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SYNTHESIS OF METHYL 2,3-DIDEOXY-DL-ALK-2-ENOPYRANOSIDES FROM FURAN COMPOUNDS

A GENERAL APPROACH TO THE TOTAL SYNTHESIS OF MONOSACCHARIDES

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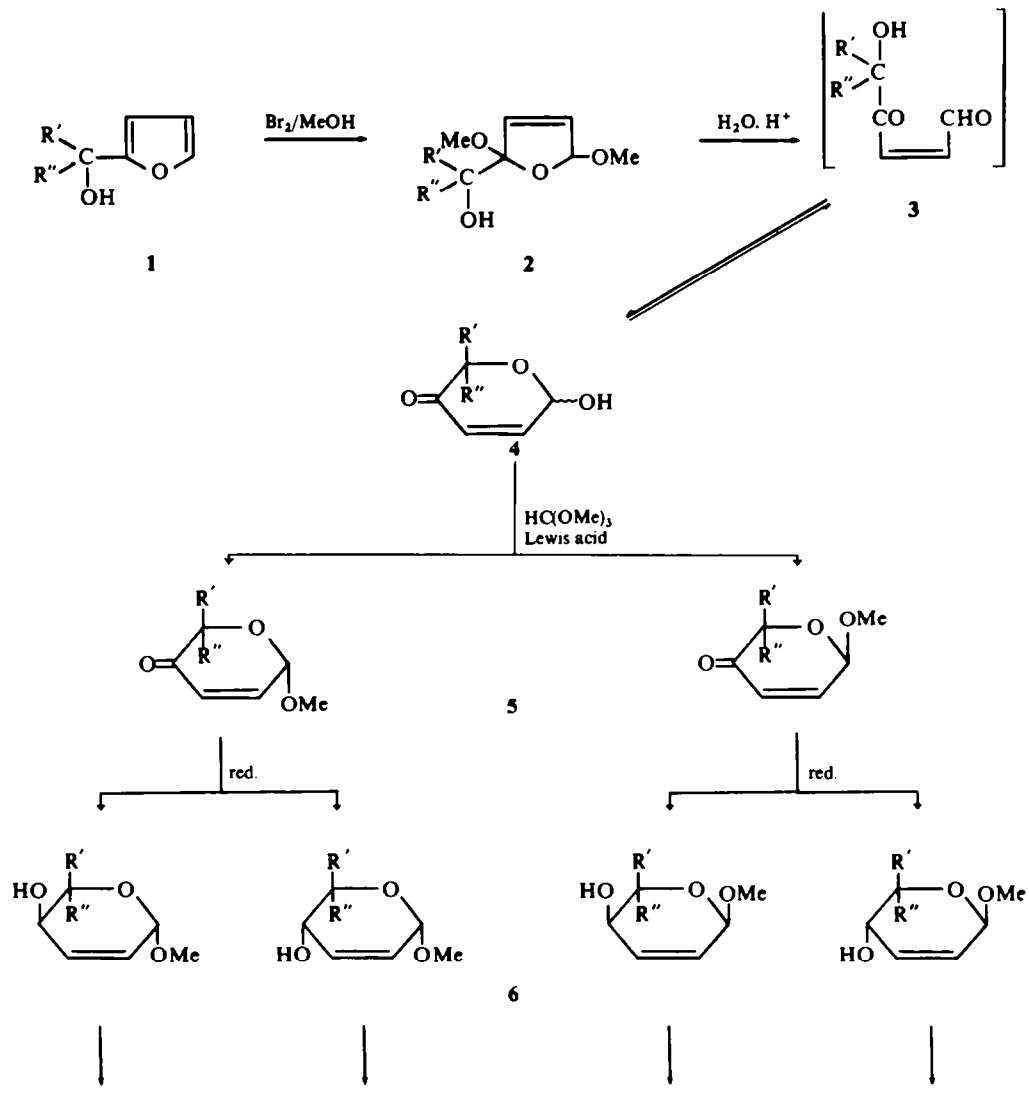
Abstract—A method of converting furan derivatives via 2,3-dideoxy-DL-alk-2-enopyranos-4-uloses, a new class of sugar compounds, into methyl 2,3-dideoxy-DL-alk-2-enopyranosides is described. Furfuryl alcohol, 2(1,2-O-isopropylidene-1,2-dihydroxyethyl)furan, 1(2-furyl)ethanol and 2(2-furyl)glycerol 1,3-diacetate treated with bromine in methanol gave corresponding 2,5-dimethoxy-2,5-dihydrofuran derivatives, which hydrolyzed with diluted sulphuric acid afforded 2,3-dideoxy-DL-pent-2-enopyranos-4-ulose, 2,3-dideoxy-DL-hex-2-enopyranos-4-ulose, 2,3,6-trideoxy-DL-hex-2-enopyranos-4-ulose and 6-O-acetyl-5-C-acetoxymethyl-2,3-dideoxy-DL-hex-2-enopyranos-4-ulose, respectively. The latter treated with methyl orthoformate in the presence of Lewis acids yielded corresponding methyl glycosides, which were reduced with sodium borohydride to give appropriate pairs of stereoisomeric methyl 2,3-dideoxy-DL-alk-2-enopyranosides. All stereoisomers were separated and their configuration was established by PMR spectra. 1-O-Acetyl derivatives of 2,3-dideoxy-DL-alk-2-enopyranos-4-uloses were obtained.

THE FORMATION of furan compounds from mono- and polysaccharides induced by mineral acids is a well known transformation. Döbereiner[1] was the first to observe, in 1832, the formation of furfural in the course of heating sugar with H_2SO_4 and MnO_2. Since then, a considerable number of studies of this problem have been performed.[2] A recent example, the transformation of sugar into a furan derivative, has been reported by Tsuji and Fujimaki[3] who obtained 2-methyl-3-formylfuran on heating a streptose derivative at pH 2–4.

Here we report on a reversal of the transformation of sugars into furan derivatives, i.e. on the route of obtaining monosaccharides from simple furan compounds. The principle of this method is presented in Scheme 1.

A compound of 2-furylcarbinol (**1**) type is converted in a known reaction,[4] by treatment with Br_2 in MeOH, to a mixture of *cis* and *trans* isomers of the corresponding 2,5-dimethoxy-2,5-dihydrofuran derivative (**2**). Mild acid hydrolysis of **2** brings about cleavage of the acetal bonds and formation of dicarbonyl compound **3** (not isolated), undergoing immediate cyclization to 2,3-dideoxy-DL-alk-2-enopyranos-4-ulose (**4**) (mixture of anomers, if $R' \neq R''$). Compound **4** is methylated with methyl orthoformate in the presence of a Lewis acid catalyst, yielding methyl glycosides (**5**). A mixture of glycosides (**5**) can be separated by column or gas chromatography. In turn, the reduction of the ketone group in compound **5** with metal hydrides leads to stereoisomeric methyl 2,3-dideoxy-DL-alk-2-enopyranosides (**6**). Compounds **6** can be obtained (in most cases) in the form of pure diastereoisomers. Individual steps of the synthesis show high or satisfactory yields.

SCHEME 1



Addition reactions to C2–C3 double bond, i.e. hydroxylation or epoxidation and oxirane ring opening

Monosaccharides

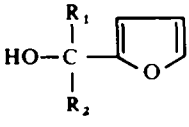
2,3-Unsaturated sugars, especially alkyl 2,3-dideoxy-hex-2-enopyranosides (optically active form) are well known in carbohydrate chemistry.[5] During the last decade, their preparations and chemistry have been widely studied.[6,7,8,9] According to the data from the literature, alkyl 2,3-dideoxy-alk-2-enopyranosides can be converted—via hydroxylation,[6b,10] epoxidation[11] and subsequent opening of the oxirane ring[12]—to a number of simple sugars. Moreover, taking into account the possibility of an inversion of the configuration at C4[7b] in compounds **6**, we assume that the above mentioned reactions represent a method of total synthesis of monosaccharides. It is noteworthy that the synthesis according to Scheme 1 permits ready preparation of a number of "deformed" sugars, e.g. of monodeoxy-, dideoxy-, alkoxy, etc. type.

However, the reported method affords pure diastereoisomers **6** in the racemic form. For various reasons, it could be desirable to obtain methyl glycosides **6** as individual enantiomers. Although we have not yet obtained enantiomeric sugars **6**, we think that—at least in some cases—the synthesis of optically active sugars according to Scheme 1 ought to be possible. Methods leading to this purpose are outlined below.

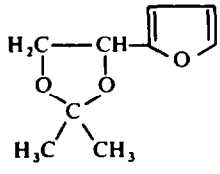
Substrates

The following compounds were chosen as substrates: furfuryl alcohol (**7**), 2(1,2-O-isopropylidene-1,2-dihydroxyethyl)furan (**8**), 1(2-furyl)ethanol (**9**), and 2(2-furyl)-glycerol 1,3-diacetate (**10**). Compounds **7**, **8** and **9** were the substrates for the synthesis of the most common sugars: pentoses, hexoses and 6-deoxyhexoses. Compound **10** served as an example for the synthesis of sugar with a branched skeleton.

Furfuryl alcohol (**7**) and 1(2-furyl)ethanol (**9**) are readily available. We have recently reported[13] on a convenient synthesis of 2(1,2-O-isopropylidene-1,2-dihydroxyethyl)-furan (**8**), involving the condensation of furan with butyl glyoxylate, reduction of the resulting butyl ester of (2-furyl)glycolic acid (**11**) with LAH, and subsequent condensation with acetone. 1,3-Diacetate of 2(2-furyl)glycerol (**10**) was prepared from ethyl ester of (2-furyl)tartronic acid (**12**)[13] by reduction and subsequent acetylation of the resulting (2-furyl)glycerol with acetic anhyd. in pyridine. Compounds **11** and **12** were also included in these studies as potential substrates for the synthesis of uronic acids.



