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.[1] 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.[1]

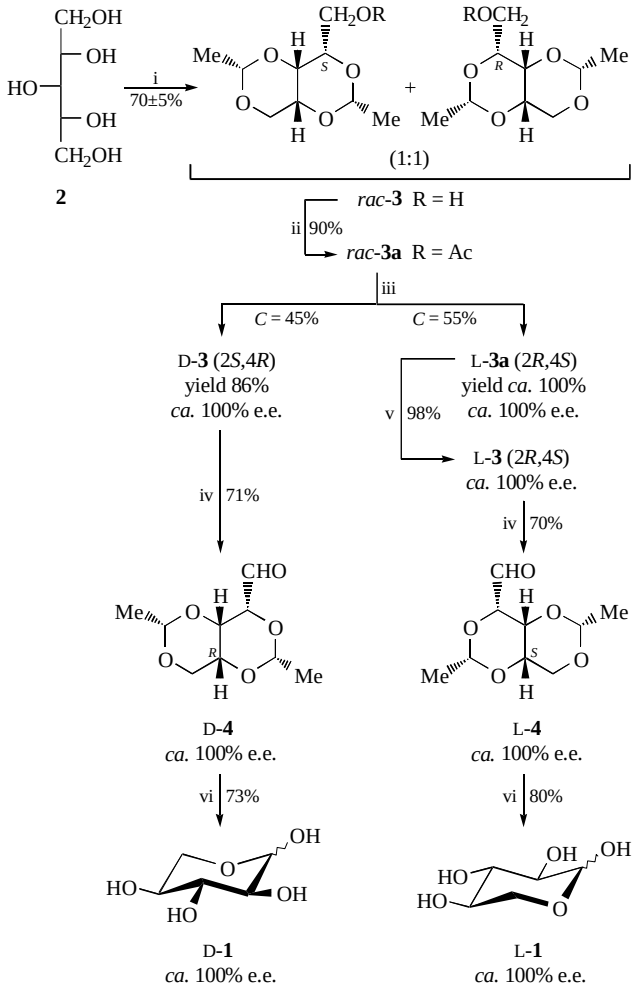
Now we report the preparation of L-xylose (L-**1**) from xylitol **2** using PPL-catalysed hydrolysis of 1-*O*-acetyl-2,4:3,5-di-*O*-ethylidene-DL-xylitol (*rac*-**3a**) as the key step. Acetate *rac*-**3a** was obtained from **2** in two conventional steps *via* racemic alcohol *rac*-**3** (Scheme 1). In contrast with its di-*O*-methylidene analogue, at 45% conversion *rac*-**3a** gave not levorotatory, but dextrorotatory alcohol D-**3** {$[\alpha]_D^{22}$ +3.6°, (*c* 1.0, H_2O)}.† Using Pfitzner–Moffatt oxidation, the latter was converted into aldehyde D-**4** {mp 164 °C (sublimed), $[\alpha]_D^{22}$ +13.4°, (*c* 1.0, H_2O)} which was deprotected to afford practically enantiopure D-xylose {$[\alpha]_D^{22}$ +73.9° (15 min) → +18.8° (2 h), (*c* 1.0, H_2O)}. The enantiomeric purity of intermediate D-**3** was confirmed by the ^{19}F and ^1H 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_2 or, better, partitioning of the products between the aqueous phase and $CHCl_3$ followed by filtration of the concentrated organic layer through a pad of SiO_2 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), $[\alpha]_D^{22}$ +7.30°, (*c* 1.0, $CHCl_3$)}. This was saponified to give enantiopure L-**3** {$[\alpha]_D^{22}$ –3.5°, (*c* 1.0, H_2O)}† whose ^1H and ^{13}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 ^{19}F and ^1H 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 $[\alpha]_D^{22}$ –13.4°, (*c* 1.0, H_2O). Lit.,[2] mp 152–160 °C, $[\alpha]_D^{20}$ –13.2° (H_2O). Acid-catalysed hydrolysis of diacetal L-**4** gave the target L-xylose with mp 145–146 °C (from EtOH) and $[\alpha]_D^{22}$ –76.3° (15 min) → –18.4° (2 h) (*c* 1.0, H_2O). Lit.,[3] mp 144 °C, $[\alpha]_D^{20}$ –79.3° → –18.6° (H_2O).

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.[3,4] 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').

