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A NEW SYNTHESIS OF FOUR DIASTEREOISOMERIC 2,6-DIDEOXY-DL-HEXOSES[a,b]

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Abstract—The synthesis of four diastereoisomeric 2,6-dideoxy-DL-hexoses from butyl E 2,3,4-trideoxy-aldehydo-DL-hex-2-enuronate (2) is described. The aldehyde 2 treated with MeMgBr affords a mixture of diastereoisomeric diols 6, which after hydroxylation and Ruff degradation gives 2,6-dideoxy-DL-hexoses 13, 14, 15 and 16.

The title compounds represent an important class of natural dideoxy sugars. All four possible stereoisomeric 2,6-dideoxy-D-hexoses and their various methyl ethers have been found in cardiac glycosides.[1] 2,6-Dideoxy-hexoses of the lyxo and arabino configuration and their derivatives occur also as the sugar components of numerous antibiotics containing aromatic aglycons.[2] The most important group of these compounds is represented by anthracycline antibiotics, which are clinically effective against various forms of cancer. These antibiotics contain the amino sugar daunosamine and rhodosamine either alone or in combination with other deoxy sugars. 2,6-Dideoxy-L-lyxohexose has been found in the antibiotic cinerubin A[3] and in the rhodomycin complex[4] as the neutral component.

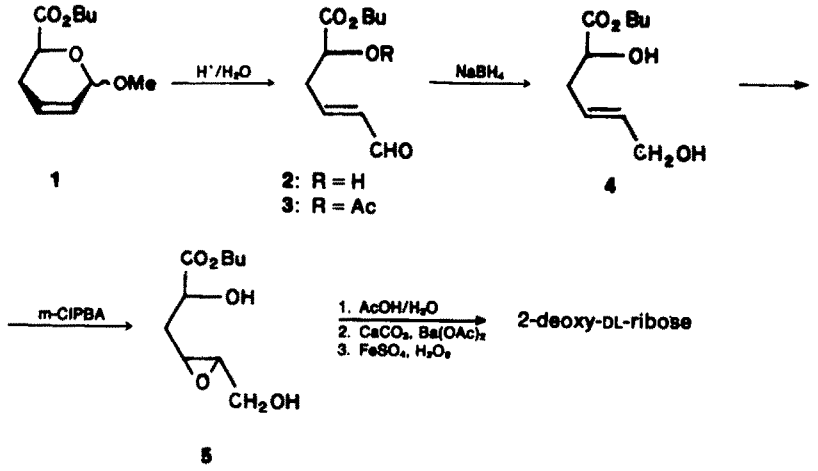
Syntheses of 2,6-dideoxyhexoses and their derivatives have often been attempted.[1] In recent years, due to interest in anthracycline antibiotics, there has been an increased interest in this class of sugars.[5-7] The syntheses comprise multi-stage transformations of natural sugars.

The readily available Diels–Alder adduct 1[c] obtained by condensation of 1-methoxy-1,3-butadiene with butyl glyoxylate easily undergoes hydrolysis in dilute mineral acids to give butyl 2,3,4-trideoxy-aldehydo-DL-hex-2-enuronate (2)[d] to which the E configuration is assigned on the basis of ^{1}H NMR data.[8] Compound 2 opens the way to deoxy sugars via suitable transformations of the functional groups. For instance, reduction of the aldehyde group leads to primary alcohol 4; epoxidation of the double bond followed by hydrolysis of the oxirane 5 and, finally, by Ruff degradation of the resulting product leads to racemic 2-deoxyribose[9] (Scheme 1).

This paper reports a new, simple synthesis of all four diastereomeric 2,6-dideoxy-DL-hexoses from butyl 2-methoxy-5,6-dihydro-2H-pyran-6-carboxylate (1), based essentially on Scheme 1.

