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Tetrahedron 59 (2003) 8405–8410

TETRAHEDRON

Stereoselective synthesis of β-functionalized α-aminophosphonates via aziridinium ions

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Received 22 May 2003; accepted 28 August 2003

This paper is dedicated with admiration to Professor Maria Michalska

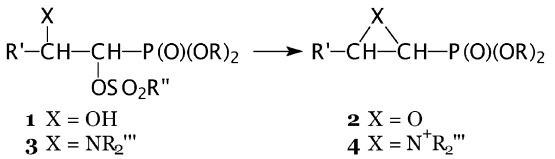
Abstract—1,2-Diamino-, 1-amino-2-hydroxy- and 1-amino-2-chloro-2-phenylethylphosphonates were obtained in a stereo- and regioselective manner from 2-amino-1-hydroxy-2-phenylethylphosphonate through the intermediacy of an aziridinium ion.

1. Introduction

1-Aminophosphonates constitute a well explored class of compounds because of their biological activity.[1] Installation of an amino group at C(1) is generally accomplished by the formation of the C–P bond via the Fields–Kabachnik reaction using imines and *H*-phosphonates.[2] Several modifications of this approach have recently been described in the literature.[3] The major drawback of this reaction is the limited stability of imines prepared from aliphatic amines and sometimes incompatibility of protecting groups with Lewis acid catalysts when structurally complex aldehydes are applied.

On the other hand, 1-hydroxyphosphonates are easily accessible via the Abramov reaction,[4] which has recently been developed to the level of advanced enantioselective syntheses.[5] Under these circumstances, efficient and safe processes of transforming 1-hydroxy- to 1-aminophosphonates would be of high demand. Unfortunately, nucleophilic substitutions at C(1) in phosphonates are difficult.[6] Although displacements of a triflate by an amine at the primary carbon in hydroxymethylphosphonate were accomplished in good yield,[7] reactions at secondary centres failed to give satisfactory results.[8] Application of the Mitsunobu reaction[9] enables the hydroxy–azide exchange[10] to occur in good yields, however, at the cost of working with hydrazoic acid. A microwave induced alumina supported transformation of 1-hydroxy- to 1-aminophosphonates has just been published.[11]

Displacements of good leaving groups (e.g. sulfonates) from C(1) in phosphonates are facilitated by the formation of the oxirane[12] or aziridine[13] rings. We reasoned that a similar approach could lead to 1-aminophosphonates via intermediacy of aziridinium ions,[14] if 2-amino-1-hydroxyphosphonates[15] would have been applied as starting materials (Scheme 1). Herein, we wish to report the evidence for the formation of an aziridinium ion next to the phosphonate group and its reactivity with various nucleophiles.



Scheme 1.

2. Results and discussion

Dimethyl (1*R**,2*S**)-2-(*N*,*N*-dibenzylamino)-1-hydroxy-2-phenylethylphosphonate,[16] (1*R**,2*S**)-**5** was treated with mesyl chloride in the presence of 5 equiv. of triethylamine and the reaction mixture containing crude mesylate (1*R**,2*S**)-**6** was reacted with benzylamine to give (1*S**,2*R**)-**7** in 72% yield after purification on a silica gel column. When dibenzylamine was used instead of benzylamine under the same conditions, (1*S**,2*R**)-**8** was isolated in 47% yield after chromatographic purification and crystallisation. Addition of tetraethylammonium chloride (1 equiv.) during mesylation of **5** gave (1*S**,2*R**)-**9**, which was obtained by column chromatography in 93%. And finally, when the purification of the reaction mixture after

Keywords: aziridines; phosphonic acids and derivatives; regiospecificity; stereospecificity.
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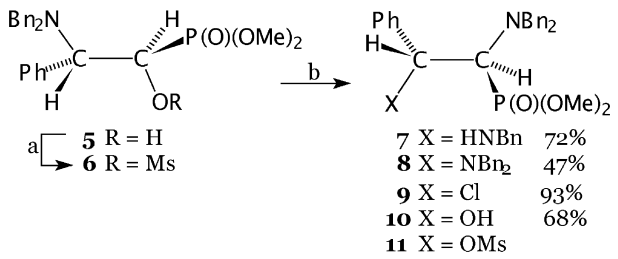
doi:10.1016/j.tet.2003.08.062



