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Selectively Tosylated Aldonolactones as Precursors for Highly Functionalized, Enantiomerically Pure Tetrahydrofurans

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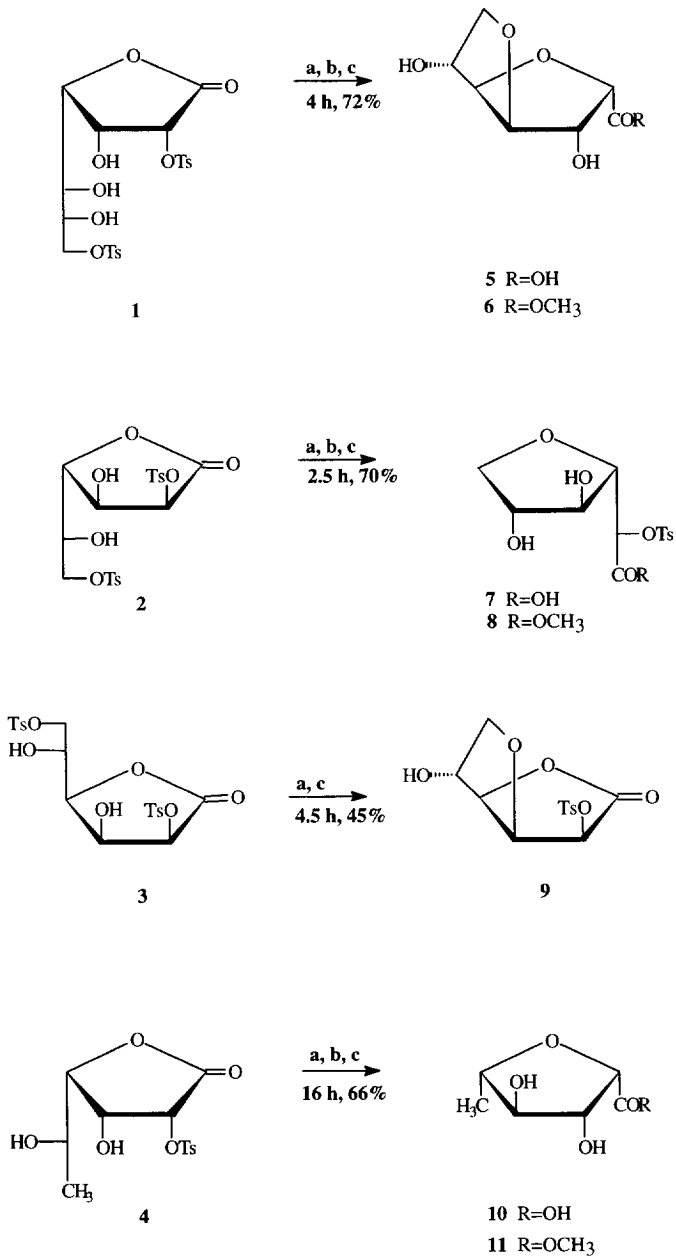
Abstract: α,ω-Di-*O*-tosylated-aldonolactones were selectively converted into functionalized tetrahydrofurans when boiled in water-dioxane. Thus, the 2,7-di-*O*-tosyl-D-*glycero*-D-*gulo*-heptono-1,4-lactone (**1**) readily gave the 2,5;4,7-di-anhydride with inversion of the configuration at C-2, while the 2,6-di-*O*-tosylated hexonolactones with D-*talo* -(**2**)- and D- *manno*- (**3**) configurations gave the 2-*O*-tosylated 3,6-anhydrides **7** and **9**, respectively. Finally, in a more slow reaction, the 2-*O*-tosylated-L-rhammono-1,4-lactone (**4**) gave the 2,5-anhydride **10**, inverted at C-2, as the only product.

