TABLE III

Solvent dependence of the hydroxyl proton chemical shift of 3,5-dichlorosalicylaldehyde*

Solvent	Concentration (mole %)	Shift (p.p.m.)†
Cyclohexane	<2.5‡	11.283
Benzene	5.0	11.410
Perfluorobenzene	<5‡	11.264
Carbondisulfide	<5‡	11.234
Chloroform-d_1	5.0	11.333
Methylene chloride	5.0	11.336
Acetone	5.0	11.363
Acetonitrile	<5‡	11.271

*Temperature: 30 °C.
†In p.p.m. to low-field of internal TMS with a precision of 0.005 p.p.m. or better in most instances.
‡Saturated solutions.

Experimental

3,5-Dichlorosalicylaldehyde from Aldrich Chemical Company was used as received and recrystallized from carbon tetrachloride, acetone, and ether. Carbon tetrachloride was redistilled and passed through Linde molecular sieve (4A). Acetone was refluxed with potassium permanganate, distilled, dried over calcium chloride, and redistilled. It was kept over alumina. Solutions in acetone were prepared on a vacuum line, in a dry box, or in air, with or without internal tetramethylsilane. The proton chemical shift did not differ by more than 0.01 p.p.m. in any of the solutions though in one, with which the least precaution had been taken, there was a coupling observable between the hydroxyl and the ring proton. Because of the small effects these precautions had on the measured hydroxyl proton shift, less stringent precautions were taken with the other solutions. They were all degassed.

The ring proton assignments were confirmed by use of mixed solvents of acetone–carbon disulfide and perfluorobenzene – carbon disulfide. This was necessary because the ring proton shifts interchange in some solvents.

Measurements were made on a DA-60-I Varian spectrometer using the frequency sweep mode and calibrations were done by period counting, using tetramethylsilane as the internal reference. The shift positions are thought to be accurate to 0.005 p.p.m. in most instances. Sample temperatures were calibrated using the Varian methanol and ethylene glycol samples. The former were used at low and the latter at high temperatures. Although the absolute temperatures may be in error by 2 °C the relative temperatures appear to be accurate to 0.5 °C.

Infrared spectra were obtained on a Perkin–Elmer 337 grating spectrophotometer. A 0.025 mm cell was used and indene line positions served to calibrate the carboxyl stretching frequencies.

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Synthesis of branched-chain sugars by the Wittig reaction

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The Wittig reaction has been extended to yield a 2,3-dideoxy branched-chain sugar from 2-deoxy-3-ketose **3**. Improvements in the procedures for the preparation of ketose (**3**) are also described.

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Renewed interest in the chemistry of the branched-chain sugars has arisen partly because of their presence in some recently discovered antibiotics (1–3). Most synthetic work in this field has involved the condensation of Grignard reagents or diazomethane with ketoses (3, 4), or the scission of carbohydrate epoxides with organometallic reagents (5). In addition, the epoxides have been cleaved with diethyl malonate carbanion (6). Application of the oxo reaction to

