Carbohydrate Research, 55 (1977) 177–192

TOTAL SYNTHESIS OF HEXURONIC ACIDS*†

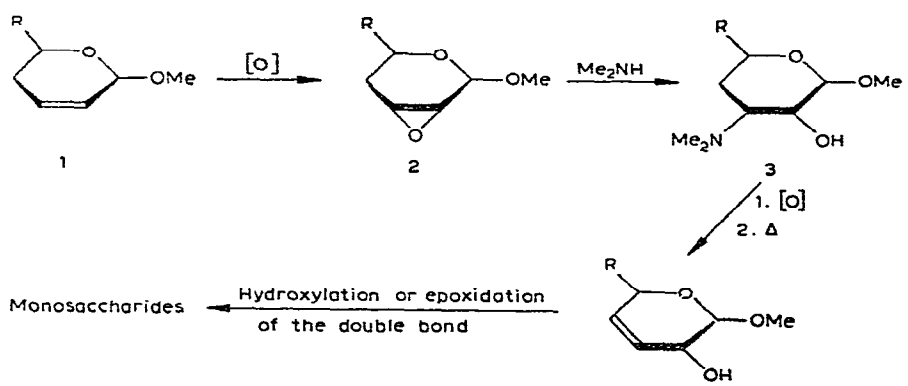
JÓZEF MIECZKOWSKI AND ALEKSANDER ZAMOJSKI‡
Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warszawa (Poland)
(Received October 28th, 1976; accepted for publication in revised form, January 30th, 1977)

ABSTRACT

Six stereoisomeric hexuronic acids (*tert*-butyl esters of methyl pyranosides) having the *altro*, *manno*, *gluco*, *gulo*, *galacto*, and *talo* configurations were obtained from *cis,trans-tert*-butyl 2-methoxy-5,6-dihydro-2*H*-pyran-6-carboxylate (**5**). The synthesis involved the following successive steps: epoxidation of the double bond in **5**, opening of the epoxides with dimethylamine, Cope degradation of the dimethylamino derivatives, and hydroxylation of the double bond in the *tert*-butyl hex-3-enuronates. All compounds were obtained as pure diastereoisomers in racemic form.

INTRODUCTION

The totally synthetic approach to monosaccharides based on derivatives of 2-alkoxy-5,6-dihydro-2*H*-pyran (Scheme I) has been applied thus far for the prepara-



Scheme 1

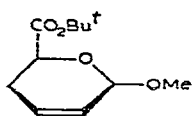
*Dedicated to the memory of Professor J. K. N. Jones, F.R.S.
†Derivatives of 2-Alkoxy-5,6-dihydro-2*H*-pyran as Substrates in the Total Synthesis of Monosaccharides. Part XXIII. Part XXII: *Tetrahedron*, 32 (1976) 2957–2959.
‡To whom inquiries should be addressed.

tion of normal pentoses[1], hexoses[2,3], 4-deoxy-[4], and 6-deoxy-hexoses[5], and several other five- and six-carbon sugars[6]. We considered that a logical supplement to these investigations, extending the generality of the approach, would be the synthesis of stereoisomeric hexuronic acids.

Following the general pattern outlined here, we were able to obtain six stereoisomeric hexuronic acids as *tert*-butyl or methyl esters of methyl α-glycosides.

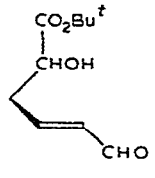
RESULTS

The necessary substrate **5**, containing six carbon atoms in the backbone, was readily obtained in 57% yield by condensation of *trans*-1-methoxy-1,3-butadiene with *tert*-butyl glyoxylate. Two additional products were isolated in low yield from the mixture; they were identified as *tert*-butyl 2-hydroxy-6-oxo-hex-4-enoate (**6**, 8% yield) and *tert*-butyl 2-[1-(*tert*-butoxycarbonyl)-5-oxo-pent-3-enyloxy]-5,6-dihydro-2*H*-pyran-6-carboxylate (**7**, 0.4% yield)*.

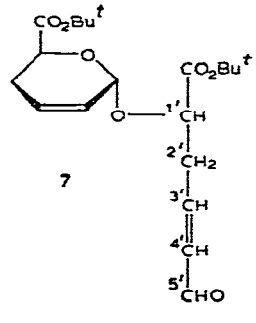


5

trans : *cis* 3 : 2

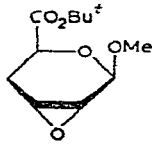


6

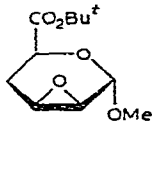


7

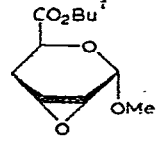
Epoxidation of **5** with 30% hydrogen peroxide and acetonitrile at room temperature afforded a mixture of four stereoisomeric epoxides **8–11** in 67% total yield. The epoxides were separated by column chromatography. Assignment of configuration to individual compounds was made on the basis of ^{1}H-n.m.r. data[7].



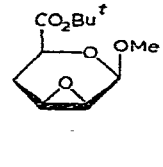
8 (10%)



9 (18%)



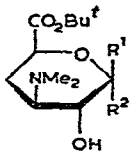
10 (36%)



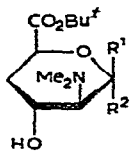
11 (3%)

*These compounds were obviously artefacts; **6** was formed from **5** through hydrolysis by residual water contained in *tert*-butyl glyoxylate, and **7** was obtained from **5** by substitution of the methoxyl group by the hydroxyl group of **6**. Although it was difficult to avoid the formation of **6** and **7** during the condensation, the separation of **5** from both side products was readily achieved by distillation.

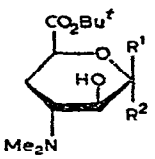
Opening of the oxirane ring in **9** and **11** with aqueous dimethylamine at room temperature afforded *tert*-butyl [methyl 3,4-dideoxy-3-(dimethylamino)-α- and β-DL-*arabino*-hexopyranosid]uronates, **14** and **17**. In the case of both *ribo* epoxides (**8** and **10**), the same reaction furnished, in addition to the desired *tert*-butyl [methyl 3,4-dideoxy-3-(dimethylamino)-β- and α-DL-*xylo*-hexopyranosid]uronates (**12** and **15**), some of the isomeric 2-deoxy-2-(dimethylamino) sugars **13** and **16**, resulting from attack of the nucleophile at C-2†.



12 R^1 = OMe, R^2 = H
15 R^1 = H, R^2 = OMe



13 R^1 = OMe, R^2 = H
16 R^1 = H, R^2 = OMe



14 R^1 = H, R^2 = OMe
17 R^1 = OMe, R^2 = H

The results are given in detail in Table I.

