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Determination of the absolute configuration of phosphinic analogues of glutamate†

Bruno Commare,‡[a,b] Delphine Rigault,‡[a] Isabelle A. Lemasson,§[a] Patrick Deschamps,[c] Alain Tomas,[c] Pascal Roussel,[d] Isabelle Brabet,[e,f] Cyril Goudet,[e,f] Jean-Philippe Pin,[e,f] Frédéric R. Leroux,*[b] Françoise Colobert*[b] and Francine C. Acher*[a]

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A series of phosphinic glutamate derivatives (*e.g.* **LSP1-2111**) have been proven to be potent agonists of metabotropic glutamate (mGlu) receptors and shown promising *in vivo* activity. However, so far all were synthesized and tested as a mixture of two diastereomers whose absolute and relative configurations are not known. In this study, the stereomers were separated on a Crownpack CR(+) column and their absolute configuration was assessed by means of a diastereoselective synthesis. Both separated L-stereomers activated the mGlu4 receptor with EC_{50}'s of 0.72 and 4.4 μM for (1*S*,1′*S*)-and (1*S*,1′*R*)-**LSP1-2111**, respectively.

Introduction

Compounds bearing phosphinate moieties are present in numerous biologically active molecules. Indeed, this chemical motif is found in herbicides like phosphinothricin, an inhibitor of glutamine synthetase.[1,2] Phosphinate derivatives like α-aminophosphinates,[3] are also frequently studied as enzyme inhibitors and more particularly ureases,[4] aminopeptidases[5–8] or metalloproteases.[9] A well-known phosphinate is fonisopril which is an ACE (angiotensin I converting enzyme) inhibitor used for the treatment of hypertension and heart failure.[10] Finally, some metal chelators have been synthetized based on a phosphinate motif and used in medical imaging.[11] Their applications are also important in neurosciences where several phosphinates are used such as γ-aminobutyric acid (GABA) and metabotropic glutamate (mGlu) receptor ligands.[12–14]

Our laboratory has developed a series of phosphinic glutamate analogues that selectively activate some mGluR subtypes.[14] Among these compounds **LSP1-2111** was thoroughly investigated, its central bioavailability was assessed[15] and its efficacy was shown *in vitro* and in animal models of Parkinson's disease (PD),[16] anxiety,[17] schizophrenia[18,19] and fear conditioning.[20] However, the tested compound is a mixture of two diastereomers. It is well known that diastereomers may display different biological activities. Accordingly access to single diastereomers and determination of their absolute configuration is required to carry out their pharmacological evaluation. In the present study, separation of the two diastereoisomers of **LSP1-2111** was achieved on a small scale. The absolute configuration of both stereogenic centers was determined by means of the synthesis of a close analogue **LSP1-2093** (Fig. 1).

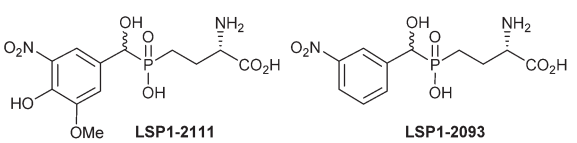

Fig. 1 Structures of **LSP1-2111** and **LSP1-2093**.

[a]*Laboratoire de Chimie & Biochimie Pharmacologiques et Toxicologiques, UMR CNRS 8601, Université Paris Descartes, Sorbonne Paris Cité, 45, rue des Saints-Pères 75270, Paris cedex 06, France. E-mail: francine.acher@parisdescartes.fr; Fax: +33 142 86 83 87; Tel: +33 142 86 33 21*

[b]*Laboratoire de Chimie Moléculaire, UMR CNRS 7509, Université de Strasbourg, ECPM, 25, rue Becquerel 76087, Strasbourg, France. E-mail: francoise.colobert@unistra.fr, frederic.leroux@unistra.fr; Fax: +33 368 8527 42; Tel: +33 368 8527 46*

[c]*Laboratoire de Cristallographie et RMN Biologiques, UMR CNRS 8015, Université Paris Descartes, 4 avenue de l'Observatoire, 75270 Paris cedex 06, France. E-mail: patrick.deschamps@parisdescartes.fr, alain.tomas@parisdescartes.fr; Fax: +33 153 73 97 32; Tel: +33 153 73 98 40, +33 153 73 98 51*

[d]*Unité de Catalyse et Chimie du solide, UMR CNRS 8012, École Nationale Supérieure de Chimie de Lille BP 90108-59652 Villeneuve d'Ascq cedex, France. E-mail: pascal.roussel@ensc-lille.fr; Fax: +33 320 43 68 14; Tel: +33 320 33 64 34*

[e]*Institut de Génomique Fonctionnelle, Centre National de la Recherche Scientifique Unité Mixte de Recherche 5203, Université de Montpellier, F-34094 Montpellier, France. E-mail: cyril.goudet@igf.cnrs.fr; Fax: +33 467 54 24 32; Tel: +33 434 35 92 77*

[f]*Inserm Unité 661, F-34094 Montpellier, France*

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‡ These authors contributed equally.

