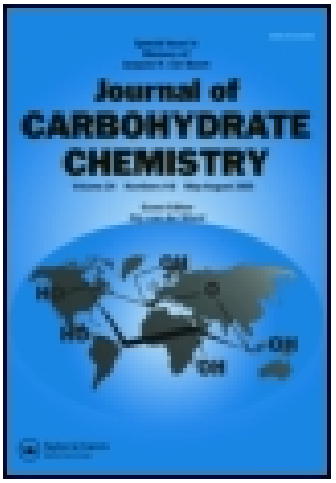

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lcar20

Direct Synthesis of the Isosteric Phosphono Analogues of α-L-Rhamnose 1-Phosphate and β-L-Fucose 1-Phosphate

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Published online: 22 Aug 2006.

To cite this article: Laura Cipolla , Barbara La Ferla , Luigi Panza & Francesco Nicotra (1998) Direct Synthesis of the Isosteric Phosphono Analogues of α-L-Rhamnose 1-Phosphate and β-L-Fucose 1-Phosphate, Journal of Carbohydrate Chemistry, 17:7, 1003-1013, DOI: 10.1080/07328309808001879

To link to this article: http://dx.doi.org/10.1080/07328309808001879

J. CARBOHYDRATE CHEMISTRY, 17(7), 1003-1013 (1998)

DIRECT SYNTHESIS OF THE ISOSTERIC PHOSPHONO ANALOGUES OF α-L-RHAMNOSE 1-PHOSPHATE AND β-L-FUCOSE 1-PHOSPHATE

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Received December 29, 1997 - Final Form May 4, 1998

ABSTRACT

The isosteric phosphono analogue of α-L-rhamnose 1-phosphate has been stereoselectively synthesized by reaction of 2,3,5-tri-*O*-benzyl-L-rhamnose with tetraethyl methylenediphosphonate and sodium hydride in diglyme, followed by deprotection with iodotrimethylsilane. To synthesize stereoselectively the isosteric phosphono analogue of β-L-fucose 1-phosphate, 2,3,5-tri-*O*-benzyl-L-fuconolactone was treated with lithiated dimethyl methylenephosphonate, and the 3,4,5-tri-*O*-benzyl-1,7-dideoxy-1-(phosphonodimethyl)-L-*galacto*heptulopyranose obtained was stereoselectively reduced with triethylsilane and boron trifluoride etherate to afford the dimethyl (2,3,4-tri-*O*-benzyl-β-L-fucopyranosyl)methanephosphonate which was finally deprotected with iodotrimethylsilane.

INTRODUCTION

The biological relevance of glycosyl phosphates, which act as glycosyl donors, metabolic regulators[1] or components of antigenic oligosaccharides,[2] has stimulated the synthesis of a variety of stable analogues. Mimetics of glycosyl phosphates could in fact interfere in metabolic processes or replace the labile phosphates in recognition phenomena. The substitution of the phosphoesteric oxygen with a carbon atom does not modify

significantly the geometry of a phosphate,[3] but the so obtained phosphono analogue, defined isosteric,[3] cannot undergo the cleavage of the phosphoesteric bond. Nonisosteric but isopolar[4] analogues of glycosyl phosphates, carrying a phosphono group at the anomeric centre of the parent sugar, and analogues of uloses 1-phosphate[5] have also been synthesized. We are however particularly interested in the isosteric analogues.

To synthesize isosteric phosphono analogues of glycosyl phosphates, in which we are particularly interested, indirect synthetic procedures have been more often employed[6] in which the phosphonic group is introduced on an electrophilic carbon atom that was previously introduced by C-C bond formation to the anomeric centre of the sugar. The usual approach requires formation of a C-glycoside, then conversion of the C-glycosidic carbon atom into a halide, which in turn is converted into a phosphonate through an Arbuzov reaction. Only a few examples in which a methylenephosphonic group was directly linked to the anomeric carbon of D-ribose, affording a mixture of the α- and the β-phosphonate, have been reported.[7] In these examples a Wittig or Horner-Emmons reagent, such as $Ph_3P{=}CHPO(OPh)_2$ or $(MeO)_2POCH_2PO(OMe)_2$ was reacted with the aldol, affording an intermediate α,β-unsaturated phosphonate, which spontaneously underwent a Michael-type cyclization.

We were interested in the synthesis of the phosphono analogues of α-L-rhamnose 1-phosphate[8] and β-L-fucose 1-phosphate.[9] The former is part of the repeating unit of *Streptococcus pneumoniae* 19F antigenic polysaccharide,[2] whereas the second is a key glycosyl donor in maturation of the glycidic part complex type glycoproteins of pharmacological relevance, such as sialyl Le^x.[10] We investigated the possibility of effecting the synthesis of these two phosphonates by direct introduction of a methylenephosphonic group at the anomeric centre of the parent sugar.

