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Synthesis of constrained cycloalkyl analogues of glutamic acid with an ω-phosphonic acid function

Bernard Bessières,[a] Angèle Schoenfelder,[a] Céline Verrat,[a] André Mann,[a,*] Paul Ornstein[b] and Conception Pedregal[c]

[a]*Laboratoire de Pharmacochimie de la Communication Cellulaire, UMR 7081 Faculté de Pharmacie, 74, route du Rhin BP 24, F-67401 Illkirch, France*

[b]*Lilly Research Laboratories, Indianapolis, IN 46285, USA*

[c]*Lilly, SA. Avd. de la industria 30, 28108 Alcobendas, Madrid, Spain*

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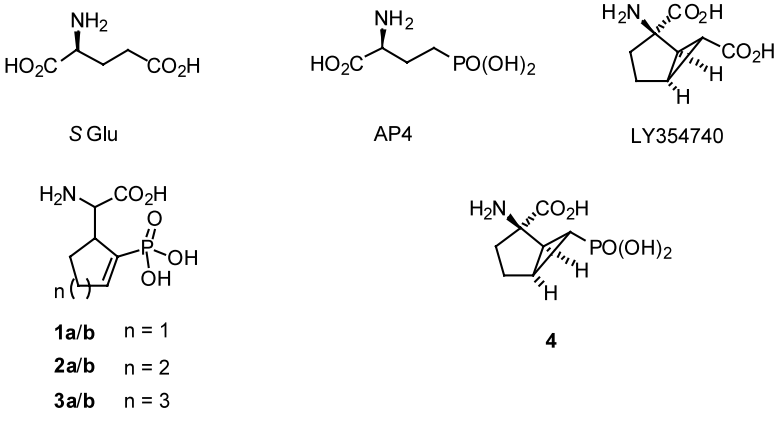
Abstract—A general method based on the sequential reactivities of bis-bromocycloalkenes (**3**–**5**) is proposed for the preparation of phosphonocycloalkanes (**1a**/**b**–**3a**/**b**), representing structural constrained analogues of AP4. For the synthesis of an additional congested AP4 analogue (**4**), an intramolecular cyclopropanation of a ketocarbene towards a vinyphoshonate, assisted by $Rh(OAc)_2$ was successfully experimented. © 2002 Published by Elsevier Science Ltd.

(*S*)-Glutamate (Glu) is an important neurotransmitter in the vertebrates, and because of its intrinsic structural flexibility, Glu binds productively to several receptor subtypes, classified as the ionotropic and metabotropic glutamate receptors (iGlu and mGlu).[1] The mGlu receptors themselves are divided in three groups (I, II and III) depending on sequence homology and pharmacology. Among them Group III mGlu receptors are auto-receptors and as such, promising targets for modulating the glutamatergic transmission. AP4, an ω isostere of Glu, is until now the most selective group III ligand,[1,2] but owing its moderate potency better ligands are highly awaited. Interestingly LY354740,[3] a congested Glu analogue, has also some affinity to the Group III mGlu receptors. These observations suggested that the restriction of rotatable bounds in the Glu backbone may have some virtue in the design of new Group III ligands.

Therefore, we embarked in a chemical program towards the synthesis of conformational restricted analogues of AP4: compounds (**1a**/**1b**, **2a**/**2b** and **3a**/**b**) in which the AP4 skeleton is incorporated into cycloalkyl frames, and compound (**4**), a phosphono isostere close



Scheme 1.

* Corresponding author.

