

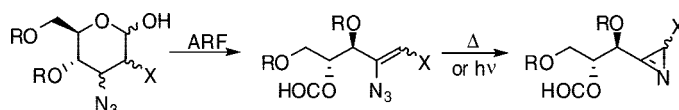
Synthesis of Polyhydroxylated 2*H*-Azirines and 2-Halo-2*H*-azirines from 3-Azido-2,3-dideoxyhexopyranoses by Alkoxy Radical Fragmentation

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ARF = Alkoxy radical fragmentation
X = H, F, Cl Br, I; R = Protective group

The reaction of 3-azido-2,3-dideoxypyranose and 3-azido-2,3-dideoxy-2-haloxyhexopyranose compounds with (diacetoxyiodo)benzene and iodine generated 2-azido-1,2-dideoxy-1-iodoalditols and 2-azido-1,2-dideoxy-1-halo-1-iodoalditols, respectively. These β -iodo azides could be transformed by chemoselective dehydroiodination into 2-azido-1,2-dideoxy-4-*O*-formyl-pent-1-enitols and (*Z,E*)-2-azido-1,2-dideoxy-1-halo-4-*O*-formyl-pent-1-enitols in good yields. Thermolysis and photochemical studies of these vinyl azides and 1-halovinyl azides for the synthesis of polyhydroxylated 3-alkyl-2*H*-azirines and the hitherto unknown 2-halo-3-alkyl-2*H*-azirines have also been accomplished.

Introduction

2*H*-Azirines, since first reported by Neber et al.,¹ have received a great deal of attention from theoretical and experimental chemists.² The highly strained imine bond confined in a three-membered ring confers unique properties to these heterocycles.³ They can act as nucleophiles, electrophiles, and also as dienophiles and dipolarophiles in cycloaddition processes. As a consequence of this reactivity, they are precursors of an impressive number of more elaborate heterocyclic systems.

Products possessing stabilized 2*H*-azirine systems have also been isolated from natural sources.⁴ The asymmetric syntheses of two of them, dysidazirine and azirinomycin, have been accomplished.⁵ On the other hand, the corresponding and even more reactive 2-halo-2*H*-azirines have been much less studied. As far as we know, there exists no general method to prepare disubstituted 3-alkyl-2-halo-2*H*-azirines and they are expected to be highly unstable on the basis of previous studies of related azirines.⁶

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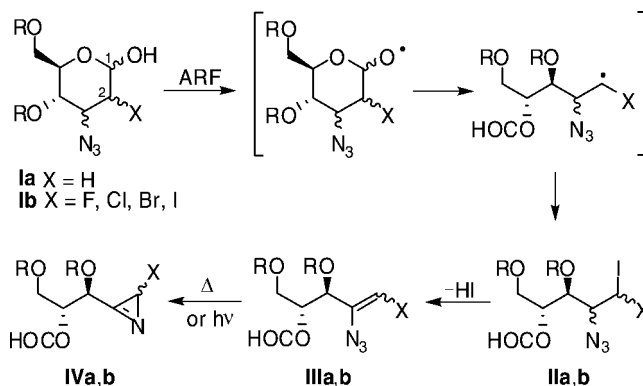
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Vinyl azides are also useful intermediates in the synthesis of heterocycles, with versatility endowed by being precursors of vinyl nitrenes.⁷ Since the pioneering work on the addition of iodine azide to olefins and the subsequent elimination of hydrogen iodine by Hassner and co-workers,⁸ several methods for the synthesis of these compounds have been developed.^{7,9} Comparatively, the synthesis of halovinyl azides whose halogen atom offers another reaction site has received much less attention. Although they can also be prepared by addition of halogen azides to vinyl halides,¹⁰ other syntheses have been developed to avoid the use of these highly reactive and dangerous reagents: (a) the reaction of α -oxophosphonium ylides with *N*-halosuccinimides in the presence of azidotrimethylsilane¹¹ and (b) the addition of hydrazoic acid to some allenyl halides.¹² However, access to halovinyl azides by these methods is limited to specific structures; e.g., none of them could apparently be used for the synthesis of fluorovinyl azides or for substances with a terminal 2-azido-1-halo-1-alkene arrangement. Indeed, there exists no general method to prepare 2-azido-1-halo-1-alkenes, the only report being on the isolation of the α -azido- β -chloro- and α -azido- β -bromostyrene from the reaction of (haloethynyl)benzene with sodium azide in low yield.¹³ One of the most interesting features of vinyl azides is their easy thermal or photochemical transformation into 2*H*-azirines.^{8a-c,14}