RESULTS AND DISCUSSION

The reaction of aldehyde 2 with methyl magnesium bromide at −70° afforded a mixture of diastereomeric diols 6 in a 60% yield (Scheme 2). Under the experimental conditions the ester group remained unchanged. The ratio of threo and erythro diols 6 was estimated to be 1:1 by integration of the well separated signals of C-3 and C-4 in the ^{13}C NMR spectrum (Table 1) recorded for the mixture. Continuation of the synthesis leading to 2,6-dideoxyhexoses did not require separation of isomeric diols 6. Further steps consisted in: (i) hydroxylation of the double bond in 6, (ii) saponification of the ester group to calcium salt of 3,7-dideoxy-heptaldonic acid and (iii) Ruff degradation of the salt obtained.



1 2: R = H 3: R = Ac 4 5

Scheme 1.

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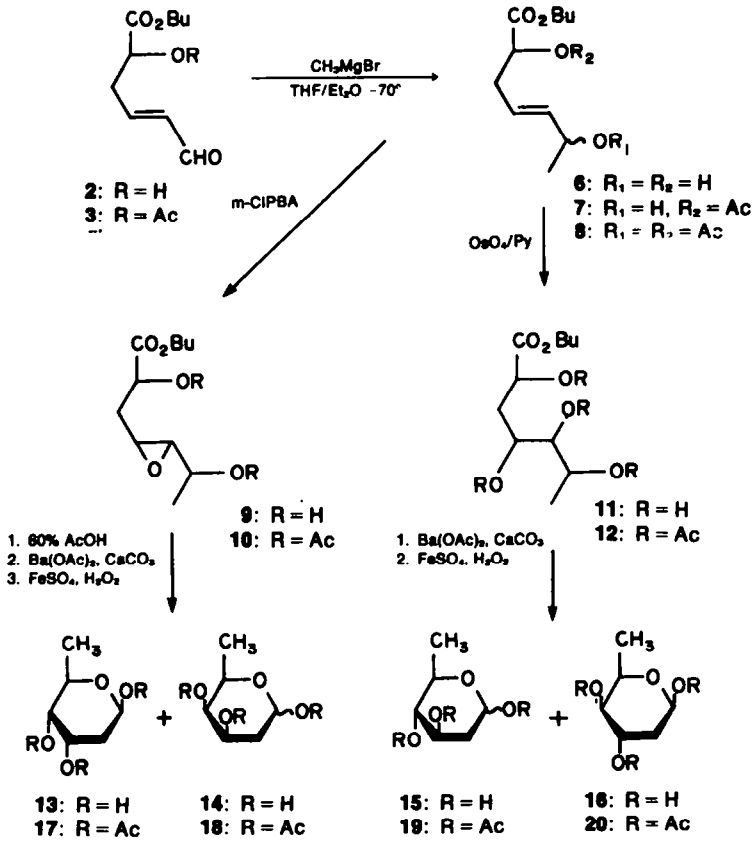
[b]The paper was presented at the 11*th Symposium on Chemistry of Natural Products* held in Golden Sands, Bulgaria, in September 1978, Abstr. papers Vol. 3, p. 137.

[c]For the sake of simplicity all formulae in this paper refer to monosaccharide D series, although in fact they represent racemic compounds.

[d]According to sugar nomenclature. Another name: butyl E 2-hydroxy-6-oxo-hex-4-enoate (2).



Scheme 2.

Table 1. ^{13}C NMR spectral data for compounds 4, 5, 6, and 9; $CDCl_3$. In brackets relative intensities are given

	C-1	C-2	C-3	C-4	C-5	C-6	C-7	
4	174.35	70.35	37.25	126.04	133.41	62.71	—	O-CH_2-CH_2-CH_2-CH_3 65.09 30.68 19.10 13.64
6	174.40	70.31	37.02 (1) 37.14 (1)	123.98 (1) 124.20 (1)	138.57	68.14	23.03	O-CH_2-CH_2-CH_2-CH_3 65.21 30.63 19.07 13.61
5	174.42	68.34	36.47 (1.4) 36.14 (1)	52.96 (1.4) 52.63 (1)	59.07 (1.4) 58.33 (1)	61.64	—	O-CH_2-CH_2-CH_2-CH_3 65.64 30.53 19.03 13.59
9	174.43	68.34	36.17 36.44	53.39 (1.5) 53.04 (1.5) 52.80 (1) 52.48 (1)	63.15 62.32 61.50	67.46	19.30	O-CH_2-CH_2-CH_2-CH_3 65.64 30.52 19.02 13.59

