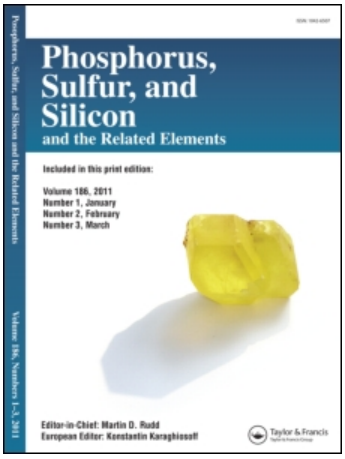

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ENANTIOSPECIFIC SYNTHESIS OF α-AMINO PHOSPHONIC ACIDS

S. HANNOUR[a], A. RYGLOWSKI[a], M.L. ROUMESTANT[a]*, PH. VIALLEFONT[a], J. MARTINEZ[a], F. OUAZZANI[b] and A. EL HALLAOUI[b]

[a]*UMR 5810 Laboratoire des Aminoacides Peptides et Protéines Place E. Bataillon – 34095 Montpellier Cédex France and* [b]*Faculté des Sciences Saiss, BP 2022 Fes Maroc*

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(S) or (R) enantiomerically pure phosphonic analogue of homoserine derivatives **1** are substrates of choice for the synthesis of various functionalized α-aminophosphonic acids in good to excellent yields.

Keywords: aminophosphonic acids; enantiospecific synthesis; chirality

INTRODUCTION

α-aminophosphonic acids are an important class of compounds that exhibit a variety of biological properties [1]. They are also interesting in the design of enzyme inhibitors [2]. Several methods for the synthesis of optically active compounds have been published, chirality being introduced by the use of chiral auxiliaries [3] or by catalytic asymmetric synthesis [4]. We have thoroughly investigated the use of 2-hydroxypinan-3-one [5] in the synthesis of enantiomerically pure α-aminophosphonic acids and we describe here our results concerning mainly the obtainment of new compounds susceptible to present biological activities.

* Corresponding author.

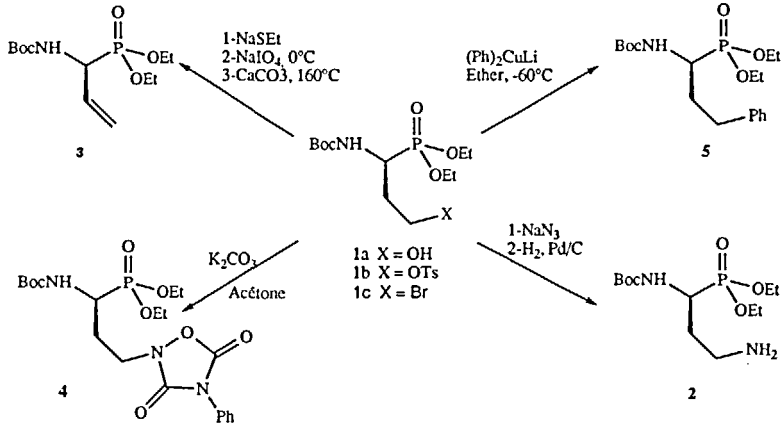
RESULTS

Recently we have published[6] an efficient synthesis of (S) enantiomerically pure phosphonic analogue of homoserine derivatives **1** and the obtainment of phospho homoserine lactone [7] from these compounds. In this paper we report the preparation of various α-aminophosphonic esters by action of several nucleophiles on these derivatives (scheme 1); the phosphonic analogue of homoserine was also used as a chiral precursor for the synthesis of homologous secondary alcohols and unsaturated functionalized aminoesters via the aldehyde **8** . (scheme 2).

