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Dual Course of Bisacetonation of D-Xylose in a System Me_2CO-$Me_2C(OMe)_2$-H_2SO_4

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Abstract—In the course of formation of a bisisopropylidene protective group by keeping D-xylose in a mixture Me_2CO–$(MeO)_2CMe_2$–H_2SO_4 alongside the expected 1,2:4,5-O-diisopropylidene derivative formed minor dimethylacetal, 2,3:4,5-O-diisopropylidene-D-xylose, inseparable from the main product by the chromatography on SiO_2. The conditions were found for the selective formation and isolation of the latter, some its one-pot transformations were studied resulting in synthetically promising orthogonally protected acyclic C^5-synthons.

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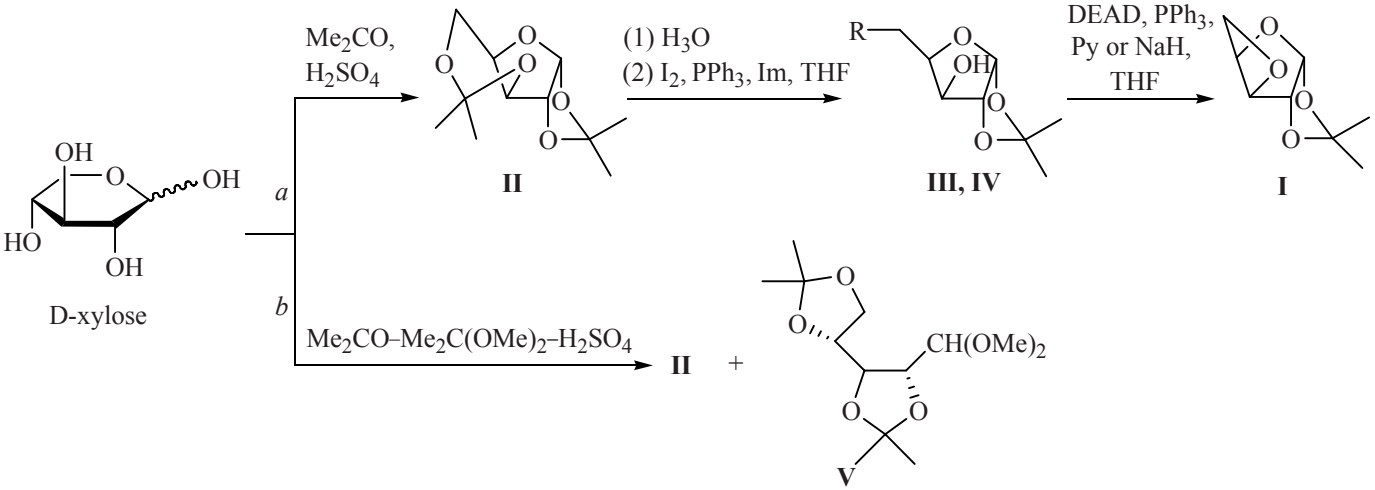
Anhydro derivatives of sugars are internally protected compounds convenient for further regio- and stereoselective transformations (cf., e.g., the structures of levoglucosan and levoglucosenone, oxetano-, epoxysugars etc. with the structures of the parent sugars [1–5]).

We synthesized 3,5-anhydro derivative of a D-xylose **I** from diol **III** by intermolecular ring closure by Mitsunobu reaction [6] along path *a* (Scheme 1). Oxetane **I** can also be obtained in a good yield by intramolecular substitution (S_N2) of iodine in compound **IV** by alkoxide.

Although the preparation of oxetane **I** by the path *a* occurred without complications, still the stage of bisacetonide **II** synthesis provided moderate yields and was time-consuming. Aiming at optimization we carried out the acetonation of D-xylose by a mixture Me_2CO–

Scheme 1.



R = OH (**III**), I (**IV**).

$Me_2C(OMe)_2$–H_2SO_4 (cat.) (path *b*) [7]. However in this event alongside the acetonide **II** formed a significant amount (~20%) of acyclic bisacetonide **V**. In various eluent systems compounds **II** and **V** appeared on TLC plates as a single spot, and we failed to separate them by column chromatography on SiO_2. Therefore the mixture of compounds **II** and **V** was involved into a sequence of transformations modified compared to procedure *a* (stages of preparation of primary iodide from alcohol **III** [8] and ring closure effected by NaH instead of intramolecular cyclization of diol **III** by Mitsunobu reaction [9]) and aimed at the preparation of oxetane **I** (Scheme 2). We hoped that in the course of the progress along the stages the mixture of compounds **II** and **V** would undergo certain "self-purification", and the main product **I** would be obtained in a plausible purity. In the experiment this reaction sequence led to the formation of two compounds: oxetane **I** and epoxy derivative **VI**.