Scheme 2. *Reagents and conditions*: (a) MsCl, NEt_3, CH_2Cl_2, 0°C; (b) $BnNH_2$, NEt_3, 40°C, 8 h; or Bn_2NH, NEt_3, 40°C, 20 h; or $Et_4N^+Cl^-$, 20°C, 20 h; or H_2O–SiO_2; or wash out Cl^-, 20°C, 48 h.

mesylation was attempted on a silica gel column, (1*S**,2*R**)-**10** was eluted from the column in 68% yield (Scheme 2).

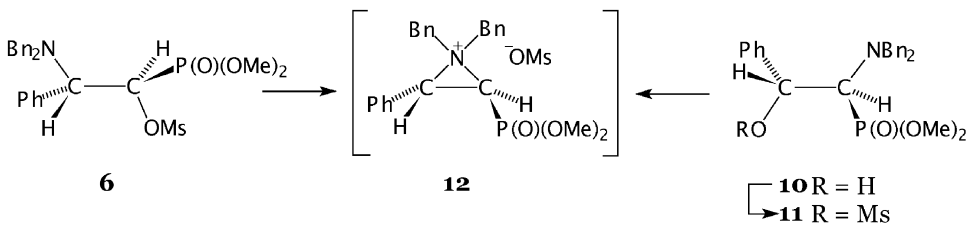
When the crude mesylate **6** (obtained in situ using mesyl chloride) was reacted with benzylamine or dibenzylamine, the respective diamines **7** and **8** were contaminated with the unreacted chloride **9** and unidentified organophosphorus compounds. Taking into account that their ^{31}P NMR resonances appeared 7–10 ppm upfield from those for diamines **7** and **8** and their high affinity to silica gel, we are convinced that cleavage of one methyl group at the phosphonate ester functions occurred. This effect was especially pronounced in the reaction with dibenzylamine leading to moderate yield of diamine **8**.

In identification of compounds **7**–**11** as 1-aminoalkylphosphonates ^1H, ^{13}C and ^{31}P NMR spectroscopic data were successfully employed. Comparisons of several spectral features of isomeric 2-(*N*,*N*-dibenzylamino)-1-hydroxy- and 1-(*N*,*N*-dibenzylamino)-2-hydroxyphosphonates **5**[16] and **10**, respectively, as well as their mesylates **6** and **11** are particularly convincing and, in most instances, take advantage of inductive effects of N and O atoms. Thus, *H*–C–P in **5** and **6** resonate downfield (4.67 and 5.68 ppm) in comparison with these protons in **10** and **11** (3.46 and 3.66 ppm). The same relationship was observed for the *C*–P resonances when comparing 69.25 ppm (**5**) and 76.8 ppm (**6**) with 62.1 ppm (**10**) and 59.0 ppm (**11**). Simultaneously, one-bond C–P couplings dropped down significantly from 161.5 Hz in **5** and 166.9 Hz in **6** to 130.3 Hz in **10** and 132.9 Hz in **11**. Similar comparisons of *H*–C–C–P and *C*–C–P chemical shifts in the isomeric pairs prove N–C(2) and O–C(2) connectivities in **5/6** and **10/11**, respectively. Furthermore, large (ca. 8 ppm) downfield shifts were noticed in the ^{31}P NMR spectra of **10** and **11** when compared to those of **5** and **6**. Taking into account *H*–C–P, *H*–C–C–P, *C*–P, *C*–C–P and ^{31}P NMR chemical shifts and one-bond C–P coupling constants of **7**, **8** and **9**, there is no doubt that they are 1-(*N*,*N*-dibenzylamino)phosphonates. It is worth noting that signals of *H*–C–C–P in all 2-aminophosphonates (**5**, **6**, **7** and **8**) appeared in the 4.1–4.3 ppm region, despite the fact that they originate from 2-amino-1-hydroxy- or 1,2-diaminophosphonates.