2,4-diaminobutyric acid (DABA) is a biological active compound of microbial origin which inhibits the GABA transaminase [8]. To prepare the phosphonic analogue of DABA **2**, nucleophilic substitution of the tosylate **1b** by sodium azide in DMF at room temperature gave the corresponding azide in nearly quantitative yield ; catalytic hydrogenation in ethanol or methanol using Pearlman catalyst (Pd(OH)2/C) afforded **2** in good yield which was easily transformed to the corresponding phosphonic acid by hydrolysis in refluxing 6 M HCl. From the same starting material **1b**, the phosphonic analogue of vinyl glycine **3** was prepared using Le Goffic's [9] method via the ethyl thioderivative which was oxidised by sodium metaperiodate to give the sulfoxide in 90% overall yield. Thermolysis in O-dichlorobenzene afforded **3** in 45% yield. Reaction of 4-phenyl-1,2,4-oxazolidine-3,5-dione prepared according to Zinner's method[10] on **1b** in acetone in the presence of K_2CO_3 gave the phosphonic analogue of homoquisqualic acid **4**, a potentially neuroactive compound, in 70% yield . In the laboratory [11] we have prepared numerous optically active α-amino esters by reaction of organocuprates on chiral bromohomoserine; this methodology has been applied to the synthesis of phosphonic analogue of homophenylalanine. Reaction of diphenylcuprate on **1c** in diethylether at – 60°C gave **5** in 75% yield, in THF **1c** was recovered. All attempts to prepare the phosphonic analogue of homotryptophane by action of an organometallic reagent (Li, Mg, Zn) on **1b** or **1c**were unsuccesful.

Except for the last reaction, **1b** and **1c** appear to be very good chiral synthons for the obtainment of various α-aminophosphonic esters.

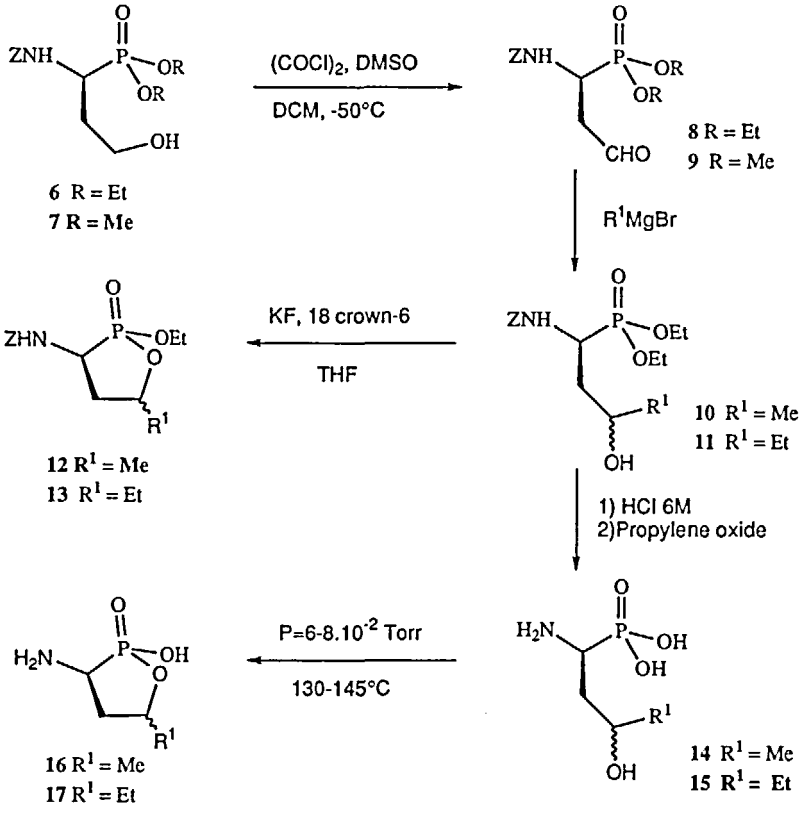
The phosphonic analogue of homoserine N-protected by a benzyloxycarbonyl group **6** was also used as chiral precursor for the synthesis of homologous secondary alcohols via the aldehyde **8**. Oxidation of **6** in



SCHEME 1

DCM using oxalyl chloride and catalytic amounts of DMSO[12] led to the aldehyde **8** in 90% yield ; oxidation of the dimethyl ester **7** in the same conditions afforded the desired aldehyde **9** in 60% yield as a mixture of several products difficult to separate by column chromatography; moreover it appears very unstable. Pyridinium chlorochromate as oxidizing agent gave the aldehyde **8** in only 45% yield. The secondary alcohols were prepared by reaction of diverse organometallic reagents (CH_3Li, CH_3MgBr, CH_3CH_2MgBr) on **8** at low temperature (-15°C). The best results were achieved using bromides to prepare organometallic compounds, the application of methylmagnesium iodide or methyl lithium was completely unsuccessful causing the decomposition of the starting material. A large excess of alkylmagnesium bromide (5–7 equivalents) in reaction with aldehyde allowed to synthesize the corresponding secondary alcohols in nearly quantitative yields as a mixture of two epimers (1/1 ratio) separable by column chromatography. In contrast the use of 2 – 2,5 equivalents of alkylmagnesium bromide gave a mixture of several products as detected by ^1H and ^{31}P NMR which mainly consisted of 20–25% of aldehyde, 30–35% of secondary alcohol (**10**, **11**) and 20–35% of cyclic lactone (**12**,**13**).

