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Rearrangements of Haloalkynol Derivatives of Glucofuranose

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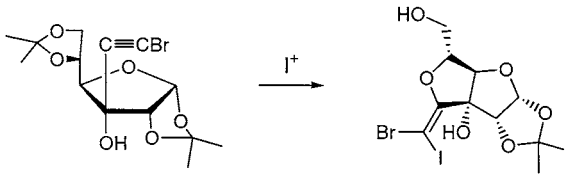
ABSTRACT

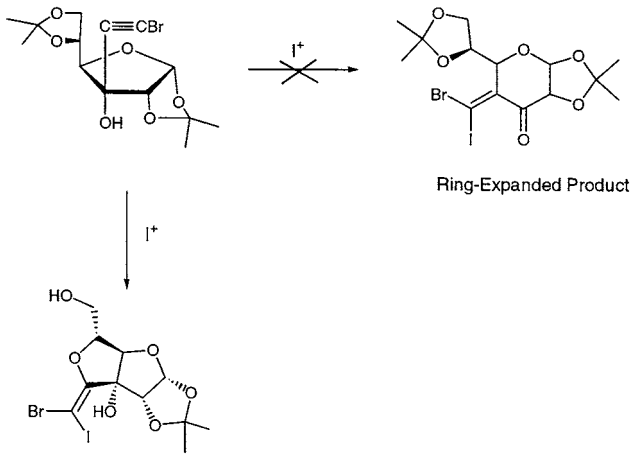


Bromoalkynol derivatives of diacetone glucose undergo rearrangements to dihaloenol ethers contained in furo[3,4-b]furan cores when treated with halonium-producing reagents.

Halonium-producing reagents such as *N*-iodosuccinimide (NIS) and catalytic amounts of protic acids such as *p*-toluenesulfonic acid (TsOH) or iodine and Lewis acids such as [hydroxy(tosyloxy)iodo]benzene (Koser's reagent) have been used to convert haloalkynols to *β*,*β*-dihaloenones.[1] Group shifts with significant stereospecificity are involved and have been applied to ring expansions of representative cyclopentyl haloalkynols to *β*,*β*-dihalocyclohexanones.[2] Efforts to extend ring expansions to the conversions of furanoses to pyranoses were undertaken but led to products of haloetherification.[3] For example, iodination of 3-iodoethynyl-1,2-*O*-(1-methylethylidene)-5-*O*-methyl-α-D-pentofuranose led not to expansion but to the formation of a furo[3,4-b]furan system. It arose by the unexpected attack by a neighboring ether on the vinyl cation formed during the reaction. Such ether cleavages are uncommon.[4] The products, with their exocyclic dihaloglycals, represent attractive starting points for novel tamoxifen-like compounds after aryl exchanges of the halogens.[5]

We report now the halogenation of haloalkynol derivatives of diacetone glucose (1,2,5,6-di-*O*-(1-methylethylidene)-α-D-glucofuranose) **1**, whose acetonide protecting group at C-5 and C-6 was expected to block the formation of haloethers and lead to ring expansions to ketopyranoses. This group, however, did not survive the halogenation conditions, and the reactions' main products were those of haloetherification at the C-5 site. (Scheme 1)

Scheme 1. Preference for Ether Formation vs Ring Expansion



Commercially available diacetone glucose was oxidized at the C-3 position with the Dess−Martin reagent in dry methylene chloride to afford 1,2,5,6-di-*O*-(1-methyleth-

(1) Koser, G. F. *Aldrichim. Acta* **2001**, *34*, 89.
(2) Herault, X.; McNelis, E. *Tetrahedron* **1996**, *52*, 10267.
(3) Djuardi, E.; McNelis, E. *Tetrahedron Lett.* **1999**, *40*, 7193.
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(5) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Suzuki, A. *Pur. Appl. Chem.* **1991**, *63*, 419.

