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Diastereoselective synthesis of 4-substituted 2-amino-4-phosphonobutanoic acids

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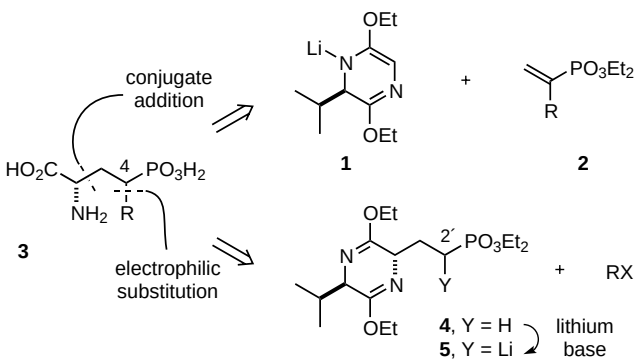
Abstract—Conjugate additions of the lithiated bis-lactim ether derived from *cyclo*-[Gly-D-Val] **1** to α-substituted vinylphosphonates **2** or electrophilic substitutions on the lithiated bis-lactim ether derived from *cyclo*-[L-AP4-D-Val] **5** allow direct and stereoselective access to a series of 4-substituted AP4 derivatives **3** in enantiomerically pure form.

The physical and structural similarity between the phosphonic acid group and the biologically important phosphate ester and carboxylic acid moieties gives 2-amino-4-phosphonobutanoic acid (AP4) derivatives the ability to act as substrate mimics and interfere with significant enzymatic and receptor-mediated processes. Thus, AP4 constitutes a glutamate analog where the distal carboxylate group is replaced by a phosphonic acid group. In this manner, several AP4 derivatives have shown potent and selective agonistic character at group III of the metabotropic glutamate receptors (mGluRs), which play fundamental roles in the central nervous system and are attractive targets for therapeutic intervention in a number of neurological diseases.[1,2] In addition, AP4 derivatives constitute non-hydrolyzable isosteres of *O*-phosphoserine and *O*-phosphothreonine where the phosphoryl ester oxygen is substituted by a methylene linkage. Such phosphonylated analogs have been incorporated into useful peptides[3] for the biochemical and immunochemical investigation of the Ser/Thr protein kinases and phosphatases, which are recognized as key elements in the regulation of cell function.[4]

The extensive interest in AP4 derivatives has led to the development of numerous syntheses, most of them related to three major methodologies. Thus, phosphites have been utilized for the conjugate addition to carbonyl compounds which were subsequently converted to amino acids via Strecker reaction,[5] or have been reacted with halides,[6a,b] triflates[3d,6c] or carbonyl[3b,d,e] functionalities located at the side chain of amino acid derivatives. Alternative syntheses have relied on glycine enolate equivalents for the alkylation,[7] 1,3-dipolar cycloaddition[8] and conjugate addition[9] of suitable functionalized phosphonates.

In this area, we have shown that conjugate additions of lithiated bis-lactim ethers, derived from *cyclo*-[Gly-D-Val] **1** (Scheme 1) and *cyclo*-[Ala-D-Val], to β-substituted vinylphosphonates enable a stereocontrolled access to enantiomerically pure 2-methyl and/or 3-substituted AP4 derivatives.[9a–c] Studying the reactivity of the lithium azaenolate derived from *cyclo*-[Ala-D-Val],



Scheme 1. Approaches to 4-substituted AP4 derivatives.

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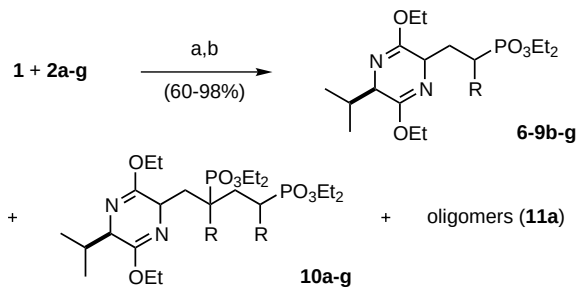
we also observed remarkable stereoselection in the 1,4-addition when *O*,*O*-diethyl 1-phenylethenylphosphonate was used as the acceptor.[9b] These precedents prompted us to explore the scope and limitations of the additions of lithiated bislactim **1** to a series of α-substituted vinylphosphonates **2**, which could result in a direct route to enantiomerically pure 4-substituted AP4 derivatives **3**, useful for delineating the requirements for receptor binding and physiological responses at group III of the mGluRs.