Hydroxylation of the double bond in **6** can be achieved directly or by epoxidation and opening of the oxirane ring. Due to the E configuration of the double bond in **6** direct hydroxylation should lead to threo configuration at C-4 and C-5 C atoms, whereas epoxidation and hydrolysis of the epoxide under acidic conditions should afford erythro diol at C-4 and C-5. It was expected therefore that ribo and lyxo 2,6-dideoxyhexoses will be obtained via epoxidation and subsequently hydrolysis, and the arabino and xylo stereoisomers via direct hydroxylation of **6**.

Epoxidation of the double bond in **6** with *m*-chloroperbenzoic acid afforded a mixture of four stereoisomeric epoxides **9** in a ratio of 1.5:1.5:1:1 (according to the ^{13}C NMR spectrum). The mixture **9** was not separated into pure components. Opening of the oxirane ring in **9** with aqueous acetic acid, followed by Ruff degradation of the calcium salt of the resulting 3,7-dideoxy-heptaldonic acid, gave a mixture of 2,6-dideoxy-DL-ribohexose (**13**) and 2,6-dideoxy-DL-lyxo-hexose (**14**).

The mixture was separated chromatographically (Experimental) into pure components. Their ratio was about 1:1.5 and the total yield was 41%. The configuration and the composition of anomers could be simply determined from the ^{13}C NMR spectra of free sugars **13** and **14**[a] (Table 2) and the ^{1}H NMR spectra of triacetates **17** and **18**. In aqueous solution compound **13** occurred

[a]Signals in the ^{13}C NMR spectra were assigned to the appropriate carbon atoms of 2,6-dideoxy-hexoses **13**, **14**, **15** and **16** by comparision of their data with the corresponding values of chemical shifts in the series of hexopyranoses, 6-deoxyhexopyranoses and 2-deoxyhexopyranoses.[10]

Table 2. ^{13}C NMR spectral data for compounds 13–16 in D_2O with dioxan as the internal standard

	C-1	C-2	C-3	C-4	C-5	C-6
13	92.22	39.24	68.26	73.19	70.23	18.16
14 α	92.21	32.50	65.62	71.31	67.19	16.90
14 β	94.43	35.41	68.93	71.57	70.25	16.72
15 α	91.97	38.43	71.01	77.71	72.68	17.76
15 β	94.03	40.61	68.52*	77.09	68.75*	17.76
16	92.64	34.64	69.33*	70.13	69.86*	16.57

*Assignments can be reversed.

exclusively as β-pyranose; likewise, after acetylation with acetic anhydride in pyridine only one β-pyranose triacetate 17 was obtained. Sugar 14 occurred in aqueous solution as a mixture of α-pyranose and β-pyranose forms in the ratio 1:1.3 (according to the ^{13}C NMR spectrum). After acetylation a mixture of isomeric α and β triacetates 18 was obtained. In the ^1H NMR spectrum of this mixture (Experimental) signals of two main components: α-pyranose and β-pyranose (about 80–90%) as well as weak signals of the protons of the α- and β-furanose forms of triacetates were visible.

Direct hydroxylation of the double bond in 6 with osmium tetroxide in pyridine led to a mixture of four isomeric esters of 3,7-dideoxy-heptaldonic acid 11. The mixture 11 was converted as before into calcium salt and treated with H_2O_2 and $FeSO_4$ to yield 2,6-dideoxy-DL-arabinohexose (15) and 2,6-dideoxy-DL-xylohexose (16). The mixture of 15 and 16 was acetylated and then the peracetyl derivatives obtained (19 and 20) were separated by chromatography. The configuration and composition of the anomers of sugars 15 and 16 were determined from the ^1H NMR spectra of their triacetates 19 and 20. Free arabinose 15 is present in aqueous solution as a mixture of α- and β-pyranose (about 1:1), whereas xylose 16 occurs exclusively as the β-pyranose form.

