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Asymmetric Synthesis of (*R*)- and (*S*)-Piperidin-2-yl-phosphonic Acid by Diastereoselective Addition of Trialkyl Phosphite onto Potential Iminium Salt.

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ABSTRACT: Two strategies have been developed to synthesize both enantiomers of piperidin-2-yl-phosphonic acid. The first one uses the double condensation of glutaraldehyde with (*R*)-(-)-phenylglycinol and triethylphosphite to give 2-ethylphosphonate-6-oxazolopiperidine **2** which furnished in few steps (*S*)-(+)-piperidin-2yl-phosphonic acid (**5**) in 58% ee. The second strategy utilizes the 2-cyano-6-oxazolopiperidine synthon **1** which upon treatment with trimethyl phosphite gave 2-cyano-6-oxazaphosphorinane **7** which gave pure (*R*)-(-)-piperidin-2-yl-phosphonic acid (**10**) in good overall yield.

INTRODUCTION

Aminophosphonic acids show are an area of interest as implied by the number of publications devoted to their synthesis as well as their uses as biologically active compounds. During the last two decades, considerable efforts have been made towards the asymmetric synthesis[1] of phosphonic analogs of naturally occurring α-aminoacids.

Like acyclic derivatives, cyclic phosphonic acids show interesting properties and in the course of our continuing efforts towards the asymmetric synthesis of piperidine derivatives[2] we launched a project related to the synthesis of the phosphonic analog of pipecolic acid. To our knowledge, only one asymmetric synthesis of a diethyl ester of this compound has been proposed.[3]

RESULTS

Some years ago we reported the preparation of the 2-cyano-6-oxazolopiperidine synthon **1** by the double condensation of (*R*-)-(-)-phenylglycinol and glutaraldehyde in the presence of potassium cyanide.[2a,b] We decided to reproduce this double condensation in the presence of trialkyl phosphite (trimethyl or triethylphosphite) in place of the cyanide ion (Scheme 1). A smooth reaction took place and gave the expected product **2** in 58% yield by reaction with triethyl phosphite. Compound **2** was in fact an inseparable

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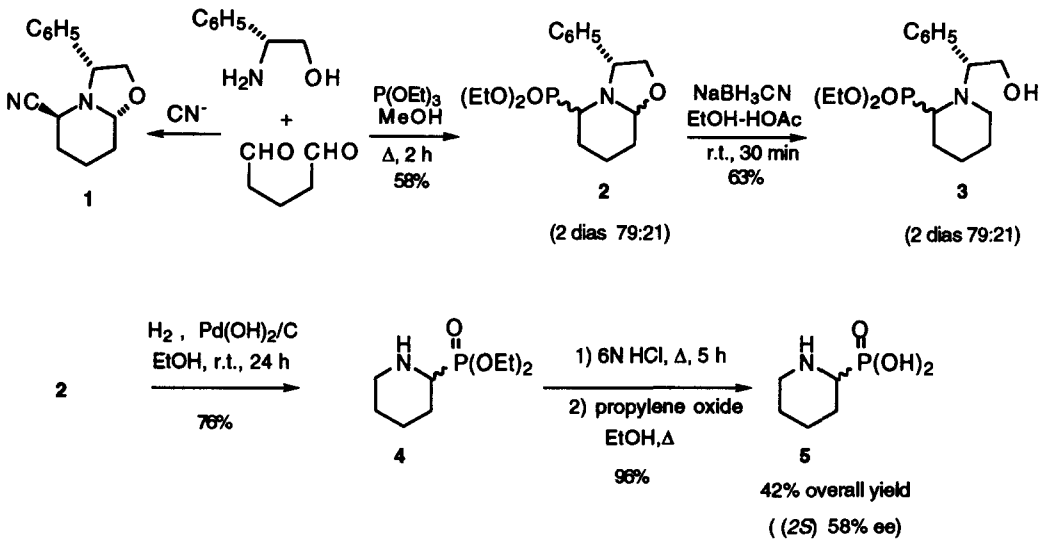
mixture of two epimers in 79:21 ratio. It was not easy to determine the epimeric center by means of conventional analytic data. Attempts to equilibrate the diastereomeric mixture **2** by treatment with a catalytic amount of $ZnBr_2$ in CH_2Cl_2 was unsuccessful and the mixture was recovered unchanged. It was eventually found that reduction of the crude reaction mixture **2** by $NaBH_3CN$ gave aminophosphonate **3** in 63% yield and as a mixture of two diastereomers in the same 79:21 ratio indicating that the epimeric center of **2** was α to the phosphonate moiety.

