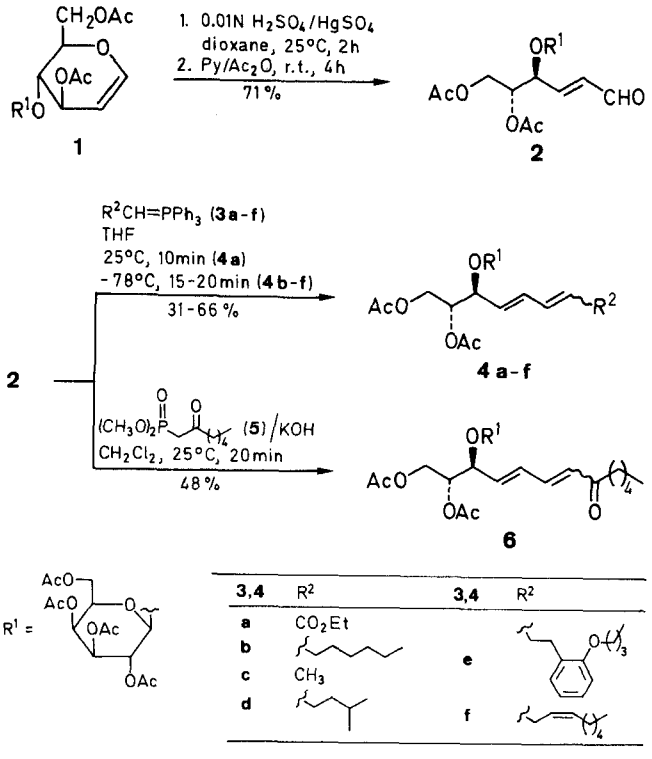
Acidic Opening of the Dihydropyran Ring of Hexa-*O*-acetyl-D-lactal and Subsequent Chain Elongation. Novel Approach to the Synthesis of Low Molecular Weight *O*-Glycosides Containing a Diacetoxypolyene Aglycone Moiety

G.A. Tolstikov, A.G. Tolstikov,* O.F. Prokopenko, L.M. Khalilov, V.N. Odinokov
Institute of Chemistry, USSR Acad. Sci. Ural Department, Bashkirian Research Centre, Ufa, USSR

Low molecular weight *O*-glycosides containing a diacetoxypolyene aglycone moiety were prepared by chain elongation with phosphoranes or with a phosphonate of (2*E*,4*S*,5*R*)-5,6-diacetoxy-4-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranyloxy)-2-hexenal **(2)**, which was prepared from hexa-*O*-acetyl-D-lactal by acidic ring opening and subsequent acetylation.

The acidic opening of glycal acetates according to the method modified by Perlin[1] has found use in the synthesis of biologically active compounds.[2-4] No similar transformations using hexa-*O*-acetyl-D-lactal are known.

We report herein the acidic opening of the hydropyran ring of hexa-*O*-acetyl-D-lactal **(1)**, which after acetylation gave (2*E*,4*S*,5*R*)-5,6-diacetoxy-4-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranyloxy)-2-hexanal **(2)** in 71% yield. This transformation of compound **1** provided a novel approach to a synthesis of low molecular weight *O*-glycosides. Chain extension of **2** with phosphoranes **3** and phosphonate **5** gave *O*-glycosides containing a diacetoxypolyene aglycone moiety. The reaction of aldehyde **2** with ethoxycarbonylmethylenetriphenylphosphorane **(3a)** is unusually easy; it is completed in a few minutes and gives compound **4a** in a 68% yield. The aldehyde **2** and nonstabilized alkylidenephosphoranes **4b–f** also react readily. In all cases, the formation of the olefination products **4b–f**, obtained as a mixture of geometric isomers at the 5,6-double bond (isomer composition was not analyzed), was complete within 20 minutes at −78°C. In contrast, (2*E*,4*S*,5*R*)-4,5,6-triacetoxy-2-hexenal[1] (a product of D-glycal opening) gives ethyl (2*E*,4*E*,6*S*,7*R*)-6,7,8-triacetoxy-2,4-octadienoate in 6 hours under the same conditions. Likewise the reaction of (2*E*,4*R*,5*R*)-4,5,6-triacetoxy-2-hexenal (a product of D-galactal opening) with heptylidenetriphenylphosphorane **(3b)** proceeds slowly at −78°C and yields (2*R*,3*R*,4*E*,6*Z*)-1,2,3-triacetoxy-4,6-tridecadiene[4] only after 2 hours at room temperature. Aldehyde **2** thus appears to react easily due to the presence of the sugar substituent. The olefination of aldehyde **2** with dimethyl 2-oxoheptylphosphonate **(5)** in the presence of alkali yields (2*R*,3*S*,4*E*)-1,2-diacetoxy-3-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranyloxy)-4,6-tridecadien-8-one **(6)** (48% yield).



