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Conjugate Addition of Lithiated Schöllkopf's Bislactim Ether to 1*E*,3*E*-Butadienylphosphonates: Stereocontrolled Access to 2,3-*anti*-4*E* 2-Amino-6-phosphono-4-hexenoic Acid Derivatives

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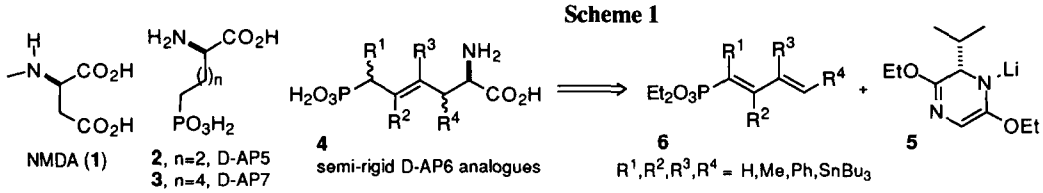
Abstract: Face-selective 1,6-addition of lithiated Schöllkopf's bislactime ether **5** to 4-substituted, 1,4- or 3,4-disubstituted 1*E*,3*E*-butadienylphosphonates **6a-d** allows a direct and stereocontrolled access to semi-rigid AP6 analogues, the 2,3-*anti*-4*E* 2-amino-6-phosphono-4-hexenoic acid derivatives **4a-c**. The relative stereochemistry was assigned from a NMR study of the cyclic derivative **12c**. Ten-membered *trans*-fused chair-boat-like transition states are invoked to rationalize the stereochemical outcome of the addition. © 1997 Elsevier Science Ltd.

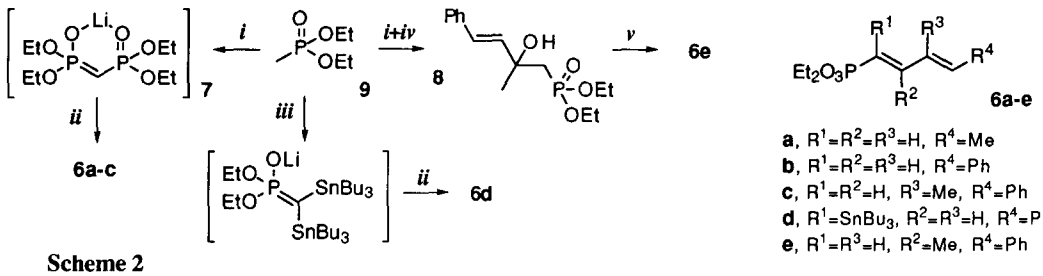
A variety of cognitive and neurodegenerative processes in the mammalian central nervous system are mediated by the *N*-methyl-D-aspartate (NMDA, **1**) receptors, a subclass of the excitatory amino acid receptors.[1] Overstimulation of the NMDA receptor-ionophore complex by an excess of glutamate in the synaptic region triggers a cascade of events leading to neuronal death. This process has been associated with the pathophysiology of a number of acute and chronic neurological disorders, such as cerebral isquemia, epilepsy and Alzheimer's or Parkinson's diseases.[2] Although the potential therapeutic use of the NMDA receptor antagonists is supported by their neuroprotectant effect on some experimental models, known competitive inhibitors are often inactive *in vivo* because of poor transport to the brain, while the non-competitive ones present serious behavioural effects. Phosphono amino acids, such as D-AP5 and D-AP7 (**2** and **3**, respectively) constitute the prototypic competitive NMDA receptor antagonists, and have focused a great deal of effort towards the improvement of their binding affinity and bioavailability in the last decade.[3] One approach to meeting this goal has been the reduction of the conformational mobility through the incorporation of ring systems, insaturations or/and hydrophobic groups into the acyclic structures of the amino acids. While a number of structure-activity relationship studies have been carried out on AP5- and AP7-length compounds, less attention has been paid to the AP6 series.[4] As part of a project directed to the design of new bioactive phosphonates we report here the diastereoselective synthesis of several 2-amino-6-phosphono-4-hexenoic acids **4**, a series of semi-rigid analogues of D-AP6 with lipophilic substituents.