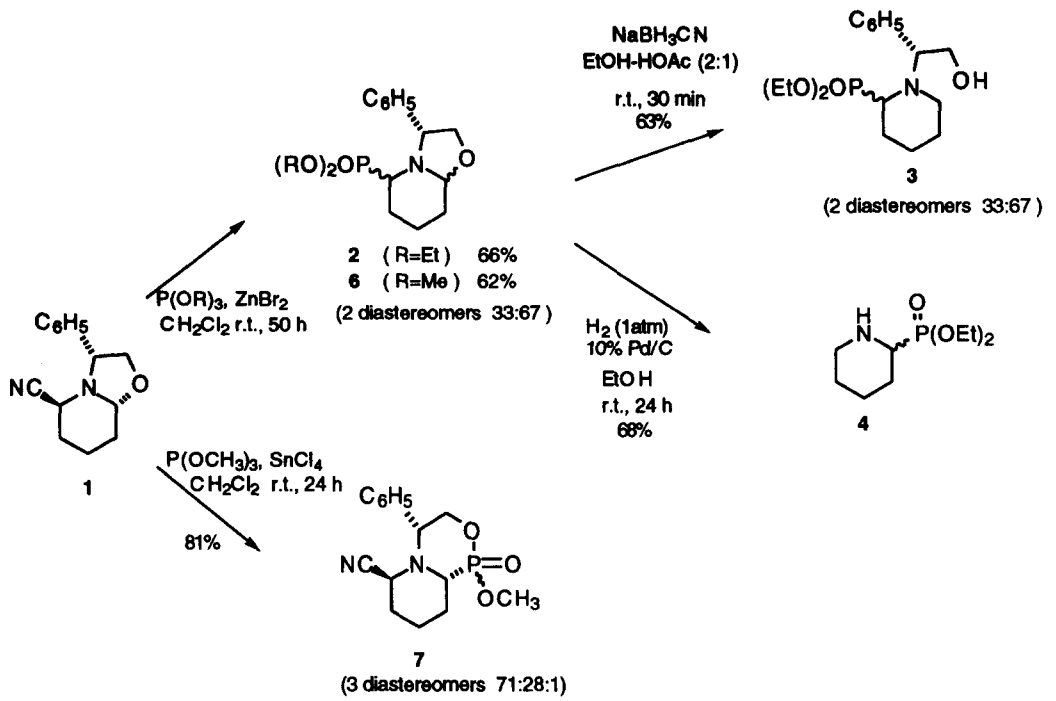


Scheme 1

Transformation of **2** into the aminoester **4** can be obtained in 76% yield in a one-pot reaction by reduction and hydrogenolysis in the presence of Pd/C as catalyst. The determination of the optical rotation would confirm the diastereoselectivity of the first reaction. Indeed we found a value of $[\alpha]_D$ 5.0° (*c* 0.6, $CHCl_3$) ($[\alpha]_{578}$ 5.0° (*c* 0.6, $CHCl_3$)) which cannot be compared to the value reported in the literature for the "pure" compound: $[\alpha]_D$ 3.59° (*c* 0.596, $CHCl_3$).[3] The free aminoacid was then obtained by acid hydrolysis followed by treatment with propylene oxide to give **5** in 96% yield ($[\alpha]_{578}$ 2.6° (*c* 1, 1N NaOH) not reported in the literature)

Facing the problem of the enantiomeric purity of **4** (and therefore **5**), we envisaged other routes to its preparation in order to confirm the obtained results. We decided to apply the Arbusov reaction to synthon **1** which contains two potential iminium salts, namely the aminonitrile and the oxazolidine functions.

Upon treatment with triethyl phosphite (or trimethyl phosphite) in CH_2Cl_2 and in the presence of 1 equivalent of $ZnBr_2$, synthon **1** was transformed in the 2-phosphono-6-oxazolidine compound **2** in 66% yield (or **6** in a similar yield) (Scheme 2). As in the previous reaction, **2** (or **6**) also consisted of a mixture of 2 isomers but with a reverse ratio 33:67 and could be reduced by $NaBH_3CN$ to give **3** in the same diastereomeric ratio. Compound **2** was transformed to aminophosphonate **4** in 68% yield (H_2, Pd/C). Optical rotation of this sample was very low (near zero) and could not be determined with accuracy but was in agreement with an estimated ee of 30% .



