STEREOSPECIFIC CHAIN-BRANCHING BY *C*-ALKYLATION AT THE KETONIC AND ENOLIC POSITIONS OF 1,6-ANHYDRO-2,3-*O*-ISOPROPYLIDENE-β-D-*lyxo*-HEXOPYRANOS-4-ULOSE*†

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ABSTRACT

Attempted base-catalyzed *C*-formylation at the enolic (C-3) position of 1,6-anhydro-2,3-*O*-isopropylidene-β-D-*lyxo*-hexopyranos-4-ulose (**1**) gives instead a dimer (**8**) of **1**. The ketone **1** is, however, *C*-alkylated stereospecifically at C-3 by the action of paraformaldehyde in methanolic potassium carbonate; concomitant reduction at C-4 occurs, and 1,6-anhydro-3-*C*-(hydroxymethyl)-2,3-*O*-isopropylidene-β-D-talopyranose (**3**) is formed. The ketone **1** undergoes stereospecific attack at C-4 by Grignard reagents, and the 4-*C*-methyl (**13**), 4-*C*-vinyl (**10**), and 4-*C*-ethynyl (**11**) derivatives of 1,6-anhydro-2,3-*O*-isopropylidene-β-D-talopyranose were so prepared. Ozonolysis of **10** and **11** gives the corresponding 4-*C*-formyl (**14**) and 4-*C*-carboxy (**16**) derivatives, respectively. The *spiro* epoxide **12** formed by action of diazomethane on the ketone **1** has been characterized as the D-*talo* isomer by its conversion on reduction into the 4-*C*-methyl derivative **13**.

INTRODUCTION

Previous papers in this series[2] have described the results of chain-extension reactions achieved by addition of unsaturated Grignard reagents to *aldehydo* sugar derivatives. The present work extends this approach to chain-branching reactions by use of *keto* sugar derivatives. In addition to the use of Grignard reagents, the feasibility of *C*-alkylation reactions at the enolic position of the *keto* derivative is explored. By use of a suitable, locked-ring, *keto* derivative, chain branching was introduced stereospecifically by *C*-alkylation at the carbonyl group, and, in the same system, it is possible to perform regiospecific and stereospecific *C*-alkylation at the enolic position. Ozonolysis of the *C*-vinyl and *C*-ethynyl derivatives provides convenient routes to the *C*-formyl and *C*-carboxy derivatives, respectively.

These reactions afford general information of utility in the design of stereo-

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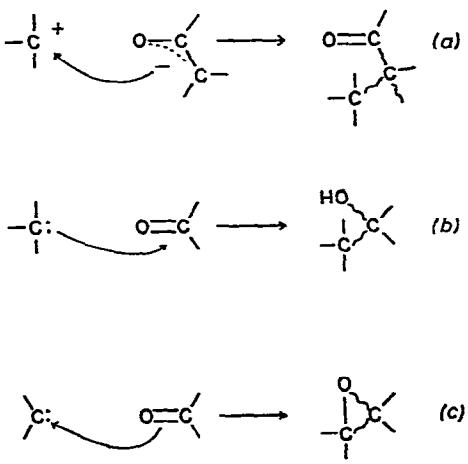
specific approaches to the synthesis of branched-chain sugar derivatives. Branched-chain sugars[3] are constituents of certain plant glycosides and polysaccharides, and are also found as constituents of various antibiotics of the oligosaccharide[4], nucleoside[5], and macrolide[6] types. Synthetic analogs of such structures are of chemotherapeutic interest.

DISCUSSION

Three general approaches to the introduction of a branched carbon chain in a straight-chain, *keto* sugar derivative can be envisaged: (*a*) attack of an electrophilic carbon species at the enolic carbon atom of the enolate anion, (*b*) attack of a nucleophilic carbon species at the carbon atom of the ketone, and (*c*) attack of a suitable electrophile, such as a carbenoid species, at the oxygen atom of the carbonyl group by an insertion type of reaction.



Scheme I

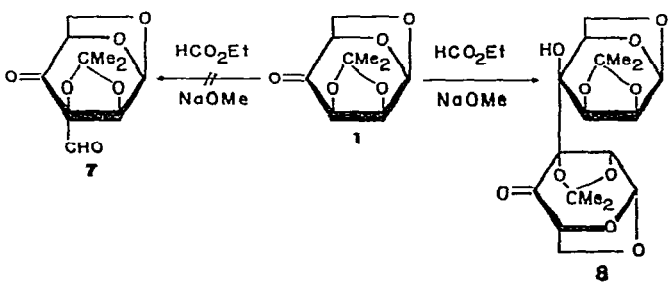
Stereochemical factors can be expected to influence the distribution of products in all three types of reaction, and factors of positional specificity (regiospecificity) are also involved in the enolate reaction, where two enolic positions are open for attack.

Each of these types of reaction has been evaluated with 1,6-anhydro-2,3-*O*-isopropylidene-*β*-D-*lyxo*-hexopyranos-4-ulose[7] (**1**), a ketone that has been shown[8] to undergo completely stereospecific reduction to 1,6-anhydro-2,3-*O*-isopropylidene-*β*-D-talopyranose, and that undergoes regio- and stereo-specific enolic exchange of the C-3 hydrogen atom[9–11].

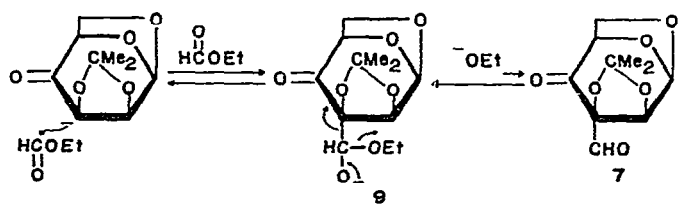
*Alkylation of 1,6-anhydro-2,3-*O*-isopropylidene-β-*D-lyxo-*hexopyranos-4-ulose* (**1**) *at the enolic (C-3) position.* — Chain-branching through alkylation of a ketose with formaldehyde has been documented by Schaffer[12] and applied with an *aldehydo*-sugar precursor by Williams and Jones[13] in a synthesis of D-apiose. In the present study,

Further evidence for the structure of **4** was adduced by removal of the *O*-isopropylidene group through the action of 9:1 trifluoroacetic acid–water[16]. A quantitative yield of a crystalline diol (**5**) was obtained, which, on acetylation with an excess of the reagents, gave a monoacetate (**6**), indicating that one of the hydroxyl groups in **5** is tertiary. The i.r. spectrum of **6** showed absorptions for acetate and hydroxyl groups, and the n.m.r. spectrum established that one of each of these groups was present.

