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Differential Reactivity of α- and β-Anomers of Glycosyl Acceptors in Glycosylations. A Remote Consequence of the *endo*-Anomeric Effect?

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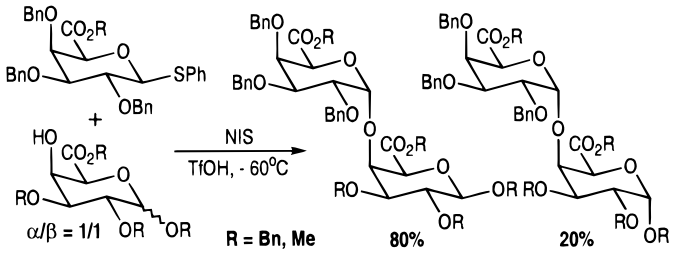
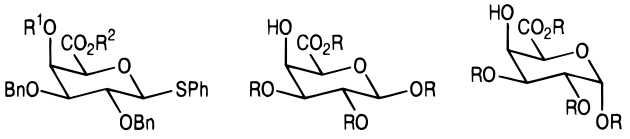
ABSTRACT



When phenyl tri-*O*-benzyl-1-thio-β-D-galactopyranosiduronic acid esters were coupled with a 1/1 mixture of α and β 2,3 di-*O*-protected D-galactopyranosiduronic acid esters, the β-anomer proved to be more reactive. Data from theoretical calculations suggested that the enhanced reactivity of this anomer compared with the α one would be due to a stronger hydrogen bond of the C-4 OH with the ring oxygen.

We recently reported that direct coupling between two D-galacturonic acid esters can be performed in good yields when 1-thioglycosides are used as donors.[1] For example, the condensation, at − 60 °C, between **1a** and **2**β (Figure 1) in the presence of *N*-iodosuccinimide and triflic acid used as promoters afforded disaccharide **4a** (Figure 2) in 88% yield.[1b] In contrast, when **1a** was reacted with disaccharide acceptor **4b** we observed that the reaction became sluggish and had to be conducted at room temperature, giving rise to the expected trisaccharide in only 45% yield.[1a] We first envisaged that the difference in reactivity between **2**β and **4b** could be due to steric effects. Indeed, the presence of the α-oriented bulky substituant at C-1′ in **4b** would force the C-2′ and



1a R^1 = Bn, R^2 = Me
1b R^1 = Bn, R^2 = Bn
1c R^1 = H, R^2 = Bn

2β R = Bn
3β R = Me

2α R = Bn
3α R = Me

Figure 1. Monosaccharide reactants.

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(1) (a) Magaud, D.; Grandjean, C.; Doutheau, A.; Anker, D.; Shevchik, V.; Cotte-Pattat, N.; Robert-Baudouy, J. *Tetrahedron Lett.* **1997**, *38*, 241−244. (b) Magaud, D.; Grandjean, C.; Doutheau, A.; Anker, D.; Shevchik, V.; Cotte-Pattat, N.; Robert-Baudouy, J. *Carbohydr. Res.* **1998**, *314*, 189−199.

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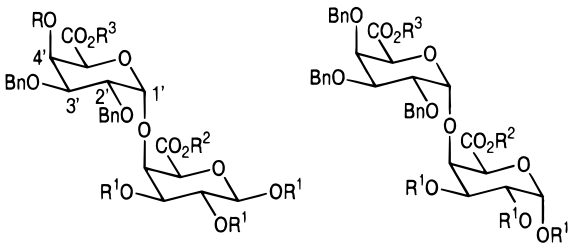

4a R = Bn, $R^1 = R^2 = Bn$ R^3 = Me
4b R = H $R^1 = R^2 = R^3$ = Bn (reactant)
4c R = Bn, $R^1 = R^2 = R^3$ = Bn
4d $R^1 = R^2 = R^3$ = Bn
4e R = Bn, $R^1 = R^2 = R^3$ = Me
4f $R^1 = R^2 = R^3$ = Me

Figure 2. Disaccharide reactants and products.

