

# Lipase-mediated transformation of D-xylose and D-galactose into less common L-aldoses

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Xylitol and dulcitol have been converted into L-xylose and L-fucose, respectively, by employing lipase-mediated enantioselective deacylation or acylation of their cyclic acetal derivatives as the key step.

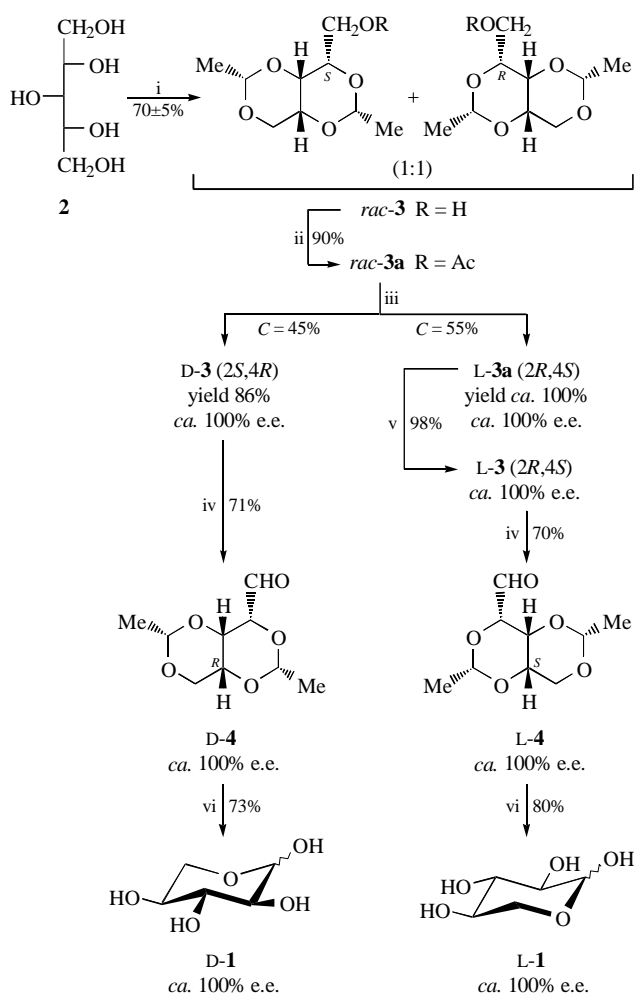
As a part of our studies on the enantioselective hydrolysis of various racemic esters catalysed by porcine pancreatic lipase (PPL), the hydrolysis of 1-*O*-acetyl-2,4:3,5-di-*O*-methylidene-DL-xylitol was shown to afford 2,4:3,5-di-*O*-methylidene-L-xylitol of *ca.* 100% enantiomeric purity.<sup>1</sup> In principle, this transformation might be used as a short cut to the 'unnatural' L-xylose from its abundant D-counterpart; however, the difficulty of removing the *O*-methylidene protecting groups was an obstacle to achieving this. On the other hand, PPL-catalysed hydrolysis of the corresponding di-*O*-benzylidene derivative was practically devoid of enantioselectivity.<sup>1</sup>

Now we report the preparation of L-xylose (L-1) from xylitol 2 using PPL-catalysed hydrolysis of 1-*O*-acetyl-2,4:3,5-di-*O*-ethylidene-DL-xylitol (*rac*-3a) as the key step. Acetate *rac*-3a was obtained from 2 in two conventional steps *via* racemic alcohol *rac*-3 (Scheme 1). In contrast with its di-*O*-methylidene analogue, at 45% conversion *rac*-3a gave not levorotatory, but dextrorotatory alcohol D-3 {[ $\alpha$ ]<sub>D</sub><sup>22</sup> +3.6°, (*c* 1.0, H<sub>2</sub>O)}.<sup>†</sup> Using Pfizner–Moffatt oxidation, the latter was converted into aldehyde D-4 {mp 164 °C (sublimed), [ $\alpha$ ]<sub>D</sub><sup>22</sup> +13.4°, (*c* 1.0, H<sub>2</sub>O)} which was deprotected to afford practically enantiopure D-xylose {[ $\alpha$ ]<sub>D</sub><sup>22</sup> +73.9° (15 min) → +18.8° (2 h), (*c* 1.0, H<sub>2</sub>O)}. The enantiomeric purity of intermediate D-3 was confirmed by the <sup>19</sup>F and <sup>1</sup>H NMR spectra of its (*S*)-MTPA ester.