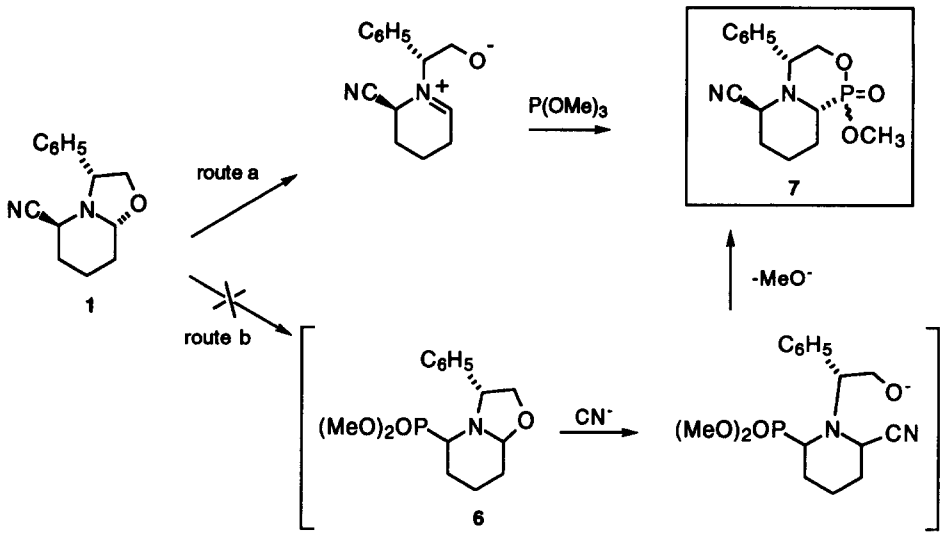
Scheme 2

In order to improve both the yield and the diastereoselectivity of the transformation of **1** into **2** we decided to perform the reaction by changing $ZnBr_2$ for $SnCl_4$ (Scheme 2). We were pleased to find that this change in Lewis acid led to a complete transformation, however product **7** (71:28:1 mixture of 3 diastereomers) was formed in 81% yield with no trace of phosphonate **6**.

In spite of this unexpected result, we assumed that **7** would be a good precursor of the desired aminophosphonic acid. Before achieving the synthesis of the phosphonic α-amino acid, we tried to determine the exact configuration of the two major diastereomers **7a** and **7b** and to understand by which mechanism they were formed.

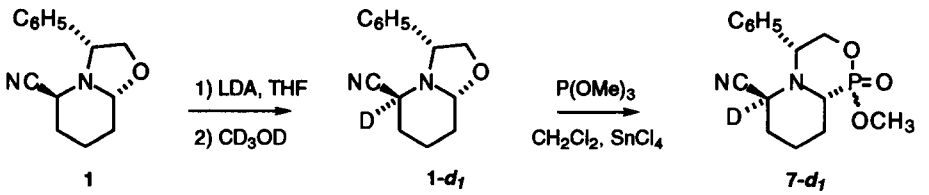
1) mechanism

It was more than surprising to notice that the simple change of Lewis acid led to the formation of a definitively different product which *a priori* arose *via* the formation of a different iminium ion. Thus the simplest mechanism implied the opening of the oxazolidine ring instead of departure of CN^- to form an iminium ion which gave an Arbusov reaction (*route a* Scheme 3). We can also imagine a different mechanism through the formation of **6** in which the oxazolidine ring could be opened by cyanide ion as proposed in Scheme 3 (*route b*).



Scheme 3

Convincing evidence for *route a* was provided by an experiment conducted with deuterated synthon **1-*d*1**. The latter was prepared (LDA, THF, -78°C, CD_3OD, 80% yield, 98% D incorporation) and consequently treated with trimethylphosphite in the presence of 1 equivalent of $SnCl_4$ to give compound **7-*d*1** whereby all the deuterium was located on C-2 (Scheme 4).

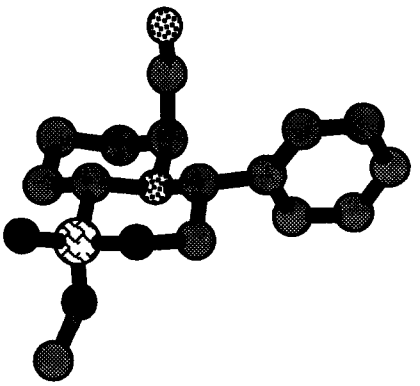


Scheme 4

2) stereochemistry

The stereochemistry of the two major diastereomers of **7** have been carefully examined. Data including IR[4] as well as ^1H ($^3J_{P-H}$) and ^{13}C NMR data[5] strongly suggested that the two components are epimeric at the phosphorus atom. On the other hand, it was not easy to assess the configuration at C-9a for the major isomer. This was fully demonstrated through a X-ray analysis of the major isomer **7a** (see experimental part) which could be isolated from the diastereomeric mixture by chromatography and crystallized.

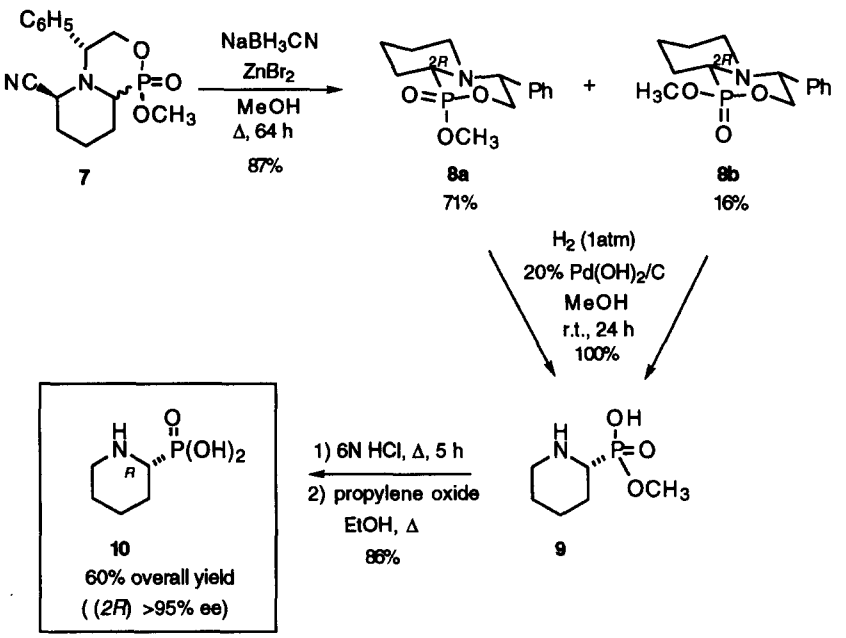
The exact configuration is as depicted in the figure.



