Tetrahedron: Asymmetry Vol. 2, No. 9, pp. 913-917, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

Synthesis of Enantiomerically Pure Phosphonic Analogues of Homoserine Derivatives

Fouad OUAZZANI, Marie-Louise ROUMESTANT, Philippe VIALLEFONT

URA468 - Université Montpellier II - Place E. Bataillon - 34095 Montpellier Cédex - France

Abdelilah EL HALLAOUI

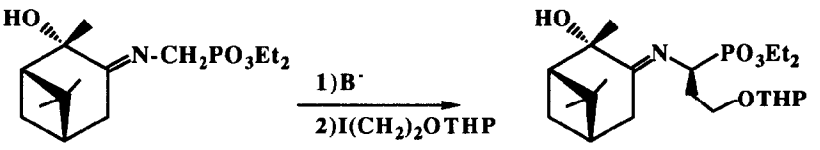
Université Sidi Mohamed Ben Abdallah - Faculté des Sciences - Fes- Maroc

(*Received* 17 *June* 1991)

Abstract : Enantiomerically pure phosphonic analogues of homoserine derivatives are synthesized, the key-step being the diastereoselective alkylation of a chiral Schiff base.

Aminophosphonic acids are receiving considerable interest because of their occurrence in nature and because their numerous properties in the agricultural, physiological and clinical domains[1]. They are probably the most important substitutes for the corresponding α-aminoacids in biological systems. Although their activity usually depends on their absolute configuration, few papers dealing with their asymmetric synthesis appeared[2].
We describe here an efficient synthesis of enantiomerically pure phosphonic analogues of homoserine derivatives using (1S,2S,5S) 2-hydroxypinan-3-one[3] as chiral auxiliary.

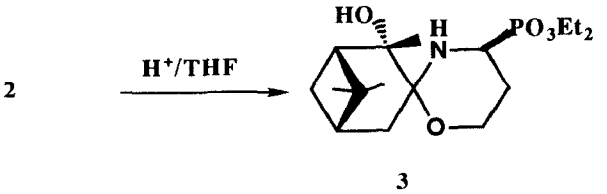
Results :
Alkylation in THF of the Schiff base **1** prepared from (1S, 2S, 5S) 2-hydroxypinan-3-one and aminomethyl phosphonic acid diethylester with the tetrahydropyranyl ether[4] of 2-iodo-ethanol using LDA or MgDA as base failed, only starting product being recovered. With t-BuOK the desired compound was obtained in 20% yield; addition of a cosolvent like HMPA did not enhance the yield (Scheme 1). However with 18-crown-6 (2 equivalents) **2** was obtained in 80% yield, and as a single diastereoisomer[5] (as detected by ^1H NMR at 250 MHz in $CDCl_3$ or C_6D_6 and by ^{31}P NMR).



1 **2**

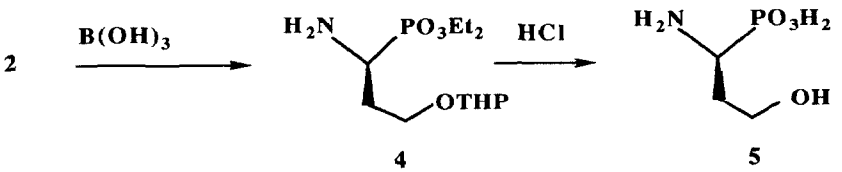
Scheme 1

Hydrolysis of **2** by 15% citric acid or 1N HCl led to the spiro compound **3** as a single diastereomer (as detected by ^1H and ^{31}P NMR) depicted in Scheme 2 arising from the intramolecular attack of the hydroxyl group on the C=N bond and to which we have assigned the configuration S, cyclisation affecting not the stereogenic centre.



