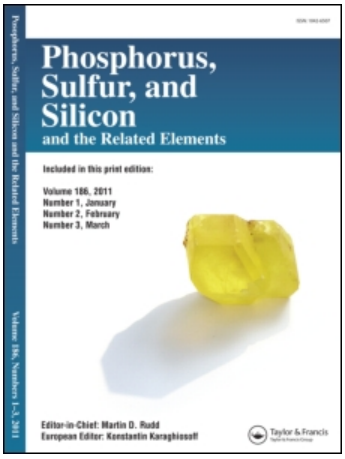

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ASYMMETRIC SYNTHESIS OF 1-AMINOALKYLPHOSPHONIC ACIDS

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ASYMMETRIC SYNTHESIS OF 1-AMINOALKYLPHOSPHONIC ACIDS

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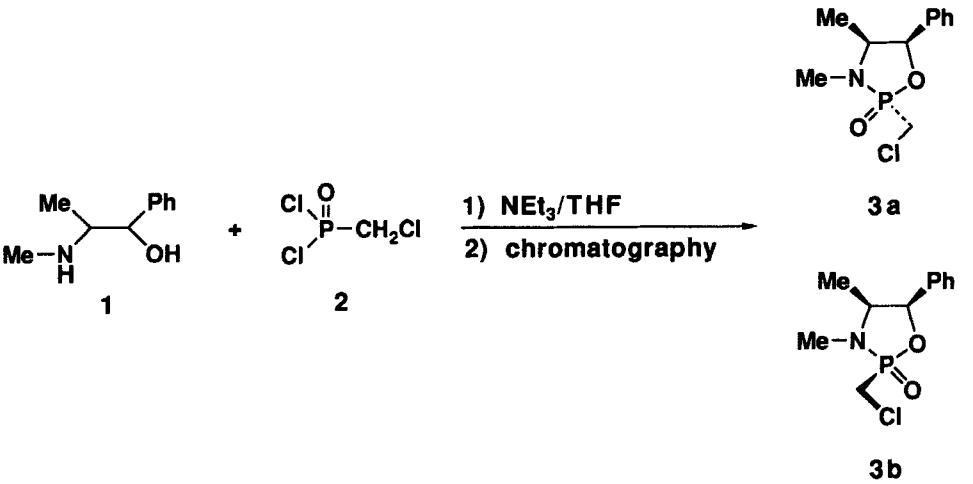
Asymmetric synthesis of Phe and Tyr phosphonic analogous has been achieved by diastereoselective alkylation of chiral 1,2,3-oxazaphospholanes, the latter being readily obtained from (-) ephedrine and chloromethylphosphonic dichloride.

Key words: (-) Ephedrine; chloromethyl phosphonic dichloride; 1,3,2-oxazaphospholanes; optically active (S) and (R) 1-aminoalkylphosphonic acids.

Strategies for the synthesis of optically active 1-aminoalkylphosphonic acids are numerous and have been reviewed by Redmore and Dhawan.[1] Some more recent papers report the synthesis of these compounds either by (a) alkylation of chiral 2-*N*-protected aminomethyl 1,3,2-oxazaphospholanes[2] or bicyclic phosphonamides,[3] or (b) asymmetric electrophilic amination of chiral phosphorus-stabilized anions.[4,5]

