Alicyclic Carbohydrates. XXXII. Synthesis of Pseudo-β-DL-gulopyranose from a Diacetoxybutadiene. Proton Magnetic Resonance Studies[1,2]

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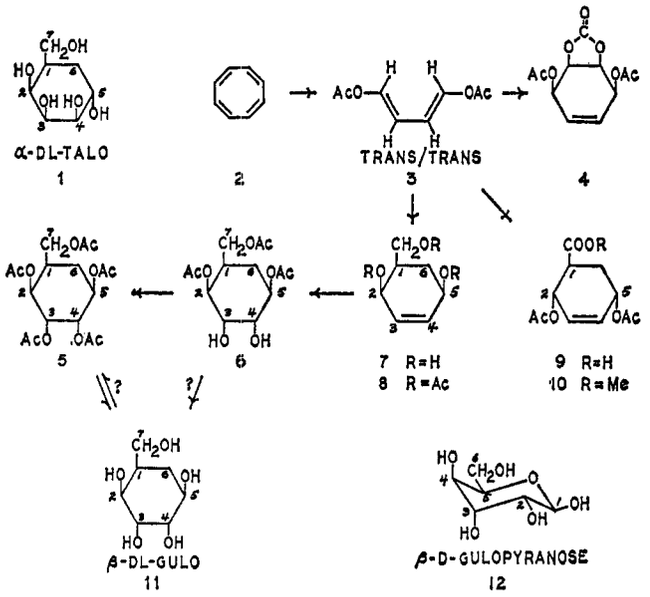
Configurations of the three diastereomeric 1,4-diacetoxy-1,3-butadienes were confirmed by nmr spectroscopy. The assignments were based on coupling constants calculated from measured frequency differences in the AA'XX' (or AA'BB') patterns present in the spectra of the *cis, cis* and *trans, trans* diastereomers. The *trans,trans* diene was used for synthesis of a pseudo-sugar (here defined as a cyclic monosaccharide whose ring-oxygen atom has been replaced by methylene). Diels–Alder reaction of the *trans,trans* diene with allyl acetate gave the all-*cis* diastereomer of 2,5-dihydroxy-3-cyclohexene-1-methanol triacetate. The carbon–carbon double bond in this adduct was remarkably inert, but did react with *t*-butyl hydroperoxide–osmium tetroxide to give 2,3,4,5-tetrahydroxy-1-cyclohexanemethanol triacetate, shown by proton magnetic double resonance to have the β-DL-gulopyranose configuration. This pentol triacetate on reaction with acetic anhydride gave the pentol pentaacetate, which on hydrolysis gave the desired free pentol, pseudo-β-DL-gulopyranose.

We recently reported the synthesis of a hydroxymethylcyclohexanetetrol which was shown by proton magnetic resonance (pmr) to have the configuration (see formula 1, Scheme I) of α-DL-talopyranose.[4a] This pseudo-talopyranose belongs to a class of compounds which have been designated *pseudo-sugars* (alicyclic analogs of cyclic monosaccharides); it appears to be the first known pseudo-hexose.[4]

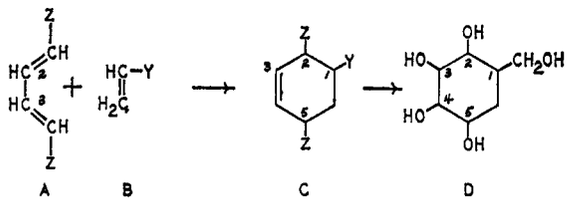
SCHEME I



We now report the synthesis of a second pseudohexose (**11**), which has been shown by pmr and spin-decoupling studies to have the configuration of β-DL-gulopyranose (**12**). It is hoped that in some cases pseudo-sugars will be accepted by enzymes or biological systems in place of corresponding true sugars, and thus may serve to inhibit the growth of malignant or pathogenic cells.[5,6]

The most general and convenient route (Scheme II) to pseudo-hexopyranoses (D) appears to be the Diels–Alder reaction of a 1,4-disubstituted 1,3-butadiene (A) with a dienophile (B) to give a 1,2,5-trisubstituted 3-cyclohexene (C), convertible into a hydroxymethylcyclohexanetetrol (D). Here Z would be a univalent group (*e.g.*, acetoxyl) readily convertible into hydroxyl, and Y would be either hydroxymethyl or some group (*e.g.*, carbomethoxyl or acetoxymethyl) readily convertible into hydroxymethyl.

SCHEME II



For our present synthesis, it appeared that a suitable diene would be 1,4-diacetoxy-1,3-butadiene,[7-9] and in particular its *trans, trans* diastereomer, whose position 2–3 single bond can readily assume the cisoid conformation (A) needed for the Diels–Alder reaction. In the course of this work, we have used pmr spectroscopy (see below) to confirm the configurations of the three diastereomers of 1,4-diacetoxy-1,3-butadiene, which previously were based on infrared spectroscopy.[10]

(1) Presented in part by G. E. M. at the Winter Meeting of the American Chemical Society, Division of Carbohydrate Chemistry, Phoenix, Ariz., Jan 1966.

(2) For preceding paper, see G. E. McCasland, M. O. Naumann, and Lois J. Durham, *Carbohyd. Res.*, **4**, 516 (1967).

(3) To whom any correspondence should be addressed: University of San Francisco.

(4) G. E. McCasland, S. Furuta, and Lois J. Durham, *J. Org. Chem.*, **31**, 1516 (1966).

(4a) NOTE ADDED IN PROOF.—H. J. Schaeffer and R. Vince have prepared nucleoside analogs in which, for example, a purine residue is attached to position 5 of *trans*-2-hydroxy-1-cyclohexanemethanol: see *J. Med. Chem.*, **11**, 15 (1968), and earlier publications there cited.

(5) With the experience gained on pseudo-talose and pseudo-gulose, efforts to synthesize pseudo-sugar analogs of the biologically more important (and optically active) natural sugars, such as D-glucose, are in progress; these isomers in all probability will be more active biologically. (Note: Preliminary results on the compound here described as pseudo-β-DL-gulopyranose appeared to indicate an α-DL-mannopyranose configuration; actually, the pseudo-mannopyranoses are still unknown.)

(6) The synthesis of pseudo-α-DL-galactopyranose has recently been completed: G. E. McCasland, S. Furuta, and Lois J. Durham, *ibid.*, **33**, 2841 (1968).

