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PRELIMINARY COMMUNICATION

Unexpected cycloreversion of a tosylated sugar oxetane under E2 conditions. The facile formation of 2-(2-furanyl)-1,3-dioxolane from a novel 2,5:4,6-dianhydro-L-idose derivative

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Abstract: 2,5:4,6-Dianhydro-3-*O*-*p*-toluenesulfonyl-L-idose ethylene acetal (**4**) was synthesized with the aim of studying its chemical behaviour in the presence of several basic agents (Bu_4NF/MeCN, NaOMe/MeOH, KOBu^t/Bu^{t}OH/THF, and NaH/DMSO). Treatment of **4** with sodium hydride in dimethyl sulphoxide at room temperature unexpectedly gave the 2-(2-furanyl)-1,3-dioxolane. The mechanism of the process presumably involved the initial conversion of **4** to the corresponding 2,3-unsaturated derivative **5**, followed by a facile oxetane ring cycloreversion by the elimination of formaldehyde.

Keywords: 2,5-anhydro-L-idose; 2,5:4,6-dianhydro-L-idose; sugar oxetanes; cycloreversion.

In a previous paper,[1] the conversion of D-glucose to 2,5-anhydro-L-threo-hex-2-enose ethylene acetal derivatives of type **1** (Scheme 1) was described. Stereospecific hydrogenation of **1**, followed by several functional groups manipulations furnished the 3,6-dideoxy derivative **3**, a convenient intermediate for the synthesis of both (+)-muscarine and (+)-*epi*-muscarine.[1,2] In the search for an alternative and presumably a more efficient route towards the divergent intermediate **3**, a new multistep sequence was planned which involves the conversion of D-glucose to **3** *via* the 2,3-unsaturated derivative **5**. It was further assumed that the postulated intermediate **5** might be available through an E2 process performed on the 3-*O*-tosyl ester **4**. Therefore the preparation of the 2,5:4,6-dianhydro-L-idose derivative **4** was first attempted starting from the known[3] tritosylate **6** (Scheme 2).

The synthesis started with a regioselective nucleophilic displacement of the primary tosyloxy function in **6** with a bromide anion. The resulting 6-bromo derivative **7** was isolated by flash column chromatography (94 %) and characterized by NMR and mass spectral data.[4] Treatment of **7** with ethylene glycol and toluene-4-sulfonic acid in refluxing benzene with azeotropic removal of water[5] afforded the corresponding 2,5-anhydro-L-idose

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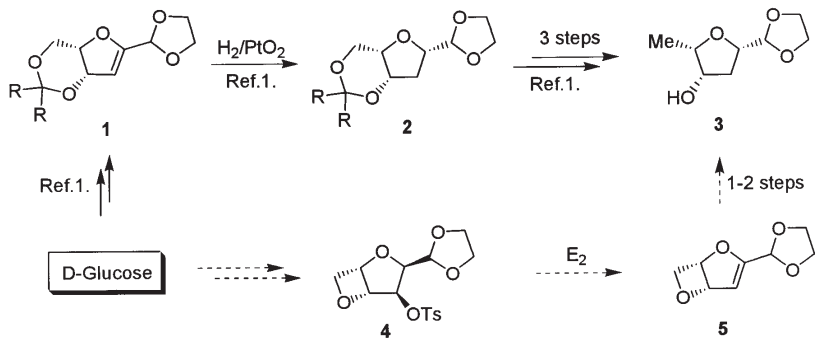
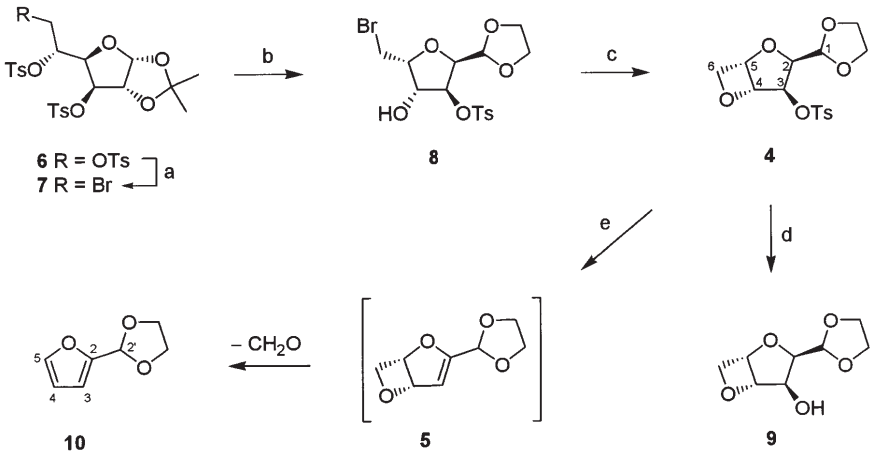


