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Note

On the regioselectivity of the Hanessian–Hullar reaction in 4,6-*O*-benzylidene protected galactopyranosides

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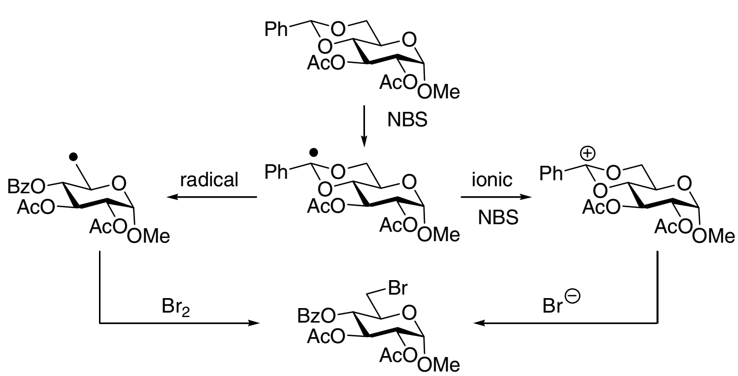
Abstract—The *N*-bromosuccinimide mediated fragmentation of methyl 4,6-*O*-benzylidene-β-D-galactopyranoside results in the formation of methyl 4-*O*-benzoyl-6-bromo-6-deoxy-β-D-galactopyranoside and methyl 4-*O*-benzoyl-3-bromo-3-deoxy-β-D-gulopyranoside, as opposed to the methyl 6-*O*-benzoyl-3-bromo-3-deoxy-β-D-gulopyranoside originally reported. The kinetic methyl 4-*O*-benzoyl-6-bromo-6-deoxy-β-D-galactopyranoside rearranges to the thermodynamic methyl 4-*O*-benzoyl-3-bromo-3-deoxy-β-D-gulopyranoside under the reaction conditions, likely via a 3,6-anhydro galactopyranoside. The NBS-mediated cleavage of 4,6-*O*-benzylidene acetals in the galactopyranoside series is therefore shown to conform to the regiochemistry observed in the corresponding gluco- and mannopyranoside series with preferential cleavage of the C6–O6 bond by an ionic mechanism.

Keywords: Deoxy sugars; Benzylidene acetal

The *N*-bromosuccinimide mediated fragmentation of benzylidene acetals is an important and facile means of access to deoxy sugars.[1–11] The reaction is accepted to proceed by an initial hydrogen atom abstraction to give a benzylidene radical, which then suffers fragmentation by either of the two potential pathways, as illustrated for the 4,6-*O*-benzylidene-type acetal in the *gluco*-series (Scheme 1). Both pathways were envisaged from the outset by Hanessian who, nevertheless, favored the ionic mode of fragmentation.[1,3] Hullar, on the other hand, initially promoted the pure radical pathway.[2] Indirect support has subsequently been provided for



Scheme 1. Radical and ionic pathways for benzylidene fragmentation.

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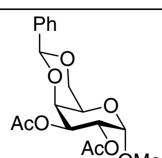
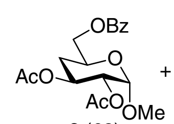
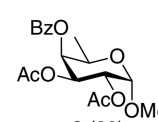
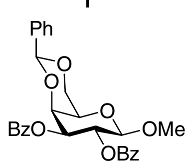
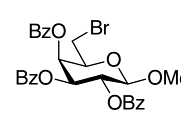
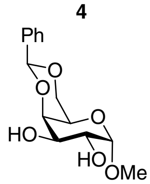
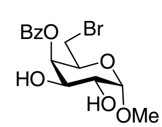
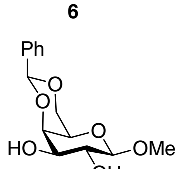
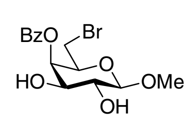
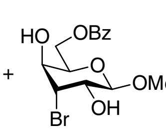
the ionic fragmentation,[12] and this is generally accepted to be the most plausible mechanism. The waters were muddied, however, by the elegant work of Roberts who, following early work by Jeppesen,[13] showed that pure radical fragmentations of 4,6-*O*-benzylidene acetals proceed with preferential cleavage of the primary C6–O6 bond in both the glucose and mannose series.[14–17] Work from this laboratory concurs with Roberts regarding the regioselectivity of fragmentation of the 4,6-*O*-benzylidene acetals in both the *gluco*- and *manno*-series under free radical conditions.[18]