The relative stereochemistry of the products was established based on ^1H and ^{13}C NMR data. The phosphonates **7**–**11** exist almost exclusively as single conformers having the phenyl and phosphonate groups antiperiplanar ($^3J_{P-C_{ipso}}$=10.9–14.3 Hz,[17] $^3J_{H1-H2}$=8.1–11.7 Hz,[18] $^3J_{P-H2}$=9.0–12.6 Hz[19]). Thus, transformation of *anti*[16] diastereoisomer **6** into *anti* diastereoisomers **7**–**11** requires two inversions of configuration to occur, undoubtedly through the participation of the aziridinium ion **12** (Scheme 3). Nucleophiles stronger than MsO^- (H_2NBn, $HNBn_2$, Cl^-, H_2O/SiO_2) exclusively attacked the benzylic position in **12** leading to 1,2-diamino-, 1-amino-2-chloro- and 1-amino-2-hydroxyphosphonates. The reaction with water is particularly interesting as a functional group transposition.

Several attempts at isolating pure mesylate (1*R**,2*S**)-**6** proved fruitless. Mesylation of **5** with mesyl chloride in the presence of triethylamine (5 equiv.) below 0°C followed by quenching of the reaction mixture at 0°C with water, water work-up and low temperature solvent evaporation led to a mixture which consisted of (1*R**,2*S**)-**6**, (1*S**,2*R**)-**9** and (1*S**,2*R**)-**11** in a 84:2:14 ratio as judged from immediate ^1H, ^{13}C and ^{31}P NMR spectroscopic studies. ^1H and ^{31}P NMR monitoring of this mixture at room temperature for 2 days revealed disappearance of the 1-*O*-mesylate **6** and the exclusive formation of 2-*O*-mesylate **11**. Thus, in the absence of strong nucleophiles MsO^- was reactive enough to open the aziridinium ion **12** at the benzylic position. The same transformations took place, when (1*R**,2*S**)-**5** was subjected to mesylation with mesyl anhydride, except for the absence of the chloride **9**. Mesylation of (1*S**,2*R**)-**10** with mesyl chloride gave a mixture of the chloride (1*S**,2*R**)-**9** and the mesylate (1*S**,2*R**)-**11** containing significant amounts of (1*S**,2*R**)-**10**. However, in a separate NMR tube experiment we observed quantitative formation of the mesylate **11** and its hydrolysis to (1*S**,2*R**)-**10** after addition of water.

The 2-chlorophosphonate (1*S**,2*R**)-**9** was also useful as a starting material in the synthesis of the 2-(*N*-benzylamino)-phosphonate (1*S**,2*R**)-**7**, which was isolated in moderate 54% yield. Undoubtedly, when the crude mesylate (1*R**,2*S**)-**6** obtained using mesyl chloride was reacted with benzylamine, two nucleophiles (Cl^- and H_2NBn) can attack the aziridinium ion **12** (formed primarily from the mesylate **6**) leading to the amine (1*S**,2*R**)-**7** and the chloro derivative (1*S**,2*R**)-**9**. The latter compound is a second, although less reactive, source of the aziridinium ion **12**.



Scheme 3. Formation of the aziridinium ion **12** from 1-*O*-mesylate **6** and 2-*O*-mesylate **11**.

When the crude mesylate (1*R**,2*S**)-**6** was washed with water to remove chlorides, the reactions with amines were complete in a shorter time and the purification of the diamines (1*S**,2*R**)-**7** and especially (1*S**,2*R**)-**8** did not require tedious separation of a residual 2-chlorophosphonate (1*S**,2*R**)-**9**.

