Synthesis of Macrolide Antibiotics. II.[1] Stereoselective Synthesis of Methyl 4,6-O-Benzylidene-2-deoxy-2-C,3-O-dimethyl-α-D-glucopyranoside. Stereochemistry of Hydrogenation of the C-2 Methylene Group of Methyl 4,6-O-Benzylidene-2-deoxy-2-C-methylene-3-O-methyl-α- and -β-D-*arabino*-hexopyranoside

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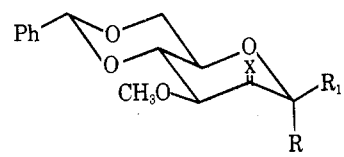
Methyl 4,6-O-benzylidene-2-deoxy-2-C,3-O-dimethyl-α-D-glucopyranoside (13) was stereoselectively synthesized by catalytic hydrogenation of methyl 4,6-O-benzylidene-2-deoxy-2-C-methylene-3-O-methyl-α-D-*arabino*-hexopyranoside (9) using W-8 Raney nickel as the catalyst and isooctane as the solvent. 2-Deoxy-2-C-methylene unsaturated sugar 9 (and its β anomer 10) was obtained by treating methyl 4,6-O-benzylidene-3-O-methyl-α-D-*arabino*-hexopyranosid-2-ulose (1) (or its β anomer 2) with triphenylmethylenephosphorane in toluene at 95°. The optimal reaction conditions for the reaction of triphenylmethylenephosphorane and 1 were investigated. The dependence of the stereochemistry of catalytic hydrogenation of unsaturated 2-deoxy-2-C-methylene hexopyranosides upon the anomeric configuration, the nature of the catalyst, and the solvent has been studied.

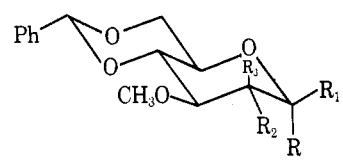
In a previous publication[2] we have reported that sodium borohydride reduction of the C-2 keto group of a methyl D-*arabino*-hexopyranosid-2-ulose derivative is highly stereoselective and strongly depends upon the anomeric configuration of the 2-ulose: the α anomer (1) yielded the corresponding D-gluco derivative (3) as the only product, whereas the β anomer (2) gave a 19:1 mixture of the D-manno (4) and D-gluco (3) derivatives. It has also been observed that the catalytic hydrogenation of methyl β-D-*arabino*-hexopyranosid-2-ulose (5)[3] and its 3,4,6-tri-O-benzyl derivative 6[4] is also highly stereoselective, giving methyl β-D-mannopyranosides 7 and 8 as the predominant products (the manno to gluco ratio was 19:1 in both cases).

In an attempt to stereoselectively synthesize methyl 4,6-O-benzylidene-2-deoxy-2-C,3-O-dimethyl-α-D-glucopyranoside (13), an intermediate in the stereoselective synthesis of erythronolides A and B, wherein the C-2 carbon will correspond to the C-2 and/or C-10 carbon of erythronolides A and B, we have undertaken a study on whether the torsional strain and/or nonbonding steric interactions between the C-1 methoxy group and the catalyst in the transition state or its vicinity can be utilized to control the stereochemistry of catalytic hydrogenation of the C-2 methylene group of methyl 4,6-O-benzylidene-2-deoxy-2-C-methylene-3-O-methyl-α-D-*arabino*-hexopyranoside (9). Such interactions have been recently postulated as a possible explanation for the high stereoselectivity observed in the addition reactions to the C-4[1] or the C-2[2] carbonyl carbon atom, as well as for the reactivity of the C-2 methyl sulfonate toward the nucleophilic displacement.[5]