C-3′ benzyloxy groups on the *upper face* and thus reduce the accessibility of the C-4′ OH group. However, we also noticed that a structural difference between the two acceptors was the configuration of the anomeric carbons C-1 and C-1′, respectively β in compound **2**β and α in compound **4b**. We thus found it interesting to compare the relative reactivity of the two anomeric acceptors **2**α and **2**β when simultaneously reacted with donor **1b**.[2]

When coupling a mixture of **2**α (0.5 equiv) and **2**β (0.5 equiv) with donor **1b** (0.6 equiv) under usual conditions,[1b] monitoring of the reaction by TLC indicated that the former compound reacted faster. After purification of the crude product we obtained, in 67% yield based on donor, a mixture of **4c** and **4d** in the ratio **4c**/**4d** = 4:1.[3] As already envisaged for acceptors **2**β and **4b**, the difference in reactivity between **2**α and **2**β would again result from a greater steric hindrance around the 4-OH group in the former compound. However molecular modeling[4] data did not confirm this hypothesis and failed to provide a rationale for the differential reactivity between **2**α and **2**β based on steric considerations.[5] Analysis of conformational space showed that in both compounds in their favored $^4C_1$ conformations, the C-4 hydroxyl group does not present steric compression and remains accessible. Therefore, we decided to examine the relative reactivity of **3**α and **3**β, the analogues of compounds **2** bearing methoxy groups at C-1, C-2, and C-3. We reasoned that, in these compounds, it would be rather unlikely that the steric hindrance around the 4-OH group would depend on the anomeric configuration.

The known acceptors[6] **3**α and **3**β were obtained in respectively 64% and 33% yields from methyl 2,3-di-*O*-methyl α− and β-D-galactopyranosides[7] by selective oxidation of the C-6 hydroxyl group (Pt/C, O_2, $NaHCO_3$, H_2O, 95 °C) followed by treating the resulting sodium carboxylate with methyl iodide in DMF. When a mixture of **3**α (0.5 equiv) and **3**β (0.5 equiv) was reacted with **1a** (0.6 equiv), we again observed that **3**β was more rapidly consumed than **3**α and we obtained a mixture of **4e** and **4f** (ratio **4e**/**4f** = 4:1[8]) in 83% yield based on donor **1a**.

To rationalize the differential reactivity[9] between the α- and β-anomers in acceptors **2** or **3**, we formulated the following hypothesis: Due to the absence of an *endo*-anomeric effect[10] the basicity of the pyranosyl oxygen atom in β-anomers would be greater than that in the α ones.[11] As a consequence, in the β-anomers the intramolecular hydrogen bonding between the axial 4-OH group and its proximal pyranosyl oxygen would be stronger than that in the α-anomers and therefore the C-4 alcoholic function should be more nucleophilic.[12] This hypothesis is supported by the results of theoretical ab initio calculations[13] (Figure 3) carried out on 5-hydroxy-2-methoxytetrahydropyrans **5** used as models of α and β galactopyranosides: the distance between the two involved atoms would be respectively 2.37 Å in **5**β

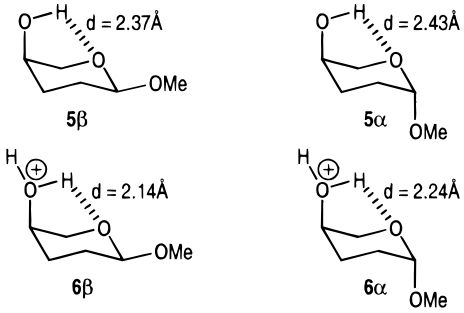

Figure 3. Ab initio 6.31G* geometries.

(2) Compounds **1a**−**c** and **2**β were prepared according to ref 1b. The acceptor **2**α was obtained as follows: **1c** was transformed into the corresponding silyl ether (TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 100%) which was reacted with benzyl alcohol (NIS, TfOH, CH_2Cl_2/Et_2O 1/2, 4 Å MS, 25 °C, 3 h) to give, in 75% yield, a mixture of anomeric benzyl glycosides (α/β = 1:1.5) which were separated by column chromatography. Cleavage of the TBDMS group in the α-anomer (TFA, 10% H_2O, 1 h 30 min, 93%) gave **2**α.

(3) This ratio was determined from the ^{1}H NMR spectrum of the mixture on the integration of the hydrogen signals at C-1′: **4c**, 5.32 (d, 0.8 H, $J_{1'-2'}$ = 2.9, H-1′), **4d**, 5.20 (d, 0.2 H, $J_{1'-2'}$ = 3.3, H-1′). The major isomer in the mixture was deduced from the integration of signals at 3.77 and 3.46 corresponding respectively to H-2 and H-3 in **4c** (values to be compared with 3.77 and 3.52 in **2**β *versus* 3.87 and 3.97 in **2**α). The ratio **4c**/**4d** was confirmed by the ratio of recovered unreacted acceptors (**2**α/**2**β = 80:20) determined from the ^{1}H NMR spectrum of the mixture (integration of H-2 and H-3 hydrogen signals).