TABLE I

PRODUCTS OF REACTION OF THE STEREOISOMERIC EPOXIDES **8–11** WITH 25% AQUEOUS DIMETHYLAMINE AT ROOM TEMPERATURE

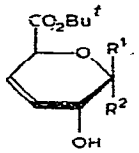
Substrate No.	*Product No.*	*Reaction time (h)*	*Yield (%)*	*M.p. (degrees)*	*Analysis[a] Found*			*Yield of salts[b] (%)*
					C	*H*	*N*	
8	**12**	24	13	61–62	56.9	9.2	5.1	38
	13		20	85–86	56.7	9.1	4.9	
9	**14**	14	71	80	56.8	9.1	5.0	23
10	**15**	48	30	62	56.8	9.3	4.8	33
	16		8	36–38	56.7	9.3	4.9	
11	**17**	14	42	[c]	56.6	9.4	5.1	35

[a]For $C_{13}H_{25}NO_5$ calc.: C, 56.7; H, 9.2; N, 5.1. [b]Internal salts of (dimethylamino)hexuronic acids (see footnote on this page). [c]Oil, distilled at 121°/0.01 torr.

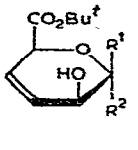
Oxidation with hydrogen peroxide readily converted compounds **12**, **14**, **15**, and **17** into their *N*-oxides. Refluxing of the *N*-oxides in xylene solution (Cope degradation) gave the corresponding *tert*-butyl (methyl 3,4-dideoxy-DL-hex-3-eno-pyranosid)uronates **18–21**. The 3,4-unsaturated products were contaminated with small proportions of isomers (such as **22** and **23**) having the double bond shifted to the 4,5-position. They were undoubtedly formed from 3,4-alkenes under the influence

†The reaction of epoxides **8–11** with dimethylamine was accompanied by partial hydrolysis of the ester group. As a result, dimethylamino acids (as acetone-insoluble internal salts) were obtained as side products (see experimental section).

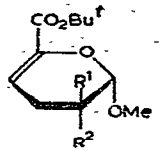
of *N,N*-dimethylhydroxylamine split off during the pyrolysis and acting as a basic catalyst.



18 R^1 = OMe, R^2 = H
20 R^1 = H, R^2 = OMe



19 R^1 = H, R^2 = OMe
21 R^1 = OMe, R^2 = H



22 R^1 = OH, R^2 = H
23 R^1 = H, R^2 = OH

The results of Cope degradation of the *N*-oxides are shown in Table II.

TABLE II

COPE DEGRADATION OF *N*-OXIDES OBTAINED FROM THE *tert*-BUTYL [METHYL 3,4-DIDEOXY-3-(DIMETHYLAMINO)-DL-HEXOPYRANOSID]URONATES (12, 14, 15, AND 17)

Substrate No.	*Product No.*	*Yield (%)*	*B.p.*[a] *degree/torr (m.p.)*	*Analysis found*[b]		*Side products (%)*
				C	*H*	
12	18	50	115/0.1	57.4	8.1	22 (5)
14	19	39[c]	110/0.05 (49–50)	57.4	8.0	22 7 recovered 14 (46)
15	20	28[d]	111/0.15 (45–46)	57.5	8.1	23 (5) recovered 15 (60)
17	21	51	100/0.1	57.5	7.8	23 (traces)

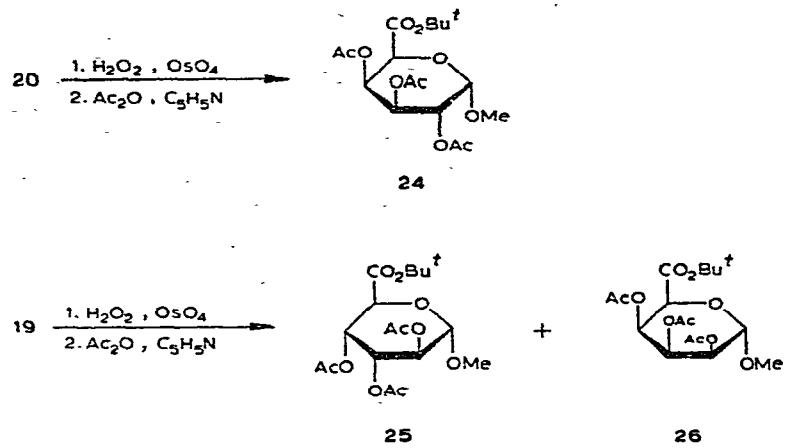
[a]Air-bath temperature. [b]For $C_{11}H_{18}O_5$ calc.: C, 57.4; H, 7.9. [c]Yield 72%, based on the substrate consumed. [d]Yield 69%, based on the substrate consumed.

Further synthetic steps were performed on the *tert*-butyl (methyl 3,4-dideoxy-α-DL-*threo*- and *erythro*-hex-3-enopyranosid)uronates, **19** and **20**, as described in the following examples.

cis-*Hydroxylation*. — Both of the *tert*-butyl 3,4-unsaturated glycosiduronates **19** and **20** were hydroxylated with the Milas reagent, namely ~6% hydrogen peroxide in *tert*-butyl alcohol containing catalytic amounts of osmium tetraoxide. From the *erythro* compound **20**, a single product was formed in 48% yield that was identified after acetylation as *tert*-butyl (methyl 2,3,4-tri-*O*-acetyl-α-DL-galactopyranosid)-uronate (**24**).

Under the same conditions, two products were obtained from the *threo* compound **19**, in 7:1 proportion. They were separated after acetylation and identified as *tert*-butyl (methyl 2,3,4-tri-*O*-acetyl-α-DL-hexopyranosid)uronates having the *altro* (**25**, major component) and *talo* (**26**) configurations.

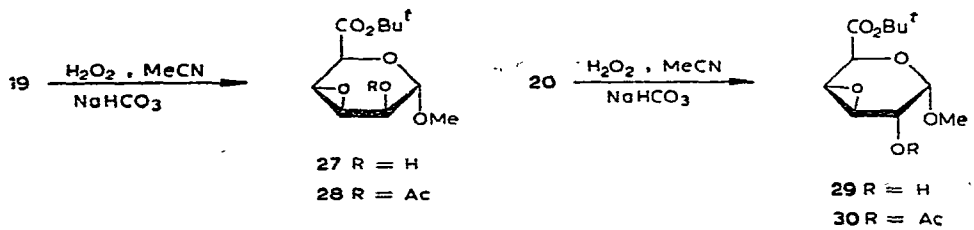
The results of *cis*-hydroxylation are in accord with the well-documented observation[8] that both hydroxyl groups enter preferentially in *trans*-relation to the



existing ring-substituents. In the *erythro* derivative **20**, the substituents at C-1 and C-2 acted in the same direction, permitting exclusive *trans* attack of the reagent molecule. In the *threo* derivative **19**, the directing influences of 2-OH and 1-OMe groups acted in opposite directions, and therefore both possible stereoisomers were formed.