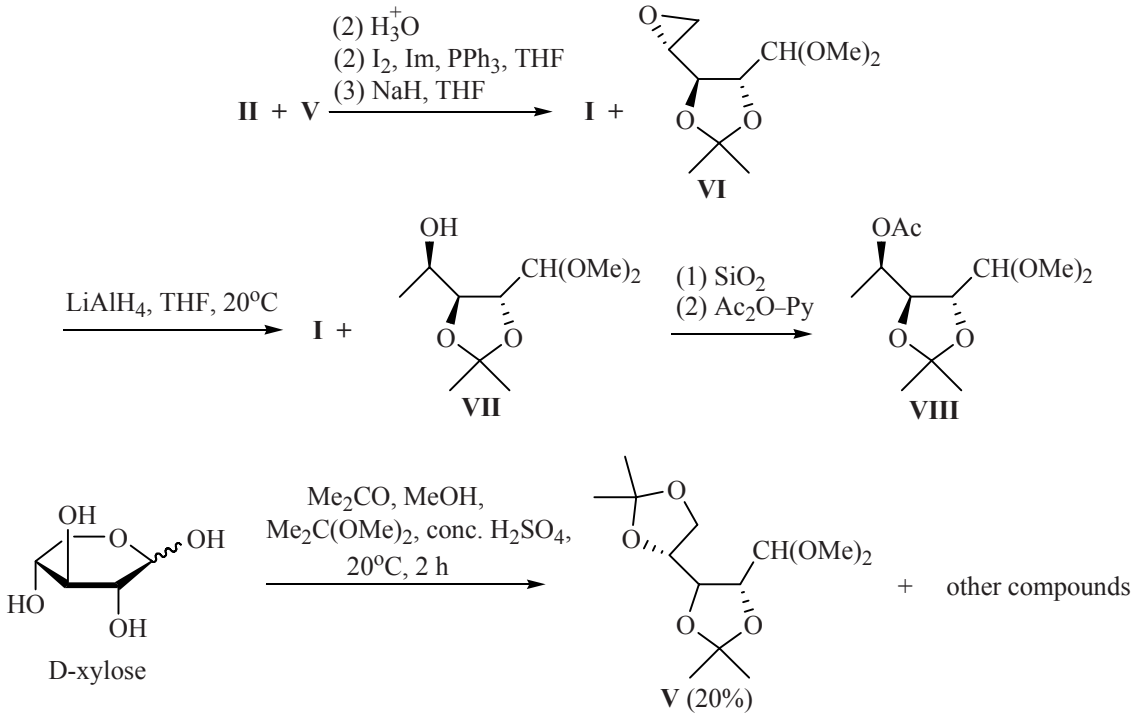
We succeeded in the complete purification of oxetane **I** after treating the mixture of compounds **I** and **VI** with $LiAlH_4$ (THF, 20°C). The formed alcohol **VII** due to its higher polarity was easily separated on SiO_2 from the unreacted oxetane I; alcohol **VII** was characterized as acetate **VIII**.

The formation of acyclic derivative **V** at the preparation of D-xylose acetal was evidently due to the use of 2,2-dimethoxypropane (the "source" of MeOH) aimed at quenching water eliminated at the acetalization of xylose with acetone. The liberated MeOH was involved in the formation of the dimethyl acetal compound **V**. In the cyclic forms of sugars (furanosides, pyranosides) the anomeric hydroxy group is especially active in the formation of glycosides catalyzed by acids in the presence of alcohols. Therefore we believe that the acetalization of D-xylose along the path leading to acyclic acetonide **V** started not by the formation of the dimethyl acetal function at C^1, but the formation of C^4,C^5- or *trans*-C^2,C^3-acetonides that block further cyclization into furanosides and pyranosides.

When at the acetonation of D-xylose along path *b* (Scheme 1) into the reaction mixture was added MeOH, then at incomplete conversion of the initial compound at the beginning of the reaction the TLC test showed a low-polar main spot corresponding to the acetonides mixture of **II** and **V**. However the spectral data of this compound showed that it was the individual minor bisacetonide **V**. As a result we obtained a sample of bisacetonide **V** lacking the impurity of compound **II**.