7: $R_1 = R_2 = H$;
9: R_1 = Me, $R_2 = H$;
10: $R_1 = R_2 = CH_2OAc$;
11: R_1 = COOBu, $R_2 = H$;
12: $R_1 = R_2$ = COOEt;



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It is possible to resolve 1(2-furyl)ethanol (**9**) into enantiomers; Duveen and Kenyon[14] have reported the preparation of laevorotatory alcohol **9**. Compound **8** may also be obtained in an optically active form.* We are of the opinion that a total synthesis of

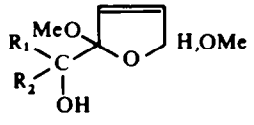
* 2(1,2-dihydroxyethyl)furan obtained by acidic degradation of methyl 4,6-O-benzylidene-2,3-dideoxy-α-D-erythro-hex-2-eno-pyranoside[8] is optically active and has D configuration. We obtained both enantiomers of this diol by condensation of furan with 1-menthyl glyoxylate, separation of the resulting diastereomeric 1-menthyl esters of (2-furyl)glycolic acid, and reduction of the latter with LAH.[15]

optically active sugars could be achieved by the route given in Scheme 1. when starting with the enantiomers of compounds **8** or **9**.

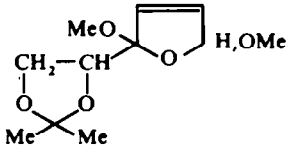
2.5-Dimethoxy-2.5-dihydrofurans (**2**)

When treated with Br_2 in MeOH. compounds **7–12** readily formed the corresponding 2.5-dimethoxy-2.5-dihydrofurans (**13–18**). Yields. b.ps and analytical data of compounds **13–18** (for mixtures of *cis* and *trans* isomers) are recorded in Table 1.*

TABLE 1. YIELDS, BOILING POINTS AND ANALYTICAL DATA OF 2,5-DIMETHOXY-2,5-DIHYDROFURANS **13–18**



13. 15–18



14

Compound	R_1	R_2	Yield %	B.p. °C/mm	Formula	Analysis % Calc. C	Calc. H	Found C	Found H
13[a]	H	H	73	71/1·0	$C_7H_{12}O_4$	52·5	7·6	52·3	7·8
14	—	—	76	74/0·5	$C_{11}H_{18}O_5$	57·4	7·9	57·4	7·8
15[b]	CH_3	H	92	72–4/1·5	$C_8H_{14}O_4$	55·2	8·1	55·4	8·2
16	CH_2OAc	CH_2OAc	64	130/0·6	$C_{13}H_{20}O_8$	51·3	6·6	51·2	6·7
17	CO_2Bu	H	73	135/0·9	$C_{12}H_{20}O_6$	55·4	7·8	55·3	8·0
18	CO_2Et	CO_2Et	47	132/0·8	$C_{13}H_{20}O_8$	51·3	6·6	51·2	6·7

[a] Lit.[16] b.p. 86–87°C/0·4 mm.
[b] Lit.[17] b.p. 104–107°C/10–11 mm.

Compounds **13–18** already show an analogy to sugars; they can be considered as diacetals of 2.3-dideoxy-DL-alk-2-enofuranosid-4-uloses.†

2.3-Dideoxy-DL-alk-2-enopyranos-4-uloses (**4**) and *methyl 2.3-dideoxy-DL-alk-2-enopyranosid-4-uloses* (**5**)

The key stage of the synthesis involves the transformation of the 2.5-dimethoxy-2,5-dihydrofurfuryl alcohol [**2**] into the 2,3-dideoxy-DL-alk-2-enopyranos-4-ulose [**4**]. When treated with 1–2% H_2SO_4 at 20–60°C, compounds **13–16** (mixtures of geometric

* Separation of the geometric isomers of compounds **13–18** and assignment of configuration will be reported in another paper.[18]

† Introduction of two OH groups at C2 and C3 should afford sugar derivatives. However, hydroxylation of 2.5-dialkoxy-2.5-dihydrofurans proceeds usually with difficulty and low yields. Elming has suggested in his review[19] on 2.5-dialkoxy-2.5-dihydrofurans: "It would be desirable to improve the yields of the hydroxylation reaction of dimethoxy-dihydrofurans. since a good general procedure for this reaction might open a simple route for the preparation of certain carbohydrates from furans". We have carried out hydroxylation of *cis*-**14** and obtained. in low yield. two substances which were assigned the structures of 3α.4α- and 3β.4β-dihydroxy-2β.5β-dimethoxy-2α(1.2-O-isopropylidene-1.2-dihydroxyethyl)tetrahydrofuran. These results have been presented at the Annual Meeting of the Polish Chemical Society in Poznan (1970).[20]

isomers) afford, in very high yields, corresponding compounds **19–22**. Compounds **19–22** show low stability in aqueous solution at room temperature, and undergo rapid decomposition, when treated with basic agents. In acid media, secondary reactions take place. For example, we observed that compound **21** stored for a few days at pH 3–4, underwent intermolecular dehydration, yielding two stereomeric compounds: the racemic and meso forms of 1-O-(2,3,6-trideoxy-α-DL-hex-2-enopyranosyl-4-ulose)-2,3,6-trideoxy-α-DL-hex-2-enopyranosid-4-ulose (**23**) and (**24**). The proof of their structure will be presented below. In pure state at 0°C, compounds **19–22** may be stored without decomposition.

The course of hydrolysis of compounds **17** and **18** was different (see below).

The structure of compounds **19–22** was evident from their analytical and spectral data. They showed strong absorption in the UV (λ_{max} ~215 nm, ε ~8000) and IR (1700 and 1640 cm^{-1}) spectra, characteristic of the α,β-unsaturated ketone system. In the IR spectra, the band due to the OH group (3500 cm^{-1}) was also present. Compound **22** showed maxima corresponding to the acetate residue (1750 and 1220 cm^{-1}). Unequivocal confirmation of the structure of compounds **19–22** followed from their PMR spectra, in which the assignment of all protons present in the molecule was possible (Table 4). The PMR spectra showed the signals of three protons in the ABX* pattern (e.g. Fig. 1); these signals were assigned to the anomeric proton and to the protons at the double bond. Coupling constants exhibited by this ABX system and the chemical shift of H1 were characteristic of 2,3-unsaturated sugars.[21]

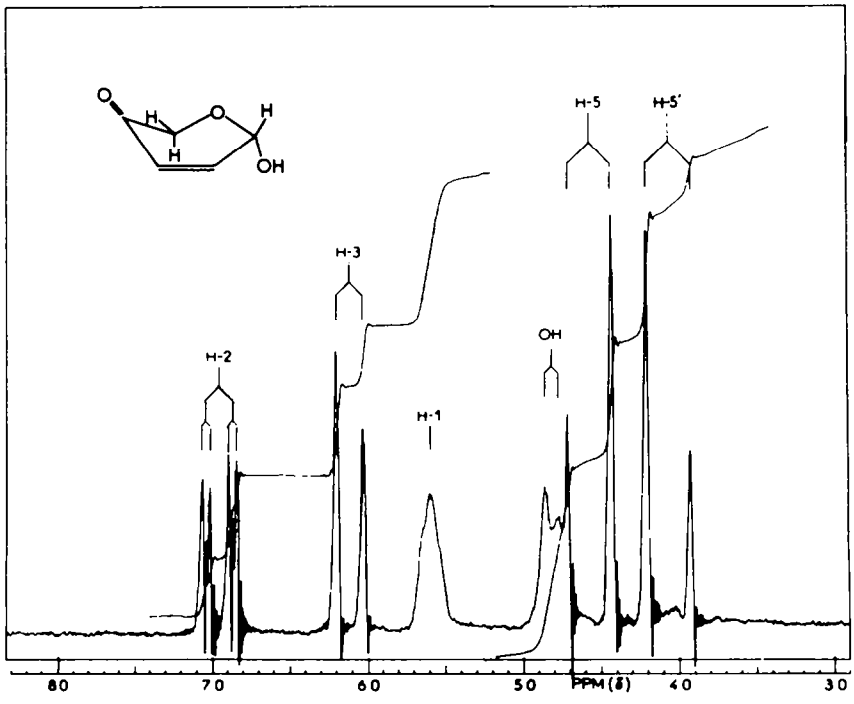
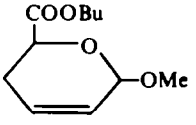


FIG 1. PMR spectrum (60 MHz, $CDCl_3$) of 2,3-dideoxy-DL-pent-2-enopyranos-4-ulose (**19**).

* After the exchange of the hydroxyl group proton.

The signals of the olefinic protons were shifted downfield, as expected for an α,β-unsaturated ketone system.[22] The signal of the proton at C5 in compound **20** appeared as a triplet, and in compound **21** as a quartet due to the coupling with the CH_2 and CH_3 group, respectively. In compound **19**, the protons on C5 gave an AB system with geminal coupling J = 15 Hz (Fig. 1). The presence of CH_3, hydroxymethyl, acetoxymethyl and OH group in the respective compounds was also confirmed by the PMR spectra. Yields, b.ps, m.ps, as well as the analytical and spectral data of compounds **19–22** are presented in Table 2.

