Synthesis of 2-Amino-2-methyl-4-phosphonobutanoic Acids by Conjugate Addition of Lithiated Bislactim Ether Derived from *Cyclo*[Ala-D-Val] to Vinylphosphonates

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Abstract: Face-selective conjugate addition of lithiated Schöllkopf's bislactim ether derived from *cyclo*[Ala-D-Val] **4** to prochiral vinylphosphonates **5a-c** allows a direct and stereocontrolled access to optically pure MAP4 analogues, the 2-amino-2-methyl-4-phosphonobutanoic acid derivatives **12**-**15**. The relative stereochemistry was assigned from NMR studies of the cyclic derivatives **16** and **17**. Eight-membered transition states are invoked to rationalize the stereochemical outcome of the additions.

Key words: phosphonobutanoic acids, α-methyl α-amino acids, conjugate addition, stereoselective synthesis, vinylphosphonates

L-Glutamic acid mediates fast excitatory transmission at the majority of central nervous system synapses, and also participates in neuronal plasticity and neurotoxicity.[1] Synaptically released glutamate exerts its effects via activation of ligand-gated cation channels (ionotropic glutamate receptors) and metabotropic glutamate receptors (mGluRs), which modulate intracellular second messengers through G protein-coupled processes. Glutamate receptors have attracted considerable attention because of their therapeutic potential for the treatment of a range of chronic and acute central nervous system disorders with social significance, such as stroke, epilepsy and Alzheimer's disease.[2] To date, mGluRs have been distinguished into three groups, based on sequence homology, signal transduction mechanisms and agonist 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 Figure 1) and competitively antagonized by the α-methylated derivatives of L-AP4 (MAP4, **2**) and 4-phosphonophenylglycine (MPPG, **3**).[3] Biological research on mGluRs function eagerly demands the development of more potent and selective agonist and antagonists. As the molecular basis for the glutamate recognition and binding at the mGluRs proteins has not been elucidated yet, the development of high affinity ligands still relies on structural modification of established structures and screening of new lead compounds. As part of a project directed to the design of new bioactive phosphonates [4] 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.

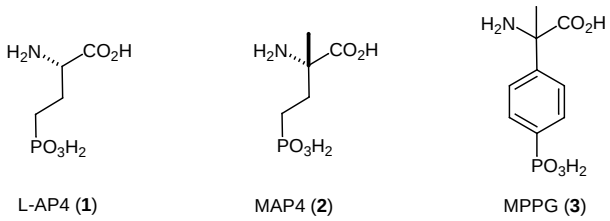
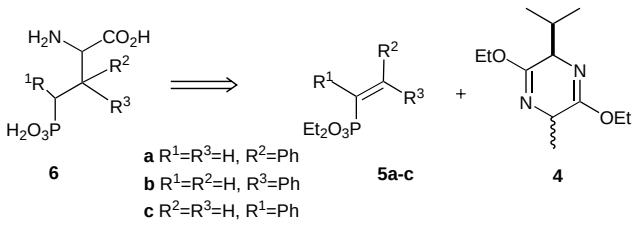


Figure 1

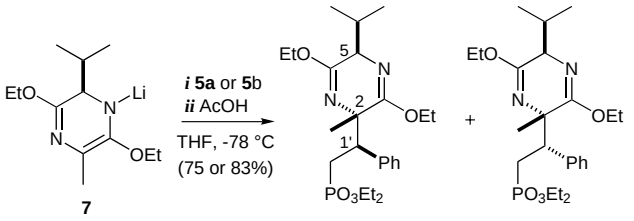
In this area, we have recently developed a direct approach to optically pure 2-amino-4-phosphonobutanoic acids, by using a highly regio and stereoselective addition of the lithium salt of bislactim ether derived from *cyclo*[L-Val-Gly] to a variety of alkenylphosphonates.[4b] The high level of π-facial selectivity found in these processes prompted us to explore the scope of the reactions between the lithium salt of bislactim ether **4**, and prochiral vinylphosphonates **5a-c**, that could result in a stereocontrolled access to the desired 2-amino-2-methyl-4-phosphonobutanoic acid derivatives **6** (see Scheme 1).