Perusal of the literature reveals that the 4,6-*O*-benzylidene galactopyranosides potentially afford the means of distinguishing between the two pathways for the NBS-mediated Hanessian–Hullar reaction. Thus, for the 4,6-*O*-benzylidene galactopyranosides the pure radical fragmentation affords mixtures of the 4- and 6-deoxy products owing to competing cleavage of the primary and secondary C–O bonds (Table 1, entry 1).[14–17] On the other hand, two out of three 4,6-*O*-benzylidene galactopyranosides studied by Hanessian in the NBS-mediated protocol gave exclusively the 6-bromo-6-deoxy product (Table 1, entries 2 and 3), thereby strongly indicating the ionic fragmentation. Curiously, however, a third NBS-mediated example was reported to afford a mixture of the expected 6-bromo-6-deoxy product **9**, and a somewhat unusual 3-bromo-3-deoxygulopyranoside **10** (Table 1, entry 4), which leaves open the possibility of alternative mechanisms. No explanation was provided by Hanessian for the formation of this unusual product **10**, whose structure was based on comparison of physical data with that of an authentic sample[19] of methyl 3-deoxy-β-D-xylopyranoside following hydrogenolytic removal of the bromine atom and saponification, but an ionic mechanism was later put forward by Gelas for its formation.[9]

With a view to better understand the regioselectivity of benzylidene acetal fragmentation, we have repeated the reaction of methyl 4,6-*O*-benzylidene-β-D-galactopyranoside **8** with NBS, and report here our results, which lead to a minor revision of the structure of the unusual 3-bromo-3-deoxy-guloside. This minor correction of structure enables a mechanism to be written bringing the regioselectivity of fragmentation in the galactose series into full agreement with that in the glucose and mannose series.

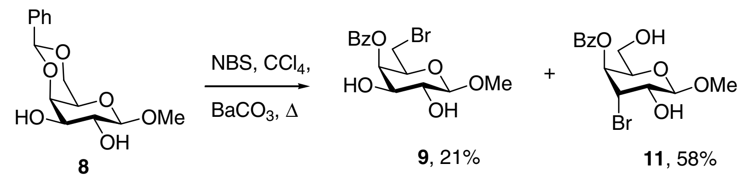
Methyl 4,6-*O*-benzylidene-β-D-galactopyranoside **8**[21] was heated to reflux with NBS and barium carbonate in 3/1 mixture of tetrachloromethane and 1,1,2,2-tetrachloroethane for 4 h. Chromatography on silica gel then enabled the isolation of two products, in yields of 21% and 58%, to which we assign the structures

Table 1. Fragmentation of 4,6-*O*-benzylidene galactopyranosides according to Hanessian and Roberts

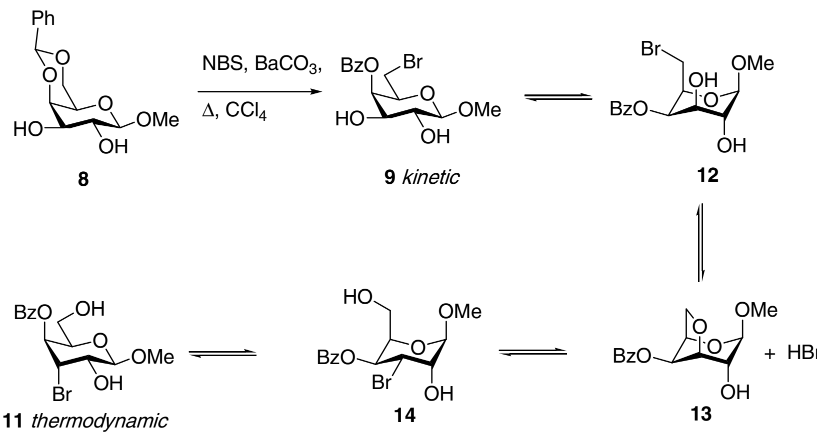
Entry	Substrate[a]	Conditions[b]	Products (% yield)
1	 **1**	DTBP/TIPST	 **2** (62) +  **3** (38)
2	 **4**	NBS	 **5** (65)
3	 **6**	NBS	 **7** (90)
4	 **8**	NBS	 **9** (15) +  **10** (19)

[a] Galactosides **4**, **6**, and **8** were originally represented[3] with the phenyl group axial to the dioxane ring. We have preferred to represent them with the phenyl equatorial in line with crystallographic structures[20] of benzylidene protected galactose derivatives.