It is noteworthy that compounds **19–22** occurred only in the hemiketal, cyclic form. Free 2,3-unsaturated sugars (e.g. pseudoglycals) show the properties of free aldehydes.[23] Likewise, compound **25**, after acid hydrolysis, occurs almost exclusively as free aldehyde.[24]



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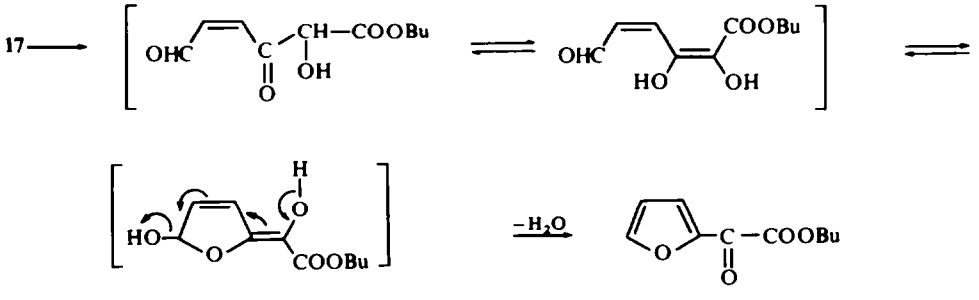
Acid hydrolysis of 2,5-dialkoxy-2,5-dihydrofurfuryl alcohols (**2**) has been till now several times reported; however, the products were either assigned an acyclic structure[4,25] or they were characterized as compounds formed in secondary reactions.[4] The formation of the 5,6-dihydro-α-pyran-5-one system, as in compounds **19–22**, has so far been reported in only one case.[26]

As mentioned above, the course of acid hydrolysis of compounds **17** and **18** was different. Namely, butyl 2-furylglyoxylate (**26**) was the only product obtained by hydrolysis of **17**. The formation of ester **26** is undoubtedly a consequence of the easy enolization of the α-hydroxy-β-ketoester system (Scheme 2). This enolization is particularly well known in the chemistry of ascorbic acid.[27]

SCHEME 2



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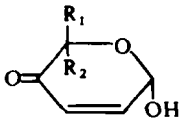
It is noteworthy that an analogous product, viz. (2-furyl)-hydroxymethyl ketone (**27**) was obtained in very small yield (~1%), in addition to compound **20**, during the hydrolysis of **14**. Because of the lack of the ester group stabilizing the enol form in **14**, the system is aromatized to a minor extent. We did not succeed in isolating the possible

TABLE 2. YIELDS, B.PS. (M.PS.), ANALYTICAL AND SPECTRAL DATA OF 2,3-DIDEOXY-DL-ALK-2-ENOPYRANOS-4-ULOSES **19–22**

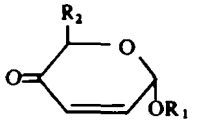


19–22

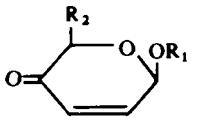
Compound	R_1	R_2	Yield %	B.p. (m.p.)	Formula	Analysis (%) Calc. C	Calc. H	Found C	Found H	Spectral data IR[a] γ_{max} cm^{-1}; UV [$\lambda_{max}(\varepsilon)$]	
19	H	H	100[b]	(54–8°C)	$C_5H_6O_3$	52·6	5·3	52·5	5·3	3500. 1710 1690. 1640	213·5 (8350)
20[c]	CH_2OH H	H CH_2OH	100[b]	—	$C_6H_8O_4$		d			3450. 1700 1640	215 (8020) 345 (30)
21	CH_3	H	98	120°/0·35 (62–65° C)	$C_6H_8O_3$	56·2	6·3	56·0	6·4	3450. 1690. 1630	215 (8160) 278 (20) 343 (40)
22	CH_2OAc	CH_2OAc	64	150°/0·8	$C_{11}H_{14}O_7$	51·2	5·5	51·3	5·8	3500. 1750. 1695. 1640 1235	217 (7900) 357 (40)

[a] Only more important bands are given. [b] Yield is given for crude, homogeneous in TLC product. [c] Mixture of anomers. [d] Compound **20** was analyzed as its 1,6-di-O-acetyl derivative **41** (Table 3).

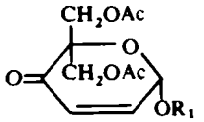
TABLE 3. YIELDS, B.PS (M.PS), ANALYTICAL AND SPECTRAL DATA OF DERIVATIVES OF 2,3-DIDEOXY-DL-ALK-2-ENOPYRANOS-4-ULOSES



29. 30. 32. 36. 38, 39, 41, 42;



31. 33. 37. 40;



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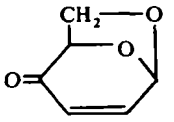

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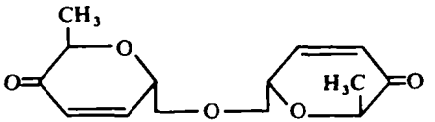

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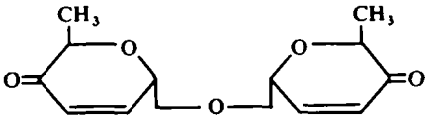

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Compound	R_1	R_2	Yield %	B.p. (m.p.)	Formula	Analysis (%) Calc. C	Calc. H	Found C	Found H	Spectral data IR[a] (γ_{max} cm^{-1})	Spectral data UV[λ_{max}(ε)]
23	—	—	9	(110°)	$C_{12}H_{14}O_5$	60·5	5·9	60·5	6·1	1700. 1635;	221 (22600) 339 (50) 352 (60)
24		—	4	(130°)	$C_{12}H_{14}O_5$	60·5	5·9	60·7	6·1	1700. 1635;	218 (20900) 357 (60)
29	CH_3	H	43	76–81°/23 mm	$C_6H_8O_3$	56·2	6·3	56·3	6·4	1700. 1640;	211 (8200)
30	CH_3	CH_2OH	12	70°/10^{-4} mm	$C_7H_{10}O_4$	53·2	6·4	52·7	6·5[b]	3500. 1700. 1640;	208 (8800) 345 (30)
31	CH_3	CH_2OH	10		$C_7H_{10}O_4$					3500. 1700. 1640;	[c]
32	CH_3	CH_3	45	82–85°/30 mm	$C_7H_{10}O_3$	59·1	7·1	59·0	7·3	1700. 1630;	211 (8000) 278 (20) 343 (50)

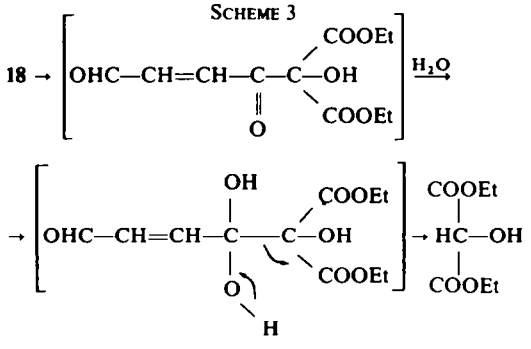
33	CH_3	CH_3	19	82–85°/30 mm	$C_7H_{10}O_3$	59·1	7·1	59·1	7·2	1700, 1630;	212 (8700) 278 (40) 343 (60)
34	CH_3	—	30	100°/0·6 mm	$C_{12}H_{16}O_7$	52·9	5·9	52·8	6·0	1750, 1695, 1640, 1230;	215 (9000) 278 345
35	--	--	26	84°/30 mm	$C_6H_6O_3$	57·1	4·8	57·3	5·0	1710, 1695, 1610;	202 (4900) 234 (4500) 356 (70)
36	CH_3	CH_2OAc	80	70°/10^{-4} mm	$C_9H_{12}O_5$	54·0	6·0	53·8	6·1	1745, 1698 1630, 1225;	211 (7900) 275 (80) 343 (30)
37	CH_3	CH_2OAc	80	70°/10^{-4} mm	$C_9H_{12}O_5$	54·0	6·0	53·8	6·0	1745, 1695, 1630, 1245;	213 (8200) 284 (40) 340 (40)
38	Ac	H	85	70–80°/0·4 mm (40–41°)	$C_7H_8O_4$	53·8	5·2	53·7	5·1	1755, 1705, 1635, 1220;	217 (11200) 353 (30)
39	Ac	CH_3	46	80°/0·4 mm	$C_8H_{10}O_4$	56·5	5·9	56·6	6·2	1755, 1700, 1635, 1225;	216 (11100) 331 (60)
40	Ac	CH_3	34	80°/0·4 mm	$C_8H_{10}O_4$	56·5	5·9	56·5	6·0	1750, 1700, 1635, 1235;	216 (10900) 346 (40)
41[c]	Ac	CH_2OAc	40	100°/10^{-4} mm	$C_{10}H_{12}O_6$	52·6	5·3	52·7	5·5	1745, 1700, 1635, 1230;	217 (10600) 271 (170) 346 (30)
42[c]	Ac	CH_2OH	17		$C_8H_{10}O_5$	--	—	--		3520, 1745, 1695, 1635, 1220;	216 (9100) 337 (40)

[a] Only important bands are given. [b] Analyzed as anomeric mixture. [c] Mixture of α and β anomers 3:1 (from PMR spectrum). [d] Not measured.

by-products, viz. 2-furyl-methyl ketone (from compound **15**) and furfural (from compound **13**). from the respective post-hydrolysis mixtures.

The hydrolysis of diester **18** afforded ethyl tartronate (**28**) in good yield (71%). It is hard to explain the formation of **28**. being a product characteristic of the basic cleavage of transitional β-ketoester. The possible mechanism accounting the formation of ethyl tartronate is presented in Scheme 3.

SCHEME 3



28

The next step of the synthesis involved the conversion of the obtained pyranosuloses **19–22** into methyl glycosides **29–34**. Glycosidation with the use of MeOH in the presence of various catalysts (HCl. TsOH. acidic ion exchange resins) yielded. in addition to the desired product. considerable amounts of by-products; the latter were formed as a result of ketalization of the C4 carbonyl group and/or an addition of the elements of MeOH to the double bond. Satisfactory results were obtained by treating compounds **19–22** with methyl orthoformate in the presence of BF_3/Et_2O or $SnCl_4$ at room temperature for 40–60 min. Under these conditions. glycosidation proceeded in a yield of 30–65% and the above mentioned side reactions were reduced to a minimum. Methyl glycosides obtained from pyranosuloses **20** and **21** were mixtures of anomers; these were separated by column and preparative gas chromatography.

Glycosides **29–34** are more stable than their parent pyranosuloses; however. treated with acid or basic reagents. they also decompose quite readily. For physical properties. analytical data and yields of glycosides **29–34** see Table 3.

In the course of glycosidation of 2.3-dideoxy-DL-hex-2-enopyranos-4-ulose (**20**). in addition to anomeric methyl glycosides **30** and **31**. considerable amount (ca. 25%) of 1.6-anhydro-2.3-dideoxy-β-DL-hex-2-enopyranos-4-ulose (**35**) was formed. Structure confirmation was on the basis of the analytical data, the UV and IR spectra (bands of the CO—CH=CH system, lack of absorption of the OH group) and the PMR spectrum (Fig. 2).

