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1,5-ANHYDRO-4,6-*O*-BENZYLIDENE-1,2,3-TRIDEOXY-3-*C*-METHYLENE-D-*erythro*-HEX-1-ENITOL: SIX SYNTHETIC ROUTES*†

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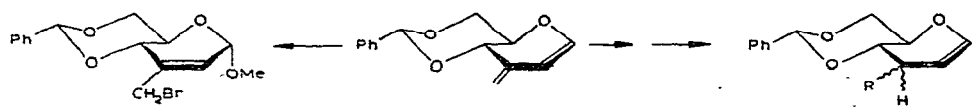
ABSTRACT

Six synthetic routes to the title compound, the conjugated diene **1**, have been developed. Many of the intermediates encountered in these routes are interesting in their own right, being highly functionalised and amenable to structural manipulation. The two best routes begin with methyl α-D-glucopyranoside and give the diene in four and seven steps, in 31 and 24% yields, respectively. For haste the former is better, but for economy and large scale-operation the latter is preferred.

INTRODUCTION

An earlier communication from this laboratory[1] reported 1,5-anhydro-4,6-*O*-benzylidene-1,2,3-trideoxy-3-*C*-methylene-D-*erythro*-hex-1-enitol, (**1**). As part of the proof of structure, the diene was methoxybrominated, and it was found that the α-D-anomer **2** was formed exclusively. This stereoselectivity was subsequently found



2 **1** **3**

R = alkyl

to be general for all alcohols, and was utilized in a synthesis of sucrose[3], thereby opening a new approach to the synthesis of α-disaccharides.

In other work in this laboratory, compounds derived from **1** were used extensively for synthetic and mechanistic studies in developing routes to such 3-deoxy-

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†For preliminary accounts of this work, see refs. 1 and 2.

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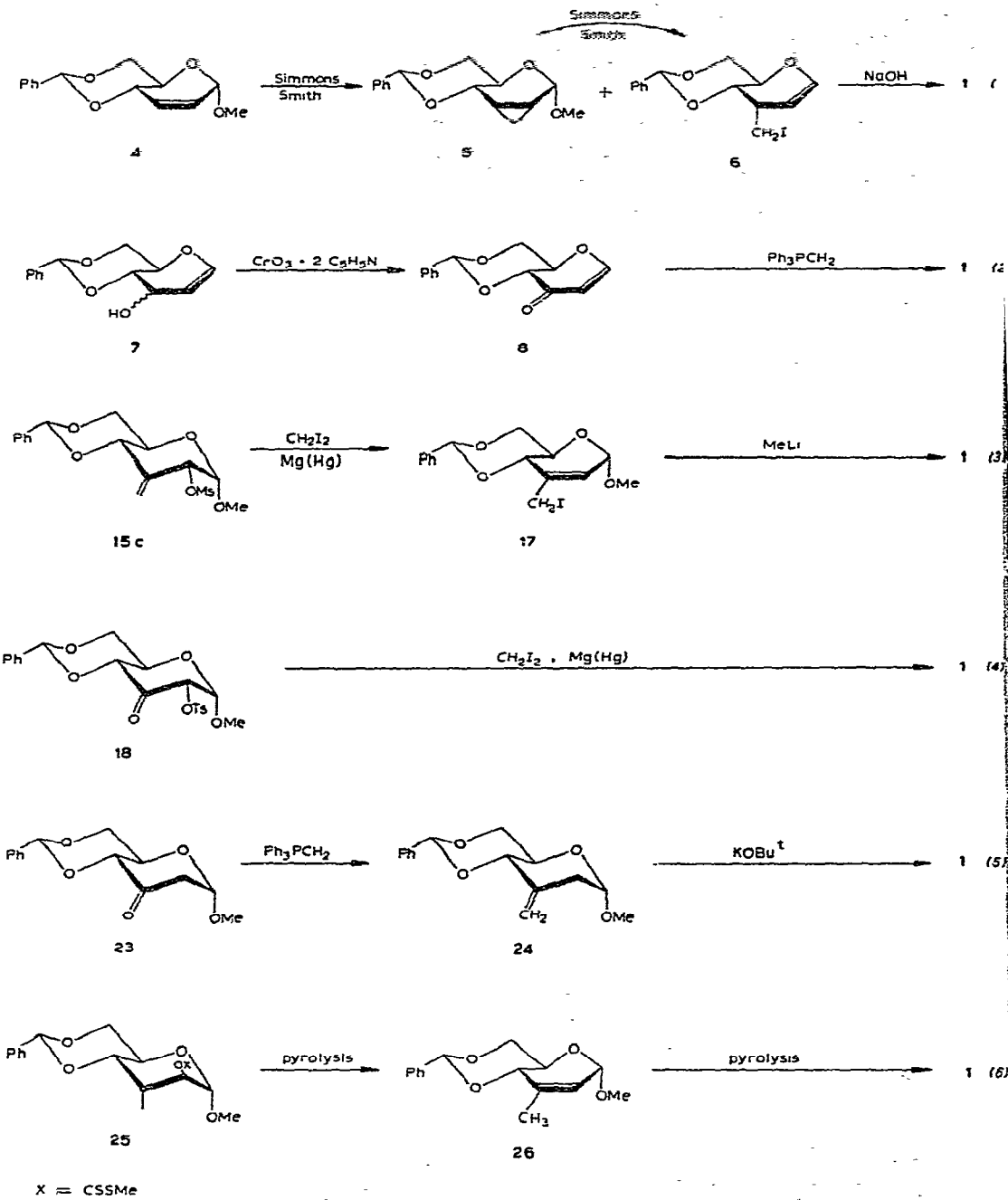

Simmons
Smith
Ph
OMe
4
5
6
CH2I
NaOH
CrO3 • 2 C5H5N
HO
7
8
Ph3PCH2
CH2I2
Mg(Hg)
OMs
15c
17
MeLi
OTs
18
23
24
KOBu t
CH2
25
pyrolysis
OX
X = CSSMe
26
CH3

Scheme 1.

glycals[4] as **3**. Availability of the latter compounds permitted the synthesis of certain important sugars of antibiotics[5], and provided simple access to specifically labelled 2-deoxynucleosides[6].