Starting from the diastereomeric mixture of alcohols **10** (**11**) and using the procedure we have previously described[7], two cyclic lactones **12** (**13**) were obtained in 35% yield after column chromatography. In this case,

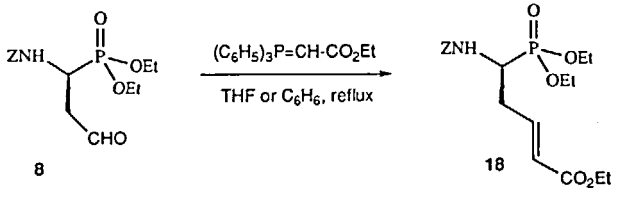


SCHEME 2

also, the precursors were recovered and an extension of reaction time did not improve the yield of cyclic compounds . After simultaneous cleavage of the diethyl esters and the benzyloxycarbonyl group with 6M HCl and subsequent treatment with propylene oxide followed by recrystallization (water-ethanol-acetone) **10** and **11** were converted into the corresponding phosphonic acids **14** and **15** in nearly quantitative yields. To obtain dry samples for the elemental analysis, an unexpected but interesting result was obtained; phosphonic acids turned out to cyclize under vacuum at elevated temperature to afford **16** and **17** ; a similar process of intramolecular cyclization under vacuum was observed by Groth [13] et al but it concerned another class of compounds. The intramolecular cyclisation of

1-amino-3-hydroxyalkyl phosphonic acids appeared to occur easier and in quantitative yield in comparison with phosphonic acid analogue of homoserine (R^1 = H) which in addition needed about 20–30°C higher temperature and cyclized only in 80–90% yield.

The aldehyde **8** was submitted to react with ethoxy carbonyl methylene triphenylphosphorane in refluxing THF or C_6H_6 to afford the diethyl-1-(N-benzyloxycarbonylamino)-4-ethoxycarbonyl-3-butenyl phosphonate in 60% yield ; in both solvents the E compound **18** was exclusively formed (scheme 3).



SCHEME 3

In conclusion from the easily available chiral precursors **1a, 1b, 1c** we have prepared numerous new optically active (pure) α-aminophosphonic acids.

EXPERIMENTAL

General : Reagents and solvents were purified in the usual way, t-BuOK was sublimed before use. All glassware was oven dried.

Thin layer chromatographic analyses were performed on silica gel $60F_{254}$ Merck plastic sheets or glass plates. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh). Melting points are uncorrected. Spectra were recorded with the following instruments. ^1H and ^{31}P NMR : Bruker 250 MHz ; Mass spectra JEOL JMS DX 100 and DX 300. Optical rotations were measured using a Perkin-Elmer Model 141 polarimeter at r.t.

The α-aminophosphonic esters **1a, 1b, 1c, 6** and **7** were obtained using the procedure we have described[6], starting from (2S, 3S, 5S) 2-hydroxypi-

nan-3-one. Their enantiomers were prepared using (2R, 3R, 5R) 2-hydroxy pinan-3-one.

Synthesis of 2

To tosylate **1b** (1mmol) dissolved in DMF (6ml), NaN_3 (2 mmol) was added and the solution was left for 15 hours at room temperature upon stirring. After evaporation of the solvent in vacuo, the oily residue was dissolved in DCM (3 ml) and then washed with water. The organic layer was dried (Mg SO_4) evaporated and chromatographed over silica gel using Et_2O and 5% MeOH in Et_2O as eluents.