Scheme 1.

derivative **8** (68 %), the structure of which was assigned unambiguously by NMR and mass spectral data.[6] The desired product **8** was thus obtained in 64 % overall yield with respect to the tri-*O*-tosyl derivative **6**. However, when the last two-step sequence was carried out without purification of the 6-bromo derivative **7**, product **8** was obtained in an overall yield of 70 % with respect to the starting compound **6**. Reaction of **8** with silver oxide and silver triflate in refluxing tetrahydrofuran gave a good yield of the corresponding oxetane **4** (83 %), which was fully characterized by the corresponding spectral and analytical data.[7]



Scheme 2. (a) LiBr, DMF, 90 ºC, 1.5 h; (b) Ethylene glycol, TsOH, C_6H_6↑↓, Dean-Stark, 71 h; (c) Ag_2O, AgOTf, THF↑↓, N_2, 40 h; (d) NaOMe, MeOH↑↓, 3 h; (e) NaH, DMSO, N_2, rt, 16 h.

The next step of the work was directed to the conversion of the tosyloxy-oxetane **4** into the corresponding unsaturated derivative **5**. In the original synthesis of (+)-muscarine,[1] the desired unsaturated intermediate **1** was readily obtained by treatment of the corresponding 3-*O*-tosyl ester with tetrabutylammonium fluoride in boiling acetonitrile. An attempted conversion of **4** to **5** under similar reaction conditions[1] was unsuccessful. According to TLC, after 24 h the reaction mixture still contained a significant amount of the starting compound **4** along with several additional components of higher polarity. No

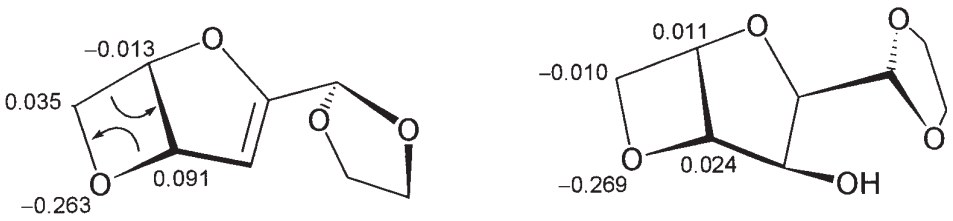
traces of the desired olefin **5** could be detected in the reaction mixture, neither could any of the polar by-products be obtained in pure form due to their similar chromatographic properties. Treatment of **4** under more basic reaction conditions, with sodium methoxide in refluxing methanol, resulted in the cleavage of the methanesulphonate ester group to afford the corresponding alcohol[8] **9**, isolated in 41 % yield along with a similar amount of the starting compound **4**. Conversely, when **4** was treated with non-nucleophilic bases, such as potassium *tert*-butoxide in tetrahydrofuran, or sodium hydride in dimethyl sulphoxide at room temperature, an unexpected reaction occurred resulting in the formation of 2-(2-furanyl)-1,3-dioxolane[9] (**10**). In the case of the NaH/DMSO reagent system, the furfural derivative **10** was isolated by flash column chromatography in 45 % yield. The ^{1}H and ^{13}C NMR spectral data of the thus obtained product **10** were in reasonable agreement with those already reported.[14] (Table I).