In view of the foregoing, diene **1** is a potentially useful synthetic intermediate. However, the initial route [eq. (*1*), Scheme 1] was handicapped by the low yield[7] of **6** in the Simmons–Smith reaction of **4**. Efforts to develop more attractive routes were therefore undertaken[2] and this paper gives a full account of these investigations.

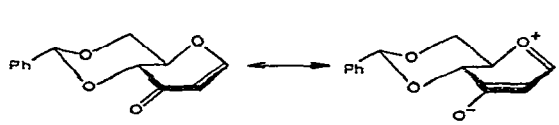
DISCUSSION

Our approaches may be categorised as follows: (*A*) introduction of the glycal double-bond first and the exocyclic double-bond subsequently; (*B*) the reverse of *A*; and (*C*) construction of both double-bonds simultaneously.

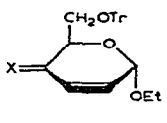
Approach (*A*). — (*a*) In investigating the occurrence of compound **6** in the original example[7a], it was found that the cyclopropyl glycoside **5** undergoes iodinolysis in the Simmons–Smith medium giving **6** in yields[7b] of up to 85%. Dehydroiodination of **6** with sodium hydroxide in 1,4-dioxane–water afforded[7b] a 97.4% yield of **1**.

(*b*) The conceptually simple approach of eq. (**2**) (Scheme 1) was appealing because hex-1-enopyran-3-uloses (**8**) are well known compounds[9], rapid routes to which have recently been developed in our laboratory[10].

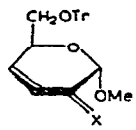
Unfortunately, the Wittig reaction of **8** afforded **1** in only ~10% yield, presumably because **8** is a vinylogous lactone, and lactones do not undergo the Wittig reaction[11]. The contributing form **9** apparently delocalises the positive charge from



8 **9**



10 X = O
12 X = CH_2



11 X = O
13 X = CH_2

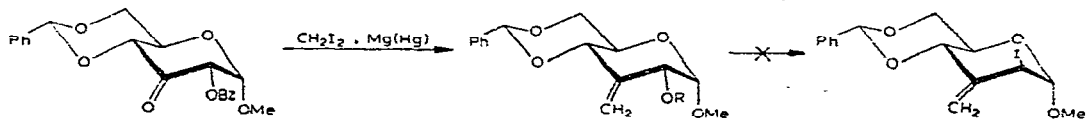
C-3, where it is required for the Wittig reaction to succeed[11]. Accordingly, such enones as **10** and **11**, where the ring-oxygen atom is in the δ-position, give methylene adducts **12** and **13**, respectively, in yields of 60% or greater[12].

The possibility of adding one carbon via 1,2-addition of a methyl group to **8** may be rejected, as these compounds react with organometallic reagents mainly by 1,4-addition[13].

Approach (*B*). — (*a*) The plan conceived in connection with approach (*B*) envisaged the intermediacy of the iodide **16**, which would undergo loss of the elements of methyl hypoiodite by reductive elimination. As far as the exocyclic methylene group is concerned, an ideal progenitor would be methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose (**14**), which may be prepared in large quantity by the method of Carey and Hodgson[14]. However, attempts to convert **14**

into **15** by the Wittig reaction afforded a complex mixture. This result is not unprecedented, as the corresponding 2-benzamido-2-deoxy analogue behaves similarly[15].

Accordingly the Cainelli methylenation procedure[16] was tried. The reaction of **14** with methylene iodide and magnesium amalgam in ether–benzene proved highly successful, giving the desired alkene **15a** and the debenzoylated material (**15b**) as the only products. As the latter compound was desired for the succeeding reaction, the total crude product was generally de-esterified and sulfonylated to give **15c**.



14 **15** **16**

a R = Bz
b R = H
c R = Ms
d R = Ts

It then remained to displace the 2-sulfonate group by iodide, a type of reaction that is usually very difficult in normal pyranosides[17]. However we were encouraged by previous experience showing that the activating influence of an endocyclic, allylic, double bond overcame this resistance[18]. Nevertheless, no reaction was observed with sodium iodide in acetone, butanone, dimethyl sulfoxide, or hexamethylphosphoric triamide.

Fortunately, lithium iodide in refluxing ether led to reaction, although the product of allylic displacement (**17**), was obtained instead of **16**. Identification of **17** was readily made because spectra of the bromine analogue **2** were available in our laboratory[1].

Loss of methyl hypoiodite from **17** was now a 1,4-process rather than the 1,2-elimination envisaged for **16**. Treatment of **17** with a 5-molar excess of methyllithium afforded the diene **1** in 85% yield.