Epoxidation and ring-opening of the oxiranes. — Epoxidation of the *threo* compound **19** with a mixture of 30% hydrogen peroxide and acetonitrile afforded a single epoxide **27** (59% yield) for which the *α-talo* configuration was deduced from ^{1}H-n.m.r. data. This assignment is in agreement with the conclusion that cyclic, allylic alcohols are preferentially epoxidized *cis* in relation to the hydroxyl group; a transient hydrogen-bond between the epoxidizing reagent (peroxyiminoacetic acid in this instance) and the hydroxyl group is assumed, in accounting for the stereochemical result of the reaction[9].

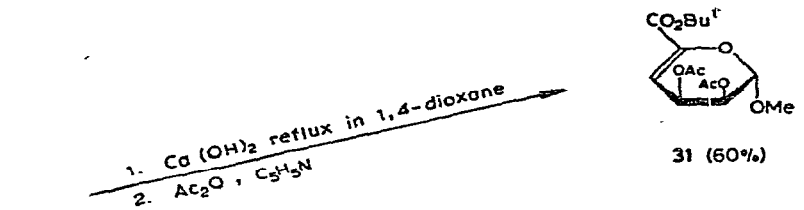
Treatment of the *α-erythro* compound **20** with the same epoxidizing reagent also gave a single product, namely **29** (56% yield). From the ^{1}H-n.m.r. data, the *α-galacto* configuration could be unequivocally established for **29**.



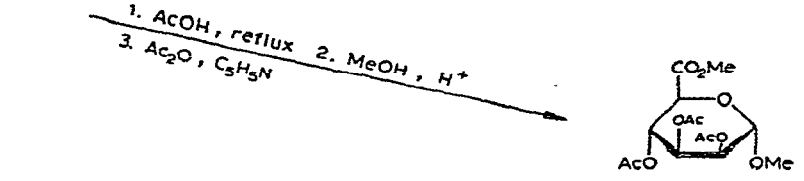
This stereochemical result is—in the light of the previous considerations—rather unexpected. We have to assume that, in this instance, steric hindrance exerted by both substituents at C-1 and C-2 prevailed decisively over hydrogen bonding to

the 2-OH group, and forced the reagent molecule to attack the double bond *trans* in respect to the substituents.

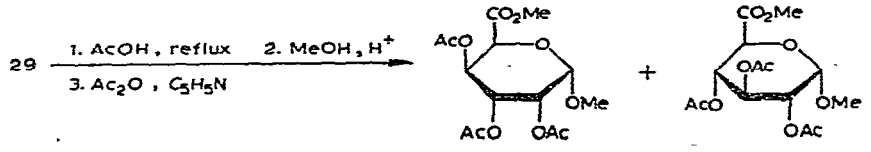
The oxirane ring-opening in **27** was first attempted under basic conditions. Heating **27** with a suspension of calcium hydroxide in 1,4-dioxane gave a single product that was isolated and characterized as a diacetate **31**. On the basis of spectral data, the structure assigned to **31** was *tert*-butyl (methyl 2,3-di-*O*-acetyl-4-deoxy-β-DL-*erythro*-hex-4-enopyranosid)uronate, indicating opening of the three-membered ring at C-4 followed by elimination of a water molecule*. Formation of 4,5-unsaturated derivatives under basic conditions is well known in the chemistry of glycuronic acids[16].



31 (60%)



32 (22%)



33 (20%) 34 (1.9%)

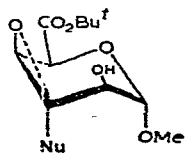
*The 4,5-unsaturated compound might also have been formed in a concerted way initiated by abstraction of H-5 by the base:

We are grateful to a referee for this suggestion.

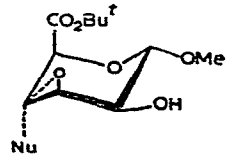
Further ring-opening reactions of oxiranes **27** and **29** were performed with acetic acid. Compound **27** gave a single product that was identified as methyl (methyl 2,3,4-tri-*O*-acetyl-α-DL-mannopyranosid)uronate (**32**).

Under the same conditions, the oxirane **29** afforded two products in 10:1 ratio and these were identified as the methyl (methyl 2,3,4-tri-*O*-acetyl-α-DL-gulo- and gluco-pyranosid)uronates (**33** and **34**), respectively.

The oxirane ring-opening behavior of **27** and **29** resembles closely the results achieved with methyl 3,4-anhydro-DL-hexopyranosides having the same configurations[3]. They may be explained in terms of "product-like" transition states[11], (such as A and B for **27**), which account for steric interactions in two possible chair-forms resulting from axial attack of the nucleophile at C-3 or C-4. This is illustrated for compound **27**.



A, axial attack at C-3



B, axial attack at C-4

It may be seen that transition state *A* (two 1,3-diaxial interactions) is less favorable than *B* (one 1,3-diaxial interaction), and therefore the product having the *manno* configuration should prevail. The same reasoning leads to the conclusion that, in the ring-opening reactions of compound **29**, products having the *gulo* configuration should preponderate.

CONCLUSION

The method depicted in Scheme I has permitted the preparation of six stereoisomeric hexuronic acids having the *altro*, *manno*, *gluco*, *gulo*, *galacto*, and *talo* configurations. There can be little doubt that the remaining two stereoisomers should be obtainable in the same way, by using appropriate changes in the substitution mode at C-1 and/or at C-2, as well as a variety of derived products, such as those obtained by oxirane ring-opening with different nucleophiles. No attempts have been made to increase the yields of intermediate or final products.

The work presented here essentially concludes the test series[1–5] in which we set out to establish the generality of a monosaccharide synthesis based on derivatives of 2-alkoxy-5,6-dihydro-2*H*-pyran.