Thus in the synthesis of oxetane **I** bisacetonide **II** should be used obtained by the H^+-catalyzed reaction of D-xylose with acetone (path *a*) in the absence of $(MeO)_2CMe_2$. Bisacetonide **V**, epoxide **VI**, and acetate

Scheme 2.



VIII formed in the side reactions are synthetically promising new chiral C^5-block synthons.

EXPERIMENTAL

IR spectra were recorded on spectrophotometers UR-20 and Specord M-80 from thin films or mulls in mineral oil. ^1H and ^{13}C NMR spectra were registered on a spectrometer Bruker AM-300 at operating frequencies 300.13 and 75.47 MHz respectively, internal reference TMS. The optical rotation was measured on a polarimeter Perkin Elmer-341. Mass spectra were obtained on an instrument Thermo Finnigan MAT 95XP, 70 eV, ionizing chamber temperature 200°C, sample admission at 5–270°C, heating rate 22 deg/min.

3,5-Anhydro-1,2-*O*-isopropylidene-α-D-xylofuranose (I). To a dispersion of 0.06 g (2.5 mmol) of NaH in 5 ml of THF under an argon atmosphere was slowly added dropwise at stirring a solution of 0.3 g (1.0 mmol) of iodide **IV** in 10 ml of THF. The reaction mixture was stirred at room temperature for 2 h, then it was quenched with a saturated water solution of NH_4Cl (1 ml). THF was distilled off, the reaction product was extracted from the water layer with $CHCl_3$ (3 × 20 ml), the combined extracts were washed with the saturated NaCl solution, dried with $MgSO_4$, evaporated, and the residue was subjected to chromatography on SiO_2. Yield 0.11 g (65%). Oily substance, $[\alpha]_D^{20}$ +11.3° (*c* 0.5, $CHCl_3$) {+11.0° (*c* 1.0, $CHCl_3$) [6], +11.9° (*c* 0.75, $CHCl_3$) [9]}. ^1H NMR spectrum, δ, ppm: 1.37 s (CH_3), 1.40 s (CH_3), 4.25 d.d (1H, H^{5A}, $J_{4,5A}$ 2.2, $J_{5A,5B}$ 7.7, long range constant 0.5 Hz), 4.72 d (1H, H^2, *J* 3.7 Hz), 4.74 d.d (1H, H^{5B}, $J_{4,5B}$ 4.3 Hz), 5.13 d.t (1H, H^4), 5.20 d (1H, H^3, *J* 4.0 Hz), 6.25 d (1H, H^1, $J_{1,2}$ 3.7 Hz). ^{13}C NMR spectrum, δ, ppm: 27.05 (CH_3), 27.75 (CH_3), 78.15 (C^3), 78.36 (C^5), 84.48 (C^4), 87.40 (C^2), 108.09 (C^1), 113.74 (CMe_2). Mass spectrum, *m/z*: 171 $[M-1]^+$, 157 $[M-CH_3]^+$, 129 $[M-C_2H_3O]^+$, 113 $[M-C_3H_7O]^+$.

1,2-*O*-Isopropylidene-α-D-xylofuranose (III) was obtained by procedure [10]. IR spectrum, cm^{-1}: 3400 (ν_{OH}). ^1H NMR spectrum, δ, ppm: 1.37 s (3H, CH_3), 1.45 s (3H, CH_3), 3.70 t (1H, *J* 5.7 Hz) and 4.13 q (1H, CH_2, *J* 3.7 Hz), 3.96 d.d (1H, OH, *J* 3.6 and 5.3 Hz), 4.25 d.t (1H, C^4H, *J* 3.6 Hz), 4.40 d (1H, C^3H, *J* 4.2 Hz), 4.48 d (1H, C^2H, *J* 3.7 Hz), 5.93 d (1H, C^1H, *J* 3.7 Hz). ^{13}C NMR spectrum, δ, ppm: 26.03 (CH_3), 26.59 (CH_3), 60.58 (C^5), 76.17 (C^4), 77.42 (C^3), 85.41 (C^2), 104.67 (C^1), 111.64 (CMe_2).

