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The Ferrier rearrangement as the key step in the synthesis of C_7–C_{16}-alkyl 2,3-dideoxy glucosides from glucose and C_7–C_{16}-alkanols[1–3]

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The Ferrier rearrangment was used as the key step in the synthesis of C_7–C_{16}-alkyl 2,3-dideoxy glucosides from glucose and C_7–C_{16}-alkanols.

Keywords: synthesis of C_7–C_{16}-alkyl 2,3-dideoxy glucosides, Ferrier rearrangement.

INTRODUCTION

The Ferrier rearrangement[4] (Scheme 1) continues to be the pinnacle of the chemistry of the 2,3-unsaturated sugars. The fact that tri-*O*-acetyl glucal[5] **1** can now be easily synthesized from glycose adds even more to its attractiveness. In the initial version,[4] the delocalized allyloxocarbenium ion **2** was trapped with an alcohol affording the α-D-product **3**. In the course of his synthetic studies, Frazer-Reed[6] quenched ion **2** with triethylsilane to give **5** and with a variety of enol silanes to give, for example, **6a**. The concurrent studies of Grynkiewicz and BeMiller[7] with enol acetates, to give **6b**, for example, were timely developments. The structures of the major anomers of C-glycosides such as **6** follows independently from a comparison of their ^{13}C-NMR data, with those of their *cis* (or β-D) counterparts.[8] However, independent proof comes from the Eschenmoser-Claisen rearrangement[9] on the axial alcohol **7** which must necesserily give the α-D amide **6c**.[10]

RESULTS AND DISCUSSION

In continuation of our investigations[1–3] on the synthesis of biodegradable surfactants wich could be obtained from renewable resources, we synthesized C_7–C_{16}-alkyl 2,3-di-

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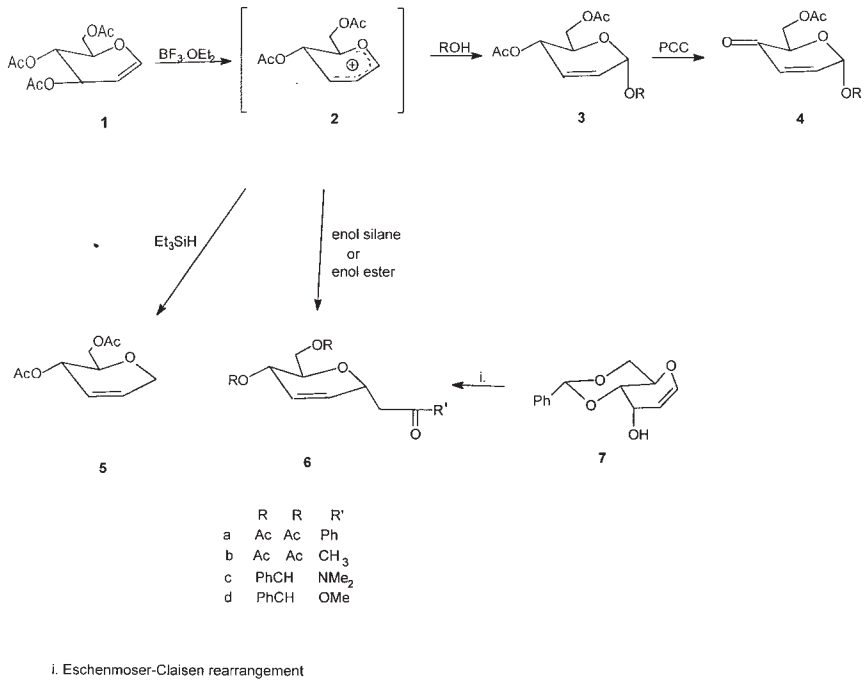


Scheme 1.

deoxy glucosides from glucose and fatty alcohols using the Ferrier reaction.[4,11] As depicted in the synthetic Scheme 2, treatment of glucose **8** with acetic anhydride and molten anhydrous sodium acetate at 120 ºC gives exclusively the β-D-glucose penta-acetate **9**, which on treatment with hydrogen bromide/acetic acid leads to the glucosyl bromide **10**. Reductive elimination with zink-copper affords tri-*O*-acetyl glucal **1**. Glycosylation with a fatty alcohol ROH (**11**) and boron trifluoride etherate proceeds by a nucleophilic attack at the anomeric center of the glucal **1**. By an allylic rearrangement, the activated ester function at C-3 leaves the molecule to give the alkyl 2,3-unsaturated glucosed **3**α/β (in 85–97 % yield) with the α-anomer largely prevailing (**3**α : **3**β = 10 : 1). Hydrogenation on paladium on charcoal (Pd/C)proceeded quantitatively affording C_7–C_{16}-alkyl 2,3-dideoxy glucosides **12**. For comparison, the reactions of **1** with methanol and 1-butanol were performed.