EXPERIMENTAL

General methods. — ^{1}H-n.m.r. spectra were recorded with a Jeol 100-MHz spectrometer with solutions in $CDCl_3$. Chemical shifts are given on the δ scale

(Me_4Si, 0 p.p.m.). *trans*-1-Methoxy-1,3-butadiene was obtained from 1,1,3-trimethoxybutane by catalytic dealkoxylation[12]. *tert*-Butyl glyoxylate was prepared in 71% yield from *tert*-butyl bromoacetate by the method of Kornblum and Frazier[13]. The product was distilled at 64–67°/20 torr through a Vigreux column; its spectral (i.r. 3450 cm^{-1}) and analytical data (calc. for $C_6H_{10}O_3$: C, 55.4; H, 7.8. Found: C, 54.8; H, 8.4) indicated the presence of some residual water.

tert-*Butyl* cis *and* trans *2-methoxy-5,6-dihydro-2H-pyran-6-carboxylate* (**5**). — A solution of 1-methoxy-1,3-butadiene (82 g) in heptane (500 ml) was mixed with *tert*-butyl glyoxylate (120 g) and boiled for 24 h under reflux. After removal of the solvent under diminished pressure, the residue was fractionated and afforded two fractions; compound **5** b.p. 70–75°/0.4 torr, 120 g (56.5%), and one having b.p. 85–115°/0.4 torr [21 g, compounds **5**, **6**, and **7** (t.l.c.)]. The Diels–Alder product **5** contained the *cis* and *trans* isomers in 3:2 ratio, as determined by integration of ^{1}H-n.m.r. methoxyl-group signals.

A sample of **5** was separated by column chromatography into the pure stereoisomers. Data for the *cis* isomer were: ^{1}H-n.m.r.: 6.13 (m, 1H, $J_{3,4}$ 10.5 Hz, H-4), 5.77 (m, 1H, H-3), 5.13 (m, 1H, H-2), 4.35 (pd, 1H, $J_{5,6}+J_{5',6}$ 12.5 Hz, H-6), 3.59 (s, 3H, OCH_3), 2.20–2.52 (m, 2H, H-5, H-5'), and 1.53 (s, 9H, CMe_3); ν_{max}^{film} 1750, 1730, 1660, 1160, 1050, and 850 cm^{-1}.

Anal. Calc. for $C_{11}H_{18}O_4$: C, 61.7; H, 8.5. Found: C, 61.7; H, 8.5.

For *trans*-**5**: ^{1}H-n.m.r. data: 6.10 (m, 1H, $J_{3,4}$ 10.2 Hz, H-4), 5.85 (m, 1H, H-3), 5.05 (m, 1H, H-2), 4.42 (pd, $J_{5,6}+J_{5',6}$ 16.0 Hz, H-6), 3.52 (s, 3H, OCH_3), 2.32 (m, 2H, H-5, H-5'), and 1.54 (s, 9H, CMe_3); ν_{max}^{film} 1740, 1660, 1160, 1085, and 855 cm^{-1}.

Anal. Calc. for $C_{11}H_{18}O_4$: C, 61.7; H, 8.5. Found: C, 61.4; H, 8.5.

The assignment of *cis* and *trans* configurations was based on the ^{1}H-n.m.r. data[14].

A 10 g-sample of the second, higher-boiling fraction was separated by column chromatography into its components: 1.1 g of *cis*- and *trans*-**5**, 7.3 g of *tert*-butyl 2-hydroxy-6-oxohex-4-enoate (**6**), and 0.8 g of *tert*-butyl 2-[1-(*tert*-butoxycarbonyl)-5-oxopent-3-enyloxy]-5,6-dihydro-2*H*-pyran-6-carboxylate (**7**). Compound **6** was identified by comparison (i.r. and ^{1}H-n.m.r. spectra, and t.l.c.) with an authentic sample obtained by hydrolysis of **5** with 2% hydrochloric acid (compare ref. 15). The structure of **7** was derived from the spectral and analytical data.

For compound **7**: ^{1}H-n.m.r. data: δ10.52 (d, 1H, $J_{4',5'}$ 7.7 Hz, H-5'), 6.85 (pt, 1H, $J_{3',4'}$ 16.0, $\Sigma J_{3',2'}$ 14.2 Hz, H-3'), 6.15 (pd, 1H, H-4'), 6.04 (m, 1H, $J_{3,4}$ 10.0 Hz, H-4), 5.80 (m, 1H, H-3), 5.18 (m, 1H, H-2), 4.50 (pd, 1H, $J_{1',2'}+J_{1',2''}$ 12.3 Hz, H-1'), 4.25 (t, 1H, $\Sigma J_{5,6}$ 15.0 Hz, H-6), 2.80 (m, 2H, H-2' and H-2''), 2.28 (m, 2H, both H-5), 1.50 and 1.47 (two s, 18H, two CMe_3); ν_{max}^{KBr} 1745, 1690, 1640, 1160, 1020, and 720 cm^{-1}.

Anal. Calc. for $C_{20}H_{30}O_7$: C, 62.8; H, 7.9. Found: 62.8; H, 7.6.

tert-*Butyl* [*methyl 2,3-anhydro-4-deoxy*-DL-*hexopyranosid*]*uronates* (**8**–**11**). — A solution of the stereoisomers of **5** (130 g) in methanol (500 ml) was treated with

300 ml of 30% hydrogen peroxide, 150 ml of acetonitrile, and 400 g of sodium hydrogencarbonate, and stirred for 5 days at room temperature. The mixture was poured into 2 liters of water and the product extracted with dichloromethane. The extract was dried (magnesium sulfate) and concentrated under diminished pressure. Acetamide was filtered off, and the residue was distilled at 80–110°/0.4 torr. The distillate (105 g) was chromatographed on a column of silica gel with 10:1 light petroleum (b.p. 60–80°)–ether. Four fractions were obtained: (*a*) 14.5 g (10%) of the *β-ribo* epoxide **8**, distilling at 101°/0.3 torr; ν_{max}^{film} 1745, 1150, 1135, 1020, and 845 cm^{-1}.

Anal. Calc. for $C_{11}H_{18}O_5$: C, 57.4; H, 7.9. Found: C, 57.3; H, 7.8.

(*b*) 25.0 g (18%) of the *α-lyxo* epoxide **9**, distilling at 97°/0.3 torr, m.p. 60°; ν_{max}^{KBr} 1740, 1170, 1040, 1125, and 825 cm^{-1}.

Anal. Calc. for $C_{11}H_{18}O_5$: C, 57.4; H, 7.9. Found: C, 57.4; H, 8.0.

(*c*) 50.1 g (36%) of the *α-ribo* epoxide **10**, distilling at 98°/0.2 torr, m.p. 33–34°; ν_{max}^{KBr} 1740, 1150, 1100, 1055, and 820 cm^{-1}.

