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

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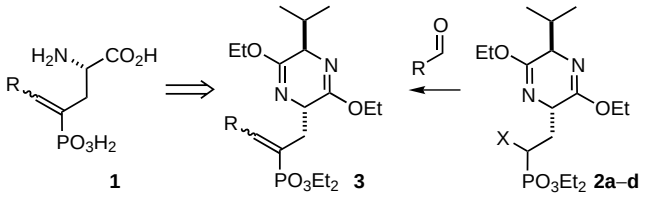
Abstract—Olefination of α-silyl-, α-phosphoryl- and α-stannyl-stabilised phosphonate carbanions derived from *cyclo*-[L-AP4-D-Val] Li^+**4b–d**$^-$ allow a (*Z*)-selective access to the α,β-substituted vinylphosphonates **7A–E** that have been transformed into enantiomerically pure 4-alkylidene AP4 derivatives **12A,B** and **13A,C**. According to semi-empirical (PM3) calculations, the preference for *like* topologies in the intermediate adducts of the phosphonate addition step accounts for the highly (*Z*)-selective course of the 'tin-Peterson-like' olefination.

1. Introduction

As the major excitatory neurotransmitter in the central nervous system, (*S*)-glutamic acid operates through different classes and subtypes of ionotropic and metabotropic glutamate receptors (iGluRs and mGluRs, respectively) which constitute potential targets for therapeutic intervention in a number of neurological disorders.[1] In particular, several phosphonic acid isosters of glutamic acid, the 2-amino-4-phosphonobutanoic acid (AP4) derivatives, have been found to have potent and selective activity at group III of mGluRs (mGluR4 and mGluR6-8).[2] Therefore, there is considerable interest in the development of practical and versatile methodology for the preparation of AP4 derivatives, that may result in useful tools for characterising the molecular pharmacology of the mGluRs.



Scheme 1. a, X = H; **b**, X = $SiMe_3$; **c**, X = PO_3Et_2; **d**, X = $SnPh_3$.

As part of an ongoing program aimed to the search of agonists and antagonists for the group III of mGluRs,[3] in this communication we wish to report the synthesis of a series of (4*Z*)- and (4*E*)-alkylidene AP4 derivatives **1** in enantiomerically pure form (see Scheme 1). In this area, we have recently found that electrophilic substitutions on the bis-lactim ether derived from *cyclo*-[L-AP4-D-Val] **2a** take place in a regioselective fashion, α to the phosphonate group, and allow a direct and stereoselective access to a variety of 4-substituted AP4 derivatives.[3a] Based on these precedents we envisaged that electrophilic substitutions on **2a** with phosphonyl, silyl or stannyl groups could be followed by Wadsworth–Emmons or Peterson-like olefinations of carbonyl compounds, giving rise to the vinylphosphonates **3**,[4] as precursors of the targeted 4-alkylidene AP4 derivatives.

2. Results and discussion

We first examined the olefination reactions of benzaldehyde, as model carbonyl compound, using the α-trimethylsilyl-, α-diethoxyphosphoryl- and α-triphenylstannyl-stabilised phosphonate carbanions derived from bis-lactim ethers **2b–d**. Towards this end, the phosphonate carbanion Li^+**4b**$^-$ was generated by the addition of α-silylvinylphosphonate **6**[5] to a solution of lithium azaenolate **5**, derived from (3*R*)-2,5-diethoxy-3-isopropyl-3,6-dihydropyrazine,[6] at −78°C in THF, while Li^+**4c**$^-$ and Li^+**4d**$^-$ were prepared by adding bis-lactim ethers **2c** and **2d**[3a] to solutions of LDA at −78°C in THF (see Scheme 2).[8] Benzaldehyde was slowly added 15 min later, and the reaction mixtures were gradually warmed to 0°C during 4 h. After