§ Present address: BioFocus DPI Ltd, Chesterford Research Park, Saffron Walden, CB10 1XL, UK.

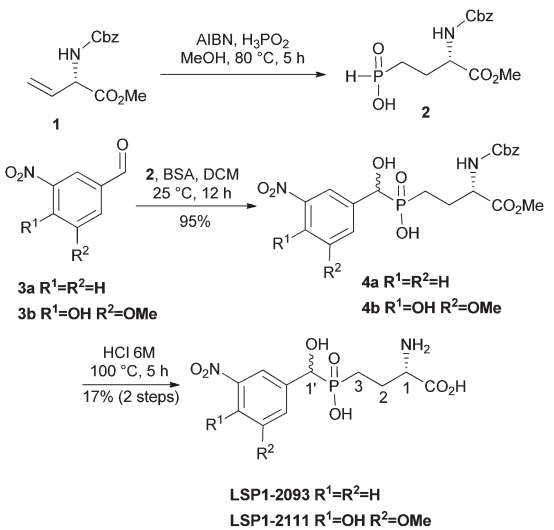
Results and discussion

LSP1-2111 and **LSP1-2093** were synthesized using the already reported general pathway depicted in Scheme 1.[14] The first step consists in the addition of phosphinic acid on (*S*)-methyl 2-(((benzyloxy)carbonyl)amino)but-3-enoate **1** *via* a radical process. After 5 hours at 80 °C, the conversion is total and the crude compound is used in the next step without further purification. α-Hydroxy-phosphinic acid **4a** and **4b** were obtained by condensation of **2** to 3-nitrobenzaldehydes **3a** and **3b**. Acid hydrolysis (HCl 6 M) afforded, after purification on ion exchange resins, the desired amino acids **LSP1-2111** and **LSP1-2093**.

The protected vinylglycine **1** used as the starting material, is enantiopure (*S*) and its stereogenic center is conserved throughout the synthesis. In contrast, the stereogenic benzylic carbinol formed by nucleophilic addition of the phosphorus derivative onto 3-nitrobenzaldehydes is epimeric. Therefore all α-hydroxy-phosphinic acids of this series were tested as a mixture of the two diastereomers.[16–20] To evaluate their respective biological activities, we describe herein the separation of both diastereomers and the determination of the absolute configuration of the newly created stereogenic center.

The first approach to separate both diastereomers of **LSP1-2111** and **LSP1-2093** involved the use of enantiopure chiral auxiliaries (Mosher acid, (*S*)-acetyllactate or (*S*)-acetylalanine) hoping to get separable diastereomers by silicagel flash chromatography. Unfortunately, this method was unsuccessful.

We thus set up a separation by chiral HPLC using a Crownpak CR(+) column (Daicel). This column is based on a chiral crown ether stationary phase that enables the resolution of amino acid racemic mixtures. CR(+) allows to separate L-amino acids and CR(−) D-amino acids.[21]



Scheme 1 Synthetic pathway of **LSP1-2093** and **LSP1-2111**.

