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Fragmentation of Carbohydrate Anomeric Alkoxyl Radicals. A New Synthesis of Chiral β-Iodo Azides, Vinyl Azides, and 2*H*-Azirines

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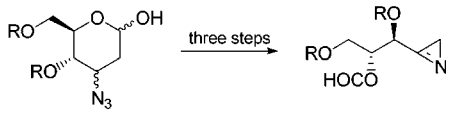
ABSTRACT



The reaction of 3-azido-2,3-dideoxy-hexopyranose compounds from the D-*gluco*, D-*galacto*, D-*lacto*, and L-*arabino* carbohydrate series, with (diacetoxyiodo)benzene and iodine, generated 2-azido-1,2-dideoxy-1-iodo-alditols with one carbon less than the starting carbohydrate. These β-iodo azides could be transformed by dehydroiodination into vinyl azides, which in turn afforded 3-monosubstituted 2*H*-azirines under thermal conditions. These β-iodo azides and 2*H*-azirines may be interesting chiral synthons for the preparation of more complex heterocyclic systems.

2*H*-Azirines have attracted considerable interest from the synthetic, mechanistic, and theoretical points of view, largely because of their manifold reactions and structural characteristics. Due to the high ring strain, they can react as nucleophiles, electrophiles, and also as dienophiles or dipolarophiles in cycloaddition processes. These strained imines are precursors of an impressive number of more complex heterocyclic systems.[1] Moreover, a few products possessing this 2*H*-azirine ring system have been isolated from natural sources.[2] Asymmetric syntheses of two of them, dysidazirine and *ent*-azirinomycin, have been reported.[3] Vinyl azides are also versatile organic compounds endowed with a rich and fascinating chemistry.[4] Probably one of the most interesting features of this class of compounds is their thermal and photochemical transformation into 2*H*-azirines.[5]

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(1) (a) Palacios, F.; Ochoa de Retana, A. M.; Martínez de Marigorta, E.; de los Santos, J. M. *Org. Prep. Proced. Int.* **2002**, *34*, 219−269. (b) Palacios, F.; Ochoa de Retana, A. M.; Martínez de Marigorta, E.; de los Santos, J. M. *Eur. J. Org. Chem.* **2001**, 2401−2414. (c) Gilchrist, T. L. *Aldrichimica Acta* **2001**, *34*, 51−55. (d) Padwa, A.; Woolhouse, A. D. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds; Pergamon Press: Oxford, 1984; Vol. 7, pp 47−93. (e) Anderson, D. J.; Hassner, A. *Synthesis* **1975**, 483−495.

(2) (a) Miller, T. W.; Tristram, E. W.; Wolf, F. J. *J. Antibiot.* **1971**, *24*, 48−50. (b) Stapley, E. O.; Hendlin, D.; Jackson, M.; Miller, A. K.; Hernandez, S.; Mata, J. M. *J. Antibiot.* **1971**, *24*, 42−47. (c) Molinski, T. F.; Ireland, C. M. *J. Org. Chem.* **1988**, *53*, 2103−2105. (d) Salomón, C. E.; Williams, D. H.; Faulkner, D. J. *J. Natural Prod.* **1995**, *58*, 1463−1466.

(3) (a) Davis, F. A.; Reddy, G. V.; Liu, H. *J. Am. Chem. Soc.* **1995**, *117*, 3651−3652. (b) Davis, F. A.; Liu, H.; Liang, C.-H.; Reddy, G. V.; Zhang, Y.; Fang, T.; Titus, D. *J. Org. Chem.* **1999**, *64*, 8929−8935. (c) Gentilucci, L.; Grijzen, Y.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1995**, *36*, 4665−4668.

(4) (a) L'abbé, G.; Hassner, A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 98−104. (b) L'abbé, G. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 775−782. (c) Smolinsky, G.; Pryde, C. A. In *The Chemistry of the Azido Group*; Patai, S., Ed.; John Wiley and Sons: London, 1971; pp 555−585. (d) Hassner, A. In *Azides and Nitrenes: Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic Press: Orlando, 1984; pp 35−94.