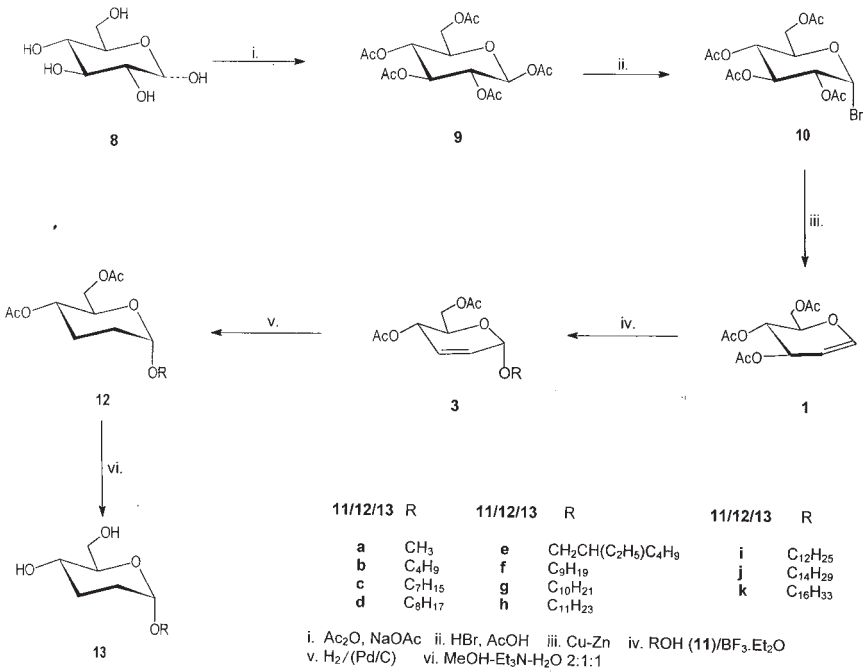
Following chromatographic purification, the peracetylated products were de-esterified with the mixture methanol : triethylamine : water (2 : 1 : 1) to give alkyl α- glucoside **13**α.

For structural assignmenta extensive NMR studies were employed (^{1}H – ^{1}H homonuclear and ^{1}H – ^{13}C heteronuclear chemical correlation spectroscopy (COSY) experiments were performed).

EXPERIMENTAL

General.

Solvents designated as "dry" were distilled prior to use: dichloromethane from calcium hydride; methanol from magnesium. TLC was performed on silica 60 plates GF 254 (Marck). Dry flash



Scheme 2.

column chromatography was carried out using Merck silica gel 60, particle size 0.04 – 0.06 mm. Spots were visualized by spraying with 10 % sulfuric acid in ethanol (carbohydrates) and 1 % anisaldehyde and 2 % sulfuric acid in glacial acetic acid (noncarbohydrate compounds) and subsequent heating. NMR spectra: Varian Gemini 200 (200 MHz) in $CDCl_3$ or Bruker 250 (62.9 MHz) in DMSO-d_6. Assignment of the signals was supported by ^1H – ^1H homonuclear and ^1H – ^{13}C heteronuclear chemical-shift correlation spectroscopy (COSY) experiments.

The tri-*O*-acetyl glucal (**1**) was prepared according to the literature procedure,[12,13] *via* the acetylated sugar **9** and glucosyl bromide **10** (Scheme 2).

*Methyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (**3a**)*

General procedure. To a stirred solution of glucal **1** (2.72 g, 9.99 mmol) in dry toluene (25 ml), methanol (**11a**, 0.40 ml, 10.00 mmol) and a catalytic amount of $BF_3 \cdot Et_2O$ (0.80 ml, 6.50 mmol) were added. The mixture was allowed to react for 1 h and then neutralized by the addition of Na_2CO_3 (2 g). After the solution had been stirred for 30 min, the solids were filtered off and the filtrate was successively washed with a saturated aqueous solution of $NaHCO_3$ and distilled water. After drying with anhydrous Na_2SO_4, the solvent was evaporated on a rotary evaporator under vacuum affording a syrup (2.28 g). The residue was purified by dry flash chromatography (toluene–ethyl acetate) to afford **3a** in 96 % yield as a 10 : 1 mixture of the α- and β-methyl glucoside. ^1H-and ^{13}C-NMR data are given in Tables I and III, respectively.

