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A novel seven-membered carbohydrate phostone

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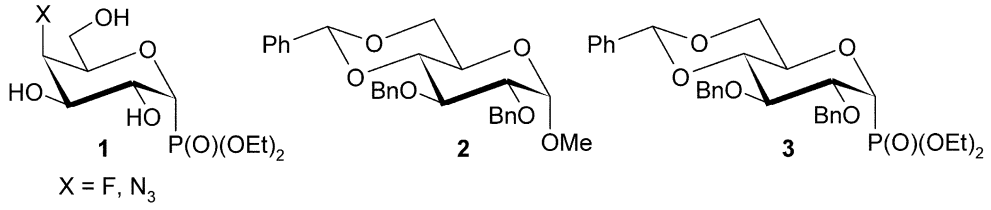
Abstract—Treatment of methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α(β)-D-glucopyranoside with triethyl phosphite and trimethylsilyl trifluoromethanesulfonate affords the seven-membered phostone arising from the attack of reagents on the acetal protecting group.

The specific binding of complex carbohydrates to lectin type receptors forms the basis of vital intercellular recognition processes. Thus, the biosynthesis of oligosaccharides and other glycosylated intracellular metabolites is of enormous importance, as these compounds are directly involved in various fundamental biological pathways.[1] The range of carbohydrate structures present in a cell wall varies in different tissues reflecting the specificity of glycosyltransferases, enzymes that catalyse the transfer of a specific monosaccharide from activated donor (glycosyl nucleotide) into a defined linkage with a specific acceptor. Replacement of the C1–O linkage in the donor with a more stable C–P bond should provide non-isosteric but isopolar donor mimetics that are more resistant to enzymic degradation and therefore have a greater potential to selective inhibition.

Continuing our search for galactosyltransferase inhibitors, we aimed to prepare α-D-galactopyranosyl-*C*-phosphonate **1** modified at the C-4 atom. For the creation of the C–P bond, we decided to follow a well-established protocol described for the Michaelis–Arbuzov reaction of benzylated 1-*O*-acetyl-D-hexopyranoses with triethyl phosphite and trimethylsilyl trifluoromethanesulfonate as catalyst,[2] which was applied successfully later to protected methyl pentofuranosides.[3] Employing methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside **2** as starting compound and hoping to take advantage of both regioselective deprotection of the OH-4 moiety and a subsequent S_N2 inversion of configuration in an intermediate glycosylphosphonate **3**, the desired phosphonate **1** would be synthesized. The reaction of glucoside **2** with triethyl phosphite in the presence of trimethylsilyl trifluoromethanesulfonate afforded smoothly a major crystalline product but instead of the expected phosphonate **3**, phostone **4** was obtained (Scheme 1).



Keywords: carbohydrates; phosphonic acid; phostone; acetal group.
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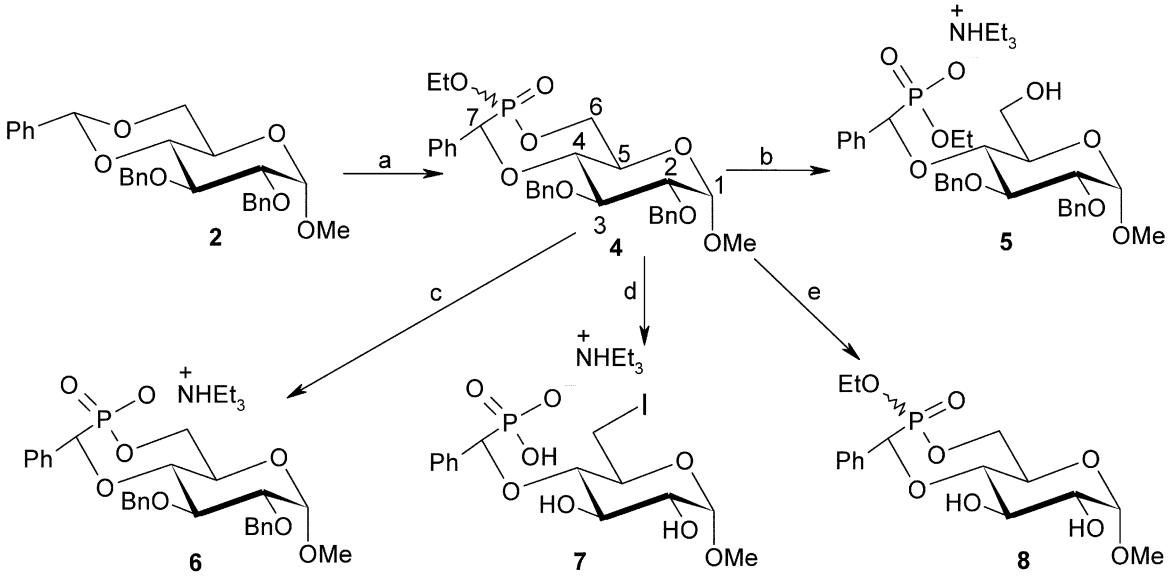