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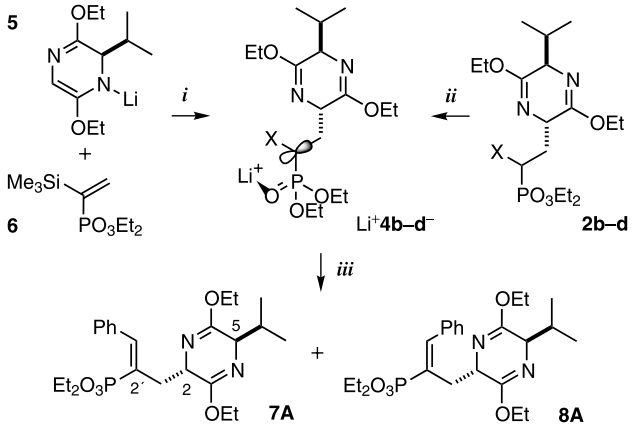
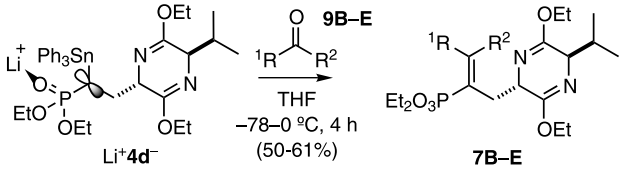


Scheme 2. *Reagents and conditions*: (i) THF, −78°C, 15 min; (ii) LDA, THF, −78°C, 15 min; (iii) benzaldehyde, THF, −78 to 0°C, 4 h (70–85%). **b**, X = $SiMe_3$; **c**, X = PO_3Et_2; **d**, X = $SnPh_3$.

quenching with acetic acid and aqueous work-up, the 2′-benzylidene substituted bis-lactim ethers **7A**/**8A** were isolated in 56–77% yield, along with 10–25% of unreacted starting materials.[9,10] The analysis of the ^{31}P NMR spectra of the crude mixtures revealed different levels of stereoselection in the formation of the new double bond. Thus, olefinations with the α-trimethylsilyl- and α-diethoxyphosphoryl-stabilised phosphonate carbanions Li^+**4b**$^-$ and Li^+**4c**$^-$ led to mixtures of 2,5-*trans*-2′*Z* and 2,5-*trans*-2′*E* bis-lactim ethers **7A**/**8A** in 3:2 and 5:1 ratio, respectively. However, starting with the 2′-triphenylstannyl substituted bis-lactim **2d**, the 'tin-Peterson-like' olefination gave rise, exclusively, to the (*Z*)-vinylphosphonate **7A**. After chromatographic separation of the 2′-benzylidenated bis-lactim ethers, evidence supporting their relative configurations was obtained from NMR analysis.[11–13]

Having shown the feasibility of performing the olefination process on the bis-lactim ethers derived from *cyclo*-[L-AP4-D-Val] without compromising the integrity of its chiral centers, a series of vinylphosphonates **7B**–**E** was prepared in moderate yield, by application of the 'tin-Peterson-like' reaction to various structurally diverse carbonyl compounds (see Scheme 3). Thus, solutions of isobutyraldehyde (**9B**), 2-thienylcarboxaldehyde (**9C**), cinnamaldehyde (**9D**) or ciclohexanone (**9E**) in THF were added dropwise to solutions of Li^+**4d**$^-$ in THF at −78°C, and the reaction mixtures were gradually warmed to 0°C during 4 h. After quenching with acetic acid and aqueous work-up, vinylphosphonates **7B**–**E** were isolated in 50–61% yield, along with 10–32% of unreacted starting materials.[9–11] As was previously encountered in the reaction of Li^+**4d**$^-$ with benzaldehyde, after inspection of the ^{31}P NMR spectra of the crude mixtures obtained in the reactions with the aldehydes **9B**, **9C**, and **9D**, we could not detect any absorption corresponding to the minor (*E*)-isomers. Thus, the 'tin-Peterson-like' olefinations of either α-branched, α,β-unsaturated, aromatic or heteroaromatic aldehydes using the α-triphenylstannylphosphonate lithium salt derived from *cyclo*-[L-AP4-D-Val] take place with an outstanding level of stereoselection giving rise, exclusively, to the kinetically favoured (*Z*)-vinylphosphonates.

