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REACTIONS OF 3-O-ACETYL-2-C-p-TOLYLSULFONYL-D-ARABINO- AND -D-RIBO-HEX-1-ENITOL DERIVATIVES WITH NUCLEOPHILES; THE S_N2' MECHANISM IS PROVED FIRSTLY IN GLYCAL DERIVATIVES

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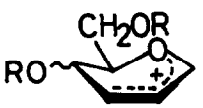
Abstract: Reactions of the title compounds with sodium methoxide and sodium borodeuteride were found to proceed mainly via the S_N2' mechanism; nucleophiles selectively attacked the anomeric carbon atom from the same side of the leaving acetoxyl group at C-3.

The Lewis acid or transition metal-catalyzed[1] reactions of glycal derivatives[2] have been studied intensively, in part because of their versatility as synthetic intermediates, in which a nucleophile attacks the C-1 and/or C-3 positions. The product ratios frequently depend on the reaction conditions, e.g., due to anomerization of product[2a] and/or [3,3] sigmatropic rearrangement.[3] These reactions are thought to proceed via a carbenium ion 1 stabilized by the ring oxygen atom.[1a] In fact we have not been aware of literature such an example as an approaching direction of a nucleophile is controlled by the configuration of a leaving group at C-3.

In order to achieve the S_N2' reaction in glycal derivatives, we took the following two factors into consideration. Firstly introduction of an electron-withdrawing group at C-2 should not only suppress the formation of cation, but also activate the double bond towards a nucleophile. Secondly 4,6-O-benzylidene derivative seems to be suitable for the present purpose based on the following reason. The most stable intermediary cation should be an oxonium ion rather than a carbenium ion. If this is true, C-5 must move up to the plane of O-5, C-1, and C-2; the movement gives rise to a strain to the 1,3-dioxane ring. In fact semi-empirical molecular orbital calculations of model compounds 2-5 with full optimization[4] showed that C-5, O-5, C-1, and C-2



1

2 X,Y = OCH_2O

3 X = Y = OMe

4 X,Y = OCH_2O

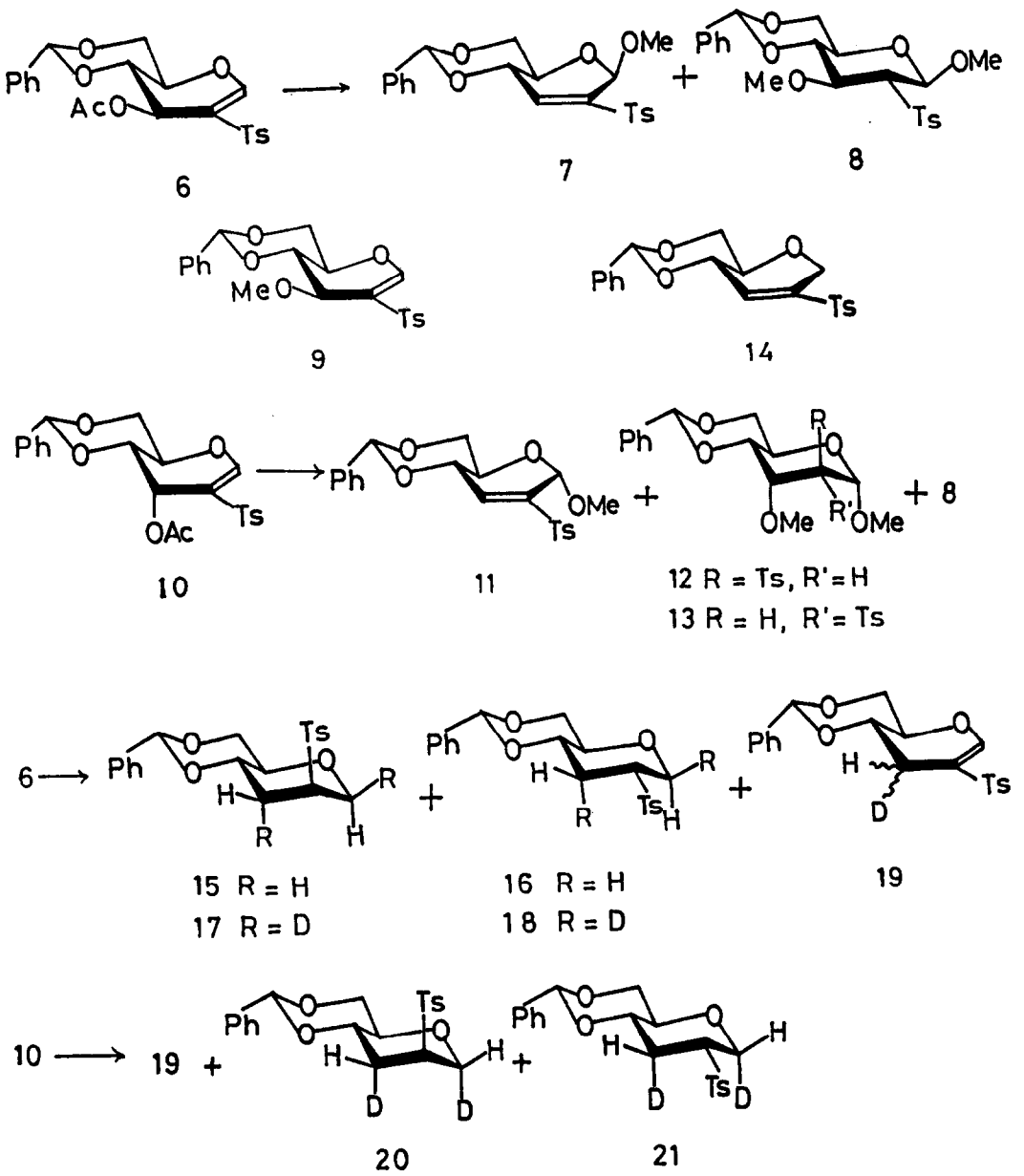
5 X = Y = OMe

of cations **4** and **5** are almost in the same plane and that difference in the heat of formation between 4,6-O-methylene derivative **2** and its cation **4** is larger than that between 4,6-di-O-methyl derivative **3** and its cation **5** by 31.4 (MINDO/3), 20.1 (MNDO), and 16.7 kJ/mol (AM1), respectively.

