Tetrahedron Letters,Vol.26,No.33,pp 3915-3918,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

STEREOSELECTIVITY IN THE ELECTROPHILE-PROMOTED CYCLIZATIONS OF A HYDROXYOLEFIN DERIVED FROM ARABINOSE. SYNTHESIS OF A PHOSPHONATE ISOSTERE OF β-D-ARABINOSE-1,5-DIPHOSPHATE

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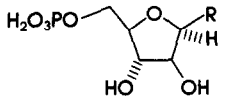
Abstract: Cyclization of hydroxyolefin **3**, either with NBS or $Hg(OAc)_2$, gives predominantly the β isomer of a C-arabinofuranoside structure. Carbohydrate phosphonate **1** was synthesized from bromide **4a** in six steps.

We have been interested in preparing carbohydrate phosphonate **1** because of its potential as a stable analogue of β-D-arabinose-1,5-diphosphate **2**, a potent inhibitor of the enzyme fructose-1,6-bisphosphatase (EC 3.1.3.11).[1] In our successful synthetic work we uncovered a strong stereoselective preference for cyclization of hydroxyalkene **3** to the C-arabinofuranoside structures **4a** and **5a**, which have a cis arrangement of substituents on carbons 2 and 3.[2] Recent interest[3,4] in stereoselective mercuriocyclizations of chiral hydroxyalkenes for the preparation of C-glycosides prompts us to report our independent studies.

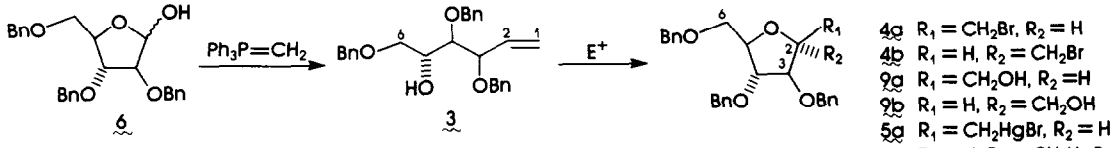
A very direct entry into a functionalized C-arabinofuranoside structure suitable for elaboration into **1** is olefination of **6** with diphosphorus reagents such as **7** or **8**, followed by Michael-type cyclization.[5,6] However, this approach was not successful in this case.[7] More auspiciously, treatment of **6** with methylidenetriphenylphosphorane (2.35 equiv from the phosphonium bromide and lithium



1 $R = CH_2PO_3H_2$
2 $R = OPO_3H_2$

$Ph_3P=CH\overset{O}{\overset{\|}{C}}P(OPh)_2$ **7**

$(EtO)_2\overset{O}{\overset{\|}{P}}\bar{C}H\overset{O}{\overset{\|}{P}}(OEt)_2\ Na^+$ **8**



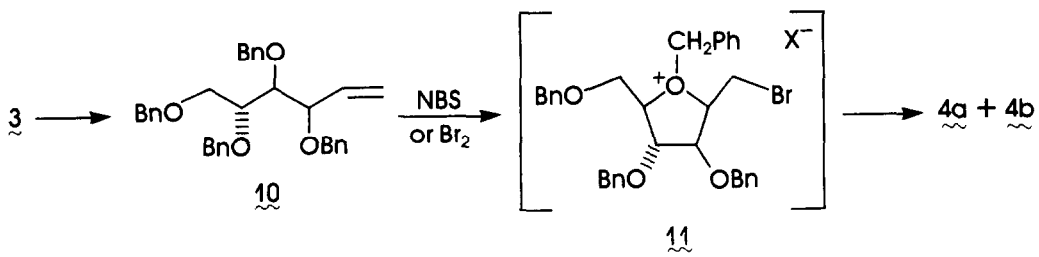
6 → ($Ph_3P=CH_2$) → **3** → (E^+)