3. Conclusions

Dimethyl (1*R**,2*S**)-2-(*N*,*N*-dibenzylamino)-1-mesyloxy-2-phenylethylphosphonate **6** reacted with nucleophiles in regio- and stereospecific manner to produce 2-substituted dimethyl 1-(*N*,*N*-dibenzylamino)-2-phenylethylphosphonates in good yields. The formation of (1*S**,2*R**)-configured products implies the intermediacy of the aziridinium ion **12**. This clear regio- and stereochemical outcome of the reactions was secured by incorporating highly reactive benzylic and relatively unreactive α to the phosphoryl group carbon atoms within the aziridinium ion framework. Under these circumstances even MsO^-, considered as non-nucleophilic, was able to open the aziridinium ion. Both mesylates (1*R**,2*S**)-**6** and (1*S**,2*R**)-**11** appeared too reactive to be isolated.

Further studies in this new area of the phosphonate chemistry employing variety of 2-(*N*,*N*-dibenzylamino)-1-hydroxyalkylphosphonates prepared from enantiomerically pure α-(*N*,*N*-dibenzylamino)aldehydes[20] are under way in this laboratory and the results will be disclosed in due course.

4. Experimental

^1H, ^{13}C and ^{31}P NMR spectra were taken in $CDCl_3$ on the Varian Mercury-300 spectrometer at 300, 75.5 and 121.5 MHz, respectively. IR spectral data were measured on an Infinity MI-60 FT-IR spectrometer. Melting points were determined on a Boetius apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of this Faculty on a Perkin–Elmer PE 2400 CHNS analyser.

The following adsorbents were used: column chromatography, Merck silica gel 60 (70–230 mesh); analytical TLC, Merck TLC plastic sheets silica gel 60 F_{254}. TLC plates were developed in various chloroform/methanol and ethyl acetate/hexanes solvent systems. Visualisation of spots was effected with iodine vapours.

4.1. Mesylation of (1*R**,2*S**)-5 (general procedure)

A solution of (1*R**,2*S**)-**5** (0.24 mmol) in anhydrous CH_2Cl_2 (2 mL) was cooled to 0°C under argon atmosphere and triethylamine (0.72 mmol) was added followed by mesyl chloride (0.29 mmol, 1.2 equiv.). After 30 min, temperature of the reaction mixture was allowed to reach 20°C and additional NEt_3 (0.48 mmol) was added.

4.1.1. Dimethyl (1*S,2*R**)-1-(*N*,*N*-dibenzylamino)-2-(*N*-benzylamino)-2-phenylethylphosphonate (1*S**,2*R**)-7.** Benzylamine (96 μL, 0.88 mmol) was added to the solution containing (1*R**,2*S**)-**6** prepared from (1*R**,2*S**)-**5** (0.340 g, 0.80 mmol) as described in Section 4.1 and the reaction mixture was kept in 40°C (bath) for 8 h and left at room temperature for 13 h. The residue was diluted with CH_2Cl_2 (20 mL), washed with water (2×10 mL), dried over $MgSO_4$ and concentrated. The crude product was chromatographed on a silica gel column with ethyl acetate/hexanes (2:1, v/v) to give (1*S**,2*R**)-**7** (0.297 g, 72%) as a colourless oil. IR (film): ν=3028, 2949, 2848, 1495, 1454, 1235, 1055, 1029, 735, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ=3.39 (dd, J=14.1, 9.6 Hz, 1H, *H*CP), 3.43 (d, J=13.2 Hz, 1H, N–*H*CH–Ph), 3.54 (d, J=13.2 Hz, 1H, N–HC*H*–Ph), 3.71 (d, J=10.8 Hz, 3H, CH_3OP), 3.75 [brd, J=8.4 Hz, 2H, N(*H*CH–$Ph)_2$], 3.80 [dd, J=8.4, 4.8 Hz, 2H, N(HC*H*–$Ph)_2$], 3.82 (d, J=10.8 Hz, 3H, $POCH_3$), 4.09 (dd, J=10.2, 9.6 Hz, 1H, *H*CCP), 6.90–7.00 (m, 5H, Ar), 7.10–7.40 (m, 15H, Ar). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=51.5, 52.1 and 52.3 (2d, J=7.3 Hz, CH_3OPOCH_3), 55.0 [d, J=1.5 Hz, $N(CH_2Ph)_2$], 61.8 (d, J=128.0 Hz, CP), 62.1 (d, J=8.3 Hz, *C*CP), 126.8, 127.0, 127.3, 128.1, 128.2, 128.4, 128.7, 129.4, 138.9, 140.0, 141.4 (d, J=12.9 Hz, C_{ipso} in PhCCP). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ=33.50. Anal. calcd for $C_{31}H_{35}N_2O_3P{\cdot}1.5H_2O$: C, 68.75; H, 7.07; N, 5.17. Found: C, 68.89; H, 6.89; N, 5.23.