The synthesis of stereoisomeric 2,6-dideoxyhexoses presented in this paper offers certain advantages which consist in its preparative simplicity and usually good or moderate yields of individual steps. It is particularly important that the products were prepared from 1 in four steps only.

The resolution of 2, the key intermediate in the presented synthesis, into enantiomers via diastereoisomeric esters with ω-camphanic acid has been attempted. So far it failed however due to the instability of the ester.[11]

EXPERIMENTAL

^1H NMR spectra were recorded for solns in $CDCl_3$ with a Jeol JNM-4H-100 spectrometer (δ scale, TMS = 0 ppm) and ^{13}C NMR spectra with a Varian CFT-20 instrument for solns in $CDCl_3$ or D_2O with TMS or dioxane as the internal standard; chemical shifts are given in ppm downfield from TMS. IR spectra were recorded on a Unicam SP-200 spectrophotometer. Tlc was performed with silica gel G Merck, and column chromatography with silica gel Merck (70–230 mesh).

M.ps and b.ps are uncorrected. B.ps denoted with asterisk refer to the air-bath temp.

Compound 2 was prepared according to Ref. 8. Compound 3 was obtained by acetylation of 2 with acetic anhydride and pyridine.[11]

Butyl E 2,6-dihydroxyhept-4-enoate (6). A soln of 2 (16.0 g, 0.08 mol) in dry THF (300 ml) was stirred and cooled to −70°. To this well stirred, cooled soln MeMgBr (0.4 mol) in ether (100 ml) was added dropwise. Then the mixture was stirred for 5 hr at −70°, poured into ice-water (750 ml) containing NH_4Cl (50 g). The separated organic layer was washed with water (20 ml) and combined with one obtained by washing the aqueous layer with chloroform (5 × 30 ml). Concentration of the combined and dried ($MgSO_4$) extracts followed by purification by chromatography using ligroin and AcOEt (7:3) as eluent gave 6 (10.4 g, 60%), b.p. 135–139°C/0.2 mm Hg. IR: 3450 (OH), 1740, 1195 cm^{-1} (ester). ^1H NMR: ($CDCl_3$): 0.96 (t, 3H, CH_2CH_3), 1.26 (d, 3H, CH_3), 1.2–1.9 (m, 4H, CH_2CH_2), 2.49 (m, 2H, CH_2), 4.19 (t, 2H, OCH_2), ~4.3 (m, 2H, $CH(OH)CO_2Bu$, $CH_3CH(OH)$), 5.64 (m, 2H, CH=CH). (Found: C, 60.7; H, 9.0. Calc. for $C_{11}H_{20}O_4$: C, 61.1; H, 9.3.)

The 2,6-diacetate 8: b.p. 150°/0.4 mm Hg*; IR: 1745, 1240 cm^{-1} (ester). ^1H NMR ($CDCl_3$): 0.96 (t, 3H, CH_2CH_3), 1.30 (d, 3H, CH_3), 1.2–1.8 (m, 4H, CH_2CH_2), 2.02, 2.12 (2xs, 6H, 2xAc), 2.56 (m, 2H, CH_2), 4.14 (t, 2H, OCH_2), 5.03 (t, 1H, ΣJ = 12.0 Hz, $CH(OAc)CO_2Bu$), 5.29 (m, 1H, ΣJ = 23.5 Hz, $CH_3CH(OAc)$), 5.64 (m, 2H, CH=CH). (Found: C, 59.9; H, 8.1. Calc. for $C_{15}H_{24}O_6$: C, 60.0; H, 8.1%).