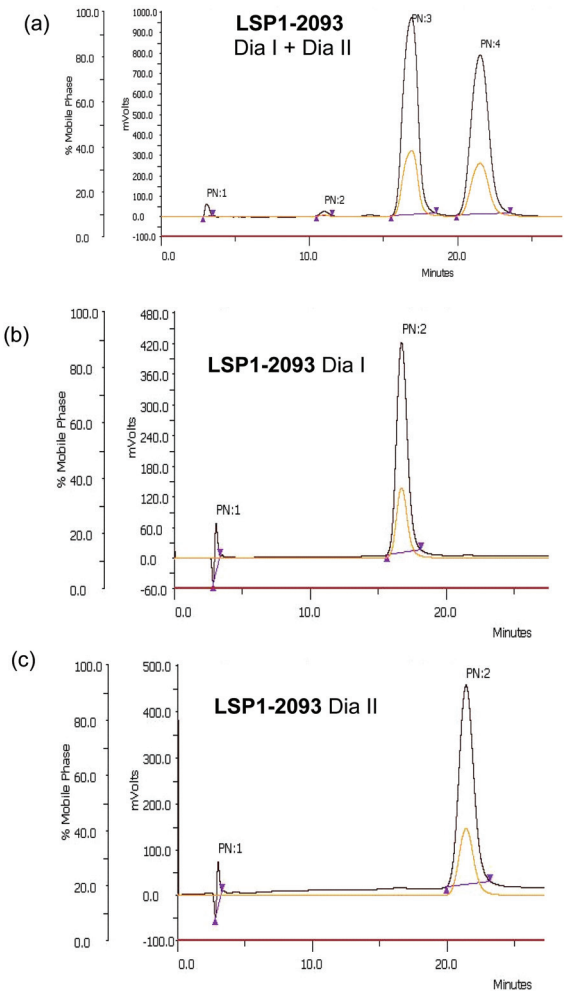


Fig. 2 Separation of (a) **LSP1-2093** diastereomers, (b) **LSP1-2093** Dia I and (c) **LSP1-2093** Dia II on a Crownpak CR(+) (150 × 4 mm, eluent $HClO_4$, pH 2.0, 0.4 mL min^{-1}, detection λ = 210/254 nm, T = 21 °C).

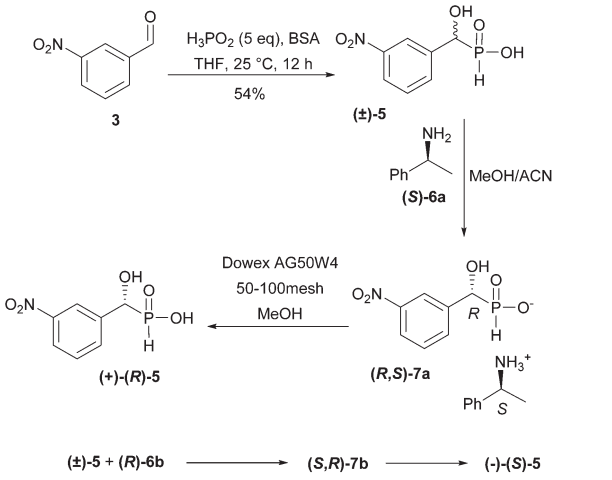
We succeeded in separating the mixtures of **LSP1-2093** (Fig. 2) and **LSP1-2111** diastereomers (ESI†) using classical analytical Crownpak conditions (150 × 4 mm, eluent $HClO_4$ pH 2.0, 0.4 mL min^{-1}, detection λ = 210/254 nm, T = 21 °C). The use of hydrochloric acid instead of perchloric acid allowed a semi-preparative separation. For both compounds, the first eluted isomer was named Dia I (Fig. 2 (b)) and the second Dia II (Fig. 2 (c)). They were characterized by their optical rotation and ^{1}H NMR analysis where the only difference was found at the H_a and H_b protons of C_3 (ESI,† Table 1). Dia I of **LSP1-2093** and **LSP1-2111** displays a small optical rotation ($[\alpha]_D^{20} = -2$ (c = 0.6, H_2O) and $[\alpha]_D^{20} = +2$ (c = 0.8, H_2O), respectively, for **LSP1-2093** and **LSP1-2111**) and the chemical shift of H_a and H_b appear as a single multiplet, at δ = 1.8 ppm, whereas Dia II displays a large optical rotation ($[\alpha]_D^{20} = +29$ (c = 0.6, H_2O) and $[\alpha]_D^{20} = +25$ (c = 0.7, H_2O), respectively, for **LSP1-2093** and **LSP1-2111**) and the chemical shifts of H_a and H_b, appear as two distinct multiplets, at δ = 1.7 and 1.9 ppm. Starting from this observation, we can thus deduce that the absolute con-

figuration of the stereogenic benzylic carbinol of Dia I and Dia II of **LSP1-2093** and **LSP1-2111** are similar. Nevertheless, we were not able to obtain suitable single crystals for X-ray analysis in order to determine the absolute configuration of the benzylic carbinol. Therefore we turned our attention to an alternative synthetic route that should allow firstly the determination of the absolute configuration of the carbinol formed and secondly the synthesis of larger amounts of pure isomers.

Our idea was to control the configuration of the benzylic carbinol before the introduction of the amino acid part to the hydroxyphosphoryl moiety. Therefore, we first added 3-nitrobenzaldehyde to hypophosphorous acid to afford racemic hydroxy(3-nitrophenyl)methylphosphinic acid (±)-**5**. Mono nucleophilic addition proceeded smoothly when a large excess (5 equiv.) of H_3PO_2 was used. Racemate **5** was thus efficiently resolved by the addition of (*S*)- or (*R*)-1-phenylethylamine **6** (1 eq.) (Scheme 2).

Salt (*R*,*S*)-**7a** was found to precipitate from a mixture of (±)-**5** and (*S*)-1-phenylethylamine in MeOH–ACN at room temperature.[22,23] The ^{31}P NMR spectrum of the crystallized salt **7a** exhibited a singlet at δ = 18.92 ppm. The selection of the (*R*)-enantiomer of *rac*-**5** with (*S*)-1-phenylethylamine was confirmed by X-ray crystallography[34] (Fig. 3) after crystallization of **7a** in EtOH.[35] Treatment of salt **7a** with resin Dowex AG50W4 gave enantiopure (+)-(*R*)-**5** in a quantitative yield. Resolving *rac*-**5** with (*R*)-1-phenylethylamine in MeOH–ACN followed by crystallization in EtOH gave access to (−)-(*S*)-**5**.