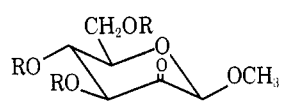
The synthesis of methyl 4,6-O-benzylidene-2-deoxy-2-C-methylene-3-O-methyl-α-D-*arabino*-hexopyranoside (9) from methyl 4,6-O-benzylidene-3-O-methyl-α-D-*arabino*-hexopyranosid-2-ulose (1) and triphenylmethylenephosphorane[5] was investigated first. In refluxing ether the reaction of 1 with triphenylmethylenephosphorane gave after 15 hr two products: 2-deoxy-2-C-methylene sugar derivative 9 in ca. 25% yield and the elimination product methyl 4-deoxy-3-O-methyl-α-D-*glycero*-hex-3-enopyranosid-2-ulose (11)[7] in ca. 10% yield. The starting material 1 has also been recovered from the reaction mixture (26%). When dimethyl sulfoxide was used as the solvent, the yield of 2-deoxy-2-C-methylene sugar 9 decreased to 17%, whereas the yield of the elimination product 11 increased to 58%, irrespective of the reaction temperature. No starting material could be, however, isolated from the reaction mixture. The increase in the formation of the unsaturated sugar 11 with the increase of the polarity of the solvent used (ϵ_{ether} 4.335 and ϵ_{Me_2SO} 46.68) indicated that in very polar solvents (e.g., dimethyl sulfoxide) the rate of deprotonation at the C-3 carbon of 1 followed by β-elimination of the 4,6-O-benzylidene group[8] is a considerably faster reaction than the addition of triphenylmethylenephosphorane to the C-2



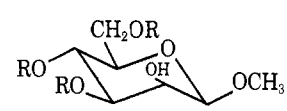
1, R = CH_3O; R_1 = H; X = O
2, R = H; R_1 = CH_3O; X = O
9, R = CH_3O; R_1 = H; X = CH_2
10, R = H; R_1 = CH_3O; X = CH_2



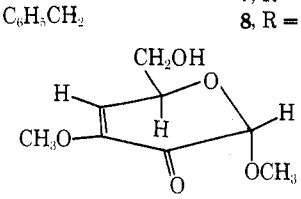
3, R = CH_3O; R_1 = R_3 = H; R_2 = OH
4, R = R_2 = H; R_1 = CH_3O; R_3 = OH
12, R = R_2 = H; R_1 = CH_3O; R_3 = CH_3
13, R = CH_3O; R_1 = R_3 = H; R_2 = CH_3
14, R = CH_3O; R_1 = R_2 = H; R_3 = CH_3



5, R = H
6, R = $C_6H_5CH_2$



7, R = H
8, R = $C_6H_5CH_2$



11

carbonyl carbon of **1**. It has been therefore concluded that the deprotonation at the C-3 carbon of **1** should be considerably slower in solvents less polar than either (e.g., toluene, ϵ 2.379) and that the β-elimination of the 4,6-*O*-benzylidene group to give **11** should be greatly impeded in such solvents. Indeed, when methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (**1**) was treated at room temperature with triphenylmethylenephosphorane in a toluene solution for 17 hr, 2-deoxy-2-*C*-methylene sugar **9** was isolated in 74% yield. Since the addition of triphenylmethylenephosphorane to the C-2 carbonyl carbon was evidently the rate-limiting step of the Wittig reaction,[6b] we raised the reaction temperature with intention to avoid prolonged contact of **1** with a base (triphenylmethylenephosphorane) which may result in deprotonation of the C-3 carbon and β-elimination of the 4,6-*O*-benzylidene group. Thus by treating **1** with triphenylmethylenephosphorane at 95° not only was the reaction time shortened (the reaction was over in 20 min), but the yield of **9** was increased as well (85%).