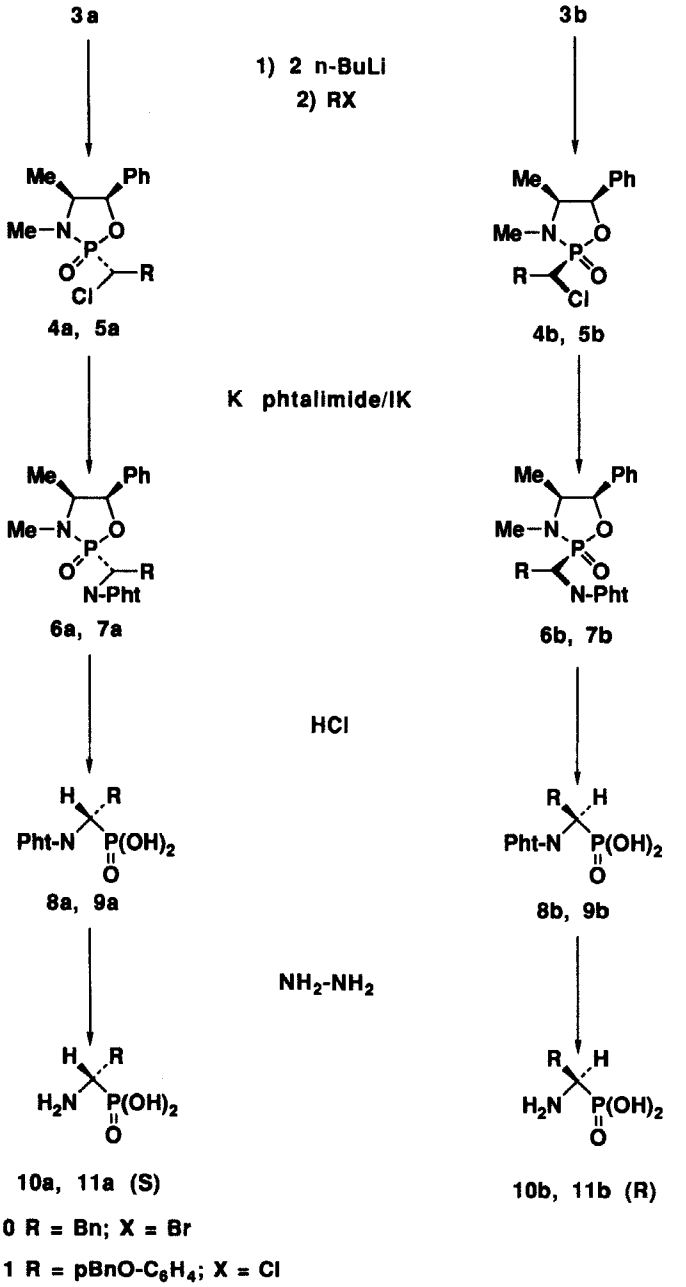
We wish to report an asymmetric synthesis of enantiomerically pure 1-aminoalkylphosphonic acids from commercially available starting materials such as (-) ephedrine and chloromethyl phosphonic dichloride instead of *N*-benzoylaminomethylphosphonic dichloride, the synthesis of which is long and tedious.[2,6]

A mixture of diastereoisomeric (2S, 4S, 5R) and (2R, 4S, 5R) 2-chloromethyl 3,4-dimethyl 2-oxo 5-phenyl 1,3,2-oxaphospholanes **3a**, **3b** was obtained from the



SCHEME I

reaction of (-) ephedrine with chloromethylphosphonic dichloride (60% yield). It should be noted that the chemical yield of the reaction was improved from 10% to 60% when the dichloride in THF solution was added to a solution of (-) ephedrine and triethylamine in THF rather than the reverse procedure. These oxazaphospholanes were stable enough to withstand diastereomeric separation by column



SCHEME II

chromatography on silica gel (isomer ratio: 3/1). The purity of each diastereoisomer was checked by ^{31}P n.m.r.: major isomer **3a** at 35.84 ppm and minor isomer **3b** at 34.47 ppm. The assignment of configuration at phosphorus in 1,3,2-oxazaphospholanes was based on ^{1}H n.m.r.: in phosphorus-containing heterocycles, protons in a 1,3-cis relation to a P=O group are deshielded.[7] Since the H_5 resonance occurs at lower field in **3a** than **3b**, in **3a** the P=O group must be cis to H_5. A deshielding effect for N—CH_3 is also noted in **3a**.

Deprotonation by butyllithium followed by alkylation of the lithium salt with benzyl bromide or p-benzyloxybenzyl chloride led to the corresponding 2-(chloro, benzyl)methyl and 2-(chloro, p-benzyloxybenzyl) methyl oxazaphospholanes **4a**, **4b** and **5a**, **5b**.

