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A common access to 2- and 3-substituted methyl β-D-xylopyranosides

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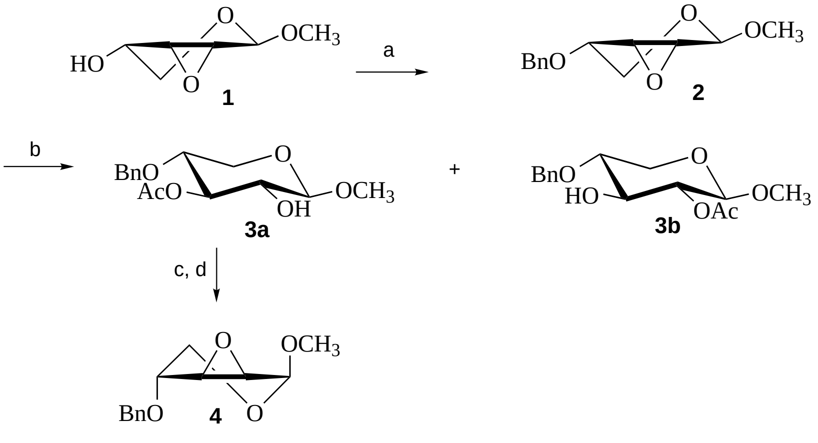
Abstract—2-Deoxy-, 3-deoxy-, 2-deoxy-2-fluoro- and 3-deoxy-3-fluoro- derivatives of methyl β-D-xylopyranoside diacetates were prepared by a new common route via 2,3-anhydropentosides. The stereo- and regioselective introduction of fluorine or hydrogen was accomplished by epoxide ring opening of methyl 2,3-anhydro-β-D-ribopyranoside and methyl 2,3-anhydro-4-*O*-benzyl-β-D-lyxopyranoside. Methyl 2,3-anhydro-4-*O*-benzyl-β-D-lyxopyranoside was originally obtained in three simple steps from readily available methyl 2,3-anhydro-4-*O*-benzyl-β-D-ribopyranoside. © 2001 Elsevier Science Ltd. All rights reserved.

Acetylxylan esterases (EC 3.1.1.72, AcXEs) are microbial enzymes which deacetylate partially acetylated 4-*O*-methyl-D-glucuronoxylan, the major plant hemicellulose. Previous investigations of the mode of action of AcXEs using diacetates of methyl β-D-xylopyranosides[1,2] showed that AcXEs deacetylate efficiently positions 2 and 3 if the adjacent OH-group is non-esterified. These results led to the hypothesis that deacetylation of positions 2 and 3 involves a common *ortho*-ester intermediate in which the acetyl group is loosely bound to both OH-groups. The verification of the hypothesis requires substrate analogues of methyl β-D-xylopyranoside diacetates in which the formation of hypothetical 2,3-*ortho*-ester intermediate is eliminated. Such analogues include, e.g. 2-deoxy-, 3-deoxy-, 2-deoxy-2-fluoro- and 3-deoxy-3-fluoro- derivatives of methyl β-D-xylopyranoside diacetates. These compounds also will be useful to evaluate the role of OH-groups at positions 2 and 3 in the enzyme–substrate interactions.

There are many synthetic methods for preparation of differently substituted deoxy[3] and deoxy-fluoro[4] derivatives of carbohydrates. All of them require a variety of different suitably protected starting compounds.



Scheme 1. *Reagents and conditions*: (a) BnBr, NaH, THF, rt, 2.5 h, 88%; (b) CH_3COONa (10 equiv.), CH_3COOH, 140°C, 3 h, 91% **3a**+**3b** (66% for **3a**); (c) TsCl, Py, rt, 48 h; (d) 0.7 M MeONa/MeOH, rt, overnight, (87% from **3a**).

Keywords: epoxide ring opening; regioselectivity; reduction; hydrofluorination; acetylxylan esterase.

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The epoxide ring opening of anhydroglycosides as versatile intermediates for reactions with a wide range of nucleophiles, is a well-established reaction. Factors leading to stereo- and regioselectivity in carbohydrate epoxide ring opening have been frequently investigated. Usually, the *trans*-diaxial opening products are formed exclusively (the Fürst–Plattner rule).