The enantiomeric ratio of the stereogenic carbinol (+)-(*R*)-**5** and (−)-(*S*)-**5** has been verified by ^{31}P NMR using L-menthol as a chiral auxiliary.[23] Indeed, menthyl phosphinates (*R*)-**8a**, (*R*)-**8a′**, (*S*)-**8b** and (*S*)-**8b′** were easily obtained from *rac*-**5** (Scheme 3).[23–25] ^{31}P NMR analysis revealed 4 peaks at δ = 27.24, 30.53, 32.13 and 35.13 ppm (in almost the same proportions) corresponding to the 4 possible stereomers resulting from the esterification of *rac*-**5** with L-menthol (Fig. 4a).



Scheme 2 Resolution of hydroxy-(3-nitrophenyl)methylphosphinic acid (±)-**5**.

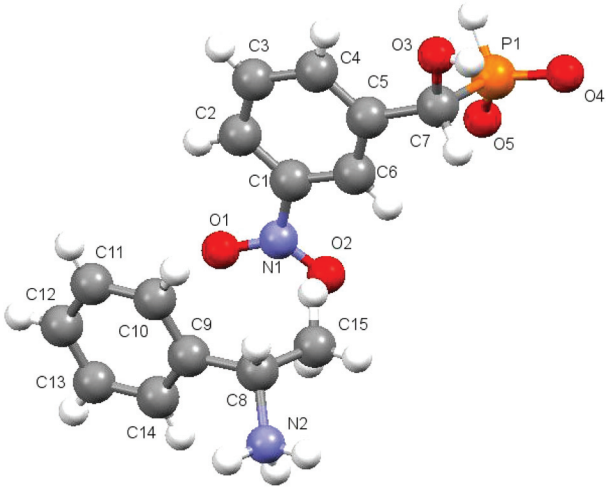
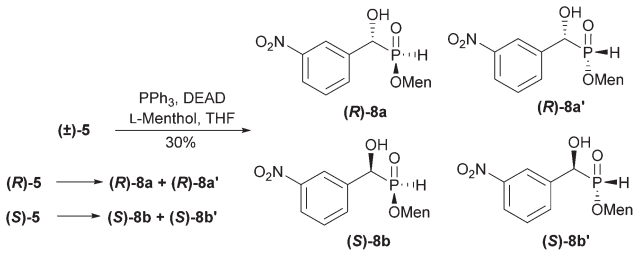


Fig. 3 X-ray crystal structure of (*S*)-1-phenylethylamonium (*R*)-[α-hydroxy-(3-nitrophenyl) methyl]phosphinate (*R*,*S*)-**7a**.



Scheme 3 Synthesis of stereomeric menthyl phosphinates (*R*)-**8a**, (*R*)-**8a′**, (*S*)-**8b** and (*S*)-**8b′**.

Starting from (+)-(*R*)-**5**, the corresponding menthyl phosphinates revealed two major peaks at δ = 30.36 and 33.18 ppm ((*R*)-**8a** and (*R*)-**8a′**) and two minor peaks at δ = 28.41 and 34.85 ppm ((*S*)-**8b** and (*S*)-**8b′**) in the ^{31}P NMR spectrum (Fig. 4b). On the opposite, esterification of (−)-(*S*)-**5** provided (*S*)-**8b** and (*S*)-**8b′** (δ = 28.13 and 35.07 ppm as ^{31}P NMR major peaks) (Fig. 4c). For both (+)-(*R*)-**5** and (−)-(*S*)-**5** the enantiomeric ratio was evaluated to 90% by ^{31}P NMR peak integration (Fig. 4).

The asymmetric synthesis of *para*-substituted phenylhydroxymethylphosphinates and phenylhydroxymethylphosphonates has been reported in the literature.[26–29] It was found that levogyre (negative optical rotation) isomers were constantly of (*S*) configuration. Oxidation of (−)-(*S*)-**5** and esterification of the resulting phosphonate (Scheme 4) provided (−)-(*S*)-**10** that matches these previous observations and allowed us to extend the correlation between optical rotation and absolute configuration to other substituted phenylhydroxymethylphosphinates. This correlation was verified by reproducing the reaction sequence from (+)-(*R*)-**5** to obtain (+)-(*R*)-**10**.