4.1.2. Dimethyl (1*S,2*R**)-1,2-bis(*N*,*N*-dibenzylamino)-2-phenylethylphosphonate (1*S**,2*R**)-8.** Dibenzylamine (120 μL, 0.624 mmol) was added to the solution containing (1*R**,2*S**)-**6** prepared from (1*R**,2*S**)-**5** (0.220 g, 0.520 mmol) as described in Section 4.1 and the reaction mixture was maintained at 40°C (bath) for 15 h and left at room temperature for 13 h. After dilution with CH_2Cl_2 (20 mL), the organic phase was washed with water (2×10 mL), dried over $MgSO_4$ and concentrated. The crude product was purified on a silica gel column using chloroform/methanol (50:1, v/v). The appropriate fractions were collected and recrystallised from ethyl acetate:hexanes to give (1*S**,2*R**)-**8** (0.147 g, 47%) as colourless plates. Mp 180.5–181.5°C. IR (KBr): ν=3425, 3060, 3025, 2927, 2839, 2805, 1494, 1451, 1243, 1055, 1031, 742, 695 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ=2.85 (d, J=13.8 Hz, 2H, NCH_2Ph), 3.35 (brd, J=13.8 Hz, 1H, NCH_2Ph), 3.61–3.69 (brm, 3H, NCH_2Ph), 3.73 and 3.79 (2d, J=10.8 Hz, 6H, CH_3OPOCH_3), 3.82–3.98 (brm, 2H, NCH_2Ph), 3.95 (t, J=11.7 Hz, 1H, HCP), 4.38 (dd, J=11.7, 9.3 Hz, 1H, HCCP), 6.45–6.52 (m, 2H, Ar), 6.59–6.68 (m, 2H, Ar), 6.95–7.10 (m, 5H, Ar), 7.15–7.22 (m, 2H, Ar), 7.22–7.32 (m, 9H, Ar), 7.32–7.40 (m, 1H, Ar), 7.40–7.50 (m, 4H, Ar). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=51.6 and 51.8 (2d, J=7.4 Hz, CH_3OPOCH_3), 54.3, 54.6, 55.1, 55.5 (d, J=129.1 Hz, CP), 63.6 (d, J=7.7 Hz, *C*CP), 126.8, 127.0, 127.5, 128.0, 128.6, 129.5, 131.0, 131.3, 133.7 (d, J=14.3 Hz, C_{ipso} in PhCCP), 137.6, 139.3, 139.7. ^{31}P NMR (121.5 MHz, $CDCl_3$) δ=32.02. Anal. calcd for $C_{38}H_{41}N_2O_3P{\times}0.25\ H_2O$: C, 74.92; H, 6.87; N, 4.60. Found: C, 74.87; H, 6.86; N, 4.58.