Earlier work from our laboratory revealed hypervalent iodine reagents in the presence of molecular iodine to be a valuable oxidation system for the formation of anomeric alkoxy radicals from carbohydrate alcohols.¹⁵ The glycopyran-1-*O*-yl radical thus formed triggers the facile radical β -fragmentation of the C1–C2 bond to give a C2 radical.¹⁶ An electron-withdrawing group at this position inhibits the oxidation of the C-radical, which is finally trapped by an atom of iodine from the reaction medium. This should also occur in the case of 2-deoxy carbohydrates, allowing for the efficient synthesis of 1-iodoalditols with one carbon less than the starting carbohydrate.

SCHEME 1. β -Fragmentation of 3-Azido-2,3-dideoxyhexopyranoses and 3-Azido-2,3-dideoxy-2-halohexopyranoses^a



^a ARF = alkoxy radical fragmentation reaction; R = protective groups.

It should be possible, using this methodology and taking into account the availability of the 3-azido-2,3-dideoxyhexopyranose **1a** compounds, to synthesize chiral β -iodo azides **2a** and hence vinyl azides **3a** and 2*H*-azirines **4a** from carbohydrates (Scheme 1, X = H). 3-Azido-2,3-dideoxyhexopyranose compounds were conveniently prepared in high yield by acid-catalyzed reaction of 2-deoxyhex-1-enitol derivatives (glycals) with NaN_3 . The reaction proceeded through Michael addition of the azide anion over an α,β -unsaturated aldehyde intermediate.¹⁷

This methodology could be extended to the preparation of polyhydroxylated 2-azido-1-halo-1-alkenes **3b** starting from halohydrins **1b** and after chemoselective dehydroiodination of the 1,1-dihalo alditol **2b** intermediate. In addition, the thermalolysis or photolysis of these halovinyl azide **3b** offers an unrivaled opportunity to study the properties and stability of the hitherto unknown 3-alkyl-2-halo-2*H*-azirines **4b** (Scheme 1, X = Hal).

Results and Discussion

To assess the potential scope and limitations of this method, experiments were carried out using a variety of 3-azido-2,3-dideoxyhexopyranose compounds **7–12** as outlined in Table 1. In previous communications, we described the preliminary results obtained,¹⁸ and we now disclose herein the full details of these experiments. The reaction of glycals **1–6** with NaN_3 in the presence of HgSO_4 and H_2SO_4 afforded 1,3-hydroxy azides **7–12** in good yields as diastereoisomeric mixtures at

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TABLE 1. Alkoxy Radical Fragmentation Reaction of 3-Azido-2,3-dideoxy-hexopyranoses^a

entry	lactol	time (h)	γ -hydroxy azide ^a yield (%)	time (h)	β -iodo azide ^b yield (%), dr	time (h)	vinyl azide ^c yield (%)
1		5	7 (90)	0.5	13-D-Ara (95, 9:1) 13-D-Rib	0.5	19 (80)
2		7.5	8-D-Ara (88) 8-D-Rib	0.25	14-D-Ara (91, 7:3) 14-D-Rib	3	20 (66)
3 ^d		5	9-D-Ara (76) 9-D-Rib	0.5	15-D-Ara (96, 6:4) 15-D-Rib	0.75	21 (85)
4		2.5	10 (87)	0.5	16-D-Xyl (86, 6:4) 16-D-Lyx	0.5	22 (70)
5		3	11-L-Ara (88) 11-L-Rib	0.5	17-L-Ara (93, 4:6) 17-L-Rib	0.5	23 (76)
6		2.5	12-L-Thr (87) 12-L-Ery	0.5	18-L-Thr (78, 2:8) 18-L-Ery	1	24 (91)