Figure

3) Preparation of (2*R*)-piperidin-2yl-phophonic acid :

After determining the configuration of the major epimer of **7** we went through the synthesis of the target phosphonic amino acid as described in Scheme 5. The crude mixture of **7** was reduced with $NaBH_3CN$ to give compound **8** as a mixture of 3 isomers (71:28:1) which could be separated. The major isomers **8a** and **8b** which were assigned to have the same configuration at C-2 were hydrogenolyzed separately to give the same compound **9** ($[\alpha]_D$ -6.8° (*c* 1, $CHCl_3$)) in quantitative yield. This monoester was hydrolyzed in 6N HCl to give **10** in 86% yield ($[\alpha]_{578}$ -4.3° (*c* 1, 1N NaOH).



Scheme 5

In conclusion, from the same chiral inductor, (*R*)-(-)-phenylglycinol, we have developed a strategy for the preparation of both enantiomers of piperidin-2-yl-phosphonic acid. The (*S*)-enantiomer has been obtained in 58%ee while the (*R*)-enantiomer has been isolated in a pure form. The absolute configuration of these phosphonic amino acids has been proved by the X-ray structure of one of the precursors of the (*R*)-isomer.

EXPERIMENTAL

3-Phenyl-hexahydro-oxazolo[3,2-a]pyridin-5-yl-phosphonic acid diethyl ester (2):

a) from glutaraldehyde and phenylglycinol:

A 25 wt % aqueous glutaraldehyde solution (18.0 g, 16.9 mL, 45 mmol) was added dropwise to a solution of (*R*)-(-)-phenylglycinol (4.12 g, 30 mmol) in methanol (150 mL) at 0°C, followed by addition of triethylphosphite (16.95 g, 17.75 mL, 102 mmol). The reaction mixture was then heated at reflux for 2 h. The solvent was removed by evaporation *in vacuo* and the residue was purified by column chromatography on silica gel, eluting with ether/ethyl acetate (6/1), to give compound **2** (5.85 g, 58%) as a mixture of two diastereomers in a ratio of 3.7/1.

b) from synthon **1**:

To a solution of oxazolidine **1**[2] (228 mg, 1.0 mmol), in dichloromethane (40 mL), was added sequentially redistilled triethylphosphite (332 mg, 348 µL, 2.0 mmol) and zinc bromide (450 mg, 2.0 mmol). The reaction mixture was stirred at room temperature for 50 h, then the solvent was removed by evaporation. The residue was taken up in 15% NaOH and the aqueous suspension extracted with ether. The combined etheral extracts were washed with brine, dried with Na_2SO_4, and evaporated *in vacuo*. Column chromatography on silica gel, eluting with ether/ethyl acetate (4/1), yielded 224 mg (66%) of compound **2** as a colorless oil and 30 mg (13%) of recovered starting material **1**.

2: (mixture of diastereomers) IR (film) 2981, 2944, 2906, 2869, 1256, 1231, 1169, 1131 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.46-7.20 (m, 5 H, Ar-H), 4.97 (dd, *J* = 4.8, 7.7 Hz, H-9), 4.75 (dt, *J* = 3.3, 9.5 Hz, H-6'), 4.71 (t, *J* = 3.6 Hz, H-6), 4.52 (td=q, *J* = 7.5, Hz, H-9'), 4.31 (t, *J* = 7.7 Hz, H-8), 4.17 (t, *J* = 7.5 Hz, H-8'), 4.14-3.92 (m, CH_2 and $CH_{2'}$), 3.82 (dd, *J* = 4.8, 7.7 Hz, H-8), 3.59 (t, *J* = 7.5 Hz, H-8'), 3.29 (m, H-2'), 3.06 (dt, *J* = 4.0, 8.9 Hz, H-2), 2.2-1.2 (m, 2H-3, 2H-4, 2H-5, and 2H-3', 2H-4', 2H-5', CH_3 and $CH_{3'}$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.4, 139.5, 128.4, 128.2 127.7, 127.1, 127.0 (Ar-C), 88.1 (d, *J* = 13.1 Hz, C-6), 87.6 (C-6'), 73.3 (C-8'), 69.2 C-8), 66.4 (d, *J* = 2.4 Hz, C-9), 62.8 (d, *J* = 6.3 Hz, $POCH_2$ or $POCH_{2'}$), 62.4 (C-9'), 62.1 (d, *J* = 6.5 Hz, $POCH_2$ or $POCH_{2'}$), 61.9 (d, *J* = 7.6 Hz, $POCH_2$ or $POCH_{2'}$), 61.2 (d, *J* = 7.6 Hz, $POCH_2$ or $POCH_{2'}$), 54.4 (d, *J* = 168.3 Hz, C-2), 50.7 (d, *J* = 126.6 Hz, C-2'), 31.5, 27.0, 25.7 (d, *J* = 2.6 Hz), 24.4 (d, *J* = 2.6 Hz), 19.7, 17.7 (d, *J* = 12.0 Hz), 16.5 (CH_3 or $CH_{3'}$), 16.3 (CH_3 or $CH_{3'}$); MS (CI) *m/z* 340 $[M+1]^+$.