Scheme 1



Although additions to electron deficient alkenes constitute a powerful method in asymmetric synthesis [5] and unsaturated systems bearing phosphonate groups act as acceptors with a variety of nucleophiles [6], diastereoselective additions to alkenyl and butadienyl phosphonates are scarce in the literature.[7] Studying the addition of alkenylphosphonates to a chiral glycine enolate (lithiated Schöllkopf's bislactim ether, **5**),[8] we have observed a regioselective 1,6-addition when *O,O*-diethyl-1,3-butadienylphosphonate was used as the acceptor. The high level of stereoselection found in these processes prompted us to explore the scope of the additions to prochiral 1*E*,3*E*-butadienylphosphonates **6**, that could result in direct and stereocontrolled access to a series of 2-amino-6-phosphono-4-hexenoic acids **4**, potential competitive NMDA receptor antagonists.

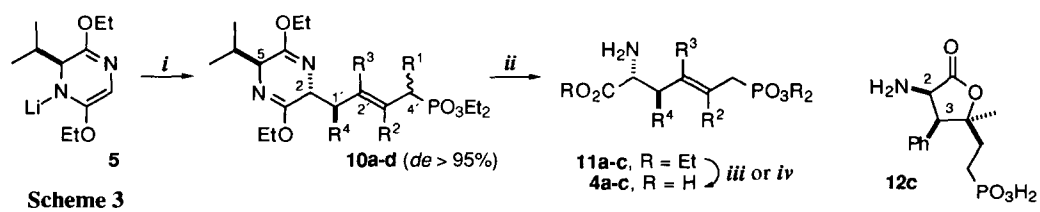
A representative series of 1*E*,3*E*-butadienylphosphonates **6a-e** was prepared as depicted in scheme 2. Condensation of lithiomethylenebisphosphonate (**7**) with the corresponding aldehydes afforded pure 1*E*,3*E*-dienylphosphonates **6a-c** in good yields.[9] α-Tributyltinbutadienylphosphonate **6d** was synthesized using a "tin-Peterson-like" alkenylation, as described in the literature.[10] As the modified Wadsworth-Emmons olefination of 4-phenyl-3-buten-2-one was unsuccessful, dienylphosphonate **6e** was prepared by dehydration of β-hydroxyphosphonate **8**, which was in turn obtained by addition of the ketone to the lithium salt of methylphosphonate **9**. In this way, compounds **6d** and **6e** could be isolated in 85% and 45% yield, respectively, after flash chromatography of the crude mixtures of isomers.



Scheme 2

i. a. 2 eq. LDA, -78 °C, THF, 10 min. *b.* $ClPO_3Et_2$, -78 °C, THF, 10 min. *ii.* RCHO, THF, -78 °C to RT. 65-85% (*i+ii or iii+ii*). *iii. a.* 3 eq. LDA, -78°C, THF. *b.* 2 eq. $ClSnBu_3$, -78°C, THF, 1h. *iv.* 4-phenyl-3-buten-2-one, THF, -78 °C to RT. 75% *v.* H_2SO_4 2.5M:THF 1:1, reflux, 4h, 45%.