(4) (a) Boswell, D. R.; Coxon, E. E.; Coxon, J. M. In *Advances in Molecular Modeling*; Liotta, D., Ed.; Jai Press Inc.: Greenwich, 1995; Vol. 3. (b) Leach, A. R. In *Molecular Modeling, Principles and Applications*; Longman, 1996.

(5) The molecular dynamic trajectories were calculated using version 6.01 of SYBYL (SYBYL Molecular Modeling System, Tripos Associates Inc., St. Louis, MO, 1993). The simulation of the two anomers was initiated with zero kinetic energy using a time step of 0.5 fs, at 300 K. The lengths of the trajectories are 1.000 ps.

(6) Synthesis of **3**α: Grishkovets, V. I.; Zemlyakov, A. E.; Chirva, V. Y. *Chem. Nat. Compd. (Engl. Transl.)* **1983**, *19*, 522−524. Synthesis of **3**β: Evtushenko, E. V.; Ovodov, Y. S. *Chem. Nat. Compd. (Engl. Transl.)* **1987**, *23*, 28−30.

(7) Williams, N. R.; Jeanloz, R. W. *J. Org. Chem.* **1964**, *29*, 3434−3435.

(8) Column chromatography of the crude product gave pure samples of **4e** and **4f** and a mixture of these two compounds. In this mixture the ratio **4e**/**4f** was determined from the integration of the signals of hydrogens H-1′ and H-5.

(9) This 4:1 ratio corresponds to a ratio of about 7 for the rate constants for the glycosylation reactions with respectively β and α acceptors.

and 2.43 Å in **5**α in favor of a stronger hydrogen bonding in the former compound. A similar distance difference was observed when modeling hydroxonium species **6**α and **6**β designed to mimic positively charged cationic intermediates formed by nucleophilic attack of acceptors on activated donors during glycosylation reactions.

To try to confirm the above hypothesis, we compared the reactivity of glucuronic acid ester derivatives **7** (Figure 4).

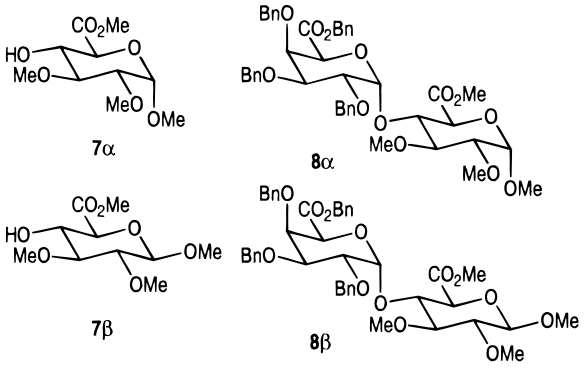

Figure 4. Glucuronic acid reactants and products.

Acceptors **7**α and **7**β were obtained by following the procedure used for the preparation of compounds **3**, from known methyl 2,3-di-*O*-methyl α- and β-D-glucopyranosides.[14]

When a mixture of acceptors **7**α (0.5 equiv) and **7**β (0.5 equiv) was reacted with donor **1b** (0.6 equiv), we obtained a mixture of disaccharides **8**α and **8**β (in 62% yield based on donor **1b** and with a **8**β/**8**α ratio of 1.2/1); some unreacted acceptors **7** were also recovered as a 1.1/1 mixture of **7**α and **7**β.[15]

Thus, as expected, with glucuronic acceptors **7**, in which the equatorial orientation of the C-4 OH group prevents the formation of an internal hydrogen bond with the pyranosyl oxygen atom, the difference in reactivity between the α- and β-anomers is far less pronounced than that with their galacturonic analogues. The residual slightly enhanced reactivity of the β-anomer could be due to the delocalization of oxygen nonbonding electrons into the σ^* orbital of the C_4-C_5 bond (Figure 5) enhancing the electron density at C-4 and consequently on the C-4 OH group.[16]

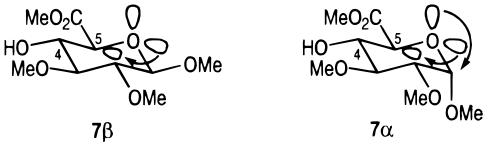

Figure 5. n → σ^* delocalization.