(7) W. Reppe, O. Schlicting, K. Klager, and T. Toepel, *Ann.*, **560**, 1 (1948). A product reported by these authors as 1,2-diacetoxy-3-cyclobutene was later shown by Criegee and coworkers[8] to be 1,4-diacetoxy-1,3-butadiene.

(8) (a) R. Criegee and P. Becher, *Chem. Ber.*, **90**, 2516 (1957); (b) R. Criegee, W. Hörauf, and W. D. Schellenberg, *ibid.*, **86**, 126 (1953).

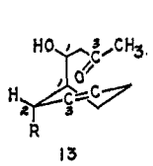
(9) A. C. Cope, N. Nelson, and D. Smith, *J. Amer. Chem. Soc.*, **76**, 1100 (1954).

(10) H. H. Inhoffen, J. Heimann-Trosien, H. Muxfeldt, and H. Krämer, *Chem. Ber.*, **90**, 187 (1957).

Although acrylic acid and methyl acrylate had previously been used as dienophiles with this same diene[11,12] we chose instead to use allyl acetate, in order to avoid possible difficulties in reduction of the carboxy or carbomethoxy group to hydroxymethyl at a later stage in the synthesis. (Such difficulties had previously been encountered in the synthesis[4] of pseudo-talopyranose.) Although allyl acetate is much less reactive than methyl acrylate, a good yield of the desired enetriol triacetate (**8**) was obtained after 2 days of reaction at 200°.

The enetriol triacetate, so far obtained only as a syrup, gave a correct microanalysis and appropriate infrared and pmr spectra. On hydrolysis it gave the free enetriol, also obtained as a syrup, which is an alicyclic analog of the true sugar derivative (see Scheme III) known as "pseudo-glucal" (**15**), although differing in configuration.[13] The configurations **7** and **8** of the enetriol and its triacetate are based primarily on chemical correlation with the pentol triacetate (see below).

Scheme III



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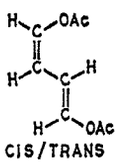
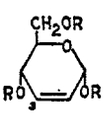


CIS/TRANS

14



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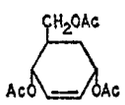

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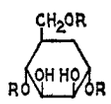
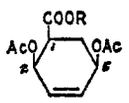


17 R=H

18 R=OAc



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Efforts to convert the enetriol triacetate **8** into the pentol 2,5,7-triacetate **6** by hydroxylation of the double bond were at first unsuccessful.[14] This double bond is extraordinarily inert to nearly all additive reagents which normally react readily with cyclohexenes, including bromine, hypobromous acid, performic acid, the Prévost reagent, and hydrogen with a catalyst (at least under low pressure). The carbon–carbon double bond was not detected by infrared spectroscopy (apparently because of near-symmetry); however its presence was readily and definitely demonstrated by pmr spectroscopy. Reaction of the enetriol triacetate with osmium tetroxide in pyridine finally did give the desired pentol triacetate **6**, but only in 11% yield. In later preparations the yield of product, isolated as pentol pentaacetate **5**, was increased to nearly 40% by use of *t*-butyl hydroperoxide catalyzed with osmium tetroxide.[15]

(11) R. McCrindle, K. H. Overton, and R. A. Raphael, *J. Chem. Soc.*, 1560 (1960).

(12) E. E. Smissman, J. T. Suh, M. Oxman, and R. Daniels, *J. Amer. Chem. Soc.*, **84**, 1040 (1962).

(13) The pseudo-glucal 4,6-diacetate (anomeric configuration unknown?) was obtained by heating tri-*O*-acetyl D-glucal with water. On acetylation of pseudo-glucal diacetate, the triacetate was obtained. See B. Helferich, *Advan. Carbohyd. Chem.*, **7**, 210 (1952).

(14) Note that the cyclohexane ring-numbering used here for pseudohexopyranoses is different from the accepted numbering of true hexopyranoses.

(15) R. Daniels and J. L. Fischer, *J. Org. Chem.*, **28**, 320 (1963).

The striking inertness of the double bond in the enetriol triacetate **8** is perhaps due to deactivation through π-complex interaction with the carbonyl group of the acetoxymethyl side chain. It appears that the side chain can assume an *"endo"* conformation which would be sterically favorable for such interaction. A similar interaction has been postulated by Kugatova-Shemyakina and Ovchinnikov[16] to account for the unique behavior of certain side-chain carbonyl derivatives of the 3-cyclohexene series, such as the 2-substituted derivatives of 1-(1-hydroxy-3-oxobutyl)-3-cyclohexene (**13**).

Our enetriol triacetate adduct was at first assigned the *endo* or DL(1/25) configuration **16** by analogy with the adduct from acrylic acid or methyl acrylate, **9** or **10**, claimed by Smissman and coworkers[12] to have this configuration, although McCrindle and coworkers[11] had favored the DL(125/0) or *exo* configuration **19**. Also, our own pmr studies at first seemed to support the DL-(1/25) configuration. However, more complete pmr studies on the enetriol triacetate, and especially on the pentol triacetate **6** derived from it (see below), now definitely have established the enetriol triacetate configuration as *exo* or DL(125/0), **8**.[5] Certain other Diels–Alder adducts also are known to have the *exo* or all-*cis* configuration, for example, the adduct **4** from vinylene carbonate, reported by Criegee and Becher.[8] It is noteworthy that vinylene carbonate (or allyl acetate) requires 2 days at about 200° for reaction, while acrylic acid or ester reacts with the diacetoxy diene under much milder conditions. The varying steric results possibly could be explained in terms of the relative rates of formation and thermodynamic equilibration of the adducts from the various pairs of reactants.

The pentol triacetate **6** was a sharp-melting, crystalline compound with appropriate microanalysis and infrared spectrum. The possibility was considered that one of the acetyl groups had migrated from position 2, 5, or 7 to position 3 or 4 to give a structurally isomeric product. However, it was demonstrated by pmr (see below) that no acetyl migration[17] takes place under the conditions of preparation used for this compound.