Scheme 1

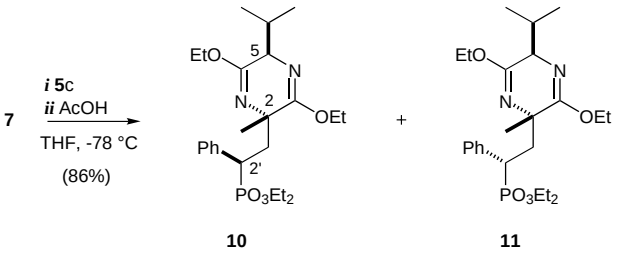
To this end, (3*R*,6*S*,*R*)-2,5-diethoxy-3-isopropyl-6-methyl-3,6-dihydropyrazine (**4**) was prepared from alanine and D-valine,[5] while vinylphosphonates **5a**[6] and **5b**[7] were prepared as described in the literature. 1-Phenylethenylphosphonate **5c**[8] was obtained by condensation of formaldehyde and the sodium salt of tetraethyl phenylmethylenebisphosphonate, which was in turn generated from diethyl benzylphosphonate.[6]

Thus, slow addition of 2-phenylethenylphosphonates **5a,b** over a solution of 1.2 equivalents of the lithium salt **7** at low temperature led (after quenching with acetic acid, aqueous workup and removal side products by flash chromatography) to mixtures of adducts **8**+**9** in good yields (see Scheme 2). Integration of the ^{1}H-decoupled ^{31}P NMR spectra of the crude reaction mixtures revealed opposite stereochemical courses in the additions to acceptors with *E*- and *Z*-geometry (**5a** and **5b**, respectively), 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 **8** in case **a** and the 2,5-*trans*-2,1'-*syn* isomer **9** in case **b**, were greater than 90%.



Scheme 2

Addition to 1-phenylethenylphosphonate **5c** also took place regio and stereoselectively, to afford a mixture of adducts **10**+**11** in a combined yield of 86%. As creation of stereocenter at C2' takes place during the quenching of the reaction, by protonation of the initially formed anionic intermediate, diastereoselective formation of the 2,5-*trans*-2,2'-*anti* isomer **10** (with a diastereomeric excess of 50% over the 2,5-*trans*-2,2'-*syn* isomer **11**) is remarkable. The asymmetric induction at C2' could not be completely suppressed by increasing the temperature of the quenching. When the addition of acetic acid was carried out at room temperature, the mixture **10**+**11** was obtained in similar yield, and **10** was formed with a diastereomeric excess of 17% over its epimer **11**. Evidence supporting the assignment of the relative configurations was obtained by NMR analyses of cyclic derivatives, as depicted in Figure 3. Absolute configurations follow from the use of **4**, derived from D-valine, as there is ample precedent.[9]



Scheme 3

The separation of the diastereomeric mixtures could be achieved by medium pressure liquid chromatography (mixtures AcOEt-hexane, SiO_2 230-400 mesh) to provide products of high purity (diastereomeric excesses higher than 98%) on a multigram scale.[10] Vigorous acid hydrolysis of the adducts **8**-**11** (12 M hydrochloric acid, reflux, 30-40 h) allowed, after removal of the auxiliary D-valine by reverse phase chromatography (H_2O, RP-18 230-400 mesh), the isolation of the amino acids **12**, **13**, **14** and **15** as their hydrochloride salts in good yields (78-95%, see Figure 2).[12]

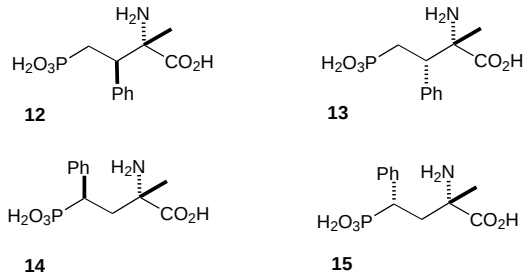
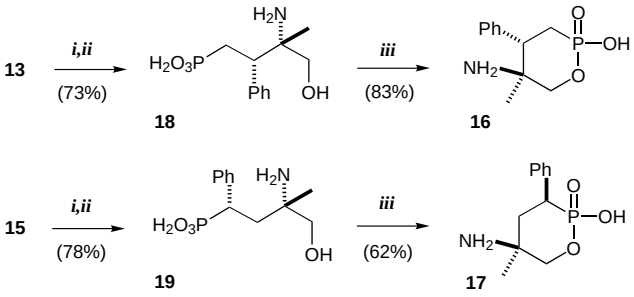


