First International Electronic Conference on Synthetic Organic Chemistry (ECSOC-1), www.mdpi.org/ecsoc/, September 1-30, 1997

[A0023]

Stereoselective Synthesis of 2-Amino-2-methyl-4-phosphonobutanoic Acid Derivatives (MAP4 Analogues)

María Ruiz, Vicente Ojea, M. Carmen Fernández, **Susana Conde, Aniana Díaz and** José M. Quintela

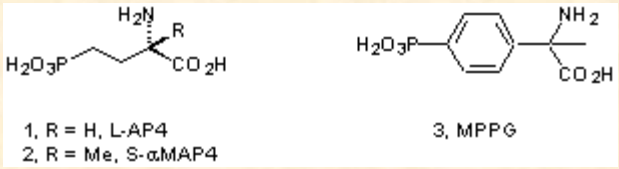
Departamento de Química Fundamental e Industrial. Facultade de Ciencias. Universidade da Coruña

Campus A Zapateira s/n, A Coruña 15071. Spain.

Received: 4 August 1997 / Uploaded: 4 August 1997

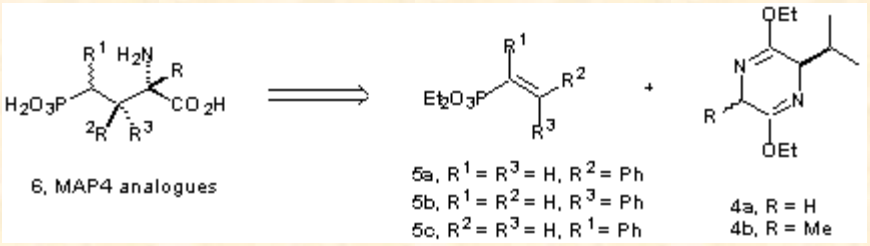
The metabotopic glutamate receptors (mGluRs) constitute a new family of excitatory amino acid receptors, which modulates the synaptic transmission by coupling to second messengers through G-proteins.[1] To date, mGluRs have been distinguished into three groups, based on sequence homology, signal transduction mechanisms and agents pharmacology. In particular, receptors of group III (mGluR4 and mGluR6-8) are characterized by their selective response to several phosphonic acid derivatives. Thus, they are selectively activated by L-2-amino-4-phosphonobutanoic acid (L-AP4, **1** in scheme 1) and competitively antagonized by the α-methylated derivatives of L-AP4 (MAP4, **2**) and 4-phosphonophenylglycine (MPPG, **3**).[2]

Figure 1. Agonists and antagonists of group III of mGluRs.



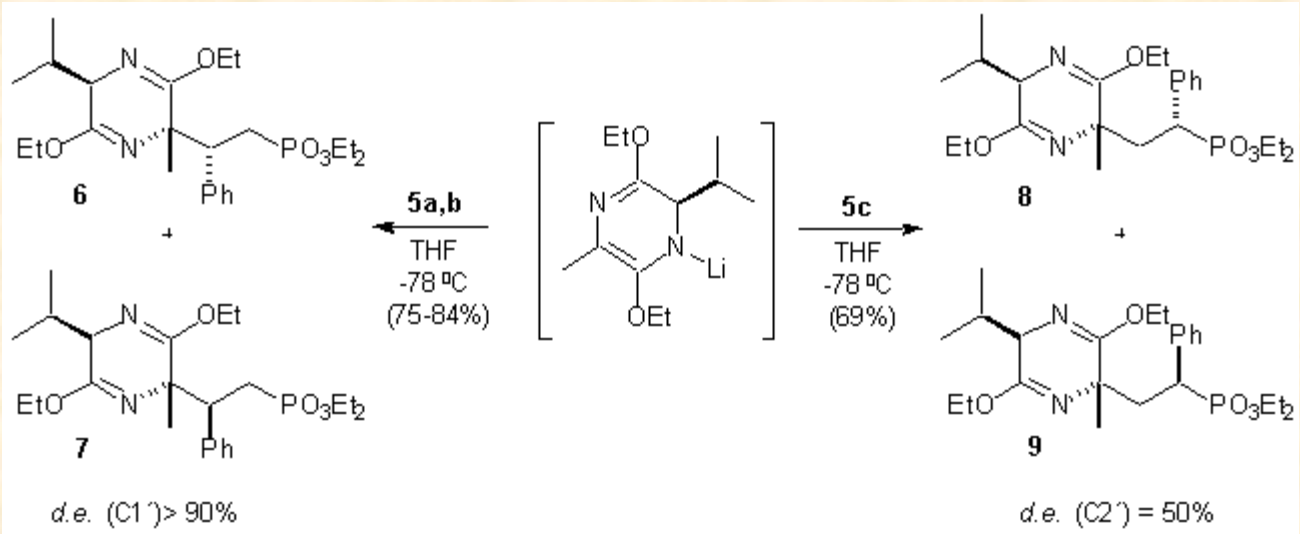
As part of a project directed to the design of new bioactive phosphonates, we report now the diastereoselective synthesis of several MAP4 derivatives, prepared in order to study the stereochemical requirements for a potent binding at group III of mGluRs. In this area, we have recently developed a direct approach to optically pure 2-amino-4-phosphonobutanoic acids, by using a highly regio and stereoselective addition of the lithium salt of bislactim ether **4a** to a variety of alkenylphosphonates.[3] The high level of π-facial selectivity found in these processes prompted us to explore the scope of the reactions between the lithium salt of bislactim ether **4b**, and prochiral alkenylphosphonates **5a-c**, that could result in a stereocontrolled access to the desired 2-amino-2-methyl-4-phosphonobutanoic acid derivatives **6**.