It would be expected, from many similar examples, that the two hydroxyl groups would add to positions 3 and 4 of the enetriol triacetate **8** in a manner *trans* to the acetoxy groups at positions 2 and 5. The resulting pentol triacetate was at first thought to have the α-DL-mannopyranose configuration **18**, because of preliminary pmr results and the assumed configuration **16** of the enetriol triacetate. However, the pentol triacetate is now known to have the β-DL-gulopyranose configuration **6**.[6]

The pentol triacetate **6**, mp 105°, on acetylation in the usual manner gave the pentol pentaacetate **5**, mp 133°, whose characterization is described below. Hydrolysis of the pentol pentaacetate finally gave the desired free pentol, pseudo-β-DL-gulopyranose **11** as a colorless syrup with appropriate infrared and pmr spectra. The configuration is based primarily on chemical correlation with the pentol triacetate and pentaacetate. The free pentol presumably could also be prepared by hydrolysis of the pentol triacetate.

(16) G. P. Kugatova-Shemyakina and Y. A. Ovchinnikov, *Tetrahedron*, **18**, 697 (1962).

(17) Recent work by S. J. Angyal, P. T. Gilham, and G. J. H. Melrose [*J. Chem. Soc.*, 5252 (1965)] indicates that such acetyl migrations are more common than formerly supposed.

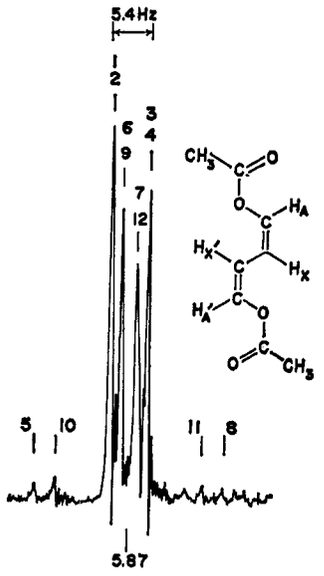

Figure 1.—Proton magnetic resonance spectrum at 60 MHz of the *cis,cis* diastereomer (mp 101–102°) of 1,4-diacetoxy-1,3-butadiene in chloroform-*d*.

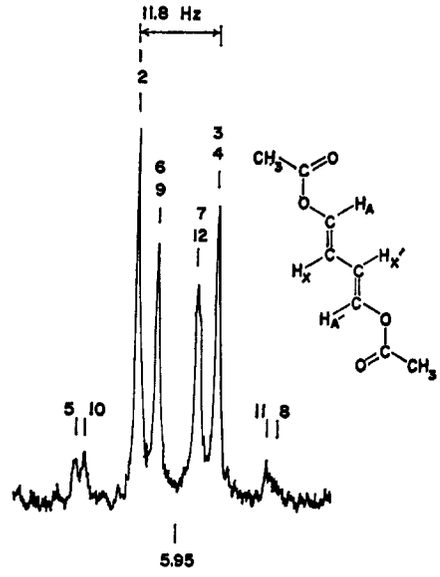

Figure 2.—Proton magnetic resonance spectrum at 60 MHz of the *trans,trans* diastereomer (mp 103–104°) of 1,4-diacetoxy-1,3-butadiene in chloroform-*d*.

Proton Magnetic Resonance Studies on the Diacetoxybutadienes.—The pmr spectrum (Figure 1) of *cis,cis*-1,4-diacetoxy-1,3-butadiene in chloroform-*d* contained only three sets of signals, with relative areas of six, two, and two protons. The two acetate methyl groups produced a sharp singlet at 2.18 ppm. The four olefinic protons produced a symmetrical pattern consisting of one two-proton component at 5.87 and another at 7.10 ppm. Such a pattern is characteristic of a set of two pairs of equivalent nuclei with unequal coupling constants, often described as an AA′XX′ (or AA′BB′) case.[18,19]

For our present analysis, the AA′XX′ approximation has been used.[20,21] Coupling constants for the *cis,cis* diene were calculated from measurements of the observed line spacings in either the AA′ or XX′ component: $J_{AX} = 6.7$, $J_{AX'} = -1.3$, $J_{XX'} = 11.0$ and $J_{AA'} = 1.6$ Hz.

The spectrum of the *trans,trans* diene (Figure 2) was very similar, with the three sets of signals located at 2.13, 5.95, and 7.35 ppm. The calculated coupling constants for this isomer were $J_{AX} = 12.5$, $J_{AX'} = -0.7$, $J_{XX'} = 11.5$, and $J_{AA'} = 0.8$ Hz. Each set of coupling constants was calculated from measurements of the observed line spacings, which correspond to energy levels given by Pople, Schneider, and Bernstein[18,19] (see Table I). Although these calculations do not in themselves permit one to distinguish J_{AX} from $J_{AX'}$ or $J_{AA'}$ from $J_{XX'}$, or to choose the relative signs, the values given are believed correct by analogy to known *cis*, *trans*, single-bond vicinal, and long-range coupling constants for other 1,4-disubstituted 1,3-dienes.[22–24] Nevertheless, the numerical values of Table I are dependent on correct assignment of the lines, and any error in these assignments might cause reversal of the relative magnitudes or signs of the coupling constants.

TABLE I

PARAMETERS USED FOR CALCULATING COUPLING CONSTANTS OF THE 1,4-DIACETOXY-1,3-BUTADIENES

Parameter	Frequency difference measured between lines[a]	Assignment	Observed values from the spectra (Hz)[b] *cis,cis*	*trans,trans*
N	1–3; 2–4	$J_{AX} + J_{AX'}$	5.4	11.8
K	5–6; 7–8	$J_{AA'} + J_{XX'}$	12.6	12.2
M	9–10; 11–12	$J_{AA'} - J_{XX'}$	−9.5	−10.7
$(K^2 + L^2)^{1/2}$	5–7; 6–8	...	±15.2	±18.3
$(M^2 + L^2)^{1/2}$	9–11; 10–12	...	±12.0	±16.7
L	(Calcd)	$J_{AX} - J_{AX'}$	(7.9)	(13.2)

[a] Designations of Pople, *et al.*[18,19] [b] Average of data taken from the AA′ and XX′ components, using two tracings of each expanded 60-MHz spectrum.

The 1,4-diacetoxy-1,3-butadiene isomers of mp 101–102° and 103–104° may thus be assigned the configurations *cis,cis* and *trans,trans*, respectively.[25] The one remaining isomer then necessarily has the one remaining, *cis,trans* configuration, **14**. Our assignments to the three diastereomers confirm those of

(18) (a) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp 138–140; (b) see also Table 6–18, p 141.

(19) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, London, 1965, Vol. 1, pp 392–99.