Yield = 97% Rf= 0.52 (MeOH/Et_2O 5/95)

^1H NMR ($CDCl_3$) δ: 4.72(m,1H); 4.22–4.04(m,4H); 3.65–3.52(m,1H); 3.5–3.33(m,2H); 2,13–1.91(m,1H); 1.84–1.64(m,1H); 1.45(s,9H); 1.28(t,6H,J=7,1Hz).

^{31}P NMR ($CDCl_3$, H_3PO_4) δ : 24.7

MS [FAB^+] : 337 [M +H]

To azide (1 mmol) dissolved in EtOH or MeOH (10 ml), 20% Pd(OH)2/C (0.1 g) was added. The mixture was hydrogenated at room temperature for 24 hours, the catalyst was filtered off and the solvent removed under reduced pressure. Resulting oil was dissolved in 5% citric acid (10 ml), the solution extracted with diethyl ether (2 × 10 ml) and basified by addition of K_2CO_3 to pH 9–10. The aqueous phase was extracted with DCM (3 × 15 ml) dried ($MgSO_4$) and evaporated to dryness.

Yield = 80–90%

(S) $[\alpha]^{20}D$ = + 8.9 (c=0.5, $CHCl_3$)

^1H NMR ($CDCl_3$) δ: 4.87(m,1H); 4.29–4.09(m,5H); 2.95–2.72(m,2H); 2.04–1.6(m,2H); 1.6(m,2H); 1.48(s,9H) ; 1.36(t,6H, J=7,1Hz).

^{31}p NMR ($CDCl_3$, H_3PO_4) δ : 26.1

MS [FAB^+] : 311 [M+H]

Synthesis of 3

To a solution of NaH (4 mmol, 0.096 g) in DMF (50 ml) was added under N_2at room temperature ethanethiol (4.3 mmol, 0.26 g). The mixture was stirred 10 min. and **1c** (4.3 mmol, 1.9 g) in DMF (5ml) was added and the solution was left for 2 hours upon stirring. The solvent was evaporated and the residue dissolved in CH_3CO_2Et (3 × 20 ml) then washed with water.

The organic layer was dried ($MgSO_4$) evaporated and chromatographed over silica gel using Et_2O as eluent.

Yield = 80% Rf = 0.48 (ether)

^1H NMR ($CDCl_3$) δ: 4.6–4.3 (d.t, 1H, J=6Hz J=18Hz); 4.25(q,4H, J=6Hz); 3.20(m,2H); 2.2(m,2H); 1.9(s,9H) ; 1.5(t,6H, J=6Hz).

To a solution of the above product (0.7 mmol, 0.25g) in MeOH (3ml) was added $NaIO_4$ (0.73 mmol, 0.16 g) in H_2O (3 ml). The reaction was left at 0°C for 4 hours. After filtration, MeOH was evaporated and the aqueous layer washed with $CHCl_3$ (3 × 5 ml). The organic layer was washed with water, dried ($MgSO_4$), filtrated and concentrated under vacuo. The crude product was chromatographed on silica gel using 5% Et_2O in MeOH.

Yield = 95% Rf = 0.55 (Et_2O/MeOH 5/95)

^1H NMR ($CDCl_3$) δ: 4.6–4.3 (d.t ,1H, J=4Hz J= 18 Hz); 4.25 (q,4H, J=6Hz); 3.20(m,2H); 2.2(m,2H); 1.9(s,9H) ; 1.5(t,6H,J=6Hz).

MS [FAB$^+$] : 382 [M+H]

To the precedent compound (0.7 mmol, 0.26 g) in o-$C_6H_4Cl_2$, $CaCO_3$ (2.1 mmol, 0.20g) was added. The mixture was left upon stirring under N_2, at room temperature for 1 hour and then heated at 160°C during 12 hours. The mixture was diluted with Et_2O (10 ml), filtered, concentrated and the residue chromatographed using Et_2O as eluent

3 : Yield = 45% Rf = 0.47 (Et_2O)

(S) $[\alpha]^{20}D$ = 18.6 (c=1.04, $CHCl_3$)

^1H NMR ($CDCl_3$) δ: 5.9 (m,1H); 5.2(m,2H); 5(m,1H); 4.6(m,1H); 4.4–4.2(d.t, 1H, J=4Hz, J=17 Hz); 4.2(q,4H, J=6Hz); 1.5(s,9H); 1.35(t,6H, J=6Hz).

