SYNTHESIS OF METHYL (METHYL α-L-ALTROPYRANOSID)URONATE AND SOME OF ITS DERIVATIVES*

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Methyl (methyl 2,3,4-tri-O-methyl-β-D-galactopyranosid)uronate (*I*) treated with Purdie reagent (a mixture of methyl iodide and silver oxide) and methyl sulphide afforded an equilibrium mixture of $C_{(5)}$- epimers, which upon chromatographic separation yielded methyl (methyl 2,3,4-tri-O--methyl-α-L-altropyranosid)uronate (*II*). Methyl (methyl 2,3,4-tri-O-benzyl-α-L-altropyranosid)-uronate *IV* was obtained by an analogous reaction from methyl (methyl 2,3,4-tri-O-benzyl-β-D--galactopyranosid)uronate (*III*). Hydrogenolysis of *IV* furnished methyl (methyl α-L-altropyranosid)uronate (*V*); subsequent acetylation gave the acetate *VI*. The role of the anomeric effect in the conversion of β-D-galacturonic acid derivatives to the corresponding α-L-altruronic acid derivatives under conditions of the described $C_{(5)}$ epimerization is discussed.

Our previous paper[1] dealt with the conversion of per-O-methyl derivative of methyl (methyl α-D-galactopyranosid)uronate to the corresponding methyl (methyl α-L--altropyranosid)uronate derivative by treatment with Purdie reagent in the presence of methyl sulphide; the reaction mechanism has been rationalized and the possibility to use this $C_{(5)}$-epimerization reaction in the synthesis of difficultly accesible derivatives of L-altruronic acid starting from D-galacturonic acid derivatives has been shown. In this paper we wish to report a further preparative application of this conversion.

As mentioned, L-altruronic acid derivatives are not easily accessible. Fischer and Schmidt[2] reported to have observed a partial conversion of sodium D-galacturonate to the corresponding L-*altro* substance when studying the epimerization of sodium uronates; other authors[3,4], however, failed to confirm their finding.

The conversion of *I* to the corresponding L-altruronate is governed by factors associated with the stability of the reaction intermediates in the reaction scheme of elimination by the E1cB mechanism. One of the most important factors influencing the stability of the pyranose compounds is the anomeric effect. The $C_{(5)}$ epimerization should, therefore, depend on the anomer used, this being also indicated by values of frontier electron densities calculated by the CNDO/2 method[1]. These values

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suggested a greater reactivity of the β-anomer. We tried to estimate qualitatively and explain the effect of the employed D-*galacto* anomer on the yield of the corresponding L-*altro* derivative by calculating the energy of the individual intermediates involved in the $C_{(5)}$-epimerization by means of the CNDO/2 method[5] and empiric procedure according to Angyal[6]. It follows from the E1cB elimination scheme[1] that the yield of the L-*altro* derivative is determined by the equilibrium between the carbanions possessing D-*galacto* and L-*altro* configurations and also by the rate of proton addition to these carbanions.

We presumed, when calculating the stability of the individual carbanions, that their geometry equalled that of the neutral saccharide derivatives[1]. The energy found for the α-D-*galacto* derivative calculated by the CNDO/2 method was by 1·1 kcal.mol^{-1} lower than that of the β-anomer. The stability of anomers is influenced by steric interactions among substituents on the pyranose ring, which, due to the presence of a methoxyl group in the axial position at carbon $C_{(1)}$ in the α-anomer, exerts a destabilizing effect when compared with the β-anomer. The α-anomer in which the segment C—O—C—O—C is in a *gauche-gauche* conformation is more stabilized by the anomeric effect than the β-anomer where the conformation of this segment is *trans-gauche*. As it follows from the energy values of both conformers calculated by the CNDO/2 method the prevailing interaction stabilizing the α-anomer is the anomeric effect. A comparison of the carbanions with L-*altro* and D-*galacto* configurations shows that an additional bulky group in axial position (the methoxycarbonyl group at $C_{(5)}$) should result in a more pronounced destabilization of the anomer bearing an axial methoxyl group at $C_{(1)}$ (β-L-*altro*) than of the carbanion with D-*galacto* configuration. Although the anomeric effect remains unaltered, its stabilizing power should be less pronounced in the β-L-*altro* than in the β-D-*galacto* carbanion. In effect, the energy of the β-L-*altro* carbanion is by 0·60 kcal.mol^{-1} lower than that of the α-anomer. The calculated energy values show that the equilibrium between D-*galacto* ⇄ L-*altro* is in the α-D-*galacto* shifted less towards the L-*altro* than in the β-D-*galacto* carbanion. (The difference in energy is by 0·5 kcal . . mol^{-1} lower than in the second case). Provided an equal activation entropy, the rate of addition of a proton to both carbanions is given by the activation energy *i.e.* by the difference in the activated complex energy of this reaction and that of the carbanion. The energy of the activated complex, the structure of which is probably close to that of the L-*altro* derivative, was calculated by means of the Angyal's scheme and the value of the anomeric effect (2·35 kcal.mol^{-1}) was calculated by the CNDO/2 method using dimethoxymethane as a model compound[7,8]. The energy of the activated α-L-*altro* complex calculated in this way is by 0·30 kcal.mol^{-1} lower than that of the β-anomer. The activation energy of the proton addition to the α-anomer of L-*altro* derivative is then by 0·3 kcal.mol^{-1} less than that of the proton addition to the carbanion of the β-anomer. As it follows from the calculated values of the individual reaction intermediates, the use of the β-anomer (as in the $C_{(5)}$-