The analytical and spectral data of glycosides **29–34** were fully consistent with their structure. The UV spectra showed an absorption (λ_{max} ~211 nm. ε ~8000) characteristic of the α.β-unsaturated ketone system. The respective absorption maxima in IR occurred at 1700 (C=O) and 1640 (C=C) cm^{-1}. As anticipated, in the IR spectra the band due to the OH group disappeared (with the exception of compound **30** and **31**). In the PMR spectra. a triproton singlet of the OMe group appeared. instead of the OH group proton signal. Other signals showed no significant changes. relative to the spectra of parent pyranosuloses **19–22** (Table 4).

The assignment of configuration α to glycosides **30** and **32**, and of configuration β to glycosides **31** and **33** was based on the analysis of the magnitude of coupling constants J_{12} and J_{13}. Assuming half-chair conformation for compounds **19–22** and **29–34**, the dihedral angle ϕ between the anomeric hydrogen and the double bond hydrogens was measured with the aid of Dreiding's models. For the pseudo-equatorial and pseudoaxial anomeric hydrogen it amounts to 40° and 80°, respectively.

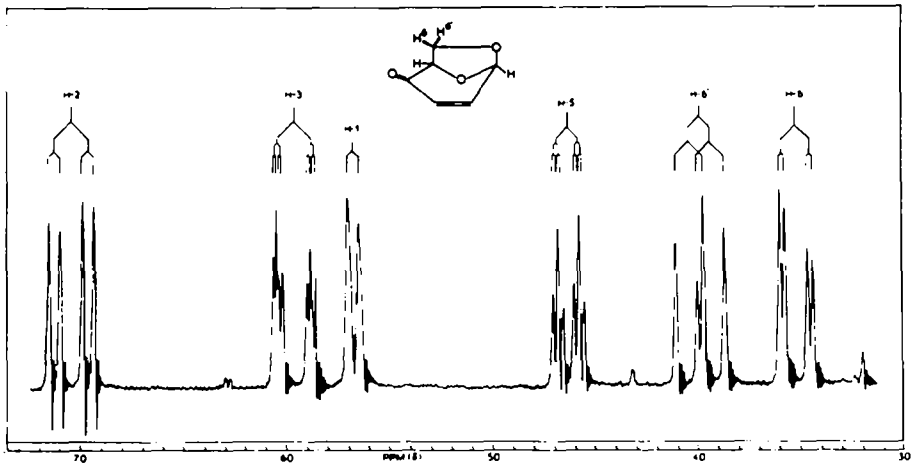


FIG 2. PMR spectrum (60 MHz, CCl_4) of 1,6-anhydro-2,3-dideoxy-β-DL-hex-2-enopyranos-4-ulose (**35**).

The relationship between the vicinal (J_{12}) and the allylic (J_{13}) coupling constants in the —CH=CH—CH system versus the dihedral angle ϕ is given by the equations (1) derived by Garbisch.[28] Equations (1) are

$$J_{vic} = \begin{cases} 6{\cdot}6\cos^2\phi + 2{\cdot}6\sin^2\phi & (0° \leqslant \phi \leqslant 90°) \\ 11{\cdot}6\cos^2\phi + 2{\cdot}6\sin^2\phi & (90° \leqslant \phi \leqslant 180°) \end{cases}$$
$$J_{allil} = \begin{cases} 1{\cdot}3\cos^2\phi - 2{\cdot}6\sin^2\phi & (0° \leqslant \phi \leqslant 90°) \\ -2{\cdot}6\sin^2\phi & (90° \leqslant \phi \leqslant 180°) \end{cases} \quad (1)$$

semi-empirical, and their parameters have been obtained from the numerical data concerning carbocyclic systems; thus, with respect to our compounds, the agreement between the calculated and experimentally found coupling constants could be expected to be of a qualitative nature. It is of importance, however, that the equations permit us to predict for the angle of 40° a large coupling constant J_{12}, and very small—J_{13}. On the other hand, for the angle of 80°, both coupling constants should be similar.*

* The magnitude of the coupling constants would not undergo any fundamental change, even if it were postulated that 2,3-dideoxy-alk-2-enopyranos-4-uloses and their methyl glycosides occurred in the "sofa" conformation (cf. ref.[29]), assuming that in this conformation five atoms of the ring: C1–C5 are situated on one plane, whereas the ring oxygen atom is located "above" or "below" the plane of the ring.

TABLE 4. PMR DATA OF 2,3-DIDEOXY-DL-ALK-2-ENOPYRANOS-4-ULOSES AND THEIR DERIVATIVES

Compound	Chemical shifts (ppm, δ scale)								Coupling constants[a] (Hz)				Solvent
	H1	H2	H3	H5	H6	OH	OCH_3	OAc	J_{12}	J_{13}	J_{23}	J_{56}	
19	5·60[b]	7·00	6·12	4·33[c]	—	4·82[d]	--	--	3·0	<0·5	10·5	—	$CDCl_3$
20[e]	5·63	7·00	6·00[f] 6·10[g]	4·90[f] 4·30[g]	3·87	4·90 −4·15	—	--	3·6[f] --	 1·2[g]	10·2	4·0	$(CD_3)_2CO$
21	5·59	6·89	6·07	4·69	1·32	4·40[d]	—	—	3·5	<0·5	10·2	6·6	$CDCl_3$
22	5·78	6·97	6·17	—	4·42[h] 4·37[h]	4·85	--	—	3·0	0	10·0	—	$CDCl_3$
23	5·63	6·83	6·12	4·53	1·40	—	--		3·5	0	10·2	6·8	$CDCl_3$
24	5·52	6·82	6·10	4·26	1·39	--	--		3·4	0	10·2	7·0	$CDCl_3$
29	5·02	6·81	6·02	4·18[i]		--	3·40	—	3·3	~0·6	10·1	—	$CDCl_3$
30	5·06	6·78	6·01	4·33	3·80	2·57	3·48	—	3·4	<0·5	10·2	4·9	CCl_4
31	5·15	6·76	6·08	4·15	3·79	2·72	3·55	—	2·4	1·2	10·2	4·0	CCl_4
32	4·69	6·35	5·81	4·37	1·32	—	3·19	--	3·3	<0·5	10·2	6·9	C_6H_6
	4·96	6·71	5·94	4·40	1·32	—	3·46	—	3·3	<0·5	10·2	6·9	CCl_4
33	4·75	6·34[j]	5·77	3·84	1·37	--	3·22	--	1·8[k]	1·5	10·2	7·0	C_6H_6
	5·13	6·78[j]	5·98	4·10	1·40		3·46	--	1·9[k]	1·5	10·2	7·0	CCl_4
34	5·02	6·81	6·10	—	4·32[l]	—	3·46	-	3·4	<0·5	10·0	—	$CDCl_3$
35	5·70	7·06	5·97	4·66	4·02[m] 3·55	--	—	—	3·25	~0·5	10·0	6·25[m] 1·5	CCl_4

TABLE 4—*contd.*

Compound	Chemical shifts (ppm, δ scale)								Coupling constants[a] (Hz)				Solvent
	H1	H2	H3	H5	H6	OH	OCH_3	OAc	J_{12}	J_{13}	J_{23}	J_{56}	
36	4·66	6·25	5·75	4·50–4·25		--	3·11	1·66	3·5	~0	10·3	[n]	C_6H_6
	5·10	6·83	6·04	4·57	4·40	—	3·47	2·02	3·5	~0	10·5		$CDCl_3$
37	4·63	6·20	5·71	3·95	4·50–7·29	--	3·15	1·65	2·1	1·5	10·5		C_6H_6
	5·21	6·83	6·10	4·60–4·25		—	3·50	2·06	2·0	1·7	10·7	[o]	$CDCl_3$
38	6·92	6·37	6·15	4·26[p]	--	--		2·08	3·7	<0·5	10·5	--	CCl_4
39	6·24	6·81	5·99	4·39	1·25	--		1·98	3·4	0	10·2	6·8	CCl_4
40	6·27	6·63	5·94	4·09	1·31	--		1·99	2·3	1·2	10·2	6·8	CCl_4
41[r]	6·49	6·88	6·18	4·66	6·42		—	2·00[s] 2·10	3·6	0	10·2	3·9	$CDCl_3$
42[r]	6·50	6·87	6·20	4·50–4·35		3·13		2·10	--	--	10·2		$CDCl_3$

[a] Coupling constants were obtained by first order treatment. [b] Broad singlet, $w/2$ = 9·0 Hz. [c] Center of AB system: $J_{55'}$ = 16·5 Hz, $\Delta\delta_{55'}$ = 25·5 Hz. [d] Doublet, J = 5 Hz. [e] PMR spectrum was obtained for anomeric mixture. [f] α-anomer. [g] β-anomer. [h] s, 2H. [i] Center of AB system: $J_{55'}$ = 16·5 Hz, $\Delta\delta_{55'}$ = 20·5 Hz. [j] Additional coupling of H2 J = ~1·0 Hz. [k] J_{15} = ~1·0 Hz. [l] s, 2H and the center of AB system: J = 11·5 Hz, $\Delta\delta$ = 22 Hz. [m] H6$_{exo}$. [n] $J_{56} + J_{56'}$ = 8·0 Hz. [o] J_{56} = 3·8 Hz, $J_{56'}$ = 6·1 Hz, $J_{66'}$ = 12·0 Hz. [p] Center of AB system: $J_{55'}$ = 17·0 Hz, $\Delta\delta_{55'}$ = 18·6 Hz. [r] Signals of α-anomer. [s] 6-OAc.