Butyl E 2-acetoxy-6-hydroxyhept-4-enoate (7). A Grignard reaction was performed on 3 (10.0 g, 0.041 mol) in THF with MeMgBr as described yielded 7 (8.0 g, 75%); b.p. 150°/0.4 mm Hg*; IR: 3450 (OH), 1750, 1235 cm^{-1} (ester). ^1H NMR ($CDCl_3$): 0.95 (t, 3H, CH_2CH_3), 1.25 (d, 3H, CH_3), 1.2–1.9 (m, 4H, CH_2CH_2), 2.12 (s, 3H, Ac), 2.55 (m, 2H, CH_2), 4.15 (t, 2H, OCH_2), ~4.3 (m, 1H, $CH_3CH(OH)$), 5.02 (t, 1H, Σ12.0 Hz, $CH(OAc)CO_2Bu$), 5.63 (m, 2H, CH=CH). (Found: C, 59.8; H, 8.4. Calc. for $C_{13}H_{22}O_5$: C, 60.4; H, 8.6%).

Butyl trans 4,5-anhydro-3,7-dideoxyheptaldonate (8). A soln of 6 (3.5 g, 0.016 mol) and *m*-chloroperbenzoic acid (3.5 g) in $CHCl_3$ (20 ml) was left at room temp. for several days. After disappearance of the substrate (tlc light petroleum-ether-methanol 45:45:10), the soln was cooled to 0°, filtered, and concentrated to dryness. The oily residue was purified by chromatography on silica gel to give 9 (2.3 g, 62%); b.p. 150°/0.4 mm Hg*; IR: 3460 (OH), 1740, 1200 cm^{-1} (ester). ^1H NMR ($CDCl_3$): 0.95 (t, 3H, CH_2CH_3), 1.28 (d, 3H, CH_3), 1.2–1.9 (m, 4H, CH_2CH_2), 2.03 (m, 2H, CH_2), 2.56, 3.16 (2xm, 2H, epoxide), 3.65 (t, 1H, $CH(OH)CO_2Bu$), 4.19 (t, 2H, OCH_2), 4.34 (m, 1H, $CH(OH)CH_3$). (Found: C, 56.0; H, 8.7. Calc. for $C_{11}H_{20}O_5$: C, 56.9; H, 8.7%).

The 2,6-diacetate 10: b.p. 150°/0.4 mm Hg*; IR: 1745, 1240 cm^{-1} (ester). ^1H NMR ($CDCl_3$): 0.96 (t, 3H, CH_2CH_3), 1.29 (2xd, 3H, CH_3), 1.2–1.8 (m, 4H, CH_2CH_2), 2.05, 2.14 (2xs, 6H, 2xAc), 2.7–3.2 (m, 2H, epoxide), 4.18 (t, 2H, OCH_2), 4.78 (m, 1H, $CH(OAc)CH_3$), 5.13 (m, 1H, $CH(OAc)CO_2Bu$). (Found : C, 56.8; H, 7.7. Calc. for $C_{15}H_{24}O_7$: C, 56.9; H, 7.6%).

Butyl 3,7-dideoxyheptaldonate (11). To a soln of 6 (1.6 g, 7.4 mmol) in pyridine (20 ml) osmium tetroxide (2.0 g) was added with cooling. After storage at room temp. for 1 hr, the mixture was treated with sat $NaHSO_3$aq, stirred for 0.5 hr, and extracted 10 times with EtOAc. The extract was dried ($MgSO_4$) concentrated, and purified by chromatography with EtOAc–light petroleum 1:1 to give 11, colourless syrup (1.7 g, 92%). IR: 3450 (OH), 1730, 1200 cm^{-1} (ester). ^1H NMR ($CDCl_3$): 0.95 (t, 3H, CH_2CH_3), 1.26 (d, 3H, CH_3), 1.2–2.0 (m, 4H, CH_2CH_2), ~2 (m, 2H, CH_2), 3.1–4.9 (m, 8H, H-2, H-4, H-5, H-6, 4xOH), 4.17 (t, 2H, OCH_2).

The tetraacetate 12: IR: 1750, 1230 cm^{-1} (ester). ^1H NMR ($CDCl_3$): 0.94 (t, 3H, CH_2CH_3), 1.24 (bd, 3H, CH_3), 1.0–1.8 (m, 4H, CH_2CH_2), 2.06, 2.16 (2xs, 12H, 4xAc), 4.22 (t, 2H, OCH_2), 4.7–5.7 (m, 4H, H-2, H-4, H-5, H-6). (Found: C, 55.1; H, 7.3. Calc. for $C_{19}H_{30}O_{10}$: C, 54.5; H, 7.2.)