[b] DTBP: di-*tert*-butylperoxide; TIPST: triisopropylsilanethiol (i-Pr_3SiSH).



Scheme 2. Reaction of **8** with *N*-bromosuccinimide.



Scheme 3. Mechanism for the formation of 3-bromo-3-deoxy-guloside **11**.

6-bromo-6-deoxygalactoside **9** and 4-*O*-benzoyl-3-bromo-3-deoxy-guloside **11**, respectively (Scheme 2).[†] For the major 3-bromo-3-deoxy product **11**, the location of the benzoate ester on the 4-position and not the 6-position as originally reported (Table 1) is readily apparent from the chemical shift of H-4, an apparent doublet at δ 5.49 ($J = 3.0$ Hz). The axial nature of the C3–Br bond is clear from the ^3J coupling constant of 3.0 Hz in the apparent triplet assigned to H3 resonating at δ 4.64.[‡]

Our structure differs from the original report of Hanessian by the placement of the benzoate ester, something that might easily have been overlooked in 1966, and which has no consequence on the conversion through saponification and hydrogenation to methyl 3-deoxy-β-D-xylopyranoside used in the original structural proof. Nevertheless, it is this different placement of the benzoate ester that enables the NBS-mediated cleavage of **8** to be brought into line with all other known NBS cleavage reactions of 4,6-*O*-benzylidene acetals, be they *galacto*-, *gluco*-, or *manno*-, with preferential cleavage of the C6–O6 bond. Thus, the initial fragmentation reaction gives the 6-bromo-6-deoxy product **9**, which under the conditions of the reaction, is in equilibrium with a ring inverted conformer **12**. The population of this minor conformer is facilitated by the switch from the equatorial to the axial glycoside and the corresponding gain in anomeric stabilization. Formation of a 3,6-anhydro sugar **13** ensues and this is finally cleaved following nucleophilic ring opening by bromide at the 3-position to give **14**, which relaxes to the observed $^4C_1$ conformer **11** (Scheme 3). In strong support of this argument we note that in a reaction taken to low conversion with 44% recovered substrate, similar to the original report of Hanessian, the yield of **9** and **11** was 18% and 14%, respectively, clearly indicating the equilibrium nature of the process with **9** as the kinetic product and **11** as the thermodynamic product.[§] The difference between the β- and α-galactopyranoyl series in the NBS cleavage (Table 1, entries 3 and 4) now is readily seen to be a consequence of the greater ability of the β-anomer to populate the higher energy inverted conformer. The mechanism proposed for the formation of **11** (Scheme 3) is more plausible than the mechanism written by Gelas for the formation of the alternative regioisomer **10**,[9] which contains a stereoelectronically improbable shift of dioxenium ion between the 4,6- and 3,4-

† Jacobsen and Mols mention the formation of methyl 4-*O*-benzoyl-3-bromo-3-deoxy-β-D-gulopyranoside, that is, **11**, from the Hanessian reaction of **8** with NBS, but give neither data nor a rationale for their structural assignment.[22]

‡ We note that Hanessian, working at 60 MHz, characterized the purported **10** by the presence of a doublet ($J = 5.0$ Hz) resonating at δ 5.54 in the ^{1}H NMR spectrum, and that, while this was obviously assigned incorrectly to the anomeric hydrogen, it is consistent with H-4 in structure **11** now proposed.

§ The mass balance in all experiments is made up of several minor unidentified products.

positions, and which does not explain the difference in behavior between the α- and β-anomers.

The high degree of regioselectivity observed in the NBS-mediated fragmentation of **9**, as contrasted with the lack of regioselectivity in the pure radical fragmentations of galactose-based 4,6-*O*-benzylidene acetals (Table 1, entry 1), provides very strong evidence that the Hanessian–Hullar fragmentation proceeds via an ionic mechanism.