(5) (a) Smolinsky, G. *J. Org. Chem.* **1962**, *27*, 3557−3559. (b) Hassner, A.; Levy, L. A. *J. Am. Chem. Soc.* **1965**, *87*, 4203−4204. (c) Fowler, F. W.; Hassner, A.; Levy, L. A. *J. Am. Chem. Soc.* **1967**, *89*, 2077−2082. (d) Hassner, A.; Fowler, F. W. *J. Org. Chem.* **1968**, *33*, 2686−2691.

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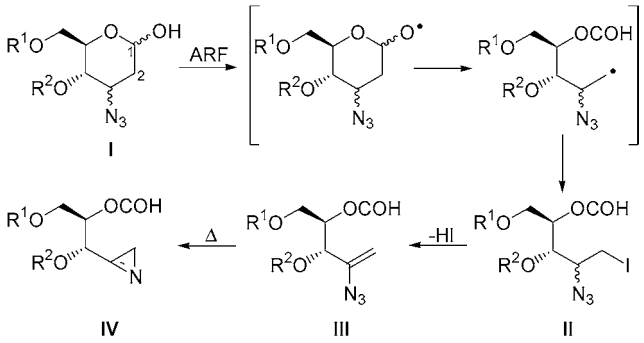
Scheme 1. β-Fragmentation of 3-Azido-2,3-dideoxy-hexopyranoses[a]



[a] ARF = alkoxyl radical fragmentation reaction; R^1, R^2 = protective groups.

On the other hand, β-iodo azide compounds, which are currently being synthesized by iodoazidation of alkenes, are precursors of vinyl azides, amines, and aziridines.[6]

The reaction of carbohydrate anomeric alcohols with hypervalent iodine reagents in the presence of iodine has been recently described by this laboratory.[7] The glycopyran-1-*O*-yl and glycofuran-1-*O*-yl radicals thus formed caused facile cleavage of the C1−C2 bond to give a C2-radical. An electron-withdrawing group at this position inhibits the oxidation of the C-radical, and this can be trapped by iodine atoms from the reaction medium. This should also occur in the case of the β-fragmentation of 2-deoxy carbohydrates, allowing for the efficient synthesis of 1-iodo-alditols with one carbon less than the starting carbohydrate (Scheme 1).

By using this methodology and taking into account the availability of the 3-azido-2,3-dideoxy-hexopyranose compounds (**I**),[8] we had the opportunity to synthesize chiral β-iodo azides (**II**), and hence vinyl azides (**III**) and 2*H*-azirines (**IV**) from carbohydrates. 3-Azido-2,3-dideoxy-hexopyranose compounds were conveniently prepared in high yield by acid-catalyzed reaction of 2-deoxy-hex-1-enitol derivatives (glycals) with NaN_3. The reaction proceeded through Michael addition of the azide anion over an α,β-unsaturated aldehyde intermediate.

To explore the generality and scope of this methodology, experiments were carried out using a variety of 3-azido-2,3-dideoxy-hexopyranose compounds **1**, **5**, **9**, **13**, and **17** as outlined in Table 1. The alkoxyl radical fragmentation (ARF) reactions were performed under the conditions stated (entries 1−5), with (diacetoxyiodo) benzene and iodine in CH_2Cl_2 at reflux temperature. In all cases, the isomeric γ-hydroxy azides were separated by chromatography and the C-3 stereochemistry assigned by a careful study of the vicinal coupling constants (particularly $J_{2a,3}$ and $J_{2e,3}$). The stereochemistries of the β-iodo azides **2**, **6**, **10**, **14**, and **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 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. The yields shown in the table 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 ARF reaction proceeded smoothly in high yield, and as observed, the sensitive glycosidic linkage and the di-*tert*-butylsilanediyl protective group survived the reaction conditions (entries 3 and 4, respectively). The dehydroiodination of the β-iodo azides with DBU in benzene at reflux temperature afforded vinyl azides **3**, **7**, **11**, **15**, and **19** 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 not necessary, and the synthesis could be realized directly from the diastereoisomeric mixture.

