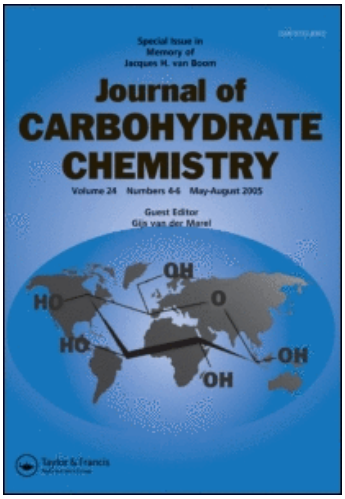

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ROUTES FROM "TRIACETYL GLUCAL"

To 6-DEOXY-HEX-2-ENOPYRANOSIDES

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ABSTRACT

Four routes from "triacetyl glucal" to methyl 2,3-dideoxy-α-D-erythro-hex-2-enopyranoside have been examined. The timing and procedure for the 6-deoxygenation step, which can be carried out before or after a Ferrier rearrangement, is of crucial importance to the yield and "ease" of the process. The preferred procedure with respect to yield (62% overall), ease, and efficiency involves (i) a Ferrier rearrangement, (ii) deacetylation, (iii) selective sulfonylation, and (iv) lithium aluminum hydride reduction.

INTRODUCTION

During the past eight years we have used 6-deoxyhex-2-enopyranosides of the D configuration in a number of our synthetic projects and, although we[1] and others[2] have previously described routes to these compounds, we have been constantly exploring methods that would make them readily available for (a) pilot and exploratory studies and/or (b) multistep syntheses. Objectives (a) and (b) are not always compatible. In this report, we describe a number of routes that have been examined, and express our preference for route (d).

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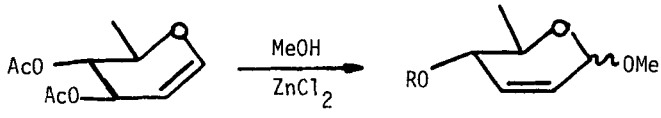
SCHEME 1



1 75% 2 (α/β=4:1)

a R=Ac
b R=H

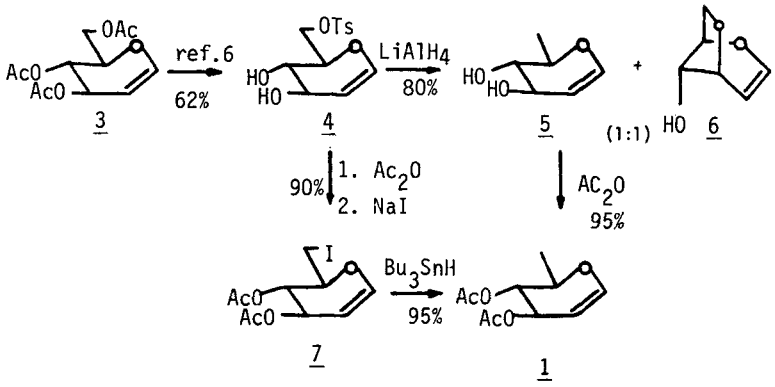
The experience gained in our earlier studies,[1] coupled with the commercial availability of "triacetyl glucal" (3)# caused us to base our recent studies upon this material. The Ferrier rearrangement[3] of 3, 4-di-O-acetyl-D-rhamnal[4] (1) outlined in Scheme 1, had been applied to the L-antipode with ethanol by Paulsen and Koebernick[5] and so an efficient route to 1 from 3 seemed all that was required. Our first efforts were therefore directed toward this objective.

(a) Compound 3 was deacetylated and selectively sulfonylated to give 4, as described previously by Brimacombe et al.[6] Treatment of 4 with lithium aluminum hydride (LAH) in refluxing THF gave a 1:1 mixture of two compounds, which were separated by column chromatography. The more polar product was identified as 5 by acetylation to 1 and comparison of the physical constants with the literature value for its enantiomer.[7] The faster-moving product was shown to be the known[6] 3,6-anhydro sugar 6.

In order to minimize formation of 6, the sulfonate 4 was acetylated and subjected to iodinolysis. Reduction of the resulting iodide 7 with tri-n-butyltin hydride went smoothly to give diacetate 1 from 3, via 4 and 7, in five steps, with a 51% overall yield.

