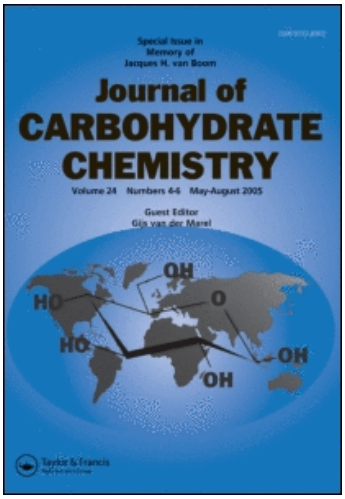

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A CONCISE AND STEREOSELECTIVE SYNTHESIS OF *C*-GLYCOSYL ANALOGUES OF β-L-FUCOPYRANOSYL PHOSPHATE AND β-L-RHAMNOPYRANOSYL PHOSPHATE

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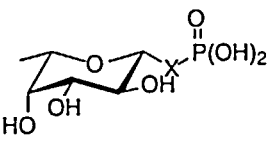
ABSTRACT

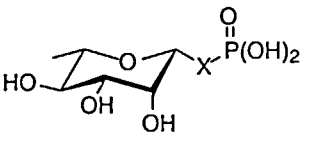
The isosteric *C*-glycosyl analogues of β-L-fucopyranosyl phosphate **1** and β-L-rhamnopyranosyl phosphate **2** have been stereoselectively synthesized from the corresponding glycono-1,5-lactones **3** and **10** via methylphosphonylation, dehydration and catalytic hydrogenation, followed by deprotection.

INTRODUCTION

Glycosyl phosphates play crucial roles in carbohydrate metabolism as metabolic regulators or ubiquitous intermediates for glycoconjugate biosynthesis. Over the past two decades, several synthetic methods have been developed for metabolically stable glycosyl phosphates, i.e., *C*-glycosyl analogues where the bridging oxygen is replaced by a methylene group[1] or a difluoromethylene group.[2] Recently, Nicotra and his associates have reported the probably most efficient route to the *C*-glycosyl analogue of β-L-



β-L-Fucopyranosyl phosphate X = O
C-Glycosyl analogue **1** X = CH_2



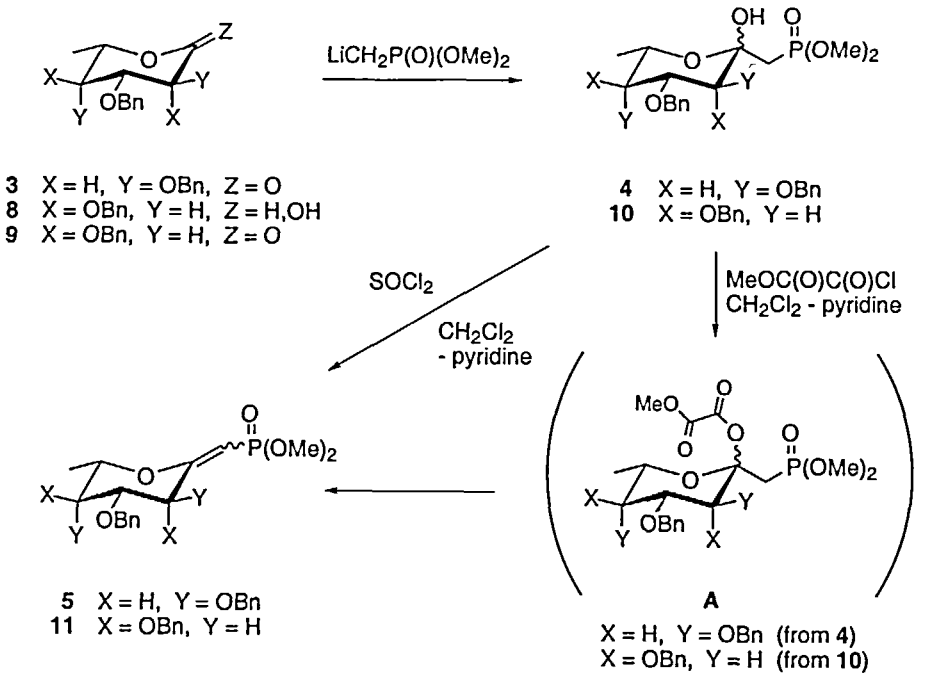
β-L-Rhamnopyranosyl phosphate X = O
C-Glycosyl analogue **2** X = CH_2

