ gave the product (*S*)-**3b** in 88% yield and 45% ee. The 2,6-difluorobenzaldehyde derivative (*S*)-**3i** was obtained in 80% ee [16] (Scheme 4). The products are assumed to have the (*S*) absolute configuration based on extensive literature precedence [14,16]. The aliphatic fluorinated allylic acetate **1a** also gave only a modest enantioselectivity (42% ee) under the same reaction conditions with a 66% yield (*S*)-**3a**.

3. Conclusion

In conclusion, we have presented a general and simple procedure for the synthesis of 4-(fluoroalkylidenyl)- and 4-(fluorobenzylidenyl) glutamic acid derivatives, which is based on the tandem conjugate addition-elimination of the Schiff base of glycine *tert*-butyl ester with fluorinated allylic acetates. The generality of the methodology has been demonstrated for the synthesis of a wide range of 4-(fluoroalkylidenyl)- and 4-(fluorobenzylidenyl) glutamic acid derivatives. In addition, enantioselective conjugate addition-elimination was also carried out to obtain chiral 4-(fluoroalkylidenyl)- and 4-(fluorobenzylidenyl) glutamic acid derivatives in modest enantioselectivities. Further investigations focused on improving the yields in the case of aliphatic fluorinated allylic acetates and the enantioselectivities of the chiral PTC process are currently underway.

4. Experimental

Unless otherwise noted, all manipulations were carried out under an inert atmosphere using flame-dried glassware. Tetrahydrofuran (THF) was freshly distilled before use from sodium benzophenone ketyl and anhydrous diethyl ether was purchased from Mallinckrodt chemicals. Sure Seal™ bottles of *n*-butyl lithium (2.5 M in hexanes), cinchonidine, $CsOH{\cdot}H_2O$, DIBAL-H, NMO, Pd/C and fluorinated aldehydes were purchased from the Aldrich Chemical Co. The benzophenone imine of glycine *tert*-butyl ester (**2**) and phase-transfer catalysts were prepared by literature procedures. Other chemicals were used without further purification, unless otherwise noted.

The ^1H, ^{13}C and ^{19}F nuclear magnetic resonance (NMR) spectra were plotted on a Varian Gemini-300 spectrometer (300, 75 and 282 MHz, respectively) with a Nalorac-quad probe. ^1H NMR spectra were obtained using $CDCl_3$ as the solvent with either tetramethylsilane (TMS: δ 0 ppm) or chloroform ($CHCl_3$: δ 7.2 ppm) as the internal standard. ^{19}F NMR spectra were recorded in $CDCl_3$ using $CFCl_3$ or trifluoroacetic acid (TFA) as the internal standard. ^1H NMR

data are reported as chemical shifts (δ ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (Hz), and integration. Enantiomeric excesses (% ee) were measured using a Dynamax HPLC fitted with an HPXL Solvent Delivery System and a Dynamax UV (λ 254 nm) detector, and a (*S*,*S*)-Whelk-O1 (Regis Technologies®) chiral HPLC column. Mass spectra were recorded using a Hewlett Packard 5989B mass spectrometer/5890 series II gas chromatograph or a Finnigan mass spectrometer model 4000. The chemical ionization gas used was isobutene. Flash chromatography was performed on 40–60 μm silica gel (230–400 mesh).

5. Experimental procedure and analytical data for products

5.1. Synthesis of fluorinated allylic acetates [(±)-*1*]

To a stirred suspension of NMO (2.1 g, 18 mmol) in anhydrous THF (50 mL) was added DIBAL-H (2.7 mL, 15 mmol) at 0 °C and the mixture was stirred for 0.5 h to dissolve the NMO. Methyl propiolate (0.89 mL, 10 mmol) was added dropwise and the mixture was stirred at 0 °C for 1 h, followed by the dropwise addition of the fluorinated aldehyde (12 mmol). The mixture was warmed to rt, stirred for 4 h, quenched with 10 mL of 1.0 M HCl, and the product was extracted with ether (3 × 50 mL). The combined ether layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated *in vacuo*. Purification by flash chromatography over silica gel (95:5, hexanes:ethyl acetate) provided the desired fluorinated allylic alcohol. These alcohols were converted to the corresponding acetates using acetyl chloride (1.2 equiv.) in the presence of pyridine (1.5 equiv.) at 0 °C for 4–6 h in dichloromethane.