Whereas the catalytic hydrogenation of methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methylene-3-*O*-methyl-β-D-*arabino*-hexopyranoside (**10**) proceeded stereoselectively giving the corresponding 2-deoxy-2-*C*-methyl-D-mannopyranoside **12** as the only reaction product (84%), the stereoselectivity of the catalytic hydrogenation of methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methylene-3-*O*-methyl-α-D-*arabino*-hexopyranoside (**9**) was, contrary to expectations, not very high and depended upon the nature of the catalyst and the solvent used (Table I). Raney nickel and nonpolar solvents favored the formation of the 2-deoxy-2-*C*-methyl-D-gluco derivative **13** (the gluco to manno ratio was 2.9:1), whereas platinum and polar solvents favored the formation of the 2-deoxy-2-*C*-methyl-D-manno derivative **14** (the gluco to manno ratio was 1:3.1). When glacial acetic acid (containing 5% acetic anhydride) was used as the solvent, the overall yield of **13** and **14** was considerably lower (86% with 10% Pt/C and 66% with 10% Pd/C) probably owing to the extensive debenzylidenation. Similarly, large amounts of catalyst (e.g., expt 13) apparently also facilitate debenzylidenation. It is interesting to note that methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*,3-*O*-dimethyl-α-D-mannopyranoside (**14**) is more susceptible to debenzylidenation than **13**, which would explain the fact that the **13**:**14** ratio was higher than expected in expt 1, 2, and 13.

Experimental Section

General. The silica gel used for all column chromatography was M. Woelm (Eschwege, Germany) silica gel, particle size <0.063 mm. The melting points are uncorrected. Optical rotations were determined with a Cary 60 spectropolarimeter in a 1.0-cm cell. The ir spectra were recorded with a Perkin-Elmer infrared spectrophotometer, Model 267. The uv spectra were recorded with a Cary 15 uv–visible spectrophotometer. The proton NMR spectra were recorded with a Varian T-60 spectrometer using tetramethylsilane as an internal standard. The chemical shifts (δ) are expressed in parts per million (ppm). The carbon-13 NMR spectra of compounds **12**, **13**, and **14** were reported elsewhere.[10]

All Wittig reactions were performed in a nitrogen atmosphere using three-necked round-bottom flasks equipped with rubber stopples and a reflux condenser. All solutions were introduced in the reaction flask via syringe. The stirring was effected with a magnetic stirrer.

Reaction of Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (1) with Triphenylmethylenephosphorane in Ether. To a suspension of methyltriphenylphosphonium bromide (179 mg, 0.5 mmol) in absolute ether (20 ml) a 2 *M* hexane solution of *n*-butyllithium (0.25 ml, 0.5 mmol) was added and the reaction mixture was stirred at room temperature for 4 hr. An ethereal solution (10 ml) of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (**1**, 162 mg, 0.55 mmol) was then added and the reaction mixture was heated at reflux for 15 hr. The precipitate was filtered off and washed with several portions of benzene and the combined filtrate was evaporated in vacuo. The oily residue (370 mg) was chromatographed on silica gel (18 g). Elution with 3:1 hexane–acetone gave four fractions. The most polar and the only chromatographically pure fraction (10 mg, 9.6%) was the elimination product **11** whereas the other three fractions, being impure, were rechromatographed. By chromatography of the first fraction (49 mg) on silica gel (5 g) using 9:1 benzene–ethyl acetate as eluent pure **9** (40 mg, 24.8%) was obtained, whereas chromatography of the second fraction (38 mg) on silica gel (4 g) using 4:1 benzene–ethyl acetate gave pure starting material **1** (32 mg, 19.7%). Finally, the chromatography of the third fraction (34 mg) on silica gel gave an additional amount of starting material (4.5 mg), raising thus the total amount of recovered **1** to 26.2% (42.5 mg). The other two fractions (12 and 7 mg) except for the fact that they did have the 4,6-*O*-benzylidene group (according to their NMR spectra) were not further investigated.