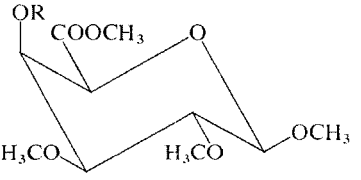
-epimerization of *I*) would shift the equilibrium between the two carbanions more in favour of the L-*altro*, than with the α-anomer, and increase the rate of the addition of a proton to this species. This has to result in the increase of the yield of α-L-*altro* derivative and consequently, in the formation of the elimination product in a lower yield when compared with the α-D-*galacto* derivatives.

From the preparative point of view this reaction should be, therefore, more advantageous to carry out in the β-D-*galacto* series. Here, the equilibrium mixture of the D-*galacto* and L-*altro* diastereoisomers should contain a larger relative proportion of the L-*altro* derivative than in the same conversion of compounds with α-D-*galacto* configuration. This presumption was experimentally confirmed: Purdie reagent and methyl sulphide treated methyl (methyl 2,3,4-tri-O-methyl-β-D-galactopyranosid)-uronate furnished the corresponding L-*altro* derivative in an approximately three times greater yield than a similar conversion of methyl (methyl 2,3,4-tri-O-methyl--α-D-galactopyranosid)uronate[1].

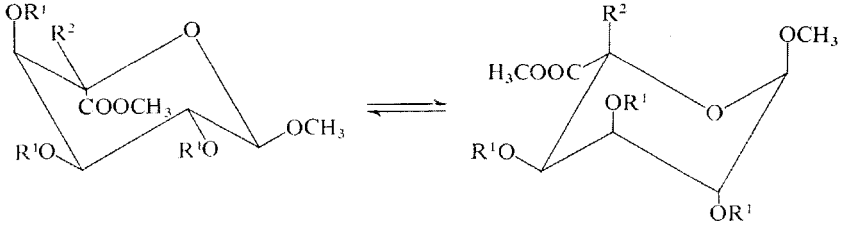
To make use of the above-mentioned reaction in obtaining methyl (methyl α-L-altropyranosid)uronate and its 2,3,4-tri-O-substituted derivatives, methyl (methyl 2,3,4-tri-O-benzyl-β-D-galactopyranosid) uronate (*III*) had to be synthesized. Since the corresponding per-O-benzyl derivative could not be perpared in a reasonable yield by benzylation of methyl (methyl α-, or β-D-galactopyranosid)uronate with benzyl bromide and silver oxide[9], compound *III* was prepared by a procedure analogous with the preparation of methyl (methyl 2,3,4-tri-O-benzyl-β-D-glucopyranosid)uronate[10] by oxidation of methyl 2,3,4-tri-O-benzyl-β-D-galactopyranoside[11] with chromium trioxide. Compound *III* was characterized as an amide and the ^{1}H-NMR spectrum of *III* proved its structure. Compound *III* was processed similarly as in the conversion of methyl (methyl α- and β-D-galactopyranosid)uronate per-O-methyl derivatives. A stronger base than silver oxide itself, generated[1,12] from Purdie reagent in the presence of methyl sulphide, caused the abstraction of the $C_{(5)}$-proton. Its subsequent readdition to the carbanion formed as intermediate during the E1cB process afforded finally, as indicated by TLC, an equilibrium mixture of $C_{(5)}$-isomeric methyl (methyl 2,3,4-tri-O-benzylhexopyranosid)uronates *III* and *IV* from which *IV* could be isolated in an ~25% yield.