TABLE I. NMR Spectral data for **10** (in $CDCl_3$)

	Chemical shift δ(ppm) and J (Hz)					
	H-2'	H-3	H-4	H-5	2×CH_2	
This work	5.94	6.46	6.37	7.44	3.98–4.19	
Ref. 14	5.91	6.43	6.34	7.40	3.92–4.25	
	$J_{3,4}$	$J_{4,5}$				
This work	3.3	1.8				
Ref. 14	3.2	1.8				
	C-2	C-2'	C-3	C-4	C-5	2×CH_2
This work	151.0	97.7	108.7	110.1	143.1	65.1
Ref. 14	151.0	97.6	108.6	110.0	143.0	65.0

Thermal decomposition of simple oxetanes has already been described in the literature. Such a transformation has been reported for the oxetane itself[10] and for some 3,3-dialkyloxetanes,[11] but in the temperature range 395–484 ºC and 407–448 ºC, respectively. Cycloreversions of several non-carbohydrate oxetanes under laser flash photolysis conditions were also recently described.[12,13] However, the room temperature decomposition of sugar oxetanes under basic conditions has not been reported in the chemical literature so far.

Presumably, the conversion of **4** to **10** occurred *via* two successive reactions. The first one is the expected E2 elimination of **4** to the corresponding 2,3-unsaturated derivative **5**. The subsequent process presumably involved a facile cycloreversion of the oxetane ring in **5** whereby the furfural derivative **10** was formed after elimination of formaldehyde. It appears that the presence of a double bond in the five-member ring of **5** activates the oxetane ring towards the cycloreversion process. This assumption was verified by molecular modelling (HyperChem Molecular Modelling Package, release 6.03; Hypercube Inc., Gainesville, FL). Preliminary MM+ modelling simulations of **5**



5a **9a**

Fig. 1. Optimised structures **5a** and **9a** with formal charge distribution in the oxetane rings. The hydrogen atoms were omitted for sake of clarity.

were performed *in vacuo* to identify the most stable conformation of the intermediate. This was done by using the conformational search module in HyperChem with a conjugate gradient limit of 0.01 kcal/mol Å. Endocyclic torsional variations were treated by applying the usage directed scheme with restricted ranges for ring torsion flexing in conjunction with a non-Metropolis criterion.[15] High energy structures were defined as those possessing energies of 6 kcal/mol greater than the lowest accepted conformation, also those with relative energy differences within 0.05 kcal/mol were discarded in the post-optimisation runs. All low energy conformers that fell within the specified acceptance criteria were further refined by second series optimisations in which only the acyclic torsional parameters were varied by applying a lower gradient limit (0.001 kcal/mol Å). This procedure identified the conformer **5a** as the most stable structure (Fig. 1). The same procedure was applied to the saturated oxetane **9** whereby the lowest energy conformation **9a** was obtained. Moreover, structures **5a** and **9a** were finally optimised by using the semiempirical PM3 method. Preliminary results of these calculations showed that the oxetane ring of **5a** has a unique distribution of positive and negative charge arranged in an alternating order that is favourable for the elimination of a mol of formaldehyde from **5** leading to the formation of **10**. Conversely, PM3 calculations performed on the saturated oxetane **9a** showed that both positive and negative charges are distributed over neighbouring atoms of the oxetane ring, with the negative charge located at the C-6 and O-6, while the positive charge was distributed over the C-4 and C-5. We believe that such a different charge distribution in **5a** and **9a** is responsible for the thermal stability of **9a**, as well as for the high reactivity of the unsaturated derivative **5**.

In conclusion, an unexpected base catalysed cycloreversion reaction of the newly synthesized sugar oxetane **4** has been described in this work. The mechanism of the process has been reasonably explained on the basis of preliminary semi-empirical PM3 calculations performed on the postulated intermediate **5**.

