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Alkylidene Carbenes as Intermediates in the Synthesis of Highly Functionalized Branched-chain Sugars and Nucleosides

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Abstract: Reaction of *O*-mesylcyanohydrins of furanos-3-ulose with sodium azide afforded isomeric vinylazido compounds. A mechanism involving an alkylidene carbene is proposed and the intermediacy of such a carbene is confirmed by standard trapping reactions such as, addition to the double bond of cyclohexene or insertion into the Si-H or O-H bonds of triethylsilane or methanol, respectively. The above mentioned reaction has been carried out in different solvents (dichloromethane, THF, nitromethane, acetonitrile) to yield a variety of highly functionalized branched-chain sugars. Finally, extension of this reaction to 3'-α-mesyloxynitriles of nucleosides has lead to 3'-vinylazido- and 3'-azido-3'-azidomethyl nucleosides.

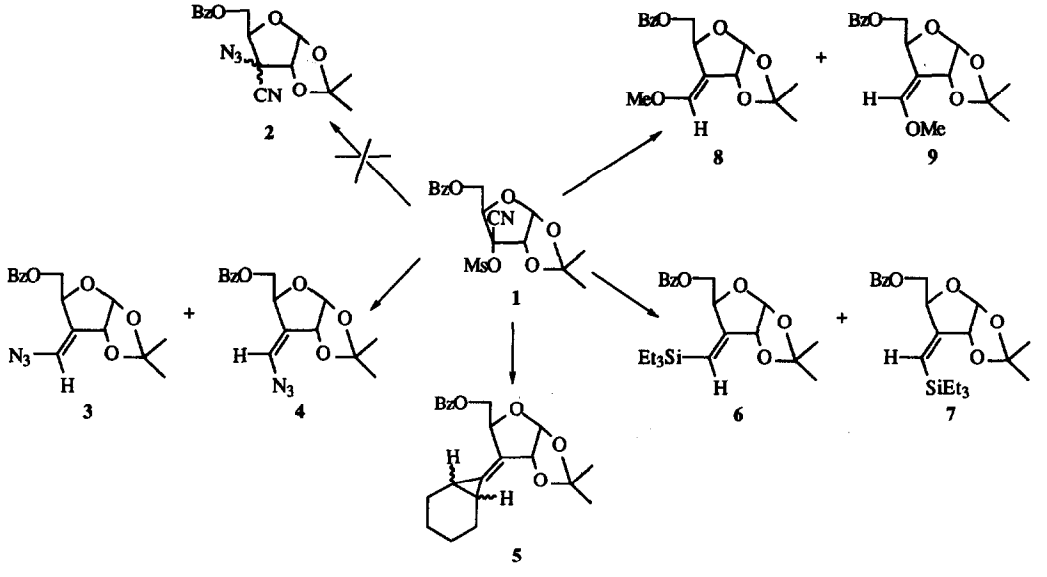
INTRODUCTION

Alkylidenecarbenes have been extensively studied in recent years.[1] These reactive intermediates have been generated from a variety of precursors, such as, vinyl halides[2], N-nitrosooxazolidones and related compounds,[3,4] vinyl triflates,[5] vinyl amines,[6] vinyl silanes,[7] (diazomethyl)phosphonates,[8] 1-diazo-1-alkenes[9] under basic or neutral conditions including photofragmentation.[1a] Many efforts have been directed towards their obtention in milder and more efficacious conditions, and now a good number of methods for their generation are at hand. However, to the best of our knowlegde, these reactive intermediates have not been studied, so far, in carbohydrate chemistry, where they would offer new possibilities of functionalization in C-branched carbohydrates.

We now report a simple method for the mild generation of alkylidenecarbenes from α-mesyloxynitriles (cyanomesylates) of carbohydrates. Cyanomesylates of carbohydrates, which are considered useful chiral synthons for the synthesis of naturally occurring branched-chain sugars,[10,11] have not been so far, used for the generation of alkylidene carbenes. These precursors can be easily obtained by reaction of uloses with sodium cyanide followed by mesylation of the corresponding cyanohydrin.[11b] In a preliminary account[12] we reported the unexpected behavior of tertiary cyanomesylates which on treatment with sodium azide afforded vinylazido derivatives through an alkylidene carbene intermediate. Here we describe this reaction in detail and extend it to the synthesis of branched-chain sugar nucleosides.