Scheme 1. *Reagents and conditions*: (a) $P(OEt)_3$ (2 equiv.), TMSOTf (2 equiv.), CH_2Cl_2, 0°C to rt, 2 h, 70%; (b) aceton/5% NaOH (1:2, v/v), 90°C, 2 h, then CH_3COOH, 77%; (c) TMSBr (2 equiv.), CCl_4, 0°C to rt, 12 h, then H_2O, 80%; (d) TMSI (5 equiv.), CCl_4, 0°C to rt, 12 h, then H_2O, 30%; (e) EtOH, Pd/C, 2 h, 60%.

Recently, there has been renewed interest in the synthesis of the cyclic phosphonate analogues (phostones) of pentoses[4,5] or hexoses[6–9] having the anomeric carbon atom replaced by a pentacovalent phosphorus. This type of glycomimetic represents a promising structural matrix for glycosidase inhibitor construction or for the generation of new types of catalytic antibodies.[10] The formation of an unexpected sugar-derived phostone has been previously reported; a Michaelis–Arbuzov reaction performed on a γ-iodoalcohol[11] or acetylation of carbohydrate-derived γ-hydroxyphosphonic acids[12] serve as good examples, however, to our knowledge, the preparation of a seven-membered phostone is unprecedented.

Phostone **4** was readily isolated by crystallization (ethyl acetate) as a single diastereoisomer (absolute configuration at the phosphorus atom was not determined) and its identity was confirmed in particular from NMR studies (^{31}P, ^{1}H, ^{13}C, HMQC, COSY, NOESY, and HMBC).[13] In ^{31}P NMR, the ring phosphorus in **4** appears at 23.49 ppm (relative to H_3PO_4). A characteristic feature of the phostone **4** is the spin–spin coupling between ^{31}P and both proton H-6 and carbon C-6. Furthermore, HMBC showed a cross peak between the nuclei C-4 and H-7 (and vice versa) being indicative of O-6 phosphonate unit (see Scheme 1 for numbering). Irradiation of the signal due to the H-4 proton resulted in a NOE enhancement of the H-7 proton, which suggests that the proton H-7 remains axial.

In view of the unique nature of phostone **4** we studied its reactivity under several conditions. Acid hydrolysis of phostone **4** failed but alkaline hydrolysis gave exclusively a ring cleavage product isolated as salt **5** by chromatography on silica gel with a mobile phase containing 1% of triethylamine. The identification of product **5** corresponds with a previous finding that seven-membered 2-ethoxy-[1,2]oxaphosphepane-2-oxide was decomposed by hydroxyl ions in an alcohol–water mixture.[14] TMSBr treatment of phostone **4** afforded phosphonic acid triethylamine salt **6** leaving the cyclic ester group intact. In contrast, treatment with TMSI led to unprotected acyclic phosphonate **7** in which the C-6 primary hydroxyl group had been transformed into a 6-iodo moiety in accord with the mechanism proposed.[15] Finally, hydrogenation of **4** with H_2 in methanol in the presence of Pd/charcoal gave the expected phostone **8** (absolute configuration at the phosphorus atom was not determined). All products **5–8** (Scheme 1) were identified and characterized by NMR experiments and MS measurements.[13] In the ^{31}P NMR spectra of phostones **6** and **8**, the phosphorus resonates at 18.01 and 23.67 ppm, respectively, while the ^{31}P signal in acyclic **5** and **7** appears at 15.96 and 19.14 ppm, respectively, Characteristic vicinal couplings between the phosphorus atom and carbon C-6 as well as proton H-6 were observed for both phostones **6** and **8**.

In conclusion, we have synthesized original carbohydrate phostones using a simple method based on the finding that the protecting acetal group can interact with triethyl phosphite and trimethylsilyl trifluoromethanesulfonate.[16] Particularly noteworthy is the fact that readily available phostone **4** can be selectively cleaved or deprotected and thus it might be an interesting scaffold for the generation of new types of potential biologically active compounds.