[1-(2-Hydroxy-1-phenyl-ethyl)-piperidin-2-yl]-phosphonic acid diethyl ester (3):

To a cooled solution of **2** (88 mg, 0.26 mmol) in 4.5 mL of ethanol/HOAc (2/1) was added sodium cyanoborohydride (163 mg, 2.6 mmol) in one portion with stirring. The resulting solution was stirred at

room temperature for 30 min, then the solvent was removed*in vacuo*. The residue was taken up in 15% NaOH, and the aqueous suspension extracted with ether. The ethereal extracts were dried over Na_2SO_4. Column chromatography on silica gel (ether/ethyl acetate = 2/1) gave compound **3** (56 mg, 63%).

3: (mixture of diastereomers) IR (film) 3394, 2981, 2938, 2869, 1369, 1292, 1252, 1220 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.40-7.26 (m, 5 H, Ar-H), 4.57 (dd, J = 4.5, 9.1 Hz, H-7'), 4.27-4.09 (m, H-7, $POCH_2$ and $POCH_{2'}$), 3.94 (m, H-8 and H-8'), 3.82 (dd, J = 4.5, 11.6 Hz, H-8), 3.70 (dd, J = 4.5, 10.9 Hz, H-8'), 3.54 (dt, J = 17.1, 4.2 Hz, H-2), 3.24-3.12 (m, H-6 and H-2'), 3.09-2.98 (m, H-6'), 2.77 (dt, J = 13.1, 3.7 Hz, H-6), 2.27-2.18 (m, H-6'), 1.98-1.26 (m, 2H-3, 2H-4, 2H-5, 2H-3', 2H-4', 2H-5'), 1.35 (t, J = 6.86 Hz, CH_3 and $CH_{3'}$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 141.2, 138.3, 128.7, 128.6, 128.3, 128.1, 127.6 (Ar-C), 68.3 (d, J = 7.1 Hz, C-7), 67.0 (d, J = 3.6 Hz, C-7'), 63.2 (C-8), 62.1 (d, J = 7.6 Hz, $CH_{2'}$), 61.9 (d, J = 6.9 Hz, CH_2), 61.8 (C-8'), 57.2 (d, J = 151.1 Hz, C-2'), 53.0 (d, J = 147.3 Hz, C-2), 48.4 (C-6), 44.5 (d, J = 8.1 Hz, C-6'), 26.2, 24.7, 24.5, 24.2, 22.5 (d, J = 8.1 Hz), 21.5 (d, J = 2.8 Hz), 16.6 (CH_3 and $CH_{3'}$); MS (CI) *m/z* 342 $[M+1]^+$, 204 $[M\text{-}PO(OEt)_2]^+$, 139 $[HOP(OEt)_2+1]^{+\cdot}$.

Piperidin-2-yl-phosphonic acid diethyl ester (4):

A mixture of **2** (68 mg, 0.20 mmol) and 10% Pd/C (34 mg) in ethanol (10 mL) was hydrogenated at room temperature under atmospheric pressure for 24 h. The catalyst was filtered off, and the filtrate evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with dichloromethane/methanol (10/1), to give compound **4** as a colorless oil (30 mg, 68%).

4: IR (film) 3459, 2918, 2931, 2854, 2791, 1391, 1286, 1244, 1223, 1173,cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.16 (qd, 4 H, $J_{H\text{-}H} = J_{P\text{-}H}$ = 7.2 Hz, $2POCH_2$), 3.12 (m, 1 H), 2.94 (td, 1 H, J = 11.7, 2.2 Hz;), 2.59 (td, 1 H, J = 11.7, 2.8 Hz), 1.91-1.25 (m, 6 H), 1.34 (t, 6 H, J = 7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 62.2 (d, J = 6.1 Hz), 54.2 (d, J = 159.9 Hz), 47.4 (d, J = 16.7 Hz), 26.2, 26.0, 24.6 (d, J = 15.2 Hz), 16.6; MS (CI) *m/z* 443 $[2M+1]^+$, 222 $[M+1]^+$, 139 $[HOP(OEt)_2+1]^{+\cdot}$, 84 $[M\text{-}PO(OEt)_2]^+$. Anal. Calcd. for $C_9H_{20}NO_3P$: C, 48.86, H, 9.11, N, 6.33; Found: C, 48.75, H, 9.17, N, 5.78.