Here we report the synthesis of diacetates of methyl β-D-xylopyranoside substituted at positions 2 and 3 by hydrogen or fluorine. The derivatives were synthesized by routes that involve regioselective nucleophilic epoxide ring opening in 2,3-anhydropentoside **1** and **4**. The methyl 2,3-anhydro-β-D-ribopyranoside (**1**) was readily prepared by slight modification of an already reported synthesis from D-arabinose[5] and, after 4-*O*-benzylation,[6] it was transformed in three steps into a methyl 2,3-anhydro-4-*O*-benzyl-β-D-lyxopyranoside (**4**)[7] (Scheme 1). The key step of this transformation was the epoxide ring opening of 4-*O*-benzylated D-*ribo*-2,3-epoxide **2** to 3-acetate **3a** by sodium acetate in acetic acid at 130°C. The reaction proceeded with high regioselectivity because only xylosides **3a** and **3b** were formed (91% overall chemical yield). Due to the acetyl migration caused by high reaction temperature and by the presence of acetic acid, only 66% of 3-acetate **3a** was isolated. D-*lyxo*-2,3-Epoxide **4** was obtained after tosylation of **3a** and alkaline treatment in 87% yield. The 4-*O*-benzyl group of **4** avoids the possibility of equilibrium of the first produced D-*lyxo*-2,3-epoxide with the D-*arabino*-3,4-epoxide formed by epoxide migration.

In the next stage, the epoxides **1** and **4** were converted to deoxy and deoxy-fluoro analogues **5**, **6a**, **7a** and **8a**[8] by a regioselective epoxide opening in 2,3-anhydropentoside **1** and **4**, either by reduction or hydrofluorination. Previous studies[5b,6,9] indicated that D-*ribo*-2,3-epoxide **1** or **2** could be regioselectively transformed to 3-substituted xylopyranosides by preferential nucleophilic attack at position 3. As an extension of these results, we observed that this reaction proceeds regioselectively also with small nucleophiles like H^- and F^- (Table 1). Reduction of 2,3-anhydro-β-D-ribopyranoside **1** by $LiAlH_4$ in THF under room temperature gave only methyl 3-deoxy-β-D-*erythro*-pentopyranoside **5**. When D-*ribo*-2,3-epoxide **1** was hydrofluorinated with $Bu_4N^+H_2F_3^-$ and KHF_2 at 130°C under solid–liquid PTC,[10] the minor 2-deoxy-2-fluoro-β-D-arabinopyranoside (**6b**) was isolated in a 6% yield beside 70% yield of the desired 3-deoxy-3-fluoro-β-D-xylopyranosides **6a** (Table 1).

We further investigated the possibility of transforming the new methyl 2,3-anhydro-4-*O*-benzyl-β-D-lyxopyranoside (**4**) into corresponding D-xylopyranosides substituted at position 2. The reduction under the same conditions as for D-*ribo*-2,3-epoxide **1** was not so straightforward and afforded D-*xylo* and D-*arabino* products in the proportion 1.8:1 (Table 1). After column chromatography on silica gel methyl 4-*O*-benzyl-2-deoxy-β-D-*threo*-pentopyranoside (**7a**) and methyl 4-*O*-benzyl-3-deoxy-β-D-*erythro*-pentopyranoside (**7b**) were obtained in 53 and 29% yield, respectively. When epoxide **4** was treated by $Bu_4N^+H_2F_3^-/KHF_2$ under the SL–PTC conditions, the product of elimination **9**[11] was isolated from the reaction mixture in the highest yield (56%, Fig. 1). Its precursor, 3-deoxy-3-fluoro-β-D-arabinopyranoside **8b**, was obtained in 15% yield and the desired 2-deoxy-2-fluoro-β-D-xylopyranoside **8a** in only 6% yield. Hydrofluorination of **4** with KHF_2 in ethane-1,2-diol at 180°C also showed a lower degree of regioselectivity, but satisfactorily afforded 2-deoxy-2-fluoro-β-D-xylopyranoside **8a** (36%), which is inaccessible using the DAST method due to the occurrence of side reactions at the glycosidic bond (Scheme 2).[4,12]

Compounds **7a** and **8a** were debenzylated by catalytic hydrogenation (Pd/C) and the resulting deoxy- and deoxy-fluoro-β-D-xylopyranosides were eventually per-*O*-acetylated to afford the desired AcXE substrates.