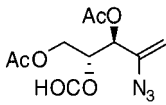
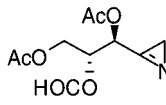
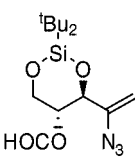
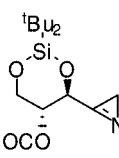
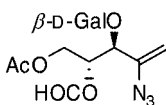
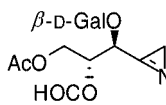
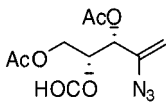
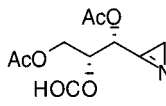
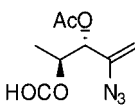
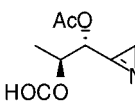
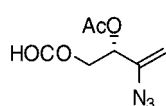
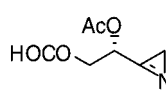
^a Reagents and conditions per mmol of substrate: HgSO₄ (0.047 mmol), H₂SO₄ (5 mM, 27 mmol), 1,4-dioxane, 30 °C, then NaN₃ (10 mmol), AcOH (1.35 mL). ^b Reagents and conditions per mmol of substrate: (diacetoxyiodo)benzene (1.5 mmol), I₂ (1.5 mmol), CH₂Cl₂, reflux. ^c Reagents and conditions per mmol of substrate: DBU (2.5 mmol), PhH, reflux. ^d For brevity, in this case β -D-Gal refers to the peracetylated moiety of galactose.

C3.¹⁷ In all cases, except for previously described compounds **7**^{17c} and **10**,^{17a,b} the mixtures were partially resolved by chromatography and the azide stereochemistry determined by means of ¹H NMR spectroscopy by a careful analysis of the vicinal coupling constants (in particular $J_{2a,3}$ and $J_{2c,3}$). It is noteworthy to mention that the major anomer of pentopyranose **12L-Thr** adopts preferentially a ¹C₄ conformation with the azido group in equatorial position and the anomeric alcohol in axial position, whereas the major anomer of compound **12L-Ery** exists in a ⁴C₁ conformation leaving also the azide equatorial and the anomeric alcohol in axial position.

The alkoxy radical fragmentation (ARF) reactions were performed under the conditions stated in Table 1 (entries 1–6),

with (diacetoxyiodo)benzene and iodine in CH₂Cl₂ at reflux temperature. The reaction proceeded smoothly in high yield, and as observed, the di-*tert*-butylsilyl protective group and the sensitive glycosidic linkage survived the reaction conditions (entries 2 and 3, respectively). The stereochemistries of the β -iodo azides **13**–**18** were then unambiguously determined by individually submitting the γ -hydroxy azides to the ARF reaction. The integrity of the adjacent azide stereogenic center was preserved during the reaction, and no generation of diastereoisomers at this carbon atom (C-3) was detected. From a practical point of view, the ARF was best accomplished with the mixture of the γ -hydroxy azides followed by a much more efficient chromatographic separation at the β -iodo azide stage.

TABLE 2. Thermolysis of Vinyl Azides 19–24^a

entry	vinyl azide	time (h)	2H-azirine yield (%)
1		22	 25 (85) ^b
2		2	 26 (58)
3 ^c		4	 27 (63)
4		2.5	 28 (84) ^d
5		1	 29 (68)
6		3.5	 30 (87) ^e

^a Toluene (12 mL/mmol), reflux. ^b Benzene (30 mL/mmol), reflux. ^c For brevity, in this case β -D-Gal refers to the peracetylated moiety of galactose. ^d By irradiation in C₆D₆ (0.07 mM) with a 450 W ACE-Hanovia medium-pressure mercury lamp, the yield was 94%. ^e Unstable; could not withstand chromatographic purification, crude yield.

The yields shown in Table 1 were determined using chromatographic homogeneous hydroxy azide mixtures giving correct elemental analysis, and in all cases complete consumption of the starting material was observed. The dehydroiodination of the β -iodo azides with DBU in benzene at reflux temperature afforded vinyl azides 19–24 in good yield. It is worth noting the stability of the sensitive formyl ester under the reaction conditions. The separation of the isomeric β -iodo azides was unnecessary; the synthesis could be realized directly from the diastereoisomeric mixture.

Under thermolysis conditions and in accord with the rules proposed by Hassner,¹⁹ acyclic vinyl azides with this 3-monoalkyl substitution pattern should give 2H-azirines. Indeed, when the vinyl azides shown in Table 2 were refluxed in the specified solvent,

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the corresponding 2H-azirines 25–30 were isolated in good yields. The azirines 25–29 were sufficiently stable to be isolated and purified by silica gel chromatography and can be stored for months in a freezer at –25 °C without significant decomposition. The azirine 30 could be isolated and fully characterized spectroscopically after aqueous workup but could not withstand silica gel chromatographic purification, probably because of its lower steric demand. The somewhat lower yields observed for azirines 26, 27, and 29 (entries 2, 3, and 5) are probably due to thermal instability of the three-membered ring at this temperature. Under photolytic conditions at room temperature, a much smoother reaction ensued, for example, irradiation of vinyl azide 22 with the unfiltered light using a 450 W Hanovia medium-pressure lamp afforded azirine 28 in 94% yield.