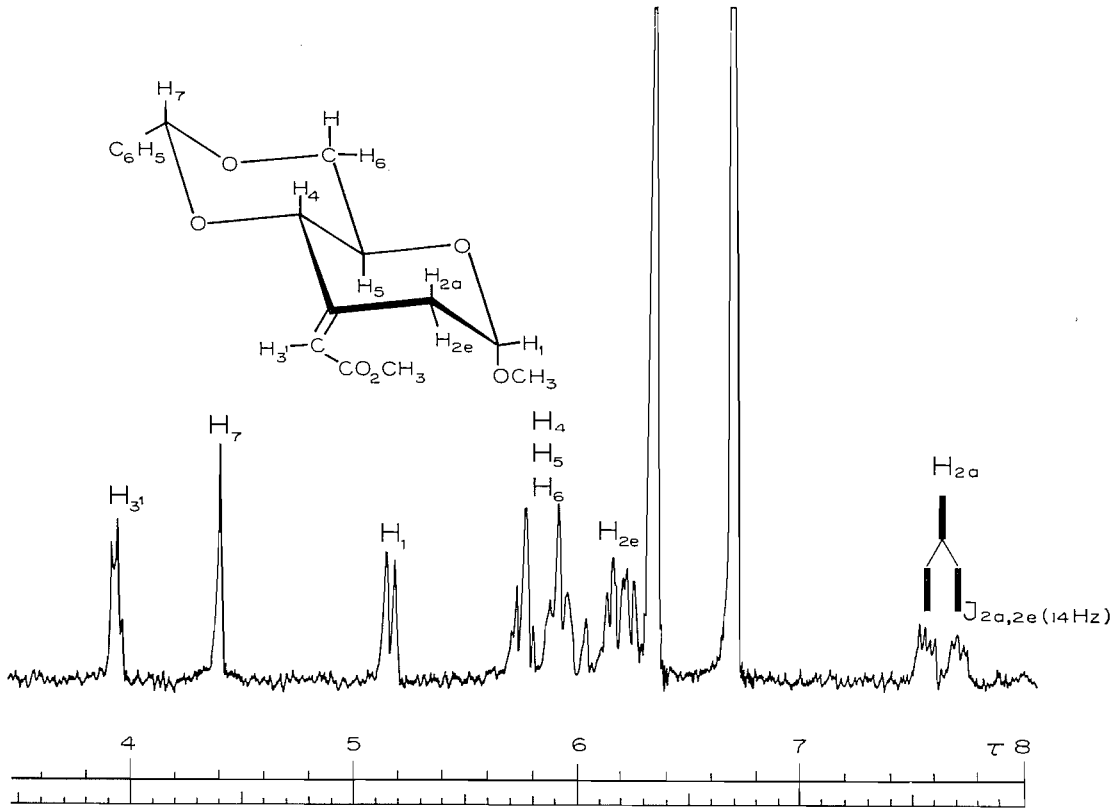


FIG. 1. Partial 100 Mc.p.s. proton magnetic resonance spectrum of methyl 4,6-*O*-benzylidene-3-*C*-(carbomethoxymethylene)-2,3-dideoxy-α-D-*erythro*-hexopyranoside in $CDCl_3$ as solvent.

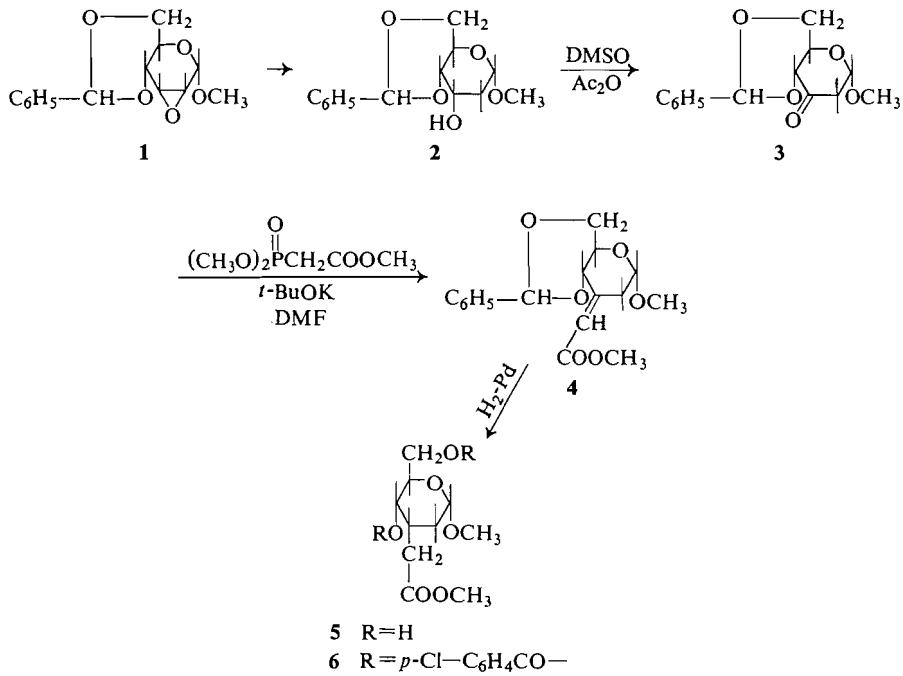
unsaturated carbohydrates has given branched-chain carbohydrates (7). Condensation of Wittig reagents with ketoses has also afforded novel branched-chain sugars (8).

The extension of the Wittig reaction to a 2-deoxy-3-ketose (**3**) to yield a 2,3-dideoxy branched-chain sugar is the subject of this paper. The work described herein is also concerned with improvements in the procedures for the preparation of the ketose (**3**).

