# Highly Diastereoselective Synthesis of Chimeras of Proline and Glutamate



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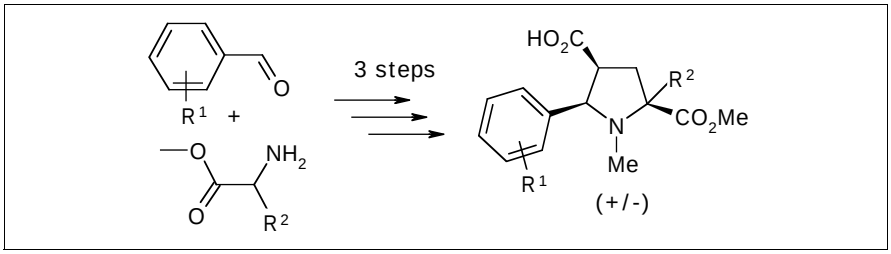


Azomethine ylides have been generated from aromatic aldimines of α-amino acid methyl esters under treatment with LiBr/$Et_3N$ and trapped with *tert*-butyl acrylate yielding racemic orthogonally protected *cis*-5-arylpyrrolidine-2,4-dicarboxylates regio- and stereo-selectively in high yields. Subsequent *N*-methylation and deprotection of 4-carboxylic group of cycloaddition products led to novel proline-glutamate *cis*-chimeras with substituents at 2 and 5 positions of pyrrolidine scaffold.

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## Introduction.

Combination of two amino acids fragments in one scaffold, typically conformationally constrained, is an actively used approach to non-proteinogenic α-amino acids and subsequent construction of peptidomimetics. Pyrrolidine 2,4-dicarboxylic acid (**1**) contains structural features of proline and glutamic acid, and can be considered as a chimera of these two proteinogenic α-amino acids. *trans*-Isomer of **1** was isolated from the seeds of *Afzelia bella* [1] and a potent competitive inhibition of glutamate transport was demonstrated for this compound [2]. Both *cis*- and *trans*-isomers of **1** have been used for synthesis of conformationally restricted glutathione analogues [3]. Bulky substituent in 5-position of proline ring influences on *cis*-/*trans*-population of a peptide bond formed by nitrogen atom of proline [4]. From other side aryl substituent in 5-position improves pharmacological properties of proline derivatives, namely mercaptoacyl 5-phenyl proline (**2**) was identified as 3-fold more active than captopril in inhibition of angiotensin converting enzyme (ACE) [5]. The insertion of a phenyl group to the 5-position of proline in a series of 2-mercapto-3-phenylpropanoyl-Gly-(5-Ph)-Pro compounds led to discovery of very potent orally active dual inhibitor **3** of neutral endopeptidase (NEP) and ACE endowed with a long duration of action [6]. During our discovery program there were needed *cis*-pyrrolidine-2,4-dicarboxylates (**4**) with diverse aryl substituents in 5-position. Additional diversity points were designed at 2- and 4-positions of pyrrolidine ring by insertion of $R^2$-substituent and stepwise modification of orthogonally protected carboxylic functions. *cis*-5-Arylpyrrolidine-2,4-dicarboxylates (**4**) have been planned to use as building blocks for construction of appropriate libraries and subsequent high throughput screening [7]. This purpose prompted us to develop stereoselective, scalable and effective approach to pyrrolidine-glutamate chimeras **4** and the results of synthetic efforts towards the goal are presented here.

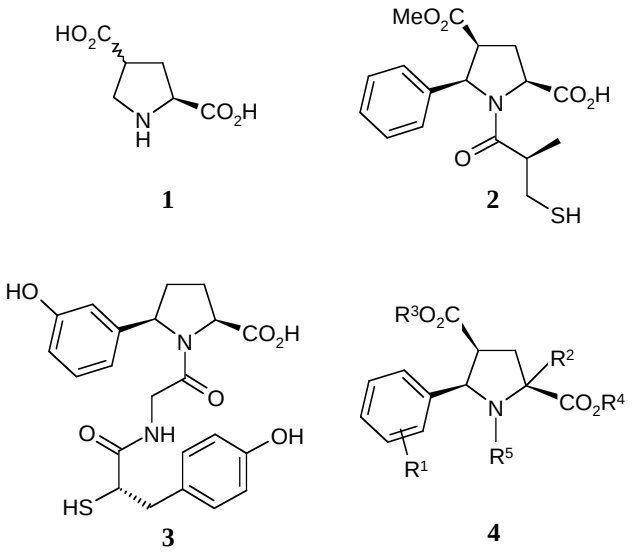



Figure 1. Structural formula of proline-glutamate chimeras and 5-aryl-prolines discussed in the introduction.

Table 1

Substituents in synthesized compounds.

| *compound* | $R^1$ | $R^2$ | *compound* | $R^1$ | $R^2$ |
|---|---|---|---|---|---|
| **a** | 2-F | H | **g** | 2-Cl | Me |
| **b** | 2,3-diF | H | **h** | 4-Cl | Me |
| **c** | 2-F-5-MeO | H | **i** | 4-MeO | Et |
| **d** | 3-Cl | H | **j** | 4-F | Et |
| **e** | H | Me | **k** | 3-pyridyl | *i*-Bu |
| **f** | 2-Me | Me | | | |

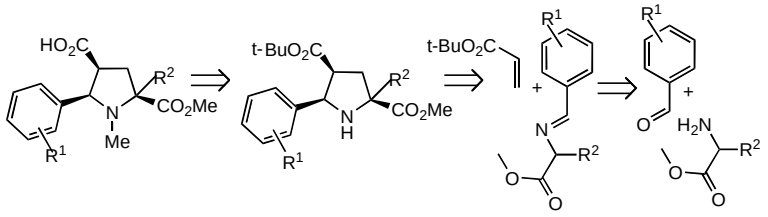
Results and Discussion.