4.1.3. Dimethyl (1*S,2*R**)-1-(*N*,*N*-dibenzylamino)-2-chloro-2-phenylethylphosphonate (1*S**,2*R**)-9.** Tetraethylammonium chloride (0.097 g, 0.586 mmol) was added to the solution containing (1*R**,2*S**)-**6** prepared from (1*R**,2*S**)-**5** (0.250 g, 0.586 mmol) as described in Section 4.1 and the reaction mixture was left at room

temperature for 20 h. The solution was diluted with CH_2Cl_2 (20 mL), washed with water (2×10 mL), dried over $MgSO_4$ and concentrated. The crude product was chromatographed on a silica gel column with ethyl acetate/hexanes (2:1, v/v) to give (1*S**,2*R**)-**9** (0.241 g, 93%) as a colourless oil which very slowly solidified. Colourless solid. Mp 73–74°C. IR (film): ν=2951, 2925, 2852, 1454, 1245, 1039 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ=3.73 (dd, *J*=13.2, 10.2 Hz, 1H, HCP), 3.75–3.90 (m, 4H, $PhCH_2NCH_2Ph$), 3.89 and 3.91 (2d, *J*=10.8 Hz, 6H, CH_3OPOCH_3), 5.15 (dd, *J*=10.2, 9.0 Hz, 1H, HCCP), 6.86–6.98 (m, 6H, Ar), 7.15–7.29 (m, 8H, Ar), 7.31–7.39 (m, 1H, Ar). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=51.6 and 52.3 (2d, *J*=7.2 Hz, CH_3OPOCH_3), 55.0 (d, *J*=1.5 Hz, NCH_2Ph), 59.8 (d, *J*=9.2 Hz, *C*CP), 61.9 (d, *J*=134.0 Hz, CP), 127.2, 127.9, 128.1, 128.2, 128.5, 129.5, 138.2, 139.8 (d, *J*=12.0 Hz, C_{ipso} in PhCCP). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ=30.10. Anal. calcd for $C_{24}H_{27}ClNO_3P$: C, 64.94; H, 6.13; N, 3.16. Found: C, 64.98; H, 5.81; N, 3.21.

4.1.4. Dimethyl (1*S,2*R**)-1-(*N*,*N*-dibenzylamino)-2-hydroxy-2-phenylethylphosphonate (1*S**,2*R**)-10.** The reaction mixture containing (1*R**,2*S**)-**6** prepared from (1*R**,2*S**)-**5** (0.405 g, 0.950 mmol) as described in Section 4.1 was diluted with CH_2Cl_2 (20 mL), washed with water (2×10 mL), dried over $MgSO_4$ and concentrated. The residue was chromatographed on a silica gel column with ethyl acetate/hexanes (2:1, v/v). The appropriate fractions (0.276 g, 68%) were recrystallised from ethyl acetate/hexanes to give (1*S**,2*R**)-**10** (0.171 g, 42%) as colourless plates. Mp 149.3–149.6°C. IR (KBr): ν=3289, 3028, 2950, 1603, 1496, 1454, 1217, 1074, 1030, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ=3.46 (dd, *J*=16.2, 8.1 Hz, 1H, HCP), 3.59 (d, *J*=11.1 Hz, 3H, CH_3OP), 3.81 (brd, *J*=13.5 Hz, 2H, NCH_2Ph), 3.84 (d, *J*=4.8 Hz, 1H, OH), 3.86 (d, *J*=11.1 Hz, 3H, CH_3OP), 3.87 (dd, *J*=13.5, 4.2 Hz, 2H, $PhCH_2N$), 5.15 (ddd, *J*=12.6, 8.1, 4.8 Hz, 1H, HCCP), 7.05–7.11 (m, 4H, Ar), 7.11–7.19 (m, 2H, Ar), 7.20–7.28 (m, 6H, Ar), 7.28–7.36 (m, 3H, Ar). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=52.2 and 52.7 (2d, *J*=7.2 Hz, CH_3OPOCH_3), 55.5 (d, *J*=2.6 Hz, NCH_2Ph), 62.1 (d, *J*=130.3 Hz, CP), 73.0 (d, *J*=6.9 Hz, *C*CP), 127.1, 127.5, 128.0, 128.2, 128.3, 129.1, 138.9, 141.9 (d, *J*=11.8 Hz, C_{ipso} in PhCCP). ^{31}P NMR (121.5 MHz, $CDCl_3$) δ=33.10. Anal. calcd for $C_{24}H_{28}NO_4P$: C, 67.75; H, 6.63; N, 3.29. Found: C, 67.83; H, 6.70; N, 3.32.

