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First synthesis of *P*-aryl-phosphinosugars, organophosphorus analogues of *C*-arylglycosides

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Abstract—The synthesis and X-ray crystal structure of the first example of arylphosphinosugar are reported. The protected polyhydroxylated 1,2-oxaphosphinane is prepared by a two steps sequence (phenylphosphinate addition on protected mannofuranose followed by intramolecular transesterification) on gram scale. Deprotection of the di-isopropylidene derivative using acidic cation-exchange resin affords the free hydroxy organophosphorus heterocycle analogous to *C*-arylglycosides.

1. Introduction

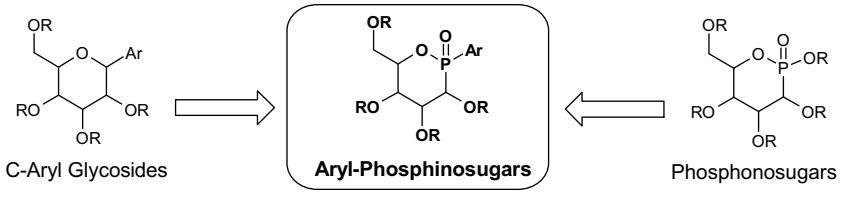
Carbohydrates are an ubiquitous class of biomolecules, with a great array of diversity, both in structure and biological function. Analogues of the natural and common sugars have the potential to modify many biological events.

Due to their increased stability towards hydrolysis as well as their presence in a number of interesting natural products, *C*-glycosides have received a great deal of attention from the synthesis and medicinal chemistry community.[1] Indeed, various examples were described exhibiting biological activity (Fig. 1).[2]

Moreover, sugars analogues containing phosphorus have received continuous attention in the literature. Numerous modified cyclic sugars in which a phosphorus atom replaces the ring oxygen were prepared.[3] So, several phosphinosugars (phostones) were synthesized. The presence of a phosphorus atom in place of the anomeric carbon (Fig. 2a–c)[4] and their similarity to natural carbohydrates suggest that they should have interesting and potentially useful biological properties. Indeed, for instance these compounds may mimic the transition state involved in glycosidase-catalyzed hydrolytic reactions. Surprisingly, despite the well known biological activity of various phosphinic derivatives,[5] phosphinosugars are still relatively unexplored (Fig. 2d).[6]

Combining *C*-arylglycosides and phosphonosugars in the same molecule would lead to cyclic polyhydroxylated *P*-aryl-oxaphosphinanes for which, to the best of our knowledge, no example of synthesis is described in the literature.

We report herein the first synthesis of 2-phenyl-1,2-oxaphosphinanes and their complete deprotection to afford



Keywords: Phostone; Sugar analogues; Arylphosphinic; Polyhydroxylated.
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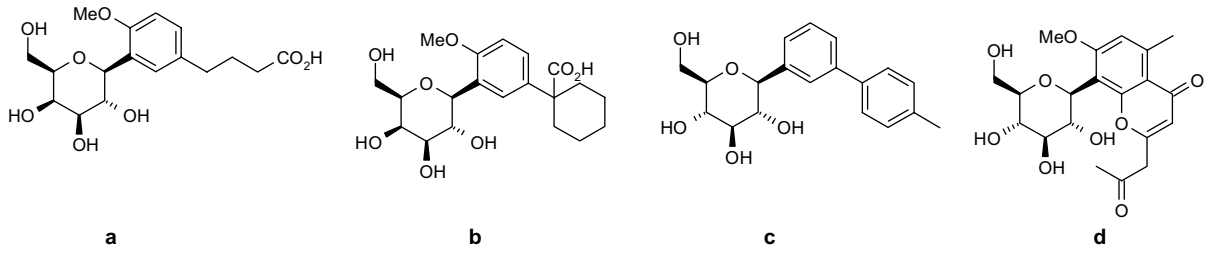


Figure 1. Some biological active synthetic *C*-arylglycosides.