Reduction of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (**1**) with lithium aluminium hydride in tetrahydrofuran gave an 88% yield of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside (**2**). Subsequent oxidation of **2** with anhydrous methyl sulfoxide and acetic anhydride afforded methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (**3**) in 90% yield. The ketose (**3**) has been prepared previously in lower yields from **2** using chromium trioxide (9) and ruthenium tetroxide (10) as oxidants.

Reaction of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (**3**) with phosphonoacetic acid trimethyl ester and potassium *t*-butoxide in anhydrous *N*,*N*-dimethyl formamide at room temperature for 20 h according to a procedure previously described (8, 11) resulted in a product (**4**) readily isolated in 76% yield. This product was a virtually pure substance as evidenced by thin-layer chromatography (t.l.c.) and by its proton magnetic resonance (p.m.r.) spectrum. This result was unexpected because Rosenthal and Nguyen (8) have found the condensation of phosphonoacetic acid trimethyl ester to 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose to give both the *cis* and *trans* unsaturated branched-chain sugars.

The structure of the unsaturated sugar **4** was deduced from its p.m.r. spectrum (shown in Fig. 1). The H-1 signal at τ 5.13, which at normal sweep appears as a doublet, was resolved into a quartet at double sweep width. Irradiation of this



1 2 3 4

5 R=H

6 R=*p*-Cl—C_6H_4CO—

signal caused the two multiplets centered at τ 7.7 to collapse to two doublets having J = 14 Hz. Therefore, this high field group of signals is due to one H-2 proton which is coupled with the other H-2 proton and with the H-1 proton. Because there are eight peaks in the signal of the first H-2, it was assumed that this proton was coupled also with the H-3[1] proton in allylic position. Confirmation of this long-range coupling was provided by irradiation of the triplet (on magnified sweep this triplet was resolved into two doublets) at τ 3.9 which also led to a collapse of the eight lines at τ 7.7 to two doublets with the characteristic large geminal coupling (J = 14 Hz), and, in addition, resulted in an alteration of the multiplets of peaks centered at τ 6.2. Therefore, the unsymmetrical triplet at τ 3.9 must be due to H-3[1], and part of the signals at τ 6.2 must arise from the other H-2 proton (believed to be H-2e). Support for the latter assignment can be adduced from the p.m.r. spectrum of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-oximino-α-D-*erythro*-hexopyranoside and its analysis as reported by Baer and Kienzle (12). These authors also found a large downfield shift of H-2e with respect to H-2a. The large downfield shift of H-2e of **4** is attributed to the strong deshielding effect of the carbomethoxymethylene group on C-3. Therefore, compound **4** is probably *trans* methyl 4,6-*O*-benzylidene-3-*C*-(carbomethoxymethylene)-2,3-dideoxy-α-D-*erythro*-hexopyranoside.

Hydrogenation of the unsaturated product (**4**) using palladium on charcoal as catalyst gave the reduced (and debenzylidated) product (**5**) which could not be crystallized. Because of overlapping of the H-2, H-3, and H-3[1] signals (in the τ 7.0 to 8.3 region), the signals of the methine hydrogen (H-3) could not be used to deduce the structure of compound **5**. Furthermore, there was also overlapping of the H-4 and H-5 peaks. As a consequence, compound **5** was converted into its *p*-chlorobenzoate ester derivative (**6**). It is known that benzoate ester groups markedly shift the signals of secondary hydrogens downfield, often below the signal of the anomeric hydrogen (13). The p.m.r. spectrum of the benzoate derivative (**6**), shown in Fig. 2, is readily analyzed and can be used to deduce the structure of the branched-chain sugar (**6**). As expected, there is a quartet at τ 4.7 downfield from the H-1 signal (at τ 5.25). Irradiation of the multiplet of peaks at τ 7.3 resulted in the collapse of the quartet at τ 4.7 to a doublet. Because high field signals are generally attributed to hydrogen atoms attached to carbon atoms which have no