The isolation of azirine 26 in crystalline form suitable for X-ray diffraction provides an opportunity to probe its solid-state structure.²⁰ Although a crystallographic analysis was performed on the palladium(II) complex of 3-(*p*-methoxyphenyl)-2H-azirine, the molecular structure of simple 3-alkylmono-substituted-2H-azirines has not been determined.²¹

Although several examples of monosubstituted 3-alkyl-2H-azirines can be found in the literature,^{7h,14,22} as far as we know, no examples of the monosubstituted 3-alkyl-2H-azirines possessing an α -hydroxyl derivative have been reported to date. Closely related stabilized 2H-azirine-3-carboxylic esters have been recently synthesized and used as dienophiles in aza-Diels–Alder cycloadditions or as radical acceptors.²³

The next goal of our work was to extend this protocol to a simple general procedure for the synthesis of 2-azido-1-halo-1-alkenes of the IIIb type (X = F, Cl, Br, and I) (Scheme 1). Previous studies in this laboratory explored the feasibility of 1,1-dihalo- and 1,1,1-trihaloalditols formation from carbohydrate halohydrin systems using the ARF reaction as the key step.²⁴

(20) X-ray data for compounds 26 and 38d-Z have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 222314 and 648303, respectively. Copies of the data may be obtained free of charge from the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. Fax: (+44) 1223-336-033. E-mail: deposit@ccdc.cam.ac.uk.

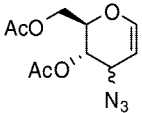
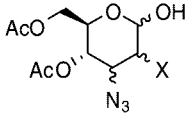
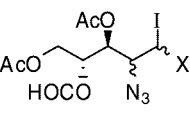
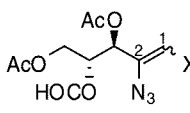
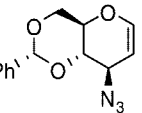
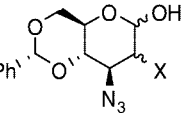
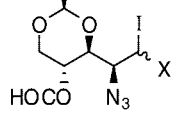
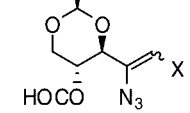
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TABLE 3. Synthesis of 2-Azido-1,2-dideoxy-1-halopent-1-enitol Compounds

entry	glycal	time	halohydrin ^a	time	β,β -dihalo azide ^b	time	halo vinyl azide ^c
		(h)	yield (%)	(h)	yield (%)	(h)	yield (%), <i>E:Z</i>
							
1	31	5	32a X = F (66)	0.75	33a X = F (85)	0.75	34a X = F (82, 1:3)
2		5.75	32b X = Cl (90)	1.25	33b X = Cl (85)	0.75	34b X = Cl (86, 1:1)
3		2	32c X = Br (94)	1	33c X = Br (81)	0.75	34c X = Br (75, 1:1) ^d
4		1	32d X = I (94)	1	33d X = I (91)	0.5	34d X = I (100, 1:2) ^e
							
5	35	17	36a X = F (65)	0.5	37a X = F (60) (6:4)	1	38a X = F (60, 1:1)
6		11	36b X = Cl (89)	2.5	37b X = Cl (100) (7:3)	1.75	38b X = Cl (92, 1:1)
7		8	36c X = Br (100)	1	37c X = Br (80) (6:4)	1	38c X = Br (60, 1:2) ^f
8		1	36d X = I (100)	1.5	37d X = I (87)	1	38d X = I (91, 1:17)

^a Reagents and conditions per mmol of substrate. Fluorohydrins: Selectfluor (1.5 mmol), nitromethane, H₂O, rt then reflux. Chlorohydrins: *N*-chlorosuccinimide (2 mmol), THF, H₂O, 50 °C. Bromohydrins: *N*-bromoacetamide (1.5 mmol), THF, H₂O, rt. Iodohydrins: *N*-iodosuccinimide (1.2 mmol), THF, H₂O, rt. ^b Reagents and conditions per mmol of substrate: (diacetoxyiodo)benzene (1.5 mmol), I₂ (1.5 mmol), CH₂Cl₂, *hν*, reflux. ^c Reagents and conditions per mmol of substrate: DBU (2.5 mmol), PhH, rt. ^d 25% of a mixture of *E*- and *Z*-vinyl iodides is also obtained. ^e Inseparable mixture of isomers. ^f 40% of a mixture of *E*- and *Z*-vinyl iodides is also obtained.