An attempt to synthesize the 3-*C*-formyl derivative (**7**) of the ketone **1** by treatment of **1** in ethyl formate with a catalytic amount of sodium methoxide resulted in the gradual conversion of **1** into a single, chromatographically faster-moving component over a period of 3 days. The faster-moving product gave a negative test with the Schiff reagent, and was isolated crystalline after chromatographic separation from unreacted, starting ketone **1**. The product, showing i.r. spectral absorptions for both hydroxyl and carbonyl groups, was found to be identical with the dimer **8**, previously described[10]. The failure of the 3,4-enediolate of **1** to condense with ethyl formate cannot be ascribed to the steric bulk of the reagent, because the 3,4-enediolate readily condenses with the sterically bulkier ketone **1**. Presumably, the transition state that would lead to **7**, by expulsion of an ethoxide anion from the intermediate **9**, is unstable with respect to the reverse reaction, the expulsion of ethyl formate leading to regeneration of the 3,4-enediolate.



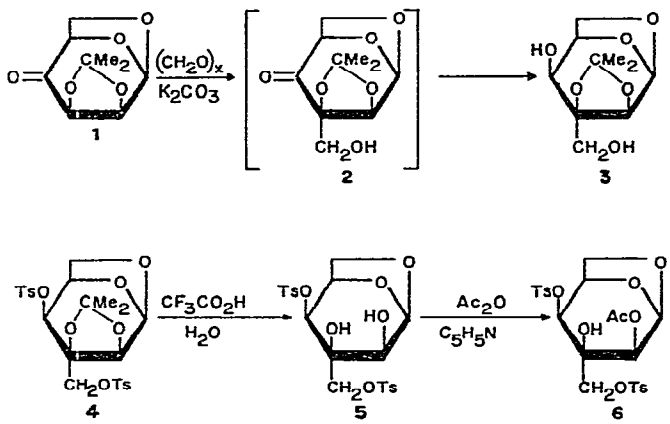
Scheme III



Scheme IV

Addition of Grignard reagents to 1,6-anhydro-2,3-O-isopropylidene-β-D-lyxo-hexopyranos-4-ulose (**1**). — The formation of branched-chain derivatives by addition of various alkyl, alkenyl, and substituted-alkynyl Grignard reagents to *keto* derivatives of sugars has been described by Overend and co-workers[17] and by Dyer and co-workers[18]; marked stereoselectivity was observed in most examples.

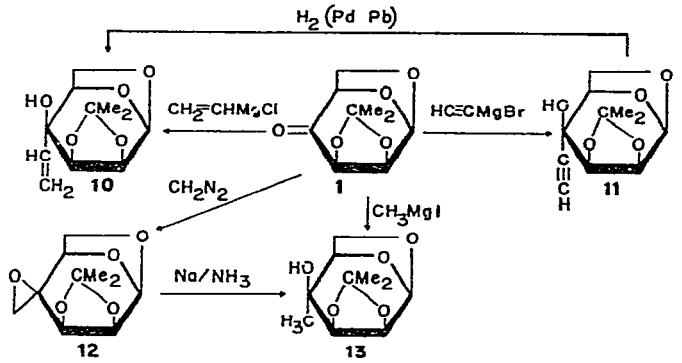
treatment of the ketone **1** with paraformaldehyde and potassium carbonate in methanol at room temperature gave a syrupy product formulated as 1,6-anhydro-3-*C*-(hydroxymethyl)-2,3-*O*-isopropylidene-*β*-D-talopyranose (**3**). This product is evidently formed by attack of the 3,4-enediolate anion of **1** on formaldehyde, to give the 3-(hydroxymethyl)-4-ketone (**2**), which subsequently undergoes reduction at C-4 by a crossed, Cannizzaro type of reaction[14]. The structure assigned to **3** is indicated by physical data and proved by subsequent conversions. The i.r. spectrum of **3** showed hydroxyl absorption, but no carbonyl band. Its n.m.r. spectrum in chloroform-*d* showed exchangeable signals corresponding to two hydroxyl groups. The H-1 and H-2 signals were observed as sharp doublets ($J_{1,2}$ 3.2 Hz) at τ 4.46 and 5.85, respectively, and the lack of additional multiplicity in the H-2 signal indicated the absence of a proton at C-3.



Scheme II

Treatment of the branched-chain diol **3** with *p*-toluenesulfonyl chloride in pyridine gave, initially, a product that appeared to be a monoester, and, subsequently, a crystalline bis(*p*-toluenesulfonate) (**4**) was isolated. Formation of such a diester indicated that neither hydroxyl group was tertiary. The n.m.r. spectrum of **4** showed sharp, one-proton doublets for H-1, H-2, and H-4, and a broadened, one-proton triplet for H-5. Irradiation of the H-5 or the H-1 signal caused collapse of the H-4 and H-2 signals, respectively, to singlets, thus demonstrating that there was no proton present at C-3 and establishing that the branching substituent had entered at C-3. The broadening of the H-5 triplet arises from $J_{5,6endo}$ coupling (0.9 Hz), the small value of which indicates a dihedral angle between H-5 and H-6endo of ~90°. The D-*talo* configuration can be assigned to **4** based on the expectation that the thermodynamically more-stable, *cis*-fused, acetal ring[10] prevails at equilibrium [exo-3-(hydroxymethyl) group], and that reduction of the keto group leads[8] to the product having the 4-substituent *cis* to C-6 and O-3. The assigned orientation of the 4-substituent accords with the observed $J_{4,5}$ coupling (5.5 Hz), which is too large to fall in the range (1–3.5 Hz) found[15] for equatorial–equatorial coupling.