Figure 1. *C*-Glycosyl analogues of β-L-fucopyranosyl phosphate **1** and β-L-rhamnopyranosyl phosphate **2**.

fucopyranosyl phosphate[3] **1** (Figure 1). Their approach was based on stereoselective hydride addition to the pyran oxonium ion derived from the methylphosphonate **4** (Scheme 1), according to the procedure devised by Kishi et al. for stereoselective β-*C*-glycosylation.[4] We disclose herein an alternative route to **1**[5] starting from the same methylphosphonate **4**. Our method is characterized by dehydration and subsequent stereoselective hydrogenation. This sequence of reactions was also proven efficient in the synthesis of the β-rhamnose analogue **2**. Although adding one extra step to the aforesaid Nicotra's protocol, our method may have general applicability for the synthesis of the *C*-glycoside analogues of β-glycopyranosyl phosphates, since Nicotra et al. reported that their approach was unsuccessful in the glucose series.[3] It is worth noting that stereoselective synthesis of **2** has never been reported prior to this communication.[6] Compound **2** is an important precursor for the *C*-glycosyl analogue of thymidine 5'-(β-L-rhamnopyranosyl diphosphate),[7] a potential donor sugar-nucleotide based inhibitor of rhamnosyltransferase (RhaT). Since RhaT is a crucial enzyme for the biosynthesis of the mycobacterial cell wall, inhibitors of RhaT have significant therapeutic potential.[8] Synthetic studies along this line are currently in progress.

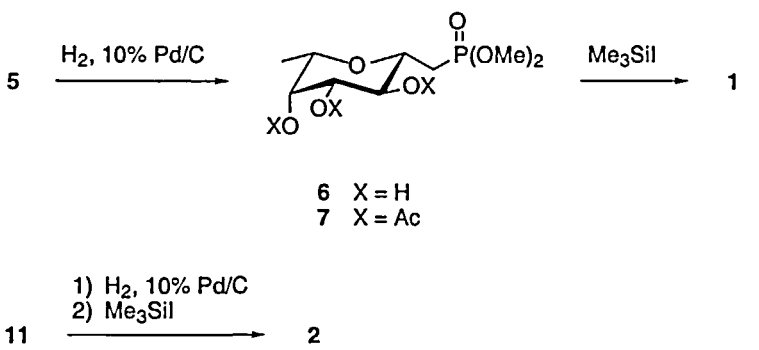
RESULTS AND DISCUSSION

Glycono-1,5-lactones are versatile starting materials for the synthesis of *C*-glycosyl analogues[9] and carba-sugars.[10] We have previously synthesized carba-β-L-



Scheme 1

fucopyranosyl phosphate from tri-*O*-benzyl-L-fucono-1,5-lactone[11] (**3**) by utilizing intramolecular Horner-Wadsworth-Emmons (HWE) olefination. One of the key intermediates for the HWE olefination was the methylphosphonate **4**,[11] that was readily prepared from **3** by reaction with lithium dimethyl methylphosphonate. We envisioned that removal of the anomeric hydroxyl group of **4** would provide a simple route to **1**. To achieve our goal we investigated radical deoxygenation, reported by Dolan and MacMillan for sterically hindered alcohols,[12] which involves reduction of the methyl oxalyl esters by stannyl radicals. To our surprise, treatment of **4** with methyl oxalyl chloride in dichloromethane containing pyridine at room temperature resulted in a rapid dehydration, yielding the olefin **5** in 82% yield. Without pyridine the reaction was sluggish and in the absence of methyl oxalyl chloride no reaction took place. It seems likely that the formation of the methyl oxalyl ester **A** was followed by a rapid elimination of methyl oxalic acid. The same transformation was also successful by use of thionyl chloride[13] in



