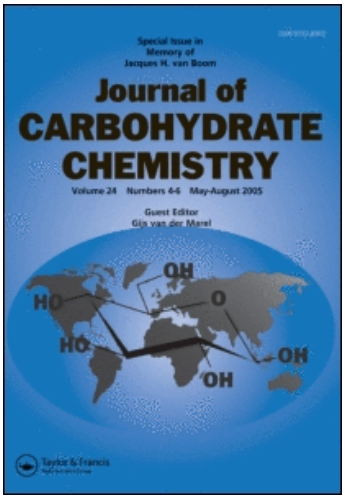


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# A SIMPLE PREPARATION OF METHYL 3,6-DIDEOXY-α-L-ARABINO-HEXOPYRANOSIDE VIA PHOTODEOXYGENATION

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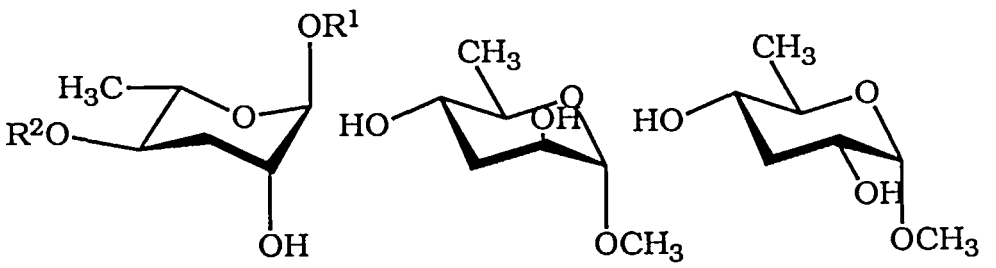
## ABSTRACT

Methyl 3,6-dideoxy-α-**L**-*arabino*-hexopyranoside (**2**, methyl ascaryloside) was synthesized in two steps by regioselective esterification of methyl α-**L**-rhamnopyranoside (**6**) with pivaloyl chloride to methyl 6-deoxy-3-*O*-pivaloyl-α-**L**-mannopyranoside (**7**) and subsequent photodeoxygenation in hexamethylphosphoric triamide/water with light of 254 nm.

## INTRODUCTION

3,6-Dideoxyhexoses are frequently found as constitutents of specific lipopolysaccharides in the cell walls of gram-negative bacteria. They occur at the nonreducing terminus of the highly branched lipopolysaccharides and in many examples they represent the immunodominant end groups, which are responsible for the serological specifity of the bacterial antigen.[3,4]




| | $R^1$ | $R^2$ |
|---|---|---|
| **1** | **H** | **H** |
| **2** | **Me** | **H** |
| **3** | **Me** | **Me** |

**4** **5**

**SCHEME 1**



3,6-Dideoxy-**L**-*arabino*-hexopyranose (**1**, ascarylose) is a constituent of the glycolipids ascaroside A, B and C isolated from the egg membrane of the tapeworm *Parascaris equorum* and has been characterized as a component of the O-antigen from *Pasteurella tuberculosis*.[3,4,5]

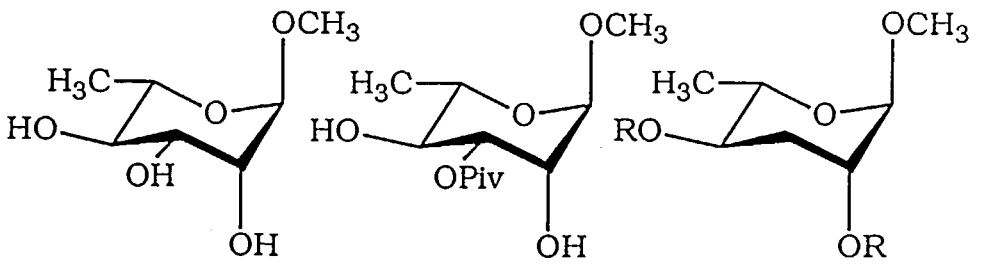
For ascarylose[6,7] (**1**) and its methyl α-**L**-glycoside[6-9] (**2**), as well as for its 4-*O*-methyl ether[10] (**3**), a number of multistep syntheses have been reported.

The irradiation of sugar esters in mixtures of hexamethylphosporic triamide (HMPT) and water has been successfully used for the preparation of deoxy sugars.[11] Since the regioselective acylation of carbohydrates can easily be executed, the photochemical deoxygenation often shortens long reaction paths leading to these important natural products.