In order to obtain the required enantiopure alcohol L-3, enzymatic hydrolysis of *rac*-3a was extended to 55% conversion. Column chromatography on SiO<sub>2</sub> or, better, partitioning of the products between the aqueous phase and CHCl<sub>3</sub> followed by filtration of the concentrated organic layer through a pad of SiO<sub>2</sub> using hexane–AcOEt (2:1, v/v) as the eluent afforded acetate L-3a as a microcrystalline solid {mp 55–56 °C (from petroleum ether, –60 °C), [ $\alpha$ ]<sub>D</sub><sup>22</sup> +7.30°, (*c* 1.0, CHCl<sub>3</sub>)}. This was saponified to give enantiopure L-3 {[ $\alpha$ ]<sub>D</sub><sup>22</sup> –3.5°, (*c* 1.0, H<sub>2</sub>O)}<sup>†</sup> whose <sup>1</sup>H and <sup>13</sup>C NMR spectra contained only signals attributable to the diequatorial diastereoisomer, while its (*S*)-MTPA ester displayed no signals attributable to the D-counterpart in its <sup>19</sup>F and <sup>1</sup>H NMR spectra. Oxidation of L-3 resulted in 2,4:3,5-di-*O*-ethylidene-L-xylose (L-4) with mp 162–164 °C (sublimed) and [ $\alpha$ ]<sub>D</sub><sup>22</sup> –13.4°, (*c* 1.0, H<sub>2</sub>O). Lit.,<sup>2</sup> mp 152–160 °C, [ $\alpha$ ]<sub>D</sub><sup>20</sup> –13.2° (H<sub>2</sub>O). Acid-catalysed hydrolysis of diacetal L-4 gave the target L-xylose with mp 145–146 °C (from EtOH) and [ $\alpha$ ]<sub>D</sub><sup>22</sup> –76.3° (15 min) → –18.4° (2 h) (*c* 1.0, H<sub>2</sub>O). Lit.,<sup>3</sup> mp 144 °C, [ $\alpha$ ]<sub>D</sub><sup>20</sup> –79.3° → –18.6° (H<sub>2</sub>O).

Allowing for 55% conversion of *rac*-3a at the enzymatic kinetic resolution step, the material yield of L-1 from 2 is about 16% over six steps of the synthesis. This is comparable with earlier syntheses of L-1 from other sugars.<sup>3,4</sup> Since *meso*-pentaol 2 is obtained directly from D-1, this work represents a formal synthesis of L-1 from D-1 based on controlled asymmetrization of a *meso* precursor ('*meso*-trick').

An alternative PPL-mediated approach from 2 to L-1,

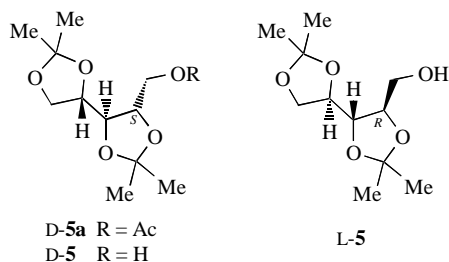


**Scheme 1** Reagents and conditions: i, MeCHO (3 equiv.)/conc. HCl, 50 °C, 3 h; ii, Ac<sub>2</sub>O–DMAP/Py, 20 °C; iii, H<sub>2</sub>O (pH 7)/PPL, 20 °C, 19–25 h; iv, dicyclohexylcarbodiimide (DCC) (3 equiv.)–H<sub>3</sub>PO<sub>4</sub> (0.5 equiv.)–DMSO, 20±2 °C, 16 h; v, KOH (1 equiv.)/MeOH, 20 °C, 3 h; vi, H<sub>2</sub>O–Me<sub>2</sub>CO (1:2, v/v)–H<sub>2</sub>SO<sub>4</sub> (cat.), 60 °C, 7 h.

