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Note

An efficient chemoenzymatic route to methyl 4-*O*-benzyl-2,3-anhydro-β-D-lyxopyranoside from methyl β-D-xylopyranoside

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Abstract—Methyl 4-*O*-benzyl-2,3-anhydro-β-D-lyxopyranoside, an intermediate for the preparation of methyl β-D-xylopyranoside derivatives modified at C-2, was obtained in five steps in 58% yield. The synthetic sequence starts from methyl β-D-xylopyranoside through two main steps involving regioselective enzymatic acetylation and deacetylation catalyzed by lipase PS.
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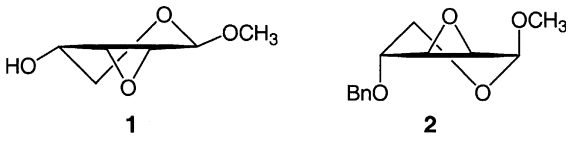
Keywords: 2,3-Anhydropyranosides; Lipase PS; Regioselective acetylation; Regioselective deacetylation

2,3-Anhydropentopyranoside derivatives find wide application in the synthesis of modified pentopyranoside compounds due to easy regioselective opening of the epoxide functionality by various nucleophiles.[1] Recently, the interest in modified or regioselectively acylated β-D-xylopyranosides increased due to the development of studies focused on substrate specificity and mode of action of acetylxylanesterases[2,3] or xylanases.[4] Methyl 2,3-anhydro-β-D-ribopyranoside (**1**)[5] and methyl 4-*O*-benzyl-2,3-anhydro-β-D-lyxopyranoside (**2**) (Fig. 1) are convenient starting materials for the preparation of β-D-xylopyranoside derivatives modified at C-3 or C-2, respectively. Recently, we have reported a four-step synthesis of **2** from **1**.[6] However, the preparation of **1** from methyl β-D-xylopyranoside (**3**) still requires four steps, which means that the preparation of **2** from **3** involves eight steps.



1 2

Figure 1. Key anhydropentopyranoside derivatives for the synthesis of modified pentopyranosides.

Use of lipases for the regioselective acylation or deacylation of carbohydrate hydroxyl groups at a preparative scale begins to be a standard protection or deprotection method in carbohydrate chemistry.[7] In our literature search, we have found lipase PS-30 (from *Burkholderia cepacia*) to be a very convenient enzyme capable to operate regioselectively at OH-3 or OH-4 of xylopyranoside compounds.[8,9] Moreover, it is relatively stable in a large variety of organic solvents and is reusable repeatedly for several times.

In this note, we report a short and efficient chemoenzymatic synthesis of methyl 4-*O*-benzyl-2,3-anhydro-β-D-lyxopyranoside (**2**) from the readily available methyl β-D-xylopyranoside (**3**). As illustrated in Scheme 1, our route to **2** begins with the known regioselective enzymatic *O*-diacetylation of **3** by lipase PS-30 (Amano).[9] We have slightly modified this step by the use of *t*-BuOH as a reaction medium instead of the toxic acetonitrile and in order to increase the solubility of the starting compound and the rate of the reaction. After 48 h of shaking, the 3,4-diacetate **4** was formed in 87% yield as the only diacetylated product. We did not observe any formation of the corresponding triacetate. Treatment of **4** with *p*-toluenesulfonyl chloride in pyridine provided the C-2-tosylate **5**, which was easily purified by

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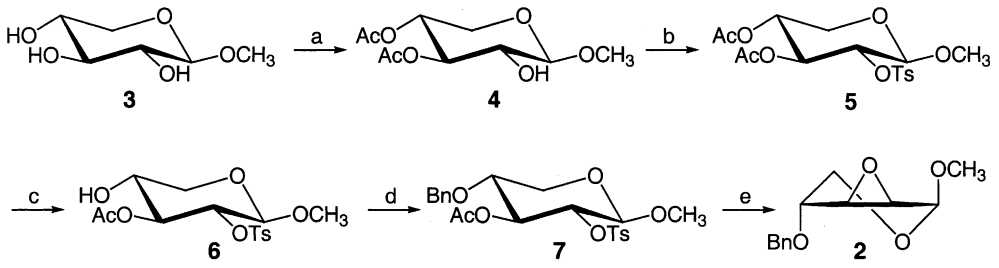