2,6-dideoxy-DL-ribohexose (13) *and 2,6-dideoxy-DL-lyxohexose* (14). A soln of 9 (2.0 g, 8.6 mmol) in 60% aqueous AcOH (10 ml) was boiled under reflux for 6 hr, and then the solvent was carefully removed under diminished pressure. A soln of the oily residue in water (10 ml) was treated with barium diacetate (0.1 g) and $CaCO_3$ (0.5 g). The mixture was boiled under reflux for 6 hr and then cooled to 40°, $FeSO_4$ (0.1 g) and 30% H_2O_2 (1.5 ml) were added, and the mixture was stirred for 1 hr, filtered and concentrated. The residue was eluted from a column of silica gel with EtOAc afforded two products: 13 (0.22 g, 17%) and 14 (0.30 g, 24%). (Found for the mixture of 13 and 14: C, 48.9; H, 8.2. Calc. for $C_6H_{12}O_4$: C, 48.6; H, 8.1%).

The 1,3,4-tri-O-acetate 17: m.p. 79–82°; IR: 1740, 1750, 1240 cm^{-1} (ester), ^1H NMR ($CDCl_3$): 1.27 (d, 3H, $J_{CH_3,H-5}$ = 6.2 Hz, CH_3), 1.8–2.2 (m, 2H, H-2, H-2'), 2.04, 2.12 (2xs, 9H, 3xAc), 4.11 (dq, 1H, $J_{H-4,H-5}$ = 9.1 hz, H-5), 4.64 (pd, 1H, $J_{H-3,H-4}$ = 3.0 Hz, H-4), 5.51 (q, 1H, $J_{H-2,H-3} + J_{H-2',H-3}$ = 6.2 Hz, H-3), 6.05 (pd, 1H, $J_{H-1,H-2}$ = 8.1, $J_{H-1,H-2'}$ = 3.8 Hz, H-1). (Found: C, 52.5; H, 6.8. Calc. for $C_{12}H_{18}O_7$: C, 52.5; H, 6.6.)

The 1,3,4-tri-O-acetate 18: IR: 1745, 1230 cm^{-1} (ester), ^1H NMR 1.19, 1.25, 1.29, 1.32 (4xd, 3H, CH_3 α and β-pyranose, α and β-furanose), 1.7–2.7 (m, 11H, H-2, H-2', acetates), 3.85 (q, J_{H-5,CH_3} = 6.2 Hz, H-5 βp), 4.07 (pd, ΣJ = 11.5 Hz, H-4 f), 4.23 (t, ΣJ = 6.4, H-4 f'), 4.20 (q, J_{H-5,CH_3} = 7.0 Hz, H-5 αp), 4.8–5.2 (m, H-3 αp and βp, H-4 αp and βp, H-5 αf and βf), 5.78 (pd, $J_{H-1,H-2}$ = 5.1, $J_{H-1,H-2'}$ = 7.5 Hz, H-1 βp), 6.29 (m, w/2 = 7.2 Hz, H-1 αp), 6.38 (m, H-1 αf and βf). (Found: C, 52.6; H, 6.8. Calc. for $C_{12}H_{18}O_7$: C, 52.5; H, 6.6.)

1,3,4-Tri-O-acetyl-2,6-dideoxy-DL-arabinohexose (19) *and 1,3,4-tri-O-acetyl-2,6-dideoxy-DL-xylohexose* (20). A soln of 11 in water (1.6 g, 6.4 mmol) was treated with barium diacetate (0.08 g) and $CaCO_3$ (0.5 g). The mixture was boiled under reflux for 6 hr and then cooled to 40°, $FeSO_4$ (0.1 g) and 30% H_2O_2 (1.5 ml) was added, and the mixture was stirred for 1 hr, filtered and concentrated. The residue was acetylated with Ac_2O and pyridine. The crude mixture of triacetates was separated on a silica gel column using light petroleum—ethyl ether 85:15 as an eluant. Two fractions were obtained; 0.32 g of 19 (19%) and 0.27 g of 20 (15%).