In conclusion, efficient and simple parallel routes for preparation of 2- or 3-deoxy and deoxy-fluoro derivatives of methyl β-D-xylopyranosides from D-arabinose are described. This approach is applicable for preparation of different 2- or 3-derivatives of xylopyranosides depending on used nucleophiles. The described compounds are currently used as enzyme substrates to elucidate the mechanisms of deacetylation by acetylxylan esterases. Details of the synthesis and results of biochemical studies will be reported in due course.

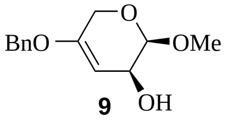

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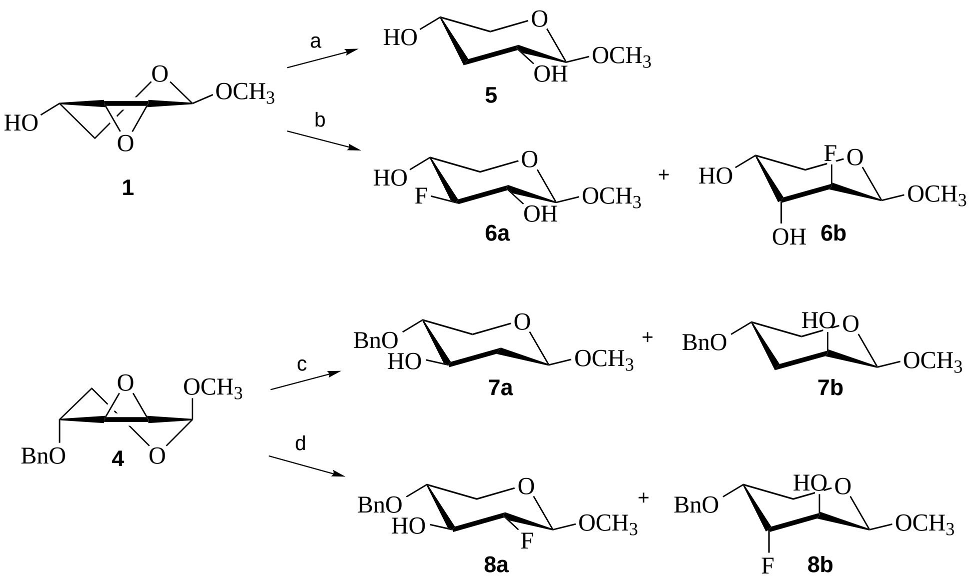
Figure 1. The structure of isolated major eliminated product **9**.

Table 1. The yields of products resulting from the epoxide ring opening of **1** and **4**

Epoxide	Reaction condition	Product yields (%)		Ratio of products *xylo*/*arabino*
1	a	**5** (74)	–	1/0
1	b	**6a** (70)	**6b** (6)	11.7/1
4	a	**7a** (53)	**7b** (29)	1.8/1
4	b	**8a** (6)	**8b** (15)	[a]
4	c	**8a** (36)	**8b** (35)	1/1

[a] The elimination reaction product **9** was isolated in 56%.



Scheme 2. *Reagents and conditions*: (a) LiAlH$_4$, THF, rt, 40 h; (b) n-Bu$_4$N$^+$H$_2$F$_3$$^-$ (3 equiv.), KHF$_2$ (6 equiv.), 130°C, 12 h; (c) KHF$_2$, (HOCH$_2$)$_2$, 180°C, 3 h.