The 80 MHZ ^{1}H NMR spectrum of 1 revealed interesting information about its conformation, since H3 was coupled to H4, H5, H2 and H1, the

SCHEME 2

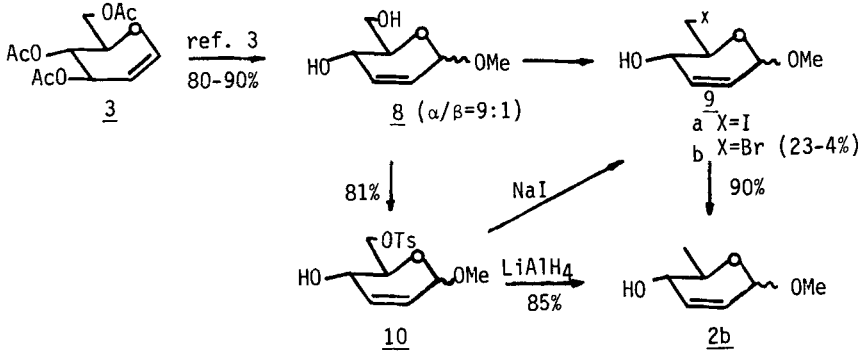


#3,4,6-Tri-O-acetyl-1,5-anhydro-2-deoxy-D-arabino-hex-1-enitol (3,4,6-Tri-O-acetyl-D-glucal).

value $J_{3,5}$=6Hz suggesting a W type relationship between H3 and H5.

In the course of these studies it was found that the use of zinc chloride in place of boron trifluoride etherate[3] for the Ferrier rearrangement of 1 gave a more readily controlled reaction. Although the product 2 (Scheme 1) appeared to be homogeneous on TLC, the 60 MHz

SCHEME 3

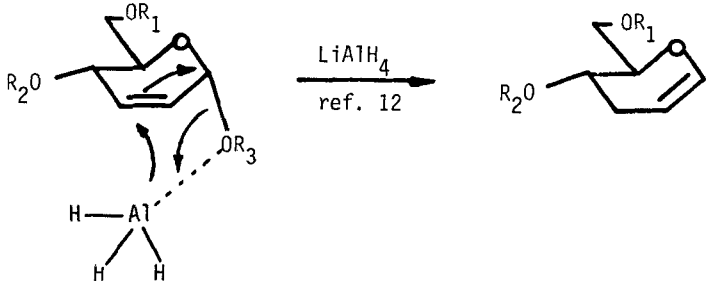


^{1}H NMR spectrum showed it to be a 4:1 mixture of α and β anomers judging from the parameters reported by Achmatowicz and co-workers for the racemic modifications.[8]

b) The diol 8 would appear to be an ideal precursor for 2b since it is obtainable in 80-90% yield from 3,[3] and the α/β ratio of 8 is 9:1 (Scheme 3) instead of 4:1 as in 2 (Scheme 1). Following our previous work,[1] 8 was converted into sulfonate 10 (Scheme 3), and thence into iodide 9a. The deactivated Raney nickel deiodination of 9a used earlier[1] was found to be reliable only on a comparatively small scale (<5 grams); hence tri-n-butyltin hydride was used, from which the yield of 2a was 90%.

c) In order to circumvent the sulfonylation step giving 10, we sought to brominate 8 directly. Using N-bromosuccinimide and triphenyl-

SCHEME 4



phosphine[9] for this task was expected to be problematic in view of the possibility of attack at the allylic sites, and the threat of acid-catalyzed rearrangements[10] brought about by traces of hydrobromic acid. It was found that these side reactions could be avoided by inclusion of one equivalent of pyridine;[11] however, on a 60 gram scale,

the 6-bromo-6-deoxy sugar 9b was isolated in only 23.4 percent yield which on reduction with tri n-butyltin hydride afforded 2b.

d) The "simplest" route from diol 8 to 2b would be by lithium aluminum hydride reduction of sulfonate 10; however, we were initially dissuaded from even attempting such a reaction because sulfonates such as 10 are comparatively unreactive, the reductive displacement requiring forcing conditions - as exemplified in the reaction of 4 (Scheme 2). Under comparable conditions, 10 would be expected to undergo the reductive rearrangement depicted in Scheme 4, which was discovered in this laboratory some years ago.[12]

To our complete surprise and gratification, treatment of the sulfonate 10 with lithium aluminum hydride overnight at room temperature afforded 2b in excellent yield, with no trace of the corresponding 3-deoxyglycal.[12]

Compound 2b can thereby be prepared in 62% yield from "triacetyl glucal" in four steps involving (i) Ferrier rearrangement, (ii) deacetylation to give 8, (iii) selective sulfonylation to 10, and (iv) lithium aluminum hydride redction.