From the PMR spectrum of glycoside **30**, we read the coupling constants J_{12} = 3·4 Hz and J_{13} < 0·5 Hz, whereas in the spectrum of glycoside **31** these constants amounted to 2·4 Hz and 1·2 Hz, respectively (Fig. 3). Likewise, for glycoside **32** we obtained J_{12} = 3·5 Hz and J_{13} < 0·5 Hz, and for **33**: 1·9 Hz and 1·5 Hz, respectively. Accordingly, configuration α was assigned to glycosides **30** and **32**, and configuration β- to compounds **31** and **33**.† It is noteworthy that the values of coupling constants J_{12} and J_{13}, both in pyranosuloses **19** and **22**, and in methyl pyranosiduloses **26**

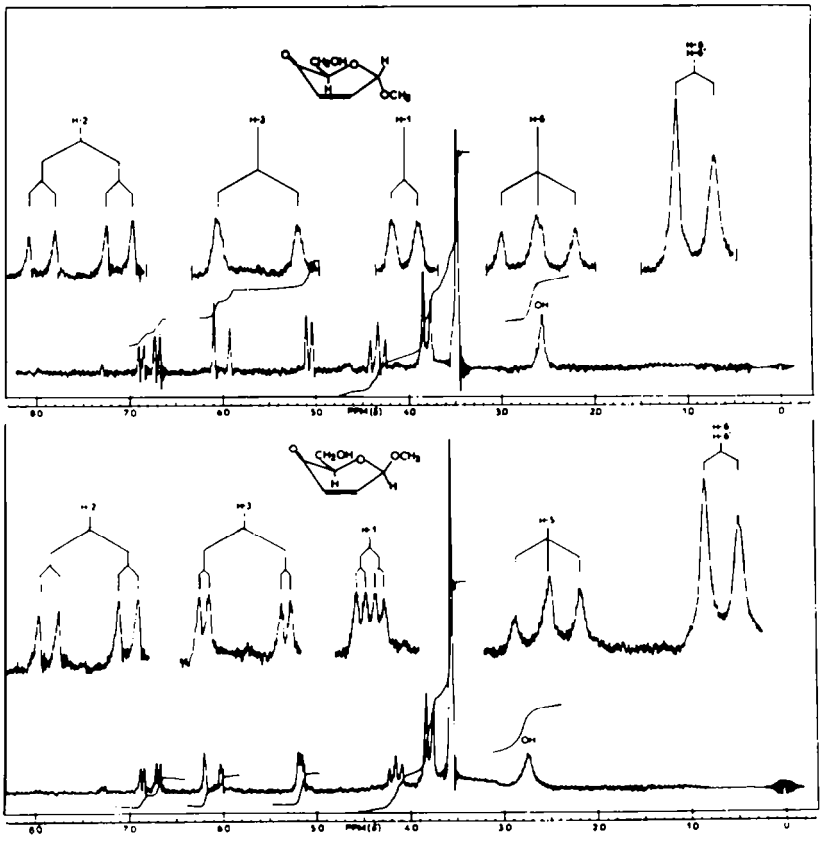
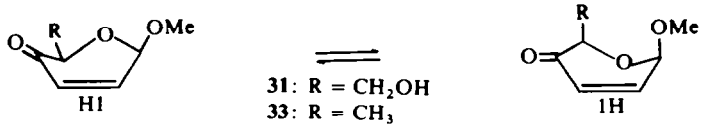


FIG 3. PMR spectra (60 MHz, CCl_4) of methyl 2,3-dideoxy-α-DL-hex-2-enopyranosid-4-ulose (**30**) and methyl 2,3-dideoxy-β-DL-hex-2-enopyranosid-4-ulose (**31**).

† From the conformational analysis it may be predicted that for α anomers (glycosides **30** and **32**) conformation with an equatorial hydroxymethyl or Me group and pseudoaxial C1-methoxy group should be preferred[30] (stabilizing anomeric effect, *cf.* also[31]). For β anomers, however, both half-chair conformations (H1 and 1H) have to be taken into consideration.



(2)

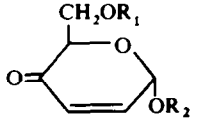
For this reason, J_{12} and J_{13} values for glycosides **31** and **33**, as obtained from the PMR spectra, should be taken as weighted average reflecting the conformational equilibrium formulated in equation (2). For the sake of simplicity, all formulae in this paper refer to D compounds.

and **29** (*cf.* Table 4), indicate that the conformational equilibrium in these compounds is markedly displaced towards the form with the pseudoaxial substituent at the anomeric carbon atom. Pyranosulose **21**, which was obtained in crystalline form, in conformity with its PMR spectrum proved to be pure α anomer.

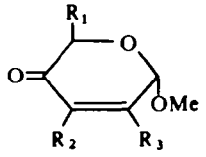
The gross structure of the above-mentioned compounds **23** and **24** followed from their analytical and spectral data (Table 3). Configuration α for both rings, in compounds **23** and **24**, was evident from their PMR spectra, in which J_{12} were 3·5 Hz and 3·4 Hz, respectively. Moreover, in the spectrum of compound **23** signals of corresponding protons of pyranose residues were perfectly superimposed, whereas in **24** they were slightly broadened; consequently, we recognized **23** to be the racemate (the molecule has C_2 symmetry), and **24**—the meso form (lack of C_2 axis).[32]

When treated with acetic anhyd. in pyridine at 0°C, 2,3-dideoxy-DL-hex-2-enopyranos-4-uloses readily form 1-O-acetyl derivatives. Thus, compound **19** afforded derivative **38** in high yield, and **21** yielded both anomers of the 1-O-acetyl derivative: α (**39**) and β (**40**), formed in a ratio 3:1. Pyranosulose **20** was acetylated in CH_2Cl_2–EtOAc solution at 0°C. Under these conditions, the 1,6-di-O-acetyl derivative (**41**) and certain amounts of the 1-O-acetyl derivative (**42**) were obtained. Both compounds (**41** and **42**) were mixtures of anomers. The spectral properties of **38**–**42** were consistent with the assigned structures (Tables 3 and 4).

2,3-Dideoxy-alk-2-enopyranos-4-uloses (**3**) are a new class of sugar compounds. So far, only the preparation of glycosides of these compounds has been described. Fraser-Reid, McLean and Usherwood[33] have obtained methyl 6-O-benzoyl-2,3-dideoxy-D-glycero-hex-2-enopyranosid-4-ulose (**43**) and ethyl 2,3-dideoxy-D-glycero-hex-2-enopyranosid-4-ulose (**44**) by oxidation of C4 hydroxyl group in the respective alkyl 2,3-dideoxy-hex-2-enopyranosides with manganese dioxide. Preparation of related sugar derivatives with substituents at C3 (**45** and **46**),[34] as well as at C2 and C3 (**47**)[35] has also been reported.



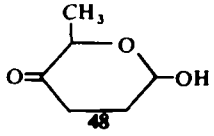
43: $R_1 = COC_6H_5$, $R_2 = Me$;
44: $R_1 = H$, $R_2 = Et$;



45: $R_1 = H$, $R_2 = N_3$, $R_3 = H$;
46: $R_1 = H$, $R_2 = NHCOOEt$, $R_3 = H$;
47: $R_1 = CH_2OH$, $R_2 = OH$, $R_3 = NH_2$;

Little is known, so far, about the reactivity of compounds of type **4** and **5** (Scheme 1); undoubtedly, however, they can be regarded as convenient substrates for synthesis of various classes of monosaccharides.*

* For example, 2,3-dideoxy-alkanopyranos-4-uloses. In this laboratory, the double bond in 2,3,6-trideoxy-DL-hex-2-enopyranos-4-ulose (**21**) was hydrogenated (H_2, Pd), yielding compound **48**. The comparison of **48** with cinerulose A[36] (as well as their methylation and acetylation products) by means of TLC pointed to the identity of both compounds.



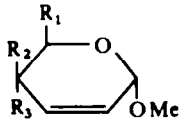
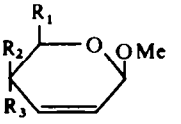
48

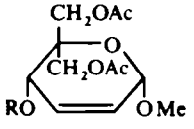
The authors are greatly indebted to Professor W. Keller-Schierlein for carrying out the comparison of cinerulose A with our synthetic sample.

Methyl 2,3-dideoxy-DL-alk-2-enopyranosides (**6**)

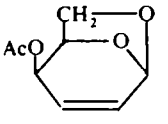
The last stage of the synthesis, leading to methyl 2,3-dideoxy-DL-alk-2-enopyranosides (**6**) (Scheme 1), consisted in the reduction of compounds **5** with $NaBH_4$ in a $THF-H_2O$ solution. Under these conditions only the C4 ketone group was reduced, whereas the double bond failed to undergo reduction to any significant extent.[37] On the other hand, we found it inadmissible to use alcohols as solvents, since their addition to the double bond (Michael's reaction) took place. The occurence of this reaction has recently been observed in $NaBH_4$ reduction of α,β-unsaturated carbonyl compounds in alcoholic solutions.[37]

From methyl pyranosid-4-uloses **29–34**, we obtained methyl 2,3-dideoxy-DL-alk-2-enopyranosides **49–57** characterized as such and/or as acetyl derivatives **58–66**. Likewise, the 1,6-anhydro-compound (**35**) yielded a product characterized as its 4-O-acetyl derivative **67**.

Compound	No.	R_1	R_2	R_3	No.	Compound
	**49**	H	H	OH	**50**	
	51	CH_2OH	H	OH	**52**	
	53	CH_3	H	OH	**55**	
	54	CH_3	OH	H	**56**	
	58	H	H	OAc	**59**	
	60	CH_3	H	OAc	**62**	
	61	CH_3	OAc	H	**63**	
	65	CH_2OAc	H	OAc	**66**	



57: R = H;
64: R = Ac;



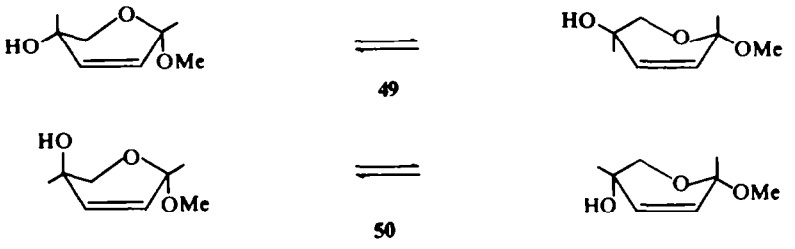
67

The analytical and spectral data of the obtained compounds are presented in Tables 5 and 6. In the IR spectra, the absorption of the conjugated carbonyl disappeared, while bands due to OH (3450 cm^{-1}) or to acetyl (1750 and 1235 cm^{-1}) appeared. The structures of compounds **49–67** were confirmed by their PMR spectra (Table 6). The latter permitted the assignment of the configuration to the respective stereoisomers.