Scheme 1. Reagents and conditions: (a) Lipase PS-30, vinyl acetate, *t*-BuOH, 87%; (b) TsCl, Pyr, rt, 88%; (c) Lipase PS-30, toluene, *n*-BuOH, 89%; (d) $BnOCNHCCl_3$, CF_3SO_3H, rt, 91%; (e) $NaOCH_3$, CH_3OH, 93%.

crystallisation from ethanol (88%). The key step of this synthetic sequence is the regioselective deacetylation at OH-4 of **5** by enzymatic alcoholysis. Fortunately, treatment of **5** with lipase PS in toluene in the presence of *n*-butanol afforded only the 4-*O*-deacetylated product **6** in high yield, the tosylated group remaining intact. Mild benzylation of OH-4 of **6** was successfully achieved with benzyl trichloroacetimidate[10] in the presence of trifluoromethanesulfonic acid giving **7** in 91% isolated yield. The introduction of a stable benzyl group at C-4 avoids further epoxide-ring migration and formation of an equilibrium between the D-*lyxo*-2,3-epoxide and its isomerisation product D-*arabino*-3,4-epoxide in solution. The preparation of methyl 2,3-anhydro-4-*O*-benzyl-β-D-lyxopyranoside (**2**) was accomplished in 93% yield by the treatment of tosylate **7** with sodium methoxide in methanol and simultaneous deacetylation.

In summary, we report an efficient and straightforward chemoenzymatic synthesis of methyl 4-*O*-benzyl-2,3-anhydro-β-D-lyxopyranoside (**2**) from methyl β-D-xylopyranoside (**3**). The preparation involves two main steps catalyzed by the same lipase but under different reaction conditions, that is regioselective 3,4-*O*-diacetylation of **3** and regioselective 4-*O*-deacetylation of **5**. The epoxide **2** is obtained in 58% overall yield from **3** in five steps.

1. Experimental

1.1. General methods

Solvents were distilled in the presence of appropriate drying agents before use. Lipase PS-30 was a gift from Amano (Japan). Methyl β-D-xylopyranoside was purchased from a commercial source (Lachema). All reactions were monitored by TLC on Silica Gel 60 (0.25 mm, E. Merck). Compounds were detected with 1% orcinol in a 10% (v/v) ethanolic soln of H_2SO_4. Column chromatography was performed on Silica Gel 60 (100–160 μm). Melting points were determined on a Kofler hot stage and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter at 20 °C. ^1H spectra were recorded at 300 MHz with a Bruker AM 300 spectrometer and chemical shifts are referred to Me_4Si as internal standard. ^{13}C NMR spectra were recorded in $CDCl_3$ at 75 MHz and shifts are referred to internal $CDCl_3$. Microanalyses were performed with a Fisons EA 1108 analyzer.

1.2. Methyl 3,4-di-*O*-acetyl-β-D-xylopyranoside (4)

Vinyl acetate (11.2 mL, 122 mmol, 20 equiv), Lipase PS (9 g) and 4 Å molecular sieves (8 g) were added to a soln of **3** (1 g, 6.1 mmol) in *t*-BuOH (150 mL). The reaction mixture was shaken at 40 °C and 200 rpm for 48 h. The reaction was stopped by filtration of lipase, which was repeatedly used for about 4 another times in the same reaction. The filtrate was concentrated and the residue was purified by column chromatography (1:2 toluene–EtOAc) to give **4** as white solid, which was washed with diethyl ether (1.32 g, 87%): mp 113–114 °C (from EtOAc); $[\alpha]_D^{20}$ −29 (*c* 1.0, $CHCl_3$); lit.[9] mp 110 °C (transition temperature) → 120 °C; $[\alpha]_D$ −32 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.05 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 2.53 (d, 1H, $J_{H-OH,H-2}$ 3.5 Hz, H–OH), 3.34 (dd, 1H, $J_{4,5a}$ 9.4, $J_{5a,5b}$ 11.7 Hz, H-5a), 3.51 (ddd, $J_{1,2}$ 7.1 Hz, $J_{2,3}$ 8.9 Hz, H-2), 3.54 (s, 3H, OCH_3), 4.09 (dd, 1H, $J_{4,5b}$ 5.3 Hz, H-5b), 4.25 (d, H-1), 4.94 (dt, 1H, $J_{3,4}$ 8.9 Hz, H-4), 5.09 (t, 1H, H-3). Anal. calcd for $C_{10}H_{16}O_7$: C, 48.39; H, 6.50. Found: C, 48.35; H, 6.88.