Tetrahydrofuran structures are present in nature in a wide range of stereochemical complexity. Thus, synthesis of enantiomerically pure tetrahydrofurans is of current interest,[1,2] not only for development of new methods[3-8] and natural product synthesis[1,9,10] but also for other purposes, such as synthesis of new biologically active compounds[11] or asymmetric catalysis.[12,13]

When carbohydrate derivatives are used as substrates for synthesis of tetrahydrofurans, the ring closure normally takes places by intramolecular nucleophilic substitution of an OH-group on an appropriate leaving group. Such leaving groups may be created simply by treatment with either strong acid to protonate a hydroxy group[14] or with hydrogen fluoride and formic or acetic acid to form acyloxonium ions.[15]

Other leaving groups such as triflyl[16,17] mesyl [9,10] and tosyl[18] have been used in tetrahydrofuran synthesis under alkaline conditions. In a previous paper[19] we have reported on a simple, general method using bromodeoxy-aldonic acids and -alditols in ring closure reactions. When these compounds were boiled in water the bromine was attacked intramolecularly by an OH-group to form tetrahydrofurans in high yields. Since we have found that α,ω-di-*O*-tosylated aldonolactones can be prepared directly from aldonolactones without any protecting group chemistry,[20] we now report on a simple procedure for the conversion of tosylated aldono-1,4-lactones into complex tetrahydrofurans.

When the crystalline 2,7-di-*O*-tosyl-D-*glycero*-D-*gulo*-heptono- (**1**), 2,6-di-*O*-tosyl-D-talono- (**2**), 2,6-di-*O*-tosyl-D-mannono- (**3**) and 2-*O*-tosyl-L-rhamnono- (**4**) -1,4-lactones[20] were heated in water-dioxane (2:1) for the time indicated (Scheme 1), a smooth and clean reaction to tetrahydrofurans took place in all cases, as seen from the ^{13}C NMR spectra of the crude products. Due to a lower solubility in water of the tosylates



1

5 R=OH
6 R=OCH3

2

7 R=OH
8 R=OCH3

3

9

4

10 R=OH
11 R=OCH3

a) H_2O/dioxane 2:1, reflux; b) MeOH, HCl; c) ion exchange resin IR-45 (OH^-)

Scheme 1

compared to the bromodeoxylactones, dioxane was added to the reaction mixture. The products **5**, **7** and **10** with a free carboxylic acid group, were separated from the liberated p-toluene sulfonic acid by esterification with MeOH/HCl to give the corresponding methylesters **6**, **8** and **11**, followed by filtration over a weakly basic ion exchange resin to give the pure products.

From the di-tosylated D-*glycero*-D-*gulo*-heptono-1,4-lactone (**1**) formation of a dianhydride (**5**) was observed within 1 h. This reaction is similar to that observed when boiling 2,7-dibromo-2,7-dideoxy-D-*glycero*-D-*ido*-heptono-1,4-lactone in water to give a dianhydride with D-*glycero*-D-*gulo*-configuration.[21] Since these two substrates are epimers at C-2, and since the two dianhydrides are different, **5** must have the D-*glycero*-D-*ido*-configuration. This shows that both reactions take place with inversion of the configuration at C 2.

The di-tosylates **2** and **3** reacted by substitution of the primary tosyl group only. The reactions took place within a few hours, and no 2,5-anhydrides were observed. A further reaction of the secondary tosyl group at C-2 in **7** and **9** is not favored, since intramolecular reaction would lead to bicyclic, bridged compounds. Thus, the 2,6-di-*O*-tosyl-D-talono-1,4-lactone (**2**) gave the 2-*O*-tosylated 3,6-anhydro acid **7**, isolated as the methyl ester **8**, while 2,6-di-*O*-tosyl-D-mannono-1,4-lactone (**3**) gave the anhydrolactone **9** due to the *cis*-orientation of OH-3 and the side chain. The retainment of the lactone ring was also observed in similar reactions of 6-bromo-6-deoxy-aldonolactones, investigated previously.[19]

The reaction of 2-*O*-tosyl-L-rhamno-1,4-lactone (**4**) giving the 2,5-anhydride **10**, required a significantly longer reaction time to be completed, because of an apparently less reactive secondary tosyl group. Thus, from the reactions leading to **7**, **9** and **10** it was revealed that the secondary tosyloxy groups were less readily substituted by internal ring formation compared to the primary ones. In contrast, the 2,5;4,7-di-anhydroacid **5** was formed readily. The tetrahydrofuran derivative formed from **4** was isolated as the methyl ester **11**.[16] The L-*gluco*-configuration of **11**, formed from **4** having L-*manno*-configuration, unambigously proves that the internal substituation at C-2 takes place with inversion of configuration at this center