The most satisfactory conditions for conducting the synthesis of compounds **4** were found to be those favored by Tsuge [8,9] and Grigg [10,11]. Both groups extensively studied 1,3-cycloaddition of electron-deficient olefins to metallo-azomethine ylides generated from α-amino acid esters Schiff bases.

majority of recent published methods of similar diversity-oriented cycloadditions [13,14]. Lithium bromide is also typical reagent for metallo-1,3-dipole generation, but in many cases cycloaddition is accompanied with Michael addition products [10]. Nevertheless we have tried to apply lithium bromide on the basis of it lower cost for production of *N*-metalated azomethine ylides **6** and succeeded in isolation of orthogonally protected prolines **7** in 80-97% yield as single stereoisomers (Table 1, Scheme 2).

Stereochemistry of synthesized racemates **7** is a result of regio- and stereo-selective *endo*-cycloaddition process controlled by lithium chelation of both *syn* dipole **6** and *tert*-butyl acrylate (Scheme 2) and has been assigned by $^1$H NMR spectroscopy. The cone anisotropy effect of the phenyl ring at C-5 causes a characteristic upfield shift on the protons of substituents at C-4 that are *cis* with regard to that phenyl group. For example, the proton signals of the

Scheme 1



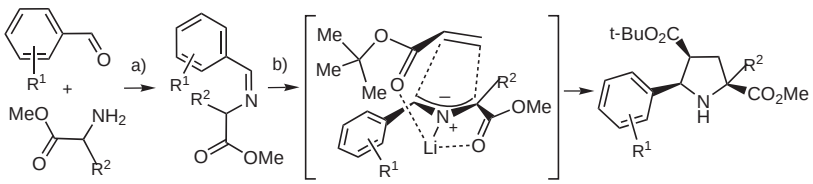

Retrosynthesis of orthogonally protected *N*-methyl-5-arylpyrrolidine-2,4-dicarboxylates.

Since we aimed to have orthogonally protected carboxylic functions and methylated nitrogen atom [12] at the pyrrolidine scaffold **4** the retrosynthetic Scheme 1 was developed. It is based on cycloaddition of *tert*-butyl acrylate with 1,3-dipole generated from iminoester obtained in its turn from benzaldehyde and α-amino acid methyl ester.

Required iminoesters **5** were readily obtained from substituted benzaldehydes and methyl esters of glycine, alanine, 2-aminobutyric acid, leucine under dehydrating conditions (Scheme 2). Silver (I) salts were used in the

*tert*-butoxycarbonyl group at C-4 in compounds **7** appear around 1.0 ppm. This value is 0.4 ppm more shielded than that of the *tert*-butoxycarbonyl groups protons in *tert*-butyl esters of aliphatic carboxylic acids (typically at 1.4 ppm). This effect is also observed in the protons of the methyl group at C-4 of similar pyrrolidine-2,4-dicarboxylates [8,15]. It is worth to note that 1,3-dipolar cycloaddition occurs with sterically hindered imine **5k** ($R^2$=*i*-Bu) under the general used conditions while the cycloaddition of iminoester with $R^2$=*i*-Pr is reported to take place only under treatment with stronger base DBU [8].

Scheme 2

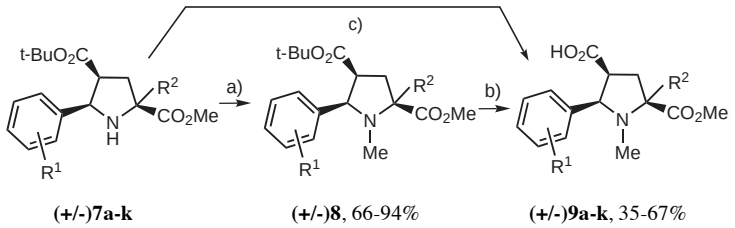



**5a-k**, 90-98% **6** **(+/-)7a-k**, 80-97%

Reaction conditions: a) $MgSO_4$, $Et_3N$, $CH_2Cl_2$, rt; b) t-Bu acrylate, LiBr, $Et_3N$, THF, rt.

Two approaches were used for subsequent *N*-methylation and appropriate deprotection of 4-carboxylic function in pyrrolidine-2,4-dicarboxylates (**7**). The first is a two-step consequent alkylation - acidic cleavage of *tert*-butyl ester procedure (Scheme 3, steps *a* and *b*). It works quite acceptable for simple 5-aryl substituents (2-F-phenyl (**a**), phenyl (**e**)) but in the case of 3-pyridyl substituent (compound **7k**) the quaternization of heteroaromatic nitrogen was the only observed process under $CH_3I$ treatment. This problem has been overcome with reductive methylation of pyrrolidine **7k** using formaldehyde and formic acid (Scheme 3, step *c*) resulted in formation of nicotine analog **9k**. The same procedure was applied for compounds **7b-d**, **f-j** and *N*-methyl-pyrrolidine-2,4-dicarboxylates (**9b-d**, **f-j**) were isolated in 35-65% yield that is comparable with 35-50% combined yield for two-step procedure.

Scheme 3




**(+/-)7a-k** **(+/-)8**, 66-94% **(+/-)9a-k**, 35-67%

Reaction conditions: a) $CH_3I$, DMF, rt; b) HCl, $CH_2Cl_2$, rt; c) $HCO_2H$, HCOH, reflux.