Once the configuration of the benzylic carbinol was confirmed, we designed a diastereoselective synthetic pathway

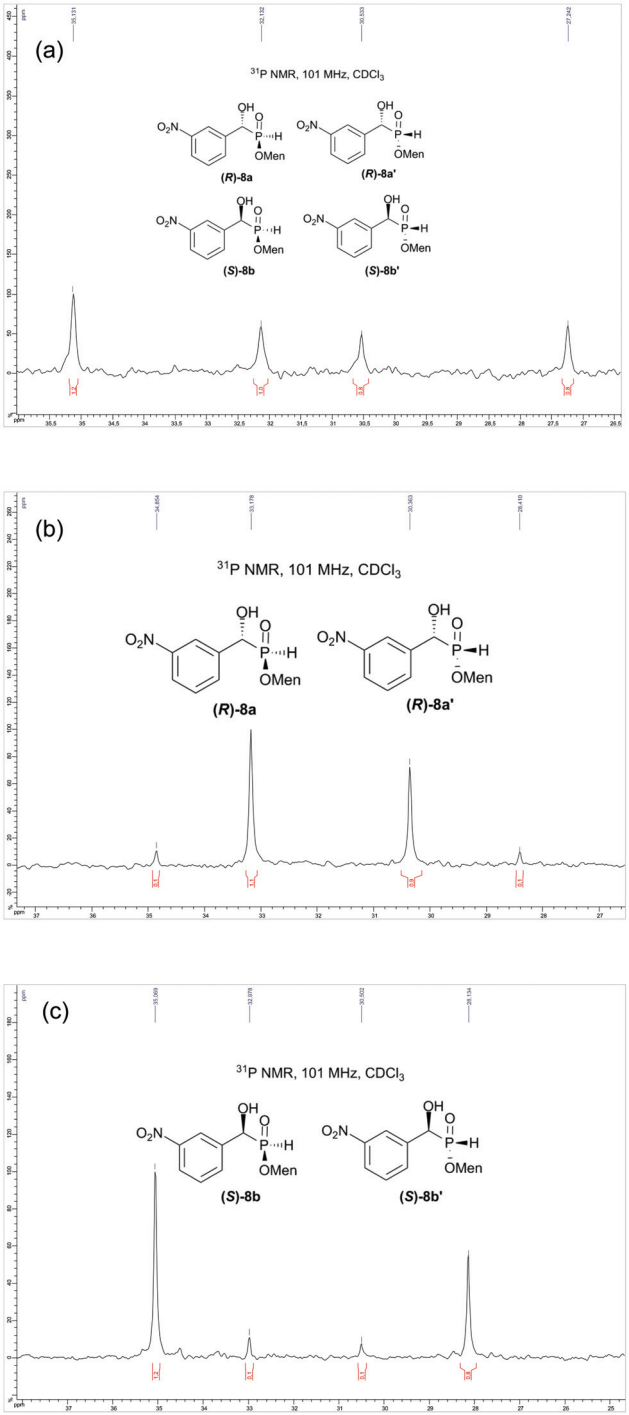
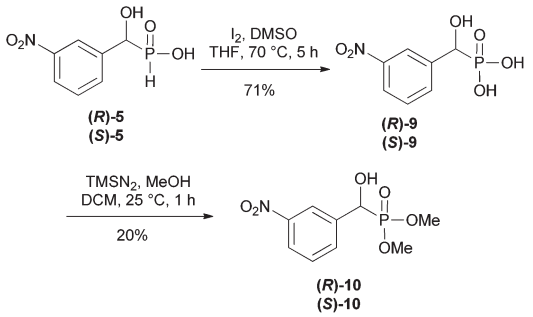


Fig. 4 ^{31}P NMR spectra of (a) the 4 stereomers **8**, (b) diastereomers (*R*)-**8a** and (*R*)-**8a′** and (c) (*S*)-**8b** and (*S*)-**8b′**.

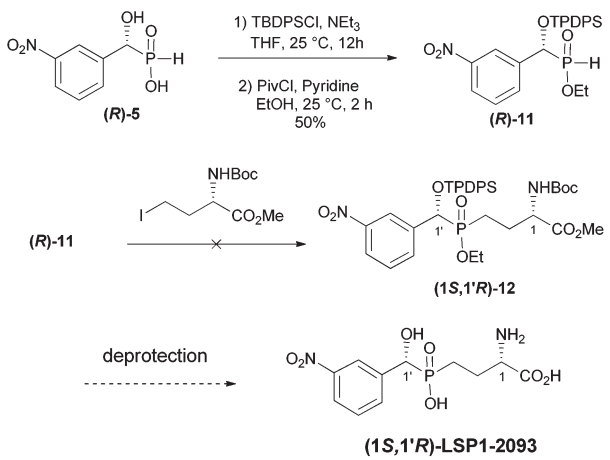
towards the two diastereoisomers of **LSP1-2093** in order to determine the absolute configuration of Dia I and Dia II (Fig. 2). Initially we developed the reaction conditions on (±)-**5** and applied them to the enantiopure compound (*R*)-**5**. Protection of the hydroxyl group of (*R*)-**5** was performed using *tert*-butyldiphenylsilyl chloride (TBDPSCl) and NEt_3, 12 h in dry