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ИЗВОД

НЕОЧЕКИВАНА ЦИКЛОРЕВЕРЗИЈА ТОЗИЛОВАНОГ ШЕЋЕРНОГ ОКСЕТАНА У УСЛОВИМА E2 ЕЛИМИНАЦИЈЕ. ЛАКО ФОРМИРАЊЕ 2-(2-ФУРАНИЛ)-1,3-ДИОКСОЛАНА ИЗ НОВОГ ДЕРИВАТА 2,5:4,6-ДИАНХИДРО-L-ИДОЗЕ

ВЕЛИМИР ПОПСАВИН, ЉУБИЦА РАДИЋ, МИРЈАНА ПОПСАВИН и ВЕРА ЋИРИН-НОВТА

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Нови дериват 2,5:4,6-дианхидро-L-идозе **4** добијен је вишефазним трансформацијама D-глукозе, а затим је испитивано његово хемијско понашање у присуству неколико базних агенаса (Bu_4NF/MeCN, NaOMe/MeOH, KOBu^t/Bu^{t}OH/THF, NaH/DMSO). Реакцијом једињења **4** са натријум-хидридом у диметилсулфоксиду, неочекивано је добијен 2-(2-фуранил)-1,3-диоксолан (**10**). Предложен је механизам ове необичне трансформације, који највероватније обухвата иницијални E2 елиминациони процес, праћен накнадним фрагментационим отварањем оксетанског прстена уз издвајање формалдехида.

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4. Compound **7** (syrup): $[\alpha]_D$ –56.88º (*c*, 0.9 in $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 1.28 and 1.45 (2×*s*, 3 H each, CMe_2), 2.45 and 2.48 (2×*s*, 3 H each, 2×*Me*$C_6H_4SO_2$), 3.52 (*dd*, 1 H, $J_{5,6a}$ = 4.2, $J_{6a,6b}$ = 12.3 Hz, H-6a), 3.57 (*dd*, 1 H, $J_{5,6b}$ = 3.2 Hz, H-6b), 4.50 (*dd*, 1 H, $J_{3,4}$ = 2.7, $J_{4,5}$ = 6.5 Hz, H-4), 4.79 (*m*, 1 H, H-5), 4.82 (*d*, 1 H, $J_{1,2}$ = 3.5 Hz, H-2), 5.00 (*d*, 1 H, H-3), 5.84 (*d*, 1 H, H-1), 7.29–7.96 (*m*, 8 H, 2×Me$C_6H_4SO_2$); ^{13}C-NMR ($CDCl_3$): δ 21.62 and 21.68 (2×*Me*$C_6H_4SO_2$), 26.33 and 26.59 (C*Me*$_2$), 31.46 (C-6), 74.97 (C-5), 77.99 (C-4), 80.39 (C-3), 82.28 (C-2), 104.42 (C-1), 113.04 (*C*Me$_2$), 128.01, 128.28, 129.71, 130.08, 132.28, 133.49, 145.22 and 145.73 (2×Me*C*$_6H_4SO_2$). FAB MS: *m*/*s* 614 (M^++Na), 592 (M^++H).
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6. Compound **8**: m.p. 154 ºC (from MeOH); $[\alpha]_D$ +95.96º (*c*, 1.15 in $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 2.46 (*s*, 3 H, *Me*$C_6H_4SO_2$), 3.40–3.60 (*m*, 2 H, $J_{6a,6b}$ = 10.9, $J_{5,6a}$ = 6.1, $J_{5,6b}$ = 7.6 Hz, 2×H-6), 3.59–3.98 (*m*, 4 H, 2×CH_2-dioxolane), 4.09 (*dd*, 1 H, $J_{1,2}$ = 6.5, $J_{2,3}$ = 3.5 Hz, H-2), 4.47 (*m*, 1 H, $J_{4,5}$ = 3.5 Hz, H-5), 4.61 (*dd*, 1 H, $J_{3,4}$ = 1.2 Hz, H-4), 4.88 (*d*, 1 H, H-1), 4.96 (*dd*, 1 H, H-3), 7.35 and 7.82 (2×*d*, 2 H each, Me$C_6H_4SO_2$); ^{13}C-NMR ($CDCl_3$): δ 21.53 (*Me*$C_6H_4SO_2$), 27.30 (C-6), 64.92 and 65.04 (2×CH_2-dioxolane), 74.28 (C-4), 79.77 (C-2), 80.88 (C-5), 84.09 (C-3), 101.18 (C-1), 127.97, 129.62, 132.66 and 145.18 (Me*C*$_6H_4SO_2$). FAB MS: *m*/*z* 446 (M^++Na), 424 (M^++H).
7. Compound **4**: m.p. 137–138 ºC (from MeOH); $[\alpha]_D$ +77.58º (*c*, 0.27 in $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 2.45 (*s*, 3 H, *Me*$C_6H_4SO_2$), 3.67–4.05 (*m*, 4 H, 2×CH_2-dioxolane), 4.32 (*dd*, 1 H, $J_{1,2}$ = 6.5, $J_{2,3}$ = 3.3 Hz, H-2), 4.42 (*dd*, 1 H, $J_{5,6a}$ = 2.5, $J_{6a,6b}$ = 8.4 Hz, H-6a), 4.81 (*dd*, 1 H, $J_{5,6b}$ = 4.7 Hz, H-6b), 5.01 (*d*, 1 H, H-3), 5.02 (*d*, 1 H, H-1), 5.07 (*m*, 1 H, $J_{4,5}$ = 3.8 Hz, H-5), 5.28 (*d*, 1 H, H-4), 7.31–7.83 (2×*d*, 2 H each, Me$C_6H_4SO_2$). ^{13}C-NMR ($CDCl_3$): δ 21.60 (*Me*$C_6H_4SO_2$), 65.17 (2×CH_2-dioxolane), 77.60 (C-5), 77.93 (C-6), 80.59 (C-2), 80.89 (C-3), 88.91 (C-4), 100.97 (C-1), 128.10, 129.64, 133.02 and 145.06 (Me*C*$_6H_4SO_2$). EI MS: *m*/*z* 343 (M^++H). Anal: Calcd. for $C_{15}H_{18}O_7S$: C, 52.62; H, 5.30; S, 9.37. Found: C, 52.82; H, 5.32; S, 9.17.
8. *2,5:4,6-Dianhydro-L-idose ethylene acetal* (**9**): To a suspension of **4** (0.1712 g, 0.50 mmol) in dry MeOH (3 mL) was added 1 M NaOMe in MeOH (2 mL). The resulting mixture was refluxed for 3 h, then neu-