(20) An AA′XX′ spectrum theoretically consists of 12 "A" transitions and 12 "X" transitions. Since the A transitions 1 and 2 are both equal to $N/2$, and 3 and 4 to $-N/2$, a maximum of 10 A lines is actually found. These ten lines theoretically consist of a high intensity doublet (lines 1,2,3,4) and two symmetrical quartets (lines 5,6,7,8 and 9,10,11, and 12), all centered on the frequency ν_A. (The predicted X spectrum, centered on ν_X, is identical with the A spectrum.) Although the inner lines of each quartet are always more intense, the numbering of the lines depends on the signs of K and M, so that in our present example the two quartets are numbered from left to right 5, 6, 7, 8 and 10, 9, 12, 11, respectively. The line 9 is coincident with line 6, and 12 with 7.

(21) For similar analysis of an AA′XX′ pattern in the spectrum of a dimercaptocyclohexanetetrol, see G. E. McCasland, S. Furuta, A. Furst, L. F. Johnson, and J. N. Shoolery, *J. Org. Chem.*, **28**, 456 (1963).

(22) R. T. Hobgood, Jr., and G. H. Goldenstein, *J. Mol. Spectrosc.*, **12**, 76 (1964).

(23) For example, the coupling constants J_{AX}, $J_{XX'}$, J_{AX}, and $J_{AA'}$ for certain 1,3-butadienes having the substituents indicated are, respectively, as follows (see ref 24): 1,4-dicarbomethoxy, *cis,cis*, 11.8, 11.3, −1.3 and ±1.3; 1,4-dicarbomethoxy, *trans,trans*, 16.5, 11.2, −0.7, and ±0.6; 1,4-dicarboxy, *trans,trans*, 15.8, 11.7, −0.71, and 0.5; 1,4-diphenyl, *trans,trans*, 15.6, 10.8, −0.94, 0.90; 1,4-dichloro, *cis,cis*, 7.3, 10.4, −1.2, 1.7; 1,4-dichloro, *trans,trans*, 13.1, 11.2, −0.69, 0.83.

(24) (a) A. A. Bothner-By and R. K. Harris, *J. Amer. Chem. Soc.*, **37**, 3445 (1965); (b) *ibid.*, **37**, 3451 (1965).

(25) Although the *cis,cis* and *trans,trans* isomers have nearly the same melting point, they are prepared from different starting materials, and are readily distinguished spectroscopically.

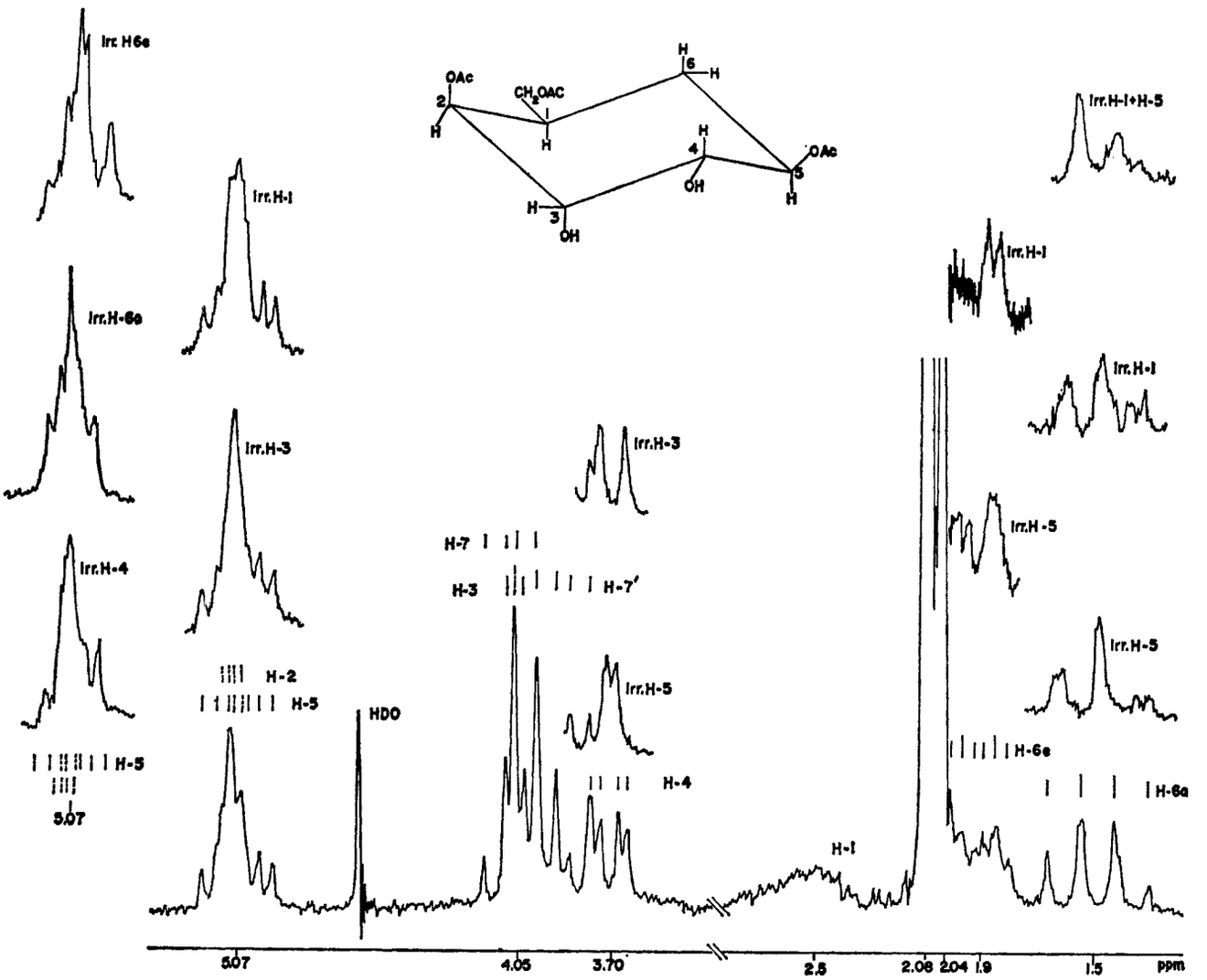

Figure 3.—Proton magnetic resonance and double resonance spectra at 100 MHz of pseudo-β-DL-gulopyranose 2,5,7-triacetate in chloroform-*d* (containing deuterium oxide).