On account of the differences in the course of reduction, the various cases are discussed separately.

The reduction of methyl 2,3-dideoxy-DL-pent-2-enopyranosid-4-ulose (**29**) afforded two methyl pyranosides **49** and **50** in a proportion of about 9:1; they were separated by column chromatography. Component **49**, with higher R_f, was predominant; in the PMR spectrum, it showed coupling constants $J_{45} = 8{\cdot}8$ Hz and $J_{45'} = 5{\cdot}3$ Hz (its acetyl derivative **58**: 8·4 Hz and 6·2 Hz, respectively). These constants pointed to the pseudoaxial position of H4. Since the anomeric effect has decisive influence on

the conformational equilibrium one may assume predominant presence of the conformer with pseudoaxial C1 methoxy group (eq. 3). Consequently, it was concluded that **49** has the structure of methyl 2,3-dideoxy-α-DL-pent-2-enopyranoside



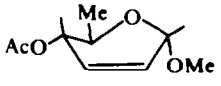
49

50

(3)

In turn, in the spectrum of methyl pyranoside **50**, we observed coupling constants $J_{12} = 2{\cdot}7$ Hz and $J_{13} = 0$ Hz, indicating the pseudoequatorial position of proton H1. Coupling constants J_{45} and $J_{45'}$ of this compound amounted to 3·1 Hz and 1·0 Hz, respectively, thus indicating the pseudoequatorial position of H4. Therefore structure of methyl 2,3-dideoxy-β-DL-pent-2-enopyranoside was ascribed to **50**. These assignments are confirmed by the agreement of the PMR data of 4-O-acetyl derivatives **58** and **59** with the numerical data recently given for compounds of this constitution.[9b]

The reduction of methyl pyranosiduloses monosubstituted in position C5 (R′ ≠ R″, *cf.* Scheme 1) should yield four diastereoisomers **6** with configuration α,β-threo and α,β-erythro. All four diastereoisomers were obtained only in reduction of compounds **32** and **33**. Thus, methyl 2,3,6-trideoxy-α-DL-hex-2-enopyranosid-4-ulose (**32**) afforded a mixture of two methyl pyranosides: **53** and **54**. This mixture was acetylated, yielding 4-O-acetyl derivatives **60** and **61**, which were separated by column chromatography. The predominant component **60**, (85% of the mixture) showed in the PMR spectrum $J_{45} = 9{\cdot}2$ Hz, this indicating the pseudoaxial position of H4 and axial of H5. Accordingly, the α-erythro configuration was assigned to compound **60**.



60

The other methyl pyranoside (**61**) exhibited coupling constant $J_{45} = 2{\cdot}6$ Hz, this unequivocally pointing to α-threo configuration (*cf.* $J_{45} = 2{\cdot}0$ Hz for methyl 4,6-O-benzylidene-α-D-threo-hex-2-enopyranoside).[9a]

The reduction of methyl 2,3,6-trideoxy-β-DL-hex-2-enopyranosid-4-ulose (**33**) also resulted in two isomeric methyl 2,3,6-trideoxy-DL-hex-2-enopyranosides: **55** and **56**, which were converted into 4-O-acetyl derivatives **62** and **63**, separated by column chromatography. The predominant component showed in the PMR spectrum coupling constant $J_{45} = 6{\cdot}0$ Hz, whereas the other, formed in a lower yield, exhibited $J_{45} = 2{\cdot}8$ Hz. Accordingly, configuration β-erythro (**62**) was assigned to the first compound, and β-threo (**63**)—to the second. The smaller coupling constant J_{45} of compound **62**, as compared with **60**, indicates that the former occurs in an equilibrium of both half-chair forms (eq. 4).

TABLE 5. YIELDS, B.PS, ANALYTICAL AND SPECTRAL DATA OF METHYL 2,3-DIDEOXY-DL-ALK-2-ENOPYRANOSIDES

Compound	R_1	R_2	R_3	Yield %	B.p. °C/mm	Formula	Analysis (%) Calc. C	Calc. H	Found C	Found H	IR[a] ν_{max} cm^{-1}
49	H	H	OH	82	64–65/0·5	$C_6H_{10}O_3$	55·4	7·8	55·6	8·2	3450;
53[b]	CH_3	H	OH	96	60/0·3	$C_7H_{12}O_3$	58·3	8·4	58·1	8·7	3450, 1660;
54	CH_3	OH	H								
57[c]	—	—	—	61	—	$C_{12}H_{18}O_7$					3500, 1740, 1240;
58	H	H	OAc	98	100/0·4	$C_8H_{12}O_4$	55·8	7·0	55·6	7·2	1745, 1240;
60	CH_3	H	OAc	67[d]	70/0·3	$C_9H_{14}O_4$	58·1	7·6	57·9	7·9	1735, 1660, 1235;
61	CH_3	OAc	H		70/0·3	$C_9H_{14}O_4$	58·1	7·6	58·3	7·6	1740, 1660, 1235;
62	CH_3	H	OAc	69[d]	70/0·3	$C_9H_{14}O_4$	58·1	7·6	58·1	7·5	1740, 1660, 1235;
63	CH_3	OAc	H		70/0·3	$C_9H_{14}O_4$	58·1	7·6	57·8	7·7	1740, 1660, 1240;
64[e]	—	—	—	50	$120/10^{-3}$	$C_{14}H_{20}O_8$	53·2	6·4	53·2	6·7	1740, 1230;
65	CH_2OAc	H	OAc	71	$90–95/10^{-3}$	$C_{11}H_{16}O_6$	54·1	6·6	54·3	6·7	1745, 1655, 1240;
66	CH_2OAc	H	OAc	46	$90–100/10^{-3}$	$C_{11}H_{16}O_6$	54·1	6·6	54·0	6·8	1745, 1655, 1235;
67	-	—	—	91	60–64/0·2	$C_8H_{10}O_4$	56·5	5·9	56·4	6·2	1740, 1640, 1235;

[a] Only more important bands are given. [b] Mixture of isomers which was not separated. [c] Mixture of anomers with α prevailing. [d] Combined yield of both acetates calculated for starting pyranosulose. [e] Analyzed as its 4-O-acetyl derivative **64**.

TABLE 6. PMR DATA OF METHYL 2,3-DIDEOXY-DL-ALK-2-ENOPYRANOSIDES

Compound	Chemical shifts (ppm. δ scale) H1	H2	H3	H4	H5	H6	OH	OCH_3	OAc	Solvent	Coupling constants Hz
49	4·68	5·65	5·90	4·10	3·50 3·85	—	4·00	3·36	—	CCl_4	$J_{12} = 2·1$, $J_{23} = 10·4$, $J_{13} = 1·0$, $J_{24} = 1·6$, $J_{34} = 1·8$, $J_{45} = 8·8$, $J_{45'} = 5·3$;
50	4·70	5·72	5·98	3·25–3·75		—	[a]	3·30		CCl_4	$J_{12} = 2·7$, $J_{23} = 10·1$, $J_{34} = 4·0$, $J_{45} = 3·1$, $J_{45'} = 1·2$;
53	4·65	5·55	5·80	3·50–3·80		1·20	3·00	3·30	—	CCl_4	$J_{45} = 9·0$, $J_{56} = 6·5$;
57	4·85	5·50–5·95		[b]	—	4·00–4·50	—	3·40	2·05[c]	$CDCl_3$	
58	4·70	5·55–6·00		5·18	3·35–3·90	—	—	3·35	2·00	$CDCl_3$	$J_{12} + J_{13} = 3·2$, $J_{45} = 8·4$, $J_{45'} = 6·2$;
59	4·70	5·70–6·15		4·78	[d]	—	—	3·33	2·00	CCl_4	$J_{45} = 2·7$, $J_{45'} = 1·0$, $J_{55'} = 12·9$;
60	4·70	5·70		4·95	3·80	1·15	—	3·33	2·00	CCl_4	$J_{45} = 9·1$, $J_{56} = 6·4$;
	4·70	5·70		5·15	3·97	1·15	—	3·30	1·80	C_6H_6	
61	4·68–4·84[e]	5·70–6·15		4·68–4·84[e]	4·08	1·13	—	3·33	2·15	CCl_4	$J_{45} = 2·6$, $J_{56} = 6·7$.
	4·67	5·55–6·10		4·79	4·05	1·12	—	3·19	1·70	C_6H_6	$J_{12} = 2·3$, $J_{34} = 4·5$;
62	4·71–5·00[e]	5·65–5·75		4·71–5·00[e]	3·74	1·25	—	3·33	2·00	CCl_4	$J_{45} = 6·0$, $J_{56} = 6·7$;
	4·90	5·55–6·00		5·07	3·80	1·22		3·30	1·63	C_6H_6	
63	4·90	5·68–6·06		4·90	3·71	1·30		3·36	2·03	CCl_4	$J_{45} = 2·8$, $J_{56} = 6·8$;
	4·78	5·55–5·95		4·90	3·53	1·16		3·33	1·72	C_6H_6	
64	4·92[e]	5·60		4·92[e]	—	4·00–4·50	—	3·41	2·06	$CDCl_3$	
65	4·77	5·73		5·17	4·15	3·70	—	3·28	2·04	CCl_4	$J_{45} = 8·9$;
	4·68	5·50–5·90		5·38	4·10–3·85	4·17		3·23	1·73 1·77	C_6H_6	
66	4·88	5·50–5·90		5·01	3·98	4·32–4·15	—	3·38	2·01	CCl_4	$J_{45} = 6·9$, $J_{56} = 4·3$;
	4·78	5·65–6·05		5·14	3·87	4·24–4·02	—	3·25	1·71 1·77	C_6H_6	
67	5·37	5·90	5·56	5·66	4·55	4·03 3·77		—	2·00	CCl_4	$J_{12} = 2·8$, $J_{23} = 10·0$, $J_{13} = 0·5$, $J_{46'} = 1·2$.
	5·32	5·75–5·40		5·52	4·42	4·03 3·65	—		1·67	C_6H_6	$J_{56} = 2·0$, $J_{56'} = 6·0$, $J_{66'} = 7·9$;

[a] Together with H4, H5 and H5' protons. [b] Signal of H4 was overlapped by methylene protons of both acetoxymethyl groups. [c] Signal corresponding to β anomer appeared at 2·08. [d] H5 – 3·68, H5' – 4·03. [e] Signals of H1 and H4 were overlapped.