Scheme 2

the place of methyl oxalyl chloride, yielding **5** in 75% yield. Although the geometry of the newly formed double bond has not yet been characterized, the ^{1}H NMR spectrum indicated the presence of only one isomer. Catalytic reduction of **5** over palladium on carbon proceeded stereoselectively with concomitant *O*-debenzylation to yield quantitatively the phosphonate **6** (Scheme 2), whose structure was assigned after conversion to the acetate **7**. Thus, the $J_{2,3}$ coupling of 9.5 Hz was in good accordance with a methylphosphonate group in an equatorial orientation. Treatment of **6** with iodotrimethylsilane afforded **1** quantitatively.

A similar sequence of reactions was also proven practical for the preparation of **2** from the corresponding phosphonate **10**, which was readily prepared as a single anomer from tri-*O*-benzyl-L-rhamnopyranose[14] (**8**) via tri-*O*-benzyl-L-rhamnono-1,5-lactone (**9**). Treatment of **10** with either methyl oxalyl chloride or thionyl chloride in dichloromethane containing pyridine gave the olefin **11** in 85% or 82% yield, respectively, as a single isomer. Although catalytic reduction of the double bond was stereoselective, simultaneous debenzylation proved to be quite difficult in this case. Therefore, complete deprotection was achieved by treatment of the reduction mixture with iodotrimethylsilane, which furnished **2** in 94% yield from **11**. The observed NOE between H-2 and H-4/H-6 established an equatorial configuration of a methylphosphonic acid group at C-2.

EXPERIMENTAL

General methods. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Optical rotations were measured with a Rudolph Research Auto P01 IV® polarimeter at 25 °C. ^{1}H NMR spectra were recorded on a Bruker AM-360 spectrometer in $CDCl_3$ or in D_2O. Chemical shift standards were Me_4Si for $CDCl_3$ and acetone for D_2O. FABMS, including HRMS, were recorded on a VG Analytical 70VSE spectrometer. TLC was performed on Merck silica gel 60F254 plates (0.25-mm thickness) and flash column chromatography on ICN silica gel 60 (0.032–0.063 mm). Elemental analyses were done by Galbraith Laboratories in Knoxville, TN.

Dimethyl (2,6-Anhydro-tri-*O*-benzyl-1-deoxy-L-*fuco*-hept-1-enopyranosyl)-phosphonate (5). (a) With methyl oxalyl chloride. Methyl oxyalyl chloride (0.45 mL, 4.70 mmol) was added dropwise to a solution of dimethyl (tri-*O*-benzyl-1-deoxy-L-*fuco*-heptulopyranosyl)phosphonate[11] (4) (290 mg, 0.522 mmol) in CH_2Cl_2 (7 mL) containing pyridine (2 mL) with vigorous stirring at rt. After 1 h, EtOH (0.5 mL) was added and the mixture was stirred at rt for 10 min. The reaction mixture was diluted with EtOAc (10 mL) and washed successively with saturated aq $NaHCO_3$ (5 mL), brine (5 mL) and water (5 mL). The organic phase was dried over anhyd Na_2SO_4 and concentrated. The product was purified by flash column chromatography on silica gel with toluene/EtOH (9:1 v/v) to give **5** (230 mg, 82%) as a colorless syrup: $[\alpha]_D$ –87.4° (*c* 4.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.35 (br d, $J_{1,P}$ = 13.5 Hz, 1H, H-1), 4.43 (br d, $J_{2,3}$ = 9.5 Hz, 1H, H-3), 3.88 (br q, $J_{6,Me}$ = 6.4 Hz, 1H, H-6), 3.73 (br s, 1H, H-5), 3.70 (d, $J_{OMe,P}$ = 11.3 Hz, 3H) and 3.68 (d, $J_{OMe,P}$ = 11.3 Hz, 3H) (2 x OMe), 1.30 (d, $J_{Me,6}$ = 6.4 Hz, 3H, Me). HRMS Calcd for $C_{30}H_{36}O_7P$ ($[M + H]^+$, 539.2199). Found: 539.2196.