1.3. Methyl 3,4-di-*O*-acetyl-2-*O*-tosyl-β-D-xylopyranoside (5)

Diacetate **4** (4.92 g, 19.8 mmol) was dissolved in pyridine (30 mL) in the presence of a catalytic amount of 4-dimethylaminopyridine (0.5 g). *p*-Toluenesulfonyl chloride (5.73 g, 30 mmol) was added at 0 °C and the mixture was stirred at room temperature. After 72 h, the soln was poured on ice (30 g) and the crude precipitate was crystallised from 95% EtOH (7.0 g, 88%): mp 152–153 °C; $[\alpha]_D^{20}$ −24 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.02 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$), 2.44 (s, 3H, CH_3), 3.27 (s, 3H, OCH_3), 3.32 (dd, 1H, $J_{4,5a}$ 9.0, $J_{5a,5b}$ 11.8 Hz, H-5a), 4.08 (dd, 1H, $J_{4,5b}$ 5.2 Hz, H-5b), 4.30

(d, $J_{1,2}$ 6.9 Hz, H-1), 4.52 (dd, $J_{2,3}$ 8.9 Hz, H-2), 4.93 (dt, 1H, $J_{3,4}$ 8.8 Hz, H-4), 4.94 (t, 1H, H-3), 7.32 (d, 2H, *J* 8.1 Hz, H-3′,5′), 7.78 (d, 2H, *J* 8.3 Hz, H-2′,6′); ^{13}C NMR ($CDCl_3$): δ 20.7 (2×CO*C*H$_3$), 21.6 (CH_3), 56.8 (OCH_3), 62.2 (C-5), 69.0 (C-4), 70.8 (C-3), 77.9 (C-2), 101.5 (C-1), 2×128.00, 2×129.5, 134.3, 144.7 (C–Ar), 169.8 (*C*OCH$_3$), 169.9 (*C*OCH$_3$). Anal. calcd for $C_{17}H_{22}O_9S$: C, 50.74; H, 5.51; S, 7.97. Found: C, 50.87; H, 5.77; S, 8.18.

1.4. Methyl 3-*O*-acetyl-2-*O*-tosyl-β-D-xylopyranoside (6)

Compound **5** (1 g, 2.5 mmol) was dissolved in toluene (100 mL), then *n*-BuOH (0.8 mL) and Lipase PS (5 g) were added. The reaction mixture was shaken at 40 °C and 200 rpm until complete disappearance of **5** (about 4–5 days). The reaction was stopped by filtration of the lipase. The regenerated lipase was used for the same reaction for another two or three runs. The solvent was eliminated under diminished pressure and the product was separated from the starting compound (about 5%) by column chromatography (2:1 toluene–EtOAc) to give **6** as a colourless oil, which precipitated in diethylether as a white solid (0.8 g, 89%): mp 108–110 °C; $[\alpha]_D^{20}$ −27 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.10 (s, 3H, $COCH_3$), 2.44 (s, 3H, CH_3), 2.74 (d, 1H, $J_{H-OH,H-4}$ 5.9 Hz, H–OH), 3.25 (s, 3H, OCH_3), 3.30 (dd, 1H, $J_{4,5a}$ 9.4, $J_{5a,5b}$ 11.8 Hz, H-5a), 3.79 (m, 1H, H-4), 4.03 (dd, 1H, $J_{4,5b}$ 5.2 Hz, H-5b), 4.28 (d, $J_{1,2}$ 7.1 Hz, H-1), 4.49 (dd, $J_{2,3}$ 8.9 Hz, H-2), 4.94 (t, 1H, $J_{3,4}$ 8.8 Hz, H-3), 7.32 (d, 2H, *J* 8.1 Hz, H-3′,5′), 7.79 (d, 2H, *J* 8.3 Hz, H-2′,6′); ^{13}C NMR ($CDCl_3$): δ 20.8 (CO*C*H$_3$), 21.6 (CH_3), 56.8 (OCH_3), 65.1 (C-5), 68.9 (C-4), 75.1 (C-3), 78.0 (C-2), 101.6 (C-1), 2×127.9, 2×129.4, 134.6, 144.6 (C–Ar), 171.8 (*C*OCH$_3$). Anal. calcd for $C_{15}H_{20}O_8S$: C, 49.99; H, 5.59; S, 8.90. Found: C, 50.35; H, 5.95; S, 8.76.