For compound 19: IR: 1740, 1220 cm^{-1} (ester). ^1H NMR: ($CDCl_3$): 1.21 (d, CH_3 αp), 1.25 (d, CH_3 βp), 1.6–2.5 (m, H-2, H-2', acetates), 3.64 (dq, J_{H-5,CH_3} = 6.2, $J_{H-4,H-5}$ = 9.0 Hz, H-5 βp), 3.96 (dq, J_{H-5,CH_3} = 6.2, $J_{H-4,H-5}$ = 10.0 Hz, H-5, αp), 4.75 (t, ΣJ = 19 Hz, H-4 βp), 4.79 (t, ΣJ = 19.5 Hz, H-4 αp), 4.98 (m, ΣJ = 27.3 Hz, H-3 βp), 5.25 (m, ΣJ = 26.5 Hz, H-3 αp), 5.77 (pd, $J_{H-1,H-2}$ = 2.2, $J_{H-1,H-2'}$ = 10.0 Hz, H-1 βp), 6.19 (m, w/2 = 6.7 Hz, H-1 αp). (Found: C, 52.2; H, 6.8. Calc. for $C_{12}H_{18}O_7$: C, 52.5; H, 6.6.)

For compound 20: m.p. 80–84°, IR: 1740, 1220 cm^{-1} (ester). ^1H NMR ($CDCl_3$): 1.2 (d, 3H, J_{H-5,CH_3} = 6.6 Hz, CH_3), 1.7–2.5 (m, 2H, H-2, H-2'), 2.06, 2.11 (2s, 9H, 3xAc), 4.18 (q, 1H, ΣJ = 20.0 Hz, H-5), 4.71 (m, 1H, w/2 = 6.5 Hz, H-4), 5.10 (m, 1H, ΣJ = 9.2 Hz, H-3), 5.94 (pd, 1H, ΣJ = 12.9 Hz, H-1). (Found: C, 52.4; H, 6.7. Calc. for $C_{12}H_{18}O_7$: C, 52.5; H, 6.6.)

Deacetylation of compounds 19 and 20 with sodium methoxide in methanol gave sugars 15 and 16 respectively.

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REFERENCES

[1]R. C. Elderfield, *Advan. Carbohydrate Chem.* 1, 147 (1945); T. Reichstein and E. Weiss, *Ibid.* 17, 65 (1962); and refs cited; T. Reichstein, *Angew. Chem.* 63, 412 (1951); J. E. Courtois and F. Percheron, *The Carbohydrates* (Edited by W. Pigman and D. Horton), p. 213. Academic Press, New York (1970).

[2]S. Hanessian, *Advan. Carbohydrate Chem.* 21, 143 (1966); S. Hanessian and T. H. Haskell, *The Carbohydrates* (Edited by W. Pigman and D. Horton), p. 139. Academic Press, New York (1970).

[3]L. Ettlinger, E. Garrmann, R. Hütter, W. Keller-Schierlein, F. Kradolfer, L. Neipp, V. Perlog, P. Reusser and H. Zähner, *Chem. Ber.* 92, 1867 (1959).

[4]H. Brockmann and T. Waehneldt, *Naturwissenschaften* 48, 717 (1961).

[5]H. S. El Khadem, D. L. Swartz, J. K. Nelson and L. A. Berry, *Carbohydr. Res.* 58, 230 (1977).

[6]T. M. Cheung, D. Horton and W. Weckerle, *Ibid.* 58, 139 (1977).

[7]P. J. Garegg and T. Norberg, *Acta Chem. Scand.* ser. B 29, 507 (1975).

[8]A. Konowal, J. Jurczak and A. Zamojski, *Rocz. Chem.* 42, 2045 (1968).

[9]M. Chmielewski, *Carbohydr. Res.* 68, 144 (1979).

[10]E. Breitmaier and W. Voelter, ^{13}C NMR *Spectroscopy* Table 5.13. Verlag Chemie (1974).

[11]M. Chmielewski, unpublished data.