(b) With thionyl chloride. The reaction was carried out similarly to the above except that thionyl chloride (0.61 mL, 8.32 mmol) was used in the place of methyl oxalyl chloride. The same work-up yielded **5** (210 mg, 75%).

(2,6-Anhydro-1-deoxy-β-L-*fuco*-heptopyranosyl)phosphonic acid[3,5] (1). A solution of **5** (230 mg, 0.428 mmol) in EtOH (8 mL) containing 10% Pd/C (23 mg) was

stirred vigorously under H_2 (1 atm) at rt for 3 days. The reaction mixture was filtered through neutral alumina and the filtrate was concentrated to give the crude dimethyl (2,6-anhydro-1-deoxy-β-L-*fuco*-heptopyranosyl)phosphonate (**6**) as a colorless syrup, which showed a single spot on TLC (R_f 0.2, EtOH/$CHCl_3$, 8:1 v/v). Without further purification, the crude **6** was dissolved in CH_2Cl_2 (5 mL). To this solution was added dropwise iodotrimethylsilane (0.13 mL, 0.886 mmol) and the mixture was stirred at 0 °C for 30 min. The reaction was then quenched by addition of ice-cold water (0.5 mL). After concentration, the product was purified by Bio-Gel P-2 column chromatography with water to give **1** (108 mg, 98%) as a colorless syrup: R_f 0.23 (4:2:2:1 n-butanol–EtOH–H_2O–AcOH); $[\alpha]_D$ –10.1° (*c* 3.4, H_2O); ^{1}H NMR (D_2O): δ 3.60 (br d, $J_{5,4}$ = 3.2 Hz, H-5), 3.55 (br q, $J_{6,Me}$ = 6.5 Hz, 1H, H-6), 3.44 (dd, $J_{4,3}$ = 9.4 Hz, $J_{4,5}$ = 3.4 Hz, 1H, H-4), 3.32 (br q-like, J = 9 Hz, 1H, H-2), 3.21 (dd, $J_{3,4}$ = 9.4 Hz, $J_{3,2}$ = 7.3 Hz, 1H, H-3), 1.99 (br t, J = 17 Hz, 1H) and 1.64 (br td-like, $J_{1',p} = J_{1',1}$ = 15.3 Hz, $J_{1',2}$ = 8.9 Hz, 1H) (H-1 and H-1'), 1.02 (d, $J_{Me,6}$ = 6.5 Hz, 3H, Me). HRMS Calcd for $C_7H_{14}O_7P$ ([M - H]$^-$, 241.0477). Found: 241.0481.

The dried compound can be stored in a freezer under Ar for at least 6 months without any decomposition.

Dimethyl (Tri-*O*-acetyl-2,6-anhydro-1-deoxy-β-L-*fuco*-heptopyranosyl)-phosphonate (7). Compound **6** (86 mg, 0.319 mmol) was acetylated with Ac_2O (3 mL) and pyridine (6 mL) at rt overnight. The mixture was concentrated and purified by flash column chromatography on silica gel with $CHCl_3$/EtOH (40:1 v/v) to give **7** (91.6 mg, 73%) as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 5.21 (br d, $J_{5,4}$ = 3.0 Hz, 1H, H-5), 5.0 (dd, $J_{3,2} = J_{3,4}$ = 9.5 Hz, 1H, H-3), 4.94 (dd, $J_{4,3}$ = 9.5 Hz, $J_{4,5}$ = 3.0 Hz, 1H, H-4), 3.80 (br q, $J_{6,Me}$ = 6.4 Hz, 1H, H-6), 3.70 (d $J_{Me,p}$ = 11 Hz) and 3.65 (d, $J_{Me,p}$ = 11 Hz) (2 x OMe), 2.11 (s, 3H), 1.99 (s, 3H) and 1.91 (s, 3H) (3 x OAc), 1.12 (d, $J_{Me,6}$ = 6.4 Hz, 3H, Me). LRMS: *m/z* 397 [M + H]$^+$.