4a $R_1 = CH_2Br$, $R_2 = H$
4b $R_1 = H$, $R_2 = CH_2Br$
9a $R_1 = CH_2OH$, $R_2 = H$
9b $R_1 = H$, $R_2 = CH_2OH$
5a $R_1 = CH_2HgBr$, $R_2 = H$
5b $R_1 = H$, $R_2 = CH_2HgBr$

Bn = $PhCH_2$

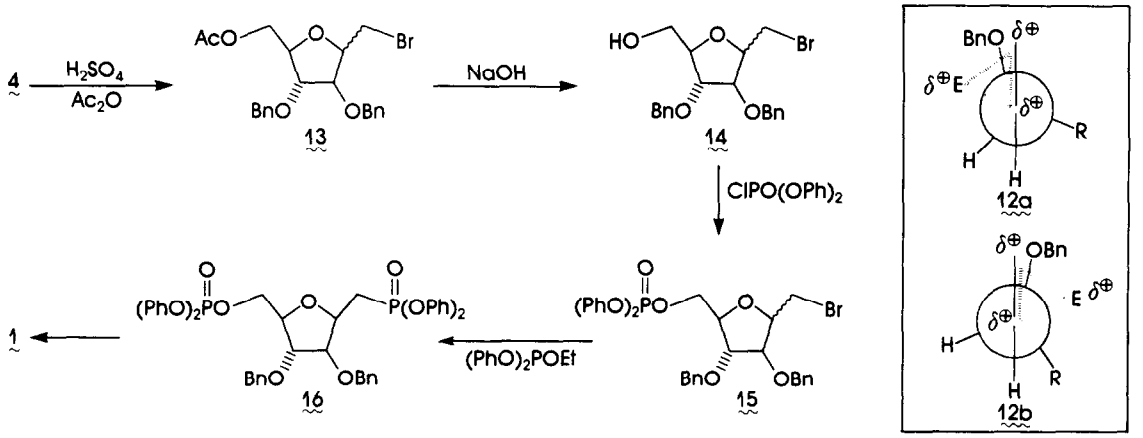
hexamethyldisilazide, 15 min, THF) gave hydroxyolefin **3** in 68% yield.[8] Cyclization of **3** with *N*-bromosuccinimide (NBS) furnished a mixture of bromomethyl compounds **4a** and **4b** (90%), which was highly enriched in the β anomer **4a** (**4a/4b** = 7.8:1).[9,10] In an attempt to prepare a larger amount of diastereomer **4b**, hydroxyalkene **3** was reacted with *m*-chloroperoxybenzoic acid in refluxing 1,2-dichloroethane (1.5 equiv MCPBA, 16 h; 65%) to give cyclized alcohols **9a** and **9b** (no intermediate epoxide was observed). This mixture was converted to a mixture of bromides **4a** and **4b** (diethyl azodicarboxylate, triphenylphosphine, $ZnBr_2$; 80%),[11] in a 55:45 ratio by ^{13}C and ^1H NMR. Thus, the NBS cyclization of **3** was highly stereoselective for the β isomer, with 2,3-cis substitution (i.e., **4a**), whereas the epoxidation was not stereoselective.

Mercuriocyclization of **3** [1.4 equiv $Hg(OAc)_2$, THF, 82% yield after exchange with NaBr] produced a mixture of **5a** and **5b** which was highly enriched in the isomer **5a**. Quantitation was best achieved by conversion to the bromomethyl compounds **4** (bromine, pyridine; 91% yield) which revealed a 6.4:1 mixture of the β and α isomers **4a** and **4b**. Mercuriocyclizations of protected ribose and glucose derivatives produce a preponderance of the 2,3-cis products, a result which has been ascribed to some form of coordination by the oxygen at C-3.[9]