Acknowledgements

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13. *Selected analytical data*: **4**: mp 188–190°C, $[\alpha]_D^{20}=14.7$ (*c* 1, CH_3OH). ^1H NMR (500 MHz, CD_3OD) δ 6.90–7.50 (m, 15H, aromatic protons), 5.13 (d, 1H, $J=5.0$ Hz, C*H*Ph), 4.58–4.74 (m, 4H, CH_2Ph), 4.75 (d, 1H, $J=3.4$ Hz, H-1), 4.49 (ddd, 1H, $J=4.6$, 12.6, 18.0 Hz, H-6), 4.28 (ddd, 1H, $J=6.6$, 12.6, 13.6 Hz, H-6), 4.02–4.14 (m, 3H, OCH_2CH$_3$, H-5), 3.87 (t, 1H, $J=9.4$ Hz, H-3), 3.66 (t, 1H, $J=9.5$ Hz, H-4), 3.52 (dd, 1H, $J=3.4$, 9.4 Hz, H-2), 3.41 (s, 3H, OCH_3), 1.26 (t, 3H, OCH_2CH_3). ^{13}C NMR (125 MHz, CD_3OD) δ 139.58 (aromatic quaternary carbon), 139.49 (aromatic quaternary carbon), 135.87 (aromatic quaternary carbon), 128.57–129.71 (aromatic carbons), 99.69 (C-1), 86.86 (C-4), 82.15 (d, $J=121.7$ Hz, *C*HPh), 80.90 (C-2, C-3), 76.77 (*C*H$_2$Ph), 74.24 (*C*H$_2$Ph), 69.95 (C-5), 68.51 (d, $J=3.6$ Hz, C-6), 64.20 (d, $J=6.4$ Hz, O*C*H$_2$CH$_3$), 55.84 (OCH_3), 16.68 ($J=3.9$ Hz, OCH_2CH_3). ^{31}P NMR (202 MHz, CD_3OD) δ 23.49. MS (EI, 70 eV) *m*/*z* 554 (M^+), 523, 463, 448, 91 (100). Anal. calcd for $C_{30}H_{35}O_8P$ (554.56): C, 64.97; H, 6.36; P, 5.59; found: C, 65.16; H, 6.27; P, 5.68.
5: $[\alpha]_D^{20}=22.0$ (*c* 1, CH_3OH). ^1H NMR (500 MHz, CD_3OD) δ 7.00–7.32 (m, 15H, aromatic protons), 5.14 (d, 1H, $J=10.3$ Hz, C*H*Ph), 4.72 (d, 1H, $J=3.5$ Hz, H-1), 4.69 (d, 1H, $J=11.0$ Hz, CH_2Ph), 4.60 (s, 2H, CH_2Ph), 4.27 (dd, 1H, $J=2.2$, 12.7 Hz, H-6), 3.96–4.02 (m, 2H, CH_2Ph, H-4), 3.76 (t, 1H, $J=9.2$ Hz, H-3), 3.66–3.72 (m, 3H, OCH_2CH$_3$, H-6), 3.59–3.62 (m, 1H, H-5), 3.53 (dd, 1H, $J=3.5$, 9.6 Hz, H-2), 3.37 (s, 3H, OCH_3), 3.09 (q, 6H, $J=7.3$ Hz, NCH_2CH$_3$), 1.23 (t, 9H, $J=7.3$ Hz, NCH_2CH_3), 1.09 (t, 3H, $J=7.0$ Hz, OCH_2CH_3). ^{13}C NMR (125 MHz, CD_3OD) δ 140.65 (aromatic quaternary carbon), 140.34 (aromatic quaternary carbon), 139.51 (aromatic quaternary carbon), 128.61–129.35 (aromatic carbons), 99.08 (C-1), 83.93 (C-3), 81.95 (d, $J=154.1$ Hz, *C*HPh), 81.94 (C-2), 77.89 (C-4), 75.58 (*C*H$_2$Ph), 73.86 (C-6), 72.62 (C-5), 61.99 (d, $J=6.5$ Hz, O*C*H$_2$CH$_3$), 61.58 (*C*H$_2$Ph), 55.40 (OCH_3), 47.54 (N*C*H$_2$CH$_3$), 17.09 ($J=6.4$ Hz, OCH_2CH_3), 9.10 (NCH_2CH_3). ^{31}P NMR (202 MHz, CD_3OD) δ 15.96. HRMS (ESI) for $C_{30}H_{37}O_9P$ (anion) calcd 571.2097, found 571.2112.
6: $[\alpha]_D^{20}=-7.0$ (*c* 1, CH_3OH). ^1H NMR (500 MHz, CD_3OD) δ 6.94–7.54 (m, 15H, aromatic protons), 4.80 (d, 1H, $J=6.6$ Hz, C*H*Ph), 4.60–4.74 (m, 5H, CH_2Ph, H-1), 4.51 (ddd, 1H, $J=5.4$, 11.9, 12.0 Hz, H-6), 3.97–4.05 (m, 2H, H-6, H-5), 3.85 (t, 1H, $J=9.3$ Hz, H-3), 3.64 (t, 1H, $J=9.2$ Hz, H-4), 3.51 (dd, 1H, $J=3.7$, 9.4 Hz, H-2), 3.38 (s, 3H, OCH_3), 3.05 (q, 6H, $J=7.3$ Hz, NCH_2CH$_3$), 1.21 (t, 9H, $J=7.3$ Hz, NCH_2CH_3). ^{13}C NMR (125 MHz, CD_3OD) δ 139.78 (aromatic quaternary carbon), 139.71 (aromatic quaternary carbon), 139.42 (aromatic quaternary carbon), 128.17–129.40 (aromatic carbons), 99.72 (C-1), 85.43 (d, $J=145.2$ Hz, *C*HPh), 85.19 (C-4), 81.61 (C-3), 81.20 (C-2), 76.52 (*C*H$_2$Ph), 74.27 (*C*H$_2$Ph), 71.10 (C-5), 67.05 (d, $J=4.8$ Hz, C-6), 55.59 (OCH_3), 47.48 (N*C*H$_2$CH$_3$), 9.06 (NCH_2CH_3). ^{31}P NMR (202 MHz, CD_3OD) δ 18.01. HRMS (ESI) for $C_{28}H_{31}O_8P$ (anion) calcd 525.1679, found 525.1674.