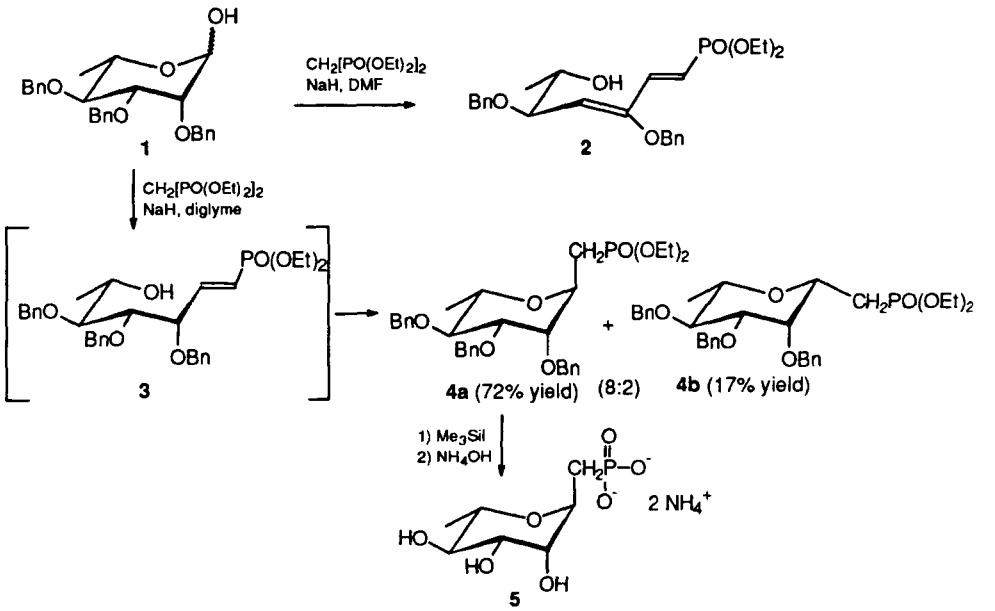
RESULTS AND DISCUSSION

Several reports indicate that the reaction of aldoses with stabilized Wittig reagents such as $Ph_3P{=}CHCOR$ afford α,β-unsaturated carbonyl derivatives which on treatment with bases undergo a Michael-type cyclization affording the thermodynamic C-glycosides.[11] In the case of C-rhamnosides, the α-anomer is more stable for steric reasons than

the β one, so we decided to effect the stereoselective synthesis of the phosphono analogue of α-L-rhamnose 1-phosphate in a direct process in which the sugar would undergo an Horner-Emmons reaction and a subsequent Michael cyclization under thermodynamic control.

2,3,4-Tri-*O*-benzyl-L-rhamnopyranose[12] **1** was treated with tetraethylmethylene-diphosphonate under different experimental conditions. Employing NaH in DMF at room temperature, the elimination product **2** was obtained in almost quantitative yield. The best result was obtained when using 6 equivalents of tetraethyl methylenediphosphonate and NaH, in diglyme at room temperature. Under such conditions the desired phosphonate **4a** was obtained in 72% yield and easily separated from the β-isomer **4b** (17% yield) by chromatography. Changing the base [$LiN(SiMe_3)_2$], the solvent (THF) and the temperature (90 °C) the same diastereometic excess (60%) was obtained in favor of the α-isomer, indicating that it is the thermodynamic product.

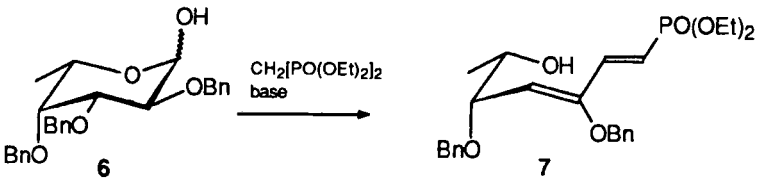
The anomeric configuration of **4a** was established by NOE experiments, which indicate the 1,3-diaxial correlation between CH_2P and two axial hydrogens in the cycle. Furthermore, the equatorial orientation of the hydrogen at the pseudo-anomeric carbon



Scheme 1

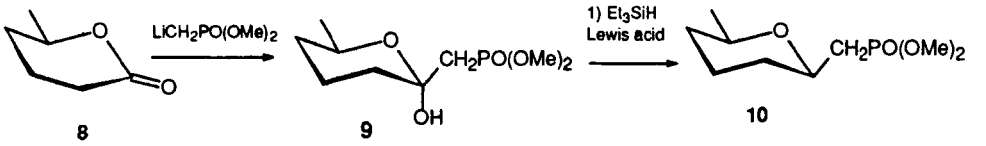
atom of **4** was confirmed by the chemical shift value δ 4.43 compared to that of its β-epimer δ 3.75. The phosphonate **4** was deprotected with Me_3SiI affording, after work-up and addition of 25% aqueous NH_3, the ammonium salt of the phosphono analogue of α-L-rhamnosyl 1-phosphate (**5**) (88% yield).