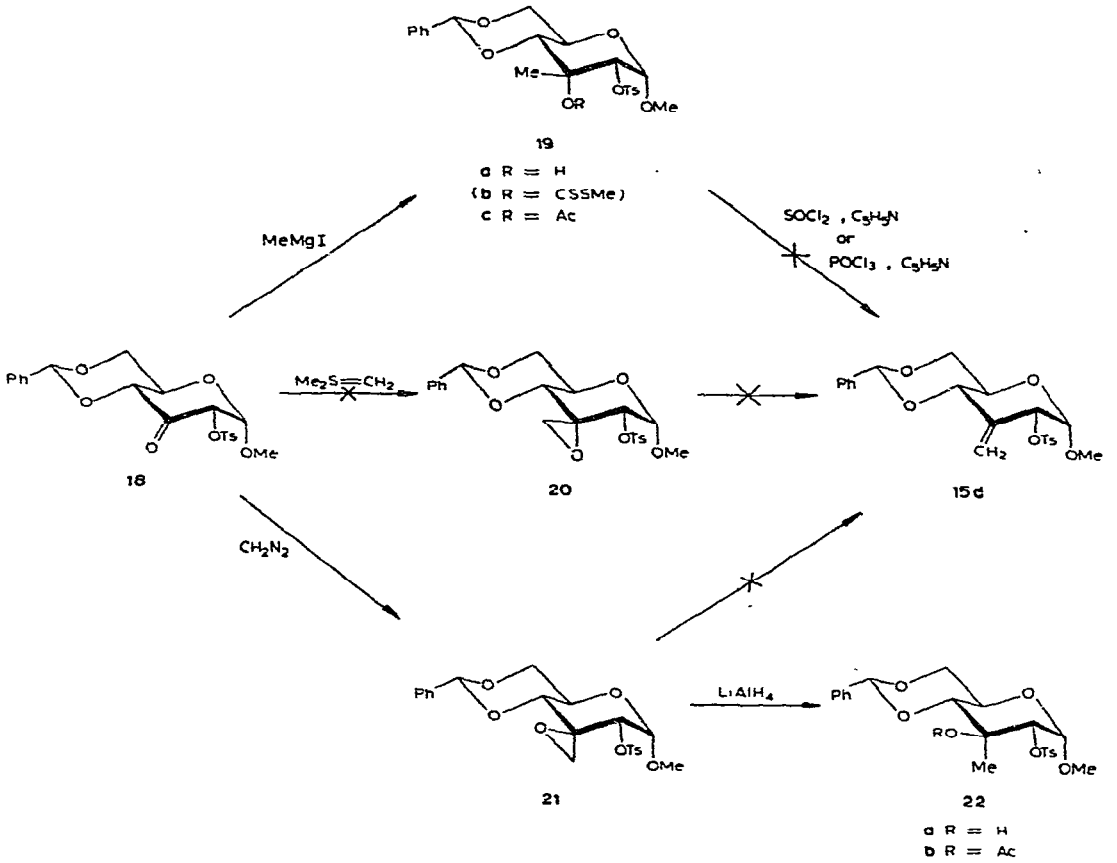
(*b*) The foregoing sequence **14**→**15a**→**15b**→**15c**→**17**→**1** could be conducted without purification of intermediates (all of which were crystalline) in an overall yield of 35%. In order to telescope the three steps **15a**→**15b**→**15c**, it was decided to use the sulfonate **18** as starting material[19]. The latter is readily obtained from the corresponding alcohol, whose large-scale preparation was reported recently from this laboratory[20].

Exposure to the Cainelli reagents converted the ketone **18** directly into **1**. The yields were variable (22–50%, see later), and chromatography was necessary to remove contaminants, one of which was the iodide **17**. It seems, therefore, that a sequence similar to that in eq. (*3*) (Scheme 1) was taking place. Evidently, after methylenation of **18**, the iodide ion generated *in situ* displaced the allylic sulfonate to give **17**, and the organomagnesium reagent (such as ICH_2MgI) was sufficiently basic to bring about the 1,4-elimination.

In spite of the successes of the processes in equations (*3*) and (*4*), procedures

involving the Cainelli reaction were seriously handicapped because the hazards of working with large amounts of mercury meant that only milligram quantities of starting ketones could be used. Efforts to improve the ratios by using highly active magnesium[21] were unavailing. Furthermore, several precautions (see Experimental) had to be observed in order to obtain a high-quality amalgam.

In view of these drawbacks, some effort was expended towards achieving indirect methylenation of **18** (Scheme 2). Attempts to dehydrate the tertiary alcohol[22] **19a** by conventional procedures caused decomposition. The xanthate ester **19b**, could not be prepared in order to try the Chugaev reaction[23].



Scheme 2.

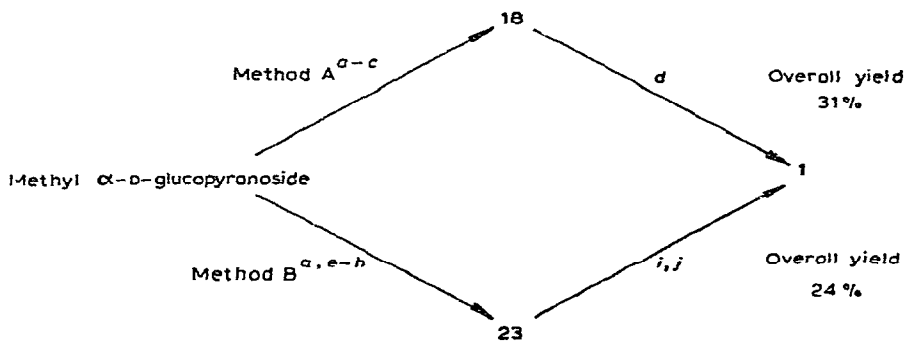
The alternative sequence **18→20→15d** was modeled after the results of Jordaan and Smedley[24]. However ketone **18** was completely decomposed by dimethylsulfonium methylide. As a result, **18** was treated with diazomethane affording **21** as a foam in 97% yield. However **21** could not be converted into **15d** by the model procedure[22].

