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Stereoselective synthesis and preliminary evaluation of (+)- and (–)-3-methyl-5-carboxy-thien-2-yl-glycine (3-MATIDA): identification of (+)-3-MATIDA as a novel mGluR1 competitive antagonist

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Abstract

The synthesis of the (+)- and (–)-isomers of 3-methyl-5-carboxy-thyen-2-yl-glycine (3-MATIDA), heterocyle isosters of carboxyphenylglycines (CPGs), a known class of competitive metabotropic glutamate receptors, was accomplished by a stereoselective Ugi condensation. The two isomers were tested as potential rat mGluR1 ligand and the (+) isomer was found to be a moderately potent antagonist, while the (–) one was inactive.

1. Introduction

The heterogenous family of GTP-binding metabotropic glutamate receptors (mGluRs) is constituted by at least eight receptor subtypes named mGluR1 to mGluR8 plus additional spliced variants which are classified into three groups on the basis of sequence homology, coupling to intracellular systems, and agonist/antagonist pharmacology. Group I mGluRs, which contain mGluR1 and mGluR5 subtypes, are currently object of an intense research activity due to their involvement in processes leading to excitotoxic neuronal death after ischemia [1]. There is indeed a general agreement that stimulation of mGluR1 subtype contributes to the progression of neurotoxicity. Several cellular mechanisms have been involved in the mGluR1-mediated neurotoxicity: (i) the Src-mediated NMDA phosporylation (and thus enhanced NMDA function) in the absence of the NR2C subunit [2]; (ii) the increased concentration of intracellular Ca^{2+} resulting from both the positive coupling to ryanodine receptors (RyR)/L-type VOCC and the IP3-mediated internal mobilization [3]; (iii) the increased synaptic glutamate concentration resulting from either an increased PKC-stimulated glutamate release or by blocking of glutamate transporters [4]; (iv) the decreased presynaptic GABA release from interneurons [5]. Furthermore, the neurotoxicity associated to stimulation of mGluR1 is confirmed by the strong neuroprotective effects played by mGluR1 antagonists in a variety of model systems of ischemia [6–10]. Thus, the potential for the development of clinically useful agents associated with pharmacological control of mGluR1 functions is the rational basis for the interest in the design, synthesis and evaluation of mGluR1 selective and potent antagonists. Recent years have seen the discovery of modulatory sites on mGluRs and the identification of a number of structurally diverse classes of mGluR noncompetitive antagonists [11–14,27].

Although noncompetitive antagonists are receiving a considerable interest in view of the improved therapeutic opportunities associated with their modulatory activities, the design and the synthesis of competitive antagonists is still a

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productive research area aimed at fully understanding the structural requirements of the glutamate-binding pocket and at the development of useful pharmacological tools to be employed in the further characterization of this family of receptors. The class of carboxyphenylglycines (CPGs, Chart 1), first discovered by Eaton et al. [15] has constituted the reservoir of mGluR1 competitive antagonists. Thus, 4CPG (**1**), 4C3HPG (**2**) and M4CPG (**3**) are mGluR1 antagonists endowed with moderate potency and poor selectivity. The 2-methyl derivative of CPG (LY367385, **4**), however, is a potent and very selective mGluR1 antagonists.

Over the last few years we have engaged ourselves in a research program finalized at the definition of the structural requirements for mGluR1 antagonism, in search of potent and selective pharmacological tools [16–19]. Thus, the prototypic structure of 4CPG (**1**) was dissected into several features that were singularly analyzed in terms of their relevance for mGluR1 binding (Chart 2).