4.2. Dimethyl (1*S**,2*R**)-1-(*N*,*N*-dibenzylamino)-2-mesyloxy-2-phenylethylphosphonate (1*S**,2*R**)-11

The phosphonate (1*R**,2*S**)-**5** (0.250 mg, 0.59 mmol) was dissolved in CH_2Cl_2 (3 mL), the solution was cooled to −5°C and treated with NEt_3 (302 μL, 2.48 mmol) and mesyl chloride (56 μL, 0.71 mmol). After 30 min at −5°C, water (5 mL) was added followed by CH_2Cl_2 (20 mL). Layers were separated, the organic phase was washed with water (2×10 mL), dried over $MgSO_4$ and concentrated to give a colourless oil (300 mg, 101%). Samples of this material: 10 mg and 150 mg were withdrawn and dissolved in $CDCl_3$ (0.7 mL) and the solutions were immediately analysed by ^1H and ^{31}P, and ^{13}C and ^{31}P NMR, respectively.

Compound (1*R**,2*S**)-**6**. Recorded together with (1*S**,2*R**)-**9** and (1*S**,2*R**)-**11** at the beginning of the NMR monitoring. ^1H NMR (300 MHz, $CDCl_3$) δ=2.23 (s, 3H, CH_3SO_2), 3.14 (d, *J*=13.2 Hz, 2H, NCH_2Ph), 3.71 and 3.74 (2d, *J*=10.5 Hz, 6H, CH_3OPCH_3), 4.00 (d, *J*=13.2 Hz, 2H, $PhCH_2N$), 4.32 (dd, *J*=9.9, 7.2 Hz, 1H, HCCP), 5.68 (dd, *J*=9.9, 7.2 Hz, 1H, HCP), 7.18–7.58 (m, 15H, Ar). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=46.4 (CH_3SO_2), 53.6 and 53.8 (2d, *J*=7.2 Hz, CH_3OPOCH_3), 54.8 (NCH_2Ph), 63.3 (d, *J*=3.2 Hz, *C*CP), 76.8 (d, *J*=166.9 Hz, CP), 127.2, 128.3, 128.4, 129.3, 130.4, 133.3 (d, *J*=12.4 Hz, C_{ipso} in PhCCP), 138.6. ^{31}P NMR (121.5 MHz, $CDCl_3$) δ=19.97.

The reaction mixture was monitored by ^1H and ^{31}P NMR for 48 h.

Compound (1*S**,2*R**)-**11**. Recorded at the end of the NMR monitoring. ^1H NMR (300 MHz, $CDCl_3$) δ=2.46 (s, 3H, CH_3SO_2), 3.66 (dd, *J*=12.9, 10.2 Hz, 1H, HCP), 3.64–3.90 (m, 4H, $PhCH_2NCH_2Ph$), 3.89 and 3.92 (2d, *J*=10.8 Hz, CH_3OPOCH_3), 5.78 (dd, *J*=10.2, 8.1 Hz, 1H, HCCP), 6.85–6.97 (m, 4H, Ar), 6.97–7.00 (m, 2H, Ar), 7.18–7.58 (m, 9H, Ar). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=46.3 (CH_3SO_2), 52.6 and 52.6 (2d, *J*=7.2 Hz, CH_3OPOCH_3), 55.1 (d, *J*=1.3 Hz, NCH_2Ph), 59.0 (d, *J*=132.9 Hz, CP), 82.4 (d, *J*=6.0 Hz, *C*CP), 127.3, 128.2, 128.7, 128.7, 129.1, 129.5, 136.2 (d, *J*=11.4 Hz, C_{ipso} in PhCCP), 138.1. ^{31}P NMR (121.5 MHz, $CDCl_3$) δ=28.01.