In previous investigations we prepared the methyl α-**D**-glycosides of 3,6-dideoxy sugars tyvelose[12] (**4**), the **D**-enantiomer of ascarylose (**1**), and paratose[13] (**5**) by the photodeoxygenation of the corresponding 3,6-di-pivaloates.

## RESULTS AND DISCUSSION

Starting from methyl α-**L**-rhamnopyranoside[14] (**6**) the 3-mono-pivaloate **7** is accessible by regioselective acylation with pivaloyl chloride in




**SCHEME 2**



pyridine at low temperature in 70% yield (Scheme 2). The structure of 7 was unambiguously proved by 300 MHz $^1$H NMR spectroscopy. Significant in the spectrum is the one-proton doublet of doublets at δ 4.98 ($J_{2,3}$ = 3.2, $J_{3,4}$ = 9.3 Hz) for 3-H. The low reactivities of the 2- and 4-hydroxyl groups in the *manno*-series can be explained by the sterically unfavorable axial orientation of 2-OH and by the steric hindrance of 4-OH through gauche interactions with the 3-hydroxyl and the 5-methyl group, respectively.[15]

Irradiation of methyl 6-deoxy-3-*O*-pivaloyl-α-L-mannopyranoside (7) in HMPT/$H_2O$ (97:3) for 48 h gave the dideoxy sugar **2**. Whereas in other systems partial ester rearrangements as side reaction lead to isomeric deoxygenated compounds during photodeoxygenation,[12] in the present example no rearrangement product could be detected. Due to its volatility and hydrophilic properties the isolation of **2** from the strongly polar and high boiling reaction mixture without losing too much yield of the desired dideoxy sugar presented a problem. However, workup was simplified by transformation of the crude deoxygenation product into the diacetate **8**, which was easily purified. Deacetylation of compound **8** with sodium methoxide in methanol gave methyl 3,6-dideoxy-α-L-*arabino*-hexopyranoside (**2**) in an overall yield of 59%.

Regioselective esterification with subsequent photochemical deoxygenation shortend the pathway to methyl 3,6-dideoxy-α-L-*arabino*-hexopyranoside (**2**) from **L**-rhamnose to three steps, in comparsion with a conventional synthesis which involved four steps from **L**-rhamnose.[6]

## EXPERIMENTAL

**General Procedures.** Melting points were determined with a Büchi 510 melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. TLC was performed on silica gel 60 $F_{254}$ analytical aluminium plates (Merck) with ethyl acetate, and column chromatography was carried out on silica gel 60 (0.063-0.1 mm, Merck). NMR spectra were recorded with a Varian VXR 300 ($^1$H, 300 MHz; $^{13}$C, 75 MHz) spectrometer, and IR spectra were recorded with a Perkin-Elmer FT 1750 spectrometer.



**Methyl 6-Deoxy-3-O-pivaloyl-α-L-mannopyranoside (7).** To a solution of methyl α-**L**-rhamnopyranoside[14] (**6**, 8.91 g, 50 mmol) in dry pyridine (150 mL, cooled to -20 °C) was added during 30 min, with exclusion of moisture, a solution of pivaloyl chloride (6.63 g, 55 mmol) in dry dichloromethane (25 mL). The resulting reaction mixture was stirred overnight. Dichloromethane and pyridine were distilled off under reduced pressure at room temperature. Dichloromethane (250 mL) was added to the residue, and the solution was washed several times with half-saturated brine. The organic layer was dried ($MgSO_4$), and solvent was evaporated. The remaining solid residue was crystallized from ether-hexane to give 9.21 g (70%) of compound **5** as colorless crystals: mp 124-126 °C, $[\alpha]_D^{21}$ - 63.3° (c 1.04, chloroform); IR (KBr) 1700 and 1200 (ester); $^1$H NMR ($CDCl_3$) δ 1.25 (s, 9H, Me, tBu, OPiv), 1.35 (d, 3H, 5-Me), 2.6 (br s, 1H, 2-OH), 2.74 (br d, 1H, 4-OH), 3.38 (s, 3H, OMe), 3.62 (td, 1H, 4-H, J ≈ 9.5/4.5 Hz), 3.70 (dq, 1H, 5-H), 3.99 (br s, 1H, 2-H), 4.65 (d, 1H, 1-H), 4.98 (dd, 1H, 3-H); $J_{1,2}$ = 1.4, $J_{2,3}$ = 3.2, $J_{3,4}$ = 9.3, $J_{4,4\text{-OH}}$ = 4.6, $J_{4,5}$ = 9.5, $J_{5,6}$ = 6.0 Hz; $^{13}$C NMR ($CDCl_3$) δ 17.55 (C-6), 27.15 (Me, tBu, OPiv), 39.09 ($C_q$, tBu, OPiv), 54.90 (OMe), 68.53, 69.59, 71.40, 74.50 (C-2,-3,-4,-5), 100.58 (C-1), 179.24 ($CO_2$).