Anal. Calc. $C_{11}H_{18}O_5$: C, 57.4; H, 7.9. Found: C, 57.2; H, 7.9.

(*d*) 4.1 g (3%) of the *β-lyxo* epoxide **11**, distilling at 95°/0.3 torr, m.p. 52–54°; ν_{max}^{KBr} 1745, 1150, 1110, 1030, and 838 cm^{-1}.

Anal. Calc. for $C_{11}H_{18}O_5$: C, 57.4; H, 7.9. Found: C, 57.1; H, 8.0.

TABLE III

^{1}H-N.M.R. DATA (100 MHz, $CDCl_3$, δ SCALE) FOR *tert*-BUTYL (METHYL 2,3-ANHYDRO-4-DEOXY-DL-HEXOPYRANOSID)URONATES (**8–11**)

Compound No.	*H-1*	*H-2*	*H-3*	*H-4pe*	*H-4pa*	*H-5*	*OCH₃*	*Coupling data (Hz)*
8	4.79	3.15	3.42	2.32	2.09	4.00	3.60	$J_{1,2}$ 0, $J_{2,3}$ 4.0, $J_{3,4pe}$ 2.0, $J_{3,4pa}$ 2.0, $J_{5,4pa}$ 10.0, $J_{5,4pe}$ 4.5, $J_{4pa,4pe}$ 14.6
9	5.12	3.05	3.43	2.10–2.30		4.27	3.57	$J_{1,2}$ 0, $J_{5,4pa+5,4pe}$ 16.5
10	5.05	3.28	3.46	2.32	1.90	4.27	3.48	$J_{1,2}$ 2.8, $J_{5,4pa}$ 12.0, $J_{5,4pe}$ 3.0
11	4.94	3.21	3.45	2.13–2.34		4.06	3.66	$J_{1,2}$ 0, $J_{3,4pa}$ 1.5, $J_{5,4pa}$ 8.8, $J_{5,4pe}$ 6.0

tert-*Butyl* [*methyl* 3,4-*dideoxy-3-(dimethylamino)*-DL-*hexopyranosid*]*uronates* (**12**, **14**, **15**, *and* **17**) *and* tert-*butyl* [*methyl 2,4-dideoxy-2-(dimethylamino)*-DL-*hexopyranosid*]*uronates* (**13** *and* **16**). — The *tert*-butyl (methyl 2,3-anhydro-4-deoxy-DL-hexopyranosid)uronates **8–11** (1 g) were each dissolved in 6 ml of 25% aqueous dimethylamine and kept at room temperature until the substrate disappeared (t.l.c.). The excess of dimethylamine and water was evaporated off under diminished pressure. Acetone was added to the oily residues and the internal salts that precipitated were filtered off. The acetone solutions of products **12–17** were dried (magnesium sulfate) and evaporated. The residues were chromatographed on a column of silica gel with 1000:8:0.3 chloroform–methanol–aq. ammonia.

TABLE IV

^{1}H-N.M.R. DATA (100 MHz, $CDCl_3$, δ SCALE) FOR *tert*-BUTYL [METHYL 3,4-DIDEOXY-3-(DIMETHYLAMINO)-DL-HEXOPYRANOSID]URONATES (12, 14, 15, AND 17), AND *tert*-BUTYL [METHYL 2,4-DIDEOXY-2-(DIMETHYLAMINO)-DL-HEXOPYRANOSID]URONATES (13 AND 16)

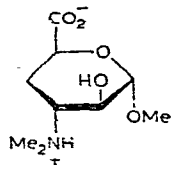
Compound No.	*H-1*	*H-2*	*H-3*	*H-4a*	*H-4e*	*H-5*	*OCH_3*	*NMe_2*	$J_{1,2}$	$J_{2,3}$	$J_{3,4a}$	$J_{3,4e}$	$J_{5,4a}$	$J_{5,4e}$	$J_{4a,4e}$
12	4.23	3.38	2.64	[a]	2.02	3.97	3.63	2.37	7.5	9.5	12.2	3.9	11.5	2.5	15.1
13[b]	4.91	2.67	4.20	2.5–2.6		4.35	3.46	2.48	3.3		10.0	4.5			
14[b]	4.75	3.38	2.55	1.75	2.25	4.64	3.67	2.36	7.7	10.5	13.0	3.9	6.7	2.5	15.0
15	5.08	3.71	3.07		2.07	4.32	3.57	2.39	3.8	11.0	11.8	4.0	12.1	2.7	14.0
16[b]	5.08	2.30		1.86		4.55	3.63	2.48	8.0	9.8	10.8		6.7	3.0	
17[b]	4.84	3.60	3.08	1.64		4.25	3.51	2.30	3.5	10.0	11.0	3.5	5.8	2.5	14.0

[a]Not resolved. [b]Coupling constants indicate conformational equilibria with preponderance of inverted [$^1C_4$(D)] chair-forms.

Reaction times, yields, melting points, and analytical data for the products obtained are collected in Table I. Table IV gives their ^{1}H-n.m.r. data.

[*Methyl 3,4-dideoxy-3-(dimethylamino)*-α-DL-arabino-*hexopyranosid*]*uronic acid* (**35**). — This product was obtained as an acetone-insoluble salt from the (methyl 2,3-anhydro-4-deoxy-α-DL-*lyxo*-hexopyranosid)uronic ester by treating it for 48 h with 25% aq. dimethylamine; yield 53%; m.p. 234–237° (decomp.); ν_{max}^{KBr} 3150, 1615, 1400, 1120, 1090, 1075, and 1030 cm^{-1}.

Anal. Calc. for $C_9H_{17}NO_5$: C, 49.3; H, 7.8; N, 6.4. Found: C, 49.3; H, 7.7; N, 6.3.



35

A sample of the salt was dissolved in methanol and esterified with diazomethane. Methyl [methyl 3,4-dideoxy-3-(dimethylamino)-α-DL-*arabino*-hexopyranosid]uronate was obtained in 73% yield, m.p. 81°.

Anal. Calc. for $C_{10}H_{19}NO_5$: C, 51.5; H, 8.2; N, 6.0. Found: C, 51.4; H, 8.3; N, 5.9.

