Nucleophilic Substitution Reactions of Pyranose Polytosylates

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The 2,3,4-tri-toluenesulfonate ester derivatives of the methyl pyranosides of L-arabinose, D-ribose, D-lyxose, and D-xylose have been prepared, and their substitution reactions with various nucleophiles have been examined. For arabinose, xylose, and ribose, highly regioselective monosubstitutions were observed with benzoate, nitrite, and azide anions. These reactions have led to short and simple routes from D-xylose to L-arabinose derivatives, from L-arabinose to D-xylose derivatives, and from D-ribose to L-lyxose derivatives. The tritosylate derived from methyl α-D-lyxopyranoside was unreactive toward nucleophilic substitution reactions, giving instead a dihydropyran product arising from an initial E2 elimination reaction of the 2-tosylate.
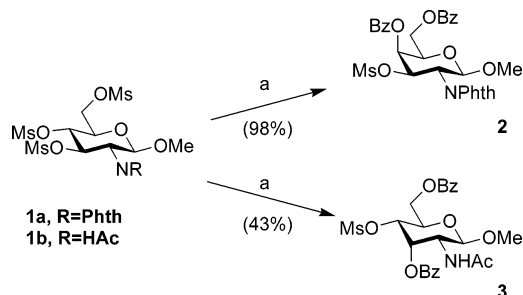
Introduction

Carbohydrates play essential roles in many biological processes, including cell–cell, cell–pathogen, and cell-signaling events.[1,2] As the functions of carbohydrates in normal biological processes and in disease states have begun to be recognized, increasing synthetic effort has been devoted to these molecules by medicinal chemists, with the result that dozens of carbohydrates and polysaccharide derivatives are now either on the market, or in clinical trials, for diseases ranging from cancer, diabetes, bacterial and viral infections, and Gaucher's disease.[3–7]

It is clear that carbohydrates will become increasingly important in the search for therapeutics for new and existing diseases.[8] Among the constraints on the development of new carbohydrate-based drugs have been the synthetic challenges involved in efficiently manipulating these stereochemically complex and densely functionalized molecules. Current methodologies for the selective functionalization of carbohydrates are often inefficient and uneconomical because they require the extensive use of protection/deprotection strategies to differentiate the often similarly reactive secondary hydroxyl groups. These multiple steps lead to low overall yield and can be very demanding in terms of time, reagents, and chromatographic separations needed to accomplish the synthesis of the desired target molecules.[9]

We are exploring a different approach to the synthesis of carbohydrate derivatives. Our strategy has been to convert all of the nonanomeric carbohydrate hydroxyl groups of carbohydrates into sulfonate ester leaving groups and then to treat these molecules with an excess of a particular nucleophile. We have shown that only one of those sulfonates derived from secondary hydroxyl groups generally reacts with nucleophiles, thus allowing for the clean and high-yielding conversion of a carbohydrate into its epimer. For example, we have shown that the trimesylate (**1a**), easily prepared from *N*-phthaloyl glucosamine,[10] undergoes nucleophilic substitution reactions at positions four and six when treated with an excess of sodium benzoate in hot DMF, to give the galactosamine derivative (**2**), in almost quantitative yield. We have also shown the corresponding *N*-acetyl derivate (**1b**) undergoes clean substitution reactions under the same conditions, this time at positions three and six, to yield the allosamine derivate (**3**) (Scheme 1).[10]

While the reactions shown in Scheme 1 are particularly short and efficient routes for converting inexpensive glucosamine to galactosamine and allosamine derivatives, the factors controlling the selectivity of the nucleophilic substitutions are unclear. We demonstrated that the configuration of the anomeric methoxyl group in either **1a** or **1b** was unimportant in determining the regioselectivities of the subsequent reactions with benzoate ion.[10] Clearly then, the courses of the reactions of **1a** and **1b** were dependent upon the nature of amine protecting groups (phthaloyl vs acetyl), but whether steric or electronic factors dominated this selectivity remains to be determined. We were also interested in examining the intrinsic reactivities of the different secondary sulfonate esters around the pyranose ring toward nucleophiles.