Sonication of a mixture of each isomer (**4a**, **4b**, **5a** or **5b**) and potassium phthalimide with a catalytic amount of potassium iodide at 50°C gave the corresponding N-phthalimido 2-methyl oxazaphospholanes **6a**, **6b**, **7a**, **7b** in good yields. By acidic hydrolysis with concentrated HCl overnight, (R) and (S) Pht-Phe(P) **8a**, **8b**, (R) and (S) Pht-Tyr(OBn)(P) **9a**, **9b** were obtained. Subsequent treatment with 1N ethanolic hydrazine solution gave rise to (R) and (S) Phe (P) **10a**, **10b**, (R) and (S) Tyr(OBn)(P) **11a**, **11b**.

Reaction yields were not optimized. The optical purity of each product was checked by ^{31}P n.m.r spectroscopy which showed only a single signal.

This synthesis reported here of chiral 1-aminoalkylphosphonic acids is of interest since the starting materials are inexpensive and readily available, and simple and clean deprotection steps give rise to products of high enantiomeric purity.

EXPERIMENTAL

All melting points are uncorrected. ^{31}P-N.M.R spectra were recorded on a Bruker WP 200 SY spectrometer with H_3PO_4 as external standard. ^{1}H-N.M.R. spectra were recorded on a Bruker WP 80 CW instrument with TMS as internal standard or sodium 3-(trimethyl-silyl)-1-propane sulfonate when D_2O was the solvent; abbreviations used are s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). FAB mass spectra were obtained on a Jeol JMS DX 300 Mass Spectrometer (matrix: NOBA). Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

2-Chloromethyl 1,2,3 oxazaphospholanes **3a** *and* **3b**. A mixture of (-) ephedrine **1** (0.2 moles) and triethylamine (0.4 moles) in 400 ml of THF was treated dropwise with chloromethyl phosphonic dichloride (0.2 moles) in the same solvent (900 ml) and stirred overnight. The precipitate was filtered and washed with THF (3 × 100 ml). The filtrate was concentrated in vacuo and the oily mixture of 2 diastereoisomers, formed in a ratio of 3/1 (yield: 60%), was separated by column chromatography on silica gel, using a 1/1 mixture of acetone/dichloromethane as eluent.

3a Rf = 0.55. mp = 85°C. $[\alpha]_D$ = −41,2 (c 2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) = 0.75 (d, 3H, J = 6.5 Hz); 2.63 (d, 3H, J = 10 Hz); 3.65–4.00 (m + d, 3H, J = 10 Hz); 5.60 (t, 1H, J = 6 Hz); 7.30 (s, 5H).
^{31}P NMR ($CDCl_3$) = 35.84. MS FAB (m/z) $(M + H)^+$: 260.

3b Rf = 0.38. mp = 80°C. $[\alpha]_D$ = −35.7 (c 2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) = 0.75 (d, 3H, J = 6.5 Hz); 2.87 (d, 3H, J = 10 Hz); 3.45–3.93 (m + d, 3H, J = 10 Hz); 5.72 (d, 1H, J = 6 Hz); 7.28 (s, 5H).
^{31}P NMR ($CDCl_3$) = 34.47. MS FAB (m/z) $(M + H)^+$: 260.

2-(Chloro, alkyl) methyl 1,3,2-oxazaphospholanes **4a**, **4b**, **5a** *and* **5b**. *General procedure*: To a well stirred cold (−78°C) solution of **3a** or **3b** (5 mmoles) in 50 ml of anhydrous THF was added dropwise a 2.5M *n*-butyllithium solution in hexane (5.5 mmoles). One hour after the end of the addition, benzyl bromide or 4-benzyloxy benzyl chloride (5 mmoles) was slowly added. The reaction mixture was left for 3–5 h at −78°C (the progress of the reaction was monitored by TLC), and poured into 15% aqueous

solution NH_4Cl (100 ml). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Acetone/dichloromethane 1/1) thus affording **4a**, **5a** and **4b**, **5b**.