Inhoffen and coworkers, which were based on infrared spectroscopy.[10] The *cis* and *trans* double bonds were reported by these authors to have characteristic C–H deformation frequencies of 760 and 940 cm^{-1}, respectively.

If one desired merely to distinguish the *cis,cis* and *trans,trans* isomers, it would be sufficient to measure the spacing of the intense doublet (lines 1 and 3, Figure 1 or Figure 2) which gives $J_{AX} + J_{AX'}$, since in such isomers $J_{AX'}$ is negligible compared to J_{AX}.

The pmr results suggest that the *cis,cis* and *trans,-trans* isomers have *trans*-coplanar favored conformations with respect to the C_2–C_3 single bond and both C=C double bonds. Apparently no evidence is yet available to indicate the favored conformations of the C_1—O or C_4—O single bonds, or of the acetoxy group C—C or C—O single bonds, in these molecules. The *cis,cis* and *trans,trans* isomers in the *trans*-coplanar conformations both belong to the symmetry point-group C_{iv}, due to possession in each case of a twofold proper rotation axis and a vertical plane (each also has an inversion center). These symmetry characteristics[26] are reflected in the spectra.

(26) (a) K. Mislow, "Introduction to Stereochemistry," W. A. Benjamin, Inc., New York, N. Y., 1966, pp 23–33; (b) M. Zeldin, *J. Chem. Educ.*, **43**, 17 (1966).

No satisfactory pmr spectrum of the *cis,trans* isomer **14** has yet been obtained, because of inadequate sample purity, resulting apparently from instability. However, since this compound in its most symmetrical conformation **14**, belongs to the less symmetrical point-group C_S, one would expect its spectrum to be quite different in certain respects. The suggested conformation has no proper rotation axis (or inversion center), but does have a plane of symmetry.

Pmr Studies on Pseudo-Gulose Derivatives.—The spectrum (not shown) of the **enetriol triacetate** (**8**) was recorded at 60 MHz only. Presence of the chemically inert carbon–carbon double bond was confirmed by a two-proton signal centered at 5.93 ppm (W_h = 7–8 Hz)

Integration revealed twelve protons in the region 1.5–2.5 ppm, nine of which belong to the three acetate methyl groups. However, only two sharp methyl singlets (2.03, 2.06 ppm) of about equal intensity, emerging from a broader signal, were actually observed. The spectral region 1.5–2.5 ppm must also contain signals for the one tertiary proton and two methylene protons of the ring.

The two side-chain methylene protons appeared at 4.07 ppm (complex multiplet) and the two AcO-CH ring protons at 5.25 ppm (overlapping multiplets).

Configurational interpretation was not attempted; however, it is known from chemical correlations that this enetriol triacetate has the all-*cis* configuration (**8**).

The spectrum (Figure 3) of the **pentol triacetate 6** was recorded at 100 MHz in chloroform-*d* (containing a little deuterium oxide). Deuterium exchange simplified this spectrum by eliminating both the hydroxyl proton signals, one a doublet (J = 7 Hz) at 3.40 ppm and the other somewhere in the region 3.7–4.2 ppm, masked by signals of H-3, 4, 7, and 7′.

Although comparisons with the 60-MHz spectrum were helpful, detailed analysis was achieved only with the aid of field-swept double resonance.[27] The assignments from left to right (Figure 3) were as follows.

At 5.07 ppm there is a presumably eight-line pattern (sum of J = 26 Hz, central four lines masked by H-2) of the axial proton H-5, due to coupling with axial H-4 and H-6_a, and equatorial H-6_e. This H-5 pattern was superimposed on that of equatorial H-2, which was a pair of doublets, with 2 and 3 Hz spacings arising from EA and EE couplings. Observation of this region while sequentially irradiating H-1, H-3, H-4, H-6_a and H-6_e (see upper traces, left side, Figure 3) revealed the expected simplifications in the H-5 and H-2 patterns.

The signal of H-3 at 4.05 ppm was nearly masked by the eight line pattern of H-7 and H-7′ centered at 3.97 ppm. However, the H-3 signal was located by irradiating H-3 while observing H-2 and H-4, and H-3 was shown to have two small couplings, about 3 Hz. This proves H-3 is equatorial, since H-4 is known to be axial.

At 3.70 ppm the axial proton H-4 appeared as a pair of doublets, due to couplings with axial H-5 and equatorial H-3 (9.5 and 3 Hz, respectively). This was shown by irradiating H-5 and H-3 while observing H-4 (upper traces, center of Figure 3).

The broad poorly resolved multiplet at about 2.5 ppm must be due to axial H-1, which is coupled to no less than five other protons.

At about 1.9 ppm, the equatorial H-6_e signal was partially masked by the three acetate methyl singlets (2.04, 2.07, and 2.08 ppm), but was still easily located by irradiation of H-1 or H-5 (upper traces, Figure 3).

At 1.5 ppm, axial H-6_a appeared as a quartet (spacing of 11–12 Hz), due to near-equal coupling with one geminal and two vicinal axial protons. Upon irradiation of H-6_e, H-1, H-5, or both H-1 and H-5 (nuclear magnetic triple resonance), the appropriate spectral changes were noted (upper traces, right side, Figure 3).

The double resonance results thus establish the DL (125/34) configuration, and the side-chain equatorial-favored conformation, for the pentol triacetate (see formula, Figure 3). Furthermore, the observed chemical shifts for H-2 and H-5 confirm the acetyl group positions 2 and 5 (no acetyl migration). It is interesting that equatorial H-2 and axial H-5 have nearly the same chemical shift, presumably due to 1,3-diaxial deshielding of H-5 by the 3-OH group. Lemieux and Stevens have discussed such effects.[28]

From chemical correlation, the **pentol pentaacetate 5** must have the same configuration (and conformation) as the triacetate; the spectrum in chloroform-*d* (not shown) was consistent with such an assignment. At

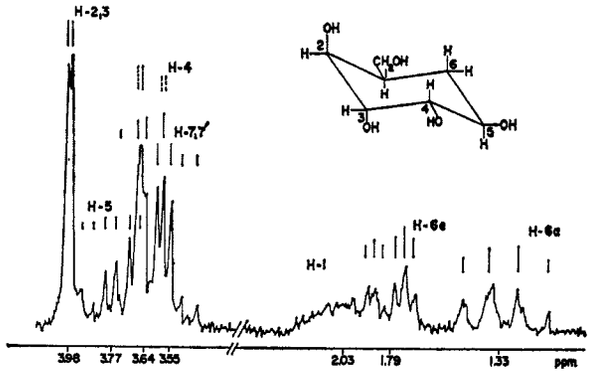

Figure 4.—Proton magnetic resonance spectrum at 100 MHz of pseudo-β-DL-gulopyranose in deuterium oxide.