62 (4)

The reduction of stereoisomeric methyl pyranosiduloses **30** and **31** took a different course. Compound **30** yielded only one reduction product **51**, which was fully characterized as 4.6-di-O-acetyl derivative **65**. The PMR spectrum of this derivative showed coupling constant J_{45} = 8·5 Hz, this indicating the pseudo-axial position of H4 and axial of H5. Consequently. we assigned configuration α-erythro to this compound. Direct comparison (TLC. IR. PMR) of the obtained product with an original sample of methyl 4.6-di-O-acetyl-2.3-dideoxy-α-D-erythro-hex-2-enopyranoside* confirmed the constitutional identity of both compounds.

The reduction of anomer β (**31**) gave also one compound **52** which was characterized as 4.6-di-O-acetyl derivative **66**. which showed in the PMR spectrum a coupling constant J_{45} = 6·9 Hz (measured at the signal of H5), which was consistent only with the pseudo-axial–axial position of protons H4 and H5. This indicated configuration β-erythro for **66** and **52**. The agreement of the numerical data for the PMR spectrum of methyl 4.6-di-O-acetyl-2.3-dideoxy-β-D-erythro-hex-2-enopyranoside. as given by Rosenthal and Whyte.[38] with the PMR data of compound **66**. is noteworthy.

The reduction of methyl 6-O-acetyl-5-C-acetoxymethyl-2.3-dideoxy-DL-hex-2-enopyranosid-4-ulose (**34**) yielded product **57**. being a mixture of two stereoisomers (not separable). The PMR spectra of **57** and of its O-acetyl derivative **64** confirmed the gross structure of the obtained product. and indicated the predominance of one component. Since in the reduction of compound **29** an attack of the reagent from the side opposite to the C1 OMe group prevailed. resulting in compound **49**. by analogy we assigned configuration α to the compound predominantly formed from **34**.

The reduction of 1.6-anhydro-2.3-dideoxy-β-DL-hex-2-eno-pyranos-4-ulose (**35**) resulted in one product. which was characterized as 4-O-acetyl derivative **67**. Because of steric hindrance due to the presence of the 1.6-anhydro bridge. attack by reducing agent would be expected to take place from the opposite side of the ring. Therefore. we assigned configuration β-threo to compound **67**. From a scale model of compound **67** we find that H4-C4-C5-C6-H6ex bonds are W shaped. Since in the PMR spectrum of **67** J_{46ex} = 1·1 Hz. according to Heyns and Weyer[39] this coupling can be regarded as an evidence for β-threo configuration of **67**.

CONCLUSION

Two aspects of the synthesis (Scheme 1) are noteworthy. Firstly. compounds with the pyranose ring are formed at an early stage in the synthesis. and all the steps leading to asymmetric carbon atoms are performed on this ring. Since the stereochemistry of six-membered rings is well known. the prediction of the reaction course. as well as the determination of the configuration and conformation of the resulting products is relatively simple. Secondly. the synthesis has the advantage that no more than two stereoisomeric compounds are formed at any stage; usually these can be separated by chromatography. Consequently. the final products can be obtained as pure diastereoisomers.

* Obtained from 3.4.6-tri-O-acetyl-D-glucal and MeOH.[6c]

So far, total syntheses of sugars have either resulted in complex mixtures of monosaccharides,[40] or consisted of stereospecific syntheses of selected types (e.g. pentoses[41]), or individual monosaccharides (e.g. L-apiose.[42] L-cladinose and L-mycarose.[43] DL-oleandrose.[44] DL-glucose.[45] etc.). Our method for total synthesis of monosaccharides seems to provide a convenient route for obtaining a number of classes of sugar compounds. The examples which we have investigated indicate the possibility of synthetizing pentoses, hexoses and 6-deoxy-hexoses. It also seems possible to synthesise by the route given in Scheme 1, nearly any type of deoxysugar (a variety of amino-, O-alkyl sugars etc.). Starting with suitably substituted derivatives of furfuryl alcohol. it should be possible to prepare ketoses and aldoses with straight or branched carbon skeletons. as well as higher sugars. Studies along some of these lines are in progress in this laboratory.

EXPERIMENTAL

M.ps were determined on a Kofler block and are uncorrected. B.ps of the small scale distillations refer to the air bath temperature. UV spectra on a Unicam SP 500 spectrometer (95% EtOH). IR spectra using a Unicam SP-200 spectrometer. KBr discs for solids and films for liquids. PMR spectra were measured on Varian HA-60-IL or Jeol JNM-4H-100 spectrometers. (TMS). Analytical glc were on 2 m × 3 mm stainless steel columns packed with 15% w/w PPE on 60–80 mesh Chromosorb W. using Willy Giede's Gaschromatograph 18/3. and for preparative scale glc Varian Autoprep 705 equipped with a 6 m × 9·5 mm column was used. All spectral and analytical measurements were performed in the Physicochemical Department of this Institute (Head: Prof. J. Dabrowski).

For column chromatography silica gel Schuchard. 100–200 mesh. or "Kieselgel für Chromatographie. unter 0·08 mm' Merck. or aluminium oxide. activity II. were used. TLC was carried out on Merck's silica gel G.

Furfuryl alcohol (**7**). b.p. 68–69°C/10 mm. was prepared by LAH reduction of furfural. 1(2-Furyl)ethanol (**9**). b.p. 98–99°C/50 mm. was prepared according to lit.[46] data. 2(1,2-O-isopropylidene-1,2-dihydroxyethyl)furan (**8**), butyl (2-furyl)glycolate (**11**) and ethyl (2-furyl)tartronate (**12**) were obtained as described before.[13]

2(2-*Furyl*)*glycerol* 1,3-*diacetate* (**10**). To a suspension of LAH (14·4 g) in abs. ether (200 ml) 38·3 g of **12** in 250 ml of abs. ether was added dropwise with stirring. After addition the stirring was continued for 1 hr. Excess LAH was decomposed with 60 ml of H_2O and 14 ml of 15% NaOH aq. Ether was removed by decantation and the residue stirred with 20 ml of H_2O. Water was separated by centrifuging and decantation. repeating 10 ×. Combined H_2O solutions were neutralized by filtration through Amberlit IRC-50. Evaporation under reduced pressure left 14·3 g (yield 60%) of crude 2(2-furyl)glycerol. To the solution of 1·1 g of 2(2-furyl)glycerol in pyridine (3 ml) chilled in ice–water bath, acetic anhyd. (3 ml) was added with stirring. After 2 hr the reaction mixture was poured into 100 ml of 1% H_2SO_4 and ice. H_2O was extracted with EtOAc and the extract washed with $NaHCO_3$ aq. After evaporation. the residue was dissolved in C_6H_6. filtered through aluminium oxide. evaporated and dried in vacuum. Yield of **10**: 0·97 g (57%). IR: 3500 (OH). 1750. 1240 (OAc). 3200. 1520. 750 (furyl) cm^{-1}. PMR ($CDCl_3$) δ 2·05 (s, 6H, $COC\underline{H}_3$), 4·40 (s, 4H, $C\underline{H}_2O$). 6·35 (m, 2H, β-hydrogens). 7·40 (m, 1H, α-hydrogen). (Found: C, 54·0; H, 6·1. Calc. for $C_{11}H_{14}O_6$: C, 54·5; H, 5·8%).

2,5-Dimethoxy-2,5-dihydrofurans **13**–**18** (Table 1) were prepared by a common method. illustrated for the case of compound **14**.

2(1,2-*O*-*isopropylidene*-1,2-*dihydroxyethyl*)-2,5-*dimethoxy*-2,5-*dihydrofuran* (**14**). To a soln of **8** (82·8 g) in a mixture anhyd. ether (150 ml) and abs. MeOH (220 ml) kept at − 35°C, bromine (86·4 g) in MeOH (290 ml) was added gradually with stirring. Reaction mixture was stirred for 30 min, saturated with gaseous NH_3 to pH 8. and allow to warm up to the room temperature. NH_4Br was filtered off, and the solvents evaporated The residue was taken into C_6H_6 and filtered through aluminium oxide. Evaporation of the solvent and distillation (74°/0·5 mm) gave **14** as colorless liquid, 86 g (76%).

2,3-*Dideoxy*-DL-*pent*-2-*enopyranos*-4-*ulose* (**19**). **13** (40 g) was dissolved in 2% H_2SO_4 (80 ml) and the solution left for 90 min at room temperature. The reaction mixture was brought to pH 4 with $NaHCO_3$. H_2O was removed below 30°C in vacuo, and the residue dissolved in ether. Ether dried ($MgSO_4$) and

evaporated to give a solid, homogeneous in TLC, yield 28·3 g (~100%). It was recrystallized from ether–hexane mixture to give **19**, m.p. 54–58°C. Analytical sample was sublimed under reduced pressure.