^{13}C-NMR spectra were obtained using a Jeol FX-90Q spectrometer (22.5 MHz). Optical rotations were measured on a Perkin-Elmer-141 polarimeter. The products were analyzed by TLC on Silufol UV-254 (CSR) plates. Hexa-*O*-acetyl-D-lactal **1** (99.9%) was prepared by literature method.[5] Nonstabilized phosphoranes **3b–d** were produced from the corresponding phosphonium bromides, prepared by heating commercial heptyl, ethyl and, 4-methylpentyl bromides with triphenylphosphine in acetonitrile; phosphorane **3e** was produced from [2-(2-butoxyphenyl)ethyl]triphenylphosphonium bromide[6] and phosphorane **3f** was produced from [(*Z*)-3-nonenyl]triphenylphosphium tosylate.[7] The yields are for chromatographically pure products.

(2*E*,4*S*,5*R*)-5,6-Diacetoxy-4-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranyloxy)-2-hexenal (2):
To a solution of lactal **1** (0.79 g, 1.4 mmol) in dioxane (5 mL), 0.01 N H_2SO_4 (15 mL) and $HgSO_4$ (0.02 g) are added sequentially. The mixture is stirred for 2 h at 25°C and extracted with CH_2Cl_2 (3 × 20 mL); the combined extract is dried (Na_2SO_4), and the solvent is evaporated. Pyridine (10 mL) and Ac_2O (0.5 mL) are added to the residue (0.56 g). After 4 h, the mixture is diluted with EtOAc (20 mL) and washed with 5% aq HCl (1 × 10 mL) and H_2O (2 × 20 mL). The organic layer is dried (Na_2SO_4), and the residue is chromatographed on silica EtOAc/hexane, 2:1); yield: 0.57 g (71%); $[\alpha]_D^{20}$ +46.7° (*c* = 1.64, $CHCl_3$).

$C_{24}H_{32}O_{15}$ calc. C 51.43 H 5.76
(560.3) found 51.45 5.74

^{13}C-NMR ($CDCl_3$/TMS): δ = 20.64, 20.81 (q, 6$\underline{C}H_3CO$), 61.41 (t, C-6'), 64.71 (t, C-6), 67.02 (d, C-4'), 68.80 (d, C-2'), 70.71 (d, C-3'), 71.02 (d, C-5'), 71.46 (d, C-5), 80.73 (d, C-4), 101.91 (d, C-1'), 133.56 (d, C-2), 152.46 (d, C-3), 169.63, 170.07, 170.23, 170.40, 171.26 8s, 6$\underline{C}OCH_3$), 193.15 (d, C-1).

Ethyl (4*E*,6*S*,7*R*)-7,8-Diacetoxy-6-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranyloxy]-2,4-octadienoate (4a)
Ethoxycarbonylmethylenetriphenylphosphorane (**3a**; 0.14 g, 0.41 mmol) is added to aldehyde **2** (0.12 g, 0.21 mmol) in dry THF (8 mL), and the mixture stirred for 10 min at 25°C. The solvent is distilled, and the residue is chromatographed on silica (EtOAc/hexane, 2:1); yield: 0.13 g (66%); $[\alpha]_D^{20}$ +36.1° (*c* = 2.02, $CHCl_3$).

$C_{28}H_{38}O_{16}$ calc. C 53.33 H 6.07
(630.6) found 53.37 6.05

^{13}C-NMR ($CDCl_3$/TMS): δ = 14.25 (q, CH_3), 20.64, 20.78, 20.91 (q, 6$\underline{C}H_3CO$), 60.41 (t, $\underline{C}H_2CH_3$), 61.76 (t, C-8), 70.71 (d, C-3'), 70.87 (d, C-5'), 72.33 (d, C-7), 79.65 (d, C-6), 107.64 (d, C-7'),

123.04 (d, C-3), 130.95 (d, C-4), 136.97 (d, C-5), 142.71 (d, C-2), 166.50 (s, C-1), 169.37, 169.80, 170.02, 170.18, 170.28 (s, $6CH_3\underline{C}O$).