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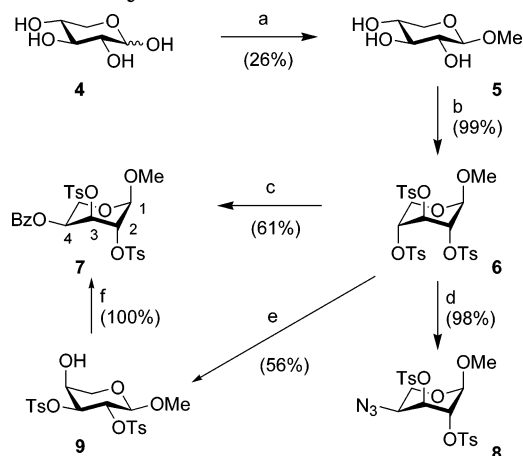
SCHEME 1[a]

[a] Reagents and conditions: (a) NaOBz, DMF, 140 °C.

SCHEME 2. Xylose Series[a]

[a] Reagents and conditions: (a) MeOH, ion-exchange resin, reflux; (b) TsCl, pyridine, rt; (c) NaOBz, DMF, 130 °C; (d) NaN$_3$, DMF, 130 °C; (e) NaNO$_2$, DMF, 130 °C; and (f) BzCl, pyridine, rt.

SCHEME 3[a]

[a] Reagents and conditions: (a) MsCl, pyridine, rt.

To clarify these issues, and to investigate the scope and potential of this synthetic strategy, we embarked upon a systematic study of the reactions that tritosylate derivatives of the four aldopentose methyl pyranosides (xylose, arabinose, ribose, and lyxose) undergo when treated with a range of oxygen- and nitrogen-based nucleophiles, namely, benzoate, nitrite, and azide. Since achieving high selectivity for these nucleophilic substitution reactions was of paramount importance to us, we deliberately chose only a moderately powerful leaving group, the 4-toluenesulfonate ester. More reactive leaving groups such as triflates might be expected to undergo much less selective displacement reactions, as well as ring contractions and other side reactions.[11] Our reason for choosing to study the tosylate leaving group, rather than the similarly reactive mesylate, was that tosylates are readily removed by several mild methods, including treatment with magnesium metal in methanol solution.[12]

The results reported here show that, in most cases, we can achieve highly regioselective displacements of a single secondary tosylate group with various nucleophiles, without the need for the usual protecting group strategies normally employed in carbohydrate chemistry.

Results and Discussion

Xylose Series. Methyl β-D-xylopyranoside (**5**) was prepared by refluxing D-xylose (**4**) in anhydrous methanol, in the presence of acidic ion-exchange resin (Scheme 2). The crude crystalline product was shown by NMR spectroscopy to be a 2:1 mixture of the β- and α-anomers. The pure β-anomer (**5**) (identified by a $^3J_{1,2}$ coupling constant of 7.6 Hz) was obtained after a single recrystallization from ethanol. Tosylation of the secondary hydroxyl groups of **5** under the usual conditions proceeded uneventfully to give the tritosylate (**6**). Examination of the ^{1}H NMR spectrum of **6**, however, revealed an unusual conformation for this molecule. Instead of adopting the expected $^4C_1$ conformation, with all substituents in equatorial orientations, it was clear from the coupling constants of the ring protons that the pyranose ring in fact adopts a $^1C_4$ conformation, with the three tosyloxy groups and the methoxyl group of **6** in axial orientations. Key coupling constants that supported this assignment were the $^3J_{1,2}$ coupling of 3.3 Hz, the $^3J_{2,3}$ coupling of 4.9 Hz, and the $^3J_{3,4}$ coupling of 5.0 Hz; values consistent with the all-axial conformation but not consistent with
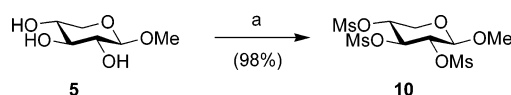
the all-equatorial conformation. Further evidence for the conformation of **6** being $^1C_4$ was the presence of long-range W-coupling (^4J coupling) between the equatorial protons at positions 3 and 5 ($^4J_{3,5}$ = 0.8 Hz) and between the protons at positions 2 and 4 ($^4J_{2,4}$ = 0.5 Hz).

Pyranose rings conformations in which most of the substituents have adopted axial orientations have been observed before, particularly when those substituents have been bulky.[13–16] The tendency of a pyranose ring to adopt the $^1C_4$ conformation appears to arise from the unfavorable 1,2-trans steric repulsions that would arise if these substituents were oriented equatorially in the $^4C_1$ pyranose conformation.