Schöllkopf described an exceptionally high level of regio and stereoselection in the 1,6-addition of lithiated bislactim ethers to prochiral 2,4-pentadienoates.[11] Although the complete stereochemical course of such process was not established, only one 1,6-adduct could be detected by NMR. In the present study we found that lithium salt **5** [12] rapidly adds to 1,3-butadienylphosphonates **6a-d** at low temperature, to afford 1,6-addition products (**10a-d**, see scheme 3) in good yields. Integration of the ^1H-decoupled ^{31}P NMR spectra of the crude reaction mixtures in cases **a**, **b** and **c** revealed a very high asymmetric induction in the formation of both new chiral centers as well as an outstanding stereoselection in the formation of the double bond geometry. In this way, the observed diastereomeric excesses (*de*) of the 2,5-*trans*-2,1′-*anti*-2′*E* isomers **10a-c** were greater than 95%. Addition to acceptor **6d**, with two stereogenic centers, also took place regio and stereoselectively, to afford a mixture of two 1,6-addition products in a 3:2 ratio. Demetalation of the mixture of allyltin derivatives **10d** (by treatment with *n*-BuLi at -78 °C and subsequent quench with HOAc) gave rise to pure adduct **10b**, confirming the exclusive formation of two epimeric 2,5-*trans*-2,1′-*anti*-2′*E* adducts also in case **d**. In contrast to the rest of the acceptors, butadienylphosphonate **6e**, characterized by substitution at position 2, reacted nonselectively with the lithium salt **5**, originating a complex mixture of addition products that could not be separated. Evidence supporting the 2,5-*trans*-2′*E* configuration of the adducts **10a-c** was obtained by NMR analysis. Thus, for these compounds, H5 resonance appears as a quasi triplet with $^5J_{H2H5}$ ~3.5 Hz, typical for a *trans* relation of substituents at the pyrazino ring,[13] with δ between 3.60-3.80 ppm. *E*-configuration at double bond was assigned on the basis of a set of NOEs observed between the alkenyl protons and substituents at positions 1′ and 4′. Assignation of a 2,1′-*anti* configuration for the addition products follows from NMR analyses of a cyclic derivative of **12c**, as depicted in figure 1.[14]



Scheme 3

i. a. **6a-d**, -78°C, THF, 5 min. *b.* AcOH, 56-88%. *ii.* HCl 0.25M/THF 1:1, RT, 24h, 78-95%. *iii.* HCl 12N, reflux, 4h, 69-85%. *iv.* TMSI, reflux, 8h, 83%.

Mild acid hydrolysis of the bislactim ether provided the amino esters **11a-c** in very good yields. Vigorous acid hydrolysis of the amino esters allowed, after purification by reverse phase chromatography (H_2O, RP-18 230-400 mesh), the isolation of the amino acids **4a,b** as their hydrochloride salts in excellent yields. On the other hand, acid hydrolysis of amino ester **11c** (HCl 12N, reflux, 6h) took place with simultaneous cyclization, to afford a mixture of lactones, from which **12c** could be isolated in 75% yield. Treatment of amino ester **11c** with iodotrimethylsilane (reflux, 8h) finally led to amino acid **4c** as its hydroiodide salt. [15]

Lactone **12c** showed in its ^1H NMR spectrum a pattern of signals suitable for the study of its relative stereochemistry by NOE difference spectroscopy. After corroborating the ^1H NMR assignments (COSY experiment), on the basis of a complete set of NOEs, supported by force field and semiempirical calculations [16] (see figure 1), a 2,3-*cis* configuration was determined for lactone **12c**. This result indicates the selective formation of the 2,1′-*anti* isomer in case **c** and let us to propose the same stereochemical outcome for all the additions of **5** to *E,E*-butadienylphosphonates **6a,b,d**.

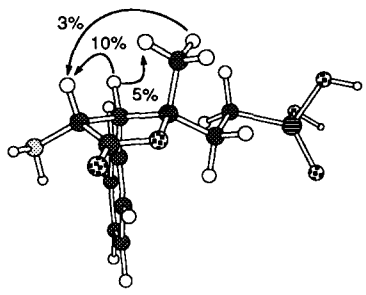


Fig. 1. PM3-optimized conformation for lactone **12c**, showing characteristic NOEs.

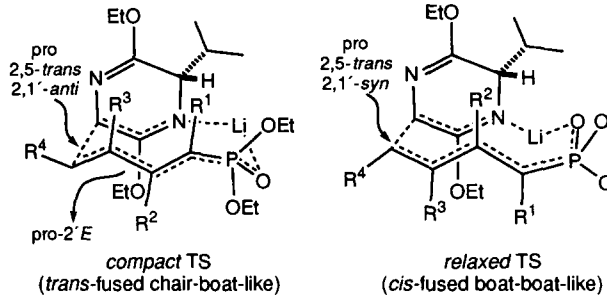


Fig. 2. *Compact* and *relaxed* transition states proposed for the 1,6-addition.