*But-1-yl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (**3b**)*

Tri-*O*-acetyl glucal (**1**, 2.72 g, 9.99 mmol) in dry toluene (25 ml) was treated with 1-butanol (**11b**, 0.90 ml, 9.83 mmol) and a catalytic amount of $BF_3 \cdot Et_2O$ (0.80 ml, 6.50 mmol) as described for **3a**. The described work-up and removal of the solvent gave 2.44 g of a syrupy residue. The residue was purified by dry flash chromatography (toluene–ethyl acetate) to afford **3b** in 85 % yield as a 10 : 1 mixture of the α- and β-but-1-yl glucoside.

TABLE I. ^{1}H-NMR data of the compounds **3a**α – **3k**α (200 MHz, $CDCl_3$)

Proton	**3a**α	**3b**α	**3c**α, **3d**α, **3f**α-**3k**α	**3e**α
H-1	4.94	5.02	5.02–5.03	4.99
H-2,3	5.85–5.88	5.80–5.97	5.80–5.97	5.77–5.94
H-4	5.29–5.35	5.27–5.34	5.27–5.36	5.27, 5.32
H-5,6	4.03–4.33	4.07–4.31	3.98–4.32	4.0–4.30
H1’	3.46	3.52	3.51	3.33–3.41
H-1b’		3.78	3.78	3.66–3.76
H-2’		1.52–1.66	1.50–1.70	1.52
$OCOOCH_3$	2.09, 2.11	2.09, 2.10	2.08, 2.10	2.04, 2.09
$–(CH_2)_n–$		1.33–1.47	1.26–1.30	1.29
$–(CH_2)_nCH_3$		0.94	0.88–0.89	0.90

TABLE II. ^{1}H-NMR data of the compounds **12a**α – **12k**α (200 MHz, $CDCl_3$)

Proton	**12a**α	**12b**α	**12c**α, **12d**α, **12f**α – **12k**α	**12e**α
H-1	4.73	4.72	4.77–4.82	4.78
H-2	1.83	1.87	1.92–1.98	1.97
H-3	1.82	1.73	1.77–1.83	1.82
H-4	4.73	4.62	4.67–4.73	4.72
H-5	3.86–3.97	3.80–3.86	3.86–3.97	3.87–3.93
H-6a	4.12	4.00	4.05–4.10	4.10
H-6b	4.27	4.16	4.22–4.27	4.24
H-1a’	3.37	3.32	3.35–3.41	3.26
H-1b’		3.60	3.60–3.67	3.58
H-2’		1.49	1.55–1.60	1.51
$OCOCH_3$	2.05, 2.09	1.95, 2.00	2.00–2.09	2.05, 2.08
$–(CH_2)_n–$		1.34	1.21–1.31	1.29
$–(CH_2)_nCH_3$		0.85	0.83–0.89	0.90

*Hept-1-yl 4,6-di-*O*-acetyl-2,3-dideoxy-*α*-D-erythro-hex-2-enopyranoside (**3c**)*

Tri-*O*-acetyl glucal (**1**, 2.72 g, 9.99 mmol) in dry toluene (25 ml) was treated with 1-heptanol (**11c**, 1.40 ml, 9.90 mmol) and a catalytic amount of $BF_3 \cdot Et_2O$ (0.80 ml, 6.50 mmol) as described for **3a**. The desribed work-up and removal of the solvent gave 2.89 g of a syrupy residue. The residue was purified by dry flash chromatography (toluene–ethyl acetate) to afford **3c** in 88 % yield as a 7 : 1 mixture of the α- and β-hept-1-yl glucoside.

Oct-1-yl 4,6-di-O-*acetyl-2,3-dideoxy*-α-*D-erythro-hex-2-enopyranoside (**3d**)*

Tri-*O*-acetyl glucal (**1**, 2.72 g, 9.99 mmol) in dry toluene (25 ml) was treated with 1-octanol (**11d**, 1.6 ml, 10.12 mmol) and a catalytic amount of $BF_3 \cdot Et_2O$ (0.80 ml, 6.50 mmol) as described for **3a**. The described work-up and removal of the solvent gave 3.06 g of a syrupy residue. The residue was purified by dry flash chromatography (toluene–ethyl acetate) to afford **3d** in 87 % yield as a 10 : 1 mixture of the α- and β-oct-1-yl glucoside.