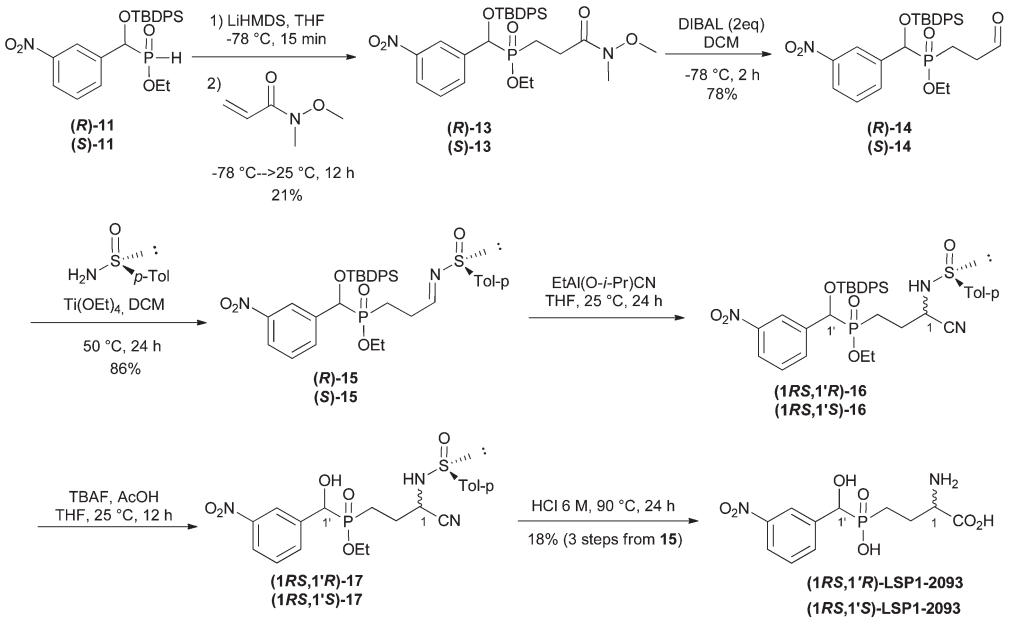
Scheme 4 Synthesis of (*S*)-hydroxyphosphonate (*S*)-**10** and (*R*)-hydroxyphosphonate (*R*)-**10**.

THF. After evaporation of the solvent, the crude residue was dissolved in EtOH and treated with pivaloyl chloride (PivCl) and pyridine to afford compound (*R*)-**11** after purification on silica gel in 51% yield[30] as a mixture of two diastereomers (phosphorus is chiral) which are not separable by chromatography on silica gel. Several attempts to couple H-phosphinate (*R*)-**11** with protected iodohomoserine giving after deprotection the desired (1*S*,1′*R*)-**LSP1-2093**, were unsuccessful (Scheme 5).

In order to circumvent this problem we decided to introduce the amino acid function through a Strecker reaction. Phosphinate (*R*)-**11** was deprotonated with lithium bis(trimethylsilyl)amide (LiHMDS) followed by the addition of acrylamide[31] to afford the Weinreb amide (*R*)-**13** in low yield (21%). For the Strecker reaction,[32] (*R*)-**13** was reduced in high yield (78%) into the aldehyde (*R*)-**14** by treatment with DIBAL-H in methylene chloride at −78 °C for 2 hours. We initially designed an asymmetric Strecker reaction using (*S*)-(+)-*p*-toluenesulfinamide as a chiral amine in order to obtain one single stereomer. Therefore, based on Midura's work,[33] imine (*R*)-**15** was synthesized by refluxing the aldehyde (*R*)-**14** in the presence of (*S*)-(+)-*p*-toluenesulfinamide, with $Ti(OEt)_4$ in DCM to afford the desired sulfinylimine which was used without



Scheme 5 Attempts to couple H-phosphinate **11** with protected iodohomoserine.



Scheme 6 Synthesis of (1*RS*,1′*R*)-**LSP1-2093** and (1R*S*,1′*S*)-**LSP1-2093**.

further purification (Scheme 6). Addition of ethylaluminium cyanoisopropoxide [EtAl(O-i-Pr)CN] with 1.0 eq. of i-PrOH at −78 °C afforded after 24 hours at 25 °C, quenching at 0 °C, a mixture of diastereomers (1*RS*,1′*R*)- and (1*RS*,1′*S*)-**16**. We observed no asymmetric induction of the chiral imine on the new stereocenter. However, since the aim of this synthesis was to determine the configuration of the benzylic carbinol of Dia I and Dia II of **LSP1-2093**, we carried out the synthesis of the corresponding (1*R*,1′*R*)- and (1*S*,1′*R*)-**LSP1-2093** to confirm their configuration on a Crownpak CR(+) column. Deprotection of the silyl ether was performed using a mixture of TBAF–AcOH (1 : 1). The use of AcOH was necessary to avoid the cleavage of the C–P bond observed under basic conditions. Indeed deprotection of the alcohol function with a base is followed by elimination of the phosphinic part by cleavage of the C–P bond.