Scheme 2

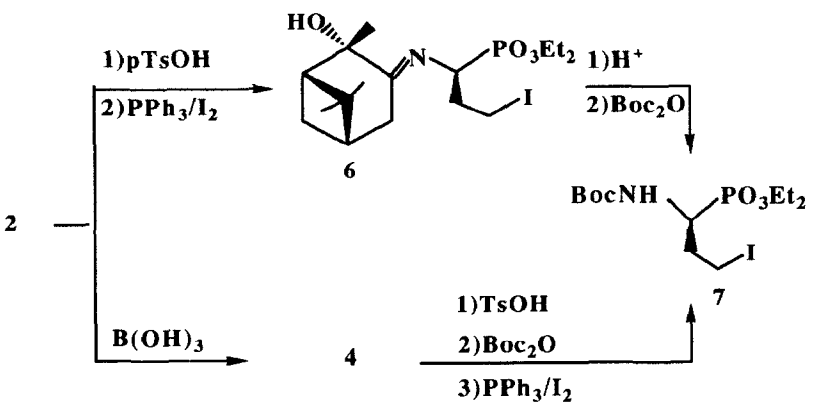
However when boric acid was used (at ambient temperature and at pH = 6-6.2) instead of citric acid, the desired aminoester was obtained (30 min) in good yield (80%).



Scheme 3

Boric acid was known to catalyze the formation and hydrolysis of hydroxyl group containing imines[6]. The suggested mechanism for this catalysis was an intramolecular transfer of a boron-coordinated hydroxide ion within a borate substrate complex.

So as to obtain the halogeno derivatives of phosphonic analogues of homoserine the two strategies depicted in Scheme 4 have been studied. Starting from **2**, we can either prepare the iodo derivative **6** via the hydroxy derivative followed by hydrolysis and protection of the amine function or hydrolyse **2** into the aminoester **4** first which is then transformed into the iododerivative. Two groups are thus available for the protection of the amine function in the subsequent reactions.



Scheme 4

The absolute configuration of the iodo derivative **6** is under investigation by X-ray crystal diffraction studies.However the configuration of the phosphonic acid **4** could be assigned by comparison with the results of Vasella[7]. Thus starting from 2-hydroxypinan-3-one with 1S,2S,5S configuration, S aminoacids were obtained.

Compounds **5** and **6** are precursors of choice for the synthesis of numerous enantiomerically pure compounds such as the phosphonic analogues of vinyl glycine, of diaminobutyric acid and potential neuroexcitatory aminoacids. This work is under active investigation.

Experimental :

Synthesis of the Schiff Base 1:

A mixture of α-aminomethyl phosphonic acid diethyl ester (O,1 mol), (1S,2S,5S) 2-hydroxypinan-3-one (0,12 mol) and a catalytic amount of boron trifluoride etherate in 150 ml of benzene was refluxed for 2 h using a water trap. The solvent was evaporated in vacuo and the oily residue was chromatographed on 70-230 mesh silica gel. Yield= (80%)

^{1}H NMR ($CDCl_3$): 0.85(s,3H); 1.32(t,6H,J=7Hz); 1.35(s,3H); 1.45(s,3H); 1.65-3.15(m,7H); 3.95 (d,2H,J=17Hz); 4.25(dxq, 4H, J=7Hz).

^{31}PNMR ($CDCl_3$) :23.76.

MS:m/z=317 $[M]^+$

Alkylation of the Schiff base of aminomethyl phosphonic acid diethyl ester : Synthesis of **2**.

To t-BuOK (22 mmol) dissolved in anhydrous THF (20 ml) under N_2 and cooled to -100°C, was added the Schiff base (10 mmol), the mixture was stirred ten minutes and 18-crown-6 (44 mmol) was added. After addition of 1-iodo 2-tetrahydropyranyl ethane (20 mmol), the reaction was followed by T.LC. (Kieselgel Merck 60F254), the temperature was allowed to warm to -20°C. The mixture was poured into a solution of NH_4Cl (60 ml), the aqueous phase extracted with ether (3 x 20 ml). The organic layer was dried ($MgSO_4$) evaporated and the residue chromatographed over silica gel.

2 : Yield=(85%) Rf=0.6 (Ether/MeOH 95/5) mp.=84°C (AcOEt/pentane)

$[\alpha]_D$ = -36.65 (c=1.2, $CHCl_3$)

Anal. Calcd for $C_{22}H_{40}NO_6P$: C,59.32 ; H,8.98 ; N,2.97. Found : C,59.15 ; H,8.97 ; N,2.98.