In summary, we have shown that α and/or ω-*O*-tosylated lactones, which can be prepared directly by selective tosylation of the lactones, can easily be converted into highly functionalized tetrahydrofurans just by boiling in water/dioxane. Substitution of the α-*O*-tosylate occours with inversion of configuration. The products may possess several different functionalities, such as hydroxy-groups, acid- or ester groups and tosyl groups. Thus, they offer possibilities for further modification and might be useful starting materials for synthetic purposes.

Table 1. ^{13}C NMR Data of Compounds **5-11**

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	OMe
5[c]	173.0	87.7[a]	77.2[b]	83.3[a]	83.6[a]	72.6[b]	72.0	-
6[c]	171.8	87.6[a]	77.2[b]	83.4[a]	83.6[a]	72.5[b]	72.0	53.3
7[d]	168.3	78.6[a]	85.0	77.9[a]	77.6[a]	74.6	-	-
8[d]	168.0	78.5[a]	85.0	77.8[a]	77.4[a]	75.0	-	52.5
9[d]	170.2	75.3[a]	77.0[a]	81.9	72.8[a]	71.4[a]	-	-
10[d]	171.8	82.9[a]	79.4[b]	81.1[b]	82.7[a]	19.2	-	-
11[c]	172.3	82.4[a]	78.9[b]	81.0[b]	82.3[a]	18.8	-	53.4

[a,b] Assignments may be reversed. [c] In D_2O. [d] In acetone-d_6.
The signals of the tosyl group are observed at 21.0-21.5 ppm for CH_3 and 128-147 ppm for aromatic carbons.

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were determined on a Perkin Elmer 241 polarimeter. NMR spectra were recorded on a Bruker AC-250 instrument. Chemical shifts were measured in ppm. Dioxane (δ = 67.4) was used as internal standard for ^{13}C NMR spectra in D_2O and HDO (δ = 4.60) for ^{1}H NMR spectra. For spectra in acetone-d_6 the solvent signals were used as internal standard, δ = 29.8 for ^{13}C NMR spectra and δ = 2.05 for ^{1}H NMR spectra. Evaporations were carried out at 40 °C *in vacuo*. For column chromatography silica gel 60, particle size 0.040-0.063 mm, from *Merck* was used. All solvents were destilled. Microanalyses were performed by *Leo Microanalytical Laboratory*.

Reaction of Tosylated Aldonolactones; General Procedure: The lactone (1.0 mmol) was dissolved in H_2O/dioxane 2:1 (v/v) and heated to reflux for the time given in Scheme 1. After cooling to r.t. the solution was concentrated and co-concentrated with toluene (2 x 20 ml) to give the crude anhydride with a free carboxylic acid group (^{13}C NMR data, see Table 1) contaminated with p-TsOH. Only in the reaction of the mannonolactone **3**, the lactone ring was preserved, and **9** was isolated as such. The acid was esterified by dissolving in MeOH (10 ml) and AcCl (0.5 ml), and the mixture was either refluxed for 2 h or kept at r.t. overnight. The solution was then poured onto a column of a weekly basic ion exchange resin (IR-45, 10 ml) and the product was eluted with MeOH (50 ml). The eluate was concentrated to give the esters or the lactone

9. All products were sufficiently pure for further reactions. Analytical samples were obtained as described below.

Methyl 2,5;4,7-dianhydro-D-glycero-*D*-ido-*heptonate* (**6**). The lactone **1** (5.0 g, 9.68 mmol) was treated as described above. Work up gave **6** as a colorless syrup (1.42 g, 6.95 mmol; 72%), which crystallized from EtOAc. Recrystallization from EtOAc gave an analytical sample, m.p. 110-111 °C, $[\alpha]_D^{20}$ -14.8° (*c* 1.0, acetone). *Anal.* Found: C, 46.60; H, 5.85. Calcd for $C_8H_{12}O_6$: C, 47.06, H, 5.92. ^{1}H NMR (D_2O): d 3.38 (dd, $J_{7,6}$ = 7.4 Hz, $J_{7,7'}$ = 9.0 Hz, H-7), 3.63 (s, OMe), 3.80 (dd, $J_{7',6}$ = 6.6 Hz, H-7'), 4.27 (ddd, $J_{6,5}$ = 4.8 Hz, H-6), 4.34-4.39 (m, H-4, H-5), 4.57 (d, $J_{2,3}$ = 3.6 Hz, H-2), 4.68 (dd, $J_{3,4}$ = 5.1 Hz, H-3).