Scheme 1. Diastereoselective synthesis of 2-amino-4-phosphonobutanoic acid derivatives.



Metalation of bislactim ether **4b** [4], by treatment with *n*-butillithium at -78 °C, followed by the slow addition of 2-phenylethenylphosphonates **5a,b** [5], led to mixtures of adducts **6**+**7** in good yields (see scheme 2). Analyses of ^{1}H-decoupled ^{31}P NMR spectra of the crude reaction mixtures revealed opposite stereochemical courses in the additions to acceptors **5a** and **5b**, as well as a very high asymmetric induction in the formation of new chiral centers in both cases. In this way, the observed diastereomeric excesses of the major adducts, the 2,5-*trans*-2,1´-*anti* isomer **6** in case **a** and the 2,5-*trans*-2,1´-*syn* isomer **7** in case **b**, were greater than 90%. Addition to alkenylphosphonate **5c** [6] also took place regio and stereoselectively, to afford a mixture of adducts **8**+**9** in a combined yield of 69%. As the creation of the stereocenter at C2´ takes place during the quenching of the addition reaction, by protonation of the initially formed anionic intermediate, the stereoselective formation of the major adduct (with a diastereomeric excess of 50% according to ^{31}P NMR analysis) is remarkably.

Scheme 2. Conjugate additions of lithiated bislactim ether **4b** to alkenylphosphonates **5a-c**.



After the separation of the diastereomeric mixtures by chromatography, vigorous acid hydrolysis of the adducts **6-9** allowed the isolation of the amino acids **10-13** as their hydrochloride salts in excellent yields (78-95%, see scheme 3). Relative stereochemistry of amino acids **10** and **11** was determined by conversion of **11** to an amino-oxaphosphorinane derivative **14**. Thus, after full trimethylsilylation of amino acid **11**, chemoselective reduction of the carboxylic ester gave rise to amino alcohol **15**, which could be cyclized by treatment with thionyl chloride in dimethylformamide at room temperature. Compound **14** showed a single chair conformation in its ^{1}H NMR spectrum (D_2O, rt), allowing to conclude a 2,3-*syn* configuration on the basis of a complete set of NOEs, that were supported by force field and semiempirical calculations. Derivatization of amino acids **12** and **13** to the corresponding amino-oxaphosphorinanes is now under progress.

Scheme 3. Amino acids **10-13** and amino-oxaphosphorinane derivative **14**.