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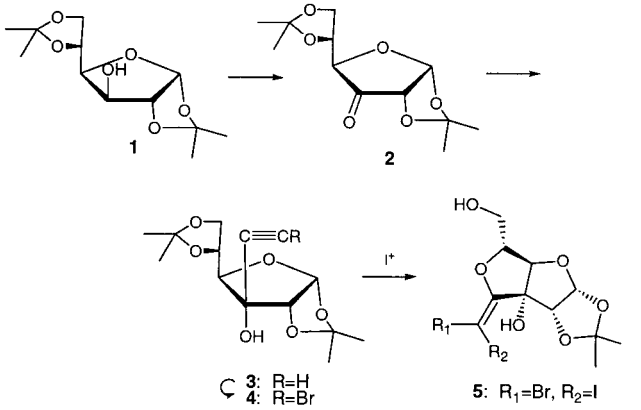
ylidene)-α-D-hex-3-ulofuranose **2** along with its hydrate in 99% yield (Scheme 2). The IR spectrum of **2** had a carbonyl

Scheme 2. Synthesis of **5**



peak at 1725 cm^{-1} and a hydrate peak at 3400 cm^{-1}. The mass spectrum had the typical fragmentation peaks at *m/z* 243 ($M^+ - 15$, from the loss of a methyl of an isopropylidene group), 142 ($M^+ - 116$, from the splitting off of the C-1/C-2 isopropylidene group and the furanose oxygen), 101 (from the $C_5H_9O_2$ group at C-4), and 157 ($M^+ - 101$).

The reaction of **2** with a nucleophile is known to give rise to a product with high stereoselectivity via attack of the nucleophile from the top face of the ring due to the bulkiness of the 1,2-isopropylidene group.[6] Upon treatment of ketose **2** with ethynylmagnesium chloride (0.5 M in THF) in anhydrous ether, one stereoisomer of 3-C-ethynyl-1,2,5,6-di-*O*-(1-methylethylidene)-α-D-allofuranose **3** was produced in 79% isolated yield as a crystalline solid with a melting point of 106−107 °C. The mass spectrum of **3** had key fragmentation peaks at *m/z* 269 ($M^+ - 15$), 183 ($M^+ - 101$), 168 ($M^+ - 116$), and 101. The IR spectrum had a hydroxyl peak at 3500 cm^{-1}, an alkyne C−H stretch at 3230 cm^{-1}, and an alkyne C−C stretch at 2100 cm^{-1}. A single proton with a signal at 2.68 ppm in the ^{1}H NMR spectrum was indicative of the alkynyl hydrogen. All data were consistent with those reported in the literature.[7]

Reaction of alkyne **3** with *N*-bromosuccinimide (NBS) and silver nitrate in acetone gave 3-bromoethynyl-1,2,5,6-di-*O*-(1-methylethylidene)-α-D-allofuranose **4** as a white solid with a melting point of 101−102 °C in 84% crude yield.[8] GCMS data confirmed the addition of a bromine to and loss of a proton from **3**. Loss of the alkynyl hydrogen was noted in the ^{1}H NMR with the absence of the singlet at 2.68 ppm and in the IR with the absence of the peak at 3230 cm^{-1}.[9]

Bromoalkynyl **4** was treated with several methods for producing iodonium ion to induce ring expansion. The expected ketopyranose would give an $M^+ - 15$ peak at m/z 473/475 in the mass spectrum as well as a peak at *m/z* 372/374 ($M^+ - 116$), and perhaps the molecular ion peak at *m/z* 488/490. After iodination with 1 equiv of NIS and a catalytic amount of TsOH monohydrate in refluxing 15% aqueous acetonitrile, compound **4** was converted to a white crystalline solid with a melting point of 202−204 °C as the major isolable product **5** in 48% yield. Loss of one isopropylidene group from this compound was shown by ^{1}H NMR and by the mass spectrum with a molecular ion peak at *m/z* 448/450. A large peak at *m/z* 332/334 in the mass spectrum indicated the loss of 116 from *m/z* 448/450. Thus, the isopropylidene group at C-1 and C-2 was still intact. In addition, there was no peak at *m/z* 101, confirming the loss of the C-5 and C-6 isopropylidene group. The complete NMR spectra for **5** were as follows: ^{1}H NMR (CD_3OD, 300 MHz) δ 5.91 (d, 1H, $J = 3.9$ Hz), 5.10 (d, 1H, $J = 3.9$ Hz), 4.65 (s, 1H), 4.39 (t, 1H, $J = 5.5$ Hz), 3.72 (d, 2H, $J = 5.3$ Hz), 1.58 (s, 3H), 1.41 (s, 3H) ppm; ^{13}C NMR (CD_3OD, 300 MHz) δ 159.5, 114.5, 107.5, 89.6, 87.9, 86.9, 84.0, 62.4, 27.6, 27.4, 25.5 ppm.