5.0–5.3 ppm, three of the four AcO-C**H** ring protons appeared as superposed multiplets; the fourth proton produced a separate multiplet at 5.38 ppm. The latter signal probably is that of H-3, formula **5**, since in the spectrum of the true sugar, β-D-gulopyranose pentaacetate, the signal of H-3, formula **12**, also appears at this location.[28] However, we do not yet have completely reliable assignments for the four pseudo-sugar protons H-2, H-3, H-4, and H-5 of **5**.

Signals of the sidechain methylene protons (H-7, H-7′) appeared as the AB part of an ABX pattern (X part is H-1), with AB centered at 4.97 ppm and having spacings of 11 (J_{AB}), 8, and 6 Hz in the 60-MHz spectrum.

The five acetate methyls (15 protons) produced the usual singlets, at 2.13 (axial, six protons), 2.04 (equatorial, six protons), and 1.98 ppm (side chain, three protons). In the same region (1.4–2.8 ppm) were seen broad poorly resolved multiplets, which must be due to H-1, H-6_a and H-6_e.

In the spectrum of the *true* sugar, β-D-gulopyranose pentaacetate, the signal of the anomeric proton and the tertiary proton (H-1 and H-5) of **12** are each shifted about 2 ppm downfield as compared with the pseudo-sugar pentaacetate, due to presence of the ring-oxygen.[28]

The spectrum (Figure 4) of the *free pentol*, pseudo-β-DL-gulopyranose, was consistent with the configuration **11** deduced by chemical correlations. Double resonance techniques were used in making the configurational assignment.[27] At 3.98 ppm the equatorial protons H-2 and H-3 appeared as a doublet. The chemical shift between H-2 and H-3 was too small, even at 100 MHz, to permit observation of J_{23}. However, irradiation of either H-1 or H-4 filled in or collapsed part of the H-2 plus H-3 "doublet," confirming its identity.

The axial H-5 pattern (3.77 ppm) presumably is a doubled triplet, resulting from couplings with axial H-4 and the two ring-methylene protons. Double resonance was used to confirm the large and small couplings with H-6_a and H-6_e, respectively.

The signals at 3.64 and 3.55 ppm are produced by H-7 and H-7′ (side-chain methylene); presumably each is a pair of doublets. These signals totally mask the signal (presumable a pair of doublets) of axial H-4 at about 3.64 ppm. The location of H-4 was shown by irradiating H-4 while observing H-2 and H-3 (see above). Since J_{45} would be large, and J_{34} and J_{23} small, the lines should be in the positions indicated in Figure 4 (compare pentol triacetate).

(27) D. W. Whiffen and R. Freeman, *Mol. Phys.*, **4**, 321 (1961).
(28) (a) R. U. Lemieux and J. D. Stevens, *Can. J. Chem.*, **43**, 2059 (1965); (b) *ibid.*, **44**, 249 (1966).

At 2.03 ppm there was a broad, unresolved multiplet, arising from axial H-1. This was confirmed by irradiation of H-1 while observing H-2 and H-3.

The signal for H-6_e, presumably a pair of triplets, appeared at 1.79 ppm, and of H-6_a (quartet) appeared at 1.33 ppm.

The free pentol is thus shown to have the DL (125/34) or β-DL- gulopyranose configuration, and the side chain-equatorial conformation (formula, Figure 4).

Experimental Section

All melting points (corrected) were measured on a Nalge-Axelrod micro hot-stage, Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Darco G-60 decolorizing charcoal[29] and Woelm alumina[30] were used. All evaporations were performed under reduced pressure. Light petroleum of bp 60–110° was used.

Infrared spectra were recorded with Perkin-Elmer Model 427 and Model 137 (Infracord) spectrometers.

Except where otherwise noted, the nmr spectra of free polyols were recorded in deuterium oxide solution, using sodium 2,2-dimethyl-2-silapentanesulfonate (SDSS) as internal reference; spectra of other compounds were recorded in chloroform-*d*, using tetramethylsilane (TMS) as internal reference; and spectra were run at *both* 60 and 100 MHz, using Varian A-60 and HR-100 spectrometers. Chemical shifts are reported in parts per million (ppm) (δ) from the SDSS or TMS reference taken as zero. Field-swept double resonance experiments were conducted with the HR-100 spectrometer according to the method of Johnson.[31] Modulation was provided by the fixed oscillator of the Varian V-3521-A nmr integrator (operated on its lower side-band), and a Hewlett-Packard hp-200-J audio oscillator (monitored by a hp Hewlett-Packard 521-C frequency counter), for fixed and variable modulation, respectively. Triple resonance experiments were conducted with additional modulation from a Hewlett-Packard 200-CD oscillator.

cis,cis-**1,4-Diacetoxy-1,3-butadiene.**—A 1.30-g portion of 4-acetoxycrotonaldehyde (prepared from commercial 1,1-diacetoxy-2-butene *via* the 4-bromo derivative by the procedures of Schmidt and Grob[32]) was treated by the procedure of Inhoffen and coworkers[10] to give a 0.11-g (11%) yield of the pure product, mp 102–103° (lit.[10] 13% yield, mp 101–102°).

The nmr spectrum was recorded (see above).

cis,trans-**1,4-Diacetoxy-1,3-butadiene (14).**—A 8.0-g portion of 4-acetoxycrotonaldehyde diacetate[32] treated by the procedure of Inhoffen and coworkers[10] gave 1.9 g of the crude product as a colorless oil, bp 92–95° (1 mm). On standing in the refrigerator the product solidified (lit.[10] mp 34–36°) but it appeared to be unstable and no satisfactory melting point or nmr spectrum could be obtained.

trans,trans-**1,4-Diacetoxy-1,3-butadiene.**—A 25.0-g portion of commercial cyclooctatetraene treated by the improved three-step synthesis of Hill and Carlson[33] gave a 56% over-all yield o the diacetoxydiene, mp 100–102° (lit.[10] mp 103–104°).