RESULTS AND DISCUSSION

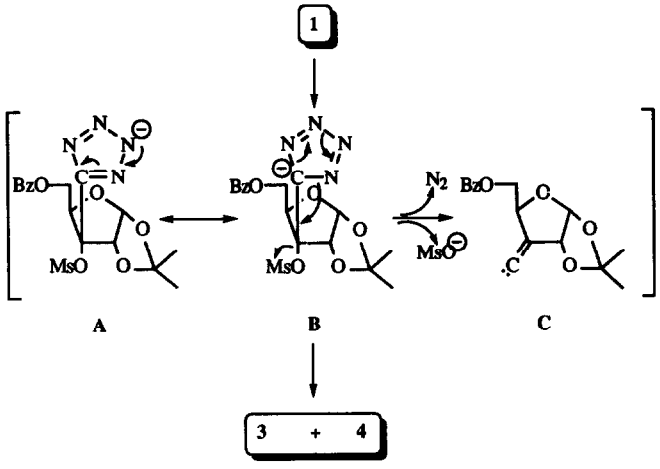
As a part of our program on the synthesis of highly functionalized branched-chain sugars, we tried to transform the α-mesyloxynitrile **1**[13] into the corresponding α-azidonitrile **2** by nucleophilic displacement of the methanesulfonate group with an azide ion. However, reaction of the α-mesyloxynitrile of ribose **1** (scheme 1) with an excess of sodium azide (NaN_3) in dichloromethane, at room temperature, and in the presence of tetrabutylammonium hydrogensulfate, afforded an isomeric mixture (2:3) of the *E* and *Z* vinylazido derivatives **3** and **4**[12] in 30% yield. Structures of **3** and **4** were assigned on the basis of the corresponding analytical and spectroscopic data. The ^1H NMR spectra (table 1) showed the disappearance of the signal corresponding to the mesyl group and the presence of a triplet at 6.85 ppm for the major compound (**4**) and a doublet at 6.94 ppm for the minor isomer (**3**) assigned to the vinylic protons of each isomer. ^{13}C NMR spectra of **3** and **4** showed the disappearance of the signals corresponding to the mesyl and cyano groups, the downfield shift of the signal corresponding to C-3 (which appeared around 126 ppm) and the presence of a new signal around 125 ppm corresponding to the vinylic carbon C-1'.



Scheme 1

The stereochemistry of the double bond of the minor (**3**) and major (**4**) isomers was established as *E* and *Z*, respectively, by NOE difference experiments[14,15] upon irradiation of the vinylic protons of both isomers. Thus, irradiation of the vinylic proton of **3** caused enhancements of the signal for H-2 (0.6%), thus indicating that was the *E* isomer. Similarly, irradiation of the vinylic proton of **4** influenced the signals of H-4 (0.5%) and H-5a (3.4%), consequently being assigned as the *Z* isomer.

A possible mechanism for the formation of the vinylazides **3** and **4** is shown in scheme 2. It implies the initial attack of the azide ion to the cyano group of **1** to give a tetrazolate (**A**), which by charge reajustment and loss of N_2 and MsO^- would generate an alkylidenecarbene or carbenoid intermediate (**C**). Subsequent reaction of **C** with the azide ion, present in the media, would afford the vinylazides **3** and **4**. According to literature data, an alkylidenecarbene intermediate has also been proposed to be involved in the synthesis of vinylazides by reaction of *N*-nitrosooxazolidones with sodium azide, under phase transfer conditions.[16] Moreover, formation of an alkylidene carbene has been also quoted by Stang in the thermolysis of a tetrazole.[17]



Scheme 2

To demonstrate the participation of the alkylidenecarbene intermediate **C** and thus the mechanism proposed, several standard trapping reactions were performed. As the intermediate proposed **C** is a β-dialkyl substituted carbene, intermolecular reactions rather than intramolecular rearrangements as in aryl or *H*-substituted alkylidenecarbenes,[1] are expected. In one hand, the preferred intermolecular reaction of alkylidenecarbenes is addition to olefines, to give methylene-cyclopropane derivatives. Such addition is commonly used to establish the intermediacy of alkylidene carbene or carbenoids in a particular reaction.[1] Thus, reaction of **1** (scheme 1) with NaN_3 in CH_2Cl_2/cyclohexene (1:4) afforded a mixture (1:1) of the two possible adducts **5** (35% yield), derived from the addition of the intermediate **C** to the double bond of cyclohexene. On the other hand, alkylidenecarbenes are known to insert into Si-H and O-H bonds to give vinylsilanes and vinylethers, respectively.[1a,1b] Therefore, reaction of α-mesyloxynitrile **1** with NaN_3 in the presence of triethylsilane afforded a (3:2) mixture of the *E* and *Z* vinylsilanes **6** and **7** in 59% yield. Similarly, reaction of α-mesyloxynitrile **1** with NaN_3 in methanol, gave a mixture (3:2) of the *E* and *Z* methylvinylethers **8** and **9**, respectively, in 56% yield. The stereochemistry of the double bond in (**6**, **7**, **8** and **9**) was assigned by NOE difference experiments upon irradiation of the vinylic protons of both isomers, as described for **3** and **4**.