1. Experimental

1.1. General methods

Optical rotations were determined with an Autopol III polarimeter for solutions in $CHCl_3$. NMR spectra were recorded for $CDCl_3$ solutions with a Bruker Avance spectrometer. Chemical shifts are in parts per million downfield from tetramethylsilane. High resolution mass spectra were recorded with a Waters Q-TOF2 instrument.

1.2. Methyl 4-*O*-benzoyl-6-bromo-6-deoxy-β-D-galactopyranoside (9) and methyl 4-*O*-benzoyl-3-bromo-3-deoxy-β-D-gulopyranoside (11)

A solution of methyl 4,6-*O*-benzylidene-β-D-galactopyranoside **8** (500 mg, 1.8 mmol) in a mixture of CCl_4 (28 mL) and 1,1,2,2-tetrachloroethane (9 mL) was treated with freshly recrystallized *N*-bromosuccinimide (360 mg, 2.0 mmol) and $BaCO_3$ (715 mg, 3.7 mmol). The solution was deoxygenated by sparging with argon for 1 h and then was heated to reflux with stirring for 4 h. After the mixture was cooled to room temperature and filtered, it was dried (Na_2SO_4), concentrated, and purified by column chromatography on silica gel (2:1, hexane/EtOAc) to give first **11** (0.388 g, 1.03 mmol, 58%) as a syrup, and then **9** (0.139 g, 0.37 mmol, 21%) in the form of a viscous oil. Compound **9**: $[\alpha]_D$ +3.7 (*c* 1.0), lit.[3] $[\alpha]_D$ +25 (*c* 1.57, $CHCl_3$); ^1H NMR (500 MHz): δ 8.06 (d, 2H, $J = 7.5$ Hz, $2 \times H_{ortho}$), 7.57 (t, 1H, $J = 7.5$ Hz, 1H, H_{para}), 7.45 (t, 2H, $J = 7.5$ Hz, $2 \times H_{meta}$), 5.68 (d, 1H, $J = 1.5$ Hz, H-4), 4.28 (d, 1H, $J = 7.2$ Hz, H-1), 3.88–3.92 (m, 2H, H-3 and H-5), 3.75 (m, 1H, H-2), 3.62 (s, 3H, CH_3), 3.43 (m 2H, $2 \times$ H-6); ^{13}C NMR (125 MHz): δ 177.97 (C=O), 133.61 (C_{para}), 130.06 (C_{ortho}), 129.03 (C_{ipso}), 128.53 (C_{meta}), 103.96 (C-1), 73.93 (C-3 or C-5), 72.35 (C-3 or C-5), 71.59 (C-2), 70.55 (C-4), 57.45 (CH_3), 28.97 (C-6); ESIMS *m*/*z* calcd for $[C_{14}H_{17}NaO_6Br]Na^+$: 383.0109. Found: 383.0104. Compound **11**: $[\alpha]_D$ +11.8 (*c* 0.56), lit.[3] $[\alpha]_D$ −6 (*c* 1.65, $CHCl_3$); ^1H NMR (500 MHz): δ 8.05 (d, 2H, *J* 7.5 Hz, $2 \times H_{ortho}$), 7.61 (t, 1H, $J = 7.5$ Hz, H_{para}), 7.47 (t, 2H, $J = 7.5$ Hz, $2 \times H_{meta}$), 5.49 (d, 1H, $J = 3.0$ Hz, H-4), 4.70 (d, 1H, $J = 7.5$ Hz, H-1), 4.64 (t, 1H, $J = 3.0$ Hz, H-3), 4.53 (t, 1H, $J = 6.5$ Hz, H-5), 3.80–3.83 (m, 2H, H-2, H-6), 3.61–3.65 (m, 1H, H-6′), 3.62 (s, 3H, CH_3); ^{13}C NMR (125 MHz): δ 165.77 (C=O), 133.98 (C_{para}), 130.02 (C_{ortho}), 128.66 (C_{meta}), 128.53 (C_{ipso}), 102.15 (C-1), 72.11 (C-5), 71.62 (C-4), 67.65 (C-2), 61.23 (C-6), 57.39 (CH_3), 51.82 (C-3); ESIMS *m*/*z* calcd for $[C_{14}H_{17}NaO_6Br]Na^+$: 383.0109. Found: 383.0117.

Acknowledgments

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Supplementary data

Copies of the ^1H and ^{13}C NMR spectra for compounds **9** and **11**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2006.02.024.

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