The procedure herein reported for the synthesis of the phosphono analogue of α-L-rhamnose 1-phosphate was first tested to synthesize the phosphono analogue of β-L-fucose 1-phosphate. Once more, from a stereochemical point of view, the desired sterically less hindered β-isomer was expected in a Michael-type cyclization. However, the reaction of 2,3,5-tri-*O*-benzyl-L-fucopyranose[13] **6** with tetraethyl methylenediphosphonate, using different bases and solvents, invariably afforded the elimination product **7** (Scheme 2).



Scheme 2

A different approach was therefore required, and we then studied the possibility of introducing the methylenephosphonic group by reaction of the protected lactone **8** with $LiCH_2PO(OMe)_2$, and subsequent Lewis acid assisted reduction of the obtained lactol **9** (Scheme 3).

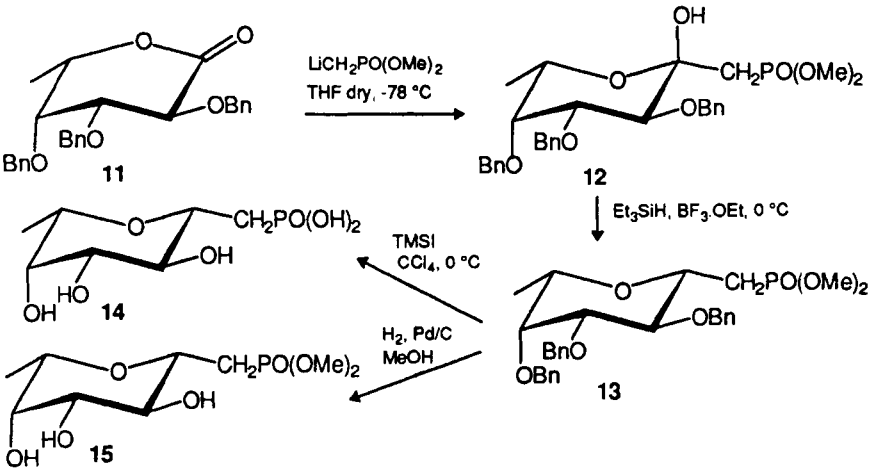


Scheme 3

The stereochemical outcome of this reduction is governed by the kinetic anomeric effect, so affording β-glycopyranosides.[14] To our knowledge this approach has never been applied to the synthesis of phosphono analogues of glycosyl phosphates. We studied its

application to the synthesis of the phosphono analogue of β-D-glucose 1-phosphate, but in that case we were unable to effect the reduction of the intermediate lactol **9**.[15] Interestingly, the procedure was applicable to the synthesis of the phosphono analogue of β-L-fucose 1-phosphate, affording the desired product in excellent yield and stereoselection.

Treatment of 2,3,4-tri-*O*-benzyl-L-fuconolactone **11** with $LiCH_2PO(OMe)_2$[16] in THF at -78 °C gave the phosphonate **12** in 90% yield according to Toyokuni et al.[17]. Reduction of **12** with Et_3SiH and $BF_3.OEt_2$ at 0 °C occurred in high yield (80%) and stereoselection (92% d.e., determined by ^{13}C NMR of the crude product) afforded **13**, the protected form of the phosphono analogue of β-L-fucose 1-phosphate. The configuration of the newly formed stereocentre in **13** was easily determined by the axial-axial (9.3 Hz) coupling constant between H-1 and H-2.[14] The deprotection of **13** was finally effected with Me_3SiI, to afford quantitatively **14**, the phosphono analogue of β-L-fucose 1-phosphate, or by catalytic hydrogenolysis in methanol to afford the phosphonic ester **15**.



Scheme 4

EXPERIMENTAL

General methods. Melting points were determined on a Büchi 535 capillary melting point apparatus. Optical rotations were measured with a Perkin Elmer 241 digital polarimeter. NMR spectra were recorded on a Bruker AC300 (300 MHz for ^1H and 75.44

MHz for ^{13}C) and on a Varian XL200 (80.96 MHz for ^{31}P). Chemical shifts are expressed in parts per million downfield from TMS or phosphoric acid for ^{31}P spectra. Reactions were followed on TLC on silica gel $60F_{254}$ (E. Merck); flash column chromatography was performed on silica gel 60 (0.040-0.063 mm, E. Merck).

