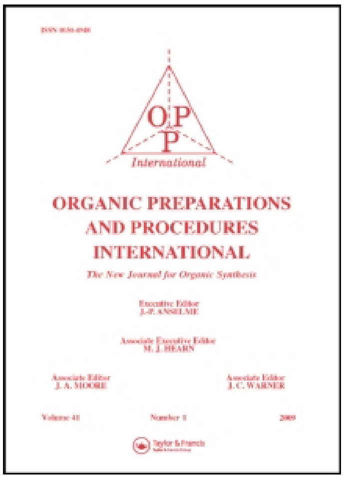

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SYNTHESIS OF 2,3-DIDEOXY-d-*arabino*-HEPTONO-1,4-LACTONE *via* A WITTIG REACTION ON UNPROTECTED d-ARABINOSE

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Anal. Calcd for $C_{15}H_{14}Br_2N_6O_2$: C, 38.32; H, 3.00; N, 17.87. Found: C, 38.50; H, 3.20; N, 17.90

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SYNTHESIS OF 2,3-DIDEOXY-D-*arabino*-HEPTONO-1,4-LACTONE *via* A WITTIG REACTION ON UNPROTECTED D-ARABINOSE

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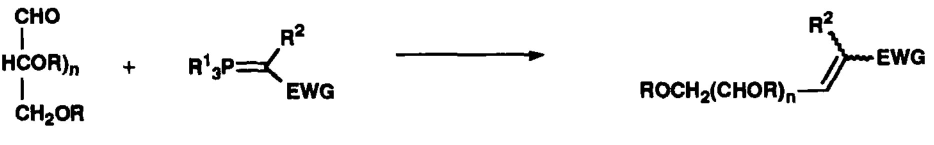
The Wittig reaction using phosphonium ylides stabilized by electron-withdrawing groups (EWG) has proven to be extremely useful for the construction of chain-extended carbohydrates.[1] Suitably protected monosaccharides (**1**) are conveniently lengthened *via* the reaction with phosphonium ylides of generic structure **2.**

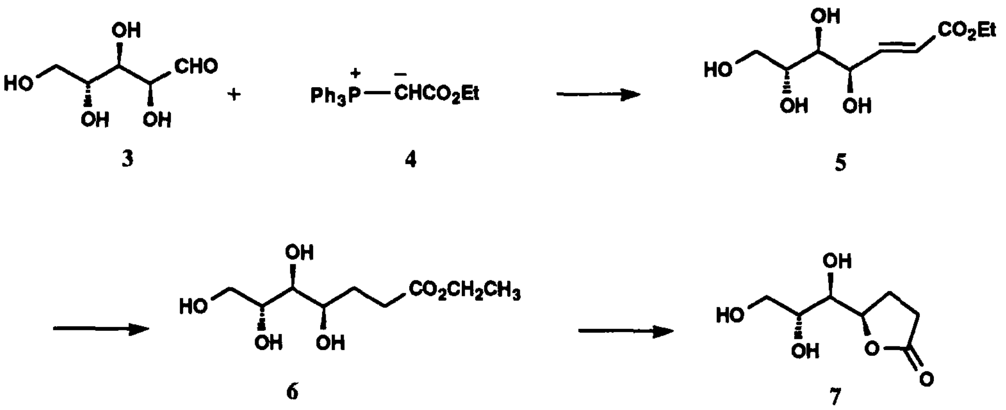
It had been reported by Kochetkov and Dmitriev that completely unprotected monosaccharides also react readily with stabilized phosphoranes, eliminating the normal three-step synthesis of the hydroxyl blocked aldose.[2] This procedure has been used for the synthesis of leukotrienes[3a] and more



1 2

recently for a four-carbon chain extention of D-arabinose.[3b] We needed to prepare D-*arabino*-heptonic acid analogues as potential inhibitors of 3-dehydroquinate synthetase[4] and examined this procedure.

A suspension of D-arabinose (3) in *p*-dioxane was combined with **4** and heated at reflux. The mixture gradually cleared over 2 hrs and **5** was obtained as the only product after recrystalization. NMR analysis indicated that only the *trans*-isomer was obtained ($J_{H}2_{H}3$ = 15.6 Hz).[5] Kochetkov and Dmitriev[2a] used DMF as the solvent, but also obtained a by-product from the reaction which they believed to be a mixture of cyclic lactones. The use of dioxane not only eliminated by-products, but also simplified work-up. This procedure works equally well with other aldoses such as D-ribose and D-glucose.



The reduction of **5** to **6** was accomplished by catalytic hydrogenation over platinum oxide. Saponification of ester **6** followed by neutralization afforded lactone **7** with an overall yield of 57% (from **3**). Compounds **5**, **6** and **7** are versatile intermediates for the synthesis of a variety of 7-carbon *arabino*-carbohydrates.

EXPERIMENTAL SECTION

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Proton and carbon NMR spectra were recorded on a General Electric® QE300 spectrophotometer. Chemical shifts are expressed in parts per million downfield (δ) from internal TMS. Elemental anaylses and optical rotations were performed by the Analytical Services Department of FMC Corporation.