According to the rules proposed by Hassner,[9] acyclic vinyl azides with this 3-monoalkyl substitution pattern should give 2*H*-azirines under thermolysis conditions. Indeed, when the vinyl azides shown in Table 1 were refluxed in toluene, the corresponding 2*H*-azirines **4**, **8**, **12**, **16**, and **20** were isolated in somewhat higher than expected yields. The lower yields observed for azirines **12** and **16** (entries 3 and 4) are probably due to thermal instability of the three-membered ring at this temperature.

The azirines **4**, **8**, **12**, and **16** were sufficiently stable to be isolated and purified by silica gel chromatography and may be stored for months in a freezer at −20 °C without significant decomposition. The azirine **20** could be isolated after aqueous workup but could not withstand silica gel chromatographic purification, probably as a consequence of its lower steric demand. The isolation of azirine **16** in crystalline form suitable for X-ray diffraction provides an

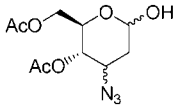
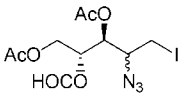
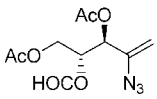
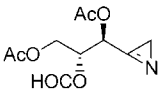
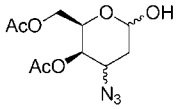
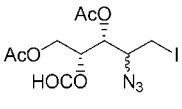
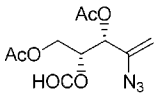
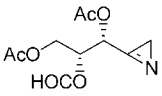
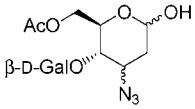
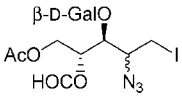
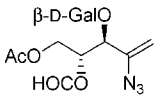
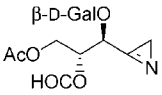
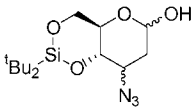
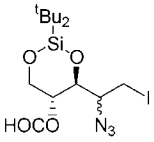
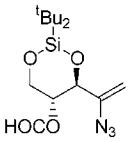
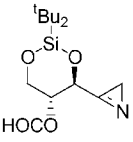
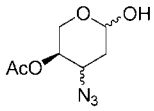
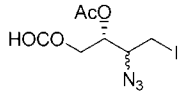
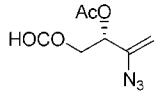
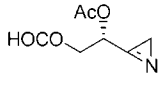
(6) For recent examples of iodoazidation of olefins, see: (a) Curini, M.; Epifano, F.; Marcotullio, M. Ç.; Rosati, O. *Tetrahedron Lett.* **2002**, *43*, 1201−1203. (b) Barluenga, J.; Álvarez-Pérez, M.; Fananas, F. J.; González, J. M. *Adv. Synth. Catal.* **2001**, *343*, 335−337. (c) Nair, V.; George, T. G.; Sheeba, V.; Augustine, A.; Balagopal, L.; Nair, L. G. *Synlett* **2000**, 1597−1598. (d) Kirschning, A.; Monenschein, H.; Schmeck, C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2594−2596. (e) Kirschning, A.; Hashem, M. A.; Monenschein, H.; Rose, L.; Schöning, K.-U. *J. Org. Chem.* **1999**, *64*, 6522−6526.

(7) (a) Armas, P.; Francisco, C. G.; Suárez, E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 772−774. (b) Armas, P.; Francisco, C. G.; Suárez, E. *J. Am. Chem. Soc.* **1993**, *115*, 8865−8866. (c) Hernández, R.; León, E. I.; Moreno, P.; Suárez, E. *J. Org. Chem.* **1997**, *62*, 8974−8975. (d) Francisco, C. G.; Freire, R.; González, C. C.; Suárez, E. *Tetrahedron: Asymmetry* **1997**, *8*, 1971−1974. (e) Francisco, C. G.; Martín, C. G.; Suárez, E. *J. Org. Chem.* **1998**, *63*, 2099−2109. (f) Francisco, C. G.; Martín, C. G.; Suárez, E. *J. Org. Chem.* **1998**, *63*, 8092−8093. (g) González, C. C.; Kennedy, A. R.; León, E. I.; Riesco-Fagundo, C.; Suárez, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 2326−2328.