Aimed toward the development of an alternative approach to the AP4 derivatives **3**, we decided to investigate the electrophilic substitution processes on the bis-lactim ether **4**,[7b] derived from *cyclo*-[L-AP4-D-Val]. Based on its potential role as first intermediate resulting from the addition of **1** to the unsubstituted vinylphosphonate,[9d] the phosphonate carbanion **5** should be accessible by treatment of **4** with an adequate base. Subsequent trapping of **5** with different electrophilic reagents (RX) could give rise to 2′-substituted bis-lactim ethers as precursors of the targeted 4-substituted AP4 derivatives.[10]

To this end, (3*R*)-2,5-diethoxy-3-isopropyl-3,6-dihydropyrazine was prepared from glycine and D-valine[11] and was transformed into (2*S*,5*R*)-3,6-diethoxy-2-[2-(diethoxyphosphoryl)ethyl]-2,5-dihydro-5-isopropylpyrazine **4**,[13] while α-substituted vinylphosphonates were obtained according to the literature. Upon addition of vinylphosphonates **2a–g** to one equivalent of **1** at −78°C in THF, reactions took place rapidly. After quenching with acetic acid and work-up, ^{31}P NMR analysis of the crude mixtures revealed the formation of mixtures of 1:1 and 1:2 addition products (**6–9b–g** and **10a–g**, respectively) along with oligomerization products in the reaction of **2a** (see Scheme 2).



Scheme 2. Conjugate additions of **1** to vinylphosphonates **2a–g**. (a) THF, −78°C, 5 min. (b) AcOH, −78°C to rt.

Both the ratio between 1:1 and 1:2 adducts and the stereoselectivity of the addition were found to be markedly dependent on the nature of the α-substituent of the acceptor (see Table 1). Thus, vinylphosphonates **2f** and **2g** with an electron-withdrawing substituent as the methoxycarbonyl or the diethoxyphosphoryl group, gave rise to the 1:1 adducts in lower proportion than vinylphosphonates **2b–e** (with phenyl, silyl, stannyl or phosphoryloxy groups) probably due to the increased electron deficiency and higher acceptor character of the former acceptors. Moreover, the addition to vinylphosphonates **2b–e** took place in a highly diastereoselective fashion and led to the exclusive formation of 2,5-*trans* adducts **6b–e** and **7b–e** (see Fig. 1), while acceptors **2f** and **2g** gave rise to mixtures of all of the possible 2,5-*trans* and 2,5-*cis* adducts.[14,15] In cases **d** and **f**, conversion to the desired 1:1 adducts could be increased simply by using an excess of the lithium azaenolate.[16] After chromatographic separation, the fractions containing the adducts **6–9b–g** were isolated in moderate to good yields. Evidence supporting their relative configuration was obtained by NMR analysis.[17,18] The assignment of absolute configurations follow from the use of bis-lactim ethers derived from D-Val, as there is ample precedent.[14]

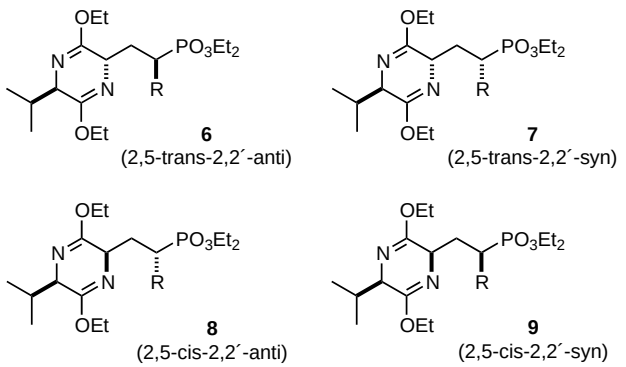


Figure 1. Diastereomeric 2′-substituted bis-lactim ethers **6–9**.

Table 1. Selectivity and yields in the conjugate addition of **1** to vinylphosphonates **2a–g**

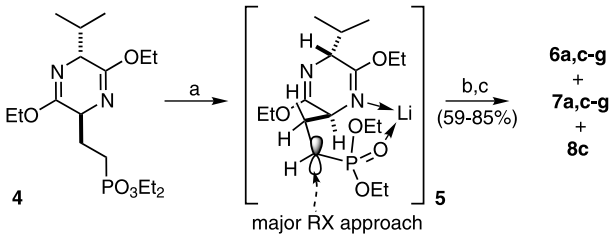
Case	R	**1** (equiv.)	1:1 adducts		**10** (%)	**11** (%)
			(%)	**6**/**7**/**8**/**9**		
2a	Me	1.1	–	–	42	27
2b	Ph	1.1	85	1:1:–:–	5	–
2c	TMS	1.2	72	1:1:–:–	11	–
2d	$SnPh_3$	1.1	42	1:1:–:–	42	–
2d	$SnPh_3$	2.2	78	1:1:–:–	15	–
2e	OPO_3Et_2	1.2	83	1:1:–:–	8	–
2f	CO_2Et	1.2	25	4:4:3:3	65	–
2f	CO_2Et	2.2	56	4:4:3:3	42	–
2g	PO_3Et_2	1.2	35	3:2[a]	25	–

[a] Refers to the **6g**/**8g** ratio (there is no *anti*/*syn* isomerism in case **g**).