Glycosides (4b–f); General Procedure:
A 0.84 M solution of BuLi in hexane (0.62 mL, 0.52 mmol) is added to a stirred suspension of the phosphonium salt (0.54 mmol) in dry THF (10 mL) under Ar at −78 °C to give the corresponding phosphorane. After 15 min, a solution of aldehyde **2** (0.2 g, 0.36 mmol) in THF (1 mL) is added dropwise to the phosphorane solution, which is then kept at −78 °C for 15–20 min, diluted with EtOAc (10 mL), and washed with 5% aq HCl (5 mL). The organic layer is Et_2O, dried (Na_2SO_4), and evaporated. The residue is chromatographed on silica (EtOAc/hexane, 2:1) to give the desired glycosides.

(2R,3S,4E)-1,2-Diacetoxy-3-(2,3,4,6-tetra-O-acetyl-β-D-galacto-pyranyloxy)-4,6-tridecadiene (**4b**); yield: 0.14 g (62%); $[\alpha]_D^{20}$ +15.8° (*c* = 1.4, $CHCl_3$).

$C_{31}H_{46}O_{14}$	calc.	C 57.93	H 7.21
(642.7)	found	58.01	7.19

^{13}C-NMR ($CDCl_3$/TMS): δ = 14.03 (q, C-13), 20.64, 20.86 (q, $6\underline{C}H_3CO$), 22.59 (t, C-12), 27.85 (t, C-8), 28.93 (t, C-9), 29.47 (t-C-10), 31.70 (t, C-11), 61.37 (t, C-6′), 62.09 (t, C-1), 10.81 (d, C-3′), 10.81 (d, C-5′), 72.60 (d, C-2), 80.47 (d, C-3), 101.15 (d, C-1′), 127.22, 127.92, 129.49, 134.42 (d, C4-C7), 170.18, 170.26, 170.44 (s, $6CH_3\underline{C}O$).

(2R,3S,4E)-1,2-Diacetoxy-3-(2,3,4,6-tetra-O-acetyl-β-D-galacto-pyranyloxy)-4,6-octadiene (**4c**); yield: 0.06 g (31%); $[\alpha]_D^{20}$ +17.9° (*c* = 0.56, $CHCl_3$).

$C_{26}H_{36}O_{14}$	calc.	C 54.54	H 6.34
(572.6)	found	54.76	6.32

^{13}C-NMR ($CDCl_3$/TMS): δ = 13.49 (q, C-8), 20.09, 20.64 (q, $6\underline{C}H_3CO$), 61.39 (d, C-6′), 62.09 (t, C-1), 70.87 (d, C-5′), 72.65 (d, C-2), 80.78 (d, C-3), 101.21 (d, C-1′), 127.81, 128.24 (d, C-6-C-7), 128.35 (d, C-4), 129.21 (d, C-5), 169.35, 170.13, 170.39, 178.04 (s, $6CH_3\underline{C}O$).

(2R,3S,4E)-1,2-Diacetoxy-3-(2,3,4,6-tetra-O-acetyl-β-D-galacto-pyranyloxy)-10-methyl-4,6-undecadiene (**4d**); yield (6): 0.071 g (32%), $[\alpha]_D^{20}$ +23.8° (*c* = 0.68 $CHCl_3$).

$C_{29}H_{42}O_{14}$	calc.	C 56.57	H 6.89
(614.6)	found	56.56	6.53

^{13}C-NMR ($CDCl_3$/TMS): δ = 20.67, 20.94 (q, $6\underline{C}H_3CO$), 22.49 (q, C-11-C-12), 25.76 (t, C-8), 27.69 (t, C-9), 38.65 (d, C-10), 61.30 (t, C-6′), 62.06 (t, C-1), 70.70 (d, C-3′), 70.84 (d, C-5′), 72.65 (d, C-2), 80.78 (d, C-3), 101.2 (d, C-1′), 127.11 (d, C-5), 127.95, 129.41 (d, C-6-C-7), 134.56 (d, C-4), 169.33, 169.34, 170.13, 170.42 (s, $6CH_3\underline{C}O$).

(2R,3S,4E)-1,2-Diacetoxy-8-(2-butoxyphenyl)-3-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranyloxy)-4,6-octadiene (**4e**); yield: 0.12 g (32%); $[\alpha]_D^{20}$ +7.4° (*c* = 3.4 $CHCl_3$).

$C_{36}H_{48}O_{15}$	calc.	C 60.48	H 6.86
(720.8)	found	60.61	6.59

^{13}C-NMR ($CDCl_3$/TMS): δ = 13.87 (q, C-15), 19.40 (t, C-14), 20.59, 20.86 (q, $6\underline{C}H_3CO$), 28.28 (t, C-8), 31.42 (t, C-13), 62.09 (t, C-1), 67.56 (t, C-12), 70.76 (d, C-5′), 70.87 (d, C-3′), 72.49 (d, C-2), 80.73 (d, C-3), 101.05 (d, C-1′), 111.12, 120.33, 127.33, 128.68 (d, $4C_{arom}$), 127.98 (d-C-1), 128.57 (s, C_{arom}-9), 129.28 (d, C-5), 129.49 (d, C-6), 131.93 (d, C-4), 159.59 (s, C_{arom}-10), 169.31, 169.85, 170.07 (s, $CH_3\underline{C}O$).