Finally, treatment with 6 M HCl afforded both diastereomers (1*R*, 1′*R*)- and (1*S*,1′*R*)-**LSP1-2093** with a global yield of 2% from (*R*)-**5**. The same synthetic pathway was applied to (*S*)-**5** to afford a mixture of the two other diastereomers (1*R*,1′*S*)- and (1*S*,1′*S*)-**LSP1-2093** which were obtained in a global yield of 3% from (*S*)-**5** (Scheme 6). Analysis of the four diastereomers **LSP1-2093** was performed on a Crownpak CR(+) column and compared to Dia I and Dia II (Fig. 2) of **LSP1-2093** to determine the absolute configuration of the latter.

The racemic mixture (1*RS*,1′*RS*)-**LSP1-2093** obtained after the reaction sequence previously described from (±)-**5** displayed 3 peaks on the Crownpak CR(+) column (Fig. 5a). Peak 1 represents the mixture of the two (1*R*)-amino acid diastereomers [(1*R*,1′*R*) and (1*R*,1′*S*)] because the CR(+) column does not resolve D-amino acids which are not retained. Peak 2 represents one of the two (1*S*)-amino acid diastereomers [(1*S*,1′*R*) and (1*S*,1′*S*)] and the peak 3 represents the other one.

On the HPLC profile of compound (1*RS*,1′*R*)-**LSP1-2093** (Fig. 5b), obtained from (*R*)-**5**, we also observed 3 peaks. Once again, the first peak represents the (1*R*)-amino acid diastereomers. As the enantiomeric ratio of the starting (*R*)-**5** is 90%, peak 2 (analogous to Dia I, Fig. 2) and peak 3 (Dia II, Fig. 2) correspond to (1*S*,1′*S*)-**LSP1-2093** (minor) and (1*S*,1′*R*)-**LSP1-2093** (major), respectively. The HPLC profile of compound (1*RS*,1′*S*)-**LSP1-2093** (Fig. 5c) obtained from (1′*S*)-**5** shows the major peak 2 (Dia I (1*S*,1′*S*)) (91%) compared to peak 3. The ratios determined by area measurement of peaks 2 and 3 are in accordance with the enantiomeric purity of (*R*)- and (*S*)-**5** measured by ^{31}P NMR of the corresponding menthylphosphinate.

Fig. 6 shows clearly the assignment of Dia I and Dia II obtained according to Scheme 1. This protocol allowing the determination of the absolute configuration of the stereogenic carbinol formed during the synthesis of phosphinic amino acids may be extended to structural analogs such as **LSP1-2111**.

Pharmacology

The separated pairs of L-diastereomers were tested for their activation of mGlu4 receptors transiently expressed in HEK293 cells. All compounds activated this receptor. Whereas a minor difference between the diastereomers of **LSP1-2093** is found, it is more pronounced for **LSP1-2111**. The 1′*S* isomer is about 6 fold more potent than the 1′*R* (Table 1).

