Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 24, pp. 2989-2992, 1996

0960-894X/96 $15.00 + 0.00

PII: S0960-894X(96)00545-8

STEREOSELECTIVE SYNTHESIS OF 2-AMINO-1-HYDROXY-3-PHENYLPROPYLPHOSPHONIC ACID

Jan Zygmunt,[#] Roman Gancarz, Barbara Lejczak, Piotr Wieczorek,[a] Paweł Kafarski[*]

Institute of Organic Chemistry, Biochemistry and Biotechnology, Technical University of Wrocław, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland and [a] Institute of Chemistry, University of Opole, Oleska 32, 45-052 Opole

Abstract: A highly stereoselective synthesis of 2-amino-1-hydroxy-3-phenylpropyl-phosphonic acid was achieved by simple addition of diethyl phosphite to enantiomeric N-blocked phenylalaninals. These compouds exhibit significant herbicidal activity.

2-Amino-1-hydroxyalkylphosphonic acids and their short peptide derivatives have recently been found to exhibit potent and selective inhibitory activities against proteolytic enzymes such as renin and human immunodeficiency virus (HIV) protease.[1] On the other hand, phosphonic acid analogues of phenylalanine have been found to be effective inhibitors of phenylalanine ammonia lyase[2] and agents affecting the growth characteristics of test plants.[3]

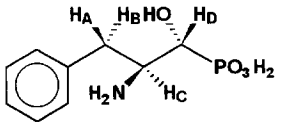
For proper determination of structure-activity relationships of these compounds their enantiomers are indispensable. Thus, their stereocontrolled synthesis is required. Addition of dialkyl phosphites to appropriate amino aldehyde derivatives constitutes one of the simplest entries to 2-amino-1-hydroxyalkylphosphonic acids. However, only few reports on the reactivity and the stereoselectivity of this reaction are available. [1] In this paper we report that simple addition of diethyl phosphite to N-blocked amino aldehydes followed by acid hydrolysis yields products of high enantiomeric purity. 2-Amino-1-hydroxy-3-phenylpropylphosphonic acids (**1**) were prepared as outlined in the Scheme. Enantiomers of N-blocked ethyl phenylalaninate (**2**) were converted into the corresponding alcohols (**3**) by action of sodium borohydride.[4] They were then oxidized with sulphur trioxide-pyridine complex yielding N-blocked phenylalaninals (**4**). Reaction of the crude aldehydes (**4**) with diethyl phosphite gave practically one diastereomer of the desired product (**5**) (95% of diastereomeric excess as established by ^{31}P-n.m.r.). Acid hydrolysis of the adduct yielded the desired acid (**1**) also with 95% distereomeric excess.[6] Yields and physicochemical data of the products are given in Table 1.

Starting from optically active amino aldehyde (**4**) one should expect a mixture of diastereomeric of 2-amino-1-hydroxyalkylphosphonic acids (**1**). Examination of the n.m.r. spectra[7] of aminophosphonic acid (**1a**) clearly indicates that strong diastereoselectivity is observed in the reaction and one of the diasteroisomers is formed in significant excess. This finding is not surprising, however, since similar effect was reported earlier for an addition of diethyl phosphite to other N-blocked amino aldehyde.[5] Starting from the opposite enantiomer of N-

[#] **Present address:** Department of Medicinal Chemistry, The University of Kansas, Lawrence, Kansas 66045, U.S.A.

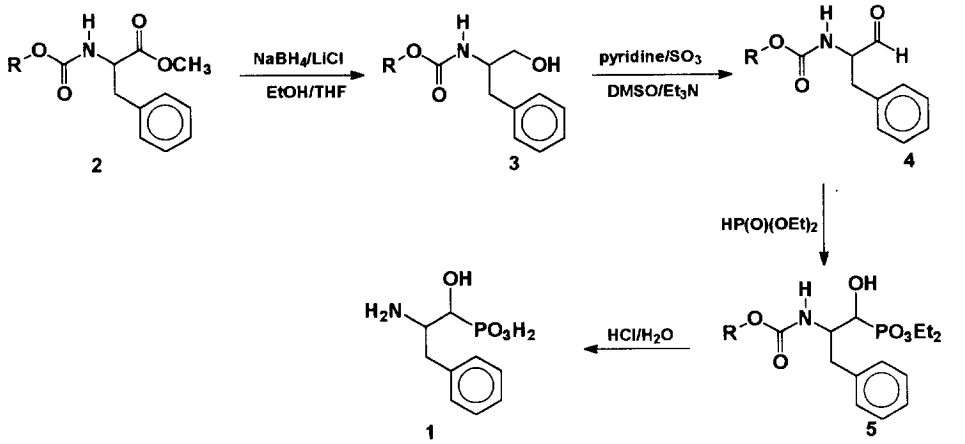
[*] **e-mail:** KAFARSKI@kchf.ch.pwr.wroc.pl **fax:** (+4871) 22-40-64

blocked phenylalaninol we obtained the enantiomeric compound (**1b**). As expected, both ^{1}H- and ^{31}P-n.m.r. spectra of the resulting acids (**1**) were identical. Moreover, in the spectra of their non-racemic mixtures a doubling of signals was observed. In order to prove that the obtained acids are enantiomers we simulated the ^{1}H-n.m.r spectra. This was performed with the set of coupling constants and chemical shift values as follows:



^{1}H n.m.r. ($CDCl_3$) in ppm: 2.08 (dxd, 1H, CH_A, J_{HAHB}= 15.3Hz, J_{HAHC}= 7.0Hz)
2.27 (dxd, 1H, CH_B, J_{HBHA}= 15.3Hz, J_{HBHC}= 8.1Hz)
2.86 (dxdxdxd, 1H, CHc, J_{HCHA}= 7.0Hz, J_{HCHB}= 8.1Hz, J_{HCHD}= 4.17, J_{HCP}= 6.0Hz)
3.05 (dxdxdxd, 1H, CH_D, J_{HDHC}= 4.17Hz, J_{HDP}=9.6Hz)

Figure 1 shows the experimental and calculated spectra in the range of 2-4 ppm, which covers the four aliphatic protons. The appropriate set of coupling constants was obtained by several decoupling experiments. The good agreement between calculated and simulated spectra strongly supports the hypothesis that the acids (**1a**) and (**1b**) are enantiomers. The relative configurations of these compounds may be supposed to be *anti* (*erythro*) based on the report by Patel et al.[1a,5] We were only able to use this analogy for the tentative structural assignment since an approach to obtain monocrystals of compounds **1a** and **1b** failed (they crystallize in form of spiral polymeric stuctures).



SCHEME

Table 1. 2-Amino-1-hydroxy-3-phenylpropylphosphonic acids **1a/1b**

Com-pound	Substrate (3)	Yield (%)	M.p. (dec.) (°C)	$[\alpha]_D^{RT}$ (c 2, 1M NaOH)	ratio of diastereoisomer (^{31}P-n.m.r.: δ in ppm)
1a	Carbobenzoxy-L-phenylalaninol	32	261-263	-10	95 : 5 (18.06/17.17)
1b	Carbobenzoxy-D-phenylalaninol	34	261-262	+10	95 : 5 (18.04/17.18)
1a	*t*-Butyloxycarbonyl-L-phenylalaninol	52	262-263	-10	95 : 5 (18.06/17.18)
1b	*t*-Butyloxycarbonyl-D-phenylalaninol	56	262-263	+10	95 : 5 (18.05/17.17)

Compounds (1) may be considered as phosphonic acid analogues of statine. Thus, we have evaluated their inhibitory potency towards cytosolic (EC 3.4.11.1) and microsomal (EC 3.4.11.2) aminopeptidases. Both enatiomers, however, were found to be weak inhibitors of these enzymes.

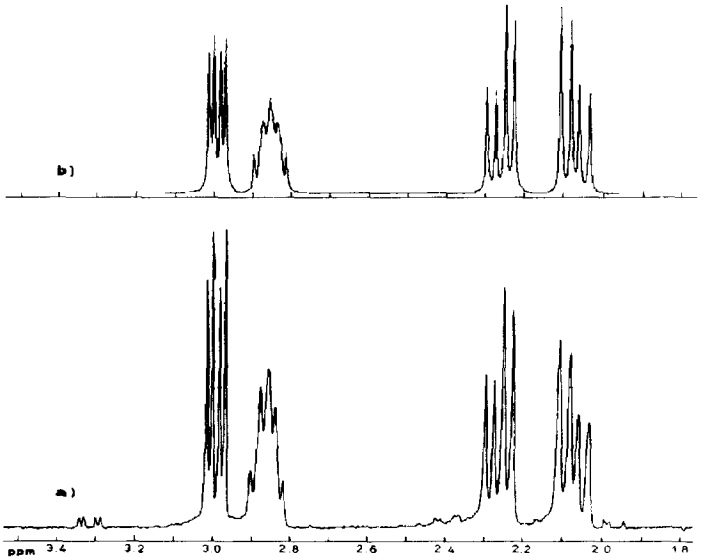


Figure 1. Experimental (a) and calculated (b) ^{1}H-n.m.r. spectrum of aliphatic region of 2-amino-1-hydroxy-3-phenylpropylphosphonic acid.