Treatment of the ketone **1** with commercial or freshly prepared vinylmagnesium chloride in tetrahydrofuran gave crystalline 1,6-anhydro-2,3-*O*-isopropylidene-4-*C*-vinyl-β-D-talopyranose (**10**), and, by using ethynylmagnesium bromide, the crystalline 4-*C*-ethynyl analog (**11**) of **10** was prepared similarly in high yield. The vinyl derivative (**10**) showed i.r. spectral absorptions for hydroxyl and vinyl groups, and the n.m r. spectrum showed an ABX pattern of signals typical of the vinyl group, together with a signal for an OH proton. The ethynyl derivative (**11**) showed i.r. and n.m.r. spectral absorptions for hydroxyl and ethynyl groups. The remaining signals in the n.m.r. spectra of **10** and **11** were in full accord with the structures assigned (see Experimental section for details). Hemihydrogenation of the ethynyl derivative **11** over Lindlar catalyst gave the vinyl derivative **10**, thus proving that both derivatives have the same configuration at C-4.



Scheme V

Treatment of the 4-ketone **1** with methylmagnesium iodide gave an almost quantitative yield of the crystalline 1,6-anhydro-2,3-*O*-isopropylidene-4-*C*-methyl-β-D-talopyranose (**13**), whose structure was confirmed by i.r. and n.m.r. spectral data (see Experimental section for details). The D-*talo* configuration assigned to the products **10**, **11**, and **13**, although not proved by classical degradative methods, can be anticipated on the basis of steric-approach control[19] of the addition of nucleophiles to the ketone, with attack from the less-hindered side of the molecule. This assignment is in accord with previous observations from this laboratory[8,20] on reduction of the ketone **1** and its oxime.

The observation that even the methyl Grignard reagent gives a single product emphasizes the stereospecificity of the reaction with the ketone **1**. In other, less sterically controlled systems, the attack of the reagent from both sides of a carbonyl group has been observed, at least with methylmagnesium iodide[17].

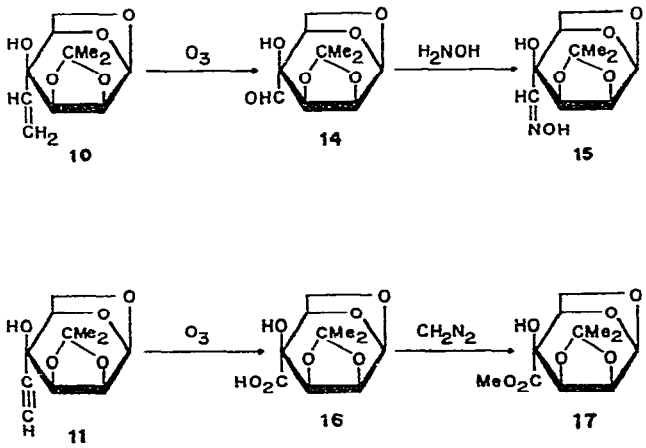
Insertion of methylene into the carbonyl group of 1,6-anhydro-2,3-O-isopropylidene-β-D-lyxo-hexopyranos-4-ulose (**1**). — Treatment of **1** with diazomethane in ether gave the crystalline *spiro* epoxide (**12**) earlier reported[7], in 77% yield. The configuration of this epoxide has not been established, but the earlier, tentative D-*talo* assignment, based on n.m.r. spectral considerations, is upheld by evidence

from the chemical transformations here presented. This route to *spiro* epoxides of sugars was utilized by Weygand and Schmeichen[21] in their synthesis of L-apiose.

The *spiro* epoxide **12** could be reduced in liquid ammonia by dissolving sodium in the solution. No products of ammonolysis of the epoxide were detected, and the product formed was identical with 1,6-anhydro-2,3-*O*-isopropylidene-4-*C*-methyl-β-D-talopyranose (**13**) prepared by treating the ketone **1** with methylmagnesium iodide. This information established that the stereochemistry of the *spiro* epoxide **12** is identical with that of the Grignard adduct **13**, and thus, by reasoning already advanced, the D-*talo* configuration is assigned to **12**.

Ozonolysis of the derivatives **10** *and* **11**, *unsaturated in the chain-branching group.* — Ozonolysis of *C*-vinyl sugar derivatives to give *C*-formyl analogs has been reported by two groups[17,18]. Treatment of the alkene **10** in methanol with ozone led to the complete conversion of **10** into a single, syrupy, Schiff-positive product formulated as the 4-*C*-formyl derivative **14**. It was characterized as its crystalline oxime (**15**), isolated in 71% yield. The oxime **15** showed i.r. absorption for hydroxyl groups, but a band at ~1660 cm^{-1}, anticipated for the C=N stretch, was not observed[22,23]. However, a sharp band at 1648 cm^{-1}, assigned to the C=N stretch, was observed in the Raman spectrum of **15** examined as a liquid (fused solid)[24]. The sharpness of the melting point and the chromatographic and n.m.r.-spectral homogeneity of **15** indicate that it is a single, geometric isomer. The configuration about the C=N bond was not assigned. This formation of a single isomer is contrasted with the *syn,anti* mixtures of oximes obtained from the ketone[7] (**1**) and methyl 2,3,6-trideoxy-α-D-*glycero*-hexopyranosid-4-ulose[23]. Possibly, the 4-OH group of **14** exerts a directive influence on the hydroxylamine reagent, by hydrogen bonding of the acidic oximino hydroxyl proton to O-4, to give the geometrically pure oxime **15**. When no such directive influence is possible, *syn,anti* mixtures of the oximes are isolated[7,23].

The n.m.r. spectrum of the oxime **15** in acetone-d_6 shows two 1-proton singlets, at τ −0.76 and 7.11, which disappear on deuteration and are assigned to the oximino



Scheme VI

hydroxyl proton and the 4-OH group, respectively. The appearance of two OH-proton signals in the n.m.r. spectrum confirms the Raman-spectral observation that the oxime **15** has a C=N double bond, because intra- or inter-molecular addition of the 4-hydroxyl group to the C=N bond would give a compound lacking the Raman absorption for the C=N group and showing only one hydroxyl-resonance signal in its n.m.r. spectrum. For the oxime, in addition to a 1-proton singlet at τ 2.51 (–N=CH–), all other ring-proton signals could be assigned on a first-order basis and are in accord with the structure **15** given for the oxime.