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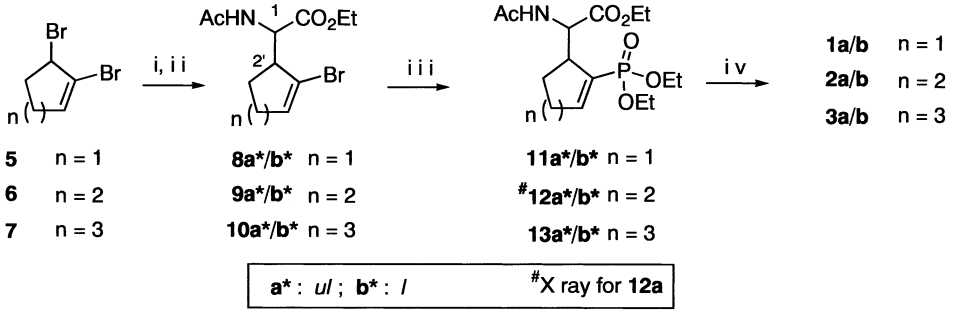
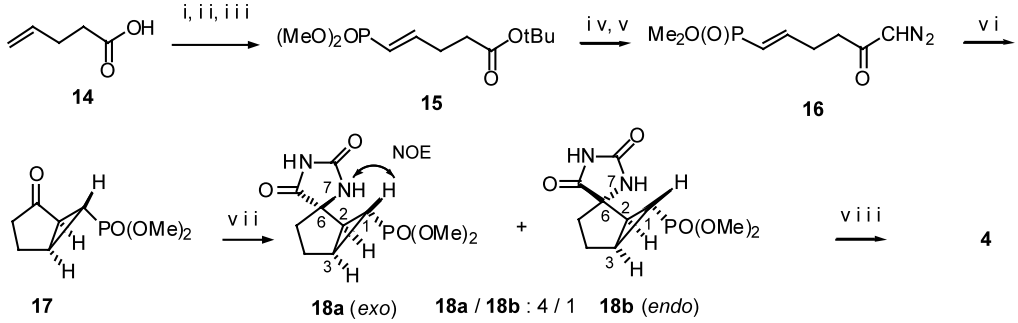
to the structure of LY354740 (Scheme 1). Indeed conformational restriction, a popular strategy in medicinal chemistry, is based on the optimization of the free energy gained during ligand/receptor association by introducing bulk, unsaturation or cyclic motives into ligand. Similar attempts have been reported in the field of the Glu ligands.[4–8] In this letter, we present our preliminary results towards the synthesis of compounds **1a**/**b**, **2a**/**b**, **3a**/**b** and **4**.

For the preparation of the first series of compounds, a general route was prospected, based on the bis-bromo intermediates **5**–**7**. Obviously the two bromines will have different reactivities: the allylic bromide would be available for a nucleophilic substitution, and the vinylic bromide possibly for a phosphorylation reaction assisted by palladium. These two reactions have some precedents in acyclic series.[9,10] We disclose our results in Scheme 2. The bis-bromo adducts **5**–**7** could be obtained following reported procedures.[11–14] Cyclopentenone was the starting material for acceding to **5**; cyclopentene and cyclohexene via their corresponding dibromocyclopropyl adducts, followed by thermal ring expansion, afforded the six and seven membered bis-bromo adducts **6** and **7**. For the introduction of the amino acid appendage at the allyl position, the acetamido route was the most convenient in our hands, even if there was an extra decarboxylative step. Gratifyingly the couple of the two diastereomers **8a**/**8b**, **9a**/**b**[15,16] and **10a**/**b** could be separated by chromatography on silica gel, and a slight diastereoselectivity was observed, the ratio of the two diastereomers in each set was nearly 3/1 (the major diastereomer having the higher R_f). The relative stereochemistry was secured in the following adducts (vide infra). The formation of the C–P bound from the vinylbromides was the most troublesome step. Under the classical conditions recommended for the palladium assisted vinylic phosphorylation no transformation was observed.[17] After some experimentation we found that the switch from triethylamine to DABCO as base,[18,19] give a clean reaction, and the expected phosphonates **11a**/**b**–**13a**/**b** could be obtained in satisfying yields. The attribution of the relative stereochemistry of the phosphono-amino acids was facilitated, because a single crystal X-ray structure was obtained for **12a**,[20] and assigned as unlike (*ul*). Thereafter a correlation based on ^{1}H and ^{13}C NMR data, allowed the determination of the relative stereochemistry of the other couples of diastereomers. The multiplicity of the methine proton at C-1 was an ideal probe. In all cases if for the unlike (*ul*) diastereomers a pseudo triplet was observed, for the like (*l*) diastereomers it was a doublet of doublet. Therefore in comparing the respective NMR spectra, the stereochemistry of the major diastereomers **11a**, **12a**, **13a** (higher R_f) and of the minor diastereomers **11b**, **12b**,[21] **13b** (lower R_f) was attributed as respectively *ul* (*R*S**) and *l* (*R*R**). Of course in a backwards sense the stereochemistry of the corresponding precursors **8a**/**b**–**10a**/**b** could also be assigned on the basis of the R_f and mass balance: **8a**–**10a** are the unlike (*ul*) diastereomers and **8b**–**10b** are the like (*l*) diastereomers. The final step was realized by an hydrolytic cleavage in acidic media, and a subsequent treatment with propylene oxide provided the zwitterions of **1a**/**b**–**3a**/**b** in crystalline form.

