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Fragmentation of carbohydrate anomeric alkoxyl radicals: synthesis of chiral 1-bromo-1-fluoro-1-iodo-alditols

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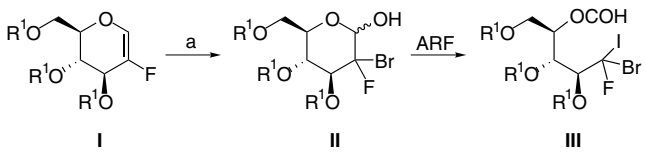
Abstract—The reaction of 2-bromo-2-deoxy-2-fluoro-hexopyranose and -pentopyranose compounds from the D-*gluco*, D-*galacto*, L-*rhamno*, L-*fuco*, and L-*arabino* carbohydrate series with (diacetoxyiodo)benzene and iodine, under visible light irradiation conditions, generated the corresponding 1-bromo-1-deoxy-1-fluoro-1-iodo-alditols with one less carbon. In the case of the D-*galacto* derivative, the diastereoisomeric mixture can be chromatographically separated and the absolute configuration determined by X-ray crystallographic analysis of the (1*R*)-isomer.

At present there appears to be no easy general methodology directed at the synthesis of asymmetric carbons bearing three different halogen atoms. Trihalomethane (CHBrClF), one of the smallest chiral molecules, has been the subject of several studies since its synthesis as early as 1893[1] but it is only recently, that its partial resolution and absolute configuration has been achieved.[2] The other three possible trihalomethanes have received considerably less attention.[3] A similar situation is found for the synthesis of carbon-substituted trihaloalkyls.[4]

In previous papers from this laboratory, we developed a new, general methodology for the synthesis of 1,1-dihalo alditols by alkoxyl radical fragmentation (ARF) of 2-deoxy-2-halo-glycopyranoses and -glycofuranoses.[5] The glyco-1-*O*-yl radical, formed by reaction of the 2-halohydrin with hypervalent iodine reagents triggers the ARF reaction, causing the formed C2 radical to be subsequently trapped by halogen atoms present in the medium. Using this ARF methodology, using either bromine or iodine as the radical trap, were we able to prepare 7 out of 10 possible 1,1-dihaloalditols, with the exceptions of 1,1-difluor-, 1,1-dichloro-, and 1-fluoro-1-chloroalditols.

With these results in hand, we turned our attention to a general protocol for the synthesis of 1,1,1-trihaloalditols, following the reactions outlined in Scheme 1. The key step in this transformation involves the ARF reaction of a 2,2-dihalohydrin. To test this methodology we decided to synthesize a hitherto practically unknown arrangement, the 1-bromo-1-fluoro-1-iodo-alkane system.[6] In this approach we take advantage of the ready availability of the 2-deoxy-2-fluoro-hex-1-enitol derivatives I.[7] These were synthesized in two steps from the corresponding 2-deoxy-hex-1-enitols (glycals) via the reaction with Selectfluor™, using magnesium bromide as the nucleophile.[8] The anomeric bromine atom in the 1-bromo-2-fluoro derivative obtained was then eliminated with TEA in CH_3CN affording the required vinyl fluoride I.[9] The bromine atom was then introduced by the reaction with NBA in the presence of water, and the 2-bromo-2-fluorohydrins II thus obtained, submitted to the ARF process to give the desired trihalo



I II III

Scheme 1. Reagents and conditions: (a) NBA (2 mmol), THF (10 mL), H_2O (1 mL), rt, 1–4 h. ARF = Alkoxy radical fragmentation reaction.

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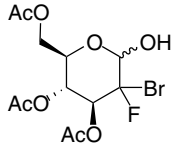
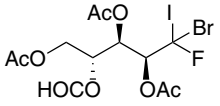
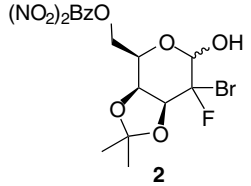
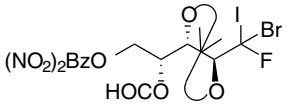
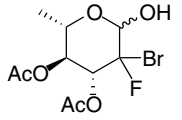
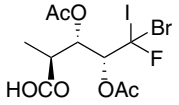
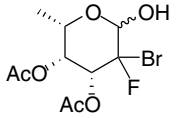
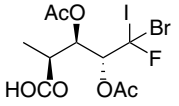
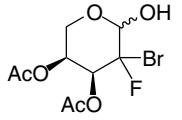
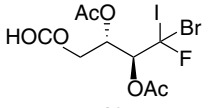
compounds III. To our knowledge, 2-bromo-2-fluorohydrins II have not been prepared previously.[10,11]

Encouraged by the ease of construction of these mixed dihalohydrins, we decided to delineate further the scope of our general protocol, particularly in regard to the influence of the stereochemistry of the saccharide on the stereoselectivity of the radical reaction. We herein report on experiments carried out using a variety of dihalohydrins belonging to the hexopyranose (entries 1–4) and pentopyranose (entry 5) series of carbohydrates as described in Table 1. The products **1**–**5** were diastereoisomeric mixtures, prepared in high yield (65–90) from derivatives of 2-fluoro-D-glucal, -D-galactal, -L-rhamnal, -L-fucal, and -L-arabinal, respectively. They are chromatographically stable compounds that can be handled without special precautions and stored in the freezer for a prolonged period of time.