One of the marked features of compounds **9** is a big magnitude of $^3J_{(H4\text{-}H5)}$ coupling constant according $^1H$ NMR experiments – 10.0-10.5 Hz. To undoubtedly establish stereochemistry of amino acids **9** X-ray analysis of dicarboxylate **9b** has been done [16]. In the molecule **9b**, all bond lengths lie in the ordinary ranges for organic compounds. In crystal, two enantiomeric molecules related by symmetry centre are combined into hydrogen-bonded dimeric units (figure 2).

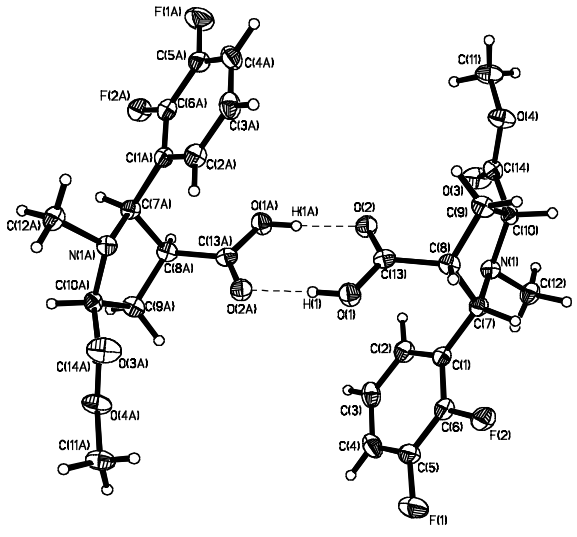



Figure 2. Hydrogen – bonded dimers in the crystal structure of **9b**. O(1)-H(1) 0.90(2), H(1)…O(2A) 1.76(2), O(1)…O(2A) 2.657(1) Å; O(1)-H(1)...O(2A) 177(2)°

In conclusion, an effective method of synthesis of *N*-methyl-*cis*-5-arylpyrrolidine-2,4-dicarboxylates (**9**) based on 1,3-dipolar cycloaddition was developed. Different protection of carboxylic functionalities in chimeras **7** and **9** allows their subsequent independent transformations.

## EXPERIMENTAL

Melting points are uncorrected. $^1H$ NMR spectra were recorded on a Bruker AMX-400 spectrometer in dimethyl sulfoxide-$d_6$ solutions. Chemical shifts (δ, ppm) were referenced to dimethyl sulfoxide-$d_5$ signal ($\delta_H$ = 2.50 ppm) and coupling constants (J) are indicated in Hz.

General Procedure for the Synthesis of Iminoesters **5** [14].

Under inert atmosphere corresponding benzaldehyde (1.0 eq) was added to a suspension of amino acid methyl ester hydrochloride (1.1 eq), $MgSO_4$ (2.0 eq), and $NEt_3$ (1.1 eq) in $CH_2Cl_2$. Resulted mixture was stirred at rt overnight. The solid was removed by filtration and the filtrate was washed once with $H_2O$. The aqueous phase was extracted once with $CH_2Cl_2$ and the combined organic layers were washed with brine. The organic phase was dried over $Na_2SO_4$, filtered and concentrated. Products were sufficiently pure by $^1H$ NMR and used in the next step without additional purification.

General Procedure for the Cycloaddition Reactions of *tert*-Butyl acrylate with Aldimines **5**.

Solution of 4.18 g (48.0 mmol) of LiBr in dry THF (16 ml) was added dropwise to the stirred mixture of 5.10 ml (35.2 mmol) of *tert*-butyl acrylate, 32 mmol of aldimine **5** and 54 ml of dry THF under inert atmosphere. After cooling to 5°C 5.40 ml (38.4 mmol) of $Et_3N$ were added dropwise with the rate not allowing the reaction temperature exceed 20°C. The mixture was stirred at rt 24 h. The reaction was quenched by addition of a saturated aqueous solution of $NH_4Cl$ (60 ml) and extracted with $Et_2O$ (3 x 40 ml). The combined organic layers were washed with brine, dried over $Na_2SO_4$, and the solvent was evaporated.

The crude products were purified by column chromatography on silica gel using hexane/AcOEt as an eluent.

(2*S**,4*S**,5*R**)-5-(2-Fluorophenyl)pyrrolidine-2,4-dicarboxylic acid 4-*tert*-butyl ester 2-methyl ester (**7a**).

This compound was obtained as a white solid, mp 53°C. Yield 93%. $^1$H NMR: δ 0.96 (s, 9H, t-$C_4H_9$); 2.15-2.23 (m, 1H, H-3); 2.26-2.34 (m, 1H, H-3); 3.23 (dd, 1H, J 14.9, 7.1, H-4); 3.70 (s, 3H, $COOCH_3$); 3.86 (dd, 1H, J 7.6, 7.6, H-2); 4.63 (m, 1H, H-5); 7.09-7.18 (m, 2H, Ar); 7.30 (dddd, 1H, J 13.5, 7.6, 5.4, 1.7, Ar); 7.51 (ddd, 1H, J 7.6, 1.7, 1.7, Ar).

*Anal.* Calcd for $C_{17}H_{22}FNO_4$: C, 63.14; H, 6.86; N, 4.33. Found: C, 62.95; H, 6.80; N, 4.24.