Figure 2

Since none of compounds **8**-**15** provided crystals suitable for X-ray diffraction analysis, we decided to transform amino acids **13** and **15** to the corresponding oxaphosphorinane derivatives **16** and **17**. The strong preference for chair conformation in solution reported for substituted 1,2-oxaphosphorinanes [4b,13] would make such six-membered cyclic compounds amenable to the assignment of their relative configuration on the basis of NMR studies. Thus, after temporary protection of the acidic functionalities at amino acids **13** and **15** (hexamethyldisilazane, reflux, 12 h), chemoselective reduction of the carboxylic ester in the presence of the phosphonate group (lithium borohydride in tetrahydrofuran at room temperature) gave rise to amino alcohols **18** and **19**, in good yields (73 and 78%, respectively). Cyclization to the corresponding amino-oxaphosphorinanes took place by heating of the amino alcohols in thionyl chloride (see Scheme 4).



i. HMDS, H_2SO_4, Δ, 12h. ***ii.*** $LiBH_4$ 2M in THF, r.t., 24 h. ***iii.*** $SOCl_2$, Δ, 14h.

Scheme 4

Both compounds **16** and **17** showed in their ^{1}H NMR spectra (200 MHz, D_2O, r.t.) a pattern of signals suitable for the study of their conformation and relative stereochemistry by NOE difference spectroscopy.[14] The analyses of the sets of observed NOEs confirmed the presence of chair conformations in solution, and allowed to conclude a *trans* disposition of the amino and phenyl groups for amino-oxaphosphorinane **16**, while a *cis* configuration was assigned for **17**. This results were supported by force field and semiempirical calculations (see Figure 3).[15]

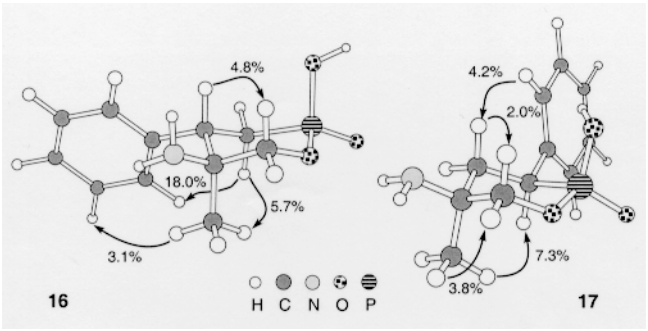


Figure 3

Translation of *Z*- or *E*-geometry of the acceptor into a *syn*- or *anti*-configuration at the 1,4-addition products was previously encountered in other conjugate additions of lithiated bislactim ethers (derived from *cyclo*[Val-Gly]) to α,β-unsaturated systems (2-alkenoates[17] and alkenylphosphonates[4b]). Thus, the stereochemical course of the additions of lithium salt of **4** to acceptors **5a,b** can be rationalized by extending the transition state model proposed for the 1,4-additions of lithiated bislactim ethers derived from *cyclo*[Val-Gly] to alkenylphosphonates.[18] In this way, an initial lithium-phosphoryl coordination to form a chelate complex, followed by a rate-determining reorganization through competitive eight-membered cyclic transition structures, can also account for the stereochemical features of these conjugate additions. According to such a model, the 2,1'-*anti/syn* stereoselection relies on the energy difference between the TSs resulting from the *like* or *unlike* approach of the *Si* face of the enolate (*trans* to the isopropyl group) to the prochiral faces of the Cβ at the alkenyl moiety. As previously found for other conjugate additions of lithiated bislactim ethers to alkenyl and 1,3-butadienylphosphonates, the stereochemical response of the reaction to the acceptor geometry can be rationalized by invoking a strong kinetic preference for the *compact* transition states over the *relaxed* counterparts (see figure 4).

