A Palladium Catalyzed Synthesis of Precursors of 2-Amino-5-Phosphonopentanoic Acid and Related Compounds

Mireille Attolini, Michel Maffei*, Bruno Principato, Gilbert Peiffer*

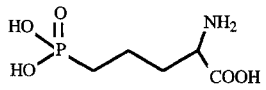
Laboratoire des Organo-Phosphorés, URA 1409 du C.N.R.S., B.P. 552, Faculté de Saint Jérôme, Avenue Escadrille Normandie Niémen, 13397 Marseille Cedex 20, France.

Fax : (33) 4 91 28 80 30. E-Mail : Michel.Maffei@LOP.u-3mrs.fr

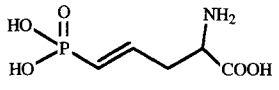
Received 10 December 1996

Abstract: The palladium(0)-catalyzed reaction of 3-acetoxy 1-alkenyl phosphonates **3** with ethyl (diphenyl methylene amino acetate) **4** and N,O bis(trimethysilyl) acetamide provides the precursors of the title compounds in high yields.

Phosphono amino acids are an important class of biologically active compounds. For example, 2-amino-5-phosphonopentanoic acid (AP-5, **1**) is known to possess NMDA antagonist activity,[1] whereas the unsaturated analogues such as **2** have been reported to inhibit threonine synthase from Escherichia coli.[2]

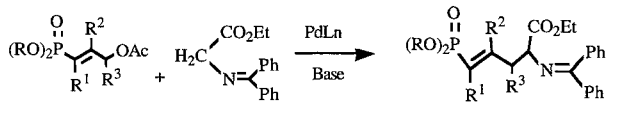


1 (AP-5)



2

Although several syntheses of these compounds have been already published,[3] we felt that the palladium(0)-catalyzed substitution of 3-acetoxy 1-alkenyl phosphonates **3** with ethyl (diphenylmethylene amino) acetate **4** would be a valuable approach to this class of amino acids (Scheme). We initiated this study having in mind the fact that the starting materials can be easily prepared by our recently reported acetoxylation of allylic phosphonates.[4] Furthermore, this methodology has been already used with success for the synthesis of numerous amino acids.[5]



3 **4** **5**

5a-d : (*E*) + (*Z*)
5e, 8 : (*E*)-*syn* + (*E*)-*anti*

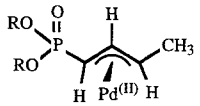
Scheme

The usual conditions used for this kind of substitution were not satisfactory. Thus, in a preliminary experiment, the reaction of dimethyl (3-acetoxy 1-propenyl) phosphonate **3a** with the sodium salt of **4** (prepared from sodium hydride in THF) at 0°C in the presence of 5% mol of palladium acetate and 10% mol of dppe (1,2 bis (diphenyl phosphino) ethane) did not afford any alkylation product, as evidenced by ^{1}H and ^{31}P NMR. Instead, we obtained a complex mixture of several compounds, presumably addition products across the activated[6] double bond of the starting phosphonate. The same result was encountered when using the lithium salt of **4** (generated from LDA in THF) at -78°C. Similar mixtures were also obtained when performing the reactions at room temperature.

However, allylic substitution occurred cleanly by reacting a mixture of **3** and **4** (1.5 eq.) in the presence of 2 equivalents of N,O bis(trimethysilyl) acetamide (BSA) in THF at 40°C using the same catalyst as above. The expected products were obtained as mixtures of *E* and *Z* isomers. The results obtained with different 3-acetoxy 1-alkenyl phosphonates **3** are displayed in Table 1.[7]

The nature of the catalyst seems to have an influence on the reaction. Thus, the use of $Pd(OAc)_2$/dppe gave slight better results than the $Pd(dba)_2$/dppe system (compare entries 3 and 4). Such a result has been already reported for the palladium(0)-catalyzed cyclization of 1-acetoxy-4-chloro-2-alkenes with dimethyl malonate.[8]

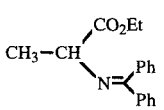
In most cases (entries 1-5), the starting acetoxy phosphonates were used as mixtures of isomers,[9] and the slight decrease of the *E*/*Z* ratio indicates a loss of stereoselectivity during the substitution process. However, the reaction of (*E*)-diisopropyl 3-acetoxy buten-1-yl phosphonate **3e** (entry 6) led to the *E* isomer exclusively.[10] These results indicate that the stereoselectivity is dictated by the steric repulsion between the substituents at the terminal positions of the (π-allyl) intermediate. Thus, the presence of a methyl group on the allyl moiety (entry 6) forces the π-allyl complex to adopt a (*syn, syn*) conformation which leads exclusively to the *E* isomer, whereas a less bulky group such as a proton (entry 3) leads to a mixture of isomers. The palladium-catalyzed acetoxylation of allyl phosphonates[4] led to similar conclusions.