5.2. Preparation of the benzophenone imine of glycine tert-butyl ester (*2*) [15a]

A mixture of *tert*-butyl chloroacetate (45.2 g, 0.30 mol), benzophenone imine (36.3 g, 0.20 mol), and anhydrous potassium carbonate (41.5 g, 0.30 mol) was stirred under argon overnight at 130 °C in a 250 mL flask equipped with a reflux condenser. After cooling to room temperature, the mixture was filtered with filter paper in a Buchner funnel using suction. The inorganic solids were washed with ethyl acetate (3 × 50 mL). The filtrates were dissolved with warming and stirring in ethyl acetate (375 mL). The organic phase was washed with water (200 mL), dried over sodium sulphate, filtered and evaporated *in vacuo*. The solid residue was dissolved in hexanes (450 mL), which required warming with stirring. After refrigeration overnight, the crystalline product was filtered to yield product as white crystals (61% yield).

5.3. General experimental procedure for the preparation of 4-(fluoroalkylidenyl)- and 4-(fluorobenzylidenyl) glutamic acid derivatives [(±)-*3*]

n-Butyl lithium (2.5 M solution in hexanes, 1.2 mmol, 1.2 equiv.) was added dropwise over 5 min by syringe to the benzophenone imine of glycine *tert*-butyl ester (**2**) (1 mmol, 1 equiv.) in THF (5 mL) at −78 °C. Then a previously prepared solution of the fluorinated allylic acetate **1** (1 mmol, 1 equiv.) in THF (2 mL) was transferred to the reaction flask via syringe. The reaction mixture was stirred for 3.5–6 h at −78 °C. After completion of the reaction (monitored periodically by TLC), the reaction mixture was warmed to ambient temperature, quenched with water (2 mL), diluted with diethyl ether (3 mL), and the phases were separated. The aqueous layer was extracted with ether (2 × 3 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography (silica, hexanes:ethyl acetate; 9:1, v/v) afforded the desired 4-(fluoroalkylidenyl)- and 4-(fluorobenzylidenyl) glutamic acid derivatives.

5.3.1. 1-(1,1-Dimethylethyl)-5-methyl-N-(diphenylmethylene)-(4E)-(1,1,1-trifluoro ethylidene)-(±)-glutamate [(±)-*3a*]

65% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.46 (s, 9H), 3.03–3.08 (m, 1H), 3.38-3.47 (m, 1H), 3.55 (s, 3H), 4.36–4.41 (m, 1H), 7.11–7.76 (m, 10H), 7.80 (s, 1H, vinyl proton).

5.3.2. 1-(1,1-Dimethylethyl)-5-methyl-N-(diphenylmethylene)-(4E)-(2,3,4,5,6-pentafluorophenyl methylene)-(±)-glutamate [(±)-*3b*]

84% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.41 (s, 9H), 2.80–2.88 (m, 1H), 3.06-3.12 (m, 1H), 3.61 (s, 3H), 4.11–4.16 (m, 1H), 7.09–7.43 (m, 11H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −137.5 (2H), −154.0 (1H), −161 4 (2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 28.0, 29.7, 32.3, 52.2, 60.4, 64.5, 81.5, 125.6, 127.9, 128.1, 128.2, 128.5, 128.6, 128.8, 130.4, 136.0, 137.2, 138.9, 166.3, 170.0, 170.7; MS (EI/CI) *m/z* calcd for $[C_{30}H_{26}F_5NO_4 + H]^+$ 559, found: 559.