involving the transformation of 2 into 1-*O*-acetyl-2,3,4,5-di-*O*-isopropylidene-DL-xylitol (*rac*-5a) *via* the corresponding alcohol (*rac*-5)<sup>5</sup> and enzymatic hydrolysis of *rac*-5a to 35–45% conversion, proved to be inefficient. In this case the e.e. of the resulting alcohol L-5 {mp 34–35 °C (from hexane, –60 °C), [ $\alpha$ ]<sub>D</sub><sup>22</sup> +3.25° (*c* 2.0, EtOH)} was only 26–28%. Lit. (for L-5),<sup>6</sup> mp 33–35 °C (from hexane, –60 °C), [ $\alpha$ ]<sub>D</sub><sup>18</sup> +12.5° (*c* 2.0, EtOH). When the unconverted fraction of the acetate (*i.e.*, mainly D-5a) was again hydrolysed in the presence of PPL to 38% conversion, and residual D-5a was saponified, the specimen of alcohol D-5 thus obtained {mp 33–35 °C (from hexane, –60 °C), [ $\alpha$ ]<sub>D</sub><sup>22</sup> –3.6° (*c* 2.0, EtOH)} had about 29% e.e.

Another example of lipase-mediated '*meso*-trick' strategy in carbohydrate chemistry is represented by the formal synthesis

<sup>†</sup> Although our specimens of D-3 and L-3 had mp 139–140 °C (from AcOEt), whereas earlier<sup>2</sup> mp 164–165 °C was reported for L-3, the [ $\alpha$ ]<sub>D</sub> values of both specimens almost coincided with those reported in ref. 2, and the NMR spectra of their (*S*)-MTPA esters were in good agreement with the assigned structures.



of L-fucose **6** from D-galactose, where dulcitol **7** was used as the starting material. At the beginning [Scheme 2(A)], **7** was converted into a mixture of two isomeric diacetonides, where the major component had a symmetric *meso* structure **8** and the minor one was racemic (*rac*-**9**  $\equiv$  **9** + *ent*-**9**, 1:1). The required *meso* diol **8** was isolated from its mixture with *rac*-**9** either by fractional crystallisation (*cf.* ref. 7) or by converting this mixture into the corresponding diacetates **8a** and *rac*-**9a**, isolating the poorly soluble **8a** by recrystallisation, and saponifying it back to **8**. Originally, it was planned to asymmetricize **8a** by PPL-catalysed hydrolysis. However, even at rather low substrate-to-enzyme ratios (**8a**:PPL = 1:2, w/w) and long exposures (72–120 h) no conversion of **8a** was detected.

As an alternative, controlled acylation of diol **8** using vinyl acetate and the lipase from *Candida rugosa* (= *C. cylindracea*, CCL, Fluka, 2U mg<sup>-1</sup>) as the catalyst was

undertaken [Scheme 2(B)]. At optimal exposures (19–23 h) the yield of levorotatory monoacetate **10** {mp 71–72 °C (from Et<sub>2</sub>O–hexane), [ $\alpha$ ]<sub>D</sub><sup>22</sup> –9.02° (c 1.0, CHCl<sub>3</sub>)} amounted to 40–43%, the recovery of diol **8** and the yield of diacetate **8a** being 47% and 8%, respectively. Longer exposures increased the yield of **10** up to 73%, but at the expense of *e.e.* ([ $\alpha$ ]<sub>D</sub><sup>22</sup> –6.4° after 44 h). Mesylation of **10** and subsequent treatment of mesylate **11** with NaI led to the wax-like iodide **12** (mp 45–47 °C) which was cleanly hydrogenolysed (with concomitant deacylation) over skeletal Ni in the presence of K<sub>2</sub>CO<sub>3</sub> in MeOH to give the known<sup>8</sup> 2,3:4,5-di-*O*-isopropylidene-L-fucitol **13** with mp 59–59.5 °C (from hexane) and [ $\alpha$ ]<sub>D</sub><sup>22</sup> +11.63° (c 1.0, EtOH).