The *gluco* configuration of **21** was established by reduction to the alcohol **22a**, the acetate of which (**22b**) was compared (n.m.r.) with **19c**. In accordance with the expected trend[25], the axial acetate in **19c** resonated at 1.98 p.p.m., whereas that in **22b** resonated at 1.83 p.p.m.

(*c*) The lability of the sulfonate **18** to base has already been noted by Szarek and coworkers[26], and this factor undoubtedly adds to the steric effects in affecting the Wittig reaction. Accordingly, the 2-deoxyketone **23** was examined and was found to give the methylene adduct **24** in 60% yield [eq. (*5*), Scheme 1]. The most satisfactory means for *β*-elimination of methanol proved to be potassium *tert*-butoxide in refluxing diethyl ether. Methyllithium was equally effective, but was more expensive. Sodium methoxide in a variety of solvents was without effect.

Approach (*C*). — (*a*) One method for the simultaneous formation of both double bonds was in fact already developed [Approach B, (a)] in connection with the conversion of **17**→**1**.

(*b*) Alternatively, in developing the synthesis of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-methyl-α-D-*erythro*-hex-2-enopyranoside (**26**), by pyrolysis of the xanthate ester **25**, it was found that prolonged heating caused[27] the formation of **1**. The best yield of **1** from **25** was 25%. However the difficulties in preparing the precursors render this route [eq. (*6*) Scheme 1] unacceptable.



[a] Benzylidination[28]. [b] Selective tosylation[20]. [c] Me_2SO, P_2O_5. [d] CH_2I_2, Mg(Hg)[16]. [e] Mesylation[29]. [f] Sodium methoxide[29]. [g] $LiAlH_4$. [h] Me_2SO, Ac_2O. [i] Ph_3PCH_2. [j] KOBu^t.

Scheme 3.

In conclusion, of the six routes indicated in Scheme 1, those involving **18** (method *A*) and **23** (method *B*) are the best (Scheme 3). The former gives marginally better yields and is considerably shorter. However the simplicity of operations, cost of reagents, and large-scale capability make method *B* the preferred route.

EXPERIMENTAL

General methods. — Melting points were determined on a Fisher–Johns heating stage or a Mel-Temp apparatus, and are uncorrected. The p.m.r. spectra were determined (unless otherwise stated) for solutions in chloroform-*d* containing 1% of tetramethylsilane as the internal standard, with either a Varian T-60, a Varian HA-100, or a Varian HR-220 spectrometer. Coupling constants (Hz) were obtained by measuring spacings of spectra judged to be first-order.

T.l.c. was performed on glass plates coated with silica gel (HF254, E. Merck) to a thickness of 0.3 mm. The chromatograms were first viewed under u.v. light, and then exposed to iodine vapor, and finally sprayed with concentrated sulfuric acid. Heating in an oven was needed for complete visibilization. For column chromatography, silica gel (E. Merck, 0.05–0.20 mm, 70–325 mesh, A.S.T.M.) was used.

Methyl 4,6-O-benzylidene-3-deoxy-3-C-methylene-α-D-ribo-hexopyranoside (**15b**) *and its 2-benzoate* (**15a**). — (All apparatus, solvents and compounds were dried for at least 1 h in an oven at 110° before use). Magnesium turnings (1.68 g, 69 mmol) that had been previously washed successively with dilute hydrochloric acid, water, abs. ethanol, and anhydrous diethyl ether, and thoroughly dried in an oven, were placed in a three-necked, round-bottom flask fitted with a dropping funnel, condenser, and mechanical stirrer. The apparatus was flushed with dry nitrogen. *All additions to the reaction vessel were made through the dropping funnel as an atmosphere of nitrogen needed to be rigorously maintained throughout the experiment.*

Triply-distilled mercury (420 g) was added to the flask. Gentle stirring for 1.5 h produced a homogeneous amalgam (0.040% wt/wt) which was cooled to −10° and covered with 1:1 anhydrous diethyl ether–benzene (25 ml). A solution of diiodomethane (6.16 g, 23.0 mmol) in the 1:1 solvent mixture (30 ml) was added during 20 minutes, and stirring was continued for 10 min. At this point, the supernatant liquid should be translucent and devoid of colour. Methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-*ribo*-hexopyranosid-3-ulose[14] (**14**, 3.00 g, 7.81 mmol) dissolved in the 1:1 solvent mixture (400 ml) was added rapidly. The mixture was stirred for 5 h at room temperature and then quenched by the cautions addition of cold, saturated, aqueous ammonium chloride. The mixture was transferred to a separatory funnel, diluted with diethyl ether (~200 ml), and washed with more saturated ammonium chloride solution. The mercury was drawn off and the ethereal layer was washed successively with saturated aqueous sodium hydrogencarbonate and water. The extract was dried (sodium sulfate) and concentrated to a syrup. Trituration with ethanol afforded a semi-crystalline material (2.8 g), which was shown [t.l.c., (1:1) ethyl acetate–petroleum ether (30–60°)] to contain mainly **15a** and **15b**.

