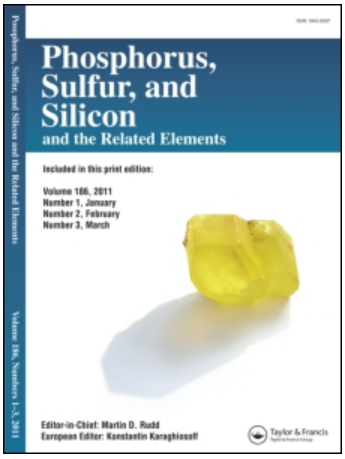

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SYNTHESIS OF ENANTIOMERICALLY PURE AMINOPHOSPHONIC ACIDS

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SYNTHESIS OF ENANTIOMERICALLY PURE AMINOPHOSPHONIC ACIDS

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An efficient general asymmetric synthesis of α-aminophosphonic acid derivatives has been achieved by alkylation of the Schiff bases **2**, prepared from (1R, 2R, 5R)(+) or (1S, 2S, 5S)(−) 2-hydroxy 3-pinanone **1** and α-aminomethyl phosphonic acid diethylester. Diastereoisomeric alkylated Schiff bases separated on column chromatography afforded after hydrolytic cleavage enantiomerically pure compounds.

1. INTRODUCTION

Interested in the synthesis of modified peptides with P–N linkage, we needed optically pure α-aminophosphonic acids. However, only a few compounds have been prepared in enantiomerically pure form, either by resolution of a racemic mixture[1] or via stereoselective reactions.[2] Several recent developments in our laboratory[3] allowed the elaboration of a general method for the preparation of such enantiomerically pure compounds.

RESULTS

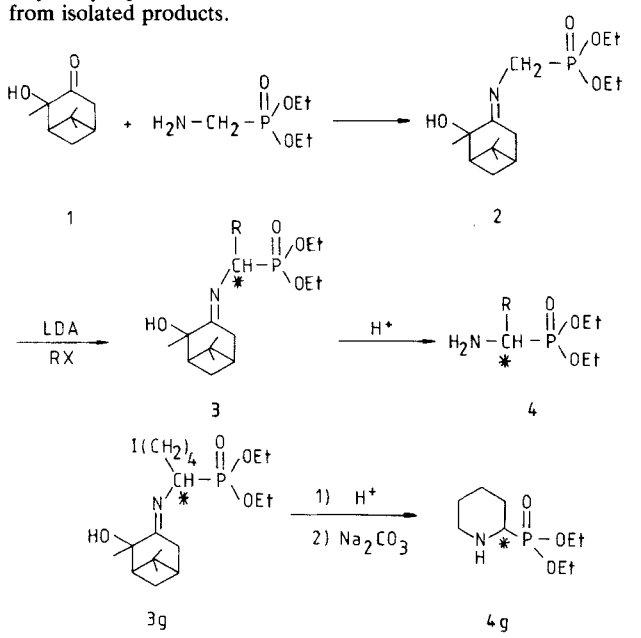
Action of two equivalents of lithium diisopropyl amide (LDA) on the Schiff base **2** (prepared by condensation of (1R, 2R, 5R)(+) 2-hydroxy 3-pinanone **1**[4] with α-aminomethyl phosphonic acid diethylester[5]) followed by the addition of methyl iodide in excess afforded the methylated Schiff base **3a** (yield: 90%, de: 85%). The two diastereoisomers detected by TLC or ^{31}P NMR spectroscopy were separated on column chromatography (silica gel, Ether-Methanol 4-1); after hydrolysis (citric acid, 15%) the two optically pure enantiomers were isolated. Enantiomeric purity was checked by ^{1}H NMR spectroscopy on the acetylated aminoester (0.15–0.2M C_6D_6/TMS solution in the presence of 0.3 molar equivalent of d-Eu(hfc)$_3$)[6].

The replacement of LDA by tBuOK led to the methylation not only of the carbanionic center but also of the ketol hydroxyl group, yield and diastereoselection were lower (70%, 42%). The results of the other asymmetric alkylations of lithiated Schiff bases using several alkylating agents are summarized in Table I.
3g after acidic hydrolysis and neutralisation with Na_2CO_3 gave the cyclic aminoester **4g** (phosphonic analog of pipecolic acid).

TABLE I

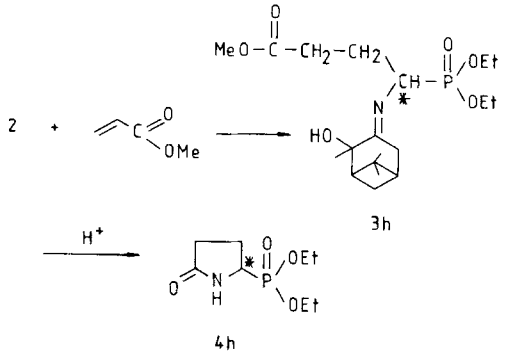
Products	RX	HP	Time (h)	Yield %	de*
3b	IC_2H_5	+	20	85	>95*
3c	$I(CH_2)_5I$	−	20	72	69
3d	$BrCH_2Ph$	+	5	71	33
3e	$BrCH_2—CH=CH_2$	+	5	70	74
3f	$BrCH_2—C\equiv CH$	−	5	85	83
3g	$I(CH_2)_4I$	−	20	82	>95

HP: 2-hydroxy 3-pinanone.
*de: from isolated products.