7: ^1H NMR (500 MHz, CD_3OD) δ 7.52–7.25 (m, aromatic protons), 4.99 (d, $J=13.4$ Hz, C*H*Ph), 4.62 (d, $J=3.5$ Hz, H-1), 3.82–3.70 (m, 2H), 3.58–3.51 (m, 1H), 3.43 (s, 3H, OCH_3), 3.40–3.28 (m, 3H), 3.14 (q, 6H, $J=7.3$ Hz, NCH_2CH$_3$), 1.28 (t, 9H, $J=7.3$ Hz, NCH_2CH_3). ^{13}C NMR (125 MHz, CD_3OD) δ 139.15 (aromatic quaternary carbon), 129.61–128.67 (aromatic carbons), 100.91 (C-1), 83.58 (C-2), 79.10 (d, $J=130$ Hz, *C*HPh), 73.40, 72.83, 71.26, 55.91 (OCH_3), 47.73 (N*C*H$_2$CH$_3$, 9.23 (NCH_2CH_3), 8.16 (C-6). ^{31}P NMR (202 MHz, CD_3OD) δ 19.14. HRMS (ESI) for $C_{14}H_{20}IO_8P$ (anion) calcd 472.9863, found 472.9876.
8: mp 215–217°C, ^1H NMR (500 MHz, DMSO-d_6) δ 7.41–7.29 (m, aromatic protons), 5.11 (d, 1H, $J=5.3$ Hz, C*H*Ph), 5.01 (d, 1H, $J=5.5$ Hz, OH), 4.95 (d, 1H, $J=6.5$ Hz, OH), 4.59 (d, 1H, $J=3.3$ Hz, H-1), 4.36 (ddd, 1H, $J=4.1$, 12.3, 18.5 Hz, H-6), 4.22 (ddd, 1H, $J=6.3$, 12.3, 13.0 Hz, H-6), 3.91–4.03 (m, 2H, OCH_2CH$_3$), 3.78–3.82 (m, 1H, H-5), 3.50 (m, 1H, H-3), 3.25 (t, $J=9.4$ Hz, H-4), 3.23–3.28 (m, 4H, OCH_3, H-2). ^{13}C NMR (125 MHz, DMSO-d_6) δ 135.3 (aromatic quaternary carbon), 127.49–128.25 (aromatic carbons), 100.22 (C-1), 79.53 (d, $J=150.3$ Hz, *C*HPh), 72.50 (C-2), 71.38 (C-3), 84.97 (C-4), 68.67 (C-5), 66.80 (d, $J=4.4$ Hz, C-6), 62.27 (d, $J=7.8$ Hz, O*C*H$_2$CH$_3$), 55.05 (OCH_3), 16.43 (d, $J=4.8$ Hz, CH_3). ^{31}P NMR (202 MHz, CD_3OD) δ 23.67.
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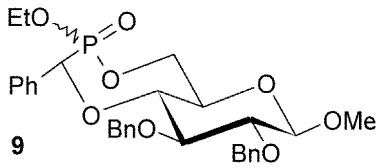
16. The attack of triethyl phosphite and trimethylsilyl trifluoromethanesulfonate on methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside resulted in the formation of phostone **9** identified as a mixture of diastereoisomers in a ratio 2:1. The major isomer **9a** was obtained by crystallization from EtOAc (mp 173–175°C, $[\alpha]_D^{20} = -26.0$ (*c* 1, CH_3OH)) and its structure was confirmed by NMR measurements. Phostone **9a** displays reactivity analogous to that of α-phostone **4** when subjected to the reagents described above. Thus, the course of this Michaelis–Arbuzov-type reaction does not depend on the anomeric configuration of the starting methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-glucopyranoside.



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In contrast to the D-*gluco* series, an attempt to prepare phostones derived from both methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-D-galactopyranosides was unsuccessful probably due to the steric hindrance of *cis* fused rings.