The synthesis of the more rigid analogues **4a** was constructed in a different way using the property of ketocarbenes to produce cyclopropanation (Scheme 3).[22,23] Compound **17** was our key intermediate in this sequence and the cyclopropanation was designed for compound **16**, an electron deficient alkene. Commercially available acid **14** constituted the starting material for the synthesis of **17**, in an uneventful sequence reported in Scheme 3. The transient aldehyde obtained after ozonolysis was transformed into the vinylphosphonate **16** (*E*/*Z*: 95/5) by a Wittig reaction. Finally, the intramolecular cyclopropanation was best performed by injecting over a 2 h period (syringe pump) a solution of **16** in acetonitrile to boiling benzene containing $Rh(OAc)_2$ as catalyst. Compound **17** was obtained after chromatography in good yield, as a single diastereomer.[24] A series of extensive NMR experiments have confirmed that the rigid cyclopentanone **17** has the *exo* geometry as desired. Its noteworthy that few examples of a carbene cyclopropanation towards electron deficient alkenes are reported. The ketone in **18** was then converted into the corresponding hydantoine. Monn's condition gave a mixture of the hydantoines **18a**/**b** in a 4/1 ratio, as an inseparable mixture of diastereomers.[3,25] The stereochemistry was assigned on the mixture by NMR experiments, and it turns out that



Scheme 2. *Reagents and conditions*: (i) diethyl acetamidomalonate, NaH, DMF, rt, 12 h; (ii) LiBr, H_2O, DMF and chromatography (for **8a**/**b**: 70%, for **9a**/**b**: 77%; for **10a**/**10b**: 53%, over the two steps, see text); (iii) diethyl phosphite (1.4 equiv.), DABCO (3 equiv.), $Pd(PPh_3)_4$ (0.03 equiv.), toluene 110°C, 6 h (from 57 to 84%); (iv) HCl (6N) reflux 24 h, then propylene oxide, rt, 12 h (from 35 to 58%).



Scheme 3. *Reagents and conditions*: (i) *t*-butyl acetate, H_2SO_4, 24 h; (ii) O_3, Me_2S; (iii) $[(MeO)_2PO]CH_2$, LDA, THF (37% over the three steps); (iv) HCO_2H, rt, 5 h; (v) $(COCl)_2$, CH_2Cl_2, then CH_2N_2 in ether (75%); (vi) **16** added to boiling benzene with 0.05 equiv. of $[RhOAc_2]_2$ (65%); (vii) KCN, $(NH_4)_2CO_3$ in H_2O, rt, 3 days (68%); (viii) HCl (6N) sealed tube, 150°C, 24 h (56%)

the adduct **18a** (the one with the carboxylate and the phosphonates function with the *exo*,*exo* stereochemistry) was the major one, in line with our expectations. In the final step harsh hydrolytic conditions were used to obtain fully deprotected amino acid **4** as a single compound after crystallization, with an HPLC purity greater than 95%.[26]