4.3. Mesylation of the phosphonate (1*S**,2*R**)-10

A cooled (0°C) solution of (1*S**,2*R**)-**10** (0.074 g, 0.17 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was treated with NEt_3 (73 μL, 0.52 mmol) followed by mesyl chloride (17 μL, 0.21 mmol). After 30 min water (10 mL) was added and the reaction mixture was diluted with CH_2Cl_2 (10 mL). Organic layer was separated, washed with water (2×5 mL), dried over $MgSO_4$ and concentrated to leave a colourless oil (80 mg). ^1H and ^{31}P NMR spectra showed the formation of a 28:46:26 mixture of the phosphonates (1*S**,2*R**)-**11**, (1*S**,2*R**)-**9** and (1*S**,2*R**)-**10**.

4.4. Synthesis of the 2-aminophosphonate (1*S**,2*R**)-7 from the 2-chlorophosphonate (1*S**,2*R**)-9

A solution of (1*S**,2*R**)-**9** (0.034 g, 0.081 mmol) and benzylamine (11 μL, 0.096 mmol) in CH_2Cl_2 (1 mL) was kept at 40°C (bath) for 18 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with water (2×5 mL), dried over $MgSO_4$ and concentrated. The crude product (30 mg) was chromatographed on a silica gel column to give (1*S**,2*R**)-**7** (0.022 g, 54%) as a colourless oil identical in all respects with the material described in Section 4.1.1.

4.5. Synthesis of the 2-aminophosphonate (1*S**,2*R**)-7 from a crude mesylate (1*R**,2*S**)-6

A solution of (1*R**,2*S**)-**5** (0.056 mg, 0.13 mmol) in CH_2Cl_2 (1.5 mL) was treated at 0°C with NEt_3 (55 μL, 0.39 mmol) followed by mesyl chloride (13 μL, 0.16 mmol). After 30 min water (5 mL) was added and the reaction mixture was diluted with CH_2Cl_2 (10 mL). The organic layer was separated, washed with water (2×5 mL), dried over $MgSO_4$ and concentrated. A solution of the crude mesylate (1*R**,2*S**)-**6**, benzylamine (17.5 μL, 0.158 mmol) and

NEt_3 (18 μL, 0.13 mmol) in CH_2Cl_2 (1.5 mL) was kept at 40°C for 6 h. The reaction mixture was purified on a silica gel column with chloroform/methanol (100:1, v/v) to give (1*S**,2*R**)-**7** (0.052 g, 76%) as a colourless oil identical in all respects with the material described in Section 4.1.1.

4.6. Synthesis of the 2-aminophosphonate (1*S**,2*R**)-8 from a crude mesylate (1*R**,2*S**)-6

The reaction was performed as described in Section 4.5 using (1*R**,2*S**)-**6** (0.250 g, 0.59 mmol), NEt_3 (246 μL, 1.77 mmol) and mesyl chloride (56 μL, 0.71 mmol). The crude mesylate (300 mg), dibenzylamine (113 μL, 0.588 mmol) and NEt_3 (82 μL, 0.59 mmol) were dissolved in CH_2Cl_2 (2 mL) and the reaction mixture was kept at 40°C for 12 h. After addition of CH_2Cl_2 (10 mL) and water (5 mL), the organic layer was separated, washed with water (2×5 mL), dried over $MgSO_4$ and concentrated. The crude product was chromatographed on a silica gel column with chloroform/methanol (50:1, v/v). The appropriate fractions (0.264 g) were crystallised from ethyl acetate/hexanes to give (1*S**,2*R**)-**8** (0.186 g, 52%) as colourless plates (Mp 180.5–181.5°C) spectroscopically identical with the material described in Section 4.1.2.

Acknowledgements

We thank Mrs Jolanta Plocka for her skilled experimental contributions. Financial support from the Medical University of Łódź (503-314-1) is gratefully acknowledged.

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