Ozonolysis[25] of the acetylene **11** in carbon tetrachloride–acetic acid afforded a chromatographically homogeneous product that gave a positive test for acid with Bromocresol Green spray-reagent and was formulated as the acid **16**. It was amorphous, but gave satisfactory elemental analyses and showed i r. absorptions for hydroxyl and carboxyl groups.

Methylation of the acid **16** with diazomethane in ethyl ether–ethanol gave the methyl ester **17**, isolated in 82% yield as a syrup, either by distillation or by chromatography. Compound **17** showed i.r. absorptions for a chelated hydroxyl group[26] and a methoxycarbonyl group. Its n.m.r. spectrum in chloroform-*d* was amenable to first-order analysis; a 3-proton singlet at τ 6.15 (OCH_3) and a 1-proton singlet at τ 2 95 (which disappeared on deuteration) were readily assigned to the methoxyl and 4-OH groups, respectively. The low field-position observed for the 4-OH proton indicates chelation of that proton with the 4-*C*-(methoxycarbonyl) group; this assignment is also indicated by the shift in the i.r. absorption band for the hydroxyl group (3.55 μm) characteristic of a chelated, OH proton[26]. Chelation of the 4-OH group with the methoxycarbonyl group, accompanied by deshielding of that group, would also help to explain the occurrence of the OMe signal in the n.m.r. spectrum at a field lower than that normally observed ($\sim\tau$ 6 50) for a methoxyl group.

EXPERIMENTAL

General. — Solutions were evaporated below 50° under diminished pressure. Melting points are uncorrected. Ozonolyses were performed with a Welsbach Corp. Ozonator Model T-408 at 2.5 liter min^{-1}, with oxygen at 8 lb. $in.^{-2}$. N.m.r. spectra were recorded at 60 and 100 MHz, and spin-decoupling experiments were performed at 100 MHz. Chemical shifts are given on the τ scale. Unless otherwise stated, spectra were measured at ~30° for solutions (~10%) in chloroform-*d*, with tetramethylsilane ($\tau = 10.00$) as the internal standard. Spectra were analyzed on a first-order basis. Microanalyses were performed by W. N. Rond. X-Ray powder diffraction data give interplanar spacings, Å, for CuK_α radiation. Relative intensities were estimated visually: m, moderate; s, strong; v, very; w, weak. The strongest lines are numbered (1, strongest), and double numbers indicate approximately equal intensities. The camera diameter was 114.59 mm. T.l.c. was effected with 250-μm layers of Silica Gel G (E. Merck, Darmstadt, Germany), activated at 110°, as the absorbent, and 3:1 chloroform–ether (solvent *A*), 5:3:1 butyl alcohol–acetic acid–

water (solvent *B*), and 10:1 benzene–methanol (solvent *C*) as the developers, and indication was effected with sulfuric acid.

1,6-Anhydro-3-C-(hydroxymethyl)-2,3-O-isopropylidene-β-D-talopyranose (**3**). — To a solution of 1,6-anhydro-2,3-*O*-isopropylidene-β-D-*lyxo*-hexopyranos-4-ulose[7,10] (**1**, 2.0 g, 10 mmoles) in methanol (500 ml) were added potassium carbonate (1.5 g) and paraformaldehyde (1.5 g, 50 mmoles). The mixture was stirred at room temperature overnight; t.l.c. then indicated complete conversion of ketone **1** into **3**; R_F 0.10, solvent *A*. The mixture was concentrated to ~20 ml at 40°/0.2 torr, diluted with chloroform (200 ml), and acidified by shaking with cold, aqueous ammonium chloride solution. The aqueous phase was extracted with two 200-ml portions of chloroform, and the chloroform extracts were combined, dried (sodium sulfate), filtered, and evaporated to a syrup that resisted crystallization; yield 0.85 g (37%); R_F 0.21 (solvent *A*); n.m.r. data (60 MHz): τ 4.46 (1-proton doublet, $J_{1,2}$ 3.2 Hz, H-1), 5.40 (1-proton triplet, $J_{4,5} \approx J_{5,6exo} \approx 6.7$ Hz, H-5), 5.63 (1-proton, broadened doublet, $J_{6exo,6endo}$ 8.0 Hz, H-6endo), 5.85 (1-proton, braodened doublet, H-2), 6.20 (1-proton, broadened quartet, H-6exo), 6.50 (2-proton, broadened singlet that disappeared on deuteration, OH), 8.31, and 8.48 (3-proton singlets, CMe_2).

Compound **3** was characterized as its crystalline bis(*p*-toluenesulfonate) (**4**).