Again this delocalization would be more important in the β than in the α-anomer due to the greater basicity of the ring oxygen in the former compound. Evidently the same effect would also contribute to some extent to the enhancement of the C-4 OH reactivity in acceptors **2**β or **3**β.

In conclusion, we report here that the reactivity of galactopyranosiduronic acid esters possessing a C-4 free hydroxyl depends significantly on the anomeric configuration. To the best of our knowledge such clear-cut differences of behavior between α- and β-anomers have been rarely observed.[17] Data from theoretical calculations suggested that the C-4 alcohol would be more nucleophilic in the β- than in the α-anomers because of a stronger hydrogen bonding of the OH group, acting as H-donor, with the ring oxygen. The greater reactivity of the β-anomers would also be due to enhancement of the electron density on the C-4 OH group in these compounds due to a more important n → σ^* delocalization. These two effects would result from the greater basicity of pyranosyl oxygen atom in the β- than in the α-anomers due to the absence of an *endo*-anomeric effect in the former compounds.[18] We will now examine if a similar differential reactivity between anomers is also observed with galactose or L-arabinopyranose derivatives.

Acknowledgment. Some of us (D.M.,D.A., A.D.) thank the European Community (Contract AIR2-CT94-1345) for financial support and undergraduate students for technical assistance.

Supporting Information Available: Typical experimental procedure for competitive glycosylation reactions. Full characterization for compound **2**α. ^{1}H NMR spectra for compounds **3**α and **3**β . ^{1}H NMR and ^{13}C NMR spectra and optical rotations for compounds **7**α and **7**β. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) (a) Deslongchamps, P. In *Stereoelectronic Effects in Organic Chemistry*; Baldwin, J. E., Ed.; Pergamon Press: Oxford, England, 1983. (b) Juaristi, E.; Cuevas, G *Tetrahedron* **1992**, *48*, 5019−5087. (c) Kirby, A. J.; Williams, N. H. In *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R., Ed.; ACS Symp. Series 539; American Chemical Society: Washington, DC, 1993.

(11) For the influence of the anomeric configuration of 1,5-dithioglucopyranosides on the ring sulfur nucleophilicity, see: Yuasa, H.; Kamata, Y.; Hashimoto, H. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 868−870.

(12) For hydrogen bonding between C-4 axial groups and ring oxygen in six-membered rings, see: (a) Alonso, J. L.; Wilson, E. B. *J. Am. Chem. Soc.* **1980**, *102*, 1248−1251. (b) Kwon, O.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 1588−1599.

(13) The calculations were carried out at the RHF 6.31G* level of theory by means of GAMESS; see: Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.;. Matsunaga, N.; Nguyen, K. A.; Su, S. J.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347−1363.

(14) Nicoll-Griffith, D. A.; Weiler, L. *Tetrahedron* **1991**, *47*, 2733−2750.

(15) In this case, due to the weaker reactivity of acceptors **7** compared with acceptors **3**, the glycosylation had to be carried out at −30 °C. Disaccharides **8**α and **8**β and recovered acceptors **7**α and **7**β were separated by column chromatography of the crude product. Structural assignments for compounds **8** were based on the signals for H-2 (3.30, dd, $J_{2-3} = 9.6$, $J_{2-1} = 3.4$) in **8**α and for H-1 (4.18, d, $J_{1-2} = 7.5$) for **8**β.

(16) Fan, Y.-H.; Haseltine, J. *Tetrahedron Lett.* **1996**, *37*, 9279−9282.

(17) For recent examples see: (a) Zhu, X. X.; Cai, M. S.; Zhou, R. L. *Carbohydr. Res.* **1997**, *303*, 261−266. (b) Rochepeau-Jobron, L.; Jacquinet, J.-C. *Carbohydr. Res*. **1997**, *305*, 181−191.

(18) Even if it turned out that the α-anomeric configuration of C-1′ in **4b** was unfavorable for the glycosylation, it seems that this factor could not account alone for the poor reactivity of this acceptor when coupled with **1a**. The difficulty of undergoing coupling in this case could be also due, in part, to a steric mismatch between donor and acceptor.