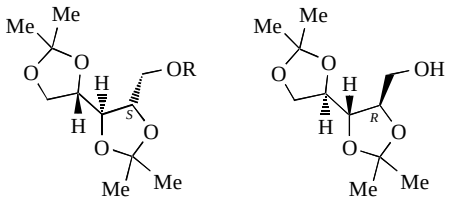
An alternative PPL-mediated approach from **2** to L-**1**, involving the transformation of **2** into 1-*O*-acetyl-2,3:4,5-di-*O*-isopropylidene-DL-xylitol (*rac*-**5a**) *via* the corresponding alcohol (*rac*-**5**)[5] and enzymatic hydrolysis of *rac*-**5a** to 35–45% conversion, proved to be inefficient. In this case the e.e. of the resulting alcohol L-**5** {mp 34–35 °C (from hexane, –60 °C), $[\alpha]_D^{22}$ +3.25° (*c* 2.0, EtOH)} was only 26–28%. Lit. (for L-**5**),[6] mp 33–35 °C (from hexane, –60 °C), $[\alpha]_D^{18}$ +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), $[\alpha]_D^{22}$ –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



Scheme 1 *Reagents and conditions*: i, MeCHO (3 equiv.)/conc. HCl, 50 °C, 3 h; ii, Ac_2O–DMAP/Py, 20 °C; iii, H_2O (pH 7)/PPL, 20 °C, 19–25 h; iv, dicyclohexylcarbodiimide (DCC) (3 equiv.)–H_3PO_4 (0.5 equiv.)–DMSO, 20±2 °C, 16 h; v, KOH (1 equiv.)/MeOH, 20 °C, 3 h; vi, H_2O–Me_2CO (1:2, v/v)–H_2SO_4 (cat.), 60 °C, 7 h.

† Although our specimens of D-**3** and L-**3** had mp 139–140 °C (from AcOEt), whereas earlier[2] mp 164–165 °C was reported for L-**3**, the $[\alpha]_D$ 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.



D-**5a** R = Ac
D-**5** R = H

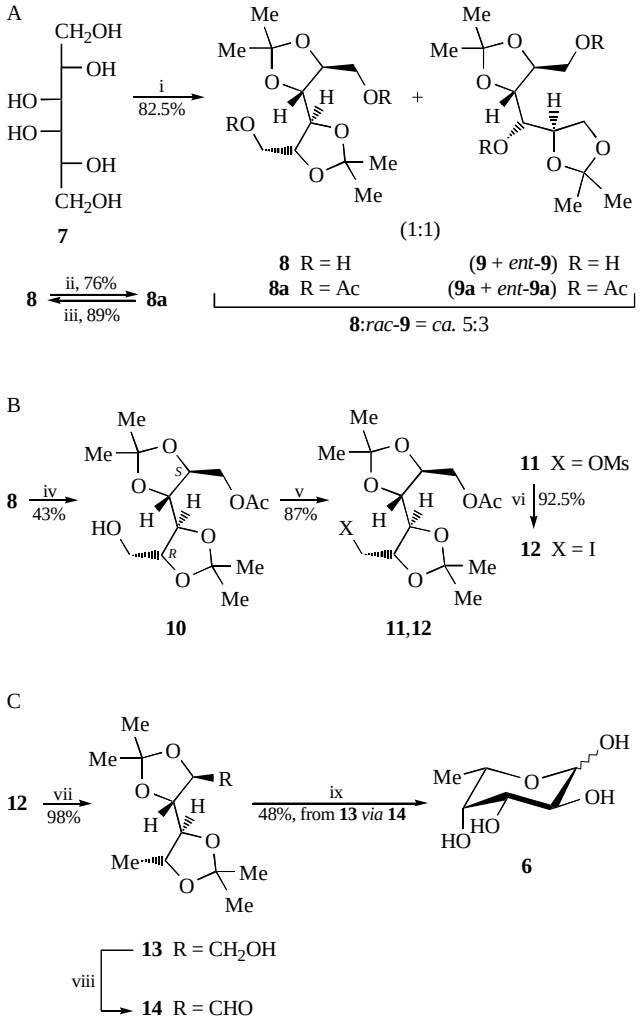
L-**5**

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**≡**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 asymmetrize **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^{-1}) 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_2O–hexane), $[\alpha]_D^{22}$ –9.02° (*c* 1.0, $CHCl_3$)} 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. ($[\alpha]_D^{22}$ –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_2CO_3 in MeOH to give the known[8] 2,3:4,5-di-*O*-isopropylidene-L-fucitol **13** with mp 59–59.5 °C (from hexane) and $[\alpha]_D^{22}$ +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), $[\alpha]_D^{22}$ –110° (15 min) → –74.7° (4 h) (*c* 0.95, H_2O)}. Lit.,[9] {mp 137–139 °C (from EtOH), $[\alpha]_D$ –75°(24 h) (*c* 0.95, H_2O)}. 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.[9,10]

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



Scheme 2 *Reagents and conditions*: i, Me_2CO–conc. H_2SO_4 (cat.), 20 °C, 1 h; ii, Ac_2O/Py; iii, KOH/MeOH, 20 °C, 90 min; iv, H_2C=CHOAc (3 equiv.)–CCL (1 equiv., w/w)/Et_2O, 22±2 °C; v, MsCl (1.1 equiv.)/Py–$CHCl_3$, 20 °C, 48 h; vi, NaI/Me_2CO, 60 °C, 48 h; vii, H_2–Ni (cat.)–K_2CO_3/MeOH, 20 °C, 1 atm, 3 h; viii, DCC (3 equiv.)–H_3PO_4 (cat.)–DMSO, 20 °C, 18 h; ix, AcOH–H_2O (6:4, v/v), 100 °C, 2 h.

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