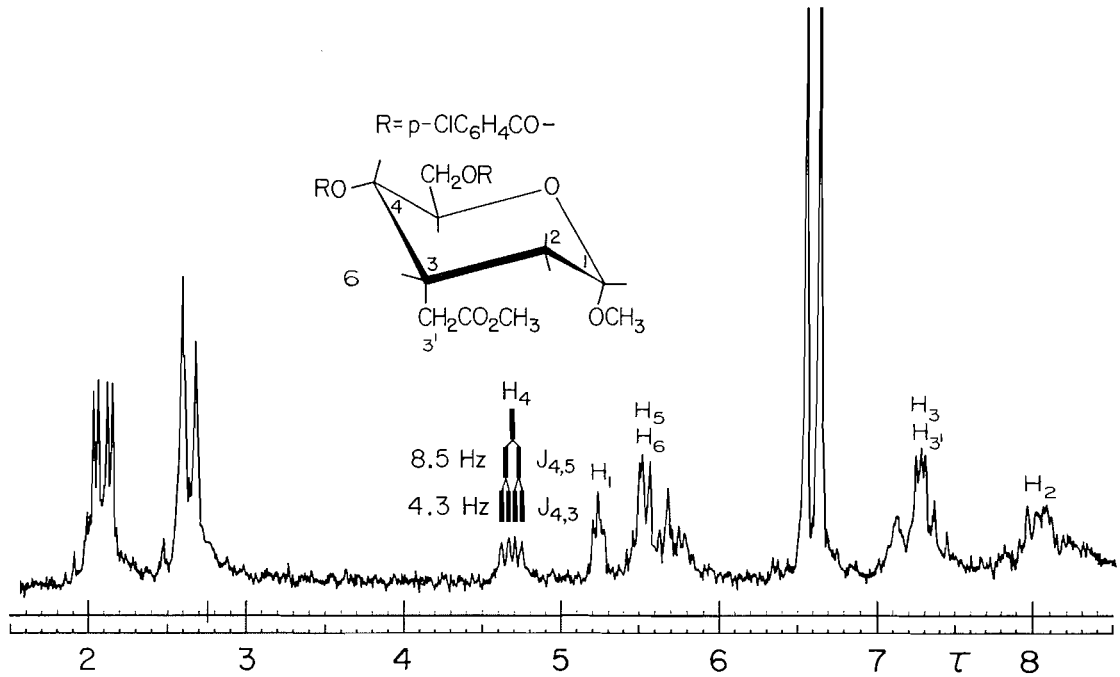


FIG. 2. The 100 Mc.p.s. proton magnetic resonance spectrum of methyl 3-*C*-(carbomethoxymethyl)-4,6-di-*O*-*p*-chlorobenzoyl-2,3-dideoxy-α-D-*ribo*-hexopyranoside in $CDCl_3$ as solvent.

oxygen atoms attached to them (13), it can be assumed that some of the peaks at τ 7.3 are due to H-3 and therefore the quartet at τ 4.7 is due to H-4. As shown in Fig. 2, the two coupling constants of the H-4 proton are 8.5 and 4.3 Hz. The larger of these must arise from the coupling of the H-4 and H-5 protons because both of these are in axial orientations. Therefore, the smaller coupling constant (J = 4.3 Hz) must be attributed to coupling between H-4 (in axial orientation) and H-3 which must be in an equatorial orientation. From this assignment it follows that the branched-chain group on C-3 must be in an axial orientation, and, therefore, compound **6** is undoubtedly methyl 3-*C*-(carbomethoxymethyl)-4,6-di-*O*-*p*-chlorobenzoyl-2,3-dideoxy-α-D-*ribo*-hexopyranoside.

Experimental

All spectra were measured with a Varian Associates 100 MHz HA spectrometer with deuteriochloroform as a solvent and tetramethylsilane as the internal standard set at τ = 10. Thin-layer chromatography was performed on silica gel G plates using benzene–methanol (97:3) as developer. The optical rotations were measured in 1 dm tubes at the D-line of sodium and room temperature (23–24°). The melting points were determined on a microstage and are uncorrected. The microanalyses were carried out by the University of British Columbia Microanalytical Laboratory.

Methyl 4,6-O-Benzylidene-2-deoxy-α-D-ribo-hexopyranoside (2)

Compound **2** was prepared using a modification of the procedure of Prins (14). To a solution of 2.5 g of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside in 70 ml of anhydrous tetrahydrofuran were added 2 g of lithium aluminium hydride (in 5 portions) over a period of ten min. After the reaction mixture was refluxed for 5 h, the excess of lithium aluminium hydride was decomposed by dropwise addition of water. The solids were removed by filtration and washed with 200 ml of chloroform. The combined filtrate was washed twice with water (100 ml), dried with magnesium sulfate, and evaporated under reduced pressure to give a solid, yield 2.25 g (88%), which on recrystallization from ethyl acetate gave pure **2**; m.p. 125–127° (lit. (14), m.p. 118–120°).