MS [FAB$^+$] : 294 [M+H]

Synthesis of 4

4-phenyl-1,2,4-oxadiazolidine-3,5-dione was obtained using Zinner's[10] method. To a solution of 4-phenyl-1,2,4-oxazolidine-3,5-dione (1.15 mmole, 0.205 g) in acetone (20 ml) under N_2 and magnetic stirring at room temperature, K_2CO_3 (2.3 mmol, 0.317 g) was added. The mixture was stirred 10 min. and **1c** (0.77 mmol, 0.3g) in acetone (5 ml) was added, left during 48 hours, filtered and concentrated. The residue was crystallized in ether. **4** : Yield = 72% m.p = 108°C (CH_2Cl_2)

Anal. calcd. for C_{20} $H_{30}N_3O_8P$ C,50.90 ; H,6.35; N,8.89 Found : C,50.95; H,6.36; N,8.91.

^{1}H NMR ($CDCl_3$) δ: 7.5(m,5H); 4.6(m,lH); 4.5–4.15(d.t,1H, J= 4Hz, J=17Hz); 4.15(q,4H, J=6Hz) ; 3.9(t,2H, J=4Hz); 2.35(m,1H); 2.15(m,1H); 1.9(s,9H); 1.5(t,6H, J=6Hz).

(S) $[\alpha]^{20}D$ =- 1.5 (c=0.66, $CHCl_3$)

Synthesis of 5

To a suspension of CuI (4.9 mmol) in anhydrous THF (10 ml) under N_2, at –60°C, a solution of diphenyllithium in ether (8 mmol) was added. The mixture was stirred for 30 min. At the same temperature a solution of **1c** (1.24 mmole) in ether (5 ml) was added dropwise. After 3 hours stirring at-60°C, a saturated solution of NH_4Cl (3 × 20 ml) was poured into the mixture. The aqueous layer was extracted with ether and the organic layer was dried ($MgSO_4$), filtered, concentrated and the residue was chromatographed.

5 : Yield = 75% Rf = 0.5 (CH_3CO_2Et)

$[\alpha]^{20}D$ = –7.5 (c=0.99, $CHCl_3$)

^{1}H NMR ($CDCl_3$) δ: 7.25(m,5H); 4.9(m,1H); 4.5–4.2(d.t,1H,J=4Hz, J=17 Hz); 4.15(q,4H, J=6Hz); 2.75(m,2H); 2.15(m,1H); 1.9(m,1H); 1.6(s,9H); 1.5(t,6H, J=6Hz).

MS[FAB$^+$] : 372[M+H]

Synthesis of aldehydes 8 and 9

To oxalyl chloride (1.2 mmol) in DCM (5 ml) at –50 to –60°C, dimethyl sulfoxide (2.4 mmol in 1 ml of DCM) and after 2 min. **6**, **7** (1 mmol in 2 ml DCM) within 5 min. were added. The stirred mixture was left at low temperature for further 30 min. and triethylamine (5 mmol) was introduced. The reaction mixture was allowed to warm to room temperature and it was washed with 5% citric acid (2 × 10 ml), water (10 ml) and saturated Na HCO_3 (10 ml). The solution was dried (Mg SO_4), evaporated in vacuo and resulting oil chromatographed over silica gel.

8 : Yield = 85–90% Rf = 0.65 ($MeOH/Et_2O$ 10/90)

R : $[\alpha]^{20}D$ = + 3.6 (c=2.2, $CHCl_3$)

^{1}H NMR ($CDCl_3$) δ: 9.68 (s,lH); 7.3(s,5H); 5,15(s,1H); 5.06(d,2H,J=5Hz); 4.67–4.46(m,1H); 4.08 (q,4H, J=7.1Hz); 2.95–2.61 (m,2H); 1.24 (m,6H, J=7.1Hz).

^{31}P-NMR ($CDCl_3$, H_3PO_4) δ : 23.4

MS [FAB$^+$] : 344 [M+H]

9 : Yield =40–50% Rf = 0.50 (MeOH/Et_2O 10/90)

^1H NMR ($CDCl_3$) δ: 9.65 (s,1H); 7.28 (s,5H); 5.36(s,1H); 5.1(s,2H); 4.35–4.25(m,1H); 3.68(dd,6H,J=10.5Hz J=2.2Hz); 2.9–2.74 (m,lH).