The selective formation of (*Z*)-vinylphosphonate **7A** in the Wadsworth–Emmons olefination of benzaldehyde with Li^+**4c**$^-$ is remarkable, since the reactions of carbonyl compounds with lithioalkylidenebisphosphonates have been reported to yield selectively β- and α,β-substituted vinylphosphonates with (*E*)-configuration.[4g–l] Conversely, the stereochemical course of the 'tin-Peterson-like' olefinations with Li^+**4d**$^-$ is similar to that previously encountered in the preparation of other α,β-substituted vinylphosphonates.[4e] The exclusive formation of the (*Z*)-vinylphosphonates **7A**–**D** in the reactions of the α-triphenylstannylphosphonate carbanion with aldehydes **9A**–**D** can be understood as a consequence of the preferential formation of the *like* α-stannyl-β-alkoxyphosphonates which then irreversibly collapse to the (*Z*)-vinylphosphonates. Presumably, the higher stereoselectivity observed in the present work may be accounted for the additional coordination of the lithium cation with a nitrogen atom of the bis-lactim ether moiety. In agreement with this proposal, semi-empirical molecular orbital calculations (PM3 Hamiltonian) for the addition process of Li^+**4d**$^-$ to benzaldehyde (**9A**) showed that the *like* transition structure and the *like* intermediate adduct are preferred to the *unlike* ones by 2.3 and 3.6 kcal/mol, respectively (see Fig. 1).[14–17]



Scheme 3. **B**, $R^1 = (CH_3)_2CH$, $R^2 = H$; **C**, R^1 = 2-(C_4H_3S), $R^2 = H$; **D**, $R^1 = C_6H_5CH{=}CH$, $R^2 = H$; **E**, $R^1 + R^2 = -(CH_2)_5-$.

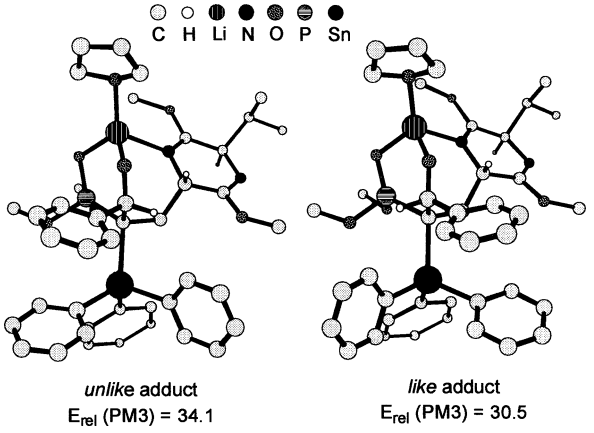


Figure 1. Competitive *like* and *unlike* intermediate adducts located at the PM3 level for the reaction of Li^+**4d**$^-$ with **9A** in the presence of one THF molecule. Hydrogen atoms are omitted, except for the chiral centers. Relative energies to the monosolvated coordination complex Li^+**4d**$^-$·**9A** are in kcal/mol.

Mild acid hydrolysis of the pyrazine moiety of the vinylphosphonates **7A–C** and **8A** (0.25N HCl, THF, rt, 1–5 h) provided the corresponding amino esters **10A–C** and **11A** in good yields (75–90%) after the removal of the valine ester by chromatography (see Fig. 2). Hydrolysis of amino esters **10A**,**B** and **11A** to the corresponding amino acids **12A**,**B** and **13A** was accomplished by heating in concentrated hydrochloric acid (12N HCl, reflux, 3 h). Hydrolysis of the thienyl substituted amino ester **10C** required a sequential treatment with trimethylsilyl bromide (CH_2Cl_2, rt, 40 h) and lithium hydroxide (H_2O, rt, 2 h). Under these conditions, complete isomerisation of the double bond to afford the corresponding (*E*)-vinylphosphonic acid **13C** was observed. After purification by reversed phase chromatography, the 4-alkylidene AP4 derivatives **12A**,**B** and **13A**,**C** were isolated in good yields (68–89%).[18]

3. Conclusion

In conclusion, reactions of benzaldehyde with α-silyl-, α-phosphoryl- and α-stannyl-stabilised phosphonate carbanions derived from *cyclo*-[L-AP4-D-Val] take place without compromising the chiral integrity of the bis-lactim ether, giving rise to vinylphosphonates with different level of (*Z*)-stereoselection. The 'tin-Peterson-like' olefination of structurally diverse carbonyl compounds using the lithiated α-triphenylstannylphosphonate were found completely (*Z*)-stereoselective, and allowed a direct access to a series of 4-alkylidene AP4 derivatives in enantiomerically pure form, that may result in useful tools for the study of group III of mGluRs. Work is now underway to explore the (Z)-selective Wadworth–Emmons olefinations with Li^+**4c**$^-$ and to extend these methodologies to the synthesis of 4-alkylidene derivatives of glutamate.