The infrared spectrum contained peaks at 3150, 1750, 1620, 1350, 1220, 1130, 950, and 910 cm^{-1}, and was essentially identical with that reported by Inhoffen and coworkers.[10] The peak at about 950 cm^{-1} reportedly is characteristic of the *trans*-substituted C=C double bond in such compounds.

The nmr spectrum was recorded (see above).

A 3.87-g portion of the diacetoxydiene treated with methyl acrylate by the procedure of Smissman and coworkers[12] gave a 5.12-g (88%) yield of methyl 2,5-diacetoxy-3-cyclohexene-1-carboxylate, as a colorless oil, bp 139–142° (1.5 mm) (lit.[12] 152–155° (3 mm)).

A 2.5-g portion of the diacetoxydiene treated with acrylic acid by the method of McCrindle and coworkers[11] gave a 1.14-g (32%) yield of 2,5-diacetoxy-3-cyclohexene-1-carboxylic acid, mp 142–145° (lit. mp[11] 142–143°).

A portion of the diacetoxydiene failed to react with allyl alcohol (1 mol) when the mixture was boiled under reflux for 24 hr. When another portion of the mixture was heated at 185° for 3 days, no pure product could be isolated.

When a portion of the diacetoxydiene was heated with *cis*-1,2-dichloroethylene (1 mol) at 190–200° for 2 days, only starting material could be isolated.

DL(**125/0**) **Diastereomer of 2,5-Dihydroxy-3-cyclohexene-1-methanol Triacetate (8).**—A mixture of 1.5 g of allyl acetate and 1.7 g of *trans,trans*-1,4-diacetoxy-1,3-butadiene[33] in a sealed Pyrex bomb tube (13 × 180 mm) was heated in an electric bomb furnace at 205–210° for 48 hr. After cooling, the tube was opened (no pressure) and the contents were evaporated, giving a brown oil. This oil was transferred to a column of neutral aluminum oxide (250 × 20 mm), and the column was eluted with 200 ml of benzene. (An ultraviolet lamp is helpful for locating the product, which is fluorescent.) Evaporation of the eluate gave a yellow oil, which was distilled under vacuum, giving 2.35 g of material, bp 142–145° (1 mm). Redistillation gave 1.9 g (70%) of the desired product in the form of a colorless syrup, bp 143–145° (1 mm).

Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.63; H, 6.73.

The infrared spectrum contained peaks at 1725 and 1230 cm^{-1}. The nmr spectrum was recorded (see above).

A portion of this triacetate was hydrolyzed by dissolving it in a 1 *N* solution of hydrogen chloride in ethanol–water (1:1). The resulting solution was boiled under reflux for 6 hr, then evaporated. A colorless syrup, presumably the desired triol, was obtained, but has not been further characterized.

Reactions which were attempted with the enetriol triacetate included: (a) *trans*-hydroxylation of the double bond with performic acid under various conditions; (b) reaction with hypobromous acid or N-bromosuccinimide under various conditions; (c) reaction with 30% aqueous hydrogen peroxide in trifluoroacetic acid; (d) reaction with potassium permanganate and magnesium sulfate. In each case, only starting material was obtained.

A 2.7-g portion of the enetriol triacetate was saponified with hot aqueous–ethanolic sodium hydroxide. The reaction mixture was neutralized, deionized, and evaporated in the usual manner, giving 1.04 g of the free enetriol as a colorless oil. The double bond in the free enetriol failed to react with (a) silver chlorate–osmium tetroxide; (b) performic acid; (c) bromine–carbon tetrachloride; (d) silver acetate and iodine (Prévost reagent); or (e) hydrogen and platinum (or nickel) catalyst. In each reaction, starting material was recovered.

DL(**125/34**) **Diastereomer of 2,3,4,5-Tetrahydroxycyclohexanemethanol 2,5,7-Triacetate (Pseudo-β-DL-Gulopyranose Triacetate) (6).**—The procedure was similar to one described by McCrindle, Overton, and Raphael.[11] A solution of 0.54 g of the enetriol triacetate in 25 ml of anhydrous ether was slowly added with stirring to a solution of 0.5 g of osmium tetroxide in 3.0 ml of anhydrous pyridine and 5.0 ml of anhydrous ether. The mixture was stirred for 5 days in the dark at 25°. The brown residue obtained upon evaporation was taken up in 25 ml of absolute methanol and the solution was saturated with hydrogen sulfide. After 30 min the mixture was filtered, and the filtrate was evaporated. The dark residue was extracted with boiling benzene (3 × 7 ml), and to the combined extract was added 15 ml of light petroleum. After 1 hr the supernatant liquid was decanted from the dark oily sediment, concentrated to about one-third volume, and kept at 25° for 3 days. The colorless needles which had separated were collected and dried: weight 65 mg (11%), mp 103–104°. The product was recrystallized, giving 40 mg of the pure pentol triacetate, mp 104–105°.

Anal. Calcd for $C_{13}H_{20}O_8$: C, 51.31; H, 6.62. Found: C, 51.27, 51.19; H, 6.74, 6.50.

The nmr spectrum was recorded (see above).

DL(**125/34**) **Diastereomer of 2,3,4,5-Tetrahydroxy-1-Cyclohexanemethanol Pentaacetate (Pseudo-β-DL-gulopyranose Pentaacetate) (5). A. From the Enetriol Triacetate.**—A stock solution of 0.5 g of osmium tetroxide in 100 ml of *t*-butyl alcohol was prepared. To a stirred solution of 4.0 ml of 30% aqueous hydrogen peroxide in 6.0 ml of the catalyst solution was added dropwise a solution of 2.16 g of the enetriol triacetate in 8 ml of *t*-butyl

(29) A product of the Darco Division, Atlas Powder Co., Wilmington, Del.

(30) A product of Alupharm Chemicals, New Orleans, La.

(31) L. F. Johnson, Varian Associates Technical Information Bulletin, Vol. III, No. 3, 1962, p 5.

(32) H. Schmidt and E. Grob, *Helv. Chim. Acta*, **32**, 77 (1949).