To achieve this objective, we decided to prepare 3-azido-2,3-dideoxyhex-1-enitols **31**²⁵ and **35**²⁶ utilizing procedures to those previously reported (Table 3). The syntheses of both compounds led to diastereoisomeric mixtures of azides. In the case of **35** the isomers could be separated and although it is not strictly necessary since C-3 is not a stereogenic center in the final product, for the sake of convenience, the study was carried out with the major isomer, which corresponds to a *D*-arabino-hex-1-enitol stereochemistry.

The 1,2-halohydrins were synthesized as outlined in Table 3. 1,2-Fluorohydrins (**32a**, **36a**), 1,2-chlorohydrins (**32b**, **36b**), 1,2-bromohydrins (**32c**, **36c**), and 1,2-iodohydrins (**32d**, **36d**) were prepared from the corresponding 2-deoxyhex-1-enitol (**31**, **35**) by reaction with Selectfluor,²⁷ *N*-chlorosuccinimide,²⁸ *N*-bromoacetamide,²⁹ and *N*-iodosuccinimide,³⁰ respectively.

(25) Glycal **31** was prepared from **7** by dehydration of the anomeric alcohol with Tf₂O and *s*-collidine: Charette, A. B.; Côté, B. *J. Org. Chem.* **1993**, *58*, 933–936. See also: Guthrie, R. D.; Irvine, R. W. *Carbohydr. Res.* **1980**, *82*, 207–224. Kawabata, H.; Kubo, S.; Hayashi, M. *Carbohydr. Res.* **2001**, *333*, 153–158.

(26) Glycal **35** was prepared starting from 1,5-anhydro-4,6-*O*-benzylidene-2-deoxy-*D*-arabino-hex-1-enitol: Chambers, D. J.; Evans, G. R.; Fairbanks, A. J. *Tetrahedron: Asymmetry* **2003**, *14*, 1767–1769, that was transformed into 1-*O*-benzoyl-4,6-*O*-benzylidene-2,3-dideoxy-*D*-erythro-hex-2-enopyranose by a Ferrier rearrangement under Mitsunobu conditions (Guthrie, R. D.; Irvine, R. W.; Davison, E. B.; Henrick, K.; Trotter, J. *J. Chem. Soc., Perkin Trans. 2* **1981**, 468–472) and finally to the required **35** by treatment with NaN₃ in HMPA (Guthrie, R. D.; Irvine, R. W.; Jenkins, I. D. *Aust. J. Chem.* **1980**, *33*, 2499–2508). See also: Guthrie, R. D.; Irvine, R. W. *Carbohydr. Res.* **1980**, *82*, 225–236.

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The ARF reactions were performed under the conditions stated in Table 3, with DIB and molecular iodine in CH₂Cl₂ at reflux temperature and irradiation with two 80 W tungsten filament lamps. The ARF reactions proceeded smoothly, and the 1-iodo-1-halo azides **33** and **37** were obtained in high yields and with modest diastereoselectivity (dr for **37a**–**37c** of 6:4–7:3).³¹ The dehydroiodination of the dihalo azides **33** and **37** with DBU in benzene at room temperature afforded halo vinyl azides **34** and **38** in good yields. As expected, the reaction occurred with high chemoselectivity except for 1-bromo-1-iodo azides **33c** and **37c** which gave significant amounts of vinyl iodides, 25% and 40%, respectively, by competitive dehydrobromination.

The stereochemistry of the double bond was assigned on the basis of 2D NOESY experiments,³² and furthermore, the structure and stereochemistry of **38d-Z** were determined unambiguously by single-crystal X-ray crystallography.²⁰

The synthesis of the halo vinyl azides **34** and **38** proceeded efficiently through the three steps, but in general with poor

(31) The reaction yields were determined using chromatographically homogeneous halohydrin mixtures giving correct elemental analyses and in all cases complete consumption of the starting material was observed.