Structural elaborations, such as conformational rigidification (AIDA, **5**) [16], aromatic ring replacement (S-CBPG, **6**; ACUDA, **7**), [17,18] and distal carboxylate bioisosteric substitution (S-TBPG, **8**) [19], were therefore introduced and the

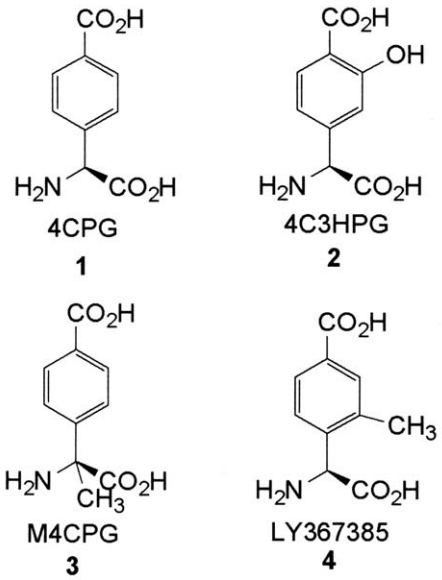


Chart 1. Representative mGluR1 competitive antagonists.

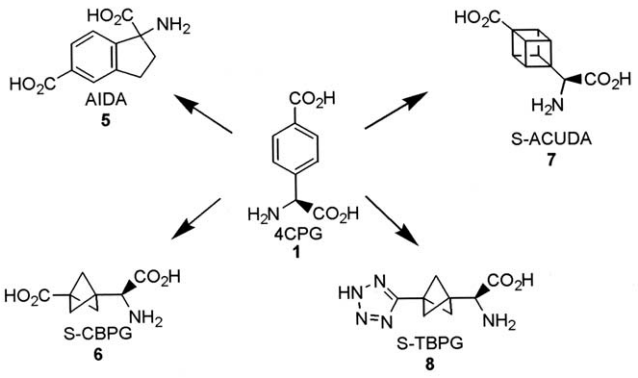


Chart 2. Structural elaborations leading to competitive mGluR1 antagonists.

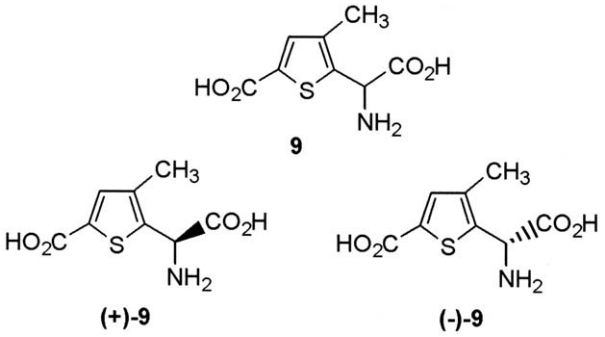


Chart 3. Thiophene derivatives as mGluR1 antagonists.

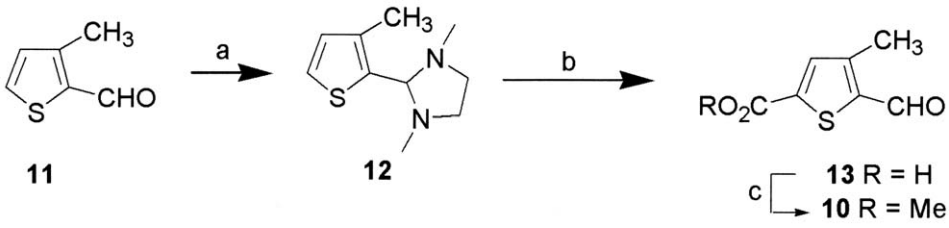
analysis of the activity data allowed for a clear delineation of the structural requirements for mGluR1 competitive antagonists. More recently, we have reported on the evaluation of thiophene analogs of CPG, some of which showed interesting activity as mGluR1 antagonists. In particular, the 3-methyl derivative of 5-carboxy-thien-2-yl-glycine (3-MATIDA, **9**, Chart 3) displayed remarkable potency and showed neuroprotective properties on in vivo models of brain ischemia [20].

Since 3-MATIDA (**9**) was originally prepared and tested as a racemic mixture, we decided to undertake the preparation and to evaluate the activity of the two individual enantiomers (+)- and (–)-3-MATIDA ((+)-**9** and (–)-**9**, respectively). The results are reported herein.