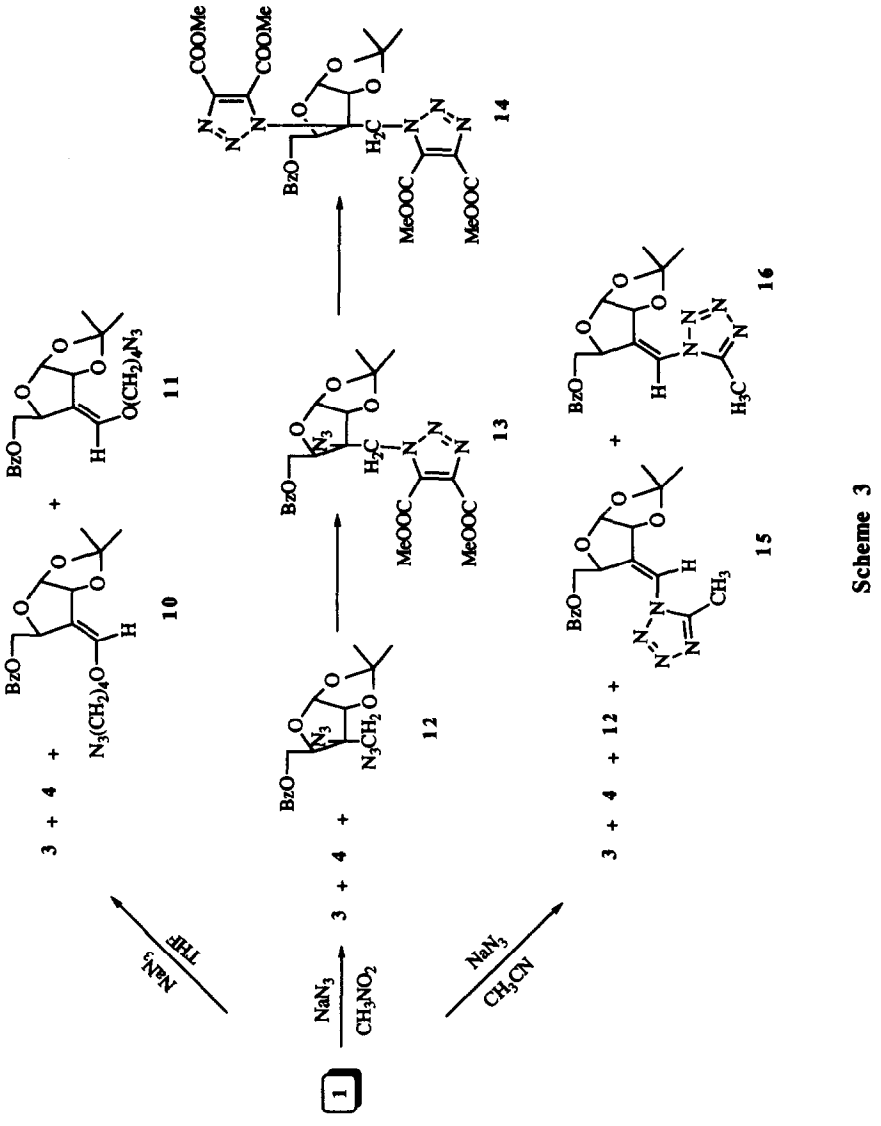
Table 1. Selected ^1H NMR Spectral Data of Carbohydrates: Chemical Shifts (ppm), Multiplicity and Coupling Constants (Hz)[a]