^{1}H NMR :0.87(s,3H) ; 1.25(t,2H,J=6Hz); 1.32(s,3H); 1.36(s,3H); 1.45(m,6H); 1.6-3(m,8H); 3.2(m,1H); 3.4(m,1H); 3.65(m,2H); 4.2(q,4H,J=6Hz); 4.1-4.3(dxt,1H, J = 4 Hz, J = 18Hz); 4.4(m,1H).

^{31}P NMR : 25.60

Hydrolysis of 2 :

a) by 15% citric acid or 1N HCl.

The Schiff base **2** dissolved in THF (7 ml) was treated by 15% citric acid or 1N HCl (6 ml) during 4 days. The solvent was evaporated and the aqueous layer extracted by ether. The aqueous phase was basified (pH=8-9) and extracted by ether, dried ($MgSO_4$) and evaporated to afford the spiro compound **3** in 73% yield as an oily product.

Rf.=0.2 (AcOEt) $[\alpha]_D$ = -29.46 (c=4.87, $CHCl_3$)

^1H NMR : 0.87(s,3H); 1.3(t,6H,J=6Hz); 1.25(s,3H); 1.5(s,3H); 2.0-3.0(m,9H); 3.4(m,1H); 3.6(m,1H); 4.1(q,4H,J=6Hz).

^{31}P=25.48

MS:m/z=362 [M+H]+

b) by boric acid

To a 0,1M phosphate buffer (pH=6.8) solution (5,44 ml) was added 1M boric acid (41,87 ml); the Schiff basc **2** (6.7 10^{-3} mol) dissolved in THF (3 ml) was added to the mixture (pH = 6.1 to 6.3) and warmed to 40°C during 40 minutes. After evaporation of the solvent, the residue was extracted first by ether to recover 2-hydroxypinan-3-one and after by methylene chloride to obtain the aminoester **4** which was purified by chromatography over silica gel.

Yield : 80% Rf=0.25 (ether/MeOH 95/5)

^1H NMR: 1.25(t,6H,J=7Hz); 1.5(m,6H); 1.5(m,2H); 1.7(td,1H,J=3Hz); 2.1(td,1H,J=3Hz); 3.1(txd,1H,J=3Hz); 3.5(txd,1H, J = 6Hz, J =17Hz); 3.65(m,2H); 4.1(q,4H,J=6Hz); 4.5(s,1H).

$[\alpha]_D$ =+5.5 (c=0.4, $CHCl_3$)

Synthesis of the acid 5 :

The aminoester **4** (1.2g ; 4.06 10^{-3} mol) in 6N HCl (120 ml) was refluxed during 6h. After evaporation, the residue was dissolved in MeOH and treated with propylene oxide, the precipitate was recrystallized in H_2O-MeOH.

mp = 214°C Lit.[7] =214-217°C

$[\alpha]_D$ =+7.3 (c=1,H_2O) $[\alpha]_D$ Lit.[7] = -6.2(c=1,H_2O)

Synthesis of the iodo derivative 7:

To the Schiff base **2** (2g) (4.5 mmol), dissolved in MeOH (100 ml), was added p-toluene sulfonic acid (0.8g) (4.6 mmol); the mixture was stirred at room temperature during 3h. The solvent was evaporated and the residue neutralised with Na_2CO_3, extracted with ether (3 x20 ml) the organic layer was dried ($MgSO_4$), concentrated and chromatographed.

Yield:75% Rf : 0.5 (Ether/MeOH 95/5)

^1H NMR:0.87(s,3H); 1.3(t,6H,J=8Hz); 1.3(s,3H); 1.5(s,3H); 2.0-3.1(m,10H); 3.2(m,2H);

4.2 (q,4H,J=8Hz); 3.8-4.4(dxt,1H, J = 4Hz,J =18Hz).

To a solution of P Ph_3 (1.4 mmol) in anhydrous CH_2Cl_2 (4 ml) and under N_2 was added imidazole (1,4 mmole) and iodine (1,4 mmol). After 10 min. was added the precedent product (1.1 mmol). The mixture was stirred during 1.5 h, filtered, the filtrate was concentrated under reduced pressure and the residue chromatographed to afford **6** in 63% yield.

Rf = 0.7 (Ether/MeOH 95/5).