Compound **15a** crystallised partially from the mixture by the use of abs. ethanol; m.p. 156.5–158.0°, $[\alpha]_D^{23}$ +141° (*c* 1, chloroform); ν_{max} 1728 cm^{-1} (benzoate), 3080, 1675 (terminal alkene); n.m.r. δ 3.43 (s, 3, OCH_3), 3.70–4.20 (m, 3, H-5, H-6a, and H-6e), 4.33 (d, 1, $J_{4,5}$ ~4.5 Hz, H-4), 5.05 (d, 1, $J_{1,2}$ 4.0 Hz, H-1), 5.25 and 5.35

(2bs, 2, H-7 and H-7'), 5.60 (bs, 2, H-2 and PhC*H*), 7.20–7.60, and 8.00–8.30 (m, 10, aromatic protons); *m/e* 383 (M), 352 (M−OCH_3).

The crude mixture (2.8 g) obtained from the foregoing reaction was dissolved in 1,4-dioxane (40 ml), and 10% sodium hydroxide (30 ml) was added to the stirred solution at room temperature. After 5 h, the mixture was extracted with chloroform, and the organic layer was washed with dilute hydrochloric acid, sodium hydrogencarbonate, and then dried (sodium sulfate). Evaporation of the solvent yielded a semicrystalline material which, after chromatography on a silica gel column, afforded 1.65 g (56% from **14**) of **15b**; R_F 0.46 in 1:1 [ethyl acetate–petroleum ether (b.p. 30–60°). After recrystallisation from ethanol it had m.p. 192.5–194°, $[\alpha]_D^{23}$ +159° (*c* 1, chloroform); ν_{max} 3080 and 1675 cm^{-1}; n.m.r.: δ 2.22 (bs, 1, OH), 3.43 (s, 3, OCH_3), 3.60–3.92 (m, 2, H-6a, and H-6e), 3.97 (m, 1, H-5), 4.18 (m, 1, H-2), 4.28 (m, 1, H-4), 4.80 (d, 1, $J_{1,2}$ 4.0 Hz, H-1), 5.26 and 5.33 (2bs, 2, H-7 and H-7'), 5.60 (s, 1, PhC*H*), 7.30–7.60 (m, 5, aromatic protons); *m/e* 278 (M), 277 (M−1), 246 (M−1−OMe).

Anal. Calc. for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.87; H, 6.66.

Methyl 4,6-O-benzylidene-3-deoxy-3-C-methylene-2-O-(methylsulfonyl)-α-D-ribo-hexopyranoside (**15c**). — Compound **15b** (1.56 g, 4.7 mmol) was dissolved in dry pyridine (15 ml) and the solution cooled to −10° with an ice–salt bath. Methanesulfonyl chloride (0.7 ml, 9.1 mmol) was added dropwise to the stirred mixture. After 3 h in the cold, the solution was poured slowly into about 20 ml of ice–water with vigorous stirring. The precipitated product (**15c**) was filtered off and washed repeatedly with water until the washings were neutral and then dried overnight in a vacuum oven at 60°; yield 1.3 g (78%). After recrystallisation from ethyl acetate–cyclohexane, it had m.p. 174°–176°, $[\alpha]_D^{23}$ +107° (*c* 0.5, chloroform); n.m.r. δ 3.10 (s, 3, OMs), 3.43 (s, 3, OMe), 3.60–4.15 (m, 3, H-5, H-6a, and H-6e), 4.30 (d, 1, $J_{4,5}$ ~4.5 Hz, H-4), 4.97 (d, 1, $J_{1,2}$ 4.0 Hz, H-1), 5.20 (d, 1, H-2), 5.30 and 5.40 (2bs, 2, H-7 and H-7'), 5.60 (s, 1, PhC*H*), 7.30–7.60 (m, 5, Ph); *m/e* 356 (M), 355 (M−1), 325 (M−OCH_3).

Anal. Calc. for $C_{16}H_{20}O_7S$: C, 53.95; H, 5.61; S, 9.00. Found: C, 53.51; H, 5.86; S, 9.27.

Methyl 4,6-O-benzylidene-2,3-dideoxy-3-C-(iodomethyl)-α-D-erythro-hex-2-enopyranoside (**17**). — Lithium iodide trihydrate was dried in a vacuum oven for 1 day at ~100° before use, to remove adsorbed water. Compound **15c** (242 mg, 0.9 mmol) and dried lithium iodide (2.5 g, 18 mmol) in 70 ml of anhydrous ethyl ether were refluxed for 2 h. The cooled solution was washed with sodium thiosulfate, water, and dried (sodium sulfate), and the ether was removed to leave **17** as a chromatographically pure solid; yield (242 mg, 90%). It was so recognized because of the similarity of its n.m.r. spectrum to that of the bromo analogue[1] **2**; n.m.r.: δ 3.42 (s, 3, OCH_3), 3.70–4.50 (m, 6, H-4, H-5, H-6a, H-6e, H-7, and H-7'), 4.80 (bd, 1, $J_{1,2}$ ~2 Hz, H-1), 5.62 (s, 1, PhC*H*), 5.80 (bs, 1, H-2), 7.30–7.60 (m, 5, Ph).

Satisfactory elemental analysis could not be obtained for compound **17** because of the ease with which it decomposed.

Methyl 4,6-O-benzylidene-2-O-p-tolylsulfonyl-α-D-ribo-hexopyranosid-3-ulose

(**18**). — The title compound was obtained by oxidation[19] of the corresponding alcohol which in turn was prepared as previously described[20].