(1*E*,3*Z*,5*R*,6*S*) Diethyl 3,5-Dibenzyloxy-6-hydroxyhepta-1,3-dien-1-phosphonate (2). To a suspension of NaH (16 mg, 0.66 mmol, 6 equiv) in dry DMF (2.5 mL), at 0 °C under inert atmosphere, a solution of tetraethyl methylenediphosphonate (170 μL, 0.66 mmol, 6 equiv) in DMF (50 mL) was slowly added; the solution obtained was left stirring at 0 °C for 30 min. Then 2,3,4-tri-*O*-benzyl-L-rhamnopyranose (**1**) (50 mg, 0.11 mmol) dissolved in DMF (50 mL), was added slowly at 0 °C. The reaction was left stirring for 7 h at rt; water was added to the reaction mixture which was then extracted with CH_2Cl_2. The organic layer was dried on Na_2SO_4 and the solvent removed under reduced pressure. Compound **2** was obtained in almost quantitative yield (50 mg). ^1H NMR ($CDCl_3$) δ 1.09 (d, 3H, $J_{6,7}$ = 6.4 Hz, H-7), 1.30 (t, 6H, $J_{H,H}$ = 7.1 Hz, $POCH_2CH_3$), 2.19 (bs, 1H, OH), 3.86 (dq, 1H, $J_{6,7}$ = 6.4, $J_{5,6}$ = 4.0 Hz, H-6), 4.10 (dq, 4H, $J_{H,H}$ = $J_{H,P}$ = 7.0 Hz, $POCH_2CH_3$), 4.24 (dd, 1H, $J_{4,5}$ = 9.0, $J_{5,6}$ = 4.0 Hz, H-5), 4.28 (d, 1H, J = 11.6 Hz, OCHPh), 4.48 (d, 1H, J = 11.6 Hz, OCHPh), 4.71 (s, 2H, OCH_2Ph), 5.43 (d, 1H, $J_{4,5}$ = 9.0 Hz, H-4), 6.00 (t, 1H, $J_{1,P}$ = $J_{1,2}$ = 16.1 Hz, H-1), 6.96 (dd, 1H, $J_{2,P}$ = 20.0 Hz, $J_{1,2}$ = 16.1 Hz, H-2), 7.22-7.41 (m, 10H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 16.37 (q, CH_3CH_2OP), 16.37 (q, CH_3CH_2OP), 18.07 (q, C-7), 61.97 (t, CH_3CH_2OP), 61.97 (t, CH_3CH_2OP), 69.25 (d), 70.59 (t, CH_2Ph), 74.17 (t, CH_2Ph), 76.96 (d), 116.0 (dd, J_{CP} = 193 Hz, C-1), 122.4 (d, C-4), 127-128 (d, Ar), 136.7 (s, C Ar), 139.3 (s, C Ar), 143.3 (dd, J_{CP} = 7.3 Hz, C-2), 155.5 (d, J_{CP} = 23.6 Hz, C-3); ^{31}P NMR ($CDCl_3$) δ 18.85.

Diethyl (2,3,4-Tri-O-benzyl-α-L-rhamnopyranosyl)methanephosphonate[18] (4a). To a suspension of NaH (317 mg, 13 mmol, 6 equiv) in diglyme (100 mL), at 0 °C under inert atmosphere, a solution of tetraethyl methylenediphosphonate (3.27 mL, 13.2 mmol, 6 equiv) in diglyme (50 mL) was slowly added; the clear solution obtained was left stirring at 0 °C for 30 min. Then 2,3,4-tri-*O*-benzyl-L-rhamnopyranose (**1**) (1 g, 2.2 mmol) dissolved in diglyme (50 mL), was added slowly at 0 °C. The reaction was left stirring for 18 h at rt; the organic layer was washed with a saturated solution of NH_4Cl, and the water layer extracted with CH_2Cl_2. The combined organic layers were dried over

