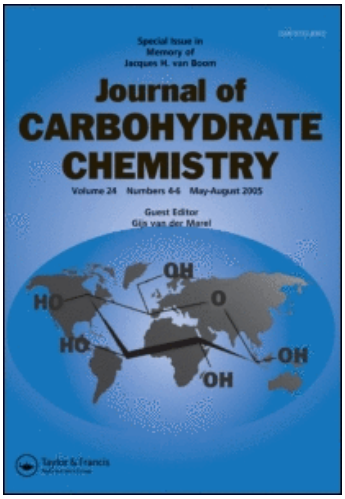

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COMMUNICATION

AN IMPROVED SYNTHESIS OF METHYL 2,3-ANHYDRO-α AND β-D-LYXOFURANOSIDES

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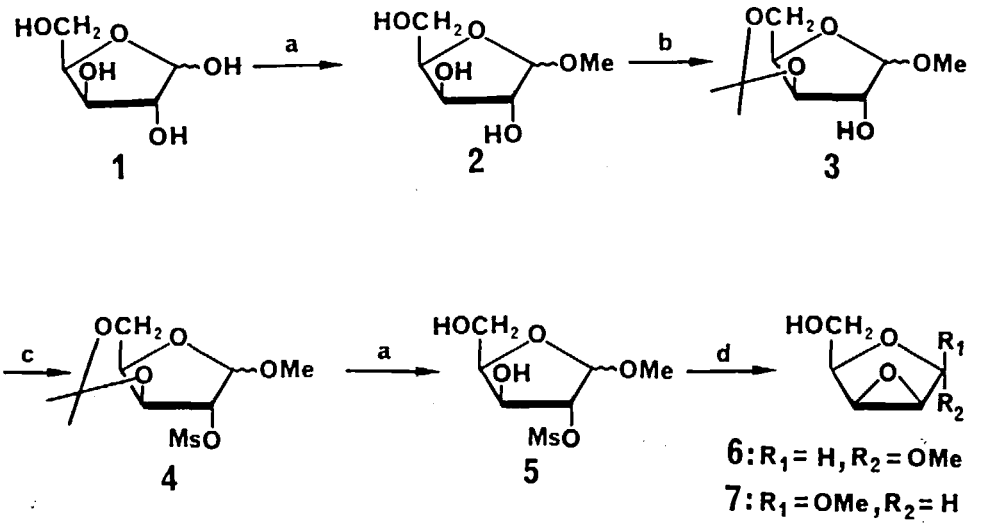
Methyl 2,3-anhydro-α (6) and β (7)-D-lyxofuranosides are important intermediates in the synthesis of C-3 substituted derivatives of D-arabinose which show biological activity as a tumor inhibitor.[1,2] Some syntheses of 6 and 7 are reported but they are either expensive or give poor yields [3-4] and generally the authors refer to Baker and coll.[5] who synthesized both α and β epoxides from D-xylose in five steps ; yields were 28 % and 22 % respectively. This synthesis is very well described but reaction times and workups are long and several intermediates are distilled with difficulty under reduced pressure. Unger and coll.[6], using Baker's method, improved the yield of compound 6 and Martin and coll.[7] described a three steps synthesis of 6 but the final purification is very difficult and the use of mercuric reagents is not consistent with biological activity ; furthermore these two publications concern only α anomer 6.

For the development of a program concerning aminofluorosugars[8] we needed a large quantity (about 10 g) of 6 and 7 ; using the same reaction pathway but changing some reagents (in order to get quantitative conversions in each step using crude intermediates before the final purification) we improved yields of the two first steps and dramatically decreased all reaction times.

Compounds 2 (α and β) were obtained in quantitative yields by treatment of D-xylose 1 with methanol/acetyl chloride. Treatment of crude 2 (α and β inseparable)

with 2-methoxypropene[9] in anhydrous acetone as solvent[10] in the presence of a catalytic amount of camphosulfonic acid led to 3α and 3β in 93 % yield (in 2 h instead of 60[5]). It is possible to separate the two epimers by flash chromatography (ether-light petroleum 1:2) but this is not necessary and **3** can be used as a crude mixture for the next step.



a) MeOH/CH_3COCl ; b) 2-methoxypropene/CSA, acetone ;
c) MsCl, Et_3N/ether ; d) MeONa/MeOH.

Mesylation was performed following Crossland and Servis[11] (2 h instead of 13-20 and neither extraction nor tedious elimination of pyridine was necessary) and the crude mesylates (4α and 4β 100 %) were then added to a mixture of acetyl chloride and methanol for 3,5-deprotection ; after 3 h a solution of sodium methoxide in methanol was added ; 12 h later[12] the reaction was over (instead of 3 days) and we obtained **6** and **7** which were easily separated by flash chromatography (light petroleum-ether 1:2 then light petroleum-acetone 1:1) in about an equal ratio with a 75 % yield. It is noteworthy that it is impossible to separate 4α and 4β on one hand and 5α, 5β, **7** on the other hand.

In conclusion, methyl 2,3-anhydro-α (**6**) and β (**7**)-D-lyxofuranosides were quickly and easily synthesized ; no intermediary purification was necessary, only a final flash chromatography led to **6** (38 %) and **7** (37 %) in five steps and only three days were required for a 10 gram scale preparation, starting from D-xylose.