*Methyl 3,3¹-anhydro-4,6-*O*-benzylidene-3-*C*-(hydroxymethyl)-2-*O*-*p*-tolylsulfonyl-α-*D*-glucopyranoside* (**21**). — A solution of methyl 4,6-*O*-benzylidene-2-*O*-*p*-tolylsulfonyl-α-*D*-*ribo*-hexopyranosid-3-ulose (**18**, 2.0 g; 4.6 mmol) in benzene (25 ml) and ethanol (75 ml) was cooled to 0°. To this was added dropwise an ethereal solution (62 ml) of diazomethane (9.2 mmol) during 30 min. The mixture was stirred for 1.5 h at 0° and then warmed to ambient temperature. After 18 h, t.l.c. showed that **18** had been consumed and a new product formed (R_F 0.38; 1:9 diethyl ether–benzene). Evaporation of the mixture afforded a yellow syrup that was dissolved in diethyl ether and decolourized with activated carbon. Evaporation gave a white foam (**21**) that failed to crystallize; yield 2.0 g (97%); $[\alpha]_D^{23}$ +35.5° (*c* 2.0, chloroform); p.m.r. (60 MHz): δ 2.40 (s, 3, Ar-Me), 2.95 (AB quartet, 2, $J_{A,B}$ 6.0 Hz, epoxy-methylene), 3.42 (s, 3, OMe), 3.6–4.5 (m, 4, H-4, H-5, H-6a, H-6e), 4.70 (d, 1, $J_{1,2}$ 4.0 Hz, H-2), 5.02 (d, 1, H-1), 5.48 (s, 1, PhC*H*), 7.2–8.0 (m, 9, aromatic protons); *m/e* 449 (M + 1), 448 (M), 447 (M − 1), 299 (M − PhCHOCH$_2$CHO), 293 (M − Ts), and those characteristic of benzylidene acetals.

Anal. Calc. for $C_{22}H_{24}O_8S$: C, 58.91; H, 5.39; S, 7.16. Found: C, 58.33; H, 5.15; S, 7.15.

*Methyl 4,6-benzylidene-3-*C*-methyl-2-*O*-*p*-tolylsulfonyl-α-*D*-glucopyranoside* (**22a**). — Compound **21** (314 mg, 0.70 mmol) was treated with lithium aluminum hydride (56 mg, 2.8 mmol) in anhydrous diethyl ether (5 ml) at 0°. After 0.5 h, the excess of reagent was composed by dropwise addition of ethyl acetate. The mixture was filtered through a bed of Celite and the filtrate concentrated to afford a colourless syrup; yield 315 mg (100%); $[\alpha]_D^{23}$ +41.9° (*c* 4.0, chloroform). This material was homogeneous in t.l.c. (R_F 0.24; 1:9 diethyl ether–benzene) and remained non-crystalline; p.m.r. (60 MHz): δ 1.40 (s, 3, C-3 methyl), 2.40 (s, 3, Ar-Me), 2.40 (bs, 1, exchangeable OH), 3.30 (s, 3, OMe), 3.4–4.4 (m, 4, H-4, H-5, H-6a, H-6e), 4.47 (d, 1, $J_{1,2}$ 4.0 Hz, H-2), 4.80 (d, 1, H-1), 5.50 (s, 1, PhC*H*), 7.2–8.0 (m, 9, aromatic protons); *m/e* 450 (M), 449 (M − 1), 301 (M − PhCHOCH$_2$CHO), 295 (M − Ts), and those characteristic of benzylidene acetals.

*Methyl 3-*O*-acetyl-4,6-*O*-benzylidene-3-*C*-methyl-2-*O*-*p*-tolylsulfonyl-α-*D*-glucopyranoside* (**22b**). — Compound **22a** (165 mg, 0.367 mmol) in anhydrous *N,N*-dimethylformamide (2 ml) and acetic anhydride (0.2 ml; 1.47 mmol) was refluxed for 4 h, after which time t.l.c. indicated that a new product had formed (R_F 0.40, 1:9 diethyl ether–benzene) at the expense of the starting material. The mixture was cooled and the excess of reagent decomposed by the dropwise addition of methanol. The mixture was then extracted with chloroform (2 × 35 ml), and the combined extracts were washed with 5% hydrochloric acid, saturated aqueous sodium hydrogencarbonate, and water. After drying (sodium sulfate) and concentrating the extracts, the product was purified on a column of silica gel with 1:9 diethyl ether–benzene to give **22b** as a colourless syrup that failed to crystallize; yield 100 mg (56%); $[\alpha]_D^{23}$ −18.6° (*c* 1.0, chloroform); p.m.r. (60 MHz): δ 1.57 (s, 3, C-3 methyl), 1.83 (s, 3,

OAc), 2.43 (s, 3, Ar-Me), 3.30 (s, 3, OMe), 3.5–4.5 (m, 3, H-5, H-6a, H-6e), 4.63 (d, 1, $J_{1,2}$ 4.0 Hz, H-1), 4.90 (d, 1, $J_{4,5}$ 8.5 Hz, H-4), 5.55 (s, 1, PhC*H*), 5.65 (d, 1, H-2), 7.2–8.0 (m, 9, aromatic protons); *m/e* 492 (M), 491 (M−1), 432 (M−HOAc), 401 (M−HOAc−OMe), 343 (M−PhCHOCH$_2$CHO), 337 (M−Ts), and those characteristic of benzylidene acetals.