5-Deoxy-5-iodo-1,2-*O*-isopropylidene-α-D-xylofuranose (IV). A solution of 2.7 g (14.2 mmol) of diole **III**, 4.32 g (18.3 mmol) of PPh_3, 1.46 g (21.5 mmol) of imidazole (Im), and 4.34 g (34.2 mmol) of I_2 in 60 ml of THF was stirred for 4.5 h under an argon atmosphere at 50–60°C [8]. The workup was the same as in preparation of compound **I**, the residue was purified by column chromatography on SiO_2 (eluent ethyl acetate–petroleum ether, 3:1). Yield 2.27 g (53%), $[\alpha]_D^{20}$ –18.5° (*c* 0.94, $CHCl_3$). ^1H NMR spectrum, δ, ppm: 1.30 s (3H, CH_3), 1.50 C (3H, CH_3), 2.90 br.s (1H, OH), 3.20 m (2H, CH_2I), 4.40 m (2H, C^3H, C^4H), 4.53 d (1H, C^2H, *J* 3.6 Hz), 5.96 d (1H, C^1H, *J* 3.6 Hz). ^{13}C NMR spectrum, δ, ppm: 8.49 (CH_2I), 26.13 (CH_3), 26.73 (CH_3), 74.52 (C^4), 80.86 (C^3), 85.02 (C^2), 105.37 (C^1), 111.83 (CMe_2).

2,3:4,5-Di-*O*-isopropylidene-D-xylose dimethylacetal (V). To a solution of 3.5 g (23.95 mmol) of D-xylose and 6.5 ml (52.69 mmol) of 2,2-dimethoxypropane in 20 ml of a mixture acetone–methanol, 1:1, was added 0.001 ml of concn. H_2SO_4, and the reaction mixture was stirred at 20°C till the complete consumption of the initial compound (~2 h, TLC monitoring). Then acetone was evaporated, and the residue was subjected to column chromatography on SiO_2 (eluent ethyl acetate–petroleum ether, 1:1). Yield 1.29 g (~20%), $[\alpha]_D^{20}$ –1.3° (*c* 0.98, $CHCl_3$). ^1H NMR spectrum, δ, ppm: 1.34 s (3H, CH_3), 1.38 s (6H, 2 CH_3), 1.40 s (3H, CH_3), 3.40 s (3H, OCH_3), 3.41 s (3H, OCH_3), 3.75–4.15 m (5H, C^3H, C^2H, C^4H, CH_2), 4.33 d (1H, C^1H, *J* 5.75 Hz). ^{13}C NMR spectrum, δ, ppm: 25.49 (CH_3), 25.94 (CH_3), 26.67 (CH_3), 26.77 (CH_3), 53.55 (OCH_3), 55.56 (OCH_3), 65.72 (C^5), 75.73 (C^4), 76.48 (C^3), 76.63 (C^2), 104.61 (C^1), 109.07 (CMe_2), 109.69 (CMe_2).

Direct transition from D-xylose to oxetane I and epoxide VI. To a solution of 3.5 g (23.95 mmol) of D-xylose and 6.5 ml (52.69 mmol) of 2,2-dimethoxypropane in 30 ml of acetone was added 0.025 ml of concn. H_2SO_4, and the reaction mixture was stirred at 20°C till the complete consumption of the initial compound (~10 h, TLC monitoring). Then acetone was evaporated, and the residue was subjected to column chromatography on SiO_2 (eluent ethyl acetate–petroleum ether, 1:1). Yield 2.73 g (62%) of a mixture of compounds **II** and **V** in a ratio 4:1 (^1H NMR data). The spectral characteristics of compounds **II** and **V** measured in the mixture coincided with the characteristics of individual bisacetonide **II** [10] and acetonide **V** prepared in modified conditions (see above).

To 2.5 g of the mixture of compounds **II** and **V** without purification was added 25 ml of water and 0.025 ml of

concn. H_2SO_4, the mixture was stirred for 2 h. Then to the reaction mixture was added dropwise 5% solution of $NaHCO_3$ till pH 7, the solvent was evaporated, and the residue was subjected to column chromatography on SiO_2 (eluent ethyl acetate–petroleum ether, 1:1). We obtained 1.8 g of a mixture of diol **III** and the corresponding 4,5-deprotected derivative of compound **V**. This mixture was dissolved in 40 ml of THF, and to the solution 3.07 g (13.0 mmol) of PPh_3, 1.02 g (15.0 mmol) of imidazole, and 3.17 g (25.0 mmol) of I_2 were added, and the mixture was stirred under argon for 4.5 h while heating at 50–60°C. The solvent was evaporated, the residue was dissolved in $CHCl_3$ and washed with a saturated water solution of $Na_2S_2O_3$. The organic layer was dried with $MgSO_4$, the solvent was evaporated, and the residue was subjected to column chromatography on SiO_2 (eluent ethyl acetate–petroleum ether, 3:1). The mass obtained (1.0 g) was dissolved in 20 ml of THF, and this solution was added dropwise to a dispersion of 0.2 g of NaH in 20 ml of THF. After keeping the reaction mixture for 2 h it was worked up as described for compound **I**. We obtained 0.4 g of oily mixture of anhydrosugars **I** and **VI** in the ratio 4:1 (^{1}H NMR data).