Na_2SO_4 and the solvent removed under reduced pressure. Gravitational chromatographic purification (eluent petroleum ether/ethyl acetate 2:8 v/v) afforded compound **4a** (900 mg, 72% yield) and the β-anomer **4b** (210 mg, 17%) [selected NMR data for the β anomer; ^{1}H NMR ($CDCl_3$) δ 1.98 (ddd, 1H, $J_{1'a,P}$ = 17.0 Hz, $J_{1'a,1'b}$ = 16.0 Hz, $J_{1'a,1}$ = 6.8 Hz), 2.21 (ddd, 1H, $J_{1'b,P}$ = 18.0 Hz, $J_{1'a,1'b}$ = 16.0 Hz, $J_{1'b,1}$ = 6.8 Hz), 3.75 (dt, 1H, $J_{1,P}$ = 9.8 Hz, $J_{1,1'}$ = 6.8 Hz), 3.89 (bs, 1H, H-2); ^{13}C NMR ($CDCl_3$) δ 28.3 (dt, $J_{C,P}$ = 154.9 Hz, C-1'), 76.7 (dd, $J_{C,P}$ = 6.9 Hz, C-1)]. **4a**: oil, $[\alpha]_D$ +8° (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.27 (dt, 6H, $J_{H,H}$ = 7.0 Hz, $J_{H,P}$ = 1.7 Hz, $POCH_2CH_3$), 1.32 (d, 3H, $J_{5,6}$ = 6.0 Hz, H-6), 2.05 (dd, 2H, $J_{H,P}$ = 19.5 Hz, $J_{1',1}$ = 7.1 Hz, H-1'a,b), 3.58 (t, 1H, $J_{4,5}$ = $J_{3,4}$ = 7.5 Hz, H-4), 3.63 (dq, 1H, $J_{4,5}$ = 7.5 Hz, $J_{5,6}$ = 6.0 Hz, H-5), 3.71 (dd, 1H, $J_{3,4}$ = 7.5 Hz, $J_{2,3}$ = 3.0 Hz, H-3), 3.83 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 3.0 Hz, H-2), 4.05 (dq, 4H, $J_{H,H}$ = $J_{H,P}$ = 7.0 Hz, $POCH_2CH_3$), 4.43 (ddt, 1H, $J_{1,P}$ = 10.0 Hz, $J_{1,1'}$ = 7.0 Hz, $J_{1,2}$ = 3.0 Hz, H-1), 4.50-4.85 (m, 6H, OCH_2Ph), 7.30 (m, 15H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 16.4 (q, CH_3CH_2OP), 16.4 (q, CH_3CH_2OP), 18.0 (q, C-6), 39.7 (dt, $J_{C,P}$ = 139.7 Hz, CH_2P), 61.7 (t, CH_2OP), 61.7 (t, CH_2OP), 69.0 (d), 70.0 (d), 71.7 (t, OCH_2Ph), 71.9 (t, OCH_2Ph), 74.6 (t, OCH_2Ph), 75.7 (d), 78.0 (d), 79.9 (d), 127.6-128.3 (d, Ar), 138.3 (2 s, C Ar), 138.5 (s, C Ar); ^{31}P NMR ($CDCl_3$) δ 29.56.

Anal. Calcd for $C_{32}H_{41}O_7P$ (568.65): C, 67.59%; H, 7.27%. Found: C, 68.97%; H, 7.34%.

(α-L-Rhamnopyranosyl)methanephosphonic Acid Diammonium Salt (5). Compound **4** (455 mg, 0.78 mmol) was dissolved in freshly distilled dry CCl_4 (18 mL); the solution was cooled to 0 °C and Me_3SiI (11.7 mmol, 1.59 mL) was added. After 1 h the solvent was removed, the residue was dissolved in absolute EtOH and a 25% aqueous NH_3 solution was added; the ammonium salt of (α-L-rhamnopyranosyl)methanephosphonic acid **5** so formed precipitated (190 mg, 88% yield). Hygroscopic solid, mp 202-204 °C; $[\alpha]_D$ 0° (*c* 2, H_2O, HCl); ^{1}H NMR (D_2O) δ 1.34 (d, 3H, $J_{5,6}$ = 5.9 Hz, H-6), 1.84 (ddd, 1H, $J_{1'a,1'b}$ = 14.8 Hz, $J_{1'a,P}$ = 10.4 Hz, $J_{1'a,1}$ = 4.4 Hz, H-1'a), 2.05 (dt, 1H, $J_{1'a,1'b}$ = 14.8 Hz, $J_{1'b,1}$ = $J_{1'b,P}$ = 10 Hz, H-1'b), 3.50 (t, 1H, $J_{3,4}$ = $J_{4,5}$ = 9.1 Hz, H-4), 3.66-3.80 (m, 2H, H-1, H-5), 3.93 (dd, 1H, $J_{3,4}$ = 9.1 Hz, $J_{2,3}$ = 3.1 Hz, H-3), 4.28 (m, 1H, H-2); ^{13}C NMR (D_2O) δ 19.91 (q, C-6) 32.6 (dt, $J_{C,P}$ 125 Hz, C-1'), 72.0 (d), 72.8 (d), 74.2 (d), 75.3 (d), 78.5 (d); ^{31}P NMR (D_2O) δ 17.81.