1,6-Anhydro-3-C-(p-tolylsulfonyloxymethyl)-2,3-O-isopropylidene-4-O-p-tolylsulfonyl-β-D-talopyranose (**4**). — A solution of the branched-chain diol **3** (0 85 g) and *p*-toluenesulfonyl chloride (3.0 g) in pyridine was kept for 1 day at room temperature. Monitoring of the reaction by t.l.c. indicated the gradual disappearance of **3** (R_F 0.21, solvent *A*), with the appearance of a component having R_F 0.53 (presumably the 3^1-mono-*p*-toluenesulfonate of **3**) and compound **4** (R_F 0.86). As the reaction progressed, **3** and the component having R_F 0.53 underwent complete conversion into **4**. The solution was then added dropwise to rapidly stirred ice–water, which caused the precipitation of **4**. The precipitate was filtered off and dissolved in chloroform; the solution was washed repeatedly with water, dried (sodium sulfate), and evaporated at 40°/0.2 torr to a syrup that crystallized from ether (10 ml) to give **4** as dense, colorless platelets; yield 0.92 g (46%), m.p. 125–126°, $[\alpha]_D^{20}$ −16.6 ±2° (*c* 0.78, chloroform); R_F 0.86 (solvent *A*); λ_{max}^{KBr} 6.27, 6.93 (aryl), 7.38, and 11.80 μm (C–O–S)[27]; n.m.r. data (100 MHz, assignments verified by spin-decoupling): τ 2.17 (2-proton doublet, aryl), 2.22 (2-proton doublet, aryl), 2.62 (4-proton doublet, aryl), 4.65 (1-proton doublet, $J_{1,2}$ 3.4 Hz, H-1), 5.20 (1-proton doublet, $J_{4,5}$ 5.5 Hz, H-4), 5.51 (1-proton broadened triplet, $J_{5,6exo}$ 5.1 Hz, $J_{5,6endo}$ 0.9 Hz, H-5), 5.72 (1-proton doublet of narrowly spaced doublets, $J_{6endo,6exo}$ 7.6 Hz, H-6endo), 6.09, 6.49 (1-proton doublets, $J_{3^1,3^{1'}}$ 9.7 Hz, H-3^1,$3^{1'}$), 6.10 (1-proton doublet, H-2), 6.37 (1-proton quartet, H-6exo), 7.53 (6-proton singlet, $ArCH_3$), 8.42, 8.69 (3-proton singlets, CMe_2); X-ray powder diffraction data: 11.11 w, 9.40 m, 7.86 s (2, 2), 6.80 s (3, 3), 6.40 s (3, 3), 5.87 s (2, 2), 5.18 broad m, 4.62 vs (1), and 4.33 m.

Anal. Calc. for $C_{24}H_{18}O_{10}S_2$: C, 53.32; H, 5.22; S, 11.86. Found: C, 53.29; H, 5.21; S, 11.71.

1,6-Anhydro-3-C-(p-tolylsulfonyloxymethyl)-4-O-p-tolylsulfonyl-β-D-talopyra-

nose (**5**). — Compound **4** (0.42 g) was deacetonated by the method of Christensen and Goodman[16] by dissolving it in 9:1 (v/v) trifluoroacetic acid–water (10 ml) at room temperature and then evaporating the solution after 4 h. A quantitative yield (0.38 g) of **5** was obtained. After recrystallization from methanol, it had m.p. 170.5–171.5°; R_F 0.15 (solvent *A*); λ_{max}^{KBr} 2.91 (OH), 3.01 (OH), 6.28, 7.34, 7.42, and 8.50 μm (SO_2).

2-O-Acetyl-1,6-anhydro-3-C-(p-tolylsulfonyloxymethyl)-4-O-p-tolylsulfonyl-β-D-talopyranose (**6**). — The deacetonated bis(*p*-toluenesulfonate) **5** (0.21 g, 0.42 mmole) was treated with acetic anhydride (10 ml) and pyridine (5 ml) overnight at room temperature; t.l.c. then indicated complete conversion of **5** into **6**, R_F 0.43 (solvent *A*). The solution was evaporated at 40°/0.2 torr to a solid residue which was extracted with hot ethanol; the extracts were combined, concentrated to 15 ml, and refrigerated, to give **6** as colorless, crystalline filaments; yield 0.15 g (68%), m.p. 195–197°, $[\alpha]_D^{20}$ −20.4 ±2° (*c* 0.12, chloroform); R_F 0.43 (solvent *A*); λ_{max}^{KBr} 2.89 (OH), 5.70 (OAc), 6.27, 7.37, 8.49 (SO_2), and 11.93 μm (C–O–S[27]); n.m.r. data (100 MHz, methyl sulfoxide-d_6): τ 2.19 (2-proton doublet, aryl), 2.34 (2-proton doublet, aryl), 2.54 (4-proton doublet, aryl), 4.55 (1-proton singlet that disappeared on deuteration, OH), 4.68 (1-proton doublet, $J_{1,2}$ 2.0 Hz, H-1), 5.59 (4-proton multiplet, width between outer peaks 10 Hz, H-2,4,5,6endo), 6.42 (1-proton, broadened quartet, $J_{6endo,6exo}$ ~6 Hz, $J_{5,6exo}$ ~3 Hz, H-6exo), 6.59 (2-proton singlet, H-3[1],3[1']), 7.56 (6-proton singlet, $ArCH_3$), 8.12 (3-proton singlet, OAc); X-ray powder diffraction data: 13.84 w, 12.18 m, 9.82 vs (1), 7.72 vw, 6.85 w, 5.78 w, 5.23 s (2, 2), 4 94 s (2, 2), 4.57 w, and 4.22 m.

Anal. Calc. for $C_{23}H_{26}O_{11}S_2$: C, 50.91; H, 4.83; S, 11.83. Found: C, 50.83; H, 4.87; S, 11.48.

Attempted formylation of ketone **1** *at C-3 and isolation of the dimer* **8** — To a solution of **1** (0.5 g, 2.5 mmoles) in ethyl formate (20 ml) was added a catalytic amount of sodium methoxide[28]. The slurry was boiled under reflux, with stirring, for 3 days; t.l.c. then indicated almost complete conversion of **1** (R_F 0.23, solvent *A*) into a single, Schiff-negative product having R_F 0.64. The mixture was filtered, made neutral with Dry Ice, refiltered, and evaporated to a syrup at 40°/0.2 torr. Components having R_F 0.23 and 0.57 were isolated by preparative t.l.c., with elution with solvent *A*. The component having R_F 0.23 was crystallized from ether–petroleum ether (b.p. 30–60°) to give 0.11 g of unchanged **1**, identical with an authentic sample of **1** by mixed m.p. and i.r. spectral comparison. The component having R_F 0.57 was crystallized from ether–petroleum ether (b.p. 30–60°) to give the dimer **8** (0.13 g, 26%), identical with an authentic sample[10] of **8** by mixed m.p. and i.r. and n.m.r. spectral comparison.