5.3.3. 1-(1,1-Dimethylethyl)-5-methyl-N-(diphenylmethylene)-(4E)-(4-fluorophenyl methylene)-(±)-glutamate [(±)-*3c*]

96% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.52 (s, 9H), 3.06–3.11 (m, 1H), 3.40–3.48 (m, 1H), 3.63 (s, 3H), 4.41–4.45 (m, 1H), 7.04–7.75 (m, 15H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −113.43; ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 28.1, 31.2, 51.8, 64.9, 81.3, 115.3, 115.6, 128.0, 128.1, 128.3, 128.5, 128.8, 128.9, 130.4, 131.3, 132.0, 132.1, 136.2, 139.2, 141.0, 168.1, 170.6, 170.8; MS (EI/CI) *m/z* calcd for $[C_{30}H_{30}FNO_4 + H]^+$ 488, found: 488.

5.3.4. 1-(1,1-Dimethylethyl)-5-methyl-N-(diphenylmethylene)-(4E)-(3-fluorophenyl methylene)-(±)-glutamate [(±)-*3d*]

92% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.52 (s, 9H), 3.07–3.13 (m, 1H), 3.42–3.50 (m, 1H), 3.64 (s, 3H), 4.40–4.45 (m, 1H), 7.10–7.64 (m, 14H), 7.75 (s, 1H, vinyl proton); ^{19}F NMR (282 MHz, $CDCl_3$) δ −112.88; ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 28.1, 31.2, 51.9, 64.9, 81.3, 115.4, 115.7, 116.4, 116.9, 125.8, 128.0, 128.1, 128.4, 128.5, 129.0, 129.9, 130.2, 130.4, 136.2, 137.3, 137.5, 139.1, 140.8, 164.3, 167.9, 170.7.

*5.3.5. 1-(1,1-Dimethylethyl)-5-methyl-N-(diphenylmethylene)-(4E)-(2-fluorophenyl methylene)-(±)-glutamate [(±)-**3e**]*

95% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.52 (s, 9H), 3.13–3.19 (m, 1H), 3.40–3.48 (m, 1H), 3.65 (s, 3H), 4.45–4.49 (m, 1H), 7.05–7.64 (m, 13H), 7.91 (s, 1H, vinyl proton), 8.04–8.09 (t, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −113.41; ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 28.1, 31.4, 51.9, 64.7, 81.3, 115.3, 115.6, 123.2, 123.4, 124.1, 127.9, 128.2, 128.3, 128.5, 128.9, 130.3, 130.5, 135.6, 131.0, 131.1, 134.6, 136.2, 139.3, 167.7, 170.7, 170.8.

*5.3.6. 1-(1,1-Dimethylethyl)-5-methyl-N-(diphenylmethylene)-(4E)-(4-trifluoromethoxyphenyl methylene)-(±)-glutamate [(±)-**3f**]*

88% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.53 (s, 9H), 3.07–3.13 (m, 1H), 3.418–3.49 (m, 1H), 3.65 (s, 3H), 4.42–4.46 (m, 1H), 7.16–7.80 (m, 14H), 7.83 (s, 1H, vinyl proton); ^{19}F NMR (282 MHz, $CDCl_3$) δ −57.67; ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 28.1, 31.1, 51.9, 64.8, 81.4, 120.7, 127.8, 128.1, 128.3, 128.5, 128.9, 129.8, 130.4, 131.6, 133.9, 136.2, 139.2, 140.5, 149.3, 168.0, 170.7, 170.8.

*5.3.7. 1-(1,1-Dimethylethyl)-5-methyl-N-(diphenylmethylene)-(4E)-(4-trifluoromethylphenyl methylene)-(±)-glutamate [(±)-**3g**]*

95% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.53 (s, 9H), 3.08–3.148 (m, 1H), 3.40–3.48 (m, 1H), 3.66 (s, 3H), 4.41–4.46 (m, 1H), 7.19–7.85 (m, 15H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −62.62; ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 28.1, 31.1, 52.0, 64.7, 81.5, 125.4, 128.0, 128.1, 128.3, 128.6, 128.9, 130.1, 130.4, 131.1, 136.1, 138.9, 139.1, 140.4, 167.8, 170.5, 170.7; MS (EI/CI) *m/z* calcd for $[C_{31}H_{30}F_3NO_4 + H]^+$ 538, found: 538.