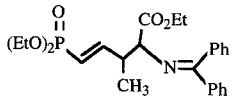
(*syn, syn*)

The beneficial influence of BSA over NaH on the course of the reaction deserves some comments. As mentioned earlier by Magnin,[11] BSA was able to limit the dialkylation in the palladium-catalyzed synthesis of γ,δ-alkenyl-1,1-biphosphonates. This was accounted for by a slow delivery of the nucleophile (since BSA serves as a weak, equilibrium base) giving rise to monoalkylation as the major pathway. In our reactions, this slow delivery of the nucleophile allows the substitution to occur exclusively. However, with NaH, the sodium salt of the nucleophile exists in a much higher concentration, thus leading mainly to addition side-products, the substitution pathway being unfavored. It is worth mentioning that the use of triethylamine as base did not promote any reaction.

Finally, in order to know more about the possible generalization of this methodology, we used the methyl substituted nucleophile **7** (entry 7) which, unfortunately, gave no conversion. On the other hand, (*E*)-diethyl (1-acetoxy 2-butenyl) phosphonate **6**[12] gave the substitution product **8** in 82% yield with complete *E* stereoselectivity (entry 8).[10]



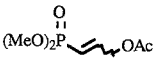
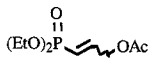
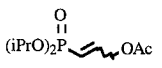
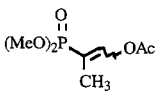
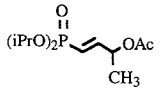
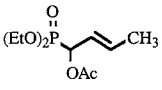
7



8

In summary, we report an effective approach for the synthesis of 2-amino-5-phosphonopentanoic acid and analogues from 3-acetoxy 1-alkenyl phosphonates **3** and ethyl (diphenyl methylene amino acetate) **4** with BSA as activator. The appropriate choice of the starting material (e.g. **3** or **6**) allows the preparation of a variety of precursors of such amino acids. Furthermore, this method should allow the synthesis of optically active compounds through the use of chiral ligands for palladium and /or chiral amino acetates.[13]

Table 1

Entry	Acetoxy phosphonate (*E*/*Z* ratio)[a]	Yield[b] (*E*/*Z* ratio)[c]	Reaction time (h)
1	 **3a** E/Z = 85:15	**5a** 77 (65/35)	2
2	 **3b** E/Z = 90:10	**5b** 74 (77/23)	2
3	 **3c** E/Z = 93:7	**5c** 93 (87/13)	1
4	**3c**	**5c** 90[d] (76/24)	2
5	 **3d** E/Z = 68:32	**5d** 75 (72/28)	2
6	 **3e** E/Z = 100:0	**5e** 92 (100/0)	1
7	**3c**	**5c** 0[e]	24
8	 **6** *E*/*Z* = 100 : 0	**8** 82 (100/0)	2

(a) See note 9. (b) Of pure product. (c) Determined by ^{31}P NMR of the crude product. (d) 5% mol $Pd(dba)_2$ was used instead of $Pd(OAc)_2$. (e) When **7** was used as nucleophile, no conversion was obtained.

References and Notes

1 Watkins, J.C. In *The NMDA Receptor*; Watkins, J.C.; Collingridge Ed.; IRL Press at Oxford Univ. Press : Oxford, U.K., **1989**.

2 Harde, C.; Neff, K.H.; Gerblig, K.P.; Laber, B.; Pohlenz, H.D. *Bioorg. Med. Chem. Lett.*, **1994**, *4*, 273.

3 Whitten, J.P.; Cube, R.V.; Baron, B.M.; McDonald, I.A. *Bioorg. Med. Chem. Lett.*, **1993**, *3*, 19. Whitten, J.P.; Baron, B.M.; McDonald, I.A. *Ibid.*, **1993**, *3*, 26. Rudisill, D.E.; Whitten, J.P. *Synthesis*, **1994**, 851.