To confirm that the steric bulk of the tosyl groups on **6** was responsible for the pyranose ring adopting an all-axial conformation, the corresponding trimesylate derivative (**10**) was prepared by treatment of triol (**5**) with methanesulfonyl chloride in pyridine (Scheme 3). ^{1}H NMR spectroscopy revealed clearly that, unlike the tritosylate (**6**), the trimesylate (**10**) adopts the expected all-equatorial $^4C_1$ conformation. The $^3J_{1,2}$ coupling constant of 7.6 Hz of **10** is diagnostic for H1 and H2 adopting a trans-diaxial orientation, and the remaining coupling constants ($^3J_{2,3}$ coupling of 9.4 Hz and the $^3J_{3,4}$ coupling of 9.3 Hz) were also consistent only with the $^4C_1$ conformation.

Treatment of the D-xylo tritosylate (**6**) with an excess of sodium benzoate in hot DMF gave the L-arabino monobenzoate (**7**), with nucleophilic substitution having

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occurred at position 4 (Scheme 2). The $J_{1,2}$ coupling constant of **7** was 4.1 Hz, indicative of a trans-diequatorial relationship between these protons, again suggesting a $^1C_4$ conformation of the ring, with the two tosyloxy substituents oriented axially at positions 2 and 3 and the newly introduced benzoate group at position 4 oriented equatorially. This was supported by the other coupling constants of the protons attached to the pyranose ring, particularly the small W-coupling (0.5 Hz) between the two equatorial protons at positions 3 and 5.

Treatment of the D-xylo tritosylate (**6**) with two molar equivalents of sodium azide in hot DMF gave a single crystalline product, in almost quantitative yield (Scheme 2). ^{1}H NMR spectroscopy identified this as the 4-azido-L-arabino derivate (**8**), and again, analysis of the coupling constants ($J_{1,2} = 4.4$ Hz) indicated that the pyranose ring of **8** adopts a $^1C_4$ conformation with all substituents adopting axial orientations, except for the azido group at position four, which lies equatorially.

When the D-xylo-tritosylate (**6**) was treated with an excess of sodium nitrite in hot DMF, the crystalline L-arabino ditosylate (**9**) was obtained. That the 4-tosylate of **6** had been displaced with inversion of configuration during this reaction was established by the conversion of **9** to its benzoate ester (**7**), which was identical to the benzoate prepared directly from the reaction of the tritosylate (**6**) with benzoate ion (Scheme 2). Although compounds **8** and **9** differ only in the substituents at position 4 (azide vs hydroxyl), this difference appears to be sufficient to control the conformation of the pyranose ring. For the alcohol (**9**), the $^3J_{1,2}$ coupling constant of 5.3 Hz, and more particularly, the $^3J_{2,3}$ coupling constant of 7.5 Hz suggest that **9** adopts a $^4C_1$ conformation. Examination of molecular models of **9** suggests that a favorable hydrogen bond can form between the hydrogen of the axial hydroxyl group at position four and one of the S=O groups of the tosylate group at position three, stabilizing the $^4C_1$ conformation. Conversion of the alcohol (**9**) to its benzoate ester (**7**) tips the ring to the $^1C_4$ conformer.

Arabinose Series. The known methyl β-L-arabinopyranoside (**12**) was prepared by refluxing L-arabinose (**11**) in anhydrous methanol, in the presence of acidic ion-exchange resin (Scheme 4). The pure β-anomer ($^3J_{1,2} = 3.5$ Hz) was obtained by recrystallization of the crude product from ethanol. Treatment of the triol (**12**) with 4-toluenesulfonyl chloride in pyridine for 7 days gave the crystalline tritosylate (**13**) in 68% yield after recrystallization (Scheme 4). The pyranose ring conformation of **13** was shown by ^{1}H NMR spectroscopy to be $^4C_1$, with the methoxyl and the tosyloxy group at position 4 oriented axially, and the two tosyloxy groups at positions 2 and 3 adopting equatorial orientations. Particularly diagnostic was the $^3J_{2,3}$ trans-diaxial coupling constant of 10.2 Hz.
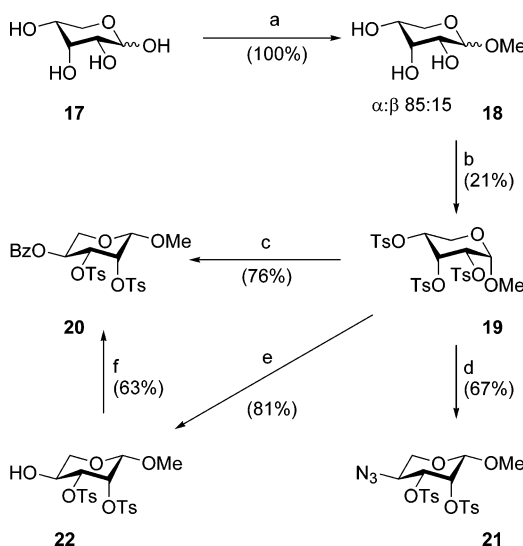
When the L-arabinose tritosylate (**13**) was treated in the usual way with an excess of sodium benzoate, a single displacement reaction occurred, yielding the D-xylose derivate (**14**) (Scheme 4). The appearance in the ^{1}H NMR spectrum of the H3 signal as a triplet (J 9.5 Hz, neighboring axial hydrogens at positions 2 and 4) confirmed that substitution had occurred at position four and that the product was the monobenzoate (**14**). This same benzoate could also be prepared by the two-step process