Reaction of Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (1) with Triphenylmethylenephosphorane in Dimethyl Sulfoxide. To sodium hydride (21 mg of 57% oil suspension) washed with several portions of hexane, dry and freshly distilled dimethyl sulfoxide (6 ml) was added and the suspension was heated at 75–80° for 45 min, whereby a pale greenish solution was obtained. The solution was then cooled to room temperature, methyltriphenylphosphonium bromide (179 mg, 0.5 mmol) was added, and the obtained solution, after stirring at room temperature for 10 min, was heated to 55–60°. Methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (167 mg, 0.57 mmol) in dimethyl sulfoxide (6 ml) was added and the reaction mixture was kept at 55–60° for 7 hr, at which time the starting material was completely consumed (monitored by TLC). The dimethyl sulfoxide was then removed in vacuo and the residue was chromatographed on silica gel (12 g). Elution with 1:1 benzene–ethyl acetate gave two fractions. The first fraction (29 mg, 17%) was pure methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methylene-3-*O*-methyl-α-D-*arabino*-hexopyranoside (**9**), whereas the second fraction (62 mg, 58%) was pure methyl 4-deoxy-3-*O*-methyl-α-D-*glycero*-hex-3-enopyranosid-2-ulose (**11**). The analytical sample of **11** was obtained by recrystallization from acetone–hexane: needles, mp 96–96.5°; NMR ($CDCl_3$) δ 5.83 (d, $J_{4,5}$ = 2.0 Hz, 1, H-4), 4.87 (s, 1, H-1), 4.79 (m, $J_{4,5}$ = 2.0, $J_{5,6}$ = 5.0 Hz, 1, H-5), 3.81 (broad d, $J_{5,6}$ = 5.0 Hz, 2, H-6 and H′-6), 3.63 and 3.53 (two s, 6, methyl from C-1 and C-3 methoxy groups).

Anal. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43. Found: C, 51.19, H. 6.41.

Reaction of Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (1) with Triphenylmethylenephosphorane in Toluene at Room Temperature. To a stirred suspension of methyltriphenylphosphonium bromide (714 mg, 2 mmol) in dry toluene (20 ml) a 2 *M* hexane solution of *n*-butyllithium (1 ml, 2 mmol) was added. After the reaction mixture was stirred at room temperature for 30 min, a toluene solution (10 ml) of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (**1**, 294 mg, 1 mmol) was added and stirring at room temperature was continued for another 17 hr. The reaction mixture was then filtered through a layer of Celite, the precipitate was washed with several portions of benzene, and the filtrate was evaporated in vacuo. The crystalline residue (625 mg) was chromatographed on silica gel (180 g). Elution with 95:5 benzene–ethyl acetate gave pure **9** (217 mg, 74%).

Reaction of Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (1) with Triphenylmethylenephosphorane in Toluene at 95°. To a stirred suspension of methyltriphenylphosphonium bromide (7.14 g, 20 mmol) in dry toluene (150 ml) a 2 *M* hexane solution of *n*-butyllithium (10 ml, 20 mmol) was added, and the reaction mixture was stirred at room temperature for 15 min. The temperature was then raised to 95° and a toluene solution (30 ml) of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (**1**, 2.940 g, 10 mmol) was added during 2 min. The reaction mixture was stirred at 95° for another 5 min, the heating bath was removed, and stirring was continued for another 15 min. Acetone was then added dropwise until the yellow color of the reaction mixture disappeared, indicating that the excess of triphenylmethylenephosphorane was destroyed and the stirring was continued for 30 min. The suspension was filtered through a layer of Celite, the precipitate was washed with several portions of benzene, and the combined filtrate was evaporated in vacuo. The yellow crystalline residue was chromatographed on silica gel (50 g). Elution with 95:5 benzene–ethyl ace-

Table I
Catalytic Hydrogenation of Methyl 4,6-O-Benzylidene-2-deoxy-2-C-methylene-3-O-methyl-α-D-*arabino*-hexopyranoside (9)