Acknowledgements

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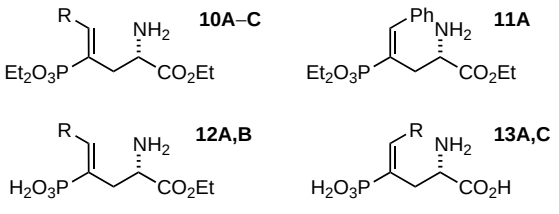

Figure 2. **A**, R = C_6H_5; **B**, R = $(CH_3)_2CH$; **C**, R = 2-(C_4H_3S).

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6. *Cyclo*-[Gly-D-Val] was obtained as described by Rose et al. Treatment of this compound with triethyloxonium tetrafluoroborate allowed the preparation of (3*R*)-2,5-diethoxy-3-isopropyl-3,6-dihydropyrazine. See: Rose, J. E.; Leeson, P. D.; Gani, D. *J. Chem. Soc. Perkin Trans. 1* **1995**, 157–165. Alternatively, both enantiomers of the related 2,5-dimethoxy-3-isopropyl-3,6-dihydropyrazine can be synthesised[7] or purchased from E. Merk.
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9. The starting material could almost be completely recovered, and showed no racemisation. Thus, the yield of the olefination could be increased to 70–85% by resubjecting recovered starting material to the same reaction conditions.