^{31}P-NMR ($CDCl_3$, H_3PO_4) δ: 26.0

MS [FAB^+] : 316 [M+H]

Synthesis of the alcohols : 10 and 11

To 3M CH_3MgBr in Et_2O (6 mmol, 2ml) stirred under N_2 and cooled to −15°C, a solution of aldehyde (1 mmol in 3 ml of anhydrous THF) was added dropwise. After 20 hours, saturated NH_4Cl (20 ml) was poured into the mixture and the aqueous phase was extracted with Et_2O (3 × 30 ml). The organic layer was dried ($MgSO_4$), evaporated and chromatographed over silica gel using Et_2O, 5% MeOH in Et_2O and 10% MeOH in Et_2O as eluents.

10: Yield = 85–90% Rf = 0.33 (MeOH/Et_2O 5/95) mixture of two epimers.

^1H NMR ($CDCl_3$) δ: 7.27 (s,5H); 5.2(s,1H); 5.08(s,2H); 4.32–3.75(m,6H); 3.45 and 2.83 (1H); 2.05–1.55(m,2H); 1.30–1.10(m,9H)

^{31}P-NMR ($CDCl_3$, H_3PO_4) δ: 25.5 and 25.9 both signals of the same intensity

MS [FAB^+] : 360 [M+H]

11 was obtained using the same procedure with 1M CH_3 CH_2 Mg Br in THF (6 mmol, 6 ml) Yield = 70–75% Rf = 0.65 (MeOH/Et_2O 10/90)

^1H NMR ($CDCl_3$) δ: 7.27(s,5H); 5.34(s,1H); 5.08(s,2H); 4.4–4.2(m,1H); 4.2–4.0(m,4H) ; 3.72–3.45(m,1H); 3.41 (s,1H); 1.80-1.57(m,2H); 1.55–1.32(m,2H); 1.30–1.13(m,6H) ; 0.9(t,3H, J=7.4Hz)

^{31}P-NMR ($CDCl_3$, H_3PO_4) δ: 25.7 and 26.1 signals of the same intensity

MS [FAB^+] : 374[M+1]

One isomer was selected in enantiomerically pure form after chromatography over silica gel Yield = 35% Rf = 0.67 (MeOH/Et_2O 10/90)

2R : $[\alpha]^{20}D$ = + 5.26 (c=0.76, $CHCl_3$)

^1H NMR ($CDCl_3$) δ: 7.35(s,5H); 5.30(s,1H); 5.18(s,2H); 4.44–4.22(m,1H); 4.21–4.06(m,4H) ; 3.80–3.52(m,1H); 3.43(s,1H); 1.90–1.65(m,2H); 1.62–1.43(m,2H); 1.40–1.25(m,6H) ; 0.97(t,3H, J=7.4Hz)

^{31}p NMR ($CDCl_3$, H_3PO_4) δ: 25.7

Synthesis of lactones 12 and 13

To **10** or **11** (1 mmol) dissolved in anhydrous THF (20 ml), KF (10 mmol) and 18-crown-6 (0.1 mmol) were added and the mixture was refluxed for 2 days. The solvent was removed in vacuo, water (3 ml) added and the aqueous phase extracted with $CHCl_3$ (3 × 5 ml). The organic layer was dried ($MgSO_4$) evaporated and chromatographed over silica gel using Et_2O, 2% MeOH in Et_2O and 5% MeOH in Et_2O as eluents.

12: Yield = 30–35% Rf = 0.71 (MeOH/Et_2O 5/95)

^1H NMR ($CDCl_3$) δ: 7.28(s,5H); 5.85–5.62(m,1H); 5.04(s,2H); 4.63–3.93(m,4H); 2.80–1.57(m,2H) ; 1.4–1.2(m,6H).

^{31}P NMR ($CDCl_3$, H_3PO_4) δ: 41.3 and 38.3 both signals of the same intensity.