^1H NMR : 1.2(s,3H); 1.65(t,6H,J=6Hz); 1.65(s,3H); 1.85(s,3H); 2.4(d,2H,J=6Hz); 1.9-3.1(m,7H); 3.25(m,1H); 3.6(m,1H); 4.5(q,4H,J=6Hz); 4.4(dxt,1H, J = 4 Hz, J=12Hz).

Hydrolysis of the Schiff base **6** was accomplished as described for **2** to give the aminoester.

$[\alpha]_D$ =-50 (c = 0.7, $CHCl_3$)

^1H NMR : 1.5 (t,6H,J=6Hz); 2.1(m,2H); 2.5(s,2H); 3.45(m,1H); 3.5(dxt 1H, J=6Hz, J =17Hz); 3.65(m,1H); 4.25(q,4H,J=6Hz).

M.S. m/z : 322 $[M+H]^+$

This aminoester was Boc protected :

Yield : 65% ; Rf : 0.65 (Ether/MeOH 95/5)

^1H NMR : 1.5 (t,6H,J=6Hz); 1.9(s,9H); 2.1(m,2H); 3.25(m,2H); 4.25(q,4H,J=6Hz); 4.3-4.6(dxt, 1H, J = 4Hz, J =18 Hz).

To a solution of dioxane/H_2O (2/1,12ml) was added at O°C the aminoester ($5.1\ 10^{-4}$ mol) and Boc_2O ($1.02\ 10^{-3}$ mol), the mixture was stirred at room temperature during 20h. The solvent was evaporated and the residue washed by EtOAc.

Yield:75% Rf:0.2 (Ether/MeOH 95/5)

$[\alpha]_D$ =-26.75 (c= 1.1, $CHCl_3$)

^1H NMR : 1.5(t,6H,J=6Hz); 1.6(s,9H); 2.1(m,2H); 3.25(m,2H); 4.25(q,4H,J=8Hz) ; 4.3-4.6(dxt,1H, J=4Hz, J = 18 Hz).

References :

1) P. Kafarski, P. Mastalerz, *"Aminophosphonates : Natural Occurence, Biochemistry and Biological Properties"* Beiträge zur Wirkstofforschung, Heft 21, Berlin 1984.

2) B. Dhawan, D. Redmore, *Phosphorus Sulfur,* **32**, 119, 1987. U. Scholkopf, R. Schutze, *Liebigs Ann. Chem.*, **45**, 1987. R. Huber, A. Vasella, *Helv. Chim. Acta,* **70**, 1461, 1987. P.A. Bartlett, K.L. Mc Laren, *Phosphorus Sulfur,* **33**, 1, 1987. M. Sting, W. Steglich, *Synthesis,* 132, 1990. M. Sawaramura, Y. Ito, T. Hayashi, *Tetrahedron Lett.* **30**, 2247, 1989. S. Hanessian, Y.L. Bennani, D. Delorme, *Tetrahedron Lett.*, **31**, 6465, 1990.

3) R. Jacquier, F. Ouazzani, M.L. Roumestant, Ph. Viallefont, *Phosphorus Sulfur*, **36**, 73, 1988.

4) N. Miyashita, A. Yoshikoshi, P.A. Grieco, *J. Org. Chem.*, **42**, 3772, 1977.

5) In alkylation reactions performed from chiral Schiff bases prepared from 2-hydroxypinan-3-one numerous factors are involved as previously described : M. Tabcheh, A. El Achqar, L. Pappalardo, M.L. Roumestant, Ph. Viallefont, *Tetrahedron*, **47**, 4611, 1991. Thus, for the moment, it is difficult to propose a model rationalizing the results.

6) H. Matsuda, H. Nagamatsu, T. Okuyama, T. Fueno, *Bull. Chem. Soc. Jpn.*, **57**, 500, 1984.
J. Hoffman, V. Sterba, *Collect. Czech. Chem. Commun* **37**, 2043, 1972.
H. Nagamatsu, T. Okuyama, T. Fueno, *Bull. Chem. Soc. Jpn.*, **57**, 2502 and 2508, 1984 .
G. Rao, M. Philipp, *J. Org. Chem.*, **56**, 1505, 1991.

7) A. Vasella, R. Voeffray, *Helv. Chim. Acta*, **65**, 1954, 1982.