4 Principato, B.; Maffei, M.; Siv, C.; Buono, G.; Peiffer, G. *Tetrahedron*, **1996**, *52*, 2087.

5 See for leading references : Ferroud, D.; Genêt, J.P.; Kiolle, R. *Tetrahedron Lett.*, **1986**, *27*, 23. Genêt, J.P.; Ferroud, D.; Montes, J.R. *Ibid.*, **1986**, *27*, 4573. Genêt, J.P.; Juge, S.; Mallart, S.; Ruiz Montes, J.; Levif, G. *Tetrahedron*, **1988**, *44*, 5263.

6 Nucleophiles add readily to α,β-unsaturated phosphonates, see : Minami, T.; Motoyoshiya, J. *Synthesis*, **1992**, 333 and references cited therein.

7 An experimental procedure is as follows (entry 3): To a stirred solution of 5 mg (0.022 mmol) of palladium acetate and 19 mg (0.048 mmol) of dppe in 1 mL THF was added a solution of 120 mg of **3c** (0.45 mmol) and 180 mg of **4** (0.67 mmol) in 2 mL THF under nitrogen atmosphere. 0.25 mL of BSA (210 mg, 1 mmol) were then added *via* syringe and the solution was stirred at 40°C (see table). After cooling to room temperature and concentration, the residue was purified by flash chromatography on silica gel. Excess of **4** and acetamide were eluted with pentane/ethyl acetate (50:50). Further elution with ethyl acetate afforded 197 mg (93%) of product **5c**. The *E* and *Z* isomers were further separated by a second chromatography on silica gel with ethyl acetate. Spectral data: *E*-(**5c**): **^{1}H NMR** ($CDCl_3$, 200 MHz): 1.20(m, CH_3CHOP and CH_3CH_2O); 2.80(m, CH_2CH=); 4.10-4.25(m, CH-N and CH_2O); 4.55(m, CHO); 5.70(dd, PCH=CH, J = 20.6, 17 Hz); 6.55(ddt, PCH=CH, J = 21.7, 17, 4.8 Hz); 7.40(m, arom.). **^{13}C NMR** ($CDCl_3$, 50 MHz): 13.1(s, CH_3CH_2O); 23.7(s, CH_3CHO); 37.8(d, CH_2CH, J = 22.7 Hz); 60.8(s, CH_3CH_2O); 63.9(s, CHN); 70.0(d, CHOP, J = 5.7 Hz); 121.0(d, PCH=CH, J = 187 Hz); 128.0-130.2(Carom.); 147.9(d, PCH=CH, J = 5.0 Hz); 170.9(s, C=O). **^{31}P NMR** ($CDCl_3$, 40 MHz): 14.47.

Z-(**5c**): **^{1}H NMR** ($CDCl_3$, 200 MHz): 1.15-1.30(m, CH_3CHO and CH_3CH_2O); 3.10-3.25(m, CH_2CH=); 4.15(m, CH-N and CH_2O); 4.55(d, CHO, J = 6.2 Hz); 5.60(ddt, PCH=CH, J = 18.7 , 13.0, 1.6 Hz); 6.50(ddt, PCH=CH, J = 52.5, 13, 6.8 Hz); 7.10-7.60(m, arom.). **^{13}C NMR** ($CDCl_3$, 50 MHz): 14.1(s, CH_3CH_2O); 23.9(s, CH_3CHO); 34.0(d, CH_2CH, J = 7.5 Hz); 61.0(s, CH_3CH_2O); 64.2(s, CHN); 70.0(d, CHOP, J = 5.4 Hz); 120.0(d, PCH=CH, J = 182 Hz); 128.0-130.0(Carom.); 148.2(d, PCH=CH, J = 6 Hz); 170.0(s, C=O). **^{31}P NMR** ($CDCl_3$, 40 MHz): 13.37.

8 Bäckvall, J.E.; Vagberg, J.O.; Zercher, C.; Genêt, J.P.; Denis, A. *J. Org. Chem.*, **1987**, *52*, 5430.

9 The starting 3-acetoxy 1-alkenyl phosphonates **3** were obtained as mixtures of *E* and *Z* isomers [4] and were used as such.