2. Chemistry

4-Methyl-5-formyl-2-thiophenecarboxylic acid methyl ester (**10**) was synthesized according to a reported method [21] as depicted in Scheme 1.

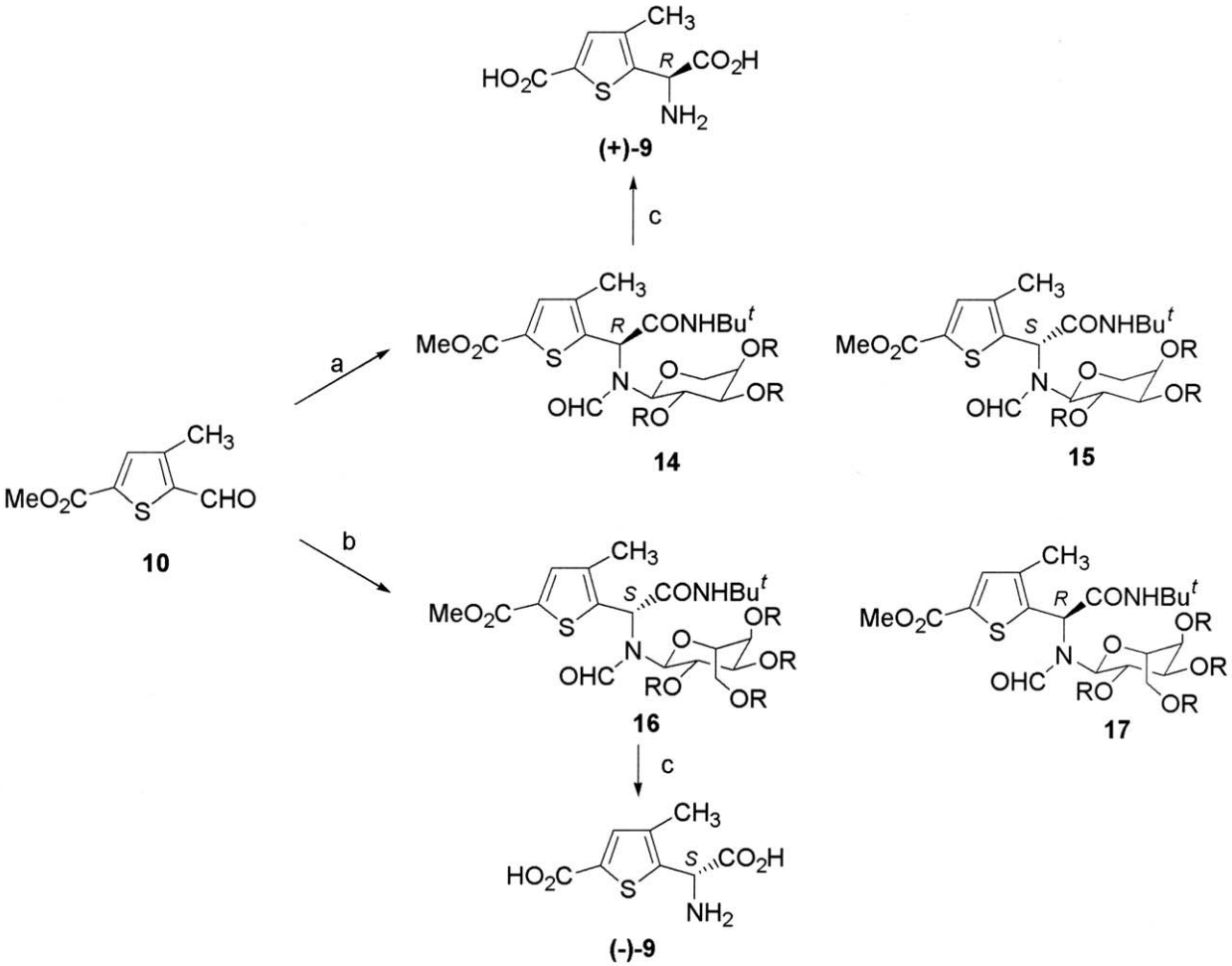
After protecting the aldehydic group of 3-methyl-2-thiophenecarboxaldehyde (**11**) by the corresponding *N,N'*-dimethylimidazolidine formation, *n*BuLi promoted lithiation at C-5 position, followed by carbonation and acidic hydrolysis, gave 4-methyl-5-formyl-2-thiophenecarboxylic acid (**13**). Acid-catalyzed esterification of **13** in methanol afforded the corresponding methyl ester **10**. Conversion of the aldehyde group into the α-aminoacidic moiety was initially accomplished through a diastereoselective Strecker reaction [22] due to our prior successful experience with this synthetic methodology, leading in this case to a racemic mixture of (±)-3-MATIDA (**9**). As analogous racemizations were not observed in our previous experiences [19,23,24] we envisaged that the presence of the sulfur-containing heteroaryl moiety could be responsible for the easier α-hydrogen abstraction from the imine generated during the removal of the chiral auxiliary under oxidative conditions. The stereoselective formation of α-aminoacid derivatives starting from an aldehyde can also be accomplished by the Ugi four-component condensation. The stereochemical control of the Ugi reaction by carbohydrate-derived amines [25] sounded attractive because circumvented the oxidative removal of the