(2*S*)-Piperidin-2-yl-phosphonic acid (5):

A solution of **4** (70 mg, 0.317 mmol) in 6N hydrochloric acid (2 mL) was refluxed for 5 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in a minimum amount of ethanol, to which was added, dropwise, an excess of propylene oxide while heating. The volatiles were removed by evaporation and the residue was recrystallized from methanol/ether to afford **5** as white solid (96%). $[\alpha]_{578}$ 2.1° (*c* 1.0, 1N NaOH), other data were identical as those of **10** (see below)

1-Methoxy-1-oxo-4-phenyl-octahydro-2-oxa-4a-aza-1-phospha-naphthalene-5-carbonitrile (7):

To a solution of oxazolidine **1** (684 mg, 3 mmol) in dichloromethane (30 mL) was added redistilled trimethylphosphite (1.8 mL, 15 mmol, 5 eq.), followed by dropwise addition of a 1 M solution of tin (IV) chloride in dichloromethane (3 mL, 3 mmol, 1 eq.). The reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure. The crude product was purified by flash-chromatography on silica gel (Et_2O/EtOAc = 4/1) to give compound **7** (775 mg, 81%) as a mixture of 3 diastereoisomers (**7a:7b:7c** = 71:28:1). The major diastereoisomer **7a** was separated by recrystallization.

MS (EI) *m/z* 306 (M^+, 19), 205 (14), 198 (15), 172 (9), 104 ($PhCH{=}CH_2$, 100), 91 ($PhCH_2$, 11), 86 (18), 84 (29), 82 (14).

Isomer **7a**: white crystals, mp 165°C (heptane-THF); ^1H NMR (250 MHz, $CDCl_3$) δ 7.40 (br s, 5 H, Ar-H), 4.24 (ddd, 1 H, *J* = 10.9, 11.5 Hz, $^3J_{H\text{-}P}$ = 2.8 Hz, H-3ax), 4.03 (ddd, 1 H, *J* = 3.0, 11.5 Hz, $^3J_{H\text{-}P}$ = 22.8 Hz, H-3eq), 3.90 (dd, 1 H, *J* = 3.0, 10.9 Hz, H-4ax), 3.88 (d, 3 H, $^3J_{H\text{-}P}$ = 10.5 Hz, OCH_3), 3.60 (d, 1 H, *J* = 3.3 Hz, H-6eq), 3.15 (td, 1 H, *J* = 2.1, 10.9 Hz, $^2J_{H\text{-}P}$ = 10.9 Hz, H-10ax), 2.20 (m, 1 H, H-9), 1.85-1.65 (m, 5 H, 2H-7, 2H-8, H-9); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 134.3/129.1-128.6 (Ar-C), 115.2 (CN), 71.0 (d, $^2J_{C\text{-}P}$ = 5 Hz, C-3), 65.3 (C-4), 54.6 (d, $^1J_{P\text{-}C}$= 150 Hz, C-10), 52.3 (d, $^2J_{C\text{-}P}$ = 7 Hz, OCH_3), 51.3 (d, $^3J_{C\text{-}P}$ = 14 Hz, C-6), 27.7 (C-7), 23.8 (d, $^2J_{C\text{-}P}$ = 4 Hz, C-9), 19.9 (d, $^3J_{C\text{-}P}$ = 15 Hz, C-8). Anal. Calcd. for $C_{15}H_{19}N_2O_3P$: C, 58.82, H, 6.25, N, 9.14; Found: C, 58.77, H, 6.22, H, 9.09

Crystal data for 7a: $C_{15}H_{19}N_2O_3P$. M_W= 306.29. A suitable crystal was investigated on a Siemens P21 diffractometer (Mo Kα radiation = 0.71069 Å, graphite monochromator). Monoclinic, space group $P2_1$, Z = 2, a = 7.274(4) Å, b = 8.694(4) Å, c = 12.265(8) Å, β = 90.74(3)°, V=775.6(8) $Å^3$, d_c = 1.31g.cm^{-3}, F(000) = 302, μ = 0.19 mm^{-1}. 1478 unique reflections measured up to 2θ = 50.26° of which 829 with $I>3\sigma(I)$ were kept in refinement calculations. The structure was solved by direct methods using SHELXS86[6] and refined by full matrix least-squares with SHELX76[7] minimizing the quantity $\sum w(F_o - F_c)^2$. Non hydrogen atoms were refined with anisotropic temperature factors; hydrogen atoms were located in difference Fourier map at observed positions. Convergence was reached at R=0.048 and R_w=0.052. The residual electron density in the final difference Fourier map shows no features up to 0.18 e.$Å^{-3}$. Lists of the fractional atomic coordinates, thermal parameters, bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre, U.K., as supplementary material.