In conclusion, we have developed two very simple and expeditive routes towards the synthesis of rigid analogues of AP4. The first sequence relays on the chemoselectivity of bis-bromocycloalkenes, the second on an intramolecular cyclopropanation of a ketocarbene towards a vinylphosphonate.[20–23]

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15. Analytical data for **9a**: mp 82°C; R_f 0.43 (hex/ether: 6/4); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ 6.25 (m, 1H), 6.08 (bd, $J=8.5$ Hz, 1H), 4.92 (dd, $J=8.5$ and 3 Hz, 1H), 4.22 (m, 2H), 3.23 (m, 1H), 2.07 (s, 3H), 2.05–1.91 (m, 3H), 1.69–1.59 (m, 3H), 1.29 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ 171.1, 169.9, 133.5, 121.8, 61.4, 54.5, 44.6, 28.0, 27.3, 23.1, 19.4, 13.8. Anal. calcd for $C_{12}H_{18}BrNO_3$: C, 47.38; H, 5.96; N, 4.60. Found: C, 47.3; H, 5.8; N, 4.5%.
16. Data for **9b**: oil, R_f 0.35 (hex/ether: 6/4); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ 6.22 (m, 1H), 6.16 (bd, $J=8.7$ Hz, 1H), 5.01 (dd, $J=8.7$ and 4.5 Hz, 1H), 4.17 (q, $J=7.1$ Hz, 2H), 2.94 (m, 1H), 2.05–2.00 (m, 2H), 2.01 (s, 3H), 1.72–1.57 (m, 4H), 1.25 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ 171.1, 170, 133.4, 122.3, 61.3, 54.3, 44.1, 27.1, 25.8, 22.8, 20.0, 13.9.
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19. *Experimental procedure for the preparation of **12a***: A mixture of **9a** (800 mg, 2.63 mmol, 1 equiv.), diethylphosphite (0.47 ml, 3.68 mmol, 1.4 equiv.) and DABCO (880 mg, 7.89 mmol, 3 equiv.) in dry toluene (27 ml) was degassed for 5 min with Ar, then palladium tetrakis (100 mg, 0.0087 mmol) was added and the yellow solution was heated at reflux. After 8 h the mixture became black and a precipitate appeared. After filtration and evaporation of the organic layer the residue was purified by silica gel chromatography eluting with AcOEt/MeOH: 95/5. Compound **12a** (680 mg, 72%) was obtained as an oil. Analyt-

ical data for **12a**: mp 92°C; R_f 0.35 (AcOEt/MeOH: 95/5); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ 8.03 (1 s, bd, $J=6.5$ Hz, 1H), 6.77 (dt, $J=3.8$ Hz, 1H), 4.47 (dd, $J=6.9$ and 1.6 Hz, 1H), 4.20 (q, $J=6.5$ Hz, 2H), 4.08 (m, 4H), 2.92 (m, 1H), 2.29 (m, 2H), 2.21 (s, 3H), 2.41–1.63 (m, 4H), 1.42–1.25 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ 171.5, 170.1, 146.6 (d, $J=7.2$ Hz), 127.7 (d, $J=180$ Hz), 62.1 (d, $J=22.5$ Hz), 61.8 (d, $J=22.5$ Hz), 60.9, 56.0, 34.8, 25.7, 25.4, 25.3, 22.7, 16.4, 16.1, 14.0. Anal. calcd for $C_{16}H_{28}NO_6P$: C, 53.17; N, 7.80; H, 3.87. Found: C, 53.3; N, 7.9; H, 3.8%.