Finally, alcohol **13** was oxidised into the corresponding oxo-diketal **14**, and the latter was immediately hydrolysed to give the target sugar **6** {mp 138–140 °C (from EtOH), [ $\alpha$ ]<sub>D</sub><sup>22</sup> –110° (15 min)  $\rightarrow$  –74.7° (4 h) (c 0.95, H<sub>2</sub>O)}. Lit.,<sup>9</sup> {mp 137–139 °C (from EtOH), [ $\alpha$ ]<sub>D</sub><sup>22</sup> –75° (24 h) (c 0.95, H<sub>2</sub>O)}. Taking into account the content of **8** in the starting mixture of isomeric diols, the yield of L-fucose from **7** was *ca.* 6% over nine steps. This is comparable with earlier syntheses of **6** from other sugar derivatives.<sup>9,10</sup>

Our results confirm the usefulness of lipases in carbohydrate synthesis (*cf.* reviews 11 and 12).

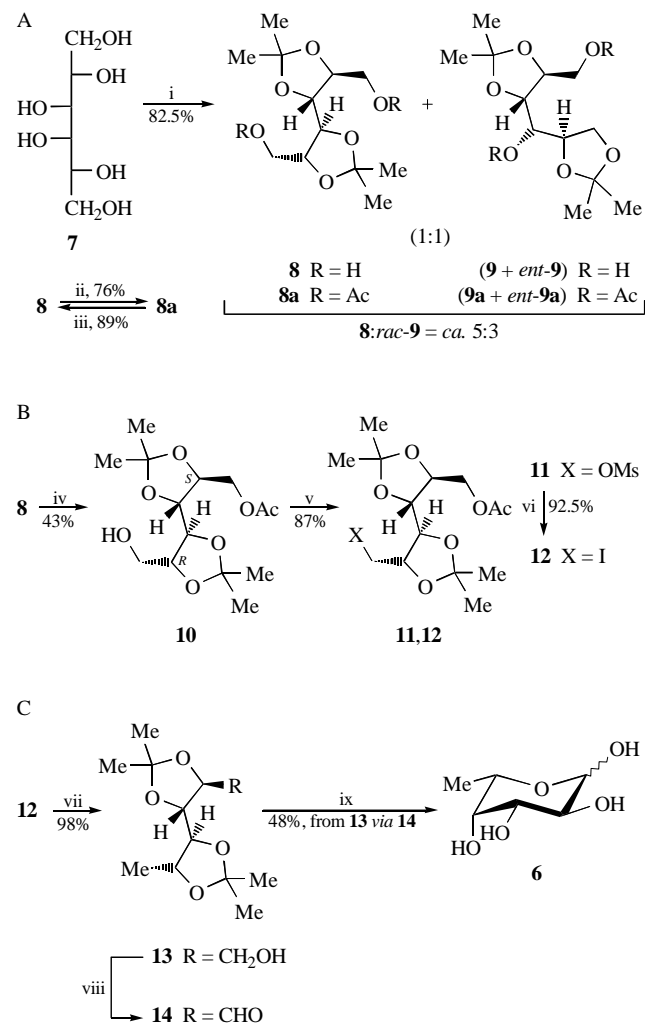
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**Scheme 2** Reagents and conditions: i, Me<sub>2</sub>CO–conc. H<sub>2</sub>SO<sub>4</sub> (cat.), 20 °C, 1 h; ii, Ac<sub>2</sub>O/Py; iii, KOH/MeOH, 20 °C, 90 min; iv, H<sub>2</sub>C=CHOAc (3 equiv.)–CCL (1 equiv., w/w)/Et<sub>2</sub>O, 22 ± 2 °C; v, MsCl (1.1 equiv.)/Py–CHCl<sub>3</sub>, 20 °C, 48 h; vi, NaI/Me<sub>2</sub>CO, 60 °C, 48 h; vii, H<sub>2</sub>–Ni (cat.)–K<sub>2</sub>CO<sub>3</sub>/MeOH, 20 °C, 1 atm, 3 h; viii, DCC (3 equiv.)–H<sub>3</sub>PO<sub>4</sub> (cat.)–DMSO, 20 °C, 18 h; ix, AcOH–H<sub>2</sub>O (6:4, v/v), 100 °C, 2 h.