(8) (a) Liberek, B.; Sikorski, A.; Melcer, A.; Konitz, A. *Carbohydr. Res.* **2003**, *338*, 795−799. (b) Dabrowska, A.; Dokurno, P.; Konitz, A.; Śmiatacz, Z. *Carbohydr. Res.* **2000**, *323*, 230−234. (c) Liberek, B.; Dabrowska, A.; Frankowski, R.; Matuszewska, M.; Smiatacz, Z. *Carbohydr. Res.* **2002**, *337*, 1803−1810. (d) Wengel, J.; Pedersen, E. B. *Synthesis* **1991**, 451−454. (e) Wengel, J.; Lau, J.; Pedersen, E. B.; Nielsen, C. M. *J. Org. Chem.* **1991**, *56*, 3591−3594. (f) Abbaci, B.; Florent, J.-C.; Monneret, C. *J. Chem. Soc., Chem. Commun.* **1989**, 1896−1897. (g) Florent, J.-C.; Monneret, C. *J. Chem. Soc., Chem. Commun.* **1987**, 1171−1172.

(9) Hassner, A.; Wiegand, N. H.; Gottlieb, H. E. *J. Org. Chem.* **1986**, *51*, 3176−3180.

Table 1. Alkoxyl Radical Fragmentation Reaction of 3-Azido-2,3-dideoxy-hexopyranoses

entry	γ-hydroxy azide[a]	time h	yield (%)	β-iodo azide[b]	time h	yield (%, dr)	vinyl azide[c]	time h	yield (%)	2*H*-azirine[d]	time h	yield (%)
1	 **1**	5	(90)	 **2-D-Ara** **2-D-Rib**	0.5	(95, 9:1)	 **3**	0.5	(76)	 **4**	22	(85)
2	 **5**	2.5	(87)	 **6-D-Xyl** **6-D-Lyx**	0.5	(86, 6:4)	 **7**	0.5	(70)	 **8**	2.5	(84)
3	 **9**	5	(74)	 **10-D-Ara** **10-D-Rib**	0.5	(96, 6:4)	 **11**	0.75	(85)	 **12**	4	(63)
4	 **13**	7.5	(88)	 **14-D-Ara** **14-D-Rib**	0.25	(91, 7:3)	 **15**	3	(66)	 **16**	2	(58)
5	 **17**	2.5	(87)	 **18-L-Thr** **18-L-Ery**	0.5	(78, 2:8)	 **19**	1	(91)	 **20**	3.5	(87)[e]

[a] Reagents and conditions per mmol of substrate: $HgSO_4$ (0.047 mmol), H_2SO_4 (5 mM, 27 mmol), 1,4-dioxane, 30 °C, then NaN_3 (10 mmol), AcOH (1.35 mL). [b] Reagents and conditions per mmol of substrate: (diacetoxyiodo)benzene (1.5 mmol), I_2 (1.5 mmol), CH_2Cl_2, reflux. [c] Reagents and conditions per mmol of substrate: DBU (2.5 mmol), PhH, reflux. [d] Reagents and conditions per mmol of substrate: toluene (12 mL/mmol), reflux. [e] Unstable, could not withstand chromatographic purification, crude yield.

opportunity to probe its solid-state structure.[10] Although a crystallographic analysis was performed on the palladium-(II) complex of 3-(*p*-methoxyphenyl)-2*H*-azirine, the molecular structure of simple 3-alkylmonosubstituted-2*H*-azirines has not been determined.[11]