Scheme 1

chiral auxiliary from the aminoacid derivatives. Thus, the reaction of the aldehyde **10** with 2,3,4-tri-*O*-pivaloyl-α-*D*-arabinopyranosylamine, [26] *tert*-butyl isocyanide and formic acid in the presence of zinc chloride in THF at –25 °C afforded the *N*-formyl-*N*-arabinosyl aminoacid amides **14** and **15** in a 32:1 diastereomeric ratio (HPLC) (Scheme 2).

The major amide **14**, expected to have an *R* configuration at the aminoacidic center according to the chiral induction, was purified by flash chromatography and submitted to a two-step hydrolysis. Treatment of the derivative **14** with hydrogen chloride/methanol resulted in the removal of the formyl group. Subsequent addition of water caused the smooth cleavage of the *N*-glycosidic bond. Final hydrolysis of the resulting amide was achieved with 6 N HCl at 80 °C. After purification on Amberlite IR 200 with 3% ammonium hydroxide the aminoacid (+)-**9** was obtained with a 73% enantiomeric excess (HPLC). To obtain the enantiomer (–)-**9** an analogous synthetic scheme was followed using in the Ugi reaction the commercial available 2,3,4,6-tetra-*O*-pivaloyl-β-*D*-galactopyranosylamine as chiral auxiliary because it is known that the asymmetric induction can be reversed using this amine in place of the 2,3,4-tri-*O*-pivaloyl-α-*D*-arabinopyranosylamine. Indeed, the reaction of the aldehyde **10** with the amine, *tert*-butyl isocyanide and formic acid in the presence of zinc chloride in THF at –25 °C afforded the *N*-formyl-*N*-galactosyl-aminoacid amides **16** and **17** in a 17:1 diastereomeric ratio (HPLC). The major diastereoisomer **16**, expected to be endowed with an *S* configuration at



Scheme 2

the aminoacidic center, was purified by flash chromatography and submitted to the hydrolysis protocol as described above to give the final (–)-**9** with a 75% enantiomeric excess.

3. Biology

The activity of the two isomers (+)- and (–)-3-MATIDA was evaluated on CHO cells permanently expressing rat mGluR1a, by measuring the variation in the concentration in intracellular calcium ([Ca2+]$_i$) caused by administration of the compounds [27]. Either (+)- or (–)-3-MATIDA ((+)-**9**, and (–)-**9**, respectively) were ineffective in stimulating mGluR1a when applied alone up to 500 μM (data not shown). When tested after administration of 10 μM glutamate, both isomers and the racemic mixture were able to decrease $[Ca^{2+}]_i$ in a dose-dependent manner. However, while the isomer (–)-**9** was only able to reach a 30% inhibition at the maximum tested concentration (500 μM) (Fig. 1), the (+)-**9** isomer at the same concentration completely abolished the glutamate-induced intracellular calcium mobilization with an IC_{50} = 54 μM (See Fig. 2a). The racemic compound had an intermediate behavior, being able to inhibit the glutamate response by a 50% at 500 μM (Fig. 1).