1,6-Anhydro-2,3-O-isopropylidene-4-C-vinyl-β-D-talopyranose (**10**). — To a stirred solution of the ketone **1** (1.0 g, 5 mmoles) in tetrahydrofuran (20 ml) was added dropwise a fresh solution (10 ml) of vinylmagnesium chloride in tetrahydrofuran (Peninsular Chemresearch Inc., Gainesville, Florida). After 20 min at room temperature, all but 10 ml of the tetrahydrofuran was evaporated from the solution at 40°/0.2 torr. Cold water was cautiously added to the solution until evolution of gas had

ceased, and the mixture was acidified by addition of ice-cold, aqueous ammonium chloride solution, and extracted with three 50-ml portions of chloroform. The extracts were combined, washed repeatedly with cold water, dried (sodium sulfate), and evaporated to a yellow syrup, which was dissolved in ether and treated with decolorizing carbon. Addition of petroleum ether (b.p. 30–60°) to incipient turbidity, and refrigeration, gave **10** as powdery, white crystals; yield 0.59 g (53%), m.p. 77.5–78.5°, $[\alpha]_D^{20}$ −61.7 ±2° (*c* 0.47, chloroform); R_F 0.64 (solvent *A*); λ_{max}^{KBr} 2.90 (OH), 6.10 (CH=CH_2), and 7.29 μm (CMe_2); n.m.r. data (100 MHz): τ 3.82 (1-proton quartet, J_{XB} 17.5 Hz, J_{XA} 10.9 Hz, H-X of vinyl group), 4.44 (1-proton quartet, J_{AB} 1.7 Hz, H-B of vinyl group), 4.70 (1-proton doublet, $J_{1,2}$ 2.3 Hz, H-1), 4.72 (1-proton quartet, H-A of vinyl group), 5.74 (1-proton doublet, $J_{6endo,6exo}$ 7.6 Hz, $J_{5,6endo}$ 0 Hz, H-6endo), 5.91 (3-proton multiplet, width between outer peaks ~7 Hz, H-2,3,5), 6.31 (1-proton quartet, $J_{5,6exo}$ 5.4 Hz, H-6exo), 6.85 (1-proton singlet that disappeared on deuteration, OH), 8.39, 8.65 (3-proton singlets, CMe_2); X-ray powder diffraction data: 9.71 m, 8.01 m, 6.76 w, 6.13 s (2), 5.69 m, 5.33 m, 4.89 vs (1), 4.31 m, and 4.16 w. Compound **10** readily sublimed at 60°/0.2 torr.

Anal. Calc. for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.74; H, 6.99.

*1,6-Anhydro-4-C-ethynyl-2,3-O-isopropylidene-β-*D*-talopyranose* (**11**). — To tetrahydrofuran (200 ml) saturated with acetylene at 0° was added, dropwise, ethylmagnesium bromide [prepared from ethyl bromide (10 ml) and magnesium turnings (5 g) in tetrahydrofuran (10 ml)]. The resulting, red solution was maintained for 30 min at 0°, with stirring, acetylene being continuously passed through it. A solution of ketone **1** (0.5 g) in tetrahydrofuran (50 ml) was then added dropwise to the stirred solution, and passage of acetylene was discontinued. After 20 min, the red solution was concentrated at 40°/0.2 torr to 10 ml, acidified by cautious addition of ice-cold, aqueous ammonium chloride solution, and the mixture extracted with three 100-ml portions of chloroform. The extracts were combined, washed with cold water, dried (sodium sulfate), and evaporated to a dark syrup which was dissolved in carbon tetrachloride, and the solution treated with decolorizing carbon, filtered, and concentrated to 10 ml. Refrigeration of the colorless solution gave **11** as colorless, flaky crystals; yield 0.44 g (77%), m.p. 147.5–148.5°, $[\alpha]_D^{20}$ −71 ±1° (*c* 0.56, chloroform); R_F 0.53 (solvent *A*); λ_{max}^{KBr} 2.88 (OH), 3.12 (C≡CH), 4.75 (C≡C), and 7.30 μm (CMe_2); n.m.r. data (100 MHz, assignments confirmed by spin decoupling): τ 4.66 (1-proton doublet, $J_{1,2}$ 2.7 Hz, H-1), 5.49 (1-proton doublet, $J_{2,3}$ 5.5 Hz, H-3), 5.56 (1-proton doublet, $J_{5,6exo}$ 5.7 Hz, H-5), 5.77 (1-proton doublet, $J_{6endo,6exo}$ 8.0 Hz, $J_{5,6endo}$ 0 Hz, H-6endo), 5.81 (1-proton quartet, H-2), 6.31 (1-proton quartet, H-6exo), 6.77 (1-proton singlet, disappeared on deuteration, OH), 7.43 (1-proton singlet, –C≡CH), 8.46, 8 68 (3-proton singlets, CMe_2); X-ray powder diffraction data: 15.07 w, 7.91 s (2), 5.47 broad s (1), 4 53 m, 4.13 m, 3.49 m, 3.17 m, 3.01 w, and 2.93 w.

Anal. Calc. for $C_{11}H_{14}O_5$: C, 58.39; H, 6.24. Found: C, 58.68; H, 6.44.

Reduction of the acetylene **11** *to the alkene* **10** *over Lindlar catalyst.* — Partially poisoned palladium (Lindlar) catalyst[29] (1.0 g) and quinoline (2 drops) were added to a solution of **11** (0.1 g) in ethyl acetate (50 ml). The mixture was hydrogenated at

25 lb. in.$^{-2}$ for 12 h at room temperature; t.l.c. then indicated complete conversion of the acetylene **11** (R_F 0.53, solvent *A*) into the alkene **10** (R_F 0.64, solvent *A*). The suspension was filtered, and the filtrate evaporated at 40°/0.2 torr to a light-yellow syrup, which was dissolved in ether. Petroleum ether (b p. 30–60°) was added to incipient turbidity, and refrigeration gave dense, colorless crystals; yield 50 mg (47%), m.p. 77–78.5°, identical with an authentic sample of **10** by mixed m.p. and i.r.- spectral comparison.