20. The X-ray structure and coordinates for compound **12a** have been deposited at the Cambridge Crystallographic Database under the deposition number CCDC 185495. Crystal data for **12a**: $C_{16}H_{28}NO_6P$, $M=361.38$, monoclinic, space group: $P12_1/C1$, $a=12.7248$ (5), $b=9.3206$ (6), $c=16.8025$ (7) Å, $U=1977.1$ Å^3, $T=294$ K, $Z=4$, μ(Mo K)$=0.167$ mm^{-1}, 7698 measured reflections, 1962 unique ($R_{int}=0.04$). The final $wR(F^2)$ was 0.062 (all data).
21. Physical data **12b**: mp 87°C; R_f 0.30 (AcOEt/MeOH: 95/5); ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ 6.95 (dt, $J=22.5$ and 3.4 Hz, 1H), 6.83 (bd, $J=7.8$ Hz, 1H), 4.83 (dd, $J=7.8$ and 3.1 Hz, 1H), 4.21–4.02 (m, 6H), 2.92 (m, 1H), 2.20 (m, 2H), 2.01 (s, 3H), 1.76–1.73 (m, 4H), 1.38–1.15 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ 170.8, 169.9, 147.7 (d, $J=7.5$ Hz), 127.3 (d, $J=177$ Hz), 61.9 (d, $J=5.5$ Hz), 61.0, 55.2, 37.0, 36.9, 25.7, 25.6, 25.5, 22.9, 19.4, 16.1, 13.9. Anal. calcd for $C_{16}H_{28}NO_6P$: C, 53.17; N, 7.80; H, 3.87. Found: C, 52.9; N, 7.9; H, 3.7%.
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24. Data for **17**: ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ 3.81–3.75 (m, rotamers of OMe, 6H), 2.52–2.45 (m, 1H), 2.27–2.12 (m, 5H), 1.27 (m, 1H); ^{31}P (81 MHz in $CDCl_3$): δ 27.8; MS (ESI-TOF) $C_8H_{13}O_4P$: M_w 204.06; found $(M+H)^+$: 205.03.
25. The NMR data for the mixture **18a**/**b** were collected at 500 MHz in DMSO at 30°C. The following experiments were performed ^{1}H,^{31}P-decoupled, ^{13}C, DEPT, COSY, 1D-TOCSY, HSQC, HMBC and 2D-NOESY. Inspection of the ^{1}H spectrum indicates that the sample is a 4:1 mixture. C-1 was easily assigned in the ^{13}C NMR spectrum (large ^{13}C–^{31}P coupling constant). H-1 was identified at 1.12 ppm through its coupling to C-1 as observed by HSQC. In the ^{31}P-decoupled proton spectrum, H-1 appears as a triplet with (J 4.0 Hz), indicating that H-2 and H-3 are *trans* to H-1 (the *cis* value would be much larger). In the minor compound H-1 also appears as triplet with a similar coupling constant, therefore the stereochemistry at the cyclopropane ring is the same for the two isomeric compounds **18a**/**b**. The configuration at C-6 has been elucidated through 1D-NOESY. A NOE effect is detected between H-1 and N-H(7) for the major isomer **18a** but not for the minor, indicating that H(1) and H(7) are on the same face in the major isomer (**18a**), and opposite in the corresponding minor one (**18b**).
26. Data for **4**: ^{1}H NMR (300 MHz, MeOH-d_4, 25°C): δ 2.43–2.25 (m, 1H), 2.25–2.00 (m, 4H), 1.72–1.58 (m, 1H), 1.38 (bs, 1H); ^{13}C NMR (75 MHz, MeOH-d_4, 25°C): δ 171.5, 65.4, 29.60, 28.5 (d, $J=3.5$ Hz), 26.1 (d, $J=4.5$ Hz), 24.2 (d, $J=3.5$ Hz), 13.9 (d, $J=187.2$); MS (electrospray +) $C_7H_{12}NO_5P$: M_w 221; found $(M+H)^+$: 222; MS (electrospray −) $(M-H)^+$: 220.