Ethyl E-2,3-Dideoxy-D-*arabino*-hept-2-enonate (5).- A suspension of 17.2 g (0.115 mol) of D-arabinose and 40 g (0.115 mol) of (carbethoxymethylene)triphenylphosphorane in 300 ml of *p*-

dioxane was heated at reflux for 3 hrs. The resulting clear solution was concentrated at reduced pressure to afford a white solid which was triturated in 100 ml of warm 1:1 diethyl ether-petroleum ether. The solid was then collected and recrystallized from 95% ethanol to yield 17 g (67%) of a white solid, mp. 138-139°, lit.[2a] mp. 133-135°, $[\alpha]_D^{25}$ = +15.4 (c = 0.4, MeOH), lit [2a] $[\alpha]_D^{18}$ = +14.5 ; IR (KBr): 1722 (CO_2Et), 1669 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.97 (dd, H-2, $J_{H_2H_3}$=15.6), 6.96 (dd, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (OCH_2CH_3), 59.8 (OCH_2CH_3), 63.5 (C-7), 70.2 (C-6), 71.6 (C-5), 73.3 (C-4), 119.9 (C-3), 151.3 (C-2), 165.9 (C-1).

Anal. Calcd for $C_9H_{16}O_6$: C, 49.09; H, 7.32. Found: C, 49.14; H, 7.05

Ethyl 2,3-Dideoxy-D-*arabino*-heptonoate (6).- A solution of 13.2 g (0.06 mol) of **5** in 200 ml of 75% aqueous ethanol was hydrogenated over 300 mg of PtO_2 at 40 lbs H_2. After the uptake of H_2 ceased, the catalyst was removed by filtration and the clear solution was concentrated at reduced pressure to afford 12.6 g (95%) of a white solid which was recrystallized from 95% ethanol, mp. 103-105°, $[\alpha]_D^{25}$ = +9.0 (c = 0.5, H_2O); IR (KBr): 1722 (CO_2Et) cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2 (OCH_2CH_3), 29.0 (C-3), 30.6 (C-2), 59.7 (OCH_2CH_3), 63.8 (C-7), 68.8 (C-4), 71.7 (C-6), 73.2 (C-5), 173.3 (C-1).

Anal. Calcd for $C_9H_{18}O_6$: C, 48.64; H, 8.16. Found: C, 48.71; H, 7.92

2,3-Dideoxy-D-*arabino*-heptono-1,4-lactone (7).- A solution of 1 g (4.5 mmol) of **7** in 5 ml of water was stirred at 25° as 2.3 ml of 2M sodium hydroxide was added. After stirring for 30 min, the solution was passed through a short column of Dowex®-50W acid ion exchange resin and washed with 50 ml of water. The water was removed under reduced pressure to afford 0.78 g (90%) of a white powder which was recrystallized from 95% ethanol, mp. 107-109°, lit.[5] mp. 111-112°, $[\alpha]_D^{25}$ = -61.1 (c = 0.2, H_2O), lit.[6] $[\alpha]_D^{25}$ = -56.9 (c = 2, H_2O); IR (KBr): 1742 (C=O) cm^{-1}; ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.3 (C-3), 28.4 (C-2), 63.5 (C-7), 71.1 (C-6), 72.5 (C-5), 79.2 (C-4), 177.7 (C-1).

Anal. Calcd for $C_7H_{12}O_5 \cdot H_2O$: C, 43.30; H, 7.26. Found: C, 42.98; H, 6.98

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AN IMPROVED SYNTHESIS OF α-CHLORODIPHENYLACETIC ACID

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(04/03/91)

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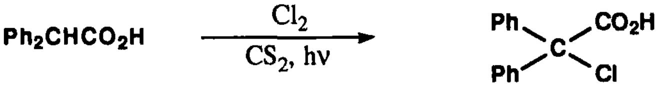
α-Chlorodiphenylacetic acid, an intermediate in the FriedelCrafts synthesis of 9-fluorenecarboxylic acid from trichloroacetic acid and benzene,[1] has also been used in the synthesis of pharmaceuticals such as *Estocin* and *Etpenal.*[2] It has also been prepared from benzilic acid and $POCl_3$ or $SOCl_2$,[3] albeit not in very good yields. This route requires long reaction times (about 24 hrs) and furnishes a mixture of products which is difficult to purify. We now report an improved procedure which involves chlorination of diphenylacetic acid in carbon disulfide, using a 250W mercury lamp as a light source. The yield of α-chlorodiphenylacetic acid is better than those previously reported. The effect of varying the chlorine gas flow rate (range 20-80ml/min),[4] temperature (20-80°, reaction times (0.5 hr to 10 hrs), solvents and light sources has been studied. The best results were obtained at 28-32° with a solution that had been saturated with chlorine.



EXPERIMENTAL SECTION

Melting points were taken with a Mettler FP5 melting point apparatus. Gas chromatographic (GC) analyses were done on a Hewlett Packard 5790 instrument using a 20m SE-52 glass capillary column. The carrier gas was hydrogen at a flow rate of 2 mL/mbn The injector and detector temperatures were maintained at 280° and the program used was 80-280°, 6°/min. Mass spectra were obtained using a Hewlett Packard Model 5987A (CG-MS). Ionization was performed at 70 eV electrons with 300 μA emission current.