EXPERIMENTAL

General Procedures. Melting points were determined on a Fischer-Johns heating stage or a Mel-Temp apparatus and are uncorrected. The ^{1}H NMR spectra were determined, unless otherwise stated, in deuteriochloroform containing 1% tetramethylsilane as internal standard with either a Varian T-60, a Brucker WP-80 or a Varian HA 100 spectrometer. Coupling constants were obtained by measuring spacings of spectra judged to be first-order.

Thin layer chromatography (TLC) was performed on glass plates coated with silica gel (HF-254, E. Merck) to a thickness of 0.3 mm. The chromatograms were first viewed under ultraviolet light, then exposed to iodine vapaor, and finally sprayed with concentrated sulfuric acid. Heating in an oven was required for complete visualisation. For column chromatography, Silica Gel (E. Merck 0.05-0.20 mm, 70-325 mesh A.S.T.M.) was used.

3,4-Di-O-acetyl-1,5-anhydro-2,6-dideoxy-D-arabino-hex-1-enitol (D-rhamnal diacetate) (1). (a) A solution of the sulfonate 4[6] (3.0 g, 10.0 mmol) in dry THF (100 mL) was cooled to 0° and to this was added lithium aluminum hydride (0.38 g, 10.0 mmol). The reaction mixture was allowed to warm up to room temperature and then heated to reflux for 8h, after which it was cooled. The excess reagent was destroyed by addition of hydrated sodium sulfate. The mixture was filtered through a pad of Celite and dried over sodium sulfate. Evaporation of the solvent gave 5 and 6[6] as a 1:1 mixture (1.04 g, 80%) which was fractionated on a column of silica gel by eluting with 10% methanol in chloroform. Compound 5, upon acetylation with acetic anhydride and pyridine, gave 1, identical with that described in (b).

(b) The sulfonate 4[6] was acetylated (Ac_2O/pyridine) in the usual way. A portion of the product (5.76 g, 15.0 mmol) in methyl isobutyl ketone (100 mL) was refluxed with sodium iodide (6.75 g, 45.0 mmol) for 6h. The solvent was then evaporated and the residue was dissolved in diethyl ether (150 mL), washed with a saturated solution of sodium thiosulfate and water, and then dried over sodium sulfate. Evaporation gave syrupy 7 (4.60 g, 90%) which exhibited the following characteristics: $[\alpha]_D^{20}$ -97.9° (c 1.8, $CHCl_3$); ^1H NMR (80

MHz) δ 2.03 (s, 3, OCOCH$_3$), 2.07 (s, 3, OCOCH$_3$), 3.40 (m, 2, H-6, H-6'), 4.1 (m, 1, H-5), 5.00-5.40 (m, 2, H-3, H-4), 4.85 (dd, 1, $J_{2,3}$ = 2.0 Hz, H-2), 6.51 (dd, 1, $J_{1,2}$ = 6.0 Hz, H-1); HRMS Calculated for $C_{10}H_{13}O_5I$: 339.98067; found: 339.97821.

A solution of the compound 7[1] (5.10 g, 15.0 mmol) in dry benzene (50 mL) was refluxed with tri-n-butyltin hydride (6.60 g, 22.5 mmol) and a catalytic amount of benzoyl peroxide for 3h. The solvent was then evaporated, and the residue was dissolved in acetonitrile and washed with petroleum ether. Evaporation of the acetonitrile layer gave 1 (3.0 g, 95%) as a syrup. Compound 1 exhibited the following characteristics: $[\alpha]^{20}_D$ -76.4° (c 0.28, $CHCl_3$); ^1H NMR (60 MHz) δ 1.30 (d, 3, J=6.0 Hz, CH$_3$), 4.18 (m, 1, H-5), 4.80 (dd, 1, $J_{1,2}$ = 6.0 Hz, $J_{2,3}$ = 3.0 Hz, H-2), 5.15 (dd, 1, $J_{4,5}$ = 6.0 Hz, H-4), 5.35 (dddd, 1, $J_{3,4}$ = 8.0 Hz, $J_{3,5}$ = 6.0 Hz, H-3), 6.45 (dd, 1, $J_{1,3}$ = 1.4 Hz, H-1); HRMS Calculated for $C_{10}H_{14}O_5$: 214.0841; found: 214.0828.