SCHEME 2

The 1,4 addition on methyl acrylate took place with good yield and diastereoselection to give **3h** (69%, de 87%). Hydrolysis of the Schiff base afforded the cyclic product **4h** (phosphonic analog of pyroglutamic acid).



SCHEME 3

To determine absolute configurations, the aminoesters were converted to aminoacids, some of them being described and configurations assigned.[7]

In summary, we have described a method which permits the access to the two enantiomers of a great variety of α-monosubstituted aminophosphonic acids; starting from (1R, 2R, 5R) hydroxy-2 pinanone-3 R aminoesters were obtained, (1S, 2S, 5S) hydroxy-2 pinanone-3 provided S aminoesters.

This method can also be applied to the synthesis of optically active α-disubstituted aminophosphonic acids and aminophosphinic acids; work is in progress and the first results are very promising.

EXPERIMENTAL

General ^{1}H NMR spectra were recorded on a VARIAN EM 360 spectrometer using tetramethylsilane as internal standard; abbreviations used are s (singulet), d (doublet), t (triplet), m (multiplet), q (quartet). ^{31}P NMR spectra were registered on a Bruker WP 80 spectrometer with H_3PO_4 as external standard. Mass spectra were obtained on a JEOL JMS DX 300 spectrometer using a glycerol matrix. Analytical data are given for the major diastereoisomer. Tetrahydrofuran was dried by distillation from lithium aluminium hydride. LDA was prepared from Buli in ether.

(1R, 2R, 5R)[(2-hydroxy-2,6,6-trimethylbicyclo[3,1,1]hep-3-ylideneamino] methyl phosphonic acid diethylester **2.** A mixture of α-aminomethylphosphonic acid diethylester (0,1 mole), 2-hydroxy pinan-3 one **1** (0,12 mole) 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. The first fractions eluted with an ether hexane (1:3) mixture, gave the unreacted **1**; the polarity of the eluent was increased (ethylacetate methanol (9:1)) and **2** was collected. The eluent was evaporated and the slightly yellow oil was pure enough for analysis.

Yield: 80%. ^{1}H NMR ($CDCl_3$) $\delta = 0.85$ (s, 3 H); 1.32 (t, 6 H, $J = 7$ Hz); 1.35 (s, 3 H); 1.45 (s, 3 H); 1.65–3.15 (m, 7 H); 3.95 (d, 2 H, $J_{P-H} = 17$ Hz); 4.25 (dq, 4 H, $J_{H-H} = J_{P-H} = 7$ Hz); ^{31}P NMR ($CDCl_3$) $\delta = 23.76$; MS: EI (m/z) M^+: 317.

General procedure for alkylation reactions. The Schiff base **2** (1 mM) was added under nitrogen, at −80°C, to a stirred suspension of LDA (2.3 mM) in dry THF (20 ml), the mixture was stirred for 30 min more. After the addition of the halogeno compound (2 mM) (or methylacrylate) the mixture was stirred at −80°C during 3 h and allowed to warm to −30°C, the reaction was followed by T.L.C. (Kieselgel Merck 60F254). The mixture was poured into a solution of Cl[NH_4] (7 ml) the aqueous phase extracted with ether (3 × 10 ml); the organic layer was dried (Na_2SO_4) evaporated and the residue chromatographed over silicagel (30 parts). The first fractions eluted with ether gave always a small quantity of **1**; the polarity of the eluent was increased (ethyl acetate and ethylacetate-methanol or ether-methanol) and the two diastereoisomers were obtained separately.

3a. NMR ($CDCl_3$): 0.8 (s, 3 H); 1.35 (t, 6 H, $J = 7$ Hz); 1.4 (s, 3 H); 1.55 (s, 3 H); 1.42 (dt, 3 H) $J = 7$ Hz, $J = 18$ Hz); 1.8–2.7 (m, 7 H); 4 (m, 1 H); 4.15 (dq, 4 H, $J = 8$ Hz); MS FAB (m/z) $(M + H)^+$: 332.

3b. NMR ($CDCl_3$) $\delta = 0.84$ (t, 3 H, $J = 7$ Hz); 0.85 (s, 3 H); 1.31 (s, 3 H); 1.30 (t, 6 H, $J = 7$ Hz); 1.55 (s, 3 H); 1.85–2.85 (m, 8 H); 3.85–4.35 (m, 5 H); MS: EI (m/z) $M^+ = 345$.

3c. ^{1}H NMR ($CDCl_3$) $\delta = 0.81$ (s, 3 H); 1.31 (s, 3 H); 1.45 (s, 3 H); 1.31 (t, 6 H, $J = 7$ Hz); 1.3–2.9 (m, 15 H); 3.2 (t, 2 H, $J = 7$ Hz); 4.1 (dt, 1 H, $J = 6$ Hz, $J = 17$ Hz); 4.2 (dq, 4 H, $J = 7$ Hz); ^{31}P NMR ($CDCl_3$) $\delta = 25$, 166; MS EI (m/z) M^+: 513.