(2*S**,4*S**,5*R**)-5-(2,3-Difluorophenyl)pyrrolidine-2,4-dicarboxylic acid 4-*tert*-butyl ester 2-methyl ester (**7b**).

This compound was obtained as a white solid, mp 89°C. Yield 92%. $^1$H NMR: δ 1.00 (s, 9H, t-$C_4H_9$); 2.16-2.33 (m, 2H, H-3); 3.25-3.31 (m, 1H, H-4); 3.69 (s, 3H, $COOCH_3$); 3.82-3.91 (m, 1H, H-2); 4.71 (dd, J 7.6, 7.6, 1H, H-5); 7.13-7.20 (m, 1H, Ar); 7.26-7.33 (m, 1H, Ar); 7.33-7.39 (m, 1H, Ar).

*Anal.* Calcd for $C_{17}H_{21}F_2NO_4$: C, 59.82; H, 6.20; N, 4.10. Found: C, 59.59; H, 6.12; N, 4.20.

(2*S**,4*S**,5*R**)-5-(2-Fluoro-5-methoxyphenyl)pyrrolidine-2,4-dicarboxylic acid 4-*tert*-butyl ester 2-methyl ester (**7c**).

This compound was obtained as a white solid, mp 62-63°C. Yield 80%. $^1$H NMR: δ 1.00 (s, 9H, t-$C_4H_9$); 2.14-2.31 (m, 2H, H-3); 3.20 (ddd, J 8.3, 8.3, 8.3, 1H, H-4); 3.69 (s 3H, $ArOCH_3$); 3.71 (s, 3H, $COOCH_3$); 3.85 (dd, J 8.5, 8.5, 1H, H-2); 4.63 (d, J 8.3, 1H, H-5); 6.81 (ddd, J 8.8, 3.3, 3.3, 1H, Ar); 7.00-7.11 (m, 2H, Ar).

*Anal.* Calcd for $C_{18}H_{24}FNO_5$: C, 61.18; H, 6.85; N, 3.96. Found: C, 60.90; H, 6.85; N, 3.89.

(2*S**,4*S**,5*R**)-5-(3-Chlorophenyl)pyrrolidine-2,4-dicarboxylic acid 4-*tert*-butyl ester 2-methyl ester (**7d**).

This compound was obtained as an oil. Yield 95%. $^1$H NMR: δ 1.02 (s, 9H, t-$C_4H_9$); 2.13-2.29 (m, 2H, H-3); 3.22 (ddd, J 7.8, 7.8, 8.6, 1H, H-4); 3.27 (s, 1H, NH); 3.69 (s, 3H, $COOCH_3$); 3.86 (dd, J 8.3, 8.3, 1H, H-2); 4.46 (d, J 8.6, 1H, H-5); 7.26-7.32 (m, 3H, Ar); 7.39-7.41 (m, 1H, Ar).

*Anal.* Calcd for $C_{17}H_{22}ClNO_4$: C, 60.09; H, 6.53; N, 4.12. Found: C, 60.30; H, 6.65; N, 4.00.

(2*S**,4*S**,5*R**)-2-Methyl-5-phenylpyrrolidine-2,4-dicarboxylic acid 4-*tert*-butyl ester 2-methyl ester (**7e**).

This compound was obtained as a white solid, mp 50-52°C. Yield 85%. $^1$H NMR: δ 0.96 (s, 9H, t-$C_4H_9$); 1.38 (s, 3H, $CH_3$); 1.97 (dd, 1H, J 13.1, 7.8, H-3); 2.47-2.55 (m, 1H, H-3); 3.30-3.37 (m, 1H, H-4); 3.71 (s, 3H, $COOCH_3$); 4.59 (d, 1H, J 8.3, H-5); 7.19-7.26 (m, 1H, Ar); 7.27-7.32 (m, 4H, Ar).

*Anal.* Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.80; H, 7.95; N, 4.59.

(2*S**,4*S**,5*R**)-2-Methyl-5-*o*-tolylpyrrolidine-2,4-dicarboxylic acid 4-*tert*-butyl ester 2-methyl ester (**7f**).

This compound was obtained as a white solid, mp 115-116°C. Yield 89%. $^1$H NMR: δ 0.89 (s, 9H, t-$C_4H_9$); 1.39 (s, 3H, $CH_3$); 1.97 (dd, J 13.0, 8.3, 1H, H-3); 2.34 (s, 3H, $ArCH_3$); 2.51-2.55 (m; 1H, H-3); 2.99 (br s, 1H, NH); 3.35-3.41 (m, 1H, H-4); 3.71 (s, 3H, $COOCH_3$); 4.75 (d, J 8.5, 1H, H-5); 7.06-7.15 (m, 3H, Ar); 7.33-7.39 (m, 1H, Ar).

*Anal.* Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.19; H, 8.20; N, 4.39.

(2*S**,4*S**,5*R**)-5-(2-Chlorophenyl)-2-methylpyrrolidine-2,4-dicarboxylic acid 4-*tert*-butyl ester 2-methyl ester (**7g**).

This compound was obtained as a white solid, mp 102-104°C. Yield 87%. $^1$H NMR: δ 0.93 (s, 9H, t-$C_4H_9$); 1.38 (s, 3H, $CH_3$); 1.96 (dd, J 13.1, 8.3, 1H, H-3); 2.59 (dd; J 13.1, 6.1, 1H, H-3); 3.14 (br s, 1H, NH); 3.44 (ddd, J 8.3, 8.3, 6.1, 1H, H-4); 3.69 (s, 3H, $COOCH_3$); 4.91 (d, J 8.3, 1H, H-5); 7.22-7.32 (m, 2H, Ar); 7.38 (dd, J 7.5, 1.8, 1H, Ar); 7.59 (dd, J 7.5, 1.8, 1H, Ar).