Table 2. Effect of compounds (1) on the growth of *Lepidium sativum* and *Cucumis sativus* measured as a percentage change in root and hypocotyl length (*L. sativum*) or weight (*C. sativus*) compared to that of the control according to published procedure.[8]

Compound	Root or shoot (hypocotyl)	Concentration (mM)			
		0.05	0.15	0.5	1.5
Lepidium sativum					
glyphosate	R	-86	-88	-90	-93
	S	-13	-16	-20	-44
1a	R	-82	-86	-87	-92
	S	-22	-46	-64	-68
1b	R	-36	-66	-74	-88
	S	+16	+9	N[a]	-54
Cucumis sativus					
glyphosate	R	-60	-71	-78	-84
	H	N	N	N	-22
1a	R	-69	-75	-81	-83
	H	-36	-45	-56	-64
1b	R	-51	-68	-73	-80
	H	-23	-33	-37	-49

[a] N = not significantly different from control[9]

Since phosphonic acid analogues of phenylalanine are known to act as plant growth regulators[3] compounds (1) were also screened for herbicidal activity against *Lepidium sativum* L. (crest) and *Cucumis sativus* L. (cucumber). As seen from Table 2 both enentiomers exhibited strong herbicidal activity being equipotent with popular herbicide glyphosate.

Acknowledgements

This work was supported in part by *Komitet Badañ Naukowych,* grant no. 3 T09A 07910

References and Notes

1. (a) D. V. Patel, K. Rielly-Gauvin, and D. E. Ryono, *Tetrahedron Lett.*, **1990**, *31*, 5587; (b) B. Stowasser, K.-H. Budt, L. Jian-Qi, A. Peyman, D. Ruppert, *Tetrahedron Lett.*, **1992**, *33*, 6625; (c) T. Yokomatsu, T. Yamagishi, S. Shibuya, *Tetrahedron: Asymmetry*, **1993**, *4*, 1401; (d) R.T. Wester, R. J. Chambers, M. D. Green, W. R. Murphy, *Bioorg. Med. Chem. Lett.*, **1994**, *4*, 2005.
2. (a) K. M. Janas, A. Filipiak, J. Kowalik, P. Mastalerz, and J. S. Knypl, *Acta Biochim. Pol.*, **1985**, *32*, 131; (b) B. Laber, H.-H. Kiltz, and N. Amrhein, *Z. Naturforsch.*, **1986**, *41c*, 49; (c) J. Zoñ,and N. Amrhein, *Liebigs Ann. Chem.*, **1992**, 625; (d) K. M.Janas, and D. Olechnowicz, *Acta Biochim. Pol.*, **1994**,*14*, 191.
3. (a) J. S. Knypl, K. M. Janas, and M.Wolska, *Physiol Plant.*, **1986**, *66*, 543; (b) P. Kafarski, B. Lejczak, E. Œlesak, E. and J. Przetocki, *Pestic. Sci.*, **1989**, *28*, 13; (c) P. Kafarski, B. Lejczak, R. Tyka, L. Koba, E. Pliszczak, P. Wieczorek, *J. Plant Growth Regul.*, **1995**, *14*, 199.
4. Y. Hamada, T. Shioiri, *Tetrahedron Lett.*, **1982**, *23*, 1193.
5. D. V. Patel, K. Rielly-Gauvin, D. E. Royno, C. A. Free, W. L. Rogers, S. A. Smithy, J. M. DeForrest, R. S. Oehl, E. W. Petrillo Jr., *J. Med. Chem*, **1995**, *38*, 4557.
6. **General procedure:** To the solution of amino alcohol (**3**; 16 mM) and triethylamine (6.6 ml; 47.7 mM) in DMSO (20 ml) freshly prepared pyridine-sulfur trioxide complex (48 mM) in DMSO (30 ml) was added and the mixture left for 20 min. at room temperature. The reaction mixture was then dissolved in icy-cold water (150 ml) and the product was extracted into ethyl ether (5x50ml). Ethereal solution was then washed succesively with: 10% solution of citric acid (2x10ml), water (3x10ml), saturated sodium hydroxide (10 ml) and water (10 ml). The solution was dried over magnesium sulphate. After removal of drying agent, diethyl phosphite (16 mM) and 3 drops of triethylamine were added and ether was removed under reduced pressure. The resulting oil was left at 24 h at room temperature in 20ml of benzene. Then concentrated hydrochloric acid (100 ml) was added and the mixture was refluxed for 10 h. The volatile components were removed *in vacuo*, the obtained oil dissolved in water (50 ml), decolorized with charcoal and water was removed under reduced pressure. The oily residue was dissolved in methanol (30 ml) and the pure aminophosphonic acid (1) precipitated with propylene oxide.
7. N.m.r. spectra were taken at 250MHz Bruker AMX apparatus.
8. For example: P. Wieczorek, D. Miliszkiewicz, B. Lejczak, M. Soroka, P. Kafarski, *Pestic. Sci.*, **1994**, *40*, 57.
9. Dixon's *Q*-test was used to reject the unreasonable results. The means for samples and controls were compared by testing the null hypothesis at the 5% significance level. See: J. C. Miller,. and J. N. Miller, *Statistics for Analytical Chemistry.* Elllis Harwood Ltd., Chichester, 1984, Chapter 3.

(*Received in Belgium* 22 *May* 1996; *accepted* 13 *November* 1996)