The ARF reactions were performed under neutral conditions with (diacetoxyiodo)benzene (DIB) and iodine in CH_2Cl_2 at room temperature and irradiation with two 80 W tungsten filament lamps to afford the trihalo compounds **6**–**10** in 65–80% yields.[12] These fragmentations are fast and clean reactions where complete consumption of the starting material was always observed by TLC analysis. No side products were detected in the crude reaction mixtures, even in those with moderate

Table 1. Synthesis of 1-bromo-1-fluoro-1-iodo-alditols[a]

Entry	Substrate	Time	Product	Yield (d.r.)[b]
1	 **1**	1	 **6**	71 (1:1)
2	 **2**	0.75	 **(*R*)-7** **(*S*)-7**	66 (2:1)
3	 **3**	1	 **8**	80 (1:1)
4	 **4**	1	 **9**	72 (1:1)
5	 **5**	1	 **10**	65 (1:1)

$(NO_2)_2Bz = 3,5$-dinitrobenzoyl.

[a] All reactions were performed in dry CH_2Cl_2 (50 mL/mmol) under irradiation with two 80 W tungsten filament lamps at room temperature containing (diacetoxyiodo)benzene (DIB) (1.5 mmol), I_2 (1 mmol) per mmol of substrate.

[b] Isolated yield.

yields (entries 2 and 5). With the exception of model **7**, (entry 2), diastereoselection was very low, if any, for the trihalo compounds, which were obtained as a chromatographically inseparable mixture of diastereoisomers. As expected, a modest increment in the selectivity (dr 2:1) was achieved in the fragmentation of dihalohydrin **2** where the steric demand increases. Fortunately, these (*R*)- and (*S*)-**7** diastereoisomers are crystalline compounds that can be separated by chromatography and their structures confirmed by ^{1}H and ^{13}C NMR spectroscopies including DEPT, COSY, HMQC, and HMBC experiments.[13] The absolute configuration was determined by an X-ray crystallographic study of a single crystal of (*R*)-**7**.[14] An interesting although not totally unexpected result of the solid-state structure is the dihedral angle O–C2–C1–F = 171.8° with a nearly antiperiplanar arrangement of C–F and C–O bonds.[15] This staggered conformation of the C1–C2 bond necessarily involves an a priori disfavored synclinal alignment of the voluminous iodine with the C2–O (−66.6°) and C2–C3 (51.9°) bonds. Other highlighted features of compound **7** are the differences between the $^{3}J_{FH}$ in both isomers (25.6 Hz for the *R* and 20.7 Hz for the *S*) and the $^{1}J_{CF}$ (332 Hz for the *R* and 327 Hz for the *S*).[16]

In summary, the ARF reaction of 2-bromo-2-fluorohalohydrins provides a facile method of preparing 1-bromo-1-fluoro-1-iodo-alditols with one carbon less than the original carbohydrate. We report for the first time on the chromatographic resolution of diastereoisomeric mixtures of 1-bromo-1-fluoro-1-iodo-alkanes of this type and the determination of their absolute configuration by X-ray crystallographic analysis. Finally, we believe that this methodology, conveniently modified, should allow the synthesis of other types of 1,1,1-trihalo alkanes and an extension of these studies in this direction is currently under way and will be reported in due course.

Acknowledgements

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11. General procedure for the synthesis of bromohydrins. A solution of the corresponding 2-deoxy-2-fluoro-hex-1-enitol (1 mmol) in THF (10 mL) and H_2O (1 mL), containing recently crystallized *N*-bromoacetamide (1.5 mmol) was stirred at room temperature for 1–4 h. The reaction mixture was then poured into water and extracted with ethyl acetate. The organic layer was dried and concentrated in vacuo. Column chromatography of the residue (hexanes–EtOAc mixtures) afforded the required bromohydrin compounds.
12. General procedure for the ARF reaction. A solution of the halohydrin (1 mmol) in CH_2Cl_2 (50 mL) containing (diacetoxyiodo)benzene (1.5 mmol) and iodine (1 mmol) was irradiated with two 80 W tungsten filament lamps at room temperature. The reaction mixture was then poured into water and extracted with CH_2Cl_2. The organic layer was washed with 10% aqueous sodium thiosulfate, dried and concentrated in vacuo. Chromatotron chromatography of the residue (hexanes–EtOAc mixtures) afforded the required halo-iodine compounds.
13. (5*R*)-5-Bromo-5-deoxy-1-*O*-(3,5-dinitrobenzoyl)-5-fluoro-2-*O*-formyl-5-iodo-3,4-*O*-isopropylidene-D-arabinitol (***R***)-**7**. Crystalline solid (44%); mp 128.7–130.3 °C (from *n*-hexane–EtOAc). $[\alpha]_D$ +19.3 (*c* 0.14); IR 3111, 2950, 1738, 1550, 1343, 1275, 1175 cm^{-1}; ^{1}H NMR (400 MHz) 1.49 (3H, s), 1.67 (3H, s), 4.58 (1H, dd, $J = 6.9$, 11.8 Hz), 4.61 (1H, dd, $J = 1.9$, 6.1 Hz), 4.77 (1H, dd, $J = 3.9$, 11.8 Hz), 4.80 (1H, dd, $J = 6.1$ Hz; $^{3}J_{FH} = 25.6$ Hz), 5.83 (1H, ddd, $J = 1.9$, 3.9, 6.9 Hz), 8.08 (1H, s), 9.15 (2H, d, $J = 2.1$ Hz), 9.24 (1H, dd, $J = 2.1$, 2.1 Hz); ^{13}C NMR (100.6 MHz) 25.5 (CH_3), 26.3 (CH_3), 55.9 (C, d, $^{1}J_{CF} = 332.0$ Hz), 65.8 (CH_2), 67.4 (CH), 74.8 (CH), 86.9 (CH, d, $^{2}J_{CF} = 20.0$ Hz), 110.7 (C), 122.6 (CH), 129.6