Methyl 2,3,6-Trideoxy-α-D-erythro-hex-2-enopyranoside (2b). (a) 3,4-Di-O-acetyl-1,5-anhydro-2,6-dideoxy-D-arabino-hex-1-enit-ol (1) (D-rhamnal diacetate) (13.8 g, 0.064 mol) was dissolved in methylene chloride (120 mL) and dry methanol (6 mL) and freshly fused anhydrous zinc chloride (4.7 g) were added. After 30 min, the solution turned black and, after an additional 20 min, TLC (10% ethyl acetate in benzene) indicated consumption of the starting material. The solution was poured into saturated sodium bicarbonate solution (100 mL), and the organic phase was separated and washed with water. Drying ($MgSO_4$) and usual processing afforded a mobile oil, which was chromatographed over silica gel (200 g) using benzene/ethyl acetate (9:1) as eluent. The yield of 2a was 9.0 g (75%)

and the α,β ratio of 4:1 was evident from the 60 MHz specturm as described in the literature.[18] Thus for 2a-α the CH_3 doublet is at 1.3 ppm and OAc at 2.15 ppm. For 2a-β the corresponding signals are at 1.4 and 2.05 ppm, respectively.

(b) The diol 8 obtained in the prescribed manner[3] from "triacetyl glucal" (30 g) was dissolved in a mixture of pyridine (50 mL) and methylene chloride (100 mL) and cooled to 0°. p-Toluenesulfonyl chloride (26 g) was added in one portion, and stirring at 0° was maintained for 2h. After standing overnight at room temperature, the product, 10, was recovered in the usual way[1] and dried in vacuo (46 g, 81% yield). A portion of the product (3.8 g, 10.1 mmol) was refluxed with sodium iodide (3.2 g, 2 mmol) in 2-butanone (100 mL) in the presence of pyridine (0.25 mL, 30 mmol) for 8h. The product 9a was isolated in the usual way and identified by comparison with the previously described ethyl glycoside.[1] Reduction with tri-n-butyltin hydride, carried out as described above (7 → 1), gave 2b in 91% yield.

(c) Methyl 2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (8[3]) (58.8 g, 0.368 mol) was dissolved in dry N, N-dimethylformamide (130 mL) under an argon atmosphere. Dry pyridine (7.8 mL) and N-bromosuccinimide (66.3 g, 0.373 mol) were added, and the solution was cooled in a carbon tetrachloride/dry ice bath (~-24°). Triphenylphosphine (98.8 g, 0.377 mol) in dimethylformamide (120 mL) was added dropwise over a 4h period, while maintaining cooling. The mixture was then allowed to warm up to room temperature, and poured into 4:1 water/ether mixture (800 mL). The ether layer was washed and dried (Na_2SO_4) and the

syrup recovered therefrom was redissolved in ether (600 mL) and left in the refrigerator for two days. The triphenylphosphine oxide crystals (18.9 g) which deposited were collected. The syrup from the mother liquors was chromatographed over silica gel using ethyl acetate/petroleum ether (1:4) and the bromide 9b (19.2 g, 23.4%) was isolated as an oil. (For purposes of identification, bromide 9b was treated with sodium iodide in acetone in the usual way.[10] The product was identical to the previously described iodide 9b[1]).

Bromide 9b (11.0 g, 0.85 mol) in benzene (300 mL) was refluxed with tri-n-butyltin hydride (74 g, 0.21 mol) and benzoyl peroxide (50 mg) for 6h. Silica gel chromatography using ethyl acetate-petroleum ether (1:4) mixture afforded 2b (9.9 g, 80.7%).

The overall yield of 2b by the route 3 → 8 → 9b → 2b was 12-15 percent.

(d) In the fourth route, sulfonate 10 (46 g) prepared in (b) was dissolved in tetrahydrofuran (100 mL), and the solution was added dropwise over 0.5h to a slurry of lithium aluminum hydride (10 g) in tetrahydrofuran (150 mL) at 0^{o}. After 2h at 0^{o}, the mixture was allowed to stand at room temperature for 2h, after which it was again cooled to 0^{o}. Redistilled diethyl ether (1L) was added slowly and water (10 mL), 15% sodium hydroxide solution (10 mL) and water (20 mL)were added slowly in succession. After stirring at room temperature for 2h, the mixture was filtered, the solvent removed, and the residue dissolved in methylene chloride and dried (Na_2SO_4). Usual recovery gave an oil which was chromatographed on a silica column using methylene chloride/diethyl ether (4:1) to afford 2b, 9.9 g (62% from 3).

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