*Preparation of 1,6:4,4^1-dianhydro-4-*C*-(hydroxymethyl)-2,3-*O*-isopropylidene-β-*D*-talopyranose* (**12**). — By a slight modification of the earlier[7] procedure, the ketone **1** (1.0 g, 5 mmoles) in ether was treated with an excess of an ethereal solution of diazomethane. The solution was stirred for 2 h at 0°, and then kept for 18 h at room temperature. Evaporation gave a colorless syrup that crystallized spontaneously. Recrystallization from ether–petroleum ether (b.p. 30–60°) gave the *spiro* epoxide **12**; yield 820 mg (77%) [lit.[7] yield 46%]. The physical properties of **12** were in agreement with those reported[7].

*Dissolving-metal reduction of 1,6:4,4^1-dianhydro-4-*C*-(hydroxymethyl)-2,3-*O*-isopropylidene-β-*D*-talopyranose* (**12**) *to give the branched-chain sugar* **13**. — To a stirred solution, maintained at the temperature of Dry Ice–isopropyl alcohol, of the *spiro* epoxide **12** (0.25 g, 1.1 mmoles) in liquid ammonia were added pieces of sodium (excess) sufficient to maintain a dark-blue color in the solution during 0.5 h The solution was removed from the refrigeration bath and allowed to warm to room temperature, with concomitant evaporation of ammonia. Sufficient water was then added dropwise to turn the solid residue into a thick paste; this was extracted with three 100-ml portions of dichloromethane, and the extracts were combined, dried (sodium sulfate), and evaporated to a white solid. T.l.c. of the solid indicated complete conversion of the *spiro* epoxide **12** (R_F 0.65) into a single component having R_F 0.45 (solvent *A*). No component that was positive to the ninhydrin spray-reagent was observed in a chromatogram of the dichloromethane extract. The solid was dissolved in ethyl ether and, on refrigeration, the solution gave 1,6-anhydro-2,3-*O*-isopropylidene-4-*C*-methyl-β-*D*-talopyranose (**13**), isolated as fine, colorless needles; yield 70 mg (30%), m.p. 152.5–153.0°, $[\alpha]_D^{20}$ −44.8 ± 1° (*c* 0.9, chloroform); λ_{max}^{KBr} 2.84 (OH), 7.15, 7.27 μm $(CMe)_2$; n.m.r. data (60 MHz): τ 4.72 (1-proton triplet, $J_{1,2\ 3}$ 2.0 Hz, H-1), 5.77 (1-proton doublet, $J_{6exo,6endo}$ 7.6 Hz, $J_{5,6endo}$ 0 Hz, H-6endo), 5.92 (3-proton multiplet, width between outer peaks 5 Hz, H-2,3,5), 6.33 (1-proton quartet, $J_{5,6exo}$ 5.4 Hz, H-6exo) 6.97 (1-proton, broadened singlet that disappeared on deuteration, OH), 8.42, 8.67 (3-proton singlet, CMe_2), 8.57 (3-proton singlet, CH_3); X-ray powder diffraction data: 9.57 m, 7.87 s (2, 2), 6.55 w, 5.98 vs (1), 5 37 s (3), 4.87 s (2, 2), 4.69 m, 4.30 m, 4.10 w, 3.90 m, 3.66 m, and 3.26 m.

Anal. Calc. for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46. Found: C, 55.46; H, 7.53.

T.l.c. of the mother liquors showed that they still contained a large proportion of **13**.

1,6-Anhydro-2,3-O-isopropylidene-4-C-methyl-β-D-talopyranose (**13**) *by addition of methylmagnesium iodide to the ketone* **1**. — An ethereal solution of methyl-

magnesium iodide, prepared from an excess of methyl iodide (5 ml) and magnesium, was added dropwise to a stirred solution of the ketone **1** (0.30 g, 1.5 mmoles) in ethyl ether. After evaporating the mixture to 5 ml and diluting the solution with chloroform (50 ml), water was carefully added until evolution of gas had subsided. The mixture was acidified (aqueous ammonium chloride), extracted with chloroform (three 100-ml portions) and the extracts were combined, dried (sodium sulfate), and evaporated to a syrup. T.l.c. (solvent *A*) indicated the presence of a single, fast-moving component, R_F 0.45. Treatment of an ethereal solution of the syrup with decolorizing carbon followed by filtration and evaporation gave a syrup that crystallized spontaneously. Recrystallization from ethyl ether in the cold gave fine, colorless needles; yield 0.31 g (>97%), m.p. 152–153°, R_F 0.45, identical with a sample of **13** by mixed m.p. and i.r. spectral comparison.

1,6-Anhydro-4-C-formyl-2,3-O-isopropylidene-β-D-talopyranose (**14**) *by ozonolysis of the alkene* **10**. — Ozone was passed through a solution of the alkene **10** (0.5 g, 2.2 mmoles) in methanol (50 ml) cooled to the temperature of Dry Ice–isopropyl alcohol. After 5 min, the solution turned blue, and ozone was passed through for an additional 20 min. The solution was then purged of ozone by bubbling pure oxygen through until the blue color had been discharged (10 min). Sodium iodide (1.5 g) and acetic acid (6 ml) were added simultaneously, and the solution was removed from the Dry Ice bath and allowed to warm to room temperature. Saturated, aqueous sodium thiosulfate solution was added dropwise to the stirred solution until the brown color of iodine had disappeared, and the solution was evaporated at 40°/0.2 torr to a solid residue, which was taken up in aqueous sodium thiosulfate solution. The mixture was extracted with three 100-ml portions of chloroform, and the extracts were combined, dried (sodium sulfate), filtered, and evaporated to a syrup that resisted crystallization; yield 0.33 g (66%). T.l.c. indicated the presence of a single component, R_F 0.21 (solvent *A*), positive to Schiff reagent. This product, the 4-*C*-formyl sugar **14**, was characterized as its crystalline oxime **15**.