2-Ethyl-hex-1-yl 4,6-di-O-*acetyl-2,3-dideoxy*-α-*D-erythro-hex-2-enopyranoside (**3e**)*

Tri-*O*-acetyl glucal (**1**, 2.72 g, 9.99 mmol) in dry toluene (25 ml) was treated with 2-ethyl-1-hexanol (**11e**, 1.56 ml, 9.98 mmol) and a catalytic amount of $BF_3 \cdot Et_2O$ (0.80 ml, 6.50 mmol) as described for **3a**. The described work-up and removal of the solvent gave 2.94 g of a syrupy residue. The residue was purified by dry flash chromatography (toluene–ethyl acetate) to afford **3e** in 86 % yield as a 13 : 1 mixture of the α- and β-ethylhex-1-yl glucoside.

Non-1-yl 4,6-di-O-*acetyl-2,3-dideoxy*-α-*D-erythro-hex-2-enopyranoside (**3f**)*

Tri-*O*-acetyl glucal (**1**, 2.72 g, 9.99 mmol) in dry toluene (25 ml) was treated with 1-nonanol (**11f**, 1.8 ml, 10.32 mmol) and a catalytic amount of $BF_3 \cdot Et_2O$ (0.80 ml, 6.50 mmol) as described for **3a**. The described work-up and removal of the solvent gave 3.79 g of a syrupy residue. The residue was purified by dry flash chromatography (toluene–ethyl acetate) to afford **3f** in 95 % yield as a 10 : 1 mixture of the α- and β-non-1-yl glucoside.

Dec-1-yl 4,6-di-O-*acetyl-2,3-dideoxy*-α-*D-erythro-hex-2-enopyranoside (**3g**)*

Tri-*O*-acetyl glucal (**1**, 2.72 g, 9.99 mmol) in dry toluene (25 ml) was treated with 1-decanol (**11g**, 1.9 ml, 9.96 mmol) and a catalytic amount of $BF_3 \cdot Et_2O$ (0.80 ml, 6.50 mmol) as described for **3a**. The described work-up and removal of the solvent gave 3.79 g of a syrupy residue. The residue was purified by dry flash chromatography (toluene–ethyl acetate) to afford **3g** in 89 % yield as a 10 : 1 mixture of the α- and β-dec-1-yl glucoside.

Undec-1-yl 4,6-di-O-*acetyl-2,3-dideoxy*-α-*D-erythro-hex-2-enopyranoside (**3h**)*

Tri-*O*-acetyl glucal (**1**, 2.72 g, 9.99 mmol) in dry toluene (25 ml) was treated with 1-undecanol (**11h**, 2.07 ml, 9.97 mmol) and a catalytic amount of $BF_3 \cdot Et_2O$ (0.80 ml, 6.50 mmol) as described for **3a**. The described work-up and removal of the solvent gave 4.05 g of a syrupy residue. The residue was purified by dry flash chromatography (toluene–ethyl acetate) to afford **3h** in 95 % yield as a 7 : 1 mixture of the α- and β-undec-1-yl glucoside.

Dodec-1-yl 4,6-di-O-*acetyl-2,3-dideoxy*-α-*D-erythro-hex-2-enopyranoside (**3i**)*

Tri-*O*-acetyl glucal (**1**, 2.72 g, 9.99 mmol) in dry toluene (25 ml) was treated with 1-dodecanol (**11i**, 1.86 ml, 9.98 mmol) and a catalytic amount of $BF_3 \cdot Et_2O$ (0.80 ml, 6.50 mmol) as described for **3a**. The described work-up and removal of the solvent gave 4.19 g of a syrupy residue. The residue was purified by dry flash chromatography (toluene–ethyl acetate) to afford **3i** in 97 % yield as a 10 : 1 mixture of the α- and β-dodec-1-yl glucoside.

Tetradec-1-yl 4,6-di-O-*acetyl-2,3-dideoxy*-α-*D-erythro-hex-2-enopyranoside (**3j**)*

Tri-*O*-acetyl glucal (**1**, 1.36 g, 4.99 mmol) in dry toluene (25 ml) was treated with 1-tetradecanol (**11j**, 1.07 ml, 4.99 mmol) and a catalytic amount of $BF_3 \cdot Et_2O$ (0.40 ml, 3.25 mmol) as described for **3a**. The described work-up and removal of the solvent gave 2.22 g of a syrupy residue. The residue was purified by dry flash chromatography (toluene–ethyl acetate) to afford **3j** in 94 % yield as a 10 : 1 mixture of the α- and β-tetradec-1-yl glucoside.