4a was prepared from **3a** and benzyl bromide. Reaction time: 3 h. Yield: 65%. Rf = 0.35. $[\alpha]_D$ = −5.1 (c 2, $CHCl_3$).
^1H NMR ($CDCl_3$) δ = 0.77 (d, 3H, J = 6.5 Hz); 2.70 (d, 3H, J = 10 Hz); 2.88–3.30 (m, 3H); 3.47–3.83 (broad s, 1H); 5.72 (d, 1H, J = 6 Hz); 7.30 (s, 10H). ^{31}P NMR ($CDCl_3$) δ = 34.95. MS FAB (m/z) $(M + H)^+$: 352.

4b was prepared from **3b** and benzyl bromide. Reaction time 3 h. Yield: 50%. Rf = 0.45. $[\alpha]_D$ = −8.6 (c 2, $CHCl_3$).
^1H NMR ($CDCl_3$) δ = 0.77 (d, 3H, J = 6.5 Hz); 2.72 (d, 3H, J = 10 Hz); 3.03–3.52 (m, 3H); 3.92–4.18 (m, 1H); 5.75 (d, 1H, J = 6 Hz); 7.35 (s, 10H). ^{31}P NMR ($CDCl_3$) δ = 34.29. MS FAB (m/z) $(M + H)^+$: 352.

5a was prepared from **3a** and p-benzyloxy benzyl chloride. Reaction time: 5 h. Yield: 40%. Rf = 0.34. $[\alpha]_D$ = −23.5 (c 2, $CHCl_3$).
^1H NMR ($CDCl_3$) δ = 0.70 (d, 3H, J = 6.5 Hz); 2.62 (d, 3H, J = 10 Hz); 2.85–3.48 (m, 3H); 3.85–4.13 (m, 1H); 5.07 (s, 2H); 5.77 (d, 1H, J = 6 Hz); 7.00 (q, 4H); 7.20–7.55 (m, 10H). ^{31}P NMR ($CDCl_3$) δ = 35.81. MS FAB (m/z) $(M + H)^+$: 457.

5b was prepared from **3b** and p-benzyloxy benzyl chloride. Reaction time: 5 h. Yield: 45%. Rf = 0.45. $[\alpha]_D$ = −29.9 (c 2, $CHCl_3$).
^1H NMR ($CDCl_3$) δ = 0.70 (d, 3H, J = 6.5 Hz); 2.72 (d, 3H, J = 10 Hz); 3.00–3.50 (m, 3H); 4.05–4.27 (m, 1H); 5.07 (s, 2H); 5.92 (d, 1H, J = 6 Hz); 7.00 (q, 4H); 7.27–7.56 (m, 10H). ^{31}P NMR ($CDCl_3$) δ = 35.82. MS FAB (m/z) $(M + H)^+$: 457.

2-(N-phthalimido, alkyl) methyl 1,3,2-oxazaphospholanes **6a**, **6b**, **7a** *and* **7b**. *General procedure*: A mixture of the alkylated oxazaphospholanes (**4a**, **5a**, **4b**, **5b**) (10 mmoles), potassium phthalimide (10 mmoles and a catalytic amount of potassium iodide in 50 ml of anhydrous toluene was sonicated at 50°C for 15 h. The solid material was removed by filtration and the filtrate is concentrated *in vacuo* to give an oil which was purified by column chromatography (acetone/dichloromethane eluent) thus affording the 2-(N-phthalimido, alkyl) methyl 1,3,2-oxazaphospholanes **6a**, **6b**, **7a**, **7b**.