2,3-*Dideoxy*-DL-*hex*-2-*enopyranos*-4-*ulose* (**20**). Hydrolysis of **14**, performed as described above, gave **20** (mixture of α and β anomers) and traces (TLC) of chromatographically more mobile component. The latter was separated by chromatography over silica gel column (~1% yield) with C_6H_6–EtOAc 9:1 as an eluant and was identified (elemental analysis, IR, PMR) as (2-furyl)-hydroxymethyl ketone (**27**), m.p. 83°C (lit.[47] 83–84·5°C). Compound **20** could be neither induced to crystallize, nor distilled in high vacuum; it was fully characterized as 1,6-di-O-acetyl derivative (**41**).

2,3,6-*Trideoxy*-α-DL-*hex*-2-*enopyranos*-4-*ulose* (**21**). Hydrolysis of **15** (15 g), carried out as for **13**, gave 11 g of **21** as yellowish oil, which solidified on standing. 1 g of **21** was chromatographed over silica gel column with C_6H_6–ether 3:1. The residue obtained after evaporation of solvents and recrystallization from ether afforded 0·7 g of **21** as colorless needles, m.p. 62–65°C.

1-*O*-(2,3,6-*trideoxy*-α-DL-*hex*-2-*enopyranosyl*-4-*ulose*)-2,3,6-*trideoxy*-α-DL-*hex*-2-*enopyranosid*-4-*uloses*: dl (**23**) and *meso* (**24**). **15** (2 g), hydrolyzed as described above, was brought to pH 6 and the water evaporated* at 80°C. Residue was dissolved in ether, and dried over anhyd. $MgSO_4$. TLC showed the presence of **21** and two more mobile components, separated by column chromatography (C_6H_6–ether 5:1). Successive fractions gave: **23**, 0·24 g (9%), colorless needles (ether), m.p. 110°C. **24**, 0·10 g (4%), colorless needles (ether), m.p. 130°C.

6-*O*-*Acetyl*-5-*C*-*acetoxymethyl*-2,3-*dideoxy*-DL-*hex*-2-*enopyranos*-4-*ulose* (**22**). Hydrolysis of 0·3 g **16**, carried out as for **13**, gave crude **22** (0·3 g). Chromatography (silica column) gave **22** (0·16 g), homogeneous to TLC. Distillation (150°C/0·8 mm) for an analytical sample.

Hydrolysis of butyl 2(2,5-*dimethoxy*-2,5-*dihydrofuryl*)*glycolate* (**17**). **17** (0·5 g), hydrolyzed and worked up as described for **13**, gave an oil (0·45 g), which was chromatographed on silica (9 g, Merck). Elution (C_6H_6–EtOAc 9:1) afforded **26** (0·12 g, 30%), colorless oil, b.p. 65–70°C/0·1 mm; IR: 3160, 1735, 1675, 1560, 1040, 885, 775 cm^{-1}. 2,4-Dinitrophenylhydrazone of **26**, m.p. 180–181°C. (Found: C, 51·3; H, 4·5; N, 14·7. Calc. for $C_{16}H_{16}O_7N_4$: C, 51·4; H, 4·3; N, 14·9%). Ketone **26**, reduced with $NaBH_4$, gave carbinol identical (TLC, IR) with compound **11**.

Hydrolysis of ethyl 2(2,5-*dimethoxy*-2,5-*dihydrofuryl*)*tartronate* (**18**). **18** (0·3 g), hydrolyzed and worked up as described for **13**, gave an oil (0·28 g), chromatographed on silica (5 g, Schuchard) with C_6H_6–EtOAc 7:3 as eluant. Evaporation of the solvents left residue, which was distilled at 88–90°/0·8 mm: ethyl tartronate (**28**), yield 0·11 g (71%). Compound **28** was identical (TLC, IR, NMR) with the product of $NaBH_4$ reduction of ethyl mesoxalate.

Methyl 2,3-*dideoxy*-DL-*pent*-2-*enopyranosid*-4-*ulose* (**29**). A soln of **19** (28·3 g) and methyl orthoformate (24·5 g) in abs. ether (600 ml) was chilled to 0°C, and 7·3 ml (16·3 g) $SnCl_4$ slowly added with stirring. After 45 min the reaction was quenched with triethylamine. The etheral layer was washed three times with water and dried with anhyd. $MgSO_4$. Evaporation of solvent left 27·3 g of crude product, distilled at 76–81°/13 mm to give **29**, 13·6 g (43%).

Methyl 2,3,6-*trideoxy*-DL-*hex*-2-*enopyranoside*-4-*ulosess*: α (**32**) and β (**33**). Glycosidation of **21**, carried out according to the procedure described above, gave anomeric mixture of **32** and **33** in proportion 5:2 (glc); this was separated by preparative glc with α (**32**) anomer first off the column.

Methyl 6-*O*-*acetyl*-5-*C*-*acetoxymethyl*-2,3-*dideoxy*-DL-*hex*-2-*enopyranosid*-4-*ulose* (**34**), was obtained by the method described for **29**.

1,6-*Anhydro*-2,3-*dideoxy*-β-DL-*hex*-2-*enopyranosid*-4-*ulose* (**35**) and *methyl* 2,3-*dideoxy*-DL-*hex*-2-*enopyranosid*-4-*uloses*: α (**30**) and β (**31**). A soln of **20** (6·57 g) and methyl orthoformate (7·3 g) in abs. ether (130 ml) was chilled to 0°C, BF_3Et_2O (1.12 ml) was added and the reaction mixture left at room temperature for 40 min. The soln was filtered (aluminium oxide column) and the neutral eluate was evaporated to dryness to give 4·01 g residue, three components (TLC). This mixture was adsorbed on silica (90 g, Schuchardt) and eluted with C_6H_6–EtOAc (5:1) mixture. Successive fractions gave: **35**, yield 1·50 g (26%), mobile colorless liquid, b.p. 84°C/30 mm, **31**, yield 0·55 g, colorless viscous oil, mixture of **30** and **31**, 0·39 g, **30**, yield 0·68 g, colorless viscous oil. Re-chromatography of mixt. fraction gave additional quantities of pure **30** and **31**. Both compounds distilled at 75–80°C/0·001 mm. (partial decomp.).

1-*O*-*Acetyl*-2,3-*dideoxy*-DL-*pent*-2-*enopyranos*-4-*ulose* (**38**). A soln of **19** (1·0 g) in acetic anhyd (3 ml) was chilled to 0°C, pyridine (1 ml) was added, and the reaction mixture left at 0°C for 3 hr. The solvent was evaporated at room temperature (~1 torr), the residue was taken into C_6H_6, filtered through a short silica gel (2·5 g) column and evaporated again. Resulting oil (1·25 g) was chromatographed on silica (17 g,

* The storage of crude **21** at pH 4–5 has the same effect as evaporation at elevated temperature.

Schuchardt). Elution with C_6H_6–ether (9:1) gave **38**, 1·15 g (85%), colorless oil, b.p. 70–80°C/0·4 mm. Compound **38** solidified on standing, m.p. 41–41·5°C.

Acetyl derivatives **36**, **37**, **39** and **40** (Table 3) were prepared by the same procedure. Chromatography over silica gel column with C_6H_6–EtOAc (9:1) afforded pure anomers **39** and **40**.

1,6-Di-O-acetyl-2,3-dideoxy-αβ-DL-hex-2-enopyranos-4-ulose (**41**) and *1-O-acetyl-2,3-dideoxy-αβ-DL-hex-2-enopyranos-4-ulose* (**42**). A soln of **20** (1·0 g) in 30 ml CH_2Cl_2–EtOAc (1:2) was placed on an ice–water bath and acetic anhyd (3 ml) and several drops of pyridine were added. After 7 hr the reaction mixture was worked up as described in the preceding experiment to give 1·39 g of an oily product, chromatographed on silica (30 g, Schuchardt). Fractions eluted with C_6H_6–ether (9:1) gave two components: **41**, 0·63 g (40%), colorless liquid, b.p. 100°/0·4 mm, **42**, 0·18 g (14%), colorless gum. Compound **42** was acetylated again to give product identical (TLC, IR) with **41**. Both compounds, **41** and **42**, were obtained as mixtures of α and β anomers in proportion 3:2 (PMR).

Methyl 2,3-dideoxy-DL-pent-2-enopyranosides: α (**49**) and β (**50**). A soln of $NaBH_4$ (1·14 g) in water (80 ml) was placed on an ice–water bath and **29** (7·6 g) in THF (20 ml) was added dropwise over 10 min. The reaction mixture was stirred for 30 min., and neutralized with AcOH. After evaporation of solvents the residue was taken up in C_6H_6–EtOAc (1:1), filtered through a short aluminium oxide column and the solvents were evaporated to give 7·1 g of an oil, chromatographed on silica (150 g, Schuchardt). Elution with C_6H_6–ether (9:1) gave at first **49**, 6·25 g (82%), colorless oil, b.p. 64–65°/0·4 mm. Successive fractions afforded small quantities of **50** (homogeneous in TLC), but not analytically pure.

4-O-Acetyl derivatives: **58** and **59** were obtained by acetylation of **49** and **50**, respectively, with acetic anhyd. and pyridine in the usual manner.

Methyl 2,3,6-trideoxy-α-DL-hex-2-enopyranosides: *erythro* (**53**) and *threo* (**54**). Reduction of **32** (2·0 g) with $NaBH_4$ (0·27 g) using the procedure described in the previous experiment gave 2·0 g of crude **53** and **54**. 1·13 g of this mixture was acetylated with acetic anhyd.–pyridine and worked up as usual to give a mixture of 4-O-acetyl derivatives **60** and **61**, which were separated on silica (80 g, Schuchardt). Elution with C_6H_6–EtOAc (9:1) and evaporation gave successively: **60**, 0·49 g (33%), mixture of **60** and **61** (0·47 g), and **61**, 0·15 g (10%). Mixed fraction after re-chromatography afforded further quantities of pure **60** and **61**.

Methyl pyranosides **57**, **62**, **63**, **64**, **65**, **66** and 1,6-anhydro compound **67** were obtained according to common procedure illustrated on the examples described above. Compounds **57** and **64** were characterized as anomeric mixtures, detected in the PMR spectra. Their separation could not be effected by chromatography over silica columns.

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