Hexadec-1-yl 4,6-di-O-*acetyl-2,3-dideoxy*-α-*D-erythro-hex-2-enopyranoside (**3k**)*

Tri-*O*-acetyl glucal (**1**, 1.36 g, 4.99 mmol) in dry toluene (13 ml) was treated with 1-tetradecanol (**11k**, 1.21 ml, 4.99 mmol) and a catalytic amount of $BF_3 \cdot Et_2O$ (0.40 ml, 3.25 mmol) as de-

TABLE III. 13C-NMR data of the compounds **3a**α – **3k**α (50 MHz, $CDCl_3$) and **12a**α – **12k**α (50 MHz, $CDCl_3$), **13a**α – **13k**α (62.5 MHz, DMSO-d_6),

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-1'	$(CH_2)_n$	CH_3
3aα	94.6	128.4	127.2	64.5	66.2	62.2	54.9		
3bα	93.7	128.3	127.5	64.8	66.4	62.5	67.8	18.8, 31.2	13.2
3cα, **3d**α, **3f**α–**3k**α	94.1–94.3	128.7–128.9	127–127.9	65.1–65.3	66.6–66.8	62.8–63.0	68.7–69.0	22.3–31.9	13.7–14.0
3eα	94.3	128.5	127.8	65.1	66.7	62.8	71.1	22.7–39.3	10.8, 13.7
12aα	97.4	23.8	28.6	67.7	68.4	63.1	54.5		
12bα	95.8	23.6	28.7	67.6	68.2	63.0	67.4	19.0, 31.2	13.4
12cα, **12d**α, **12f**α–**12k**α	95.8–96.2	23.7–23.9	28.5–29.0	67.4–67.9	68.2–68.5	62.7–63.2	66.8–67.8	22.2–31.8	13.6–14.0
12eα	96.4	23.9	28.9	67.9	68.5	63.3	67.7	22.9–41.7	10.8, 13.9
13aα	96.5	27.5	29.0	74.6	65.2	61.4	53.8		
13bα	95.0	27.3	29.1	74.5	65.1	61.3	65.5	19.1, 31.3	13.9
13cα, **13d**α, **13f**α–**13k**α	95.0–95.1	27.3	29.0–29.1	74.5	65.0–65.1	61.2–61.3	65.8–65.9	22.1–31.3	13.9

scribed for **3a**. The described work-up and removal of the solvent gave 2.41 g of a syrupy residue. The residue was purified by dry flash chromatography (toluene–ethyl acetate) to afford **3k** in 96 % yield as a 12 : 1 mixture of the α- and β-hexadec-1-yl glucoside.

1-Octyl 4,6-di-O-*acetyl-2,3-dideoxy*-α-D-*erythro-hex-2-enopyranoside (**12d**)*

General procedure. A solution of 0.47 g (1.37 mmol) of the unsaturated **3d** in 25 ml of ethyl acetate was hydrogenated in the presence of of 0.25 g of 10 % palladium-on-carbon for 24 h. The catalyst was removed by filtration and the solvent was evaporated to give 0.47 g of a syrup. The residue was purified by dry flash chromatography (toluene-ethyl acetate) to afford **12d** in 97 % yield as a 10 : 1 mixture of the α- and β-octyl glucoside. ^{1}H and ^{13}C NMR data are given in Tables II and III, respectively.

The resulting material was deacetylated by treatment of the purified sample (100–200 mg) with 2 ml of MeOH-Et_3N-H_2O 2 : 1 : 1 at room temperature for 24 h to give the alkyl 2,3-dideoxy-α-D-erythro-hexopyranoside (**13**α).

И З В О Д

FERRIER-ОВО ПРЕМЕШТАЊЕ КАО КЉУЧНИ СТУПАЊ У СИНТЕЗИ C_7–C_{16}-АЛКИЛ-2,3-ДИДЕОКСИ-ГЛУКОЗИДА ИЗ ГЛУКОЗЕ И C_7–C_{16}-АЛКАНОЛА

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Ferrier-ово премештање је примењено као кључни ступањ у вишестепеној синтези C_7–C_{16}-алкил-2,3-дидеокси-глукозида која полази од глукозе и C_7–C_{16}-алканола.

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