Five different structures seemed plausible for compound **5** (structures A−E, Figure 1). Structures A and B, the two

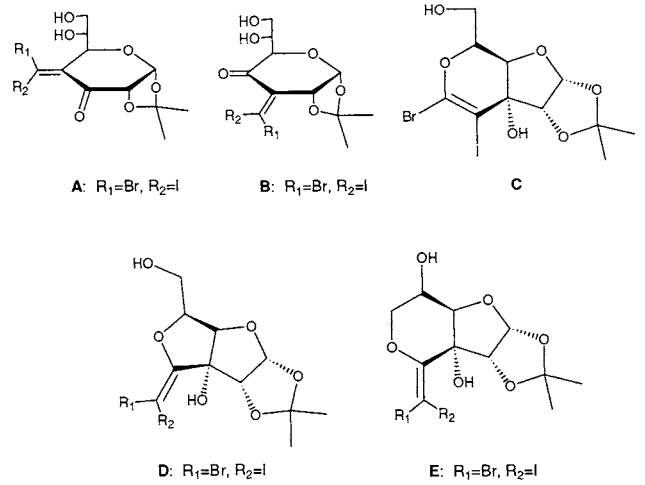


Figure 1. Possible structures for compound **5**.

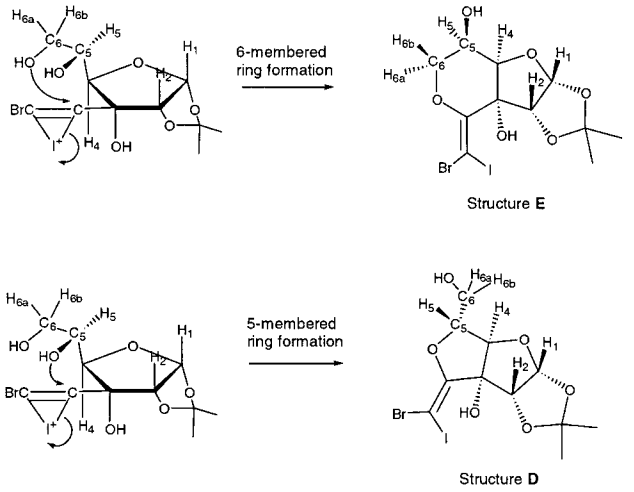
regioisomers of the ring-expanded ketopyranose with loss of the 5,6-protecting group, were ruled out due to the lack of carbonyl signals in the IR and ^{13}C NMR spectra. This confirmed that ring expansion to a ketopyranose did not occur. Since ring expansion did not take place and the 5,6-protecting group was lost, the possibility of ether formation as seen with the xylose compound in Scheme 1 seemed likely. New peaks in the ^{13}C NMR at 159.53 ppm (methylidene carbon) and 25.5 ppm (methylidene carbon with

(6) Baker, D. C.; Brown, D. K.; Horton, D.; Nickol, R. *Carbohydr. Res.* **1974**, *32*, 299.
(7) Kakinuma, K.; Iihama, Y.; Takagi, I.; Ozawa, K.; Yamauchi, N.; Imamura, N.; Esumi, Y.; Uramoto, M. *Tetrahedron* **1992**, *48*, 3763.
(8) Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 727.
(9) Structures of all new compounds described herein agreed with elemental analyses provided by Schwarzkopf Microanalytical Laboratories, Woodside, NY.