Methyl 3,6-anhydro-2-O-*tosyl-D-talonate* (**8**). The lactone **2** (464 mg, 0.95 mmol) gave compound **8** as a colorless syrup (230 mg, 0.66 mmol; 70%). Column chromatography (EtOAc-hexane 2:1) gave an analytical sample, $[\alpha]_D^{20}$ + 14.2° (*c* 1.0, acetone). *Anal.* Found: C, 48.63; H, 5.47. Calcd for $C_{14}H_{18}O_8S$: C, 48.55; H, 5.24. ^{1}H NMR (acetone-d_6): δ 2.43 (s, Me), 3.55 (s, OMe), 3.70 (dd, $J_{3,2}$ = 7.4 Hz, $J_{3,4}$ 2.0 Hz, H-3), 3.90 (dd, $J_{6,5}$ = 4.2 Hz, $J_{6,6'}$ = 5.0 Hz, H-6), 3.94 (dd, $J_{6',5}$ = 2.2 Hz, H-6'), 4.09 (dd, $J_{4,5}$ = 2.0 Hz, H-4), 4.12 (ddd, H-5), 4.97 (d, H-2), 7.47, 7.78 (OTs).

3,6-Anhydro-2-O-*tosyl-D-mannono-1,4-lactone* (**9**). The lactone **3** (2.0 g, 4.11 mmol) was treated as described above, but after refluxing in water and cooling to r.t., the solution was immediately filtered through ion exchange resin. After work up, **9** was obtained as a syrup (580 mg, 1.84 mmol; 45%), which crystallized from Et_2O. Recrystallization from Et_2O-$CHCl_3$ gave an analytical sample, m.p. 120-121 °C, $[\alpha]_D^{20}$ + 112.8° (*c* 1.0, acetone). *Anal.* Found: C, 49.57; H, 4.61; S, 10.17. Calcd for $C_{13}H_{14}O_7S$: C, 49.68; H, 4.49; S, 10.20. ^{1}H NMR (acetone-d_6): δ 2.45 (s, Me), 3.49 (dd, $J_{6,6'}$ = 8.2 Hz, $J_{6,5}$ = 9.2 Hz, H-6), 4.01 (dd, $J_{6',5}$ = 7.2 Hz, H-6'), 4.49-4.59 (m, H-5), 4.67 (dd, $J_{3,2}$ = 5.2 Hz, $J_{3,4}$ = 3.4 Hz, H-3), 4.99 (dd, $J_{4,5}$ = 3.8 Hz, H-4), 5.48 (d, H-2), 7.52, 7.88 (OTs).

Methyl 2,5-anhydro-6-deoxy-L-gluconate (**11**). The lactone **4** (1.50 g, 4.74 mmol) was treated as described above. After work-up **11** (5.50 mg, 3.12 mmol; 66%) was obtained as syrup, which crystallized on storage, m.p. 65-71 °C. Column chromatography (EtOAc-hexane 4:1) gave an analytical sample, m.p. 81-82 °C, $[\alpha]_D^{20}$ -12.5° (*c* 1.0, CH_3CN) [Lit.[17]: m.p. 84-85 °C, $[\alpha]_D^{20}$ -9.3° (*c* 1.0, CH_3CN)]. ^{1}H NMR (D_2O): δ 1.16 (d, $J_{6,5}$ = 6.4 Hz, Me-6), 3.58 (s, OMe), 3.66 (dd, $J_{4,5}$ = 4.4 Hz, $J_{4,3}$ = 2.6 Hz, H-4), 3.72 (dq, H-5), 4.17 (dd, $J_{3,2}$ = 5.0 Hz, H-3), 4.49 (d, H-2).

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