A 2,5-*trans*-2,1′-*anti* addition was previously encountered in other conjugate additions of lithiated bislactim ethers to α,β-unsaturated compounds (nitroolefins,[13] 2-alkenoates,[18] and alkenylphosphonates[8]), while a 2′*E* selectivity was also reported in the corresponding additions to 2,4-pentadienoates.[11] The observed stereochemical course can be rationalized by extending a semiempirically optimized transition state model initially developed for the 1,4-additions to alkenylphosphonates.[19] Thus, an initial lithium-phosphoryl coordination to form a chelate complex, followed by a rate-determining reorganization through competitive ten-membered cyclic transition structures, can account for the stereochemical features of the reaction. According to such a model, the selective formation of the 2,5-*trans*-2,1′-*anti*-2′*E* adducts is explained by invoking a strong kinetic preference for a *compact* (*trans*-fused chair-boat-like) transition state over a *relaxed* counterpart (*cis*-fused boat-boat-like, see figure 2).[20]

In conclusion, the conjugate addition of lithiated bislactim ethers to 1*E*,3*E*-butadienylphosphonates takes place regioselectively, with a variable level of stereoselection, depending on the pattern of substitution at acceptor. For 4-substituted and 1,4- or 3,4-disubstituted butadienylphosphonates, the reaction results in an almost complete translation of the 1*E*,3*E* geometry into a 2,1′-*anti*-2′*E* configuration at the adduct. The process constitutes a convenient approach to a variety of optically pure 2-amino-6-phosphono-4-hexenoic acids, potential competitive NMDA receptor antagonists with improved bioavailability.

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9. 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. Stereochemistry of butadienylphosphonates was assigned according to the $^3J_{HP}$ coupling constants or a set of NOEs in the ^1H NMR spectra. Compounds **6a-c,e** and **6d** were obtained with >98% 1*E*- and 1*Z*-configuration, respectively (^{31}P NMR analyses). Spectral data obtained for compounds **6d** are in full agreement with those previously reported in ref. 10.
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15. Salient data for the amino phosphonic acids: the ^{13}C NMR spectra (50 MHz, D_2O, RT) of compounds **4a-c** exhibit typical signals for C-1 (172.0-172.3), C-2 (51.3-58.4), C-3 (38.5-58.9), C-4 (130.8-137.5, d, ^3JCP~ 10-14 Hz), C-5 (119.8-128.8, d, ^2JCP~ 9-11 Hz), C6 (28.4- 33.3, d, ^1JCP~ 131-134 Hz). ^1H NMR (200 MHz, D_2O, RT) data for **12c**: 1.14-1.79 (m, 4H, H-1′,2′); 1.44 (s, 3H, Me); 3.79 (d, *J* = 8.5 Hz, 1H, H-3); 4.96 (d, *J* = 8.5 Hz, 1H, H-2); 6.96-7.00 (m, 2H, Ar); 7.21-7.24 (m, 2H, Ar) **12c**: $[\alpha]_D^{20} = -37.5$ (H_2O, c = 0.43). **4a**: $[\alpha]_D^{20} = +19.4$ (H_2O, c = 2.4). **4b**: $[\alpha]_D^{20} = +11.4$ (H_2O, c = 2.0). **4c**: $[\alpha]_D^{20} = -14.4$ (HCl 1.0M, c = 1.45).
16. Minimum energy conformations for compound **12c** were located using MMX force field as implemented in PCModel v5 and GMMX v1.6 programs.[17a] The geometries of the most important conformers were fully optimised by semiempirical molecular orbital calculations, using the PM3 Hamiltonians included in MOPAC93.[17b] The refined geometry in the gas phase was in agreement with the conformation in solution deduced from ^1H NOE spectroscopy, as depicted in Fig.1.
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