(32) A NOE interaction was observed between H-C-1 and H-C-3 in the **34-Z** and **38-Z** isomers, although such an interaction was not observed for the *E*-isomers. Product structures were also established by spectroscopic (¹H, ¹³C, and ¹⁹F NMR) correlation among *Z*- and *E*-isomers, e.g., in the ¹⁹F NMR spectra a difference of 8–10 ppm can be observed in the chemical shift of fluorine atoms between the *Z*- and *E*-isomers of fluoro vinyl azides **34a** and **38a**. For NOE-based stereochemistry of related trisubstituted vinyl halides, see: (a) Kim, J.; Zhang, Y.; Ran, C.; Sayre, L. M. *Bioorg. Med. Chem.* **2006**, *14*, 1444–1453. (b) Kattuboina, A.; Kaur, P.; Timmons, C.; Li, G. *Org. Lett.* **2006**, *8*, 2771–2774. (c) Cheng, C.; Shimo, T.; Somekawa, K.; Baba, M. *Tetrahedron* **1998**, *54*, 2031–2040. (d) Manfre, F.; Kern, J.-M.; Biellmann, J.-F. *J. Org. Chem.* **1992**, *57*, 2060–2065. (e) McCarthy, J. R.; Matthews, D. P.; Stemerick, D. M.; Huber, E. W.; Bey, P.; Lippert, B. J.; Snyder, R. D.; Sunkarall, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 7439–7440.

TABLE 4. Thermolysis and Photolysis of 2-Azido-1,2-dideoxy-1-halopent-1-enitol Compounds

entry	substrate	method ^a	temp (°C)	time (h)	product	yield (%, dr)
1 ^b	34a-E X = F	A	80	1.25	39 X = F	(71, 7:3)
2 ^b	34a-Z X = F	A	120	2	39 X = F	(78, 7:3)
3	34a-Z X = F	B	rt	0.5	39 X = F	(96, 6:4)
4 ^b	34b-E X = Cl	A	80	1.25	40 X = Cl	(94, 6:4)
5 ^b	34b-Z X = Cl	A	90	4.75	40 X = Cl	(90, 6:4)
6	34b-Z X = Cl	B	rt	0.5	40 X = Cl	(95, 6:4)
7	34c-E X = Br	A	80	1.5	--- ^c	
8	34c-E X = Br	B	rt	0.5	41 X = Br	(83, 6:4)
9	34c-Z X = Br	A	80	2	--- ^c	
10	34c-Z X = Br	B	rt	0.5	41 X = Br	(95, 6:4)
11	34d-EZ X = I	A	80	3	--- ^c	
12	34d-EZ X = I	B	rt	0.5	42 X = I	(87, 6:4)
13	38a-E X = F	A	80	1	43 X = F	(98, 7:3)
14	38a-Z X = F	A	120	6	43 X = F	(83, 6:4)
15	38b-E X = Cl	A	80	2.5	44 X = Cl	(98, 1:1)
16	38b-Z X = Cl	B	rt	0.5	44 X = Cl	(86, 6:4)
17	38c-E X = Br	A	80	1	45 X = Br	(72, 6:4)
18	38c-Z X = Br	B	rt	0.5	45 X = Br	(96, 1:1)
19	38d-E X = I	B	rt	0.75	46 X = I	(91, 1:1)
20	38d-Z X = I	B	rt	1	46 X = I	(87, 1:1)

^a Method A: Thermal conditions. All reactions were carried out in benzene (0.1 mM); the thermolysis of the Z-isomers was carried out in a heavy-walled Pyrex tube, sealed with a screw cap fitted with a Teflon gasket. Method B: Photochemical conditions. All reactions proceeded in C₆D₆ (0.03 mM) under irradiation with a 450 W ACE-Hanovia medium-pressure mercury lamp. Due to instability of the products on silica gel yields were not calculated. ^b Similar results were obtained using method B, rt, 0.5 h. ^c These conditions gave mainly insoluble brown tar material.

diastereoselectivity. Only when the steric volume of the alkyl group and the halogen increased did the diastereoselectivity improve significantly (Table 3, compare drs of **34d** with **38d** or **38c** with **38d**).