1,6-Anhydro-4-C-formyl-2,3-O-isopropylidene-β-D-talopyranose oxime (**15**). — To a solution of the *C*-formyl derivative **14** (0.33 g, 1.4 mmoles) in methanol (20 ml) were added hydroxylamine hydrochloride (0.6 g, 8.7 mmoles), potassium hydrogen carbonate (0.7 g), and water (0.1 ml), and the mixture was boiled under reflux for 20 min; t.l.c. then indicated the complete conversion of the aldehyde **14** into the oxime **15**, R_F 0.25 (solvent *A*). The mixture was evaporated to dryness at 40°/0.2 torr, the solid residue was extracted with three 50-ml portions of hot chloroform, and the extracts were combined, and evaporated to a solid, which was dissolved in hot carbon tetrachloride (10 ml). Refrigeration gave **15** as white, flaky crystals; yield 0.25 g (71%), m.p. 153–154°, $[\alpha]_D^{20}$ −87.2 ±2° (*c* 0.3, chloroform); R_F 0.25 (solvent *A*); λ_{max}^{KBr} 2.85, 2.99 (OH), and 7.34 μm (CMe_2); n.m.r. data (100 MHz, acetone-d_6): τ −0.76 (1-proton singlet that disappeared on deuteration, oxime OH), 2.51 (1-proton singlet, –N=CH–), 4.81 (1-proton doublet, $J_{1,2}$ 3.0 Hz, H-1), 5.39 (1-proton doublet, $J_{2,3}$ 5.8 Hz, H-3), 5.43 (1-proton doublet, $J_{6endo,6exo}$ 7.4 Hz, $J_{5,6endo}$ 0 Hz, H-6endo), 5.72 (1-proton doublet, $J_{5,6exo}$ 6.0 Hz, H-5), 6.10 (1-proton quartet, H-2), 6.37

(1-proton quartet, H-6exo), 7.11 (1-proton singlet that disappeared on deuteration, OH), 8.50, 8.73 (3-proton singlets, CMe_2); X-ray powder diffraction data: 15.10 vs (1, 1), 7.77 m, 5.54 vs (1, 1), 5.23 w, 4.99 w, 4.51 m, 4.14 w, 3.91 w, and 3 67 w.

Anal. Calc. for $C_{10}H_{15}NO_6$: C, 48.97; H, 6.16; N, 5.70. Found: C, 49.16; H, 6.17; N, 5.63.

Details of the Raman spectrum of this compound have been published[24].

*1,6-Anhydro-4-*C*-carboxy-2,3-*O*-isopropylidene-β-*D*-talopyranose* (**16**) *by ozonolysis of the acetylene* **11**. — Following the procedure of Criegee and Lederer[25], acetic acid (15 ml) was added to an ice-cold solution of the acetylene **11** (0.1 g, 0.4 mmole) in carbon tetrachloride (85 ml). The solution was maintained at 0°, and ozone was passed through it. After 5 min, the solution turned blue; passage of ozone was continued for an additional 40 min, and then pure oxygen was passed in until the blue color of ozone had been discharged (10 min). T.l.c. indicated the complete conversion of **11** [R_F 0.53 (solvent *A*)] into a new product, R_F 0.14 (solvent *B*), presumably **16**, as it gave a positive test for an acid with the Bromocresol Green spray-reagent. The solution was evaporated at 20°/0.1 torr to a syrup, and toluene was added to and evaporated from the residue to remove traces of acetic acid. The resulting syrup (0.17 g) was dissolved in ether (5 ml), and petroleum ether (b.p. 30–60°) was added to incipient turbidity. Refrigeration gave a few mg of the acid **16**, as a fine, white precipitate, λ_{max}^{KBr} 2.95 (OH), 5.76 (CO_2H), and 7.29 μm (CMe_2).

Anal. Calc. for $C_{10}H_{14}O_7$: C, 48.78; H, 5.73. Found: C, 48.45; H, 5.53.

*1,6-Anhydro-2,3-*O*-isopropylidene-4-*C*-(methoxycarbonyl)-β-*D*-talopyranose* (**17**). — To a solution of the ethynyl derivative **11** (250 mg, 1.1 mmoles) in carbon tetrachloride (80 ml) chilled to 0° was added acetic acid (15 ml). The solution was ozonized at 0° for 45 min, and then oxygen was passed through to purge it of the excess of ozone; t.l.c. then indicated complete conversion of the starting material into a slow-moving compound. No change was chromatographically discernible after refrigeration of the colorless solution for 1 day. After evaporation of the solution under diminished pressure to a syrup at 10°, and addition and evaporation of toluene to remove traces of acetic acid, the residue was dissolved in ethanol (10 ml), and the solution was diluted with ethyl ether (100 ml). The solution was treated with an excess of diazomethane in ether, stirred for 1 h, chilled to 0°, and finally treated with acetic acid until the bright-yellow color had disappeared and evolution of nitrogen had ceased. Evaporation of the solution to a syrup, and addition and evaporation of toluene, to remove traces of acetic acid, gave a colorless syrup for which t.l.c. indicated a major component, R_F 0.74, and a very minor one, R_F 0.61. Distallation of the syrup at 110°/0.2 torr gave the ester **17** as a colorless, viscous liquid; yield 0.23 g (82%), $[\alpha]_D^{20}$ −136.1 ±1° (*c* 0.64, chloroform); R_F 0.74; λ_{max}^{film} ~3.55 (OH)[26], 5.66 (CO_2Me), and 7.47 μm (CMe_2); n.m.r. data (60 MHz, chloroform-*d*): 2.95 (1-proton singlet that disappeared on deuteration, OH), 4.62 (1-proton doublet of narrowly spaced doublets, $J_{1,2}$ 3.1 Hz, $J_{1,5}$ 1.0 Hz, H-1), 4.88 (1-proton doublet of narrowly spaced multiplets, $J_{2,3}$ 6.0 Hz, H-3), 5.44 (1-proton doublet of narrowly spaced multiplets,

$J_{5,6exo}$ 6.0 Hz, $J_{5,6endo}$ 0 Hz, H-5), 5.51 (1-proton doublet, $J_{6exo,6endo}$ 8.0 Hz, H-6endo), 5.72 (1-proton quartet, H-2), 6.15 (3-proton singlet, OMe), 6.20 (1-proton quartet, H-6exo), 8.44, 8.68 (3-proton singlets, CMe_2).

Anal. Calc. for $C_{11}H_{16}O_7$: C, 50.77; H, 6.20. Found: C, 50.92; H, 6.12.

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