Expt	Solvent	Catalyst	Substrate/catalyst ratio	13, %	14, %	13/14 ratio	Total yield, %
1	CH_3COOH + 5% Ac_2O	10% Pt/C	3:1	25.2	60.9	0.4	86.1
2	CH_3COOH + 5% Ac_2O	10% Pd/C	3:1	36.4	29.8	1.2	66.2
3	2:1 dioxane–water	10% Pt/C	3:1	23.8	74.1	0.3	97.9
4	2:1 dioxane–water	10% Pd/C	3:1	47.0	50.3	0.9	97.3
5	2:1 dioxane–water	Raney Ni (W-1)	~3:1	62.2	36.4	1.7	98.6
6	Dioxane	Raney Ni (W-8)	~3:1	55.6	43.0	1.3	98.6
7	Toluene	10% Pt/C	3:1	41.0	59.0	0.7	100.0
8	Toluene	10% Pd/C	3:1	62.2	37.7	1.6	99.9
9	Toluene	Raney Ni (W-1)	~3:1	66.2	32.4	2.0	98.6
10	Toluene	10% Pd/C	30:1	55.6	43.0	1.3	98.6
11	Toluene	10% Pd/C	1:1.7	59.6	38.4	1.5	98.0
12	Toluene	Raney Ni (W-8)	1:1.2	70.8	29.1	2.4	99.9
13	Toluene	Raney Ni (W-8)	1:5	68.8	22.5	3.0	91.3
14	Isooctane	Raney Ni (W-8)	1:1.2	73.5	25.2	2.9	98.7

tate gave pure methyl 4,6-O-benzylidene-2-deoxy-2-C-methylene-3-O-methyl-α-D-*arabino*-hexopyranoside (**9**, 2.500 g, 85%). An analytical sample was obtained by recrystallization from acetone–isopropyl ether as needles: mp 151–151.5°; $[\alpha]^{27}D$ +57° (*c* 1.0, $CHCl_3$); NMR ($CDCl_3$) δ 7.6–7.2 (m, 5, phenyl), 5.55 (s, 1, methine H from benzylidene group), 5.37 and 5.18 (two m, $J_{gem} \sim 2$ Hz, 2, olefinic protons from the C-2 methylene group), 5.01 (s, 1, H-1), 4.43–3.63 (m, 5, H-3, H-4, H-5, H-6, H′-6), 3.59 and 3.37 (two s, 6, methyl from C-1 and C-3 methoxy groups).

Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.97; H, 7.05.

Methyl 4,6-O-Benzylidene-2-deoxy-2-C-methylene-3-O-methyl-β-D-*arabino*-hexopyranoside (10). To a suspension of methyltriphenylphosphonium bromide (357 mg, 1 mmol) in absolute toluene (20 ml) a 2 *M* solution of *n*-butyllithium in hexane (0.5 ml, 1 mmol) was added and the mixture was stirred at room temperature for 5 hr. A toluene solution (20 ml) of methyl 4,6-O-benzylidene-3-O-methyl-β-D-*arabino*-hexopyranosid-2-ulose (**2**, 293 mg, 1 mmol) was then added, and the reaction mixture was stirred for 1 hr at room temperature and then at 70° for 4 hr. The precipitate was filtered off and washed with two 20-ml portions of benzene and the combined filtrate was evaporated in vacuo. The residue (351 mg) was chromatographed on silica gel (17 g). Elution with 7:1 benzene–ethyl acetate gave pure crystalline **10** (172 mg, 59%). An analytical sample was obtained by recrystallization from acetone–isopropyl ether: mp 156°; $[\alpha]^{27}D$ − 100° (*c* 0.9, $CHCl_3$); NMR ($CDCl_3$) δ 7.6–7.3 (m, 5, phenyl), 5.55 (s, 1, methine H from benzylidene group), 5.50 and 5.43 (two d, J_{gem} = 2.0 Hz, 2, olefinic protons from C-2 methylene group), 4.80 (broad s, 1, H-1), 3.58 and 3.55 (two s, 6, methyl from C-1 and C-3 methoxy groups).

Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.91; H, 6.90.