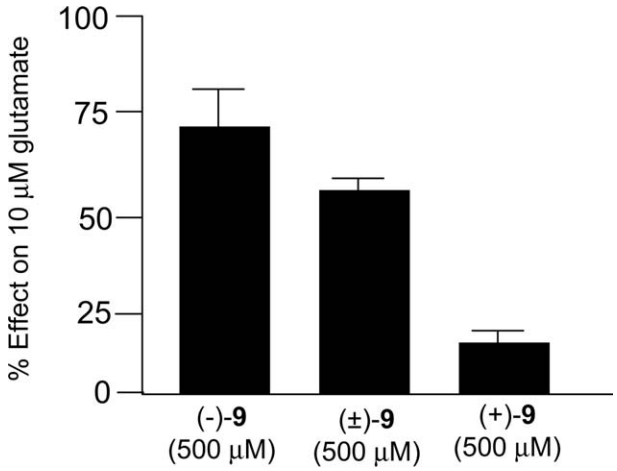


Fig. 1. Effect of 500 μM (–)-**9** and (+)-**9** and of the racemic mixture on rat mGluR1a stimulated by 10 μM glutamate.

For comparison purposes, we also evaluated the activity of LY367385 (**4**), a potent and subtype selective mGluR1 antagonist, on the same conditions. As it can be seen from Fig. 2b, **4** potently antagonized the effect of 10 μM glutamate, with an IC_{50} = 22 μM.

4. Discussion

The application of the Ugi's methodology has allowed us to prepare the two enantiomers of 3-MATIDA and to individually assess their activity in a $[Ca^{2+}]_i$-based assay on CHO cells expressing mGluR1a. As it was expected, antagonist activity only resides in an individual isomer, (+)-**9** thus confirming the stereopreference of the glutamate-binding pocket of mGluR1. Although the data obtained with the $[Ca^{2+}]_i$ assay are not directly comparable with those obtained in the IP/DAG assay, some extension of the structure–activity relationship for mGluR1 antagonists can be done. The present result confirms the need for a co-planar disposition of the pharmacophoric moieties and indicates that the phenyl ring of CPGs can be substituted by a heterocycle ring. In this respect, our results point out the thienyl ring as a suitable bioisosteric replacer of the phenyl ring when employed in search for competitive mGluR1 antagonist. This observation is further confirmed by the notion that 2-methyl substitution parallels the analogous pattern on CPG derivatives. Indeed, (+)-**9**, although showing half of the potency of **4**, keeps a good potency as mGluR1 antagonist. An issue which will require further investigation is the attribution of the absolute configuration of the chiral center of the α-amino acidic center. It can be anticipated, however, that since all the competitive mGluR1 antagonists so far reported have an *L*-stereochemistry at the glycine moiety, there is no apparent