10. All new compounds gave satisfactory microanalysis, IR, MS and NMR data.
11. For either **7B–E** or **8A** H-5 resonance appears between 3.86 and 3.98 ppm, as a triplet with ^5JH2H5 close 3.5 Hz, typical for a *trans* relation of substituents at the pyrazine ring.[12] The configurations of the vinylphosphonate moiety were assigned on the basis of the ^3JHP and the ^3JCP observed in the ^{1}H and ^{13}C NMR spectra, due to the coupling of H-3′ and C-4′ with the phosphorous atom at the β position. Thus, for **7A–D**, ^3JH3′–P (*trans*) values range from 44.4–49.3 Hz and ^3JC4′–P (*cis*) values range from 7.8–12.1 Hz, which are characteristic for the vinylphosphonates with a (*Z*)-configuration. Conversely, for **8A**, with a (*E*)-configuration, ^3JH3′–P (*cis*) = 24.9 Hz and ^3JC4′–P (*trans*) = 23.1 Hz.
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13. Selected data for compound **7A**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.72 (d, J=6.8 Hz, 3H ($C\underline{H}_3$)CH), 1.07 (d, J=6.8 Hz, 3H ($C\underline{H}_3$)CH), 1.08 (t, J=7.0 Hz, 3H, $OCH_2C\underline{H}_3$), 1.09 (t, J=7.0 Hz, 3H, $OCH_2C\underline{H}_3$), 1.25 (t, J=7.0 Hz, 3H, $OCH_2C\underline{H}_3$), 1.29 (t, J=7.0 Hz, 3H, $OCH_2C\underline{H}_3$), 2.28 (dsp, J=6.8, 3.4 Hz, 1H (CH_3)C$\underline{H}$), 2.48 (ddd, J=20.5, 14.5, 8.8 Hz, 1H, H-1′), 3.17 (ddd, J=14.3, 12.7, 4.4 Hz, 1H, H-1′), 3.80–4.23 (m, 9H, H-5, $OC\underline{H}_2CH_3$), 4.25–4.34 (m, 1H, H-2), 7.27–7.51 (m, 5H, Ph), 7.20 (d, J=44.4 Hz, 1H, H-3′); $[\alpha]_D^{20}$ = −24 (CH_2Cl_2, c=1.1). Selected data for compound **8A**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.75 (d, J=6.8 Hz, 3H ($C\underline{H}_3$)CH), 1.02 (d, J=6.8 Hz, 3H ($C\underline{H}_3$)CH), 1.17–1.38 (m, 12 H, $OCH_2C\underline{H}_3$), 2.21 (dsp, J=6.8, 3.9 Hz, 1H (CH_3)C$\underline{H}$), 2.67–3.08 (m, 2H, H-1′), 3.91 (t, J=3.4 Hz, 1H, H-5), 3.93–4.27 (m, 8H, $OC\underline{H}_2CH_3$), 4.41–4.50 (m, 1H, H-2), 7.24–7.49 (m, 5H, Ph), 7.66 (d, J=24.9 Hz, 1H, H-3′); $[\alpha]_D^{22}$ = +142 (CH_2Cl_2, c=0.4).
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15. Calculations have been performed with MOPAC93.[16] Structures were fully optimised at the restricted Hartree–Fock level of theory with the PM3 method,[17] using the eigenvector following routine (TS keyword for transition state refinement) under the more rigorous criteria of the keyword PRECISE (gradient norm <0.01). The reported intermediate adducts were verified as minima by the absence of negative eigenvalues in the vibrational frequency analysis. For each located transition structure only one imaginary frequency was found in the diagonalised Hessian matrix, and their nature verified by internal reaction coordinate calculations to the chelate complexes and intermediate adducts. Conformational space accessible for each reported structure was studied considering two different rotamers for the isopropyl (with the tertiary carbon pointing to the nitrogen or to the imidate group) and the methoxy groups (pointing to the nitrogen atom or to the substituents of the bis-lactim ether), three rotamers for the THF molecule and *gg*, *ga*, *ag* and *aa* conformations for the COPOC moiety. Ethyl groups were replaced by methyl groups to remove additional degrees of conformational freedom in the models.
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18. Selected data for amino acid **12A**: ^{1}H NMR (200 MHz, D_2O) δ 2.64 (ddd, J=17.1, 14.9, 8.6 Hz, 1H, H-3), 2.98 (dt, J=15.0, 4.7 Hz, 1H, H-3), 4.01 (dd, J=8.5, 4.5 Hz, 1H, H-2), 6.97 (d, J=41.5 Hz, 1H, H-5), 7.15–7.32 (m, 5H, Ph); $[\alpha]_D^{28}$ = −14 (H_2O, c=1.1). Selected data for amino acid **13A**: ^{1}H NMR (200 MHz, D_2O) δ 2.75 (ddd, J=15.9, 9.2 Hz, 1H, H-3), 3.03 (dt, J=15.9, 4.9 Hz, 1H, H-3), 3.97 (dd, J=9.2, 4.9 Hz, 1H, H-2), 7.14–7.32 (m, 6H, H-5, Ph); $[\alpha]_D^{28}$ = −49 (H_2O, c=1.1). Selected data for amino acid **12B**: ^{1}H NMR (200 MHz, D_2O) δ 0.76 (d, J=6.1 Hz, 6H ($C\underline{H}_3$)CH), 2.37–2.70 (m, 2H, H-3), 2.70–2.91 (m, 1H, H-6), 3.97 (t, J=6.7 Hz, 1H, H-2), 5.84 (dd, J=44.1, 11.0 Hz, 1H, H-5); $[\alpha]_D^{28}$ = +8 (H_2O, c=0.7). Selected data for amino acid **13C**: ^{1}H NMR (200 MHz, D_2O) δ 2.67 (td, J=15.5, 11.6 Hz, 1H, H-3), 3.23 (ddd, J=18.3, 15.4, 3.3 Hz, 1H, H-3), 3.76 (dd, J=11.6, 3.5 Hz, 1H, H-2), 6.98 (dd, J=4.9, 3.7 Hz, 1H, Ar), 7.22 (d, J=3.7 Hz, 1H, Ar), 7.31 (d, J=22.0 Hz, 1H, H-5), 7.41 (d, J=5.5 Hz, 1H, Ar); $[\alpha]_D^{23}$ = −62 (H_2O, c=0.2).