*Anal.* Calcd for $C_{18}H_{24}ClNO_4$: C, 61.10; H, 6.84; N, 3.96. Found: C, 61.29; H, 6.90; N, 4.09.

(2*S**,4*S**,5*R**)-5-(4-Chlorophenyl)-2-methylpyrrolidine-2,4-dicarboxylic acid 4-*tert*-butyl ester 2-methyl ester (**7h**).

This compound was obtained as a white solid, mp 110-111°C. Yield 97%. $^1$H NMR: δ 0.98 (s, 9H, t-$C_4H_9$); 1.35 (s, 3H, $CH_3$); 1.91 (dd, J 13.1, 7.8, 1H, H-3); 2.44-2.54 (m; 1H, H-3); 3.13 (br s, 1H, NH); 3.25-3.36 (m, 1H, H-4); 3.68 (s, 3H, $COOCH_3$); 4.60 (d, J 8.8, 1H, H-5); 7.27-7.38 (m, 4H, Ar).

*Anal.* Calcd for $C_{18}H_{24}ClNO_4$: C, 61.10; H, 6.84; N, 3.96. Found: C, 61.25; H, 6.80; N, 4.19.

(2*S**,4*S**,5*R**)-2-Ethyl-5-(4-methoxyphenyl)pyrrolidine-2,4-dicarboxylic acid 4-*tert*-butyl ester 2-methyl ester (**7i**).

This compound was obtained as an oil. Yield 97%. $^1$H NMR: δ 0.79 (t, J 7.3, 3H, $CH_2CH_3$); 1.00 (s, 9H, t-$C_4H_9$); 1.57-1.77 (m, 2H, $CH_2CH_3$); 1.98 (dd, J 13.5, 7.8, 1H, H-3); 2.43 (dd, J 13.5, 5.6, 1H, H-3); 2.95 (d, J 9.5, 1H, NH); 3.20 (ddd, J 7.8, 7.8, 5.6, 1H, H-4); 3.71 (s, 3H, $COOCH_3$); 3.72 (s, 3H, $ArOCH_3$); 4.43 (dd, J 9.5, 7.8, 1H, H-5); 6.87 (d, J 8.6, 2H, Ar); 7.18 (d, J 8.6, 2H, Ar).

*Anal.* Calcd for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04; N, 3.85. Found: C, 65.95; H, 8.00; N, 3.70.

(2*S**,4*S**,5*R**)-2-Ethyl-5-(4-fluorophenyl)pyrrolidine-2,4-dicarboxylic acid 4-*tert*-butyl ester 2-methyl ester (**7j**).

This compound was obtained as a white solid, mp 39°C. Yield 95%. $^1$H NMR: δ 0.80 (t, J 7.3, 3H, $CH_2CH_3$); 1.00 (s, 9H, t-$C_4H_9$); 1.59-1.78 (m, 2H, $CH_2CH_3$); 1.99 (dd, J 13.5, 7.8, 1H, H-3); 2.45 (dd, J 13.5, 5.7, 1H, H-3); 3.04 (br s, 1H, NH); 3.24 (ddd, J 7.8, 7.8, 5.7, 1H, H-4); 3.70 (s, 3H, $COOCH_3$); 4.51 (m, 1H, H-5); 7.10-7.16 (m, 2H, Ar); 7.28-7.35 (m, 2H, Ar).

*Anal.* Calcd for $C_{19}H_{26}FNO_4$: C, 64.94; H, 7.46; N, 3.99. Found: C, 65.05; H, 7.58; N, 3.79.

(2*S**,4*S**,5*R**)-2-Isobutyl-5-pyridin-3-yl-pyrrolidine-2,4-dicarboxylic acid 4-*tert*-butyl ester 2-methyl ester (**7k**).

This compound was obtained as an oil. Yield 92%. $^1$H NMR: δ 0.83 (d, 3H, J 6.4, $CH_2CH(CH_3)_2$); 0.91 (d, 3H, J 6.4, $CH_2CH(CH_3)_2$); 0.99 (s, 9H, t-$C_4H_9$); 1.61-1.81 (m, 3H, $CH_2CH(CH_3)_2$; 2.05 (dd, 1H, J 13.2, 7.8, H-3); 2.45 (dd, 1H, J 13.2, 6.4, H-3); 3.36 (ddd, 1H, J 7.8, 7.8, 6.4, H-4); 3.73 (s, 3H, $COOCH_3$); 4.60 (m, 1H, H-5); 7.37 (dd, 1H, J 7.8, 4.9, Ar); 7.69 (ddd, 1H, J 7.8, 1.7, 1.7, Ar); 8.46 (dd, 1H, J 4.9, 1.7, Ar); 8.52 (d, 1H, 1.7, Ar).

*Anal.* Calcd for $C_{20}H_{30}N_2O_4$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.18; H, 8.30; N, 7.90.

General Procedure for *N*-Methylation of Compounds **7** with $CH_3I$.

$CH_3I$ (0.38 ml, 6.1 mmol) was added dropwise to the mixture of 4.1 mmol of **7**, 2.31 g (18.3 mmol) of $K_2CO_3$ and 17 ml of dry DMF. The mixture was stirred 24 h at rt. The solid was removed by filtration and the filtrate was concentrated in vacuum. Chromatography of the residue on silica gel using hexane/AcOEt as an eluent afforded pure product **8**.