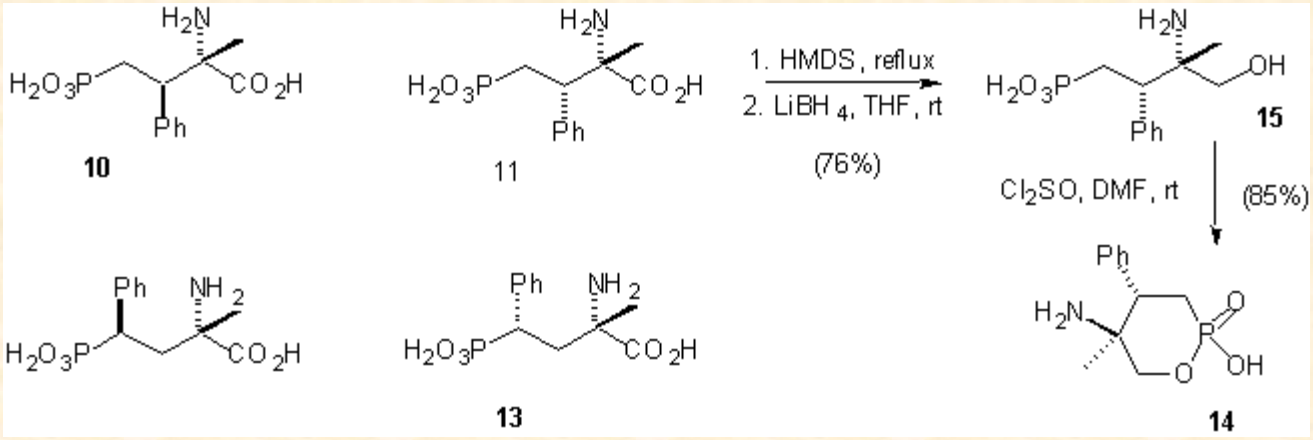
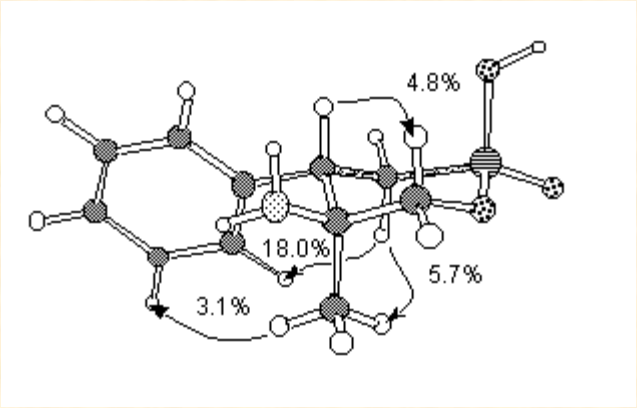


Figure 2. PM3-optimized conformations for amino-oxaphosphorinane **14**, showing characteristic NOEs.



Acknowledgments

We are grateful to the CICYT (Project SAF970184) for supporting this research. M.C.F. and S.C. thank *Xunta de Galicia* and *Ministerio de Educación y Cultura*, respectively, for their Predoctoral grants.

References and notes

[1] Knöpfel, T.; Kuhn, R.; Allgeier, H. *J. Med. Chem.* **1995**, *38*, 1417-1426.

[2] a. Jane, D.E.; Jones, P.L.St.J.; Pook, P.C.-K.; Tse, H.-W.; Watkins, J.C. *Br. J. Pharmacol.* **1994**, *112*, 809-816. b. Jane, D.E.; Pittaway, K.; Sunter,D.C.; Thomas, N.K.; Watkins, J.C. *Neuropharmacology* **1995**, *34*, 851.

[3] a. Ojea, V.; Ruiz, M.; Shapiro, G.; Pombo-Villar, E. *Tetrahedron Lett.* **1994**, *35*, 3273.b. Ojea, V.; Fernández, M.C.; Ruiz, M.; Quintela, J.M. *Tetrahedron Lett.* **1996**, *37*, 5801.

[4] Schöllkopf, U.; Groth, U.; Westphalen, K.-O.; Deng. C. *Synthesis* **1981**, 969. Alternatively, (2*R*,5*RS*)- and (2*S*,5*RS*)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-methylpyrazine can be purchased from Merck-Schuchardt.

[5] a. Aboujaoude, E.E.; Liétje, S.; Collignon, N.; Teulade, M.P.; Savignac, P. *Tetrahedron Lett.* **1985**, *26*, 4435-4438. b. Mimouni, N; Al Badri, H.; About-Jaudet, E.; Collignon, N. *Synth. Commun.* **1995**, *25*, 1921-1932.

[6] Alkenylphosphonate **5c** was obtained by condensation of formaldehyde and the lithium salt of *O,O,O,O*-

tetraethylbenzylidenediphosphonate, which was in turn generated from *O,O*-diethylbencilphosphonate (see: Teulade, M.P.; Savignac, P.; Aboujaude, E.E.; Liétge, S.; Collignon, N. *J. Organomet. Chem.* **1986**, *304*, 283-300).

Comments

During 1-30 September 1997, all comments on this poster should be sent by e-mail to ecsoc@listserv.arizona.edu with **A0023** as the message subject of your e-mail. After the conference, please send all the comments and reprints requests to the author(s).