MS [FAB$^+$] :314 [M+H]

13: Yield = 30–35% Rf = 0.84 (MeOH/Et_2O 10/90)

^1H NMR ($CDCl_3$) δ: 7.27 (s,5H); 5.7–5.5(s,1H); 5.05(s,2H); 4.38–3.9(m,4H); 2.78–2.0(m,2H) ; 1.8–1.47(m,2H); 1.35–1.16(m,3H); 0.92(t,3H, J=7.4 Hz)

^{31}P NMR ($CDCl_3$, H_3PO_4) δ : 41.2 and 38.0 both signals of the same intensity

MS [FAB$^+$] :328 [M+H]

Synthesis of aminophosphonic acids 14 and 15

Diethylaminoalkylphosphonates **10** and **11** (1 mmol) were refluxed in 6M HCl (5ml) for 3 hours and after evaporation to dryness, the residue was dissolved in EtOH (5 ml) and propylene oxide (lml) was added. The mixture was diluted with 5 fold volume of acetone and stored for several hours in the refrigerator. The precipitated product was isolated by filtration and recrystallized from H_2O/EtOH.

14 : Yield = 90%

^1H NMR (D_2O) δ: 4,15–4(m,1H); 3.5–3.42 (m,1H); 2.13–1.55(m,2H); 1.24 (dxd,3H, J=2.4Hz)

^{31}P NMR (D_2O, H_3PO_4) δ: 13.6 and 14.3 both signals of the same intensity

MS [FAB$^+$] :170 [M+H]

15 : Yield = 90%

^{1}H NMR (D_2O) δ: 3.96–3.75(m,1H); 3.61–3.46(m,1H); 2.38–1.20(m,4H); 0.98(t,3H)

^{31}P NMR (D_2O, H_3PO_4) δ: 13.4 and 14.0 both signals of the same intensity

MS [FAB$^+$] :182 [M+H]

Synthesis of lactones 16 and 17

The hydroxyamino phosphonic acids **14** and **15** were heated under vacuum at high temperature for several hours yielding the cyclic lactones.

16 : Yield = 100%

Reaction conditions : P=6–8.10^{-2} Torr T=130–140°C t = 4 hours

^{1}H NMR (D_2O) δ: 4.58–4.42 and 4.36–4.21 (m,1H); 3.66–3.51(m,1H); 2.85–2.62 and 2.48–2.19 and 1.96–1.77 (m,2H) ; 1.42–1.33(d,3H, J = 5.2 Hz)

^{31}p NMR (D_2O) δ: 28.5 and 30.5 both signal of the same intensity

MS [FAB$^+$] : 152 [M+H]

17: Yield = 90–100%

Reaction conditions : P=6–8.10^{-2} Torr T = 135–145°C t = 6hours

^{1}H NMR (D_2O) δ: 4.35–4.22 and 4.14–4.02(m,1H); 3.63–3.45 (m,1H) ; 2.88–1.45(m,4H) ; 0.94(t,3H, J=7.1Hz).

MS [FAB$^+$] :166 [M+H]

Synthesis of 18

To ethoxycarbonylmethyl triphenylphosphonium chloride (10 mmol) dissolved and stirred in cold water (100 ml) was added dropwise an aqueous solution of 0.25 M NaOH until pH 8–9. The precipitated solid was isolated by filtration, washed with water and dried in vacuo. The product was recrystallized (AcOEt/ Petroleum ether).

Yield = 85–90% m.p. = 116–118°C

A stirred solution of the aldehyde **8** (1 mmol) and ethoxycarbonylmethylene triphenylphosphorane (1.2 mmol) in dry THF or C_6H_6 (20ml) was refluxed for 4 hours. The solvent was evaporated in vacuo and the crude product chromatographed over silica gel using Et_2O, 2% MeOH in Et_2O, 5% MeOH in Et_2O as eluents.

Yield = 60–65% Rf = 0.69 (5% MeOH in Et_2O)

(R)$[\alpha]^{20}$D = – 5.07 (c=1, $CHCl_3$)

^{1}H NMR ($CDCl_3$) δ: 7.27(s,5H); 6.85(d t,1H, J=7.3Hz J=15.6 Hz); 5.84 (d,1H, J=15.6 Hz); 5.06(s,2H); 5 (s,1H); 4.27–3.97(m,7H); 2.79–2.6(m,1H); 2.58–2.39(m,1H); 1.3–1.13(m,9H).

^{31}P NMR ($CDCl_3$, H_3PO_4) δ : 23.7

MS [FAB$^+$] :414 [M+H]

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