Isomer **7b**: oil; ^1H NMR (250 MHz, $CDCl_3$) δ 7.40 (br s, 5 H, Ar-H), 4.53 (ddd, 1 H, *J* = 10.8, 12.0 Hz, $^3J_{H\text{-}P}$ = 3.1 Hz, H-3ax), 4.25 (m, 1H, signal overlapped, H-3eq), 3.90 (m, 1 H, signal overlapped, H-4), 3.88 (d, 3 H, $^3J_{H\text{-}P}$ = 10.6 Hz, OCH_3), 3.63 (d, 1 H, *J* = 4.5 Hz, H-6eq), 3.05 (ddd, 1 H, *J* = 2.8, 8.9 Hz, $^2J_{H\text{-}P}$ = 11.5 Hz, H-10ax), 2.20-1.50 (m, 6 H, 2H-7, 2H-8, 2H-9); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 133.1/129.1-128.6 (Ar-C), 115.4 (CN), 70.2 (d, $^2J_{C\text{-}P}$ = 5 Hz, C-3), 65.7 (C-4), 54.2 (d, $^1J_{C\text{-}P}$ = 150 Hz, C-10), 53.6 (d, $^2J_{C\text{-}P}$ = 7 Hz, OCH_3), 52.3 (d, $^3J_{C\text{-}P}$ = 7 Hz, C-6), 27.6 (C-7), 24.2 (d, $^2J_{C\text{-}P}$ = 4 Hz, C-9), 19.6 (d, $^3J_{C\text{-}P}$ = 14 Hz, C-8).

Isomer **7c**: oil; ^1H NMR (250 MHz, $CDCl_3$) δ 7.70-7.30 (m, 5 H, Ar-H), 4.79 (td, 1 H, *J* = 2.7, 11.6 Hz, $^3J_{H\text{-}P}$ = 2.7 Hz, H-3ax), 4.49 (ddd, 1 H, *J* = 1.5, 11.6 Hz, $^3J_{H\text{-}P}$ = 21.9 Hz, H-3eq), 3.90 (m, 1 H, signal overlapped, H-4), 3.79 (d, 3 H, $^3J_{H\text{-}P}$ = 11.0 Hz, OCH_3), 3.63 (m, 1 H, H-6), 2.97 (m, 1 H, H-10), 2.20-1.50 (m, 6 H, 2H-7, 2H-8, 2H-9); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 132.8/130.1-128.8 (Ar-C), 118.8 (CN), 71.6 (d, $^2J_{C\text{-}P}$ = 6 Hz, C-3), 60.9 (C-4), 53.0 (d, $^1J_{C\text{-}P}$= 149 Hz, C-10), 54.2 (d, $^2J_{C\text{-}P}$ = 7 Hz, OCH_3), 51.1 (d, $^3J_{C\text{-}P}$ = 7 Hz, C-6), 29.9 (C-7), 23.7 (d, $^2J_{C\text{-}P}$ = 5 Hz, C-9), 22.0 (d, $^3J_{C\text{-}P}$ = 16 Hz, C-8).

1-Methoxy-4-phenyl-octahydro-2-oxa-4a-aza-1-phospha-naphtalene-1-oxide (8) :

To a solution of **7** (850 mg, 2.78 mmol) in methanol was added sodium cyanoborohydride (1.05 g, 16.68 mmol) and zinc bromide (1.88 g, 8.33 mmol). The resulting solution was refluxed for 64 h. The solvent was removed by evaporation, and the residue was dissolved in dichloromethane, washed sequentially with 5%

NaOH and brine. The organic phase was dried ($MgSO_4$), and concentrated. Chromatography of the residual oil on silica gel (gradient elution with ether/ethyl acetate = 4/1 then 1/2) produced 555 mg (71%) of **8a**, 125 mg (16%) of **8b**.

Isomer **8a**: white solid, mp 129-130°C; $[\alpha]_D$ -71° (*c* 1.5, $CHCl_3$); IR (film) 2938, 2856, 2800, 1452, 1288, 1264, 1232, 1097, 1041, 1022cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.33 (m, 5 H, Ar-H), 4.19 (td, 1 H, *J* = 11.2, 2.5 Hz, H-9), 3.97 (ddd, 1 H, *J* = 22.2, 11.2, 3.1 Hz, H-9), 3.86 (d, 3 H, *J* = 10.5 Hz, OCH_3), 3.49 (dd, 1 H, *J* = 11.2, 3.1 Hz, H-10), 2.68 (m, 2 H, H-6 and H-2), 2.15 (m, 1 H), 1.86-1.23 (m, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 137.9, 129.7, 129.2, 128.9 (Ar-C), 72.6 (d, *J* = 5.8 Hz, C-9), 68.9 (d, *J* = 3.0 Hz, C-10), 60.4 (d, *J* = 147.6 Hz, C-2), 54.5 (d, *J* = 14.0 Hz, C-6), 52.3 (d, *J* = 6.8 Hz, OCH_3), 25.4, 25.0 (d, *J* = 4.9 Hz), 24.3 (d, *J* = 14.7 Hz); MS (CI) *m/z* 282 $[M+1]^+$.