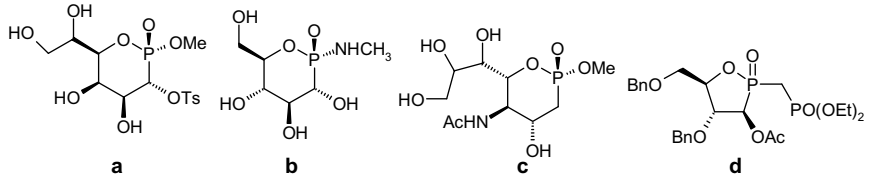


Figure 2. Several examples of phosphono- and phosphino-sugars.

the free hydroxyl organophosphorus heterocyclic compound (R = H).

2. Results and discussion

Starting material is the low-cost D-mannose, which is easily protected with acetone in the presence of iodine to give [2,3:5,6]-di-*O*-isopropylidene-β-D-mannofuranose **1** in high yields.[7] The preparation of methylphenylphosphinate **2** follows a recent procedure described by Afarinkia and Yu using phenylphosphinic acid and methyl chloroformate.[8]

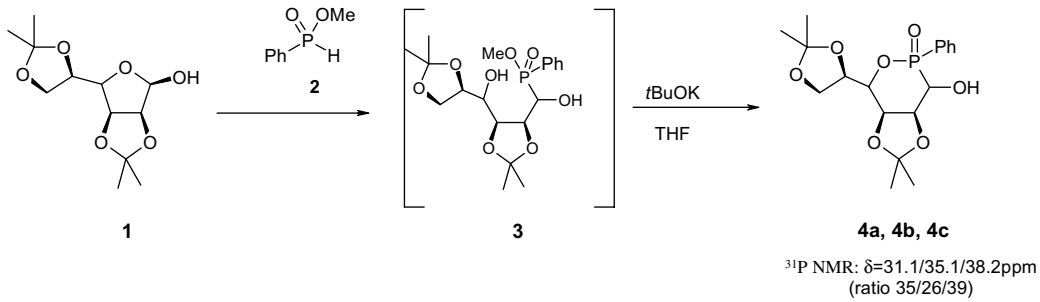
Methylphenylphosphinate **2** is added to the protected mannofuranose **1** under basic activation with potassium *tert*-butoxide (Scheme 1), affording a mixture of three cyclic *P*-phenyl-oxaphosphinanes **4** (92%) and side products (8%). The basic activation not only enhances nucleophilicity of the hydrogenophosphinate **2** by removing its acidic proton but also deprotonates the open intermediates **3** allowing the spontaneous in situ transesterification. The addition is stereoselective as demonstrated by the presence of only three diastereoisomers in different amounts (δ = 31.1 (**4a**, 39%)/35.1 (**4b**, 26%)/38.2 (**4c**, 35%) ppm), among the four possible. One diastereoisomer (δ = 31.1 ppm, **4a**) precipitates from the reaction mixture and can be easily isolated by filtration. The two others can be separated by column chromatography and the total yield reaches 85%.

Suitable crystals for X-ray analysis were obtained in DMSO for compound **4a**. According to the ORTEP structure, we were able to assign the absolute configuration of the new created asymmetric centers of the diastereoisomer **4a** (δ = 31.1 ppm) (Fig. 3).

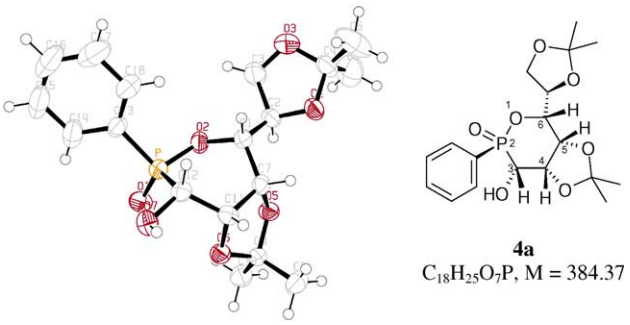
The phosphinosugar **4a** (δ = 31.1 ppm) analogous to *C*-arylated heptopyranose shows a[2,5] *B* boat structure with $P_2(S)$, $C_3(R)$ configuration.

Deprotection of phosphinosugar **4a** could be done efficiently and quantitatively using Amberlyst 15 as acidic proton exchange resin and monitoring the reaction by ^{31}P NMR. Completion occurs after several days of stirring at room temperature (also easily deduced from complete dissolution of reaction mixture) and no racemization is observed ($[\alpha]_D$ +50 (*c* 0.1, MeOH)). Indeed, partial racemization should induce the formation of diastereoisomers, which were not detected either by ^{31}P NMR or ^{1}H NMR. Recrystallization in ethanol afforded the pure fully deprotected arylphosphinosugar **5** (Scheme 2).