(33) R. K. Hill and R. M. Carlson [*J. Org. Chem.*, **30**, 2414 (1965)] report that many Diels–Alder adducts from 1,4-diacetoxy-1,3-butadiene undergo spontaneous aromatization. (It appears that little, if any, aromatic product is formed when the less reactive dienophiles, such as allyl acetate or vinylene carbonate, are used.)

alcohol. Stirring was continued at 25° for 5 days. On evaporation, a colorless syrup was obtained, and to it was added 6.0 ml of anhydrous pyridine and 6.0 ml of acetic anhydride. The mixture was kept at 25° for 1 day, then evaporated. The residual brown syrup was taken up in 15 ml of chloroform, and the chloroform solution processed in the usual manner, giving a pale yellow syrup. This syrup was crystallized from 2-propanol, giving 1.62 g of colorless crystals, mp 126–131°. This product was recrystallized, giving 1.19 g (38%) of the pure pentaacetate, mp 132–133°.

Anal. Calcd for $C_{17}H_{24}O_{10}$: C, 52.60; H, 6.23. Found: C, 52.45; H, 6.35.

The infrared spectrum (KBr) contained peaks at 3000, 1750, 1350, 1220, 1050, 900, and 820 cm^{-1}.

The nmr spectrum was recorded (see above).

B. From the Pentol Triacetate.—Acetylation of a 12-mg portion of the pentol triacetate with acetic anhydride and pyridine in the usual manner gave a 9-mg (58%) yield of the pentaacetate, mp 131–132°. A mixture melting point with a sample prepared by procedure A was not depressed, and the infrared spectra were identical.

DL(125/34) Diastereomer of 2,3,4,5-Tetrahydroxy-1-cyclohexanemethanol (Pseudo-β-DL-gulopyranose) (11).—To 175 mg of the pentaacetate was added 4.0 ml of a *M* solution of hydrogen chloride in ethanol–water (1:1). The resulting solution was boiled for 6 hr under reflux. The solution was then treated with decolorizing charcoal, and evaporated. The syrupy residue was repeatedly evaporated after additions of small volumes of absolute ethanol. The product (70 mg, 88%) was obtained as a colorless syrup; a correct microanalysis was obtained on the crystalline pentaacetate derivative (see above).

The same product was obtained by hydrolysis with hot sodium hydroxide (1 *M*) in ethanol–water (1:1), in somewhat lower yield.

The nmr spectrum was recorded (see above).

Registry No.—*cis,cis*-1,4-diacetoxy-1,3-butadiene, 10489-24-4; *trans,trans*-1,4-diacetoxy-1,3-butadiene, 15910-11-9; **5**, 16656-57-8; **6**, 16656-59-0; **8**, 16703-82-5; **11**, 16656-62-5.

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Alicyclic Carbohydrates. XXXIII. Epimerization of Pseudo-α-DL-talopyranose to Pseudo-α-DL-galactopyranose. Proton Magnetic Resonance Studies[1]

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The expression pseudo-sugar is used to denote an alicyclic analog of a cyclic monosaccharide. For example, a hydroxymethylcyclohexanetetrol (formula **1**) may be described as a "pseudo-hexose," or more explicitly, as a "pseudo-hexopyranose." When pseudo-α-DL-talopyranose (**2**) was heated with 95% acetic acid containing sulfuric acid, it underwent the expected epimerization at position 4 (position 2 by usual hexopyranose numbering). The crude product was treated with acetic anhydride. The yield of pure crystalline pentol pentaacetate (**8**, mp 147–148°) was less than 15%. This pentaacetate was readily converted in high yield by acidic hydrolysis into the desired free pentol, pseudo-α-DL-galactopyranose (**7**), mp 173–174°. The DL(123/45) or α-DL-galactopyranose configuration, **7**, which should exist in the (EAEEA) or side chain–equatorial favored conformation, **13**, was assigned for mechanistic reasons. Proton magnetic resonance studies on the pentol and its pentaacetate were consistent with this configuration and conformation. An improved preparation of pseudo-α-DL-talopyranose is described.

Recently we reported[3,4] the synthesis of pseudo-α-DL-talopyranose (**1** or **2**) (Scheme I). This was the first member of a new series of compounds which we propose to designate pseudo-sugars, *i.e.*, cyclic forms of monosaccharides in which the usual ring-oxygen atom is replaced by methylene.[3,4] It is hoped that pseudo-sugars will be found acceptable to some although not all enzymes or biological systems, and thus may have useful biological properties.

More recently, we reported the synthesis of a second pseudohexose, which had the β-DL-gulopyranose configuration.[1b]

We now wish to report synthesis and pmr characterization of a third diastereomer in the pseudo-hexopyranose (formula **1**) series, namely pseudo-α-DL-galactopyranose (**7**). In order to prepare this isomer, we utilized the valuable epimerization method recently developed by Angyal, Gorin, and Pitman.[5–7] Our starting material was the already available talopyranose isomer (**2**). This was heated for a prolonged period with the Angyal reagent,[5] 95% acetic acid (containing a little sulfuric acid). According to Angyal,[5] epimerization takes place most readily at a hydroxy or acetoxy group which has one *cis* and one *trans* neighboring functional group. Thus we predicted epimerization would take place at position 4 of formula **3** to give the acetylated α-DL-galactopyranose diastereomer **8**, and, in fact, the only new product isolated did have this configuration, as shown by pmr studies. The epimerization is believed to take place through the anchimeric effect of the neighboring *trans*-acetoxy group at position 5 of formula **3**, *via* the bicyclic acetoxonium intermediate **4**, which has not been isolated.

The yield of the α-DL-*galacto* pentaacetate product

(1) For the two preceding papers, see (a) G. E. McCasland, M. O. Naumann and L. J. Durham, *Carbohyd. Res.*, **4**, 516 (1967); (b) G. E. McCasland, S. Furuta, and L. J. Durham, *J. Org. Chem.*, **33**, 2835 (1968).

(2) To whom any correspondence should be addressed at the University of San Francisco.

(3) G. E. McCasland, S. Furuta, and L. J. Durham, *ibid.*, **31**, 1516 (1966).

(4) See also G. E. McCasland, *Advan. Carbohyd. Chem.*, **20**, 41 (1965).

(5) S. J. Angyal, P. A. J. Gorin, and M. E. Pitman, (a) *J. Chem. Soc.*, 1807 (1965); (b) *Proc. Chem. Soc.*, 337 (1962).

(6) P. A. J. Gorin, K. Horitsu, and J. F. T. Spencer, *Can. J. Chem.*, **43**, 2259 (1965).

(7) P. A. J. Gorin, *ibid.*, **41**, 2417 (1963).