*5.3.8. 1-(1,1-Dimethylethyl)-5-methyl-N-(diphenylmethylene)-(4E)-(3-fluoropyridinyl methylene)-(±)-glutamate [(±)-**3h**]*

82% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.46 (s, 9H), 3.03–3.08 (m, 1H), 3.38–3.47 (m, 1H), 3.55 (s, 3H), 4.36–4.41 (m, 1H), 7.11–7.76 (m, 13H), 7.80 (s, 1H, vinyl proton); ^{19}F NMR (282 MHz, $CDCl_3$) δ −136.32; ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 28.1, 31.3, 51.8, 64.9, 81.2, 127.8, 128.0, 128.2, 128.3, 128.5, 128.7, 129.0, 130.0, 130.2, 135.3, 136.3, 139.4, 142.0, 168.3, 170.5, 170.9.

*5.3.9. 1-(1,1-Dimethylethyl)-5-methyl-N-(diphenylmethylene)-(4E)-(2,6-difluorophenyl methylene)-(±)-glutamate [(±)-**3i**]*

61% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.47 (s, 9H), 2.96–3.04 (m, 1H), 3.11–3.17 (m, 1H), 3.63 (s, 3H), 4.26–4.30 (m, 1H), 6.86–6.92 (m, 2H), 7.19–7.50 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 28.1, 32.5, 51.8, 64.6, 81.2, 111.5, 111.8, 127.7, 128.2, 128.3, 128.4, 128.7, 128.9, 129.9, 130.1, 134.9, 136.3, 139.4, 167.0, 170.4, 170.6; MS (ESI) *m/z* calcd for $[C_{30}H_{29}F_2NO_4 + H]^+$ 505, found: 505.

*5.4. Synthesis of 4-(4-fluorobenzyl) glutamic acid (±)-**6** [10a]*

*5.4.1. Synthesis of 4-(4-fluorobenzylidenyl) pyroglutamate (±)-**4***

Excess 15% aqueous citric acid (5 mL) was added to compound **3c** (0.33 g, 0.68 mmol) dissolved in THF (3 mL). The suspension was stirred overnight at room temperature. After completion of the reaction (monitored periodically by thin layer chromatography), the reaction mixture was extracted with EtOAc (3× 5 mL) and then the aqueous layer was made basic by adding 10% aqueous K_2CO_3 (5 mL), followed by additional EtOAc (5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by column chromatography (silica, hexanes:ethyl acetate; 8:2, v/v to remove benzophenone and hexanes:ethyl acetate; 1:1, v/v to elute product) afforded the desired 4-(4-fluorobenzylidenyl) pyroglutamate (±)-**4** (87% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.50 (s, 9H), 3.19–3.27 (m, 1H), 3.38–3.49 (m, 1H), 4.28–4.33 (m, 1H), 6.61 (bs, 1H), 7.30–7.58 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 28.2, 30.2, 53.7, 82.9, 128.1, 128.8, 129.1, 129.6, 131.8, 135.2, 170.6, 171.3.

*5.4.2. Hydrogenation of 4-(4-fluorobenzylidenyl) pyroglutamate: preparation of 4-(4-fluorobenzyl) pyroglutamate (±)-**5***

To a solution of [(±)-**4**] (0.15 g, 0.51 mmol) in ethyl acetate (5 mL) was added 10% Pd/C (90 mg). Hydrogenation was carried out under a hydrogen atmosphere at room temperature and atmospheric pressure for 12 h. After completion of the reaction (monitored periodically by thin layer chromatography), the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (silica, hexanes:ethyl acetate; 9:1, v/v) afforded the desired reduced product (±)-**5** (82% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.44 (s, 9H), 2.05–2.22 (m, 2H), 2.65–2.74 (m, 2H), 3.09–3.14 (m, 1H), 3.84–3.90 (m, 1H), 6.33 (bs, 1H), 6.93–7.15 (m, 4H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −116.58; ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 27.9, 30.9, 36.8, 43.4, 55.0, 82.3, 126.1, 128.6, 128.9, 139.4, 171.1, 178.7.