SCHEME 4. Arabinose Series[a]
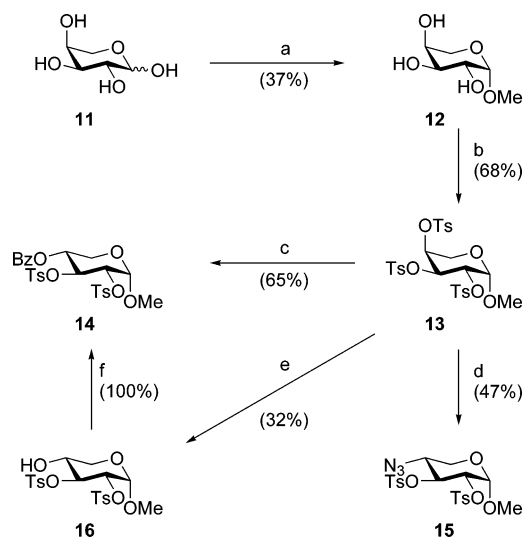
[a] Reagents and conditions: (a) MeOH, ion-exchange resin, reflux; (b) TsCl, pyridine, rt; (c) NaOBz, DMF, 130 °C; (d) NaN₃, DMF, 130 °C; (e) NaNO₂, DMF, 130 °C; and (f) BzCl, pyridine, rt.

SCHEME 5. Ribose Series[a]

[a] Reagents and conditions: (a) MeOH, AcCl, 50 °C; (b) TsCl, pyridine, rt; (c) NaOBz, DMF, 130 °C; (d) NaN₃, DMF, 130 °C; (e) NaNO₂, DMF, 130 °C; and (e) BzCl, pyridine, rt.

outlined in Scheme 4, employing first the reaction of the L-arabinose tritosylate (**13**) with sodium nitrite in hot DMF, to give the D-xylose ditosylate (**16**), followed by esterification of **16** to give the benzoate (**14**). This sequence demonstrated that nucleophilic attack by nitrite anion on **13** also occurred at position 4 and with inversion of configuration at that location.

Single substitution at the 4-position of the L-arabinose tritosylate (**13**) had also occurred when excess azide ion in hot DMF was employed, giving the 4-azido-D-xylose derivative (**15**) (Scheme 4).

Ribose Series. Methyl α-D-ribose (**18**) was prepared by treating a methanolic solution of D-ribose (**17**) with acetyl chloride (Scheme 5). A sample of the crude syrupy product was acetylated to aid in the NMR interpretation. The NMR spectrum of the triacetate, which corresponded

SCHEME 6.   Lyxose Series[a]
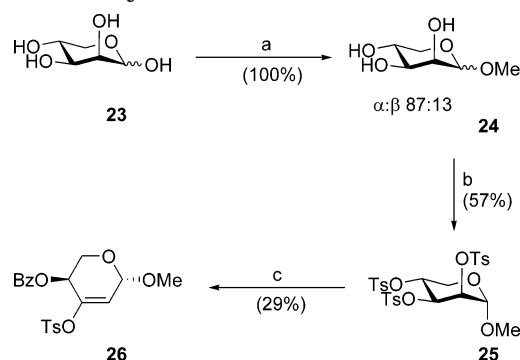
[a] Reagents and conditions: (a) MeOH, AcCl, 50 °C; (b) TsCl, pyridine, rt; and (c) NaOBz, DMF, 130 °C.

well with that reported by Dahlhoff et al.[17] indicated that the crude α-anomer (**18**) was contaminated with approximately 15% of the β-anomer. The crude syrup was used directly for subsequent steps.