4,5-Anhydro-2,3-*O*-isopropylidene-D-xylofuranose dimethylacetal (VI). ^{1}H NMR spectrum, δ, ppm: 2.75 d.d (1H, H^{5a}, *J* 2.7 and 5.3 Hz), 2.81 d.d (1H, H^{5b}, *J* 4.2, 5.3 Hz), 3.10 d.d.d (1H, H^4, *J* 2.7, 4.2, 4.9 Hz), 3.45 s (3H, OCH_3), 3.46 s (3H, OCH_3), 3.83 d.d (1H, H^3, *J* 4.9, 7.6 Hz), 4.10 d.d (1H, H^2, *J* 6.2, 7.6 Hz), 4.40 d (1H, H^1, *J* 6.2 Hz). ^{13}C NMR spectrum, δ, ppm: 26.44 (CH_3), 26.77 (CH_3), 44.71 (C^5), 51.90 (OCH_3), 57.76 (OCH_3), 55.49 (C^4), 77.84 (C^2), 77.21 (C^3), 104.49 (C^1), 110.41 (CMe_2). Mass spectrum, *m/z*: 218 $[M]^+$, 203 $[M - CH_3]^+$, 143 $[M - C_3H_7O_2]^+$, 75 $[C_3H_7O]^+$.

Reduction of a mixture of compounds I and VI with $LiAlH_4$. To a solution of 0.1 g of a mixture of compounds **I** and **VI** in 5 ml of THF was added 0.03 g of $LiAlH_4$ powder, and the reaction mixture was stirred for 2 h at room temperature, then it was quenched with a saturated water solution of NH_4Cl (1 ml). The separated precipitate was filtered off, washed with CH_2Cl_2 (3 × 20 ml), the combined organic solutions were washed with a saturated water solution of NaCl, dried with $MgSO_4$, evaporated, and the residue was subjected to column chromatography on SiO_2 (eluent petroleum ether–ethyl acetate, 7:1). We obtained 60 mg of oxetane **I** and 20 mg of alcohol **VII** which was used in the next stage.

(2*R*,3*S*,4*R*)-5-Deoxy-4-acetyl-2,3-*O*-isopropylidene-D-xylose dimethylacetal (VIII). In 2 ml of a mixture Py–Ac_2O, 2:1, was dissolved 20 mg of alcohol **VII**, and the reaction mixture was stirred till the disappearance of the initial compound (TLC monitoring). The reaction mixture was poured into 2 ml of ice water, and the reaction product was extracted into $CHCl_3$ (3 × 3 ml), the organic extracts were washed with water and dried with $MgSO_4$. Yield 19.5 mg (82%), $[\alpha]_D^{20}$ +6.6° (*c* 1.0, $CHCl_3$). ^{1}H NMR spectrum, δ, ppm: 1.40 d (3H, CH_3, *J* 6.5 Hz), 1.42 s (3H, CH_3), 1.43 s (3H, CH_3), 2.07 s (CH_3), 3.42 s (3H, OCH_3), 3.44 s (3H, OCH_3), 3.92 d.d (1H, C^2H, *J* 5.9, 7.0 Hz), 3.98 d.d (1H, C^3H, *J* 3.1, 7.0 Hz), 4.34 d (1H, C^1H, *J* 5.7 Hz), 4.90 d.d.d.d (1H, C^4H, *J* 3.1, 3.4, 6.5 Hz). ^{13}C NMR spectrum, δ, ppm: 16.06 (CH_3), 20.32 (CH_3), 25.93 (CH_3), 26.42 (CH_3), 53.45 (OCH_3), 54.96 (OCH_3), 68.49 (C^4), 75.36 (C^3), 79.63 (C^2), 104.14 (C^1), 109.29 (CMe_2), 169.51 (CH_3CO).

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