If a reaction proceeds via the cation **1**, the same results should be obtained regardless of the configuration at C-3 of starting materials. Therefore, 3-O-acetyl-1,5-anhydro-4,6-O-benzylidene-2-deoxy-2-C-p-tolylsulfonyl-D-arabino-hex-1-enitol (**6**) and its 3-epimer[5] **10** were chosen as substrates and subjected to the reactions with methanolic sodium methoxide and sodium borodeuteride, respectively.

To a methanolic dispersion (2.5 mL) of **6** (21 mg) was added M sodium methoxide (0.06 mL; ca. 1.2 equivalent amounts of **6**) and the mixture was stirred for 45 min at room temperature to give methyl 4,6-O-benzylidene-2,3-dideoxy-2-C-p-tolylsulfonyl-β-D-erythro-hex-2-enopyranoside[6] (**7**) (36%) and methyl 4,6-O-benzylidene-2-deoxy-3-O-methyl-2-C-p-tolylsulfonyl-β-D-glucopyranoside[6a] (**8**) (44%), together with unreacted starting material **6** (20% yeild). No evidence was obtained for formation of the corresponding methyl α-D-anomers and 3-O-methyl-D-glucal derivative **9**. Although compound **8** was likely to be formed via methyl 2-enopyranoside **7**, the possibility is not excluded that the 3-O-methyl derivative **9**, formed via S_N1' reaction, is a precursor of **8**. Therefore, the following reactions were performed. Treatment of **7** with methanolic sodium methoxide under the same conditions afforded **8** almost quantitatively, whereas similar reaction of **9** gave a 1 : 3 mixture of **8** and **9**, indicating that the reactivity of **9** is lower than that of the 1-enitol[7] **6** and **7**. In spite of the fact that more reactive **6** and **7** were partially isolated, **9** was not detected in the reaction of **6** with methanolic sodium methoxide, suggesting that **9** was not a precursor of **8**. Similar treatment of **10** (3-epimer of **6**) with methanolic sodium methoxide afforded the methyl α-D-2-enopyranoside **11** (60% yield) as the major products, together with the unreacted **10** (13%) and a 1 : 1 : 1.2 mixture (15%) of α-D-altro **12**, α-D-allo **13**, and β-D-gluco isomers **8**. These products were identical with each of the corresponding authentic samples by ^{1}H NMR spectroscopy.[6,8]

Reduction of **6** with sodium borohydride gave the 2-enitol **14**, identical with an authentic sample[6b], as a primary product, however, the signals due to the protons at C-1 were overlapped. Reduction of **14** with sodium borohydride in acetonitrile gave the D-arabino **15** (24%) {m.p. 171-172°, $[\alpha]_D^{20}$ 33° (c 0.8, chloroform)} and D-ribo isomers **16** (73%) { m.p. 210-211°, $[\alpha]_D^{20}$ -18° (c 0.47, chloroform)} ; these two products were readily separated by column chromatography. Furthermore it was found that sodium borodeuteride almost exclusively attacked C-3 from the axial side of **14**. On the basis of these results, the 3-O-acetyl-D-arabino-1-enitol derivative **6** was subjected to the reduction with excess of sodium borodeuteride in acetonitrile to afford the D-arabino **17**, D-ribo isomers **18**, and 3-deoxy-1-enitol derivative[5] **19** in 22, 46, and 20% yields, respectively. The ^{1}H NMR spectra of **17** and **18** revealed that



the signals due to the anomeric equatorial protons at δ 4.53 for **17** and 4.27 for **18** in $CDCl_3$ almost completely disappeared. Ratio of deuteration at the axial and equatorial position at C-3 of **19** was ca. 1 : 2 according to its ^1H NMR spectroscopy, indicating that **19** was not a precursor of **17** and **18** because the axial position at C-3 of the saturated products almost exclusively deuterated. Similar reduction of the 3-O-acetyl-D-ribo-1-enitol derivative **10** afforded the 3-deoxy-1-enitol derivative **19**, D-arabino **20**, and D-ribo isomers **21** in 9, 29, and 62% yields, respectively. In contrast with the reaction of its 3-epimer **6**, the anomeric axial protons of **20** and **21** (δ 3.73 and 3.64,

respectively, in $CDCl_3$) were almost completely deuterated and the axial position at C-3 of **19** derived from **10** was predominantly deuterated (the ratio of deuteration at the axial to equatorial positions was ca. 2 : 1).

Thus we have firstly shown that the stereoselectivity of nucleophilic addition reaction to glycal derivatives was controlled by the configuration of the leaving group at C-3, namely cis addition occurred as the main reaction path. These results well demonstrate characteristics of the general S_N2' mechanism.[9]

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NOTES AND REFERENCES

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7 It was noteworthy that the reaction of **6** with methanolic sodium methoxide performed herewith should be retarded as the reaction proceeds, because of the neutralization of the catalyst by acetic acid generated.

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