The stereoselective protonation of the phosphonate carbanion resulting from the addition to **5c** suggests the involvement of a cyclic chelate complex like **20** (see Figure 5). Axial protonation (under stereoelectronic control) or the approach of the electrophile to the less hindered face of the cyclic phosphonate carbanion, may account for the 2,2'-*anti* stereoselection in this case.

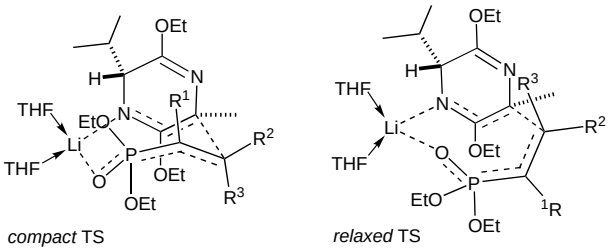


Figure 4

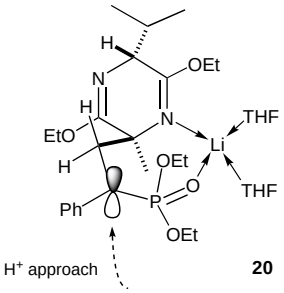


Figure 5

In conclusion, the conjugate addition of lithiated bislactim ethers derived from *cyclo*[Ala-Val] to prochiral vinylphosphonates takes place regio and stereoselectively. For β-substituted vinylphosphonates, the reaction results in an almost complete translation of the *E* (or *Z*) geometry into a 2,1'-*anti*- (or 2,1'-*syn*) configuration at the adducts. Thus, the level of π-facial discrimination delivered by this reagent/substrate couple enables a stereoregulated access to a variety of optically pure 2-amino-2-methyl-4-phosphonobutanoic acid derivatives, potential antagonists at mGluRs of type III.

Acknowledgement

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References and Notes

(1) *CNS Neurotransmitters and Neuromodulators: Glutamate.* Stone, T. W., Ed.; CRC: Boca Raton, FL, 1995.
(2) a) Knöpfel, T.; Gasparini, F. Drug Discovery Today **1996**, 1, 103. b) Knöpfel, T.; Kuhn, R.; Allgeier, H. *J. Med. Chem.* **1995**, *38*, 1417.
(3) 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. b) Jane, D. E.; Pittaway, K.; Sunter, D. C.; Thomas, N. K.; Watkins, J. C. *Neuropharmacology* **1995**, *34*, 851.
(4) a) Ojea, V.; Conde, S.; Ruiz, M.; Fernández, M. C.; Quintela, J. M. *Tetrahedron Lett.* **1997**, *38*, 4311. b) Ojea, V.; Fernández, M. C.; Ruiz, M.; Quintela, J. M. *Tetrahedron Lett.* **1996**, *37*, 5801.