(2×CH), 133.2 (C), 148.7 (2×C), 159.8 (CH), 162.2 (C); MS (EI) m/z (rel intensity) 607/605 (M^+−Me, 10/10), 483 (16), 437/435 (7/7), 385 (16), 195 (100); HRMS calcd for $C_{15}H_{12}^{81}BrFIN_2O_{10}$ 606.8684, found 606.8659. Anal. Calcd for $C_{16}H_{15}BrFIN_2O_{10}$: C, 30.94; H, 2.43; N, 4.51. Found: C, 30.95; H, 2.46; N, 4.26. (5*S*)-5-Bromo-5-deoxy-1-*O*-(3,5-dinitrobenzoyl)-5-fluoro-2-*O*-formyl-5-iodo-3,4-*O*-isopropylidene-D-arabinitol (***S***)-**7**. Crystalline solid (22%); mp 142.7–143.8 °C (from *n*-hexane–EtOAc); $[\alpha]_D$ −21.0 (*c* 0.1); IR 3098, 2984, 1740, 1550, 1342, 1275, 1175 cm^{-1}; ^1H NMR (400 MHz) 1.49 (3H, s), 1.69 (3H, s), 4.57 (1H, dd, $J = 6.6$, 11.7 Hz), 4.64 (1H, ddd, $J = 2.9$, 6.4 Hz; $^4J_{FH} = 0.8$ Hz), 4.77 (1H, dd, $J = 4.0$, 11.7 Hz), 4.90 (1H, dd, $J = 6.4$ Hz; $^3J_{FH} = 20.7$ Hz), 5.88 (1H, ddd, $J = 2.9$, 4.0, 6.6 Hz), 8.10 (1H, s), 9.16 (2H, d, $J = 2.1$ Hz), 9.24 (1H, dd, $J = 2.1$, 2.1 Hz); ^{13}C NMR (100.6 MHz) 25.3 (CH_3), 26.2 (CH_3), 56.9 (C, d, $^1J_{CF} = 327.0$ Hz), 65.5 (CH_2), 66.8 (CH), 75.8 (CH), 86.3 (CH, d, $^2J_{CF} = 21.3$ Hz), 111.1 (C), 122.4 (CH), 129.3 (2×CH), 133.9 (C), 148.4 (2×C), 159.4 (CH), 161.9 (C); MS (EI) m/z (rel intensity) 607/605 (M^+−Me, 7/7), 483 (15), 437/435 (6/6), 385 (13), 195 (100); HRMS calcd for $C_{15}H_{12}^{81}BrFIN_2O_{10}$ 606.8684, found 606.8685. Anal. Calcd for $C_{16}H_{15}BrFIN_2O_{10}$: C, 30.94; H, 2.43; N, 4.51. Found: C, 31.06; H, 2.41; N, 4.48.

14. Crystallographic data (excluding structure factors) for the structure of (***R***)-**7** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 219090. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). Crystal data and structure refinements: $C_{16}H_{15}BrFIN_2O_{10}$, $M_\tau = 621.11$, monoclinic, space group C_c2, $a = 29.7108$ (8), $b = 6.5966$ (2), $c = 10.5583$ (3) Å, $\beta = 97.414$ (1)°, $V = 2052.02$ (10) Å^3, $Z = 4$, $\rho_{calcd} = 2.010$ mg/m^3, $\mu(Mo_{K\alpha}) = 0.71073$ Å, $F(000) = 1208$, $T = 123$ (2) K, colorless crystal, 0.30×0.12×0.05 mm, collected reflections 19723. The structure was solved by direct method, all hydrogen atoms were refined anisotropically using full-matrix least-squared based F_2 to give $R_1 = 0.0329$, $wR_2 = 0.0606$ for 4534 independently observed reflections ($|F_o| > 2\sigma(|F_o|)$) and 284 parameters. Selected structural data: O–C(2)–C(1)–I = −66.6°; O–C(2)–C(1)–Br = 56.8°; O–C(2)–C(1)–F = 171.8°.
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