Tri-*O*-benzyl-L-rhamnono-1,5-lactone (9). A solution of tri-*O*-benzyl-L-rhamnopyranose[13] (**8**) (2.4 g, 5.53 mmol) in Me_2SO (18 mL) and Ac_2O (14 mL) was stirred at rt overnight. Lyophilization followed by flash column chromatography on silica

gel with hexane/toluene (5:2 v/v) gave **9** (2.2 g, 92%) as a colorless solid. An analytical sample (colorless needles) was obtained by recrystallization from Et_2O–hexane: mp 121.5–122.0 °C; $[\alpha]_D$ –2.2° (*c* 5.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.35 (d, $J_{2,3}$ = 2.8 Hz, 1H, H-2), 4.12 (dq, $J_{5,4}$ = 7.8 Hz, $J_{5,Me}$ = 6.3 Hz, 1H, H-5), 4.06 (dd, $J_{3,2}$ = 2.8 Hz, $J_{3,4}$ = 1.1 Hz, 1H, H-3), 3.48 (dd, $J_{4,5}$ = 7.8 Hz, $J_{4,3}$ = 1.1 Hz, 1H, H-4), 1.32 (d, $J_{Me,5}$ = 6.3 Hz, 3H, Me). HRMS Calcd for $C_{27}H_{29}O_5$ ($[M + H]^+$, 433.2015). Found: 433.2024.

Anal. Calcd for $C_{27}H_{28}O_5$ (432.52): C, 74.98; H, 6.53. Found: C, 74.52; H, 6.70.

Dimethyl (Tri-*O*-benzyl-1-deoxy-L-*rhamno*-heptulopyranosyl)phosphonate (10). A 2.5M solution of *n*-BuLi in hexane (2.25 mL) was added dropwise to a solution of dimethyl methylphosphonate (0.89 mL, 7.97 mmol) in THF (15 mL) with stirring at –77 °C under Ar. After 30 min at –77 °C, a solution of **9** (0.75 g, 1.74 mmol) in THF (8 mL) was added dropwise. The mixture was stirred at –77 °C for 30 min, warmed to 0 °C, and poured into a mixture of chilled 10% aq NH_4Cl (20 mL) and EtOAc (60 mL). The organic layer was separated, washed with H_2O (2 x 40 mL), and dried over anhyd Na_2SO_4. After solvent evaporation, the residue was purified by flash column chromatography on silica gel with toluene/EtOAc (4:1 v/v) to give **10** (880 mg, quantitative) as a colorless syrup: $[\alpha]_D$ –16.2° (*c* 6.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.64 (s, 1H, OH), 4.07 (dd, $J_{4,5}$ = 9.5 Hz, $J_{4,3}$ = 2.7 Hz, 1H, H-4), 3.90 (dq, $J_{6,5}$ = 9.6 Hz, $J_{6,Me}$ = 6.2 Hz, 1H, H-6), 3.72 (d, $J_{OMe,p}$ = 11 Hz, 3H) and 3.58 (d, $J_{OMe,p}$ = 11 Hz, 3H) (2 x OMe), 3.63 (d, $J_{3,4}$ = 2.7 Hz, 1H, H-3), 3.52 (dd, $J_{5,4} = J_{5,6}$ = 9.6 Hz, 1H, H-5), 2.48 (dd, $J_{1,p}$ = 18.2 Hz, $J_{1,1'}$ = 15.3 Hz, 1H) and 1.58 (dd, $J_{1',p}$ = 17.5 Hz, $J_{1',1}$ = 15.3 Hz, 1H) (H-1 and H-1'), 1.20 (d, $J_{Me,6}$ = 6.2 Hz, 3H, Me). HRMS Calcd for $C_{30}H_{36}O_7P$ ($[M + H - H_2O]^+$, 539.2199). Found: 539.2206.