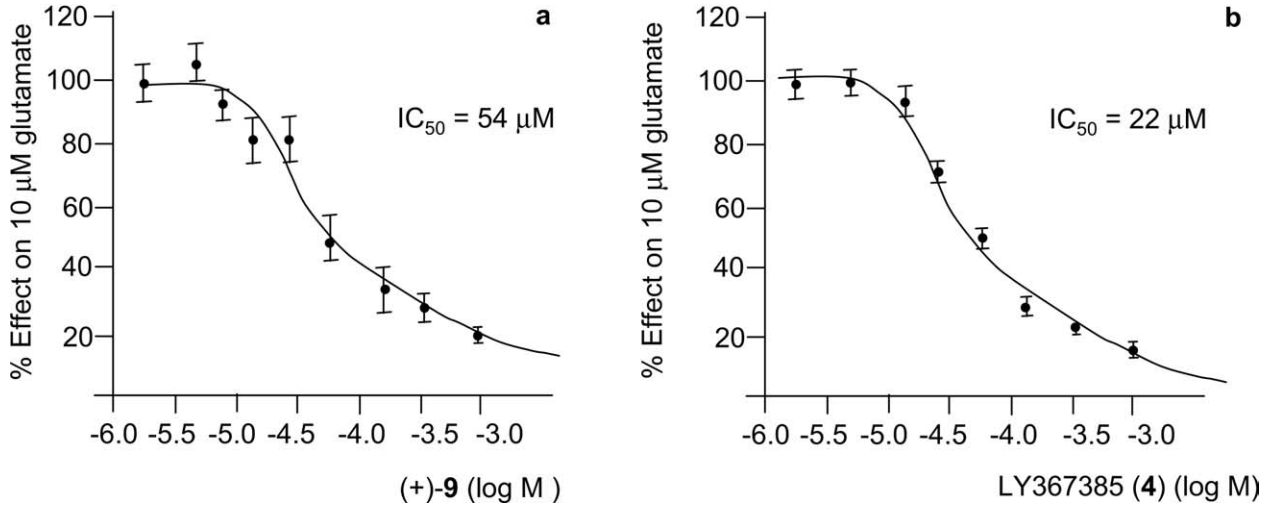


Fig. 2. (a). Dose–response curve for (+)-**9**.and (b) for **4**.

reasons for the novel derivative not to follow the same trend. (Note, however, that because of the presence of a sulfur atom in the 2 position, the *L*-isomer would be endowed with an *R* absolute configuration and not with an *S* one as in the case of CPGs.) Thus, the active isomer (+)-**9** can tentatively be attributed with the *R* configuration at the aminoacidic center, also in line with the expected chiral induction of the Ugi reaction.

In conclusion, the present results indicate (+)-3-MATIDA [(+)-**9**] as a fairly potent mGluR1a antagonist which can be used as a novel pharmacological tool for the study of metabotropic glutamate receptors.

5. Experimental

Melting points were determined with a Buchi 535 electrothermal apparatus and are uncorrected. NMR spectra were obtained with a Bruker AC 200 MHz spectrometer. The abbreviations used are as follows: s, singlet; bs, broad singlet; d, doublet; dd, double doublet and m, multiplet. TLC were carried out on pre-coated TLC plates with silica gel 60 F-254 (Merck). Flash column chromatography was performed on Merck silica gel 60 (0.040–0.063 mm).

*5.1. 1,3-Dimethyl-2-(3'-methyl-2'-thienyl)imidazolidine (**12**)*

A solution of 3-methyl-2-thiophenecarboxaldehyde (**11**) (25 g, 198.1 mmol) and *N,N'*-dimethylethylenediamine (199 mmol) in benzene (250 ml) was heated under reflux for 24 h with azeotropic removal of water. The solvent was removed in vacuo and the residue distilled under reduced pressure thus obtaining derivative **12** (33.8 g, 87% yield) as a colorless oil.

Boiling point: 90–100 °C at 0.37 mmHg; ^{1}H NMR ($CDCl_3$) δ: 2.20 (9H, bs, NCH_3 and CH_3), 2.49 (2H, m, CH_2), 3.30 (2H, m, CH_2), 3.74 (1H, s, 2-CH), 6.68 (1H, d, *J* = 5.48 Hz, 4'-CH), 7.16 (1H, d, J = 5.48 Hz, 5'-CH).