10 As shown by ^{1}H NMR, (*E*)-**5e** and (*E*)-**8** were obtained as a 2:1 mixture of *syn* and *anti* diastereomers which could not be separated. (These diastereomers were not distinguished by ^{31}P NMR). Stereochemical assignment was not possible on the basis of the following spectral data (an asterisk denotes the signals corresponding to the minor isomer). *E*-(**5e**): **^{1}H NMR** ($CDCl_3$, 200 MHz): 1.0(d, CH_3CH, J = 6.8 Hz); 1.05-1.40(m, CH_3CH_2O and CH_3CHOP); 3.05-3.20(m, CH_3CH); 3.95(d, CHN, J = 6.2 Hz); 4.05*(d, CHN, J = 5.8 Hz); 4.15(q, CH_2O, J = 7.1 Hz); 4.45-4.70(m, CH-O-P); 5.68*(dd, PCH=CH, J = 18.9, 17.2 Hz); 5.72(dd, PCH=CH, J = 20.0, 17.1 Hz); 6.58*(ddd, PCH=CH, J = 22.2, 17.1, 7.0 Hz); 6.74(ddd, PCH=CH, J = 22.0, 17.1, 7.9 Hz); 7.1-7.7(m, arom.). **^{13}C NMR** ($CDCl_3$, 50 MHz): 14.2(s, CH_3CH); 16.3(s, CH_3CH_2O); 23.8(d, CH_3CHOP, J = 4.4 Hz); 41.9(d, CH_3CH, J = 21.4 Hz); 60.9(s, CH_3CH_2O); 69.8(s, CHN); 70.1(d, CHOP, J = 5.4 Hz); 117.4*(d, PCH=CH, J = 186.0 Hz); 117.7(d, PCH=CH, J = 186.8 Hz); 128-138(Carom.); 139.9(s, C=N); 154.6(d, PCH=CH, J = 4.8 Hz); 170.5(s, C=O). **^{31}P NMR** ($CDCl_3$, 40 MHz): 15.47.

E-(**8**): **^{1}H NMR** ($CDCl_3$, 200 MHz): 1.0(d, CH_3CH, J = 6.8 Hz); 1.13-1.27(m, CH_3CH_2O); 3.03-3.17(m, $CHCH_3$); 3.54-3.70(m, CHN); 3.85-4.20(m, CH_2O); 5.65*(ddd, PCH=CH, J = 20.4, 17.2, 1.3 Hz); 5.70(ddd, PCH=CH, J = 18.3, 17.2, 1.1 Hz); 6.60*(ddd, PCH=CH, J = 22.2, 17.2, 7.1 Hz); 6.76(ddd, PCH=CH, J = 22.0, 17.2, 8.0 Hz); 7.1-7.7(m, arom.). **^{13}C NMR** ($CDCl_3$, 50 MHz): 14.0(s, CH_3CH); 16.0(d, CH_3CH_2OP, J = 4.7 Hz); 16.2(s, CH_3CH_2O); 42.0(d, $CHCH_3$, J = 21.6 Hz); 60.9(s, CH_3CH_2OC); 61.4(d, CH_2OP, J = 5.5 Hz); 69.6(s, CHN); 117.2*(d, PCH=CH, J

= 184.3 Hz); 117.5(d, PCH=CH, J = 184.5 Hz); 126.0-136.0(Carom.); 139.1(s, C=N); 154.6(d, PCH=CH, J = 6.3 Hz); 170.8(C=O). **^{31}P NMR** ($CDCl_3$, 40 MHz): 17.48.

11 Sulsky, R.; Magnin, D.R. *Synlett*, **1993**, 933.

12 **6** was prepared by acetylation of the corresponding α-hydroxy phosphonate, which in turn was obtained from diethyl phosphite and crotonaldehyde, see : Villemin, D.; Racha, R. *Tetrahedron Lett.*, **1986**, *27,* 1789 and Öhler, E.; Zbiral, E. *Chem. Ber.*, **1991**, *124*, 175. α-Acetoxy allyl phosphonates have been used in palladium(0)-catalyzed nucleophilic substitution with amines as well as stabilized carbon nucleophiles: Zhu, J.; Lu, X. *J. Chem. Soc., Chem. Comm.*, **1987**, 1318. Zhu, J.; Lu, X. *Tetrahedron Lett.*, **1987**, *28,* 1897. Lu, X.; Sun, J.; Zhu, J. *Heteroatom. Chem.*, **1992**, *3*, 551. Öhler, E.; Kanzler, S. *Synthesis*, **1995**, 539. Öhler, E.; Kanzler, S. *Phosphorus, Sulfur, Silicon and Rel. Elmts*, **1996**, *112*, 71.

13 Genêt, J.P.; Juge, S.; Ruiz Montes, J.; Gaudin, J.M. *J. Chem. Soc., Chem. Comm.*, **1988**, 718. Genêt, J.P.; Kopola, N.; Juge, S.; Ruiz Montes, J.; Antunes O.A.C.; Tanier, S. *Tetrahedron Lett.*, **1990**, *31,* 3133.