Conversion of the methyl ribopyranoside (**18**) to its tritosylate derivative (**19**) proved to be extremely difficult. Prolonged exposure of **18** to excess tosyl chloride in pyridine gave mainly a ditosylated product, identified by mass spectrometric analysis of the crude mixture. Only after subjection of the reaction mixture to prolonged reaction times and sonication in a cleaning bath could any of the tritosylate (**19**) be obtained (Scheme 5). This was separated from the ditosylated product by column chromatography, then further purified by recrystallization to remove a small amount of the undesired β-anomer.

The reaction of the D-ribose tritosylate (**19**) with excess sodium benzoate in hot DMF gave the L-lyxose benzoate (**20**) in good yield, substitution having again occurred at position 4 with inversion of configuration (Scheme 5). The ^{1}H NMR spectrum showed that **20** exists in the $^1C_4$ conformation, as shown in Scheme 5. The $^3J_{3,4}$ coupling constant of 7.7 Hz was indicative of a trans-diaxial relationship between these two hydrogens.

The L-lyxose ditosylate (**22**) was prepared by reacting **19** with sodium nitrite in hot DMF. The structure of **22** was confirmed by its conversion to the benzoate (**20**), identical to the material prepared directly from the tritosylate (**19**). Selective displacement of the 4-tosylate of **19** also occurred when it was treated with sodium azide, giving the 4-azido-4-deoxy-L-lyxose derivative (**21**) in 67% yield. Again, the $^3J_{3,4}$ coupling constant of 7.8 Hz in the ^{1}H NMR spectrum of **21** suggested that these hydrogens were oriented trans-diaxially to each other.

Lyxose Series. D-Lyxose (**23**) was treated with acetyl chloride in methanol to give the methyl glycoside (**24**) (Scheme 6). Although a mixture of isomers was obtained, crystals of the α-anomer slowly formed on standing. A sample of the syrupy crude product was analyzed by ^{1}H NMR spectroscopy after conversion to its triacetate, and this showed that the ratio of α- and β-anomers was 87: 13. Conversion the triol (**24**) to its tritosylate (**25**) was achieved under the usual conditions, to give the product

as a crystalline solid. The ^{1}H and ^{13}C NMR spectrum of this compound exhibited significant broadening of the ring proton and carbon signals (but not for the signals associated with the tosyl groups), suggesting some significant conformational exchanges on the NMR time scale.

The D-lyxose tritosylate (**25**) proved to be completely resistant to nucleophilic substitution reactions. When treated with either sodium azide or sodium nitrite in hot DMF, only the starting material could be detected by TLC and MS analysis, even after reaction times of 7 days. Workup of the reaction after this time led to high recovery of the starting tritosylate (**25**). Although the 4-tosylate may have been expected to undergo displacement with nucleophiles, the steric bulk of the axial tosylate at position 2 of **25** would be expected to severely inhibit the approach of nucleophiles to position 4.

Treatment of **25** with sodium benzoate in hot DMF for 5 days led to the production of the dihydropyran (**26**), in modest yield. This product presumably arises via an initial anti-elimination of the axial toluenesulfonate group at position 2, promoted by the removal of an axial proton at position three by the benzoate ion, which acts as a base. This initially formed allylic tosylate intermediate would then be expected to undergo facile nucleophilic displacement with additional benzoate ion to give the dihydropyran (**26**).

Conclusions

The 2,3,4-tritosylate derivatives of the methyl pyranosides of L-arabinose, D-ribose, D-lyxose, and D-xylose have been prepared, and their reactions with sodium azide, sodium nitrite, and sodium benzoate in hot DMF have been examined. In the case of the tritosylate derivatives of arabinose, ribose, and xylose, high regioselectivities were observed, and only a single nucleophilic substitution reaction occurred, even when these substrates were treated for prolonged periods with an excess of nucleophile. In all cases, substitution occurred exclusively at position four of the pyranoside, regardless of whether the tosylate substituent occupied an axial or an equatorial orientation in its ground state. Thus, simple and direct routes have been established for the conversion of D-ribose to L-lyxose derivatives, from L-arabinose to D-xylose derivatives, and from D-xylose to L-arabinose derivatives. The tritosylate derived from a-D-lyxopyranoside was unreactive toward azide and nitrite nucleophiles. When treated for prolonged periods with sodium benzoate in hot DMF, a dihydropyran product, arising from an initial elimination reaction of the tosylate group at position two, was obtained.

Supporting Information Available: Full experimental details and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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