(5) Schöllkopf, U.; Groth, U.; Westphalen, K.-O.; Deng. C. *Synthesis* **1981**, 969. Alternatively, (3*R*,6*S*,*R*)- and (3*S*,6S,*R*)-3-isopropyl-2,5-dimethoxy-6-methyl-3,6-dihydropyrazine can be purchased from Merck-Schuchardt.
(6) Teulade, M. P.; Savignac, P.; Aboujaoude, E. E.; Liétge, S.; Collignon, N. J. *Organomet. Chem.* **1986**, *304*, 283.
(7) Mimouni, N; Al Badri, H.; About-Jaudet, E.; Collignon, N. *Synth. Commun.* **1995**, *25*, 1921.
(8) Tavs, P.; Weitkamp, H. *Tetrahedron* **1970**, *26*, 5529.
(9) See Williams, R. M. *Synthesis of Optically Active α-Amino Acids*. Baldwin, J. E., Magnus, P. D. Eds.; Organic Chemistry Series, Vol. 7; Pergamon: Oxford, 1989.
(10) All new compounds have been isolated in a pure analytical form after chromatography (on SiO_2 or RP-18), and their spectral data (EIMS or FABMS, NMR and IR) were consistent with the proposed structure. Spectral data obtained for compounds **5a-c** are in full agreement with those previously reported in refs. 6, 11 and 8, respectively.
(11) Cristau, H.-J.; Yangkou Mbianda, X.; Beziat, Y.; Gasc, M.-B. *J. Organomet. Chem.* **1997**, *529*, 301.
(12) Selected data for amino acids:**12**·HCl:^{13}C NMR (50 MHz, D_2O) δ:21.7 (CH_3), 29.7 (d, *J* = 134.6 Hz, C-4), 48.3 (d, *J* = 2.0 Hz, C-3), 65.1 (d, *J* = 17.3 Hz, C-2), 129.5, 130.0, 130.2, 137.0 (d, *J* = 2.0 Hz) (Ph), 174.7 (C-1); $[\alpha]_D^{20}$ = −23.7 (c = 0.5, H_2O). **13**·HCl:^{13}C NMR (50 MHz, D_2O) δ:21.0 (CH_3), 29.8 (d, *J* = 136.4 Hz, C-4), 48.8 (d, *J* = 2.2 Hz, C-3), 66.5 (d, *J* = 17.2 Hz, C-2), 130.9, 131.3, 132.0, 138.5 (Ph), 176.2 (C-1); $[\alpha]_D^{20}$ = −3.4 (c = 0.7, H_2O). **14**·HCl:^{13}C NMR (50 MHz, D_2O) δ:21.7 (CH_3), 37.4 (C-3), 41.9 (d, *J* = 133.0 Hz, C-4), 60.9 (d, J = 17.6 Hz, C-2), 129.0 (d, *J* = 3.3 Hz), 130.0 (d, *J* = 3.0 Hz), 130.2 (d, *J* = 6.3 Hz), 135.9 (d, *J* = 8.3 Hz) (Ph), 173.6 (C-1); $[\alpha]_D^{27}$ = +8.1 (c = 0.4, H_2O). **15**·HCl:^{13}C NMR (50 MHz, D_2O) δ:23.4 (CH_3), 37.4 (C-3), 41.0 (d, *J* = 134.7 Hz, C-4), 60.9 (d, *J* = 16.6 Hz, C-2), 128.8 (d, *J* = 3.6 Hz), 129.5 (d, *J* = 2.7 Hz), 130.2 (d, *J* = 6.6 Hz), 135.1 (d, *J* = 8.3 Hz) (Ph), 173.2 (C-1); $[\alpha]_D^{23}$ = +20.6 (c = 0.8, H_2O).
(13) a) Berkowitz, D. B.; Eggen, M. J; Shen, Q.; Shoemaker, R. K. *J. Org. Chem.* **1996**, *61*, 4666. b) Tasz, M. K.; Rodriguez, O. P.; Cremer, S. E.; Sakhawat Hussain, M.; Mazhar-ul-Haque *J. Chem. Soc., Perkin Trans. 2* **1996**, 2221. c) Bergesen, K.; Vikane, T. *Acta Chem. Scand.* **1972**, *26*, 1794.
(14) Kinns, M.; Sanders, J. K. N. J. Mag. Res. **1984**, 53, 518. ^{1}H NOE experiments were recorded in a BRUKER AC200 spectrometer, using the NOEMULT.AU software for ASPECT3000 computers.
(15) Minimum energy conformations for compound **16** and **17** were located using MMX force field as implemented in PCModel v5 and GMMX v1.6 programs.[16a] The geometries of the most important conformers were fully optimised by semiempirical molecular orbital calculations, using the PM3 Hamiltonians included the MOPAC97 [16b] module of CS Chem3D Pro.[16c] The refined geometry in the gas phase was in agreement with the conformation in solution deduced from ^{1}H NOE spectroscopy, as depicted in Fig.3.
(16) a) PCModel version 5 (Molecular Modelling Software) and GMMX version 1.6. (Global Conformational Search Program), from Serena Software, Bloomington, IN 47402, USA. b) Revised version of MOPAC93, Fujitsu Ltd, Tokyo, Japan 1993. c) CS Chem3D Pro, version 4.0. Molecular Modeling and Analysis Program from CambridgeSoft Corporation, Cambridge, MA 02139, USA.
(17) Schöllkopf, U.; Pettig, D.; Busse, U.; Egert, E.; Dyrbusch, M. *Synthesis* **1986**, 737.
(18) Ojea, V.; Ruiz, M.; Vilar, J.; Quintela, J. M. *Tetrahedron: Asymmetry* **1996**, *7*, 3335.

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