EXPERIMENTAL

Methyl α and β-D-Xylofuranosides (2). D-xylose (13.5 g) was dissolved in a mixture of methanol (270 mL) and acetyl chloride (2.7 mL). After 30 mn a clear solution was obtained and 3 h later the transformation was completed (TLC acetone) ; silver carbonate (8.1 g) was then added and the mixture was stirred for 2 h (turning pink) followed by filtration through Celite and solvent evaporation yielding 14.6 g (100 %) of 2.

Methyl 3,5-O-Isopropylidene-α and β-D-xylofuranosides (3). The compound 2 (14.6 g) and camphosulfonic acid (0.4 g) were dissolved in anhydrous acetone (130 mL) then cooled to 0 °C before the addition of 2-methoxypropene (9.3 mL, 1.2 eq).[13] After 2 h (TLC methylene chloride-methanol 15:1), potassium carbonate (0.45 g) was added and the mixture was stirred for 1 h then concentrated in vacuo (15 mm, 40 °C) ; ether was added, salts were filtered off and the solvent evaporated to give 3 (17.1 g ; 93 %). By flash chromatography (ether-light petroleum 1:2) it was possible to separate 3α and 3β (5/4 ratio).

Methyl 3,5-O-Isopropylidene-2-O-methanesulfonyl-α and β-D-xylofuranosides (4). Crude 3 (17.1 g) was dissolved in ether (160 mL) and triethylamine (17.6 mL, 1.5 eq). This mixture was cooled to -20 °C then methanesulfonyl chloride (7.1 mL, 1.1 eq) was added dropwise. After 2 h (TLC methylene chloride-methanol 15:1), the solution was filtered and the solvent evaporated to give 4 (23.5 g, 100 %).

Methyl 2-O-Methanesulfonyl-α and β-D-xylofuranosides (5). A mixture of acetyl chloride (1.2 mL, 0.2 eq) in methanol (170 mL) was added to crude 4 (23.5 g). After 30 mn at room temperature, the reaction was completed (TLC methylene chloride-methanol 15:1).

Methyl 2,3-Anhydro-α (6) and β (7)-D-lyxofuranosides. A solution of sodium methoxide (9.2 g, 2eq) in methanol (20 mL) was poured into the preceding mixture and the solution was left 12 h at room temperature.[12] Acetic acid (10 g, 2 eq) was then added and after evaporation of methanol and the addition of ether (800 mL), the solution was filtered through Celite, the filtrate was coevaporated with toluene (until no acetic acid odor remained) and the crude mixture (13 g) was purified by flash chromatography (Merck 60H ether-light petroleum 2:1 then acetone-light petroleum 1:1) to give 5.03 g of 6 (first eluted 38 %) : mp 79 °C (cyclohexane) ; lit.[5] 80-82 °C (benzene) ; $[\alpha]^{22}$ +66.5° (c 1.02, water) ; lit.[5] +67° (c 2, water) ; ^{1}H NMR (300 MHz, $CDCl_3$) 4.96 (s, 1H, H-1) 4.11 (t, 1H, H-4, $J_{4,5}$ = 5.6 Hz) 3.80 (d, 2H, H-5) 3.78* (d, 1H, H-2, $J_{2,3}$ = 2.8 Hz) 3.66* (d, 1H, H-3) 3.42 (s, 3H, OCH_3)

3.30 (m, 1H, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$) 102.2 (C-1) 76.5 (C-4) 61.3 (C-5) 55.9* (C-2) 55.5 (OCH_3) 54.1*(C-3), and 4.9 g of 7 (37 %) : mp 74 °C (ether) ; lit.[5] 74-75 °C (ether) ; $[\alpha]^{25}$ -106.8° (c 1.00, water) ; lit.[5] -102° (c 2, water) ; ^1H NMR (300 MHz, $CDCl_3$) 5.03 (s, 1H, H-1) 4.03 (t, 1H, H-4, $J_{4,5}$ = 5.7 Hz) 3.85 (d, 2H, H-5) 3.76* (d, 1H, H-2, $J_{2,3}$ = 3 Hz) 3.72* (d, 1H, H-3) 3.52 (s, 3H, OCH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$) 102.4 (C-1) 76.8 (C-4) 61.3 (C-5) 56.9 (OCH_3) 55.4* (C-2) 54.9* (C-3).

* δ values can be inverted

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10. Without 2-methoxypropene and even in the presence of anhydrous $CuSO_4$, compounds 3α and 3β were obtained in only 59 % yield after 120 h.
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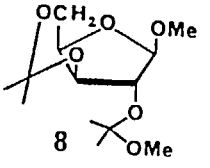
12. It was difficult to know the exact time necessary to complete the reaction. When isomers α and β were used separately, 6 is obtained in only 1 h starting from 5α, but 5β and 7 are inseparable by TLC so we left it to react for 12 h to be sure the transformation was completed.
13. When we used a larger excess of 2-methoxypropene, we observed the formation of a by product 8 whose structure was confirmed by ^1H and ^{13}C NMR. We did not observe the α anomeric compound probably because of steric hindrance.



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