The relationship of *IV*, and thereby also of products of its further conversion, with the L-series was based upon a negative Cotton effect in the characteristic (210 nm) region[13] found in the CD spectrum of *V*. Similarly as in the conversion of per-O--methyl derivative of α-D-galactouronate[1], thin layer chromatography indicated a more favoured conversion to the L-*altro* derivative than we were actually able to isolate. A part of the starting material or of the product underwent a nonspecific destruction, although to a lesser extent than with the substrate having the α-D-*galacto* configuration[1]. The formation of an olefinic substance, analogous with that formed during a similar conversion of methylated derivatives, was not observed.

The hydrogenolysis of *IV* over palladium-on-charcoal catalyst led to methyl (methyl

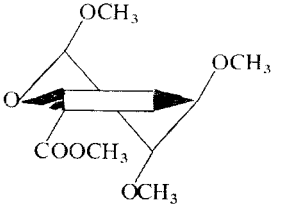


I, R = CH_3
III, R = $C_6H_5CH_2$



IV, $R^1 = C_6H_5CH_2$, $R^2 = H$
V, $R^1 = R^2 = H$
VI, $R^1 = CH_3CO$, $R^2 = H$

II, $R^1 = CH_3$, $R^2 = H$
IVa, $R^1 = C_6H_5CH_2$, $R^2 = {}^2H$
Va, $R^1 = H$, $R^2 = {}^2H$



VII

α-L-altropyranosid)uronate (*V*) in a virtually theoretical yield. Its acetylation afforded an acetate and methylation a methyl ether identical with that obtained from the conversion of methyl (methyl 2,3,4-tri-O-methyl-β-D-galactopyranosid)uronate.

The conversion of *III* to *IV* in [O—^{2}H] methanol gave the benzylated derivative *IVa*; its hydrogenolysis yielded the $C_{(5)}$ deuterium labelled methyl (methyl α-L-altropyranosid)uronate *Va*. The mass spectrum of *Va* showed, on comparison with that[14] of methyl (methyl α-D-galactopyranosid)uronate, a nearly complete deuterization at $C_{(5)}$. Compound *Va* was a key model in elucidating the mass spectrometric fragmentation of methyl (methylhexopyranosid)uronates[15].

Considering the data obtained in structure determination of methyl (methyl 2,3,4-tri-O-methyl-β-L-altropyranosid)uronate[1], the ^{1}H-NMR spectra of *II*, *III*, *IV* and particularly the coupling constants $J_{4,5}$ (Table I) it can be concluded that *II*–*IV* exist, in solution at room temperature, as a mixture of $^4C_1$(L) and $^1C_4$(L) conformers.

EXPERIMENTAL

General methos were reported in[1]. The solvent systems for thin layer chromatography on Silica gel G and preparative chromatography on silica gel were: A tetrachloromethane–acetone 4 : 1, B benzene–acetone 25 : 1, C chloroform–methanol 5 : 1, D benzene–acetone 10 : 1. Methyl (methyl 2,3,4-tri-O-methyl-β-D-galactopyranosid)uronate (*I*) was prepared by a described reaction sequence[16].

Methyl (Methyl 2,3,4-tri-O-methyl-α-L-altropyranosid)uronate (*II*)

a) A mixture of *I* (100 mg, 0·378 mmol), CH_3I (0·024 ml, 0·38 mmol), $(CH_3)_2S$ (0·028 ml, 0·38 mmol) and Ag_2O (0·2 g) was shaken in absolute methanol (1·5 ml) in the dark for 4 h. TLC (system A) clearly showed a higher conversion of the starting material (R_F 0·4) to the L-*altro* derivative (R_F 0·5), than in the reaction of the α-anomer (*cf.*[1]) and the reaction mixture contained olefinic product *VII* (R_F 0·6) in a trace amount only. No spot could be detected on the base line of the chromatogram. The separation of the reaction mixture on a silica gel column (system A) gave approximately 1·5 mg (0·006 mmol, 1·7%) of the olefin *VII* the mass spectrum of which was comparable with that of the β-L-*threo* isomer recovered from the conversion of the α-D-*galacto* compound to the β-L-*altro* substance[1], 29 mg (0·11 mmol, 29%) of α-L-*altro* derivative *II*, $[\alpha]_D^{24}$ −68° (*c* 1·0, CH_3OH), 63 mg (0·238 mmol, 63%) of the starting material *I*. Total recovery 0·354 mmol (93·7%). For $C_{11}H_{20}O_7$ (264·3) calculated: 49·99% C, 7·62% H, 58·71% CH_3O; found: 50·17% C, 7·88% H, 59·04% CH_3O. Mass and CD spectra were closely related with those of the β-L-*altro* analogue[1].