(2R,3S,4E,9Z)-1,2-Diacetoxy-3-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranyloxy]-4,6,9-tetradecatriene (**4f**); yield: 0.1 g (32%); $[\alpha]_D^{20}$ +14.6° (*c* = 1.6, $CHCl_3$).

$C_{32}H_{46}O_{14}$	calc.	C 59.26	H 7.08
(654.7)	found	59.56	7.01

^{13}C-NMR ($CDCl_3$/TMS): δ = 14.03 (q, C-14), 20.64, 20.91 (q, $6\underline{C}H_3CO$), 22.54 (t, C-13), 27.25 (t, C-8), 29.26 (t, C-11), 31.48 (t, C-12), 62.04 (t, C-1), 70.81 (d, C-3′, C-5′), 72.60 (d, C-2), 80.67 (d, C-3), 101.21 (d, C-1′), 126.68 (d, C-5), 127.38 (d, C-7), 128.57 (t, C-9), 129.11 (d, C-10), 131.12 (d, C-6), 132.15 (d, C-4), 169.31, 169.91, 170.07, 170.28, 170.45 (s, $CH_3\underline{C}O$).

(2*R*,3*S*,4*E*)-1,2-Diacetoxy-3-(2,3,4,6-tetra-O-acetyl-β-D-galacto-pyranyloxy)-4,6-tridecadien-8-one (6):
Powdered KOH (0.03 g, 0.6 mmol) is added to a mixture of aldehyde **2** (0.24 g, 0.42 mmol) and dimethyl 2-oxoheptylphosphonate (**5**) (0.14 g, 0.64 mmol) in CH_2Cl_2 (10 mL) at 25 °C. The mixture is stirred for 20 min, diluted with CH_2Cl_2, and washed with 5% aq HCl (5 mL) and H_2O (2 × 5 mL). The organic layer is dried (Na_2SO_4), and the residue is chromatographed on silica EtOAc/hexane, 3:1); yield: 0.13 g (48%); $[\alpha]_D^{20}$ +26° (*c* = 4.5, $CHCl_3$).

$C_{31}H_{44}O_{15}$	calc.	C 56.70	H 6.75
(656.7)	found	56.54	6.61

^{13}C-NMR ($CDCl_3$/TMS): δ = 13.92 (q, C-13), 20.63, 20.81 (q, $6\underline{C}H_3CO$), 22.43 (t, C-12), 23.89 (t, C-10), 31.42 (t, C-11), 40.74 (t, C-9), 61.28 (t, C-6′), 61.71 (t, C-1), 70.71 (d, C-3′), 70.87 (d, C-5′), 72.44 (d, C-2), 79.54 (d, C-3), 101.64 (d, C-1′), 131.01 (d, C-7), 131.44 (d, C-5), 137.56 (d, C-4), 140.38 (d, C-6), 169.30, 169.82, 170.01, 170.26, 170.38 (s, $6\underline{C}H_3CO$), 200.57 (s, C-8).

Received: 12 May 1988; revised: 28 August 1989

(1) Gonzales, F.; Lesage, S.; Perlin, A.S. *Carbohydr. Res.* **1975**, *42*, 267.
(2) Tulshian, D.E.O.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1981**, *103*, 474.
(3) Rama Rao, A.V.; Purandare, A.V.; Reddy Rajaeathnam, E.; Gurjar, M.K. *Synth. Commun.* **1987**, *17*, 1095.
(4) Tolstikov, A.G.; Khakhalina, N.V.; Odinokov, V.N.; Khalilov, L.M.; Spirikhin, L.V. *J. Org. Chem. USSR* **1989**, *25*, 296.
(5) Harris, T.L.; Herbert, R.W.; Hirst, E.L.; Wood, C.E.; Woodward, H. *J. Chem. Soc.* **1936**, 1403.
(6) Tolstikov, G.A.; Tolstikov, A.G.; Miftakhov, M.S.; Spirikhin, L.V. *J. Org. Chem. USSR* **1986**, *22*, 1620; *C. A.* **1987**, *107*, 77466s.
(7) Ernest, J.; Main, A.J.; Menasse, R. *Tetrahedron Lett.* **1982**, *23*, 167–169.