N-*Oxides of* tert-*butyl* [*methyl 3,4-dideoxy-3-(dimethylamino)*-DL-*hexopyranosid*]*uronates*. — These products were prepared by treatment of 10% methanolic solutions of compounds **12**, **14**, **15**, or **17** with an excess of 30% aqueous hydrogen peroxide. After disappearance (t.l.c.) of the substrate, the solvents were removed by distillation (<40°) under diminished pressure, and the remaining syrup was dried *in vacuo* over potassium hydroxide pellets for 48 h. The *N*-oxides were not characterized in detail. They melted at 128–135° with decomposition.

tert-*Butyl* (*methyl 3,4-dideoxy*-DL-*hex-3-enopyranosid*)*uronates* (**18–21**). — The dried *N*-oxide (1 g) from each of the previous experiments was covered with dry xylene and the mixture boiled under reflux until the substrate disappeared (1–1.5 h). Xylene was evaporated off and the residue was chromatographed on a column of silica gel.

(*a*) *Degradation of the* N-*oxide of* **12**. The product **18** was eluted with 10:1 benzene–ethyl ether.

(*b*) *Degradation of the* N-*oxide of* **14**. Elution with 1000:100:0.2 benzene–ethyl ether–methanol afforded compound **19** (see Table II), followed by compound **22**. Compound **22** distilled at 105°/0.04 torr, m.p. 75°; ^{1}H-n.m.r. data: 6.10 (pd, 1H, $J_{4,3}$ 3.5 Hz, $J_{4,3}$ 4.6 Hz, H-4), 4.97 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.91 (m, 1H, H-2), 3.60 (s, 3H, OCH_3), 2.59 (s, 1H, OH), 2.55 (pq, 1H, $J_{3',2}$ 3.5, $J_{3',3}$ 19.2 Hz, H-3'), 2.20 (pt, 1H, $J_{3,2}$ 8.3 Hz, H-3), and 1.55 (s, 9H, CMe_3); ν_{max}^{KBr} 3400, 1720, 1650, 1140, 1110, and 1030 cm^{-1}.

Anal. Calc. for $C_{11}H_{18}O_5$: C, 57.4; H, 7.9. Found: C, 57.3; H, 7.8.

Further elution with 1000:20:0.1 ether–methanol–aq. ammonia gave 46% of recovered compound **14**.

(*c*) *Degradation of the* N-*oxide of* **15**. Elution with 100:10:1 light petroleum (b.p. 60–80°)–ethyl ether–methanol gave compound **20** and a small amount of compound **23** (which was acetylated with acetic anhydride and pyridine after isolation). Physical data of acetylated **23**: distilled at 120°/0.1 torr; ^{1}H-n.m.r. data: 5.95 (t, 1H, $J_{4,3}$ 8.6 Hz, H-4), 5.01 (d, 1H, $J_{1,2}$ 2.5 Hz, H-1), 4.95 (m, 1H, H-2), 3.52 (s, 3H, OCH_3), 2.40 (m, 2H, both H-3), 2.09 (s, 3H, CH_3CO), and 1.50 (s, 9H, CMe_3); ν_{max}^{film} 1740, 1660, 1245, 1120, 1090, 1050, and 1020 cm^{-1}; λ_{max} 236 nm.

Anal. Calc. for $C_{13}H_{20}O_6$: C, 57.3; H, 7.4. Found: C, 57.4; H, 7.4.

Continuation of the elution with 19:1 ethyl ether–methanol gave 60% of regenerated **15**.

(*d*) *Degradation of the* N-*oxide of* **17**. Elution with 10:1 benzene–ethyl ether gave compound **21**.

The yields and analytical data for compounds **18**–**21** are collected in Table II; ^{1}H-n.m.r. data are recorded in Table V.

TABLE V

^{1}H-N.M.R. DATA (100 MHz, $CDCl_3$, δ SCALE) FOR *tert*-BUTYL (METHYL 3,4-DIDEOXY-DL-HEX-3-ENOPYRANOSID)URONATES (**18**–**21**)

Compound No.	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*OCH_3*	tert-*Bu*	*Coupling data (Hz)*
18	4.60	4.11	5.88	6.27	4.78	3.64	1.52	$J_{1,2}$ 4.8, $J_{3,4}$ 10.6
19	4.89	4.00	6.11		4.83	3.66	1.54	$J_{1,2}$ 3.9
20	5.10	4.30	5.97	6.17	4.75	3.65	1.53	$J_{1,2}$ 4.0
21	4.71	4.12	5.75	5.95	4.57	3.56	1.50	$J_{1,2}$ 3.8

tert-*Butyl* (*methyl 2,3,4-tri*-O-*acetyl*-α-DL-*galactopyranosid*)*uronate* (**24**). — The *tert*-butyl ester **20** (0.35 g) was dissolved in Milas' solution (2 ml) containing 5 mg of osmium tetraoxide, and kept at room temperature until t.l.c. (4:1 ethyl acetate–methanol) showed that hydroxylation was complete. The solution was evaporated under diminished pressure and the residue was acetylated with acetic anhydride and pyridine. The product of acetylation was chromatographed on a column of silica gel with 100:10:1 light petroleum (60–80°)–ethyl ether–isopropyl alcohol as eluent. Compound **24** distilled at 145–150°/10^{-3} torr; yield 0.29 g (49%), m.p. 135°; ν_{max}^{KBr} 1755, 1250, 1150, 1080, and 1050 cm^{-1}.

Anal. Calc. for $C_{17}H_{26}O_{10}$: C, 52.3; H, 6.7. Found: C, 52.2; H, 6.8.

The ^{1}H-n.m.r. data for **24** (Table VII) clearly indicated the *galacto* configuration. A sample of **24** was reduced with sodium borohydride in water; the product was found to be identical (t.l.c., i.r.) with methyl α-D-galactopyranoside (except for its specific rotation).

tert-*Butyl* (*methyl 2,3,4-tri*-O-*acetyl*-α-DL-*altropyranosid*)*uronate* (**25**) *and* tert-*butyl* (*methyl 2,3,4-tri*-O-*acetyl*-α-DL-*talopyranosid*)*uronate* (**26**). — The ester **19** (0.43 g) was hydroxylated with Milas' reagent and acetylated after completion of the reaction as just described. Chromatography on a column of silica gel with the same eluent afforded two products: **25** (0.28 g, 38%) and **26** (0.04 g, 5.5%). Compound **25** distilled at 141°/10^{-3} torr, m.p. 100°. The *altro* configuration of **25** was proved by reduction (sodium borohydride in water) to methyl α-DL-altropyranoside and comparison (t.l.c. and i.r.) with the authentic D-enantiomer; ν_{max}^{KBr} 1760, 1260, 1220, 1140, and 1070 cm^{-1}.

Anal. Calc. for $C_{17}H_{26}O_{10}$: C, 52.3; H, 6.7. Found: C, 52.3; H, 7.0.