The repeated experiment with a tenfold amount of reagents furnished after 2·5 h the α-L-*altro* derivative *II*, a greater amount of methyl (methyl 4-deoxy-2,3-di-O-methyl-α-L-*threo*-hex-4-eno-pyranosid)uronate (*VII*) and destruction products visible on the base line of the chromatogram. After 3 h we were able to isolate, in contrast to the same conversion of the α-D-*galacto* derivative[1], 5·3 mg (0·023 mmol, 6%) of α-L-*threo* olefin *VII*, $[\alpha]_D^{22}$ −38°, ref.[17] $[\alpha]_D$ −34°; 22·58 mg (0·085 mmol, 22·5%) of the α-L-*altro* derivative *II*, $[\alpha]_D^{22}$ −67° and 52·5 mg (0·198 mmol, 52·5%) of the starting material *I*. Total recovery 0·306 mmol (81%).

b) Compound *V* (0·3 g) dissolved in acetone (2 ml) was shaken in a dark flask with methyl iodide (3 ml) and silver oxide (0·5 mg) for 16 h. The partially methylated product was isolated and methylated by this procedure three times. The mixture was chromatographed since TLC (system D) still showed the presence of the undermethylated material. The fastest moving compound *II* (0·24 g, 67·3%) had $[\alpha]_D^{22}$ −73° (*c* 1·02 CH_3OH) after drying at 30°C and 2 kPa. The ^{1}H-NMR and CD spectra were superimposable with those of the above-described compound.

Methyl (Methyl 2,3,4-tri-O-benzyl-β-D-galactopyranosid)uronate (*III*)

A solution of chromium trioxide (16 g) in 3·5M sulphuric acid (70 ml) was portionwise added to a stirred solution of methyl 2,3,4-tri-O-benzyl-β-D-galactopyranoside[11] (28 g) in acetone (350 ml) at 20°C and the reaction mixture was worked up[10] after 1 h. The 2,3,4-tri-O-benzyl-β-D-galacto-

TABLE I

Chemical Shifts (δ) and Coupling Constants (Hz) Observed for *II*—*VI*

Compound	Solvent	Chemical shifts[a]							Coupling constants			
		H-1	H-2	H-3	H-4	H-5	$COOCH_3$	CH_3	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
II	$CDCl_3$	4·67 m[b]	3·30—3·62 m		3·88 m[b]	4·60 d	3·80	3·48; 3·52[c]	[d]	[d]	[d]	5·2
II	$(CD_3)_2CO$	4·59 m[b]	3·25—3·55 m		3·83 m[b]	4·53 d	3·72	3·36; 3·40[c]	[d]	[d]	[d]	5·3
III[e]	$CDCl_3$	4·26 d	3·88 q	3·55 q	4·22 q	4·00 d	3·63	3·59	7·3	9·2	2·2	1·4
IV[f]	$CDCl_3$	4·73 d	3·77 q	3·55 q	4·06 q	4·62 d	3·67	3·51	4·7	7·1	2·7	5·2
V	D_2O	4·65 m[b]	3·70—3·90 m		4·22 m[b]	4·57 d	3·82	3·50	[d]	[d]	[d]	5·1
V	$(CD_3)_2CO$	4·61 m[b]	3·70—3·90 m		4·18 m[b]	4·48 d	3·77	4·43	[d]	[d]	[d]	6·0
VI	$CDCl_3$	4·75 bd	4·95—5·20 m		5·43 q	4·58 d	3·80	3·49; 2·07[g]; 2·08[g]; 2·10[g]	3·6	[d]	2·7	6·4