*5.2. 5-Formyl-4-methylthiophene-2-carboxylic acid (**13**)*

Distilled TMEDA (8.96 ml, 59.4 mmol) and 1.4 N *n*BuLi in hexane (42.4 ml, 59.4 mmol) were added to a solution of **12** (11.30 g, 57.7 mmol) in dry THF (500 ml) cooled at –78 °C in an argon atmosphere; the reaction mixture was stirred for 2 h at –78 °C. The mixture was then poured onto a slurry of solid carbon dioxide and diethyl ether (400 ml) and allowed to warm to room temperature and stirred for 16 h. Solvents were removed in vacuo and the residue was stirred with 10% w/w H_2SO_4 aqueous. (500 ml). The reaction mixture was then extracted with dichloromethane (5× 100 ml), the organic phase dried (Na_2SO_4) and the solvent removed in vacuo to give the acid derivative used for the following reaction without purification thus obtaining derivative **13** (8.3 g, 84% yield) as solid.

Melting point: 177–180 °C; ^{1}H NMR ($CDCl_3$) δ: 2.53 (3H, s, CH_3), 7.54 (1H, s, 3-CH), 10.02 (1H, s, CHO).

*5.3. 5-Formyl-4-methylthiophene-2-carboxylic acid methyl ester (**10**)*

A solution of **13** (8.2 g, 48.2 mmol) in dry methanol (400 ml) was saturated with gaseous HCl and stirred for 36 h in an argon atmosphere. Methanol was then removed in vacuo and the residue was dissolved in ethyl acetate (250 ml), the solution washed with saturated $NaHCO_3$, dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give the derivative **10** (7.1 g, 80% yield) as white solid that was used for the following reaction without purification.

Melting point: 166–168 °C; ^{1}H NMR ($CDCl_3$) δ: 2.48 (3H, s, CH_3), 3.81 (3H, s, CO_2CH_3), 7.51 (1H, s, 3-CH), 9.96 (1H, s, CHO).

5.4. N-*Formyl*-N-*(2,3,4-tri*-O-*pivaloyl-β*-D-*arabino-pyranosyl)-(*R*)-(3'-methyl-5'-methoxycarbonyl) thienylglycine*-N'-tert-*butyl amide (**14**)*

Zinc chloride (4.98 mmol as a 2.2 M solution in dichloromethane) was added to a –25 °C cooled and stirred solution of **10** (0.89 g, 4.83 mmol), 2,3,4-tri-*O*-pivaloyl-β-*D*-arabinopyranosylamine (2.0 g, 4.98 mmol), formic acid (0.24 g, 5.48 mmol) and *tert*-butylisocyanide (0.43 g, 5.22 mmol) in dry THF (30 ml) kept in an argon atmosphere. The reaction mixture was stirred at –25 °C for 3 h and then kept in a refrigerator at –20 °C for 45 h. The solvent was evaporated and the residue dissolved in dichloromethane (50 ml), washed with a saturated solution of sodium bicarbonate (2× 20 ml) and water (2× 20 ml). The organic layer was dried over Na_2SO_4, filtered and evaporated in vacuo to give a residue which was submitted to a silica gel flash chromatography. Elution with hexane-ethyl acetate 80:20 afforded the major amide **14** (1.60 g, 48% yield) as an oil. Further elution with the same solvent mixture gave the minor amide **15** (0.06 g, 2% yield).

14: $[\alpha]^D_{20}$ + 11.1 (c 0.95, $CHCl_3$); ^{1}H NMR ($CDCl_3$), typical signals of the major rotamer) δ 2.15 (3H, s, 3'-CH), 3.75 (3H, s, CO_2CH_3), 7.45 (1H, s, 4'-CH), 8.25 (1H, s, N-CHO).