Compound **26** distilled at 145°/10^{-3} torr, and was obtained as a syrup that could not be induced to crystallize. The mass spectrum of **26** was practically identical to that of **24**. The *talo* configuration of **26** was deduced from ^{1}H-n.m.r. data (Table VII); ν_{max} 1740, 1260, 1230, 1145, 1070, and 1030 cm^{-1}.

Anal. Calc. for $C_{17}H_{26}O_{10}$: C, 52.3; H, 6.7. Found: C, 52.0; H, 6.6.

tert-*Butyl* (*methyl 3,4-anhydro*-α-DL-talo-*pyranosid*)*uronate* (**27**). — The ester **19** (0.82 g) in acetonitrile (5 ml) was treated with 30% hydrogen peroxide (10 ml) and sodium hydrogencarbonate (4 g), and the mixture stirred for 24 h at room temperature, with monitoring by t.l.c. (1:1:0.1 benzene–ethyl ether–methanol). The mixture was extracted with chloroform, and the extract was dried (magnesium sulfate). The residue, after removal of chloroform, was distilled (110–115°/10^{-2} torr) to afford **27** (0.52 g, 59%), m.p. 118°-120°; ^{1}H-n.m.r. data, see Table VI; ν_{max}^{KBr} 3550, 1755, 1140, 1095, and 1055 cm^{-1}.

Anal. Calc. for $C_{11}H_{18}O_6$: C, 53.7; H, 7.4. Found: C, 53.7; H, 7.6.

Acetylation of **27** with acetic anhydride in pyridine gave *tert*-butyl (methyl 2-*O*-acetyl-3,4-anhydro-α-DL-*talo*-hexopyranosid)uronate (**28**) in 50% yield; it distilled at 112°/10^{-2} torr, m.p. 110°; ^{1}H-n.m.r. data, see Table VI; ν_{max}^{KBr} 1745, 1250, 1150, 1120, and 1050 cm^{-1}.

Anal. Calc. for $C_{13}H_{20}O_7$: C, 54.2; H, 7.0. Found: C, 54.0; H, 7.0.

tert-*Butyl* (*methyl 3,4-anhydro*-α-DL-*galactopyranosid*)*uronate* (**29**). — From **20** (0.53 g), 30% hydrogen peroxide (10 ml), acetonitrile (5 ml) and sodium hydrogencarbonate (3 g), by following the procedure described for **27**, product **29** (0.29, 51%) was obtained as an oil distilling at 115–117°/10^{-2} torr; ^{1}H-n.m.r. data, see Table VI; ν_{max}^{film} 3500, 1750, 1160, 1120, and 1040 cm^{-1}.

Anal. Calc. for $C_{11}H_{18}O_6$: C, 53.7; H, 7.4. Found: C, 53.6; H, 7.1.

Compound **29** was acetylated with acetic anhydride in pyridine to afford *tert*-butyl (methyl 2-*O*-acetyl-3,4-anhydro-α-DL-galactopyranosid)uronate (**30**) in 61% yield, distilling at 115–118°/10^{-2} torr, m.p. 102°; ^{1}H-n.m.r. data, see Table VI; ν_{max}^{KBr} 1750, 1260, 1240, 1170, 1130, and 1050 cm^{-1}.

Anal. Calc. for $C_{13}H_{20}O_7$: C, 54.2; H, 7.0. Found: C, 54.3; H, 7.1.

tert-*Butyl* (*methyl 2,3-di*-O-*acetyl-4-deoxy*-β-DL-erythro-*hex-4-enopyranosid*)-*uronate* (**31**). — A solution of the epoxide **27** (0.32 g) in 1,4-dioxane (5 ml) was refluxed with a suspension of calcium hydroxide (1 g) in 1:1:0.1 benzene–ethyl

TABLE VI

^{1}H-N.M.R. (100 MHz, $CDCl_3$, δ SCALE) FOR *tert*-BUTYL (METHYL 3,4-ANHYDRO-α-DL-TALO- AND GALACTO-PYRANOSID)URONATES (27 AND 29) AND THEIR 2-ACETATES (28 AND 30)

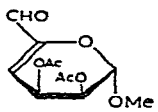
Compound No.	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*OAc*	tert-*Bu*	*OCH$_3$*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
27	4.75	3.86	[a]	3.77	4.62		1.57	3.60	4.6	3.5	4.1	2.7
28	4.88	4.91	3.59	3.73	4.61	2.13	1.52	3.54	6.3	2.3	4.0	3.3
29	4.77	3.96	3.40	[a]	4.55		1.52	3.57	3.5	1.1	4.0	2.9
30	4.92	5.02	3.37	3.58	4.58	2.15	1.53	3.52	3.4	1.0	4.0	2.8

[a]Not resolved.

ether–methanol. After evaporation of the 1,4-dioxane, the residue was applied to a column of silica gel and chromatographed with 5:1 chloroform–methanol. The product obtained was acetylated as before and the acetate **31** distilled at 120°/10^{-2} torr (0.22 g, 60%); ^{1}H-n.m.r. data: 6.04 (pd, 1H, $J_{4,3}$ 3.0, $J_{4,2}$ 1.6 Hz, H-4), 5.81 (pd, 1H, $J_{3,2}$ 4.7 H-3), 5.35 (m, 1H, H-2), 5.20 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 3.62 (s, 3H, OCH_3), 2.15 and 2.12 (2s, 6H two CH_3CO), and 1.58 (s, 9H, CMe_3); ν_{max}^{film} 1760, 1660, 1250, 1140, 1080, 1060 cm^{-1}.

Anal. Calc. for $C_{15}H_{22}O_8$: C, 54.5; H, 6.7. Found: C, 54.7; H, 6.7.

The ^{1}H-n.m.r. data for **31** strongly resembled those recorded by Mackie and Perlin[16] for the aldehyde **36**.



36

*Methyl (methyl 2,3,4-tri-*O*-acetyl-α-*DL*-mannopyranosid)uronate* (**32**). — The epoxide **27** (0.25 g) was boiled under reflux with acetic acid (1 ml) until the substrate disappeared (t.l.c. in 4:1 ethyl acetate–methanol, 52 h). After evaporation of the acetic acid under diminished pressure, the residue was esterified with 10% methanolic hydrogen chloride (72 h, room temperature). The solution was neutralized with potassium carbonate and the solids were filtered off. Methanol was evaporated off and the residue was reacetylated with acetic anhydride and pyridine. The product was purified on a column of silica gel with 10:1 benzene–ethyl ether as eluent to give **32** as a syrup (0.08 g, 22%), distilling at 140–145°/10^{-3} torr; ^{1}H-n.m.r. data, see Table VII; ν_{max}^{film} 1760, 1725, 1260, 1220, 1140, 1090, and 1030 cm^{-1}.