Because of the stereochemical disparity in the electrophile-induced cyclizations of **3**, between the NBS and mercury(II) cyclizations vs. the MCPBA reaction, we decided to probe this chemistry further. The MCPBA reaction proceeds through an epoxide, formation of which is presumably irreversible. Since bromonium ion formation is known to be reversible,[12] we considered that one of the bromonium ions in the transformation of **3** to **4a** and **4b** might be siphoned off. In an effort to separate the selectivity of bromonium ion formation from that in the ring closure, we attempted to convert tetrabenzyl ether **10** (prepared from **3** with NaH, DMF, and benzyl chloride in 85% yield) to the corresponding bromohydrin (NBS, DMSO/water)[13] or dibromide (bromine, CCl_4). Only cyclized product **4** was obtained in 74% and 65% yields (**4a/4b** was 6.9:1 and 9.3:1, respectively), in analogy with oxonium ion-mediated haloetherifications reported by Bartlett.[14] Similar stereochemical results were obtained when the oxygen at C-5 in **3** was protected with dimethyl-*t*-butylsilyl and trimethylsilylethoxymethyl ether groups (**4a/4b** = 6.7:1 and 6.8:1, respectively), unlike the large variations seen in Bartlett's study (see below).

Clearly, the bromonium ion from **10** is rather transient, reacting intramolecularly before capture by solvent (DMSO or water)[12]. Thus, the stereochemical preference in the transformation of **10**, as well as **3**, to **4** may arise from kinetic bromonium ion formation, the lifetime of these diastereomeric ions being too short for thermodynamic equilibration. In our case, the stereoselectivity appears to be dominated by the benzyl ether on C-3 of **3**, as opposed to steric interactions in an intermediate cyclic oxonium ion (viz. **11**),[14] as reflected in the similar isomer ratios observed for alcohol **3**, benzyl ether **10**, and the C-5 silyl ether derivative.



The question remains as to the source of the stereoselectivity for isomers **4a** and **5a** in cyclizations of **3**. Houk and coworkers have presented ab initio and MM2 calculations indicating that an allylic alkoxy substituent prefers to adopt an "inside" position during [3 + 2] cycloadditions of nitrile oxides to alkenes.[15] This analysis can be extrapolated to electrophilic reactions of alkenes in general to explain, for example, the stereoselectivity observed in halolactonizations of allylic alcohols.[16] Both conformers **12a** and **12b**, representing pericyclic transistion states from attack of **3** by an electrophile, reflect the "inside alkoxy" preference. Structure **12a**, which leads to the major product, may be favored because of the lower steric hindrance of the proximal hydrogen (H) compared with the proximal alkyl chain (R) in **12b**. Conformer **12b** gives the minor product after partial bond rotation.

The 7.8:1 mixture of **4a** and **4b** was selectively acetolyzed to acetate **13** (1% w/w conc. sulfuric acid/Ac_2O; 85%),[17] which was hydrolyzed to alcohol **14** (NaOH, water/MeOH; 85%). Phosphorylation of **14** gave phosphate **15** [$ClPO(OPh)_2$/pyridine; 73%], which was subjected to an Arbusov reaction [$EtOP(OPh)_2$, 160°C; 40%][18] to provide 2,5-anhydroglucitol derivative **16** [mp 72-73°C; ^{13}C NMR: CH_2P 25.2 ppm, $J(CP)$ = 141.6 Hz].[2,17] Intermediate **16** was transformed to **1** by treatment with $Me_4N^+OH^-$ (partial hydrolysis to remove two phenyl esters), H_2 and Pd/C (to remove the benzyl ethers), and H_2/PtO_2 (for the remaining phenyl esters). The

target phosphonate **1** was obtained as the disodium salt (hydrate).[20]

Phosphonate isosteres, such as **1**, have attracted considerable chemical and biological interest.[21] We will report on the biological activity of phosphonate **1** in due course.[22]

References and Notes

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22. We thank Drs. Kirk Sorgi (McNeil), Lanny Liebeskind (Emory University), and Derek Horton (Ohio State University) for helpful discussions. We also thank Carmello Rizzo (Univ. of Pa.) for technical assistance.

(Received in USA 13 May 1985)