In summary, we have described the first synthesis on large scale of *P*-phenyl-phosphinosugars under base-catalyzed

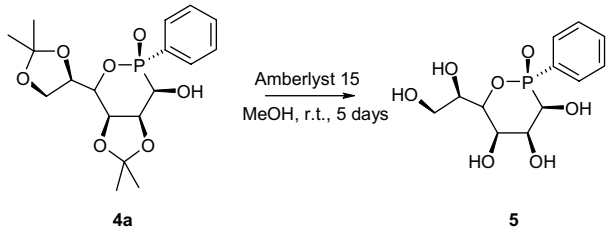


Scheme 1. Synthesis of protected *P*-phenyl-phosphinosugars **4a**–**c**.



4a
$C_{18}H_{25}O_7P$, M = 384.37

Figure 3. ORTEP structure of compound **4a**.



4a **5**

Scheme 2. Deprotection of *P*-phenyl-phosphinosugar **4a**.

transesterification conditions. The selective cleavage of di-isopropylidene protective groups without oxaphosphinane ring opening affords an efficient access to polyhydroxylated organophosphorus heterocycles analogous to *C*-arylglycosides. Further developments by variation of the substituents on phosphorus are in progress and will be reported in due course.

3. Experimental

3.1. General methods

All reactions involving air or moisture sensitive reagents or intermediates were carried out under dry nitrogen in flame-dried glassware. Reagents and solvents were distilled before use and stored under nitrogen over sodium wires (THF) or molecular sieves (dichloromethane). All reactions were monitored by ^{31}P NMR. Merck silica gel (35–70 μm) was used for column chromatography. NMR spectra were recorded on Bruker AC 200, 250, or 400 (^1H frequency: 200.13, 250.13, or 400.13 MHz; ^{13}C frequency: 50.32, 62.89, or 100.62 MHz, ^{31}P frequency: 81.02, 101.25, or 162.04 MHz, respectively). Chemical shifts are given in δ units with respect to TMS (^1H, ^{13}C NMR) or H_3PO_4 85% (^{31}P), coupling constants are expressed in hertz. Infrared spectra were recorded on Perkin–Elmer 377 or FT-NICOLET 210 spectrometer. Mass spectra were measured on JEOL JMS DX-300 spectrometer (positive FAB ionization and high resolution using *p*-nitrobenzyl alcohol NBA).

3.2. Synthesis of [2,3:5,6]-di-*O*-isopropylidene-β-D-mannofuranose 1

To a suspension of D-mannose (50.8 g, 0.282 mol) in 2.5 L of acetone was added iodine (14.3 g, 56.4 mmol) and the mixture was stirred for 2 h at 25 °C. The reaction mixture was quenched at 0 °C with sodium thiosulfate and sodium bicarbonate and the organic residues extracted with chloroform. After three washings with sodium bicarbonate (ca. 300 mL), the organic layer was dried over $MgSO_4$, concentrated, and crystallized from an acetone/hexane mixture to produce **1** (62.4 g, 0.24 mol, 85%): colorless solid; ^1H NMR (250.13 MHz, $CDCl_3$): δ 1.34 (s, 3H); 1.39 (s, 3H), 1.47 (s, 3H), 1.48 (s, 3H), 3.45 (d, 1H, J = 2.4 Hz), 4.08 (dd, 2H, J = 5.5 Hz, 1.0 Hz), 4.19 (dd, 1H, J = 7.0, 3.7 Hz), 4.41 (q, 1H, J = 5.5 Hz), 4.62 (d, 1H, J = 5.9 Hz), 4.82 (dd, 2H, J = 5.9, 3.7 Hz), 5.38 (d, 1H, J = 2.1 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ 112.4, 108.9, 100.9, 85.3, 79.9, 79.5, 73.2, 66.3, 26.7, 25.8, 25.1, 24.4.