We reasoned that the formation of 1:1 mixtures of adducts **6b–e**/**7b–e** should take place with quenching by a non-selective protonation of the 2,5-*trans*-phosphonate carbanions arising from the stereoselective addition to vinylphosphonates **2b–e**. Such phosphonate carbanions should be sufficiently stabilized,[19] thus suppressing transmetallation processes that could compromise the integrity of the newly formed stereogenic center at position 2. With these ideas in mind and pursuing a more general and stereoselective route to 4-substituted AP4 derivatives, we decided to explore the scope and limitations of the electrophilic substitution process, 'via enolate', on the bis-lactim ether **4**.

Slow addition of bis-lactim ether **4** to a solution of LDA in THF at −78°C was followed, after 15 min at the same temperature, by the dropwise addition of the electrophilic reagent. The reactions were quenched 5 min later by adding a proton source. After the work-up, the ^{31}P NMR analysis of the crude mixtures revealed a highly regioselective course for the substitution process, which, in spite of the literature,[20] led to the exclusive formation of 2′-substituted bis-lactims **6–8a**,**c–g** (see Scheme 3).

Integration of the ^{1}H decoupled ^{31}P NMR spectra also revealed moderate levels of asymmetric induction at the substitution position, depending upon the nature of the electrophilic reagent (see Table 2). In this way, for the cases **a**,**d–g**, the substitution processes took place with a complete retention of the 2,5-*trans* configuration, affording mixtures of the 2,2′-*anti* and 2,2′-*syn* products **6**/**7** in 1:2 or 2:3 ratios. In contrast, the silylation of **5**, though regio- and stereoselective at the 2′-position, took place with a significant degree of racemization at position 2, and led to mixtures of the 2,5-*cis* and 2,5-*trans* products **6c**/**7c**/**8c** in a 1:4:1 ratio.



Scheme 3. Electrophilic substitutions on bis-lactim ether **4**. (a) LDA, THF, −78°C, 15 min. (b) RX, THF, −78°C, 5 min. (c) AcOH or H_2O, −78°C to rt.

Table 2. Selectivity and yields in the electrophilic substitutions on **5**

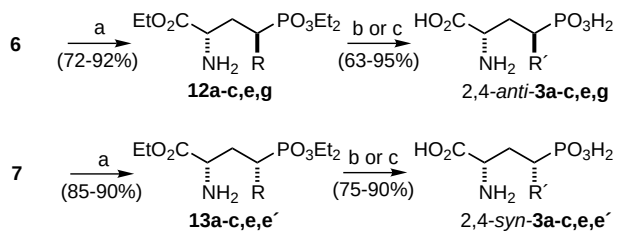
Case	R	Electrophile	H^+ source	(%)	**6**/**7**/**8**
a	Me	MeI	–	84	2:3:–
c	TMS	TMSCl	–	85	1:4:1
d	$SnPh_3$	$SnPh_3Cl$	–	75	2:3:–
e′	OH	MoOPH	H_2O	59	1:2:–
f	CO_2Et	CO_3Et_2	AcOH	66	2:3:–
g	PO_3Et_2	Et_2PO_3Cl	AcOH	83	1:–[a]

[a] Refers to the **6g**/**8g** ratio (there is not *anti*/*syn* isomerism in case **g**).

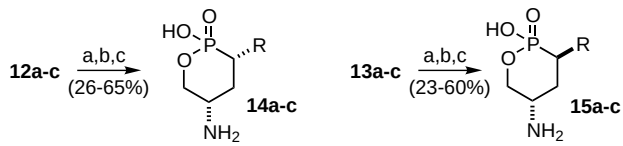
Mild acid hydrolysis of the 2′-substituted bis-lactims **6a–c**,**e**,**g** and **7a–c**,**e**,**g** provided the corresponding 2,4-*anti* or 2,4-*syn* amino esters **12** or **13** (see Scheme 4) in high yields after removal of the valine ester by chromatography. Hydrolysis of these amino esters was accomplished by either heating in concentrated hydrochloric acid (in cases **a**, **b**, and **g**) or sequential treatment with lithium hydroxide and trimethylsilyl bromide (in cases **c** and **e**). After purification by reversed phase chromatography, the 4-substituted AP4 derivatives **3a–c**,**e**,**g**, either in the 2,4-*anti* or in the 2,4-*syn* series, were isolated in high yields.