6a (from **4a**). Reaction time: 10 h. Yield: 75%. Rf (acetone/dichloromethane 2/1) = 0.51. $[\alpha]_D$ = −13.5 (c 2, $CHCl_3$).
^1H NMR ($CDCl_3$) δ = 0.73 (d, 3H, J = 6.5 Hz); 2.75 (d, 3H, J = 10 Hz); 2.95–3.45 (m, 3H); 3.85 (d, 1H, J = 14 Hz); 5.75 (d, 1H, J = 6 Hz); 7.27 (s, 10H); 7.52–7.90 (m, 4H). ^{31}P NMR ($CDCl_3$) δ = 34.45. MS FAB (m/z) $(M + H)^+$: 461.

6b (from **4b**). Reaction time: 10 h. Yield: 70%. Rf (acetone/dichloromethane 2/1) = 0.59. $[\alpha]_D$ = −21.2 (c 2, $CHCl_3$).
^1H NMR ($CDCl_3$) δ = 0.62 (d, 3H, J = 6.5 Hz); 2.70 (d, 3H, J = 10 Hz); 3.00–3.52 (m, 3H); 3.80 (d, 1H, J = 14 Hz); 5.80 (d, 1H, J = 6 Hz); 7.25 (s, 10H); 7.55–7.90 (m, 4H). ^{31}P NMR ($CDCl_3$) δ = 35.81. MS FAB (m/z) $(M + H)^+$: 461.

7a (from **4a**). Reaction time: 14 h. Yield: 70%. Rf (acetone/dichloromethane 3/1) = 0.45. $[\alpha]_D$ = −31.4 (c 2, $CHCl_3$).
^1H NMR ($CDCl_3$) δ = 0.75 (d, 3H, J = 6.5 Hz); 2.77 (d, 3H, J = 10 Hz); 3.05–3.55 (m, 3H); 3.95 (d, 1H, J = 14 Hz); 5.20 (s, 2H); 5.85 (d, 1H, J = 6 Hz); 6.77–7.55 (m, 14H); 7.65–8.00 (m, 4H). ^{31}P NMR ($CDCl_3$) δ = 35.82. MS FAB (m/z) $(M + H)^+$: 567.

7b (from **4b**). Reaction time: 14 h. Yield: 70%. Rf (acetone/dichloromethane 3/1) = 0.51. $[\alpha]_D$ = −48.6 (c 2, $CHCl_3$).
^1H NMR ($CDCl_3$) δ = 0.70 (d, 3H, J = 6.5 Hz); 2.75 (d, 3H, J = 10 Hz); 3.05–3.55 (m, 3H); 3.92 (d, 1H, J = 14 Hz); 5.20 (s, 2H); 5.90 (d, 1H, J = 6 Hz); 6.70–7.50 (m, 14H); 7.62–8.00 (m, 4H). ^{31}P NMR ($CDCl_3$) δ = 33.08. MS FAB (m/z) $(M + H)^+$: 567.

1-Phathlimido 2-aryl ethylphosphonic acids **8a**, **8b**, **9a** *and* **9b**. *General procedure*: A stirred solution of **6a**, **6b**, **7a** or **7b** (5 mmoles) and 25 ml 12N HCl was refluxed for 20 h. The mixture was evaporated to dryness, taken up in ethanol and evaporated once again to dryness. This operation was repeated three times in order to remove HCl completely. The residue was precipitated by adding a cooled mixture of 9/1 ethanol/ether. The precipitate was filtered, dried over P_2O_5 and purified by crystallization from 1/1 ethanol/ether.

8a (from **6a**). Yield: 85%. mp = 167–168°C. $[\alpha]_D$ = +17.2 (c 2, 1N-NaOH).
^{1}H NMR ($DMSOd_6$) δ = 2.90–3.17 (m, 2H); 3.22–3.54 (broad s, 1H); 7.13 (s, 5H); 7.70 (s, 4H). ^{31}P NMR ($DMSOd_6$) δ = 18.59. MS FAB (m/z) $(M + H)^+$: 332.