iodine and bromine) supported either structures D or E as the product and ruled out compound C.[10]

Analysis of the ^{1}H NMR data along with examination of molecular models supported structure D over E. The chiral center at C-5 had an absolute configuration of *R* since it was *R* in starting material **1**, and there was no evidence for bond breaking at C-5 during the intermediate steps. With C-5 as *R*, molecular models showed that if the hydroxyl group at C-6 attacked the vinyl cation to form the six-membered ring (structure E), hydrogens H-4 and H-5 would be syn. (Scheme 3) If the hydroxyl group at C-5 attacked the vinyl cation to

Scheme 3. Preference for Structure D



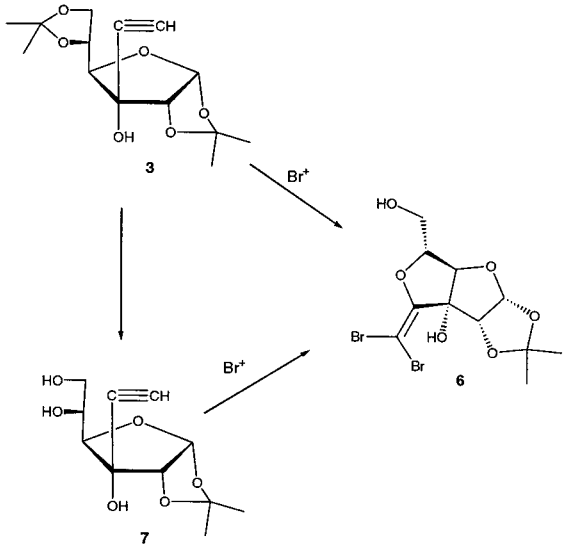
form the five-membered ring (structure D), H-4 and H-5 would be anti to one another and C-6 would be pseudoequatorial. In the ^{1}H NMR of **5**, H-4 appeared as a singlet. H-4 could only appear as a singlet if H-5 were anti to it, as in structure D. This effect was noted in the pentofuranose case[3] and by the Tsuchiya group for this type of heterocycle, as well as by the Yoshimura and Baker groups.[6,11]

Further support for structure D came from the fragmentation pattern in the mass spectrum. The base peak of *m/z* 301/303 occurs from a splitting off of 116 from the parent *m/z* 448/450 and then further cleavage of 31. The loss of 31 likely comes from protonated formaldehyde, which can be cleaved from structure D, but not structure E.

On the basis of iodonium-induced shifts, it is most likely that the stereochemistry of bromoiodoenol **5** is *E*.[12] Those findings were consistent with the shift anti to an iodonium bridging effect on the alkynyl groups. By extension, attack by an alcohol to form an enol ether should be anti to the iodine. Thus, **5** is assigned as structure D, 4-(*E*)-bromoiodomethylene-(*cis*)-3a-hydroxy-6-(*cis*)-hydroxy methyl-2,3-*O*-(1-methylethylidene)-2,3,3a,4,6,6a-hexahydrofuro[3,4-b]furan.

The dibromo analogue of **5**, namely, **6**, was prepared directly from **3** in 50% crude yield by using 2.4 equiv of NBS with catalytic $AgNO_3$ in acetone (Scheme 4). Com-