Anal. Calcd for $C_7H_{15}O_7P$. $2NH_3$ (276.23): C, 30.44%; H, 7.66%, N, 10.14%. Found: C, 30.12%, H, 7.23%, N, 9.87%.

(1*E*,3*Z*,5*S*,6*S*) Diethyl 3,5-Dibenzyloxy-6-hydroxyhepta-1,3-dien-1-phosphonate (7). To a suspension of NaH (16 mg, 0.66 mmol, 6 equiv) in diglyme (5 mL), at 0 °C under inert atmosphere, a solution of tetraethyl methylenediphosphonate (164 μL, 0.66 mmol, 6 equiv) in diglyme (2.5 mL) was slowly added; the clear solution obtained was left stirring at 0 °C for 30 min. Then 2,3,4-tri-*O*-benzyl-L-fucose (**6**) (50 mg, 0.11 mmol) dissolved in diglyme (2.5 mL), was added slowly at 0 °C. The reaction was left stirring for 3 days at rt; the reaction was then treated with a saturated solution of NH_4Cl, and the water layer extracted with CH_2Cl_2. The combined organic layers were dried on Na_2SO_4 and the solvent removed under reduced pressure. After chromatographic purification (eluent petroleum ether/ethyl acetate 1:9 v/v), compound **7** was obtained in 46% yield (23 mg), along with a 27 % yield of a mixture of the two anomers of diethyl (2,3,4-tri-*O*-benzyl-L-fucopyranosyl)methanephosphonate. Compound **7** is an oil: ^{1}H NMR ($CDCl_3$) δ 1.10 (d, 3H, $J_{6,7}$ = 6.4 Hz, H-7), 1.28 (t, 3H, $J_{H,H} \leq 2$ Hz, $POCH_2CH_3$), 1.48 (t, 3H, $J_{H,H}$ = 5.0 Hz, $POCH_2CH_3$), 3.66 (m, 2H, H-5, H-6), 4.12 (dq, 4H, $J_{H,H} = J_{H,P}$ = 6.9 Hz, $POCH_2CH_3$), 4.23 (d, 1H, J = 11.6 Hz, $OCHPh$), 4.49 (d, 1H, J = 11.6 Hz, $OCHPh$), 4.75 (m, 2H, OCH_2Ph), 5.31 (d, 1H, $J_{4,5}$ = 9.2 Hz, H-4), 6.11 (t, 1H, $J_{1,P} = J_{1,2}$ = 16.1 Hz, H-1), 6.95 (dd, 1H, $J_{2,P}$ = 20.7 Hz, $J_{1,2}$ = 16.1 Hz, H-2), 7.35 (m, 10H, Ar); ^{13}C NMR ($CDCl_3$) δ 16.60 (q, CH_3CH_2OP), 16.60 (q, CH_3CH_2OP), 19.77 (q, C-7); 62.21, (t, CH_3CH_2OP), 62.21 (t, CH_3CH_2OP), 70.04 (d), 71.03 (t, OCH_2Ph), 74.40 (t, OCH_2Ph), 79.44 (d), 117.3 (dd, J_{CP} = 188 Hz, C-1), 123.3 (d, C-4), 129.1-129.9 (d, Ar), 136.7 (s, C Ar), 139.3 (s, C Ar), 143.3 (dd, J_{CP} = 7.3 Hz, C-2), 155.5 (d, J_{CP} = 23.6 Hz, C-3); ^{31}P NMR ($CDCl_3$) δ 19.01.

3,4,5-Tri-O-benzyl-1,7-dideoxy-1-(dimethoxyphosphonyl)-L-*galacto*-heptulopyranose (12). Dimethyl methylphosphonate (413 μL, 4.83 mmol, 2.5 equiv) was dissolved in dry THF under inert atmosphere, cooled down to -78 °C and then *n*-butyllithium (4.83 mmol, 2.5 equivalents) was added; after 10 min a cold solution (-78 ° C) of 2,3,4-tri-*O*-benzyl-L-fuconolactone (**11**) (840 mg, 1.93 mmol) in THF was added, and the reaction allowed to warm up to rt. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 and washed with a saturated solution of NH_4Cl and H_2O, affording, after chro-