3d. ^{1}H NMR ($CDCl_3$) $\delta = 0.09$ (s, 3 H); 1.2 (s, 3 H); 1.35 (s, 3 H); 1.4 (t, 6 H, $J = 7$ Hz); 1.55–3.35 (m, 8 H); 4.2 (dq, 4 H, $J = 7$ Hz); 7.30 (s, 5 H); ^{31}P NMR ($CDCl_3$) $\delta = 24.46$; MS FAB (m/z) $(M + H)^+$: 408.

3e. ^{1}H NMR ($CDCl_3$) $\delta = 0.85$ (s, 3 H); 1.4 (t, 6 H, $J = 7$ Hz); 1.4 (s, 3 H); 1.5 (s, 3 H); 1.65–2.90

(m, 8 H); 3.85 (s, 1 H); 4.35 (dt, 1 H, $J = 6$ Hz, $J = 17$ Hz); 4.45 (dq, 4 H, $J = 7$ Hz); 5.4 (m, 2 H); 6.05 (m, 1 H); MS FAB (m/z) $(M + H)^+$: 358.

3f. ^{1}H NMR ($CDCl_3$) $\delta = 0.85$ (s, 3 H); 1.3 (t, 6 H, $J = 7$ Hz); 1.4 (s, 3 H); 1.5 (s, 3 H); 1.8–2.9 (m, 10 H); 3.75–4.25 (m, 5 H); MS FAB (m/z) $(M + H)^+$: 356.

3h. ^{1}H NMR (CCl_4) $\delta = 0.91$ (s, 3 H); 1.25 (t, 6 H, $J = 7$ Hz); 1.3 (s, 3 H); 1.37 (s, 3 H); 1.65–3.35 (m, 10 H); 3.7 (s, 3 H); 4.25 (m, 5 H); NMR (C_6D_6) δ: 0.71 (s, 3 H); 1.1 (t, 6 H, $J = 6$ Hz); 1.15 (s, 3 H); 1.6 (s, 3 H); 1.65–3.1 (m, 10 H); 3.38 (s, 1 H); 3.39 (s, 3 H); 4.25 (m, 5 H); MS FAB (m/z) $(M + H)^+$: 404.

Hydrolysis of alkylated Schiff bases. The purified Schiff base (1 mmole) was dissolved in THF (7 ml) and hydrolysed at 25°C with 15% aqueous citric acid (6 ml) during 72 h. The solvent was evaporated at ambient temperature and the aqueous layer extracted with benzene; the benzene layer containing the ketol was extracted with 15% aqueous citric acid. The combined aqueous layer was basified with sodium carbonate and extracted with diethyl ether. The ethereal extracts were dried (Na_2SO_4), concentrated and the residue purified by column chromatography on silica gel.

4a. Yield: 70% $[\alpha] = +14.6$ (C = 2.05, $CHCl_3$) (S); ^{1}H NMR ($CDCl_3$): 1.35 (dd, 3 H, $J = 7$ Hz, $J = 17$ Hz); 1.36 (t, 6 H, $J = 7$ Hz); 2.2 (m, 2 H); 3.15 (m, 1 H); 4.25 (d.q., 4 H, $J_{H-H} = J_{P} - H = 7$ Hz).

4d. Yield 64% $[\alpha] = -18.07$ (C = 1.66, $CHCl_3$) (R); ^{1}H NMR δ: 1.29 (t, 6 H, $J = 7$ Hz); 2.5–3.8 (m, 5 H); 4.2 (dq, 4 H, $J = 7$ Hz); 7.35 (s, 5 H).

4e. Yield: 72% $[\alpha] = -4.31°$ (C = 0.92 $CHCl_3$) (R); ^{1}H NMR δ: 1.29 (t, 6 H, $J = 7$ Hz); 1.9–2.5 (m, 2 H); 2.85 (m, 1 H); 4.15 (dq, 4 H, $J = 7$ Hz); 5.2 (m, 2 H); 5.85 (m, 1 H); MS EI (m/z) $M^+ = 207$.

4g. Yield: 77% $[\alpha] = +3.59$ (c = 0.596, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 1.32 (t, 6 H, $J = 7$ Hz); 1.5 (m, 4 H); 1.85 (m, 2 H); 2,3–3,3 (m, 3 H); 4.2 (dq $J_{H-H} = J_{P-H} = 7$ Hz) MS. FAB (m/z) $[M + H]^+ = 222$.

4h. Yield: 58% $[\alpha]$ −1.6 (C = 0.614, $CHCl_3$) (R); ^{1}H NMR δ: 1.35 (t, 6 H, $J = 7$ Hz); 2–2.65 (m, 4 H); 3.57 (m, 1 H); 4.25 (dq, 4 H, $J = 7$ Hz); 7.97 (m, 1 H).

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