As far as we know, no examples of these monosubstituted 3-alkyl-2*H*-azirine compounds possessing an α-hydroxyl derivative have been reported to date, but a few examples are documented for the preparation of monosubstituted 3-alkyl-2*H*-azirines.[5a,12] Related 2*H*-azirine-3-carboxylic esters have been recently synthesized and used as dienophiles in hetero Diels−Alder cycloadditions.[13]

In summary, using mild reactions, chiral β-iodo azides, vinyl azides, and 2*H*-azirines allowed the preparation of

(10) Crystal data and structure refinement for **16**: $C_{14}H_{25}NO_4Si$, M_r = 299.44, monoclinic, space group C_2, a = 16.4478 (8), b = 6.2864 (3), c = 16.1368 (8) Å, β = 95.529 (2)°, V = 1660.74 (14) Å^3, Z = 4, ρ_{calcd} = 1.198 Mg/m^3, μ(Mo Kα) = 0.71073 Å, F(000) = 648, T = 123(2) K; colorless crystal, 0.60 × 0.30 × 0.02 mm, collected reflections 8917. The structure was solved by direct methods, all hydrogen atoms were refined anisotropically using full-matrix least-squares-based F^2 to give R_1 = 0.0413 and wR_2 = 0.0734 for 3245 independently observed reflections ($|F_o| > 2\sigma(|F_o|)$) and 200 parameters. 2*H*-Azirine data: C(2)−C(3) = 1.438 (4) Å; C(2)−N = 1.565 (4) Å; C(3)−N = 1.255 (3) Å; C(2)−C(3)−N = 70.7 (2)°; C(3)−N−C(2) = 60.10 (18)°; C(3)−C(2)−N = 49.20 (15)°.

(11) (a) Hassner, A.; Bunnell, C. A.; Haltiwanger, K. *J. Org. Chem.* **1978**, *43*, 57−61. For recent crystallographic studies with other than 3-monosubstituted 2*H*-azirines, see: (b) Piquet, V.; Baceiredo, A.; Gornitzka, H.; Dahan, F.; Bertrand, G. *Chem. Eur. J.* **1997**, *3*, 1757−1764. (c) Alcaraz, G.; Wecker, U.; Baceiredo, A.; Dahan, F.; Bertrand, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1246−1248. (d) Villalgordo, J. M.; Heimgartner, H. *Helv. Chim. Acta* **1992**, *75*, 1866−1870. (e) Heimgartner, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 238−264. (f) Kanehisa, N.; Yasuoka, N.; Kasai, N.; Isomura, K.; Taniguchi, H. *J. Chem. Soc., Chem. Commun.* **1980**, 98−99.

(12) (a) Komatsu, M.; Ichijima, S.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1973**, *38*, 4341−4342. (b) Wade, T. N.; Khéribet, R. *J. Org. Chem.* **1980**, *45*, 5333−5335. (c) Njar, V. C. O.; Dueerkop, J.; Hartmann, R. W. *Steroid* **1996**, *61*, 138−143. (d) Ray, C. A.; Risberg, E.; Somfai, P. *Tetrahedron* **2002**, *58*, 5983−5987.

(13) (a) Alves, M. J.; Gilchrist, T. L. *Tetrahedron Lett.* **1998**, *39*, 7579−7582. (b) Alves, M. J.; Bickley, J. F.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1399−1401. (c) Gilchrist, T. L.; Mendonça, R. *Synlett* **2000**, 1843−1845. (d) Álvares, Y. S. P.; Alves, M. J.; Azoia, N. G.; Bickley, J. F.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1911−1919.

derivatives of alditols, with one carbon less than the starting carbohydrate, in good yields. The interest in these compounds owes a great deal to the ease with which they are synthesized from readily accessible starting materials. It is hoped that these compounds will serve as powerful synthetic building blocks for the preparation of complex heterocyclic systems. The methodology is also highly attractive from a strategic standpoint since it is amenable to the preparation of stereochemical and structural analogues of complex targets.

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Supporting Information Available: Experimental procedure and characterization for all pure compounds and an X-ray crystallographic file (CIF) for azirine **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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