(2*S**,4*S**,5*R**)-5-(2-Fluorophenyl)-1-methylpyrrolidine-2,4-dicarboxylic acid 4-*tert*-butyl ester 2-methyl ester (**8a**).

This compound was obtained as an oil. Yield 94%. $^1$H NMR: δ 0.93 (s, 9H, t-$C_4H_9$); 2.13 (s, 3H, N-$CH_3$); 2.18-2.37 (m, 2H, H-3); 3.20-3.35 (m, 2H, H-2, H-4); 3.70 (s, 3H, $COOCH_3$); 4.09 (d, 1H, J 10.0, H-5); 7.07-7.22 (m, 2H, Ar); 7.24-7.35 (m, 1H, Ar); 7.47(ddd, 1H, J 7.6, 7.6, 1.0, Ar).

*Anal*. Calcd for $C_{18}H_{24}FNO_4$: C, 64.08; H, 7.17; N, 4.15. Found: C, 63.96; H, 7.20; N, 4.30.

(2*S**,4*S**,5*R**)-1,2-Dimethyl-5-phenylpyrrolidine-2,4-dicarboxylic acid 4-*tert*-butyl ester 2-methyl ester (**8e**).

This compound was obtained as an oil. Yield 66%. $^1$H NMR: δ 0.90 (s, 9H, t-$C_4H_9$); 1.25 (s, 3H, $CH_3$); 1.87 (dd, 1H, J 12.0, 7.9, H-3); 2.03 (s, 3H, N-$CH_3$); 2.59 (dd, 1H, J 12.0, 12.0, H-3); 3.40 (ddd, 1H, J 10.7, 10.7, 7.9, H-4); 3.69 (s, 3H, $COOCH_3$); 3.95 (d, J 10.7, 1H, H-5); 7.15-7.34 (m, 5H, Ar).

*Anal*. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.66; H, 8.20; N, 4.37.

General Procedure for the Preparation of Compounds **9** from **8**.

4.0 mmol of corresponding compound **8** were dissolved in 50 ml of dry $CH_2Cl_2$. Dry HCl was passed through the solution during 1 h at 5°C. The mixture was stirred overnight at rt, washed with $H_2O$ (2 x 10 ml), 10% aqueous solution of $NaHCO_3$ (2 x 10 ml). Aqueous phases were extracted with $CH_2Cl_2$ (2 x 20 ml). The combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated. The residue was purified by column chromatography on silica gel using hexane/AcOEt as an eluent.

(2*S**,4*S**,5*R**)-5-(2-Fluorophenyl)-1-methylpyrrolidine-2,4-dicarboxylic acid 2-methyl ester (**9a**).

This compound was obtained as a white solid, mp 126°C. Yield 51%. $^1$H NMR: δ 2.15 (s, 3H, N-$CH_3$); 2.23-2.36 (m, 2H, H-3); 3.24-3.35 (m, 2H, H-4, H-2); 3.70 (s, 3H, $COOCH_3$); 4.11 (d, 1H, J 10.0, H-5); 7.09 (ddd, 1H, J 9.5, 8.3, 1.0, Ar); 7.15 (ddd, 1H, J 7.6, 7.6, 1.0, Ar); 7.23-7.30 (m, 1H, Ar); 7.50 (ddd, 1H, J 7.6, 7.6, 1.7, Ar); 11.80 (s, 1H, COOH).

*Anal*. Calcd for $C_{14}H_{16}FNO_4$: C, 59.78; H, 5.73; N, 4.98. Found: C, 60.01; H, 5.69; N, 4.79.

(2*S**,4*S**,5*R**)-1,2-Dimethyl-5-phenylpyrrolidine-2,4-dicarboxylic acid 2-methyl ester (**9e**).

This compound was obtained as a white solid, mp 156°C. Yield 50%. $^1$H NMR: δ 1.27 (s, 3H, $CH_3$); 1.89 (dd, 1H, J 11.7, 7.8, H-3); 2.06 (s, 3H, N-$CH_3$); 2.60 (dd, 1H, J 11.7, 11.7, H-3); 3.40 (ddd, 1H, J 10.5, 10.5, 7.8, H-4); 3.70 (s, 3H, $COOCH_3$); 3.99 (d, 1H, J 10.5, H-5); 7.16-7.29 (m, 3H, Ar); 7.31-7.35 (m, 2H, Ar); 11.72 (s, 1H, COOH).

*Anal*. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.78; H, 6.93; N, 5.25.

General One-step Procedure for the Preparation of Compounds **9** from **7**.

Corresponding compound **7** (36.0 mmol) was dissolved in 180 ml of 98% formic acid, 27 ml of 37% aqueous formaldehyde were added and reaction mixture was heated at 100°C during 30-40 min. After cooling to rt 150 ml of water were added and the mixture was neutralized with $Na_2CO_3$. Resulting mixture was extracted with $CHCl_3$ (5 x 70 ml). Organic extracts were dried over $Na_2SO_4$, and the solvent was evaporated. The crude products were purified by column chromatography on silica gel using hexane/AcOEt as an eluent.

(2*S**,4*S**,5*R**)-5-(2,3-Difluorophenyl)-1-methylpyrrolidine-2,4-dicarboxylic acid 2-methyl ester (**9b**).

This compound was obtained as a white solid, mp 140°C. Yield 40%. $^1$H NMR: δ 2.18 (s, 3H, N-$CH_3$); 2.24-2.33 (m, 2H, H-3); 3.29-3.40 (m, 2H, H-4, H-2); 3.70 (s, 3H, $COOCH_3$); 4.17 (d, J 10.0, 1H, H-5); 7.13-7.20 (m, 1H, Ar); 7.24-7.34 (m, 2H, Ar); 11.90 (s, 1H, COOH).