tralized with 1 M AcOH in MeOH (2 mL) and evaporated. Flash column chromatography (9:1 toluene–Me_2CO) of the residue gave pure **9** (0.0384 g, 41 %) as a colourless syrup, $[\alpha]_D$ +9.26º (*c*, 1.1 in $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 3.07 (*bs*, 1 H, exchangeable with D_2O, OH), 3.89–4.14 (*m*, 4 H, 2×CH_2-dioxolane), 4.33 (*d*, 1 H, $J_{2,3}$ = 3.0 Hz, H-3), 4.42 (*m*, 2 H, H-2 and H-6a), 4.81 (*dd*, 1 H, $J_{5,6b}$ = 8.3 Hz, H-6b), 5.05 (*m*, 1 H, H-5), 5.14 (*d*, 1 H, $J_{4,5}$ = 3.8 Hz, H-4), 5.30 (*d*, 1 H, $J_{1,2}$ = 4.5 Hz, H-1); ^{13}C-NMR ($CDCl_3$), δ 65.10 and 65.41 (2×CH_2-dioxolane), 74.19 (C-3), 77.18 (C-5), 77.75 (C-6), 81.16 (C-2), 91.35 (C-4), 102.32 (C-1). FAB MS: *m*/*z* 189 (M^++H), 187 (M^+–H), 171 (M^+–OH).

9. *2-(2-Furanyl)-1.3-dioxolane* (**10**): To a solution of **4** (0.3424 g, 1.00 mmol) in dry DMSO (7 mL) was added NaH (80 % dispersion in mineral oil, 0.06 g, 1.00 mmol). The mixture was stirred for 16 h at room temperature, then poured into 5 % aq NH_4Cl and extracted with Et_2O (6×10 mL). The combined extracts were dried (Na_2SO_4) and evaporated to a yellow liquid (0.0913 g). Flash column chromatography of the residue gave pure **10** (0.0628 g, 45 %) as a colourless liquid. ^{1}H and ^{13}C-NMR data are presented in Table I. FAB MS: *m*/*z* 141 (M^++H); HR MS (ES+): *m*/*z* 163.0370 (M^++Na). Calcd. for $C_7H_8O_3Na$: 163.0371.
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