5.5. Catalytic enantioselective PTC alkylations

*5.5.1. 1-(1,1-Dimethylethyl)-5-methyl-N-(diphenylmethylene)-(4E)-(1,1,1-trifluoro ethylidene)-L-glutamate [(S)-**3a**]*

Fluorinated allylic acetate **1a** (1 mmol, 1 equiv. in 1 mL CH_2Cl_2) was added dropwise at −78 °C to a mixture of the benzophenone imine of glycine *tert*-butyl ester (**2**) (1 mmol, 1 equiv.), *O*-allyl-*N*-(9-anthracenylmethyl) cinchonidium bromide (0.1 mmol, 0.1 equiv.) and $CsOH{\cdot}H_2O$ (10 mmol, 10 equiv.) in CH_2Cl_2 (3 mL). The reaction mixture was stirred vigorously in a cryobath for 48 h. The suspension was diluted with ether, washed with water, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography (silica, hexanes:ethyl acetate; 9:1, v/v) afforded the desired 4-(trifluoroethylidenyl) glutamic acid

derivative (*S*)-**3a**, which was identical with analytical data listed previously for (±)-**3a**.(66% yield and 42% ee.): Chiral HPLC conditions: column, (*S*,*S*)-Whelk-O1; solvent, hexanes:2-propanol, 95:5, v/v; flow rate, 1.0 mL/min; λ = 254, retention times, t_R = 13.97 (minor) 19.97 (major) min.

*5.5.2. 1-(1,1-Dimethylethyl)-5-methyl-N-(diphenylmethylene)-(4E)-(2,3,4,5,6-pentafluorophenyl methylene)-L-glutamate [(S)-**3b**]*

Fluorinated allylic acetate **1b** (1 mmol, 1 equiv. in 1 mL CH_2Cl_2) was added dropwise at −78 °C to a mixture of the benzophenone imine of glycine *tert*-butyl ester (**2**) (1 mmol, 1 equiv.), *O*-allyl-*N*-(9-anthracenylmethyl) cinchonidium bromide (0.1 mmol, 0.1 equiv.) and $CsOH{\cdot}H_2O$ (10 mmol, 10 equiv.) in CH_2Cl_2 (3 mL). The reaction mixture was stirred vigorously in a cryobath for 36 h. The suspension was diluted with ether, washed with water, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography (silica, hexane:ethyl acetate; 9:1, v/v) afforded the desired 4-(2,3,4,5,6-pentafluorobenzylidenyl) glutamic acid derivative (*S*)-**3b**, which was identical with analytical data listed previously for (±)-**3b**.(88% yield and 45% ee.): Chiral HPLC conditions: column, (*S*,*S*)-Whelk-O1; solvent, hexanes:2-propanol, 95:5, v/v; flow rate, 1.0 mL/min; λ = 254, retention times, t_R = 10.09 (minor) 13.33 (major) min.

*5.5.3. 1-(1,1-Dimethylethyl)-5-methyl-N-(diphenylmethylene)-(4E)-(2,6-difluorophenyl methylene)-L-glutamate [(S)-**3i**]*

Fluorinated allylic acetate **1i** (1 mmol, 1 equiv. in 1 mL CH_2Cl_2) was added dropwise at −78 °C to a mixture of the benzophenone imine of glycine *tert*-butyl ester (**2**) (1 mmol, 1 equiv.), *O*-allyl-*N*-(9-nthracenylmethyl) cinchonidium bromide (0.1 mmol, 0.1 equiv.) and $CsOH{\cdot}H_2O$ (10 mmol, 10 equiv.) in CH_2Cl_2 (3 mL). The reaction mixture was stirred vigorously in a cryobath for 48 h. The suspension was diluted with ether, washed with water, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by flash chromatography (silica, hexane:ethyl acetate; 9:1, v/v) afforded the desired 4-(2,6-difluorobenzylidenyl) glutamic acid derivative (*S*)-**3i**, which was identical with analytical data listed previously for (±)-**3i**.(68% yield and 80% ee.): Chiral HPLC conditions: column, (*S*,*S*)-Whelk-O1; solvent, hexanes:2-propanol, 95:5 (v/v); flow rate, 1.0 mL/min; λ = 254, retention times, t_R = 11.24 (major) 13.18 (minor) min.

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