Scheme 4. Synthesis of **6**



pound **6** was also observed as a side-product in the formation of **4** (Scheme 2). Compound **6** contained two bromine atoms with the loss of one protecting group as shown by key fragments in the mass spectrum at *m/z* 400/402/404 (M^+), 385/387/389 ($M^+ - 15$), 284/286/288 ($M^+ - 116$), and 253/255/257 ($M^+ - 116 - 31$). The proton NMR for **6** was nearly identical to that of **5**, as was the carbon NMR with the major difference being the dibromo methylidene carbon's signal at 68.2 ppm vs the bromoiodo methylidene carbon of **5**'s signal at 25.5 ppm. The NMR spectra for **6** were as follows: ^{1}H NMR (CD_3OD, 300 MHz) δ 5.91 (d, 1H, J = 3.9 Hz), 5.09 (d, 1H, J = 3.9 Hz), 4.62 (s, 1H), 4.43 (t, 1H, J = 5.6 Hz), 3.73 (d, 2H, J = 5.3 Hz), 1.57 (s, 3H), 1.40 (s, 3H) ppm; ^{13}C NMR (CD_3OD, 300 MHz) δ 158.9, 114.7, 107.7, 89.5, 88.1, 87.7, 83.1, 68.2, 62.5, 27.7, 27.5 ppm.

Dibromo **6** was also derived from **7** (**3** without its 5,6-isopropylidene group) in 74% yield with 2.2 equiv of NBS. Compound **7**, mp 97−98 °C, was prepared from **3** by acetic acid treatment in 94% yield.[13] In addition to a peak at *m/z* 229 ($M^+ - 15$), the mass spectrum of **7** displayed a major peak at 98 corresponding to losses of 116 and 30. The reaction from **7** to **6** confirms that the loss of the protecting group at C-5 and C-6 of **3** is required to form **6** as well as **5**.

(10) An alkylidene carbon bearing two halogens has an upfield peak in the ^{13}C NMR spectrum. (See ref 12 below and: Brunel, Y.; Rousseau, G. *Tetrahedron Lett.* **1995**, *36*, 2619.)

(11) (a) Tsuchiya, T.; Aito, K.; Umezawa, S.; Ikeda, A. *Carbohydr. Res.* **1984**, *126*, 45. (b) Yoshimura, J.; Kobayashi, K.; Sato, K.; Funabashi, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1806.

(12) (a) Bovonsombat, P.; McNelis, E. *Tetrahedron Lett.* **1994**, *35*, 6431; (b) *Tetrahedron* **1993**, *49*, 1525; (c) *Tetrahedron Lett.* **1993**, *34*, 4277. (d) Djuardi, E.; Bovonsombat, P.; McNelis, E. *Tetrahedron* **1994**, *50*, 11793. (e) Bovonsombat, P.; McNelis, E. *Synth. Commun.* **1995**, *25*, 1223.

(13) Qureshi, S.; Shaw, G. *J. Chem. Soc., Perkin Trans. 1* **1985**, 875. NMR data for **7**: ^{1}H NMR (CD_3OD, 300 MHz) δ 5.76 (d, 1H, J = 3.58 Hz), 4.56 (d, 1H, J = 3.58 Hz), 3.95 (dd, 1H, J = 5.63 Hz, J = 2.60 Hz), 3.90 (d, 1H, J = 8.47 Hz), 3.78 (dd, 1H, J = 11.58 Hz, J = 2.29 Hz), 3.59 (dd, 1H, J = 11.62 Hz, J = 5.60 Hz), 3.16 (s, 1H), 1.54 (s, 3H), 1.35 (s, 3H) ppm; ^{13}C NMR (CD_3OD, 300 MHz) δ 114.8, 105.4, 86.4, 83.0, 80.8, 78.53, 77.0, 73.4, 65.5, 27.4, 27.3 ppm.

Thus, the ether formation does occur with preference for a possible ring expansion. The latter reaction may be inhibited by the poor migrating aptitude of carbons bearing oxygen atoms, although there are reports of ring expansions of glycosides and xylofuranoses with diazomethane in a methanol/ether (3:1, v/v) mixture.[14] Since the shift reactions of haloalkynols proceed best in acidic aqueous solvents, hydrolysis of the 5,6-isopropylidene masking group proceeds prior to haloetherification. Efforts to minimize or eliminate aqueous acid in the reaction to promote ring expansion in these systems is being tested, as well as examination of acid insensitive protecting groups at the C-5 position.

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Supporting Information Available: Experimental procedures for the preparations of compounds **4**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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