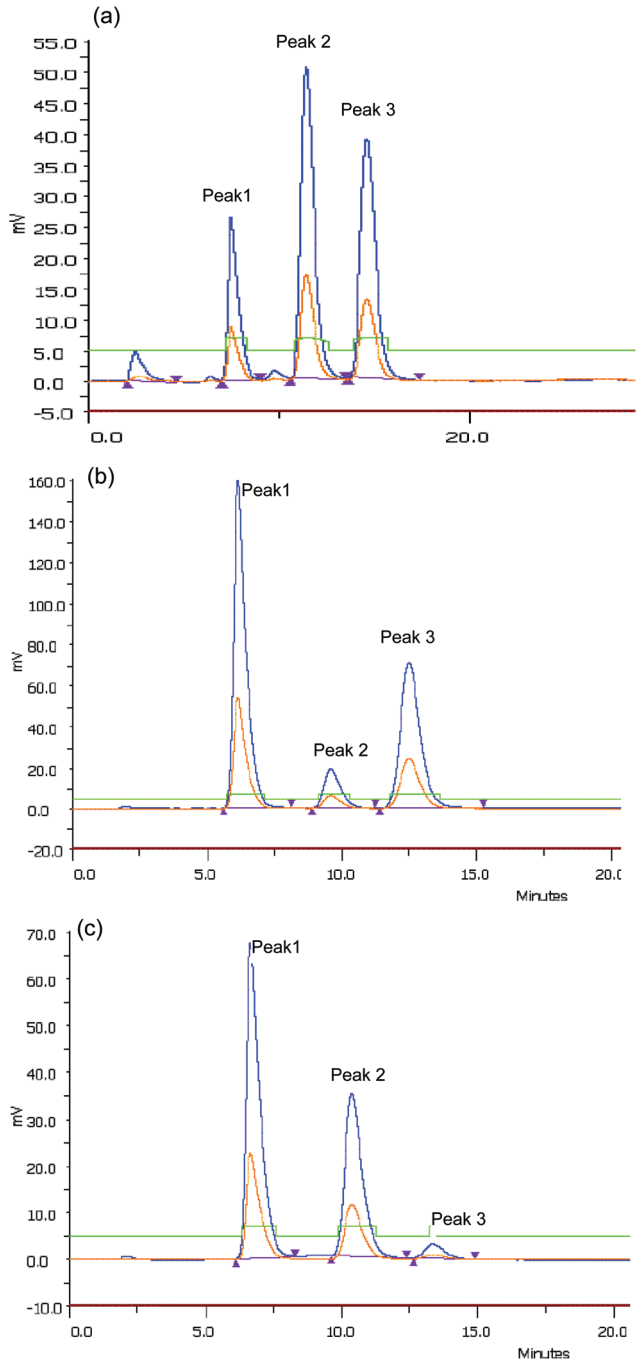


Fig. 5 Analysis of (a) (1*RS*,1′*RS*)-**LSP1-2093**, (b) (1*RS*,1′*R*)-**LSP1-2093** and (c) (1*RS*,1′*S*)-**LSP1-2093** on a Crownpak CR(+) column at 25 °C.[36]

Table 1 Pharmacological data of **LSP1-2093** and **LSP1-2111** L-diastereomers at the mGlu4 receptor

LSP1-2093 EC_{50} (μM)	(1*S*,1′*RS*)- 0.6 ± 0.3	(1*S*,1′*S*)- 1.0 ± 0.4	(1*S*,1′*R*)- 0.32 ± 0.10
LSP1-2111 EC_{50} (μM)	(1*S*,1′*RS*)- 0.9 ± 0.13	(1*S*,1′*S*)- 0.72 ± 0.08	(1*S*,1′*R*)- 4.4 ± 0.5

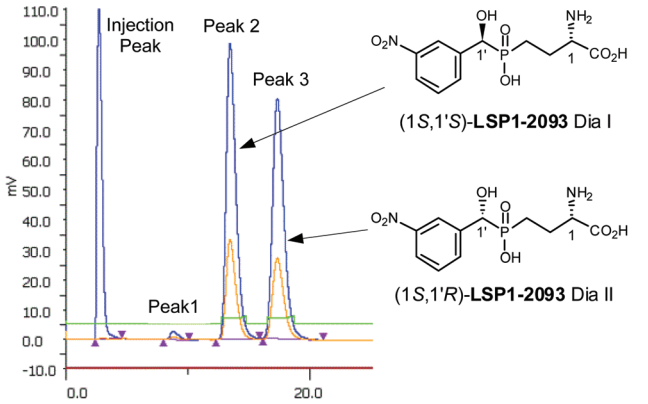


Fig. 6 Assignment of **LSP1-2093** diastereomers obtained in Scheme 1 on a Crownpak CR(+) column at 25 °C.

Conclusions

To evaluate the bioactivity of the stereomers of **LSP1-2111** and other phosphinic analogues of glutamate, it is essential to be able to isolate and characterize each stereomer. Separation of the stereomers was thus efficiently achieved by semi-preparative chiral HPLC on a Crownpak CR(+) column. Absolute configuration was assigned by means of a diastereoselective synthesis of **LSP1-2093**, a close analogue. Further studies will aim at adjusting an asymmetric Strecker reaction in order to obtain each stereomer in pure form. An application of the protocol to other phosphinic amino acids such as **LSP4-2022** is possible. The pharmacological activity of the single L-stereomers reveals that all are agonists of the mGlu4 receptor and that (1*S*,1′*S*)-**LSP1-2111** is more potent than (1*S*,1′*R*)-**LSP1-2111**.

Acknowledgements

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34 CCDC 1016374 contains the supplementary crystallographic data for this paper.
35 The known chirality of the (*S*)-1-phenylethylamine moiety was used as an internal reference.
36 Retention times on Crownpack columns are very sensitive to temperature. Consequently those recorded for **LSP1-2093** stereomers in Fig. 2 ((mixture, Dia I and Dia II)) and Fig. 5 ((1*RS*,1′*R*) and (1*RS*,1′*S*)) are slightly different.