3.3. Synthesis of 4-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-6-oxo-6-phenyl-tetrahydro-6λ*5*-1,3] dioxolo [4,5-*d*] [1,2]oxaphosphinin-7-ol 4a–c

In a 250 mL flask containing 30.3 g of **1** (0.116 mol) dissolved in 150 mL of tetrahydrofuran, 15 mL of phenylphosphinate **2** (0.116 mol) was added under stirring. Then, 38.5 mL of a 0.6 N potassium *tert*-butoxide solution in tetrahydrofuran (0.02 mmol) was added dropwise at ambient temperature. After 2 h stirring, compound **4a** precipitated as a white solid. After 24 h stirring, compound **2** has completely disappeared and three diastereoisomers **4a**,**b**,**c** were obtained in a (35/26/39) ratio. The white precipitate of **4a** was filtered off (15.5 g, 35% yield). A saturated $NaCl_{aq}$ solution was added to the yellow filtrate (pH ~ 7) and extracted with chloroform. Organic layer was dried over sodium sulfate and evaporated to dryness. Ether was added to the foamy white solid in order to precipitate residual **4a**. After filtration, of **4a** (1.5 g, 4% yield), a crude **4b**–**c** mixture is collected (23.2 g) and was separated by column chromatography on SiO_2 (gradient of ether/ethyl acetate: 100/0–70/30) affording **4b** (5.2 g, 12% yield) and **4c** (15.7 g, 36% yield) as pure diastereoisomers.

3.4. Protected diastereoisomer 4

3.4.1. 4-(2,2-Dimethyl-[1,3]-dioxolan-4-yl)-2,2-dimethyl-6-oxo-6-phenyl-tetrahydro-6λ*5*-[1,3]dioxolo[4,5-*d*] [1,2]-oxaphosphinin-7-ol. Compound **4a**: ^{31}P NMR (101.25 MHz, DMSO-d_6): δ = 31.01; ^1H NMR (250.13 MHz, DMSO-d_6): δ 1.29 (s, 3H), 1.32 (s, 3H), 1.35 (s, 3H), 1.50 (s, 3H), 3.86 (dd, 1H, J = 5.4, 8.1 Hz), 4.04 (t, 1H, J = 8.6 Hz), 4.26 (q, 1H, J = 5.4 Hz), 4.44 (m, 2H), 4.53 (m, 1H), 4.68 (ddd, 1H, J = 2.6, 8.1, 24.8 Hz), 5.81 (t, 1H, J = 8.6 Hz), 7.55–7.90 (m, 5H); ^{13}C NMR (62.90 MHz, DMSO-d_6): 25.20, 25.98, 26.62, 27.24, 65.97 (d, J = 103.2 Hz), 66.43, 74.46, 74.88 (d, J = 8.6 Hz), 76.15 (d, J = 7.2 Hz), 76.95 (d, J = 4.8 Hz), 109.52, 110.07, 129.41 (d, J = 12.5 Hz), 131.54 (d, J = 10.1 Hz), 132.51, 133.50 (d, J = 125.2 Hz); IR (KBr) : ν = 3220, 3070, 2880, 2930, 2970, 2990, 1450, 1480, 1590, 1440, 1375, 1385, 1200, 1230, 1280, 1070, 1080, 1120, 980, 1015, 960, 735, 690; HRMS(FAB^+): calcd for $C_{18}H_{25}O_7P$: 384.1416. Found: 384.1415; m/z = 769

$[2M+H]^+$ (5%), 385 $[M+H]^+$ (80%), 185 (70%), 93 (100%). $[\alpha]_D$ +62 (*c* 0.2, MeOH).

Compound **4b**: ^{31}P NMR (101.25 MHz, $CDCl_3$): δ 37.51; ^1H NMR (250.13 MHz, $CDCl_3$): δ 1.28 (s, 6H), 1.35 (s, 3H), 1.36 (s, 3H), 4.03 (m, 2H), 4.35 (m, 2H), 4.44 (m, 2H), 4.78 (m, 1H, J = 24.2 Hz), 6.11 (m, 1H), 7.27–7.90 (m, 5H); ^{13}C NMR (62.90 MHz, $CDCl_3$): 24.56, 25.54, 26.09, 27.23, 63.69 (d, J = 93.1 Hz), 67.18, 72.51 (d, J = 3.4 Hz), 73.96 (d, J = 8.6 Hz), 74.47 (d, J = 5.3 Hz), 76.37, 109.55, 110.24, 128.69 (d, J = 13.4 Hz), 132.34 (d, J = 11.0 Hz), 133.29, 129.11 (d, J = 135.8 Hz); IR (KBr) : 3200, 3030, 2860, 2900, 2960, 2980, 1435, 1460, 1580, 1420, 1360, 1370, 1190, 1230, 1040, 1060, 1115, 1030, 950, 710, 680; HRMS(FAB^+): calcd for $C_{18}H_{25}O_7P$: 384.1416. Found: 384.1402; m/z = 769 $[2M+H]^+$ (15%), 385 $[M+H]^+$ (100%), 327 (60%), 269 (50%), 73 (35%). $[\alpha]_D$ +50 (*c* 0.2, MeOH).