Acknowledgements

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7. **4** (^{1}H NMR, 300 MHz, CDCl$_3$): δ 3.33 (ddd, 1H, $J_{2,3}$ 3.7, $J_{3,4}$ 1.9 Hz, H-3), 3.37 (t, 1H, $J_{1,2}$ 2.9 Hz, H-2), 3.46 (s, 3H, OCH$_3$), 3.59 (dt, 1H, $J_{4,5a}$ 3.1, $J_{3,5a}$ 1.6, $J_{5a,5b}$ 12.1 Hz, H-5a), 3.76–3.78 (m, 1H, H-4), 3.80 (dd, 1H, $J_{4,5b}$ 2.1 Hz, H-5b), 4.67 (dd, 2H, CH$_2$), 4.93 (d, 1H, H-1), 7.29–7.37 (m, 5H, H-Ph).
8. All synthesized compounds gave satisfactory elemental analyses and were characterized by NMR spectroscopy. For example: **5** (^{1}H NMR, 300 MHz, D$_2$O): δ 1.58 (dt, 1H, $J_{2,3a}=J_{3a,4}$ 9.1, $J_{3a,3b}$ 12.8 Hz, H-3a), 2.26 (ddt, $J_{2,3b}=J_{3b,4}$ 4.4, $J_{3b,5b}$ 1.8 Hz, H-3b), 3.38 (dd, $J_{4,5a}$ 7.8, $J_{5a,5b}$ 11.3 Hz, H-5a), 3.50 (s, 3H, OCH$_3$), 3.52 (ddd, $J_{1,2}$ 6.1 Hz, H-2), 3.85 (ddd, $J_{4,5b}$ 4.1 Hz, H-4), 3.95 (ddd, H-5b), 4.36 (d, H-1). **6a** (^{1}H NMR, 300 MHz, CDCl$_3$): δ 2.42 (bs, 1H, OH), 2.58 (bs, 1H, OH), 3.30 (dd, 1H, $J_{4,5a}$ 9.4, $J_{5a,5b}$ 11.6 Hz, H-5a), 3.55 (s, 3H, OCH$_3$), 3.61 (ddd, 1H, $J_{1,2}$ 6.9, $J_{2,3}$ 7.9, $J_{2,F}$ 12.9 Hz, H-2), 3.88–4.00 (m, 1H, H-4), 4.06 (ddd, 1H, $J_{4,5b}$ 5.6 Hz, $J_{5b,F}$ 5.8 Hz, H-5b), 4.22 (d, 1H, H-1), 4.38 (ddd, $J_{3,4}$ 8.1, $J_{3,F}$ 52.0 Hz). **7a** (^{1}H NMR, 300 MHz, CDCl$_3$): δ 1.78 (dt, 1H, $J_{1,2a}=J_{2a,3}$ 4.2, $J_{2a,2b}$ 14.1 Hz, H-2a), 2.27 (dt, 1H, $J_{1,2b}=J_{2b,3}$ 3.5, H-2b), 3.43 (s, 3H, OCH$_3$), 3.36–3.45 (m, 1H, H-3), 3.58 (dd, 1H, $J_{4,5a}$ 3.6, $J_{5a,5b}$ 12.6 Hz, H-5a), 3.87 (dt, 1H, $J_{3,4}$ 4.2 Hz, H-4), 4.05 (dd, 1H, H-5b), 4.65 (dd, 2H, CH$_2$), 4.72 (t, 1H, H-1), 7.29–7.37 (m, 5H, H-Ph). **8a** (^{1}H NMR, 300 MHz, CDCl$_3$): δ 3.06 (bs, 1H, OH), 3.23 (dd, 1H, $J_{4,5a}$ 9.7, $J_{5a,5b}$ 11.7 Hz, H-5a), 3.41–3.57 (m, 1H, H-4), 3.52 (s, 3H, OCH$_3$), 3.82 (ddd, 1H, $J_{2,3}$ 8.5, $J_{3,4}$ 8.4, $J_{3,F}$ 15.2 Hz, H-3), 3.94 (ddd, 1H, $J_{4,5b}$ 5.0 Hz, H-5b), 4.15 (ddd, 1H, $J_{2,F}$ 50.5 Hz, H-2), 4.34 (dd, 1H, $J_{1,2}$ 7.2, $J_{1,F}$ 3.7 Hz, H-1), 4.67 (dd, 2H, CH$_2$), 7.35 (m, 5H, Ph).
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11. For **9**: (^{1}H NMR, 300 MHz, CDCl$_3$): δ 2.21 (d, $J_{2,OH}$ 9.1 Hz, H-OH), 3.54 (s, 3H, OCH$_3$), 3.98 (dt, 1H, $J_{3,5a}$ 1.3, J_{5a,CH_2} 1.2, $J_{5a,5b}$ 15.2 Hz, H-5a), 4.15 (dt, 1H, $J_{3,5b}$ 1.3, J_{5b,CH_2} 1.4 Hz, H-5b), 4.31 (m, 1H, H-2), 4.66 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 4.78 (dd, 2H, CH$_2$), 4.84 (bd, 1H, $J_{2,3}$ 3.4 Hz, H-3), 7.29–7.37 (m, 5H, H-Ph).
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