Methyl 4,6-O-benzylidene-2,3-dideoxy-3-C-methylene-α-D-erythro-hexopyranoside (**24**). — A three-necked, round-bottom flask was fitted with a rubber stopper, an addition funnel, and a gas-inlet tube so that a nitrogen atmosphere could be maintained throughout the reaction. Methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose[30] (**23**, 5.28 g, 20 mmol) was dissolved in anhydrous dimethoxyethane (275 ml) and placed in the addition funnel. The Wittig reagent was preformed by the addition of butyllithium (30 mmol) to a suspension of methyltriphenylphosphonium bromide (10.7 g, 30 mmol) in anhydrous diethyl ether (100 ml) during 15 min. The mixture was stirred for 30 min after which time a bright-orange coloured solution of the ylid was produced. The solution of **23** was added rapidly and the mixture stirred for 1 h at room temperature. After this time, t.l.c. showed that a single product had formed [R_F 0.60; 1:1 diethyl ether–petroleum ether (b.p. 40–60°)]. After addition of diethyl ether (~300 ml) to the flask, the solids formed were removed by filtration through a bed of Celite. The filtrate was concentrated and absorbed onto silica gel (10 g). This was placed on a column of silica gel (100 g) and eluted with 1:1 diethyl ether–petroleum ether (b.p. 30–60°) to give **24** as white crystals; yield 3.0 g (60%).

Recrystallization from ethanol afforded pure **24**; m.p. 121–122.5°, $[\alpha]_D^{23}$ +163.5° (*c* 1.04, chloroform); p.m.r. (60 MHz): δ 2.58 (m, 2, H-2a, H-2e), 3.37 (s, 3, OMe), 3.7–4.4 (m, 4, H-4, H-5, H-6a, H-6e), 4.82 (m, 1, H-1), 5.00 and 5.23 (m, 2, exocyclic methylene), 5.68 (s, 1, PhC*H*), 7.3–7.7 (m, 5, Ph).

Anal. Calc. for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.63; H, 6.94.

1,5-anhydro-4,6-O-benzylidene-1,2,3-trideoxy-3-C-methylene-D-erythro-hex-1-enitol (**1**). — *Method* (*1*) (*Scheme* 1). For the iodinolysis of **5** to give **6**, see ref. 7b. 1,5-anhydro-4,6-*O*-benzylidene-1,2,3-trideoxy-3-*C*-(iodomethyl)-D-*ribo*-hex-1-enitol (**6**, 1.374 g, 38.4 mmol) was dissolved (50 ml of 1,4-dioxane), M sodium hydroxide (50 ml) was added, and the solution was boiled for 5 min under reflux. The cooled solution was then extracted with chloroform to afford 0.862 g (37.4 mmol; 97.4%) of crystalline compound **1**.

Method (*2*). The Wittig reaction with compound[9,10] **8** (232 mg, 1 mmol) was conducted with an equimolar amount of methylenetriphenylphosphorane as described for the preparation of **24**. After 2 h, the reaction was stopped and the product (**1**) isolated by chromatography with 1:4 ethyl acetate–petroleum ether (b.p. 30–60°); yield 25 mg (10%).

Method (*3*). To a solution of compound **17** (150 mg, 0.386 mmol) in absolutely dry diethyl ether (18 ml) that had been cooled in ice–salt, methyllithium (1 ml of a 2.1M solution, 2.1 mmol) was added slowly under anhydrous conditions. The solution was then boiled for 2 h under reflux under nitrogen. The solution was then

poured into a separatory funnel containing about 10 ml of cold water. The ether layer was separated and the aqueous layer extracted with another portion of ether. The combined ether extracts were then washed with sodium thiosulfate solution and water, dried (sodium sulfate), and evaporated to afforded 80.5 mg (91%) of white, crystalline **1**.

Method (*4*). The Cainelli reagent was prepared in the same manner, and using the same quantities of reagents, as already described for the synthesis of **15a**. When the translucent supernatant layer had formed, the ketone **18** (2.00 g, 4.60 mmol) in 1:1 ether–benzene (200 ml) was added and the reaction allowed to proceed for 5 h. After conventional processing, t.l.c. indicated that the major product was fast-migrating [R_F 0.65, 1:4 ethyl acetate–petroleum ether (b.p. 30–60°)] and was accompanied by many other, slower-migrating compounds. Purification of the major product by column chromatography [1:4 ethyl acetate–petroleum ether (b.p. 30–60°)] afforded compound **1**; yield 530 mg (50%). In several experiments, the yield varied, ranging from 22–50%.

Method (*5*). A solution of methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-methylene-α-D-*erythro*-hexopyranoside (**24**, 3.0 g, 11.4 mmol) in anhydrous 1,4-dioxane (90 ml) was treated with potassium *tert*-butoxide (6.4 g, 57.0 mmol) and the mixture was refluxed for 6 h. The diene **1** was observed to be the only product by t.l.c. (R_F 0.62; 1:9 diethyl ether–benzene). The mixture was concentrated, diluted with diethyl ether (~200 ml) and washed with brine (75 ml) and water (2 × 75 ml). The dried (sodium sulfate) extract was evaporated to afford white, crystalline **1**; yield 2.0 g (76%).