Since none of compounds **3**, **6–9**, **12** or **13** provided crystals suitable for X-ray diffraction analysis, we decided to derivatize the amino esters to the corresponding 1,2-oxaphosphorinanes. The strong preference for chair conformations in solution reported for related oxaphosphorinanes[3d,9a–c,21] would make such derivatives amenable for the assignment of their relative configuration on the basis of NMR studies. Thus, after protection of the amino group as a *tert*-butylcarbamate, chemoselective reduction of the carboxylic ester took place with partial cyclization to *N*-Boc-amino-oxaphosphorinanes. Finally, cleavage of the *N*-Boc and *O*-ethyl ester groups by treatment with trimethylsilyl bromide yielded **14a–c** and **15a–c** (see Scheme 5).

The analysis of the sets of observed NOEs confirmed a *cis* configuration for all the oxaphosphorinanes **14a–c**, while a *trans* relationship was assigned to the oxaphosphorinanes **15a–c**. These results allow us to assume a 2,2′-*syn* configuration for the major substitution products. The *syn* selectivity in the substitution process can



Scheme 4. Hydrolysis of 2′-substituted bis-lactim ethers **6** and **7**. (a) 0.25N HCl, THF, rt, 1–15 h. (b) 12N HCl, reflux, 6 h. (c) i: LiOH, H_2O, rt, 1 h. ii: TMSBr, CH_2Cl_2, rt, 48 h. iii: MeOH. Legend: **a**, R = R′ = Me; **b**, R = R′ = Ph; **c**, R = R′ = TMS; **e**, R = OPO_3Et_2, R′ = OPO_3H_2; **e′**, R = R′ = OH; **g**, R = PO_3Et_2, R′ = PO_3H_2.



Scheme 5. Transformation of amino esters **12**,**13a–c** into their oxaphosphorinane derivatives **14**,**15a–c**. (a) $(Boc)_2O$, dioxane:H_2O, rt, 2–7 h. (b) i: $LiBH_4$, THF, 0°C, 15 h–4 d. ii: H_2O. (c) i: TMSBr, CH_2Cl_2, rt, 15 h. ii: MeOH. Legend: **a**, R = Me; **b**, R = Ph; **c**, R = TMS.

be rationalized considering the involvement of a cyclic phosphonate carbanion such as **5** with preferential approach of the electrophile with an axial trajectory to its less hindered face (see Scheme 3).

In conclusion, either the conjugate additions of lithiated bis-lactim ether derived from *cyclo*-[Gly-D-Val] to α-substituted vinylphosphonates or the electrophilic substitutions on the bis-lactim ether derived from *cyclo*-[L-AP4-D-Val] take place regio- and stereoselectively. Although the level of stereoselection attained in these processes depends on the nature of the α-substituent or the electrophilic reagent, they allow a direct access to a variety of 4-substituted AP4 derivatives in enantiomerically pure form. Work is now underway to extend these methodologies to the synthesis of 4-alkylidene derivatives of glutamate and AP4. Evaluation of the biological activity of these amino acids is currently in progress.

Acknowledgements

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13. Compound **4** was prepared as described by Shapiro et al. in Ref. 9d, but using a *O*,*O*-diethyl phosphonate instead of the *O*,*O*-diallyl one. All new compounds gave satisfactory IR, MS, and ^{1}H, ^{13}C and ^{31}P NMR data.
14. We have not found any precedent for such non-selective conjugate additions in the Schöllkopf's bis-lactim chemistry. 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.
15. The poor selectivity in these additions may well derive from an increased reactivity of acceptors **2f** and **2g**, as was suggested by the Editor.
16. The excess of the Schöllkopf reagent could be almost completely recovered and showed no racemization.
17. For either **6b–e** or **7b–e** the H-5 resonance appears between 3.67 and 3.91 ppm, as a triplet with ^{5}JH2H5 close to 3.5 Hz, typical for a *trans* relation of substituents at the pyrazine ring (see Ref. 17). The relative configurations at position 2′ were assigned on the basis of the sets of NOEs observed for the 1,2-oxaphosphorinane derivatives **14a–c**.
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19. Probably by chelation of the lithium with the phosphoryl oxygen and a nitrogen atom of the bis-lactim ring, as depicted in Scheme 3.

20. The lithium salt of the bis-lactim ether derived from *cyclo*-[D-AP4-L-Val] was reported to react with alkyl bromides to yield, exclusively, 2-alkylated bis-lactims. See Ref. 7b.

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