1.5. Methyl 3-*O*-acetyl-4-*O*-benzyl-2-*O*-tosyl-β-D-xylopyranoside (7)

Compound **6** (3.6 g, 10 mmol) and benzyl trichloroacetimidate (3.72 mL, 20 mmol) were dissolved in dry 2:1 cyclohexane–CH_2Cl_2 (90 mL). After cooling to −5 °C, trifluoromethanesulfonic acid (0.44 mL, 5 mmol) was added slowly and the reaction mixture was stirred for 3 h under N_2 at room temperature. Then CH_2Cl_2 (200 mL) was added and the soln was washed with aq saturated $NaHCO_3$, dried over $MgSO_4$ and evaporated. The crude oil was chromatographed (1:0 → 5:1 toluene–EtOAc) to obtain a slowly solidifying product **7** (4.10 g, 91%): mp 71–73 °C (from *i*-PrOH); $[\alpha]_D^{20}$ −29 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.02 (s, 3H, $COCH_3$), 2.42 (s, 3H, CH_3), 3.24 (s, 3H, OCH_3), 3.26 (dd, 1H, $J_{4,5a}$ 9.9, $J_{5a,5b}$ 11.8 Hz, H-5a), 3.60 (dt, 1H, $J_{3,4}$ 9.2 Hz, H-4), 3.96 (dd, 1H, $J_{4,5b}$ 5.2 Hz, H-5b), 4.22 (d, $J_{1,2}$ 7.4 Hz, H-1), 4.44 (dd, $J_{2,3}$ 9.3 Hz, H-2), 4.56 (s, 2H, CH_2), 5.21 (t, 1H, H-3), 7.24–7.34 (m, 7H, H–Ph, H-3′,5′), 7.76 (d, 2H, *J* 8.3 Hz, H-2′,6′); ^{13}C NMR ($CDCl_3$): δ 20.8 (CO*C*H$_3$), 21.6 (CH_3), 56.9 (OCH_3), 63.7 (C-5), 72.7 (C-3), 73.0 (CH_2), 75.2 (C-4), 78.7 (C-2), 101.8 (C-1), 127.7, 128.0, 128.5, 129.4, 129.6 (7×CH–Ar), 134.5, 137.5, 144.5 (3×C–Ar), 169.9 (*C*OCH$_3$). Anal. calcd for $C_{22}H_{26}O_8S$: C, 58.66; H, 5.82; S, 7.12. Found: C, 58.55; H, 6.12; S, 7.10.

1.6. Methyl 4-*O*-benzyl-2,3-anhydro-β-D-lyxopyranoside (2)

The soln of **7** (2.50 g, 5.6 mmol) in 0.7 M sodium methoxide (22 mL) was stirred overnight at room temperature. It was then neutralised with 1 M H_2SO_4 and the product was extracted with CH_2Cl_2 (3×40 mL). The organic layer was washed twice with water, dried over Na_2SO_4 and concentrated under diminished pressure. The crude syrup was purified by column chromatography (2:1 toluene–EtOAc) to afford epoxide **2** (1.23 g, 93%) as a colourless oil: $[\alpha]_D^{20}$ −77 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 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); ^{13}C NMR ($CDCl_3$): δ 50.5 (C-3), 51.5 (C-2), 55.8 (OCH_3), 58.6 (C-5), 70.4 (C-4), 72.0 (CH_2), 94.9 (C-1), 2×127.9, 128.1, 2×128.6, 137.6 (C–Ph). Anal. calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.67; H, 6.97.

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