matographic purification (eluent petroleum ether/ethyl acetate 6:4 v/v), the α-anomer **12** (972 mg, 90% yield). Oil, $[\alpha]_D$ + 16° (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 1.10 (d, 3H, $J_{5,6}$ = 6.6 Hz, H-6), 1.76 (dd, 1H, $J_{1'a,P}$ = 20.0 Hz, $J_{1'a,1'b}$ = 12.8 Hz, H-1'a), 2.37 (dd, 1H, $J_{1'b,P}$ = 16.0 Hz, $J_{1'a,1'b}$ = 12.8 Hz, H-1'b), 3.61 (d, 3H, $J_{H,P}$ = 11.1 Hz, POC*H*$_3$), 3.67 (bs, 1H, H-4), 3.72 (d, 3H, $J_{H,P}$ = 10.8 Hz, POC*H*$_3$), 3.72 (d, 1H, $J_{2,3}$ = 10.4 Hz, H-2), 4.08 (dd, 1H, $J_{2,3}$ = 10.4 Hz, $J_{3,4}$ = 2.8 Hz, H-3), 4.14 (q, 1H, $J_{5,6}$ = 6.6 Hz, H-5), 4.62 (d, 1H, J = 11.6 Hz, OC*H*Ph), 4.69 (d, 1H, J = 11.7 Hz, OC*H*Ph), 4.75 (d, 1H, J = 11.7 Hz, OC*H*Ph), 4.79 (d, 1H, J = 11.7 Hz, OC*H*Ph), 4.97 (d, 1H, J = 11.7 Hz, OC*H*Ph), 4.99 (d, 1H, J = 11.6 Hz, OC*H*Ph), 5.70 (bs, 1H, OH), 7.20-7.50 (m, 15H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 16.7 (q, C-6), 32.9 (dt, J_{CP} = 135 Hz, C-1'), 51.5 (dq, J_{CP} = 7.3 Hz, POC*H*$_3$), 53.5 (dq, J_{CP} = 7.3 Hz, POC*H*$_3$), 72.8 (t, OCH_2Ph), 74.7 (t, OCH_2Ph), 75.1 (t, OCH_2Ph), 67.2 (d), 78.7 (d), 79.0 (d), 80.6 (d), 96.9 (d, J_{CP} = 6.6 Hz, C-1), 128.2-128.7 (d, Ar), 138.5 (s, C Ar), 138.5 (s, C Ar), 138.1 (s, C Ar); ^{31}P NMR ($CDCl_3$) δ 32.26;

Anal. Calcd for $C_{30}H_{37}O_8P$ (556.59): C, 64.74%; H, 6.70%. Found: C, 64.40%, H, 6.55%.

Dimethyl (2,3,4-Tri-O-benzyl-β-L-fucopyranosyl)methanephosphonate (13). Compound **12** (707 mg, 1.3 mmol) was dissolved in dry CH_3CN, then at 0 °C Et_3SiH (333 μL, 2.7 mmol, 1.5 equiv) and then $BF_3.OEt_2$ (425 μL, 1.5 equiv) were added. After 5 h a saturated solution of $NaHCO_3$ was added to the reaction until pH 7, then the organic layer was washed with H_2O until neutral, dried with Na_2SO_4 and the solvent evaporated. After chromatographic purification (eluent toluene/ethyl acetate 1:1; 4:6 v/v) the protected phosphonate **13** (568 mg, 1.07 mmol) was obtained in 80% yield. Oil, $[\alpha]_D$ + 8° (*c* 1, $CHCl_3$). ^1H NMR (C_6D_6) δ 1.17 (d, 3H, $J_{5,6}$ = 6.3 Hz, H-6), 1.99 (dt, 1H, $J_{1'a,P}$ = $J_{1'a,1'b}$ = 15.8 Hz, $J_{1'a,1}$ = 9.0 Hz, H-1'a), 2.41 (ddd, 1H, $J_{1'b,P}$ = 19.4 Hz, $J_{1'a,1'b}$ = 15.8 Hz, $J_{1'b,1}$ = 1.9 Hz, H-1'b), 3.15 (q, 1H, $J_{5,6}$ = 6.3 Hz, H-5), 3.23 (d, 1H, $J_{3,4}$ = 2.6 Hz, H-4), 3.33 (dd, 1H, $J_{2,3}$ = 9.0 Hz, $J_{3,4}$ = 2.6 Hz, H-3), 3.43 (d, 3H, $J_{H,P}$ = 10.8 Hz, POC*H*$_3$), 3.77 (ddd, 1H, $J_{1,2}$ = 9.3 Hz, $J_{1,1'a}$ = 9.0 Hz, $J_{1,1'b}$ = 1.9 Hz, H-1), 3.86 (t, 1H, $J_{1,2}$ = $J_{2,3}$ = 9.3 Hz, H-2), 4.47 (s, 2H, OCH_2Ph), 4.48 (d, 1H, J = 11.8 Hz, OC*H*Ph), 4.52 (d, 1H, J = 11.8 Hz, OC*H*Ph), 4.92 (d, 1H, J = 11.4 Hz, OC*H*Ph), 4.94 (d, 1H, J = 11.4 Hz, OC*H*Ph), 7.02-7.48 (m, 15H, H_{Ar}); ^{13}C NMR ($CDCl_3$) δ 17.2 (q, C-6), 28.1 (dt, J_{CP} = 143.5 Hz, C-1'), 51.8 (dq, J_{CP} = 7.3 Hz, POC*H*$_3$), 52.6 (dq, J_{CP} = 7.3 Hz, POC*H*$_3$), 72.4