*5.5. (2*R*)-*N*-2-(5'-Carboxy-3'-methyl-2'-thienyl)glycine ((+)-**9**)*

A saturated solution of hydrogen chloride in methanol (2.2 ml) was added to a magnetically stirred solution of **14** (1.20 g, 1.50 mmol) in methanol (7.3 ml) cooled at 0 °C. After 1 h at 0 °C and 5 h at room temperature, water (4 ml) was added and the mixture was stirred for 24 h. The solvent was evaporated in vacuo, the residue taken up in 20 ml of water and washed with pentane (2× 15 ml). The aqueous layer was evaporated to yield the aminoacid amide hydrochloride as white solid, which was heated at 80 °C in 6 N

hydrochloric acid (20 ml) for 12 h. After evaporation in vacuo, the residue was dissolved in water (5 ml) and purified by ion exchange resin chromatography (Amberlite IR 200). Elution with 3% aqueous ammonia gave the aminoacid (+)-**9** as white crystalline solid.

$[\alpha]^{D}_{20}$ + 10.3 (c 1.0, 3% NH_4OH); m.p. > 300 °C; ^{1}H NMR (D_2O) δ 2.15 (3H, s, CH_3), 5.01 (1H, s, 2-CH), 7.35 (1H, s, 4'-CH); ^{13}C-NMR ((D_2O + Py – d_6) δ 16.83, 55.72, 136.47, 137.37, 142.13, 144.81, 171.47, 174.99.

5.6. N-*Formyl*-N-*(2,3,4,6-tetra*-O-*pivaloyl-β*-D-*galacto-pyranosyl)-(*S*)-(3'-methyl-5'-methoxy carbonyl) thienylglycine*-N'-tert-*butyl amide (**16**)*

Zinc chloride (2.4 mmol as a 2.2 M solution in dichloromethane) was added to a –25 °C cooled and stirred solution of **10** (0.43 g, 2.3 mmol), 2,3,4,6-tetra-*O*-pivaloyl-β-*D*-galactopyranosylamine (1.20 g, 2.4 mmol), formic acid (0.12 g, 2.64 mmol) and *tert*-butylisocyanide (0.21 g, 2.52 mmol) in dry THF (15 ml) kept in an argon atmosphere. The reaction mixture was stirred at –25 °C for 3 h and then kept in a refrigerator at –20 °C for 45 h. The solvent was evaporated and the residue dissolved in dichloromethane (50 ml), washed with a saturated solution of sodium bicarbonate (2× 20 ml) and water (2× 20 ml). The organic layer was dried over Na_2SO_4, filtered and evaporated in vacuo to give a residue which was submitted to a silica gel flash chromatography. Elution with hexane-ethyl acetate 80:20 afforded the major amide **16** (1.35 g, 74%). Further elution with the same solvent mixture gave the minor amide **17** (0.11 g, 8.7%).

16: $[\alpha]^{D}_{20}$ – 32.5 (c 0.92, $CHCl_3$); m.p. 111–113 °C; ^{1}H NMR ($CDCl_3$, typical signals of the major rotamer) δ 2.1 (3H, s, 3'-CH_3), 3.7 (3H, s, CO_2CH_3), 7.30 (1H, s, 4'-CH), 8.25 (1H, s, N-CHO).

*5.7. (2*S*)-*N*-2-(5'-Carboxy-3'-methyl-2'-thienyl)glycine ((–)-**9**)*

A saturated solution of hydrogen chloride in methanol (2.2 ml) was added to a magnetically stirred solution of **18** (1.20 g, 1.50 mmol) in methanol (7.3 ml) cooled at 0 °C. After 1 h at 0 °C and 5 h at room temperature, water (4 ml) was added and the mixture was stirred for 24 h. The solvent was evaporated in vacuo, the residue taken up in 20 ml of water and washed with pentane (2× 15 ml). The aqueous layer was evaporated to yield the amino acid amide hydrochloride as white solid, which was heated at 80 °C in 6 N hydrochloric acid (20 ml) for 12 h. After evaporation in vacuo, the residue was dissolved in water (5 ml) and purified by ion exchange resin chromatography (Amberlite IR 200). Elution with 3% aqueous ammonia gave the aminoacid (–)-**9** as white crystalline solid.

$[\alpha]^{D}_{20}$ – 9.4 (c 1.0, 3% NH_4OH); m.p. > 300 °C.

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