Dimethyl (2,6-Anhydro-tri-*O*-benzyl-1-deoxy-L-*rhamno*-hept-1-enopyranosyl)-phosphonate (11). (a) With methyl oxalyl chloride. Compound **10** was treated with methyl oxalyl chloride as described in the preparation of **7** to give **11** in 85% yield as a colorless solid. An analytical sample (colorless powder) was obtained by recrystallization from Et_2O–hexane: mp 78–78.5 °C; $[\alpha]_D$ –44.8° (*c* 6.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.90 (d, $J_{1,p}$ = 12.4 Hz, 1H, H-1), 4.07 (d, $J_{3,4}$ = 2.7 Hz, 1H, H-3), 3.77

(dq, $J_{6,5}$ = 8.2 Hz, $J_{6,Me}$ = 6.2 Hz, 1H, H-6), 3.67 (dd, $J_{4,5}$ = 5.5 Hz, $J_{4,3}$ = 2.7 Hz, 1H, H-4), 3.62 (d, $J_{OMe,p}$ = 11.4 Hz, 6H, 2 x OMe), 3.57 (dd, $J_{5,6}$ = 8.2 Hz, $J_{5,4}$ = 5.5 Hz, 1H, H-5), 1.35 (d, $J_{Me,6}$ = 6.2 Hz, 3H, Me). HRMS Calcd for $C_{30}H_{36}O_7P$ ($[M + H]^+$, 539.2199). Found: 539.2173.

Anal. Calcd for $C_{30}H_{35}O_7P$ (538.58): C, 66.90; H, 6.55; P, 5.75. Found: C, 66.76; H, 6.80; P, 5.67.

(b) With thionyl chloride. The reaction was carried out as described above except that thionyl chloride was used in the place of methyl oxalyl chloride, yielding **11** in 82% yield.

(2,6-Anhydro-1-deoxy-β-L-*rhamno*-heptopyranosyl)phosphonic Acid[3] (2). A solution of **11** (0.17 g, 0.316 mmol) in EtOH (5 mL) containing 10% Pd/C (20 mg) was stirred vigorously under H_2 (1 atm) at rt for 3 days. The reaction mixture was filtered through neutral alumina, and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2 (5 mL) and to this solution was added dropwise iodotrimethylsilane (0.26 mL, 1.77 mmol). The mixture was stirred at 0 °C for 30 min and quenched by addition of ice-cold water (1 mL). After concentration, the product was purified by Bio-Gel P-2 column chromatography with water to give **2** (71.5 mg, 94%) as a colorless syrup: R_f 0.26 (4:2:2:1 n-butanol–EtOH–H_2O–AcOH); $[\alpha]_D$ +11.3° (*c* 3.3, H_2O); ^1H NMR (D_2O): δ 3.81 (d-like, $J_{3,4}$ = 3.3 Hz, H-3), 3.65 (br q-like, J = 7.5 Hz, 1H, H-2), 3.43 (dd, $J_{4,5}$ = 9.1 Hz, $J_{4,3}$ = 3.4 Hz, 1H, H-4), 3.26–3.16 (m, 1H, H-6), 3.18 (t-like, J = 9.0 Hz, 1H, H-5), 1.82 (ddd, $J_{1,p}$ = 17.6 Hz, $J_{1,1'}$ = 15.0 Hz, $J_{1,2}$ = 7.5 Hz, 1H) and 1.70 (ddd, $J_{1',p}$ = 18.5 Hz, $J_{1',1}$ = 15.0 Hz, $J_{1',2}$ = 6.0 Hz, 1H) (H-1 and H-1'), 1.09 (d, $J_{Me,6}$ = 5.7 Hz, 3H, Me). HRMS Calcd for $C_7H_{14}O_7P$ ($[M - H]^-$, 241.0477). Found: 241.0480.

The dried compound can be stored in a freezer under Ar for at least 6 months without any decomposition.

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