(t, OCH_2Ph), 74.8 (t, OCH_2Ph), 75.1 (t, OCH_2Ph), 74.4 (d), 76.8 (d), 78.3 (d), 78.5 (d), 85.0 (d), 127.6-128.5 (d, Ar), 138.3-138.5 (3s, C Ar); ^{31}P NMR ($CDCl_3$) δ 33.07.

Anal. Calcd for $C_{30}H_{37}O_7P$ (540.59): C, 66.65%; H, 6.90%. Found: C, 66.72%, H, 7.02%.

(β-L-Fucopyranosyl)methanephosphonic Acid (14). Compound **13** (120 mg, 0.22 mmol) was dissolved in freshly distilled dry CCl_4; the solution was cooled to 0 °C and Me_3SiI (487 μL) was added. After 1.5 h, the solvent was removed, the brown residue was dissolved in a few mL of MeOH and precipitated by addition of Et_2O, affording quantitatively the phosphono analogue of β-L-fucose 1-phosphate (**14**). Oil, $[\alpha]_D$ - 10° (*c* 1.5, CH_3OH). ^1H NMR (CD_3OD) δ 1.22 (d, 3H, $J_{5,6}$ = 6.3 Hz, H-6), 1.86-2.20 (m, 1H, H-1'a), 2.33 (bt, 1H, H-1'b), 3.34-3.50 (m, 3H, H-1, H-2, H-3), 3.59 (q, 1H, $J_{5,6}$ = 6.3 Hz, H-5), 3.64 (bs, 1H, H-4); ^{13}C NMR (CD_3OD) δ 17.1 (q, C-6), 31.5 (dt, J_{CP} = 135.0 Hz, C-1'), 72.9 (d), 73.7 (d), 75.7 (d), 76.3 (d), 77.0 (d). ^{31}P NMR (D_2O) δ 26.16.

Anal. Calcd for $C_7H_{15}O_7P$ (242.17): C, 34.72%; H, 6.24%. Found: C, 34.41%, H, 6.58%.

Dimethyl (β-L-Fucopyranosyl)methanephosphonate (15). Compound **13** (120 mg, 0.22 mmol) was catalytically hydrogenated (Pd/C, MeOH). After 3 days, removal of the catalyst by filtration on celite and solvent evaporation afforded quantitatively (60 mg) the dimethyl phosphonate **15**. Oil, $[\alpha]_D$ + 1° (*c* 1.5, CH_3OH). ^1H NMR (CD_3OD) δ 1.23 (d, 3H, $J_{5,6}$ = 6.6 Hz, H-6), 2.00 (dt, 1H, $J_{1'a,P} = J_{1'a,1'b}$ = 15.7 Hz, $J_{1'a,1}$ = 9.7 Hz, H-1'a), 2.42 (ddd, 1H, $J_{1'b,P}$ = 19.7 Hz, $J_{1'a,1'b}$ = 15.7 Hz, $J_{1'b,1}$ = 1.3 Hz, H-1'b), 3.30-3.48 (m, 3H), 3.58, 3.67 (m, 2H), 3.72 (d, 3H, $J_{H,P}$ = 10.8 Hz, $POCH_3$), 3.73 (d, 3H, $J_{H,P}$ = 11.0 Hz, $POCH_3$); ^{13}C NMR (CD_3OD) δ 17.1 (q, C-6), 28.7 (dt, J_{CP} = 142.4 Hz, C-1'), 52.8 (dq, J_{CP} = 7.3 Hz, $POCH_3$), 53.6 (dq, J_{CP} = 7.3 Hz, $POCH_3$), 73.6 (d), 75.7 (d), 76.2 (d), 76.4 (d), 76.2 (dd, J_{CP} = 15.1 Hz, C-1); ^{31}P NMR (D_2O) 33.20.

Anal. Calcd for $C_9H_{19}O_7P$ (270.22): C, 40.00%; H, 7.09%. Found: C, 40.25%, H, 6.99%.

ACKNOWLEDGEMENTS

This work was supported by EU (contract n. BIO CT96 0158).

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