The synthetic usefulness of these compounds for the synthesis of heterocycles has been preliminarily assessed through thermolysis (method A) and photolysis (method B) experiments, and the results are summarized in Table 4. Two series of halovinyl azides **34** and **38** with different substituents at the adjacent carbon were studied. According to Hassner, thermolysis of these vinylhalo azides with this 3-monoalkyl substitution pattern should also give 3-alkyl-2-halo-2H-azirines.¹⁹ As far as we know, no examples of these disubstituted 3-alkyl-2-halo-2H-azirines have been reported to date, and they are expected to be highly reactive and unstable on the basis of previous studies of related azirines.⁶

As is evident from Table 4, thermolyses of the E-isomers occurred faster and at a lower temperature than those of the Z-isomers (entries 1 and 2, 4 and 5, or 13 and 14), a fact that has already been reported for the thermolysis of dehalogenated

vinyl azides.³³ Neither the stereochemistry of the double bond nor the reaction method used appear to greatly influence the stereochemical outcome at the halogen center (e.g., entries 1, 2, and 3 or 4, 5 and 6).

Unfortunately, we were unable to obtain 2H-azirines **41** (X = Br) and **42** (X = I) from the thermolysis of **34c** and **34d**, respectively (entries 7, 9, and 11). On heating in benzene, increasing amounts of polymeric substances were observed and the substrate completely decomposed at reflux temperature. Therefore, the preparation of 2-halo-2H-azirines from halo vinylazides was most conveniently achieved by irradiation with an unfiltered UV light using a medium-pressure mercury lamp (450 W) at room temperature (entries 3, 6, 8, 10, and 12). This was especially facile with the Z-isomers or when the halogen atom was bromine or iodine.

All of the 2-halo-2H-azirines **39–46** synthesized proved to be unstable, could not withstand chromatographic purification, and decomposed gradually, as dilute benzene solutions, within a few days in a freezer (−25 °C) under nitrogen. Notwithstanding, the instability increases in both series from 2H-azirines **39**,

43 (X = F) to **42**, **46** (X = I). We managed to fully characterize 2*H*-azirines **39**, **43** (X = F) and **40**, **44** (X = Cl) since the crude reaction products were sufficiently pure to give clean ¹H and ¹³C NMR spectra, HRMS, and correct elemental analyses. From the most unstable 2*H*-azirines **41**, **45** (X = Br) and **42**, **46** (X = I) only ¹H NMR spectra could be obtained.

In summary, we have developed a new general methodology for the synthesis of polyhydroxylated 2-azido-1-alkenes from 2-deoxycarbohydrates making use of the ARF reaction. This methodology, which avoids the use of halogen azides, has been extended to a general synthesis of 1-fluoro-, 1-chloro-, 1-bromo-, and 1-iodo-2-azido-1-alkenes under mild conditions compatible with common carbohydrate protecting groups. These carbohydrate-derived 2-azido-1-deoxy-1-iodo-alditols, 2-azido-1,2-dideoxy-pent-1-enitols, and 2-azido-1,2-dideoxy-1-halo-pent-1-enitols may be of interest as chiral synthons for the preparation of polyhydroxylated heterocyclic systems.

Experimental Section

CAUTION: Azide compounds can be toxic and potentially explosive. In particular, the reaction of glycals with NaN₃ in the presence of catalytic amounts of HgSO₄ and H₂SO₄ has the potential to form mercuric azide which is highly susceptible to spontaneous detonation. We have never encountered any problem when using the reaction scales and general procedures described below, but recommend special care be taken.

General Procedure for the Synthesis of 3-Azido-2,3-dideoxy-aldoses 7–12.^{17b,c} A solution of the corresponding 2-deoxyhex-1-enitol (1 mmol) in 1,4-dioxane (1.35 mL) containing HgSO₄ (0.047 mmol) and aqueous H₂SO₄ (5 mM, 5.4 mL) was stirred at 30 °C for 1–5 h. Then NaN₃ (10 mmol) and AcOH glacial (1.35 mL) were added, and the stirring continued for 1.5 h. The reaction mixture was then poured into water and extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄ and concentrated under vacuum and the residue purified by column chromatography (hexanes–EtOAc, mixtures) to give the required 3-azido compounds.

General Procedure for the Synthesis of β-Iodo Azides 13–18, 33, and 37. A solution of the 3-azido-2,3-dideoxy compounds (1 mmol) in CH₂Cl₂ (25–50 mL) containing (diacetoxyiodo)benzene (1.5 mmol) and iodine (1.5 mmol) was irradiated with two 80 W tungsten-filament lamps at reflux temperature for a specific period of time (Tables 1 and 3). The reaction mixture was then poured into water and extracted with CH₂Cl₂. 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 iodo azides.