*Anal*. Calcd for $C_{14}H_{15}F_2NO_4$: C, 56.19; H, 5.05; N, 4.68. Found: C, 56.35; H, 5.10; N, 4.89.

(2*S**,4*S**,5*R**)-5-(2-Fluoro-5-methoxyphenyl)-1-methylpyrrolidine-2,4-dicarboxylic acid 2-methyl ester (**9c**).

This compound was obtained as a white solid, mp 95°C. Yield 46%. $^1$H NMR: δ 2.15 (s, 3H, N-$CH_3$); 2.27 (td, 2H, J 8.3, 4.0, H-3); 3.23-3.31 (m, 2H, H-4, H-2); 3.69 (s, 6H, $COOCH_3$, $ArOCH_3$); 4.06 (d, J 9.9, 1H, H-5); 6.79 (dt; J 8.8, 3.7, 1H, Ar); 6.98-7.05 (2H, m; Ar); 11.85 (br s, 1H, COOH).

*Anal*. Calcd for $C_{15}H_{18}FNO_5$: C, 57.87; H, 5.83; N, 4.50. Found: C, 57.99; H, 5.75; N, 4.71.

(2*S**,4*S**,5*R**)-5-(3-Chlorophenyl)-1-methylpyrrolidine-2,4-dicarboxylic acid 2-methyl ester (**9d**).

This compound was obtained as a white solid, mp 120-122°C. Yield 57%. $^1$H NMR: δ 2.15 (s, 3H, N-$CH_3$); 2.17-2.34 (m, 2H, H-3); 3.23-3.33 (m, 2H, H-4, H-2); 3.70 (s, 3H, $COOCH_3$); 3.85 (d, J 10.0, 1H, H-5); 7.26-7.33 (m, 3H, Ar); 7.38 (dd, J 1.7, 1.7, 1H, Ar).

*Anal*. Calcd for $C_{14}H_{16}ClNO_4$: C, 56.48; H, 5.42; N, 4.70. Found: C, 56.54; H, 5.46; N, 4.81.

(2*S**,4*S**,5*R**)-1,2-Dimethyl-5-*o*-tolylpyrrolidine-2,4-dicarboxylic acid 2-methyl ester (**9f**).

This compound was obtained as a white solid, mp 121-122°C. Yield 50%. $^1$H NMR: δ 1.28 (s, 3H, $CH_3$); 1.93 (dd, J 12.0, 8.1, 1H, H-3); 2.02 (s, 3H, N-$CH_3$); 2.33 (s, 3H, $ArCH_3$); 2.61 (dd, J 12.0, 10.3, 1H, H-3); 3.43 (ddd, J 10.3, 10.3, 8.1, 1H, H-4); 3.70 (s, 3H, $COOCH_3$); 4.22 (d, J 10.3, 1H, H-5); 7.03-7.14 (m, 3H, Ar); 7.50 (d, J 7.3, 1H, Ar).

*Anal*. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.70; H, 7.20; N, 5.03.

(2*S**,4*S**,5*R**)-5-(2-Chlorophenyl)-1,2-dimethylpyrrolidine-2,4-dicarboxylic acid 2-methyl ester (**9g**).

This compound was obtained as a white solid, mp 130-131°C. Yield 35%. $^1$H NMR: δ 1.30 (3H, s, $CH_3$); 1.97 (dd, J 12.2, 8.1, 1H, H-3); 2.06 (s, 3H, N-$CH_3$); 2.61 (dd, J 12.2, 9.8, 1H, H-3); 3.45 (td, J 10.0, 8.1, 1H, H-4); 3.70 (s, 3H, $COOCH_3$); 4.43 (d, J 10.0, 1H, H-5); 7.23 (ddd, J 7.6, 1.7, 1.7, 1H, Ar); 7.30 (ddd, J

7.6, 1.5, 1.5, 1H, Ar); 7.34 (dd, J 7.6, 1.5, 1H, Ar); 7.58 (dd, J 7.6, 1.7, 1H, Ar).

*Anal.* Calcd for $C_{15}H_{18}ClNO_4$: C, 57.79; H, 5.82; N, 4.49. Found: C, 57.85; H, 5.80; N, 4.30.

(2*S**,4*S**,5*R**)-5-(4-Chlorophenyl)-1,2-dimethylpyrrolidine-2,4-dicarboxylic acid 2-methyl ester (**9h**).

This compound was obtained as a white solid, mp 135-137°C. Yield 50%. $^1$H NMR: δ 1.27 (s, 3H, $CH_3$); 1.90 (dd, J 11.7, 7.8, 1H, H-3); 2.06 (s, 3H, N-$CH_3$); 2.56 (dd, J 11.7, 11.7, 1H, H-3); 3.41 (ddd, J 10.5, 10.5, 7.8, 1H, H-4); 3.70 (s, 3H, $COOCH_3$); 4.02 (d, J 10.5, 1H, H-5); 7.30-7.37 (m, 4H, Ar); 11.81 (br s, 1H, COOH).

*Anal.* Calcd for $C_{15}H_{18}ClNO_4$: C, 57.79; H, 5.82; N, 4.49. Found: C, 57.77; H, 5.70; N, 4.32.