Method (*6*). For the formation of **1** by pyrolysis of **25** or **26** see ref. 26. Compound **1** was recrystallised from ethanol; m.p. 98–100°, $[\alpha]_D^{23}$ +98.4° (c, 3.6 in chloroform); ν_{max} 3012 cm^{-1} (terminal = CH_2) 2849, 1645 (vinyl ether), 1600 (terminal = CH_2) 978, and 894 (terminal = CH_2); λ_{max} (ethanol) 243 nm (ε 4600); n.m.r.: δ 3.79–3.94 (m, 2, $J_{5,6a}$ 10.0 Hz, $J_{5,6e}$ 4.5 Hz, H-5 and H-6a), 4.33 (dd, 1, $J_{4,7}$ or $J_{4,7'}$ 2.0 Hz, $J_{4,5}$ 8.0 Hz, H-4), 4.40 (distorted q, 1, $J_{6a,6e}$ 10.5 Hz, H-6e), 4.89, and 5.09 (2bs, 2, H-7 and H-7') 5.47 (d, 1, $J_{1,2}$ 6.0 Hz, H-2), 5.70 (s, 1, PhC*H*), 6.40 (bd, 1, $J_{1,7} \leqslant 0.5$ Hz, $J_{1,7'}$ 1.0 Hz, H-1), 7.47 (m, 5, Ph)

Anal. Calc. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 72.90; H, 6.38.

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REFERENCES

1 B. FRASER-REID AND B. RADATUS, *Chem. Commun.*, (1970) 779–780.
2 S. Y-K. TAM, D. E. ILEY, N. L. HOLDER, D. R. HICKS, AND B. FRASER-REID, *Can. J. Chem.*, 51 (1973) 3150–3152.
3 D. E. ILEY AND B. FRASER-REID, *J. Am. Chem. Soc.*, 97 (1975) 2563–2565.
4 B. FRASER-REID AND B. RADATUS, *J. Am. Chem. Soc.*, 92 (1970) 6061–6663; B. FRASER-REID, S. Y-K. TAM, AND B. RADATUS, *Can. J. Chem.*, 53 (1975) 2005–2016.

5 M. KUGELMAN, A. K. MALLAMS, AND H. F. VERNEY, *J. Chem. Soc. Perkin I*, (1976) 1113–1126.
6 B. RADATUS, M. B. YUNKER, AND B. FRASER-REID, *J. Am. Chem. Soc.*, 93 (1971) 3086–3087.
7 (a) B. FRASER-REID AND B. RADATUS, *Can. J. Chem.*, 47 (1969) 4095; (b) *ibid.*, 50 (1972) 2919–2927.
8 B. RADATUS AND B. FRASER-REID, *Can. J. Chem.*, 50 (1972) 2909–2918.
9 P. M. COLLINS, P. GUPTA, AND R. IYER, *J. Chem. Soc. C*, (1972) 1670–1677; P. M. COLLINS, *Carbohydr. Res.*, 11 (1969) 125–128; P. J. BENYON, P. M. COLLINS, P. T. DOGANGES, AND W. G. OVEREND, *J. Chem. Soc. C*, (1966) 1131–1136.
10 B. FRASER-REID, D. L. WALKER, S. Y-K. TAM, AND N. L. HOLDER, *Can. J. Chem.*, 51 (1973) 3950–3954.
11 A. MAERCKER, *Org. Reactions*, 14 (1965) 270–490.
12 N. L. HOLDER AND B. FRASER-REID, unpublished results.
13 B. FRASER-REID, N. L. HOLDER, AND M. B. YUNKER, *Chem. Commun.*, (1972) 1286–1287, M. B. YUNKER, Ph.D. THESIS, University of Waterloo, 1975.
14 F. A. CAREY AND K. O. HODGSON, *Carbohydr. Res.*, 12 (1970) 463–465.
15 J. H. JORDAAN AND S. SMEDLEY, *Carbohydr. Res.*, 16 (1971) 177–183.
16 F. BERTINI, P. GRASSELLI, G. ZUBIANI, AND G. CAINELLI, *Tetrahedron*, 26 (1970) 1281–1290.
17 A. C. RICHARDSON, *Carbohydr. Res.*, 10 (1969) 395–402.
18 N. L. HOLDER AND B. FRASER-REID, *Can. J. Chem.*, 51 (1973) 3357–3365.
19 K. ONODERA AND N. KASHIMURA, *Methods Carbohydr. Chem.*, 6 (1972) 331.
20 D. R. HICKS AND B. FRASER-REID, *Synthesis*, (1974) 203.
21 R. D. RIEKE AND S. E. BALES, *J. Am. Chem. Soc.*, 96 (1974) 1775–1781.
22 G. B. HOWARTH, W. A. SZAREK, AND J. K. N. JONES, *Can. J. Chem.*, 46 (1968) 3375–3379.
23 H. R. NACE, *Organic Reactions*, 12 (1962) 57–100.
24 J. H. JORDAAN AND S. SMEDLEY, *Carbohydr. Res.*, 18 (1971) 303–309.
25 R. U. LEMIEUX AND J. D. STEVENS, *Can. J. Chem.*, 43 (1965) 2059–2070.
26 W. A. SZAREK, A. DMYTRACZENKO, AND J. K. N. JONES, *Carbohydr. Res.*, 35 (1974) 203–219.
27 D. R. HICKS AND B. FRASER-REID, *Can. J. Chem.*, 53 (1975) 2017–2023.
28 M. E. EVANS, *Carbohydr. Res.*, 21 (1972) 473–475.
29 L. F. WIGGINS, *Methods Carbohydr. Chem.*, 2 (1963) 189–190.
30 A. ROSENTHAL AND P. CATSOULACOS, *Can. J. Chem.*, 46 (1968) 2868–2872.