Preparation of Methyl 4,6-O-Benzylidene-2-deoxy-α-D-erythro-hexopyranosid-3-ulose (3)

To a solution of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside (1.85 g) in anhydrous methyl sulfoxide (50 ml) was added anhydrous acetic anhydride (20 ml) and the resulting solution was kept at room temperature for 60 h. This solution was then mixed with a saturated aqueous solution of sodium bicarbonate. The precipitate which formed was removed by filtration, washed well with water, and air-dried, yield 1.65 g (90%).

The product was recrystallized from ethyl acetate, m.p. 174–176° (lit. (10), m.p. 176–178°). The phenylhydrazone derivative of **3** was prepared in the usual way, m.p. 177–178° (lit. (10), m.p. 176–177°).

Application of Wittig Reaction to 3 to Yield trans-Methyl 4,6-O-Benzylidene-3-C-(carbomethoxymethylene)-2,3-dideoxy-α-D-erythro-hexopyranoside (4)

An ice-cold solution of phosphonoacetic acid trimethyl ester (1.2 ml) and potassium *t*-butoxide (0.30 g) in anhydrous *N,N*-dimethyl formamide (2 ml) was added to a magnetically stirred solution (kept at 0°) of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (0.5 g) in 6 ml of anhydrous *N,N*-dimethyl formamide. The mixture was stirred at room temperature for 20 h and was then poured into ice-water. The precipitate was removed by filtration, washed with water, and air-dried, yield 0.45 g, m.p. 124–126°. One recrystallization of the solid from ethyl acetate – light petroleum ether (b.p. 30–60°) afforded 0.38 g of product **4** (76%), m.p. 128–129°; $[\alpha]_D^{22}$ +213° (*c*, 2 in chloroform). Infrared spectrum: ν_{max} (Nujol) 1720 cm^{-1} (ester C=O) and 1660 (C=C). The proton magnetic resonance (p.m.r.) spectrum of **4** is shown in Fig. 1.

Anal. Calcd. for $C_{17}H_{20}O_6$: C, 63.75; H, 6.25. Found: C, 63.79; H, 6.09.

Methyl 3-C-(Carbomethoxymethyl)-2,3-dideoxy-α-D-ribo-hexopyranoside (5) and its p-Chlorobenzoate Derivative (6)

Compound **4** (0.20 g) dissolved in ethanol (40 ml), was allowed to react with hydrogen at room temperature and 1 atm pressure using 10% palladium on charcoal (0.3 g) as catalyst until the gas pressure remained constant. Work-up of the product (**5**) in the usual way gave an oil, yield 0.145 g (99%); $[\alpha]_D^{22}$ +130° (*c*, 3 in ethanol). Infrared spectrum: ν_{max} 3350 cm^{-1} (OH), 1720 (C=O). Nuclear magnetic resonance spectrum: overlapping multiplets at τ 7–8.4 equal to 5 hydrogens; multiplets centered at τ 7.32, 7.53, and 8.18, due to H-3, H-3^1, and H-2; triplet at τ 5.35 attributed to H-1; and two singlets, each equal to 3 H's at τ 6.35 and 6.70.

An amount of 0.035 g of compound **5** was allowed to react with *p*-chlorobenzoyl chloride (0.2 g) dissolved in pyridine (2 ml) at room temperature for 20 h followed by heating at about 80° for 1 h. The reaction mixture was poured into ice-water, extracted several times with chloroform, and the combined chloroform extracts washed with sodium bicarbonate and water, and then dried over magnesium sulfate. After the solvent was removed by evaporation under reduced pressure, the solid residue was recrystallized several times from ethanol (several recrystallizations or a chromatographic separation were necessary to remove the *p*-chlorobenzoic acid anhydride which accompanies the ester derivative), m.p. 104–105°, $[\alpha]_D^{22}$ +65° (*c*, 1 in chloroform). The p.m.r. spectrum of **6** is shown in Fig. 2.

Anal. Calcd. for $C_{24}H_{24}O_8Cl_2$: C, 56.36; H, 4.69. Found: C, 56.35; H, 4.70.

Acknowledgments

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