(2*S**,4*S**,5*R**)-2-Ethyl-5-(4-methoxyphenyl)-1-methylpyrrolidine-2,4-dicarboxylic acid 2-methyl ester (**9i**).

This compound was obtained as a white solid, mp 94-95°C. Yield 36%. $^1$H NMR: δ 0.84 (t, J 7.3, 3H, $CH_2CH_3$); 1.53 (ddd, J 7.3, 7.3, 7.3, 1H, $CH_2CH_3$); 1.92 (ddd J 7.3, 7.3, 7.3, 1H, $CH_2CH_3$); 2.00 (dd, J 12.5, 7.8, 1H, H-3); 2.17 (s, 3H, N-$CH_3$); 2.67 (dd, J 12.5, 12.5, 1H, H-3); 3.24-3.33 (m, 1H, H-4); 3.69 (s, 3H, $COOCH_3$); 3.71 (s, 3H, $ArOCH_3$); 4.01 (d, J 10.3, 1H, H-5); 6.81 (d, J 8.8, 2H, Ar); 7.18 (d, J 8.8, 2H, Ar); 11.69 (br s, 1H, COOH).

*Anal.* Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.66; H, 7.20; N, 4.57.

(2*S**,4*S**,5*R**)-2-Ethyl-5-(4-fluorophenyl)-1-methylpyrrolidine-2,4-dicarboxylic acid 2-methyl ester (**9j**).

This compound was obtained as a white solid, mp 123-125°C. Yield 67%. $^1$H NMR: δ 0.85 (t, J 7.3, 3H, $CH_2CH_3$); 1.50-1.60 (m, 1H, $CH_2CH_3$); 1.88-1.98 (m, 1H, $CH_2CH_3$); 2.02 (dd, J 13.0, 7.8, 1H, H-3); 2.18 (s, 3H, N-$CH_3$); 2.66 (dd, J 13.0, 10.8, 1H, H-3); 3.33 (ddd, J 10.8, 10.3, 7.8, 1H, H-4); 3.69 (s, 3H, $COOCH_3$); 4.09 (d, J 10.3, 1H, H-5); 7.04-7.10 (m, 2H, Ar); 7.29 (ddd, J 12.0, 5.4, 3.1, 2H, Ar); 11.78 (s, 1H, COOH).

*Anal.* Calcd for $C_{16}H_{20}FNO_4$: C, 62.13; H, 6.52; N, 4.53. Found: C, 62.31; H, 6.38; N, 4.54.

(2*S**,4*S**,5*R**)-2-Isobutyl-1-methyl-5-pyridin-3-yl-pyrrolidine-2,4-dicarboxylic acid 2-methyl ester (**9k**).

This compound was obtained as a white solid, mp 156°C. Yield 37%. $^1$H NMR: δ 0.81 (d, 3H, J 6.6, $CH_2CH(CH_3)_2$); 0.94 (d, 3H, J 6.6, $CH_2CH(CH_3)_2$); 1.43 (dd, 1H, J 13.0, 5.1, $CH_2CH(CH_3)_2$); 1.53-1.62 (m, 1H, $CH_2CH(CH_3)_2$); 1.78-1.87 (m, 2H, H-3, $CH_2CH(CH_3)_2$); 2.15 (s, 3H, N-$CH_3$); 2.73 (dd, 1H, J 12.7, 12.7, H-3); 3.04 (ddd, 1H, J 12.7, 10.5, 7.1, H-4); 3.66 (s, 3H, $COOCH_3$); 3.84 (d, 1H, J 10.5, H-5); 7.14 (dd, 1H, J 7.8, 4.7, Ar); 7.60 (ddd, 1H, J 7.8, 1.7, 1.7, Ar); 8.27 (dd, 1H, J 4.7, 1.7, Ar); 8.38 (d, 1H, J 1.7, Ar).

*Anal.* Calcd for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74. Found: C, 63.61; H, 7.48; N, 8.84.

Crystal Structure Determination of Compound **9b**.

The single crystal of **9b** of approximate dimensions 0.30 x 0.20 x 0.10 mm was mounted in inert oil on the top of glass fibre and transferred to a cold nitrogen stream on the Bruker SMART CCD diffractometer. Crystal data: $C_{14}H_{15}F_2N_1O_4$, M = 299.27, monoclinic, $a$ = 10.2002(7), $b$ = 10.9433(7), $c$ = 12.4771(8) Å, $\beta$ = 98.236(1)°, $V$ = 1378.38(16) Å$^3$, space group $P2_1/n$, $Z$ = 4, $D_c$ = 1.442 g/cm$^3$, $F(000)$ = 624, μ(Mo-Kα) = 0.123 mm$^{-1}$. Total of 8677 reflections (3318 unique, $R_{int}$ = 0.0247) were measured using graphite monochromatized Mo-Kα radiation (λ = 0.71073 Å) at 120.0(2) K. Data were collected in the range $2.42 < \theta < 28.00$ ($-8 \le h \le 13$, $-14 \le k \le 14$, $-16 \le l \le 14$). Omega scan mode with the step of 0.3 deg (15 sec. per step) was used. The structure was solved by direct methods [17] and refined by full matrix least-squares on $F^2$ [18] with anisotropic thermal parameters for all non-hydrogen atoms. All H atoms were found from difference Fourier syntheses and refined in an isotropic approximation. The final residuals were: $R_1$ = 0.0366, w$R_2$ = 0.0867 for 2621 reflections with $I > 2\sigma(I)$ and 0.0530, 0.0926 for all data and 250 parameters. Goof = 1.036, maximum Δρ = 0.314 e/Å$^3$.

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