8b (from **6b**). Yield: 80%. mp = 161–162°C. $[\alpha]_D$ = −17.3 (c 2, 1N-NaOH).
^{1}H NMR ($DMSOd_6$) δ = 2.80–3.05 (m, 2H); 3.10–3.37 (m, 1H); 7.12 (s, 5H) 7.65 (s, 4H). ^{31}P NMR ($DMSOd_6$) δ = 17.90. MS FAB (m/z) $(M + H)^+$: 332.

9a (from **7a**). Yield: 80%. mp = 179–181°C. $[\alpha]_D$ = +11.5 (c 2, 1N-NaOH).
^{1}H NMR ($DMSOd_6$) δ = 2.75–3.25 (m, 2H); 3.45–4.00 (broad s, 1H); 5.05 (s, 2H); 6.60–7.45 (m, 9H); 7.85 (s, 4H). ^{31}P NMR ($DMSOd_6$) δ = 25.24. MS FAB (m/z) $(M + H)^+$: 438.

9b (from **7b**). Yield: 70%. mp = 174–176°C. $[\alpha]_D$ = −12.6 (c 2, 1N-NaOH).
^{1}H NMR ($DMSOd_6$) δ = 2.60–3.10 (m, 2H); 3.80–4.30 (m, 1H); 5.00 (s, 2H) 6.72–7.55 (m, 9H); 7.87 (s, 4H). ^{31}P NMR ($DMSOd_6$) δ = 26.94. MS FAB (m/z) $(M + H)^+$: 438.

1-Amino 2-aryl ethylphosphonic acids **10a**, **10b**, **11a** *and* **11b**. *General procedure*: Following the method of Yamauchi, Kinoshita and Imoto.[8] A solution of **8a**, **8b**, **9a** or **9b** (5 mmoles) in ethanol (18 ml) and 5.4 ml 1N ethanolic hydrazine were stirred for 24 h at room temperature. The precipitate was filtered. The filtrate was evaporated using a rotary evaporator at a temperature below 45°C. Since a white solid appeared upon addition of THF to the residue, the solution was filtered. Evaporation of the solvent gave the product which was crystallized from 1/1 C_2H_5OH/H_2O.

[Phe(P) (S)] **10a** (from **8a**). Yield: 75%. mp = 264–266°C. $[\alpha]_D$ = +41.2 (c 2, 1N-NaOH). ^{1}H NMR ($NaOD/D_2O$) δ = 2.50–2.80 (m, 2H); 3.35–3.87 (broad s, 1H); 7.85 (s, 5H). ^{31}P NMR (1N-NaOH) δ = 17.33. MS FAB (m/z) $(M + H)^+$: 202.

[Phe(P) (R)] **10b** (from **8b**). Yield: 75%. mp = 261–262°C. $[\alpha]_D$ = −39.5 (c 2, 1N-NaOH). ^{1}H NMR ($NaOD/D_2O$) δ = 2.70–3.10 (m, 2H); 3.27–3.55 (m, 1H); 7.40 (s, 5H). ^{31}P NMR (1N-NaOH) δ = 17.31. MS FAB (m/z) $(M + H)^+$: 202.

[(OBn)Tyr(P) (R)] **11a** (from **9a**). Yield: 61%. mp = 230–232°C. $[\alpha]_D$ = +49.1 (c 2, 1N-NaOH). ^{1}H NMR ($NaOD/D_2O$) δ = 3.04–3.25 (m, 2H); 3.40–3.75 (m, 1H); 5.15 (s, 2H); 6.85–7.60 (m, 9H). ^{31}P NMR ($DMSOd_6$) δ = 20.59. MS FAB (m/z) $(M + H)^+$: 308.

[(OBn)Tyr(P) (S)] **11b** (from **9b**). Yield: 60%. mp = 222–224°C. $[\alpha]_D$ = +51.3 (c 2, 1N-NaOH). ^{1}H NMR ($NaOD/D_2O$) δ = 2.97–3.70 (m, 3H); 5.12 (s, 2H); 6.80–7.59 (m, 9H). ^{31}P NMR ($DMSOd_6$) δ = 21.84. MS FAB (m/z) $(M + H)^+$: 308.

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