Isomer **8b**: white solid, mp 143-145°C; $[\alpha]_D$ -110° (*c* 1.0, $CHCl_3$); IR (film) 2938, 2919, 2800, 1452, 1385, 1280, 1255, 1094, 1005, 954 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5 H, Ar-H), 4.44 (td, 1 H, *J* = 11.4, 2.8 Hz, H-9), 3.97 (ddd, 1 H, *J* = 22.3, 11.4, 3.1 Hz, H-9), 3.85 (d, 3 H, *J* = 10.6 Hz, OCH_3), 3.47 (dd, 1 H, *J* = 11.4, 3.1 Hz, H-10), 2.78-2.69 (m, 1 H, H-6), 2.57 (td, 1 H, *J* = 9.7, 4.1 Hz, H-2), 2.04-1.19 (m, 7 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.2, 128.8, 128.3, 128.2 (Ar-C), 71.5 (d, *J* = 3.8 Hz, C-9), 68.9 (d, *J* = 2.9 Hz, C-10), 59.7 (d, *J* = 149.3 Hz, C-2), 54.2 (d, *J* = 14.0 Hz, C-6), 53.2 (d, *J* = 7.7 Hz, OCH_3), 25.3 (d, *J* = 4.7 Hz), 25.2, 24.0 (d, *J* = 15.3 Hz); MS (CI) *m/z* 282 $[M+1]^+$.

Piperidin-2-yl-phosphonic acid monomethyl ester (9):

A mixture of **8a** (140 mg, 0.5 mmol) and 20% $Pd(OH)_2/C$ (140 mg) in methanol (20 mL) was hydrogenated at room temperature under atmospheric pressure for 24 h. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure to afford **9** (89 mg, 100%).

Hydrogenolysis of **8b**, under identical conditions as described for **8a**, afforded the same compound **9** (100%).

9: white solid,, mp 231-233°C; $[\alpha]_D$ -6.9° (*c* 0.96, $CHCl_3$); IR (nujol) 3406, 2925, 2856, 1638, 1463, 1375, 1288, 1200, 1156, 1144, 1094, 1025 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.7 (br s, NH and P-OH), 3.65 (d, 3H, *J* = 10.2 Hz), 3.26 (m 1 H), 3.02 (m, 1 H), 2.83 (m, 1 H), 2.01-1.40 (m, 6 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 54.0 (d, *J* = 143.3 Hz), 52.9 (d, *J* = 5.7 Hz), 46.0 (d, *J* = 7.9 Hz), 25.0, 23.2 (d, *J* = 11.9 Hz), 22.3; MS (CI) *m/z* 180 $[M+1]^+$, 84 $[M\text{-}PO(OH)OMe]^+$. Anal. calcd. for $C_6H_{14}NO_3P$, 0.3 H_2O(%) C, 39.04; H, 7.97; N, 7.58 Found:C, 38.85; H, 7.43; N, 7.47.

(2*R*)-Piperidin-2-yl-phosphonic acid (10)

A solution of **9** (116 mg, 0.65 mmol) in 6N hydrochloric acid (3 mL) was refluxed for 5 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in minimum amount of ethanol, to which was added, dropwise, an excess of propylene oxide while heating. The volatiles were removed by evaporation *in vacuo* and the residue recrystallized from methanol/ether to afford **10** as a white solid (86%).

10: white solid,, mp 230°C; $[\alpha]_D$ -4.5° (*c* 1.0, 1N NaOH), $[\alpha]_{578}$ -4.3° (*c* 1.0, 1N NaOH); IR (nujol) 3388, 2956, 2850, 2731, 2531, 2438, 2369, 1625, 1600, 1456, 1375, 1244, 1169, 1031, 913 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 3.41 (br d, 1 H, *J* = 13.0 Hz), 3.13 (dt, 1 H, *J* = 2.7, 12.8 Hz), 2.99 (dt, 1 H, *J* = 3.0, 12.8 Hz), 2.09 (m, 1 H), 1.89 (m, 2 H), 1.75-1.48 (m, 3 H); ^{13}C NMR (50 MHz, D_2O) δ 56.0 (d, *J* = 142 Hz), 47.0 (d,

J = 5.5 Hz), 25.3, 23.0, 22.8; MS (FAB) *m/z* 353 $[2M+23]^+$, 331 $[2M+1]^+$, 188 $[M+23]^+$, 166 $[M+1]^+$. Anal. calcd. for $C_5H_{12}NO_3P$ (%) C, 36.37; H, 7.32; N, 8.48 Found:C, 36.55; H, 7.03; N, 8.57.

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