Catalytic Hydrogenation of Methyl 4,6-O-Benzylidene-2-deoxy-2-C-methylene-3-O-methyl-α-D-*arabino*-hexopyranoside (9). A solution (20 ml) of **9** (150 mg, 0.5 mmol) in various solvents was hydrogenated at atmospheric pressure and room temperature using different catalysts (see Table I). The hydrogenation was interrupted when the consumption of hydrogen ceased. The catalyst was then filtered off and washed with several portions of the solvent which was used for the particular hydrogenation, and the combined filtrate was evaporated in vacuo. The residue was chromatographed on silica gel (the silica gel:substance ratio was always 200:1) using 98:2 benzene–ethyl acetate as eluent. Those fractions which were mixture of C-2 epimers **13** and **14** were rechromatographed on silica gel using again 200:1 silica gel to substance ratio and 98:2 benzene–ethyl acetate as eluent. The results are given in Table I.

An analytical sample of **13** was obtained by recrystallization from *n*-hexane: mp 97°; $[\alpha]^{27}D$ +125° (*c* 0.94, $CHCl_3$); NMR ($CDCl_3$) δ 7.6–7.2 (m, 5, phenyl), 5.58 (s, 1, methine H from benzylidene group), 4.56 (d, $J_{1,2}$ = 3.6 Hz, 1, H-1), 4.4–3.2 (m, 5, H-3, H-4, H-5, H-6, H′-6), 3.57 and 3.32 (two s, 6 methyl from C-1 and C-3 methoxy groups), 2.1–1.5 (m, 1, H-2), 1.05 (d, *J* = 6.0 Hz, 3, C-2 methyl group).

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.47; H, 7.54.

Pure 2-deoxy-2-methyl manno derivative **14** was an oil: $[\alpha]^{27}D$ +57° (*c* 0.43, $CHCl_3$); NMR ($CDCl_3$) δ 7.6–7.2 (m, 5, phenyl), 5.55 (s, 1, methine H from benzylidene group), 4.53 (broad s, 1, H-1), 4.3–3.5 (m, 5, H-3, H-4, H-5, H-6, H′-6), 3.38 and 3.30 (two s, 6, methyl from C-1 and C-3 methoxy groups), 2.7–2.2 (m, 1, H-2), 1.05 (d, *J* = 6.6 Hz, 3, C-2 methyl group).

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.36; H, 7.49.

Hydrogenation of Methyl 4,6-O-Benzylidene-2-deoxy-2-C-methylene-3-O-methyl-β-D-*arabino*-hexopyranoside (10). An ethyl acetate solution (10 ml) of **10** (177 mg, 0.6 mmol) containing 10% Pt/C as the catalyst (40 mg) was hydrogenated at 0° and atmospheric pressure. After 15 min the consumption of hydrogen ceased and the hydrogenation was interrupted. The catalyst was filtered off and washed with several portions of ethyl acetate, and the combined filtrate was evaporated in vacuo. The residue (172 mg) was chromatographed on silica gel (35 g). Elution with 9:1 benzene–ethyl acetate gave pure **12** as an amorphous solid (150 mg, 84%): $[\alpha]^{27}D$ −60° (*c* 1.12, $CHCl_3$); NMR ($CDCl_3$) δ 7.6–7.2 (m, 5, phenyl), 5.53 (s, 1, methine H from benzylidene group), 4.46 (d, $J_{1,2}$ = 2.2 Hz, 1, H-1), 3.47 and 3.40 (two s, 6, methyl from C-1 and C-3 methoxy groups), ca. 2.45 (m, 1, H-2), 1.00 (d, *J* = 6.8 Hz, 3, C-2 methyl group).

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.46; H, 7.50.

Registry No.—**1**, 29774-59-2; **2**, 29774-60-5; **9**, 56614-98-3; **10**, 56614-99-4; **11**, 56615-00-0; **12**, 53011-02-2; **13**, 53011-00-0; **14**, 53011-01-1; methyltriphenylphosphonium bromide, 1779-49-3.

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