Anal. Calc. for $C_{14}H_{20}O_{10}$: C, 48.3; H, 5.8. Found: C, 48.2; H, 6.0.

A sample of **32** was reduced with sodium borohydride in water; the product obtained was identified as methyl α-DL-mannopyranoside by comparison (t.l.c. and i.r.) with an authentic sample of the D enantiomer.

TABLE VII

^{1}H-N.M.R. DATA (100 MHz, $CDCl_3$, δ SCALE) FOR ESTERS OF (METHYL 2,3,4-TRI-*O*-ACETYL-α-DL-HEXOPYRANOSID)URONIC ACIDS

Compound No.	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*OCH_3*	tert-*Bu*	*OAc*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
24	5.13	5.19	5.42	5.81	4.48	3.47	1.45	2.00, 2.09, 2.12	3.2	10.0	3.5	1.9
25	4.99	5.07	5.40	5.71	4.61	3.63	1.58	2.10, 2.15, 2.18	5.0	[a]	3.0	5.0
26	5.05	5.16	5.46	5.78	4.59	3.55	1.43	2.04, 2.12, 2.16	1.6	4.2	3.1	2.2
32	4.85	5.28	5.36	5.51	4.32	3.49	3.81[b]	2.03, 2.07, 2.18	2.0	4.7	[a]	9.7
33	5.03	5.19	[a]	5.42	4.85	3.45	3.78[b]	2.09, 2.12, 2.16	3.4	[a]	[a]	1.3
34	5.15	5.04	5.28	5.64	4.42	3.55	3.83[b]	2.06, 2.06, 2.11	3.9	10.2	9.9	10.1

[a]Not determined. [b]Ester OCH_3.

Methyl (methyl 2,3,4-tri-O-acetyl-α-DL-gulopyranosid)uronate (**33**) *and methyl (methyl 2,3,4-tri-O-acetyl-α-DL-glucopyranosid)uronate* (**34**). — The epoxide **29** (0.64 g) was boiled under reflux with acetic acid (1.5 ml) for 70 h (t.l.c. in 4:1 ethyl acetate–methanol). After isolation according to the procedure described for **32**, two products were eluted from the chromatographic column: **33** (0.18 g, 20%) and **34** (0.02 g, 2%). Compound **33** distilled at 152–155°/10^{-3} torr; ^{1}H-n.m.r. data, see Table VII; ν_{max}^{film} 1755, 1250, 1220, 1150, and 1060 cm^{-1}.

Anal. Calc. for $C_{14}H_{20}O_{10}$: C, 48.3; H, 5.8. Found: C, 48.6; H, 6.0.

A sample of **33** was reduced with sodium borohydride in water, and the product obtained was acetylated and identified (t.l.c., i.r.) as methyl 2,3,4,6-tetra-*O*-acetyl-α-DL-gulopyranoside by comparison with acetylated methyl α-D-gulopyranoside.

The acetate **34** distilled at 145–150°/10^{-3} torr; ^{1}H-n.m.r. data, see Table VII, ν_{max}^{film} 1760, 1260, 1230, 1150, 1070, and 1030 cm^{-1}.

Anal. Calc. for $C_{14}H_{20}O_{10}$: C, 48.3; H, 5.8. Found: C, 48.4; H, 5.8.

Product **34** was identified (t.l.c., i.r. and ^{1}H-n.m.r.) by direct comparison with methyl (methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosid)uronate.

REFERENCES

1 M. CHMIELEWSKI AND A. ZAMOJSKI, *Rocz. Chem.*, 46 (1972) 2223–2231.
2 A. BANASZEK, *Bull. Acad. Pol. Sci., Sér. Sci. Chim.*, 20 (1972) 925–933.
3 A. BANASZEK, *Bull. Acad. Pol. Sci., Sér. Sci. Chim.*, 22 (1974) 79–89.
4 A. KONOWAŁ AND A. ZAMOJSKI, *Rocz. Chem.*, 45 (1971) 859–868.
5 A. BANASZEK, *Bull. Acad. Pol. Sci., Sér. Sci. Chim.*, 23 (1975) 585–592.
6 M. CHMIELEWSKI AND A. ZAMOJSKI, *Bull. Acad. Pol. Sci., Sér. Sci. Chim.*, 20 (1972) 751–754; A. BANASZEK, *ibid.*, 22 (1974) 1045–1051; J. MIECZKOWSKI AND A. ZAMOJSKI, *ibid.*, 23 (1975) 581–583.
7 A. KONOWAŁ, A. ZAMOJSKI, M. MASOJIDKOVA, AND J. KOHOUTOVA, *Rocz. Chem.*, 44 (1970) 1741–1750 and references cited therein.
8 S. MCNALLY AND W. G. OVEREND, *J. Chem. Soc., C*, (1966) 1978–1980.
9 G. BERTI, *Top. Stereochem.*, 7 (1972) 95–250.
10 J. KISS, *Adv. Carbohydr. Chem. Biochem.*, 29 (1974) 229–303; P. KOVAČ, J. HIRSCH, AND V. KOVAČÍK, *Carbohydr. Res.*, 32 (1974) 360–365; P. HEIM AND H. NEUKOM, *Helv. Chim. Acta*, 45 (1962) 1735–1736.
11 R. A. B. BANNARD, A. A. CASSELMAN, E. J. LANGSTAFF, AND R. Y. MOIR, *Can. J. Chem.*, 45 (1968) 35–42.
12 A. E. MONTAGNA AND D. J. HIRSH, U. S. PAT. 2,905,722; *Chem. Abstr.*, 54 (1960) 2168.
13 N. KORNBLUM AND H. W. FRAZIER, *J. Am. Chem. Soc.*, 88 (1966) 865–866; J. JURCZAK AND A. ZAMOJSKI, *Rocz. Chem.*, 44 (1970) 2257–2260.
14 O. ACHMATOWICZ, JR., J. JURCZAK, A. KONOWAŁ, AND A. ZAMOJSKI, *Org. Magn. Reson.*, 2 (1970) 55–62.
15 A. KONOWAŁ, J. JURCZAK, AND A. ZAMOJSKI, *Rocz. Chem.*, 42 (1968) 2045–2059.
16 D. M. MACKIE AND A. S. PERLIN, *Carbohydr. Res.*, 24 (1972) 67–85.