[a] Observed multiplicities: d doublet; bd broadened doublet; q quartet; m multiplet; [b] the large $J_{2,3}$ coupling constant together with the small difference in the chemical shift of H-2 and H-3 are responsible for the further splitting of the H-1 and H-4 signals; [c] 9-proton singlet; [d] first-order coupling constants were not observed; [e] aromatic protons appeared at δ 7·25 as a 15-proton singlet, chemical shifts and coupling constants observed for the benzylic protons: δ 4·89 d, 4·75 d (J^2 = 11·1 Hz), δ 4·88 d, 4·63 d (J^2 = 11·7 Hz), δ 4·75 (2-proton singlet); [f] aromatic protons appeared at δ 7·25 as a 15 proton singlet, chemical shifts and coupling constants observed for the benzylic protons: δ 4·53 d, 4·60 d (J^2 = 11·5 Hz); δ 4·58, 4·69 d (J^2 = 11·5 Hz), 4·57 (2-proton singlet); [g] acetyl protons.

pyranosiduronic acid thus obtained was esterified with ethereal diazomethane. Purification of the crude product by chromatography on silica gel (system B) afforded compound III (17·5 g, 59%). Its m.p. after repeated crystallization from isopropyl ether was 59–61°C, $[\alpha]_D^{22}$ +4·7° (*c* 1·05, $CHCl_3$). For $C_{29}H_{32}O_7$ (492·6) calculated: 70·71% C, 6·55% H, 12·60% CH_3O; found: 70·53% C, 6·40% H, 12·70% CH_3O.

Ammonolysis[18] of *III* afforded methyl 2,3,4-tri-O-benzyl-β-D-galactopyranosiduronamide, m.p. 190–191°C, $[\alpha]_D^{22}$ +30° (*c* 1·02, $CHCl_3$) in a quantitative yield. For $C_{28}H_{31}NO_6$ (477·5) calculated: 70·42% C, 6·54% H, 2·93% N; found: 70·31% C, 6·43% H, 2·81% N. Hydrogenolysis of *III* led to methyl (methyl β-D-galactopyranosid)uronate identical with that described[17] earlier.

Methyl (Methyl 2,3,4-tri-O-benzyl-α-L-altropyranosid)uronate (*IV*)

A mixture of *III* (2 g, 4 mmol), dry silver oxide (0·92 g), methyl sulphide (0·28 ml, 0·038 mol) and methyl iodide (0·24 ml, 0·38 mol) in methanol (20 ml) was shaken in a dark flask at room temperature; the reaction was monitored by thin layer chromatography (system B). After 5 h, when the ratio between the starting material (R_F 0·2) and the product (R_F 0·3) equilibrated, the reaction mixture was filtered, the silver salts washed with methanol and the combined filtrates concentrated. Chromatography of the residue on a silica gel column (system B) gave the faster moving substance *IV* (480 mg, 24%) and the starting material *III* (1·22 g, 61%). Compound *IV* failed to crystallize; $[\alpha]_D^{22}$ −39° (*c* 1·0 $CHCl_3$) (dried at 30°C and 2 kPa). For $C_{29}H_{32}O_7$ (492·6) calculated: 70·71% C, 6·55% H, 12·60% CH_3O; found: 70·68% C, 6·31% H, 12·87% CH_3O.

Methyl (Methyl α-L-altropyranosid)uronate (*V*)

A solution of *IV* (2 g) in methanol (50 ml) was stirred in a hydrogen atmosphere in the presence of 5% palladium on charcoal (200 mg) until thin layer chromatography (system C) confirmed complete conversion of the starting material to the product *V* (R_F 0·4, system C). The catalyst was filtered off, the solvent removed and *V* (0·9 g, ~100%) dried at 30°C and 2 kPa; $[\alpha]_D^{24}$ −77·5° (*c* 2·0, CH_3OH). The CD spectrum of *V* displayed a negative Cotton effect at 210 nm. For $C_8H_{14}O_7$ (222·2) calculated: 43·21% C, 6·35% H, 27·93% CH_3O; found: 43·12% C, 6·34% H, 28·13% CH_3O. The deuterization degree at $C_{(5)}$ of compound *Va* determined by mass spectrometry, was ~96%.

Methyl (Methyl 2,3,4-tri-O-acetyl-α-altropyranosid)uronate (*VI*)

A mixture of substance *V* (100 mg), pyridine (1 ml) and acetic anhydride (0·2 ml) was allowed to stand at a room temperature for 16 h. Product *VI*, isolated in a usual way (0·15 g, 96%, R_F 0·5, solvent system D) had $[\alpha]_D^{23}$ −71° (*c* 1·0, CH_3OH). For $C_{14}H_{20}O_{10}$ (348·3) calculated: 48·27% C, 5·78% H, 17·82% CH_3O; found: 48·03% C, 5·60% H, 17·49% CH_3O.

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