Compound **4c**: ^{31}P NMR (81.02 MHz, DMSO-d_6): δ 40.84; ^1H NMR (250.13 MHz, DMSO-d_6): δ 1.41 (s, 3H), 1.43 (s, 3H), 1.49 (s, 3H), 1.56 (s, 3H), 4.15 (m, 2H), 4.26 (ddd, 1H, J = 1.9, 6.2, 8.1 Hz), 4.49 (tq, 1H, J = 5.4, 9.6 Hz), 4.57 (d, 1H, J = 3.4 Hz), 4.64 (dd, 1H, J = 1.3, 7.4 Hz), 4.93 (ddd, 1H, J = 3.3, 7.4, 26.7 Hz), 5.25 (br s, 1H), 7.38–8.04 (m, 5H); ^{13}C NMR (62.90 MHz, DMSO-d_6): δ 24.52, 25.43, 25.93, 27.38, 66.94, 68.63 (d, J = 108.0 Hz), 73.99 (d, J = 9.1 Hz), 74.27, 74.88 (d, J = 5.8 Hz), 76.37, 110.31, 110.43, 127.28 (d, J = 152.1 Hz), 128.39 (d, J = 13.4 Hz), 133.16 (d, J = 2.4 Hz), 133.49 (d, J = 11.1 Hz); IR (KBr) : 3240, 3040, 2870, 2920, 2970, 1450, 1585, 1430, 1365, 1375, 1160, 1190, 1235, 1070, 1120, 980, 1015, 950, 690; HRMS(FAB^+): calcd for $C_{18}H_{25}O_7P$: 384.1416. Found: 384.1431; m/z = 769 $[2M+H]^+$ (2%), 385 $[M+H]^+$ (70%), 307 (100%), 289 (70%), 107 (100%). $[\alpha]_D$ +27 (*c* 0.2, MeOH).

3.5. Deprotection of compound 4a

3.5.1. 6-(1,2-Dihydroxyethyl)-2-oxo-phenyl-2λ*5*-[1,2]-oxaphosphinane-3,4,5-triol 5. In a 50 mL flask, 2.0 g of compound **4a** (5.2 mmol), 2.0 g of Amberlyst® 15 resin, and 70 mL of methanol are stirred over 5 days until the white suspension disappeared (monitoring by ^{31}P NMR).

Resin is filtered off and the crude filtrate is evaporated to dryness and recrystallized from ethanol to afford colorless solid of the fully deprotected compound **5**.

^{31}P NMR (101.25 MHz, D_2O): δ 40.77. ^1H NMR (250.13 MHz, D_2O): δ 3.67–3.76 (m, 2H), 3.83–3.89 (m, 2H), 3.99–4.03 (m, 2H), 4.73 (m, 1H), 7.50–7.70 (m, 5H); ^{13}C NMR (62.90 MHz, D_2O): δ 62.39, 67.42 (d, J = 92.6 Hz), 68.94 (d, J = 9.6 Hz), 69.01 (d, J = 3.8 Hz), 69.66 (d, J = 10.1 Hz), 78.22 (d, J = 5.8 Hz), 126.15 (d, J = 119.0 Hz), 130.00 (d, J = 13.0 Hz), 130.32 (d, J = 10.6 Hz), 134.51 (d, J = 2.9 Hz); IR (KBr) : 3360, 2995, 2940, 1200, 1175, 1160, 1105, 1010; HRMS(FAB^+): calcd for $C_{12}H_{17}O_7P$: 305.0790. Found: 305.0774; m/z = 154 (100%), 289 (70%), 136 (65%), 77 (16%). $[\alpha]_D$ +50 (*c* 0.1, MeOH).

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