Anal. Calcd for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45. Found: C, 55.10; H, 8.62.

**Methyl 3,6-Dideoxy-α-L-*arabino*-hexopyranoside (2).** A solution of **7** (2.62 g, 10 mmol) in HMPT-$H_2O$ (100 mL; 97:3, v/v) was irradiated in a Gräntzel model 400 photoreactor[16] for 48 h whilst a slow stream of nitrogen was bubbled through the mixture. The reaction mixture was concentrated in high vacuo to about three quarters of the original volume. The residue was then acetylated conventionally with dry pyridine (100 mL) and acetic anhydride (50 mL) for 24 h at room temperature. The acetylation mixture was diluted with ether (500 mL) and washed three times with ice-cooled 20% sulfuric acid (first portion half-saturated with brine, the other two portions saturated with brine), saturated sodium bicarbonate and water. The organic solution was dried ($MgSO_4$) and concentrated leaving a yellow syrup (1.6 g) of methyl 2,4-di-*O*-acetyl-3,6-dideoxy-α-**L**-*arabino*-hexopyranoside **8**: $^1$H NMR ($CDCl_3$) δ 1.20 (d, 3H, 5-Me), 1.92 (ddd, 1H, 3a-H), 2.01-2.17 (m, 1H, 3e-H), 2.05, 2.11 (2 s, 6H, OAc), 3.39 (s, 3H, OMe), 3.81 (dq, 1H, 5–H), 4.53 (br s, 1H, 1-H), 4.79 (ddd, 1H, 4-H), 4.90 (ddd, 1H, 2-H); $J_{1,2}$ = 1.5, $J_{2,3a}$ = $J_{2,3e}$ = 3.3, $J_{3a,3e}$ = 13.6, $J_{3a,4}$ = 11.3, $J_{3e,4}$ = 4.8, $J_{4,5}$ = 9.8, $J_{5,6}$ = 6.3 Hz; $^{13}$C NMR ($CDCl_3$) δ 17.65 (C-6), 21.09, 21.14 (OAc), 29.36 (C-3), 54.84 (OMe), 66.35, 69.72, 69.78 (C-2,-4,-5), 97.36 (C-1), 170.02, 170.22 ($CO_2$). The crude diacetate was dissolved in dry methanol (30 mL) and treated with sodium methoxide (0.1 g) for 2 h at ambient temperature. Alkali was neutralized with Amberlite IRC 50, and after filtration solvent was evaporated in vacuo. The colorless syrup crystallized from ether-hexane (1:1) to give 0.96 g (59 %) of compound **2**: mp 85-87 °C (lit.[6] 80-81 °C, lit.[7,8] 82-84 °C; $[\alpha]_D^{23}$ - 101° (c 1.21, water), lit.[6] $[\alpha]_D^{20}$ - 103° (c 1.12, water), lit.[7] $[\alpha]_D^{20}$ - 101° (c 0.8, water), lit.[8] $[\alpha]_D$ - 118.7° (c 0.9, water), lit.[8] $[\alpha]_D$ - 127.7° (c 1, chloroform); $^1$H NMR ($CDCl_3$) δ 1.29 (d, 3H, 5-Me), 1.80 (ddd, 1H, 3a-H), 2.03 (dt, 1H, 3e-H, J= 13.1/3.3 Hz), 3.17 (s, 2H, OH), 3.38 (s, 3H, OMe), 3.56 (dd, 1H, 4-H), 3.60 (dq, 1H, 5-H), 3.86 (dt, 1H, 2-H, J = 3.1/1.6 Hz), 4.47 (br s, 1H, 1-H); $J_{1,2}$ = 1.6, $J_{2,3a}$ = 3.2, $J_{2,3e}$ = 3.3, $J_{3a,3e}$ = 13.2, $J_{3a,4}$ = 10.6, $J_{5,6}$ = 5.8 Hz; $^{13}$C NMR ($CDCl_3$) δ 17.73 (C-6), 35.08 (C-3), 54.78 (OMe), 67.68, 68.41, 69.52 (C-2,-4,-5), 100.06 (C-1).

Anal. Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.94; H, 8.88.

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