General Procedure for the Synthesis of Vinyl Azides 19–24. To a solution of the β-iodo azide (1 mmol) in dry benzene (34 mL) was added DBU (2.5 mmol) and the mixture stirred at 90 °C for a specific period of time (Table 1). After this time, the reaction mixture was poured into a saturated solution of NaHSO₄ and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated under vacuum. Column chromatography (hexanes–EtOAc, mixtures) of the residue afforded the required vinyl azides.

General Procedure for the Synthesis of Vinyl Azides 34 and 38. To a solution of the β-iodo azide (1 mmol) in dry benzene (34 mL) was added DBU (2.5 mmol) and the mixture stirred at room temperature for a specific period of time (Table 3). After this time, the reaction mixture was poured into a saturated solution of NaHSO₄ and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄, and concentrated under

vacuum. Column chromatography (hexanes–EtOAc, mixtures) of the residue afforded the required vinyl azides.

General Procedure for the Synthesis of 2*H*-Azirines 25–30. A solution of the vinyl azide (1 mmol) in dry toluene (12 mL) was heated at reflux temperature under nitrogen for a specific period of time (Table 2). After concentration under vacuum, the residue was purified by Chromatotron chromatography (hexanes–EtOAc, mixtures) to give the required 2*H*-azirines.

General Procedure for the Preparation of Fluorohydrins 32a and 36a. To a solution of the corresponding 3-azido-2,3-dideoxyhex-1-enitol (1 mmol) in nitromethane (10 mL) were added H₂O (1.5 mL) and F-TEDA-BF₄ (Selectfluor) (1.5 mmol) and the mixture stirred at room temperature for a specific period of time (Table 3) until the disappearance of the starting material was noted by TLC. The reaction mixture was then heated to reflux for 0.5 h, poured into brine, and extracted with EtOAc. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. Chromatography of the residue (hexanes–EtOAc mixtures) afforded the required fluorohydrin compounds.

General Procedure for the Preparation of Chlorohydrins 32b and 36b. A solution of the corresponding 3-azido-2,3-dideoxyhex-1-enitol (1 mmol) in THF (20 mL) and H₂O (10 mL), containing *N*-chlorosuccinimide (2 mmol), was stirred at 50 °C for a specific period of time (Table 3). The reaction mixture was then poured into water, extracted with EtOAc, and washed with Na₂S₂O₃. The organic layer was dried and concentrated under reduced pressure. Chromatotron chromatography of the residue (hexanes–EtOAc mixtures) afforded the required chlorohydrin compounds.

General Procedure for the Preparation of Bromohydrins 32c and 36c. A solution of the corresponding 3-azido-2,3-dideoxyhex-1-enitol (1 mmol) in THF (34 mL) and H₂O (4 mL), containing recently crystallized *N*-bromoacetamide (1.5 mmol), was stirred at room temperature for a specific period of time (Table 3). The reaction mixture was then poured into brine and extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. Chromatotron chromatography of the residue (hexanes–EtOAc mixtures) afforded the required bromohydrin compounds.

General Procedure for the Preparation of Iodohydrins 32d and 36d. A solution of the corresponding 3-azido-2,3-dideoxyhex-1-enitol (1 mmol) in THF (10 mL) and H₂O (10 mL), containing *N*-iodosuccinimide (1.2 mmol), was stirred at room temperature for 1 h. The reaction mixture was then poured into 10% aqueous sodium thiosulfate and extracted with EtOAc. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. Chromatotron chromatography of the residue (hexanes–EtOAc mixtures) afforded the required iodohydrin compounds.

General Procedure for the Preparation of 2-Halo-2*H*-azirine Compounds 39–46 under Photolytic Conditions. The corresponding halo vinyl azide was dissolved in C₆D₆ (0.03 mM) and placed in a NMR tube. The reaction mixture was irradiated with the unfiltered light of a 450 W ACE-Hanovia medium-pressure mercury at 10 cm and the course of the reaction was monitored by ¹H NMR until complete conversion (approximately 30 min).

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Supporting Information Available: Detailed experimental procedures and spectral and analytical data for all new compounds. X-ray crystallographic files (CIF) for compounds **26** and **38d-Z**. Copies of ¹H and ¹³C NMR spectra for compounds **13–30**, **34a–34c**, and **37d–38d**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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