Compd.	H-1 ($J_{1,2}$)	H-2	H-4	H-5 ($J_{4,5a}$, $J_{4,5b}$)	H-Vinylic (J)	Others
3[b]	5.90 d (4.1)	5.24 m	5.14 m	4.42 m	6.85 dd (1.9, 1.5)	
4[b]	5.93 d (4.1)	5.14 m	5.07 m	4.42 m	6.93 dd (2.2, 1.4)	
6	5.89 d (4.1)	4.88 m	5.00 m	4.38 m	5.72 t (1.9, 1.8)	
7	5.93 d (4.6)	5.00 m	5.09 m	4.38 m	6.06 t (1.9, 2.0)	
8	5.90 d (4.2)	5.34 m	5.08 m	4.45 dd, 4.32 dd (2.4, 4.9)	6.22 dd (1.7)	3.71 s (OCH_3)
9	5.93 d (4.0)	5.08 m	5.22 m	4.61 dd, 4.46 dd (3.2, 5.8)	6.37 dd (1.0, 2.2)	3.65 s (OCH_3)
10	5.86 d (4.0)	5.31 m	5.15 m	4.54 dd, 4.42 dd (2.4, 4.8)	6.35 dd (0.9, 2.2)	3.87 m, 3.74 m (CH_2O), 3.23 dd (CH_2N_3)
11	5.82 d (4.1)	5.24 m	4.99 m	4.34 m (4.9)	6.18 t (1.3, 1.8)	3.87 m, 3.74 m (CH_2O), 3.18 dd (CH_2N_3)
12	5.99 (3.6)	4.73 d	4.24 dd	4.56 dd, 4.46 dd (5.1, 6.2)	—	3.84 d, 3.65 d (AB system, J=12.7, CH_2N_3)
13	5.90 d (3.6)	4.50 d	— 4.44 m —		—	5.02 s (CH_2-N), 3.89 s, 3.91 s (CO_2CH_3)
14	6.25 d (3.6)	5.64 d	4.65 dd	4.36 dd, 4.16 dd (4.6, 6.1)		5.86 d, 5.32 d (AB system, J=15.8, CH_2-3), 3.67 s, 3.83 s, 3.92 s, 4.05 (CO_2CH_3)
15	6.04 (4.4)	5.22 m	5.83 m	4.72 dd, 4.39 dd (2.8, 2.4)	6.96 t (1.9)	2.56 s (CH_3-tetrazole)
16[c]	5.98 (4.1)	5.62 m	5.27 m	4.68 dd, 4.52 dd (4.2, 3.9)	6.91 t (1.4)	2.53 s (CH_3-tetrazole)

[a] $CDCl_3$ at 300 MHz. [b] $(CD_3)_2CO$. [c] 200 MHz.

It is known in the literature the influence of the media in the reactions where azide ion is involved.[18,19] Therefore, the reaction of cyanomesylate **1** with NaN_3 was studied in different solvents, in order to investigate whether the solvent would modify the nature and/or relative rates of the vinylic compounds **3** and **4**.

Thus, reaction of **1** with NaN_3 in THF, and in the presence of tetrabutylammonium hydrogensulfate, afforded the vinylazides **3** and **4** (4% yield) and a (1:10) mixture of the *E* and *Z* isomers **10** and **11**, respectively (60% yield) (scheme 3). Formation of **10** and **11** could be explained by reaction of the carbene or carbenoid (C) with the oxigen atom of THF followed by reaction of this intermediate with the nucleophile present in the medium



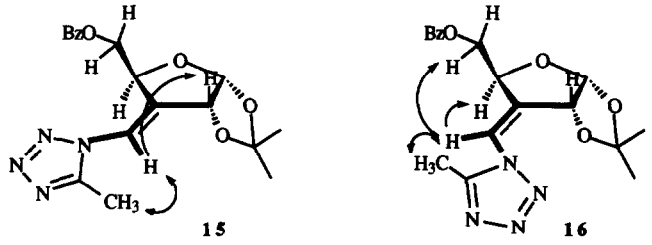
Scheme 3

(azide ion). Such result would not be unexpected as THF has available lone pairs on the oxygen atom and alkylidenecarbenes are electrophilic.[1a,20] Gilbert *et al.*[21] have also reported the obtention of enol ethers derived from THF in reactions where alkylidenecarbenes are generated and THF is used as the solvent.

When the reaction of α-mesyloxynitrile **1** with NaN_3 was carried out in nitromethane, the *E* and *Z* vinylazides **3** and **4** were obtained in a ratio of 3:2 (in 18% yield), together with a less polar compound that was unequivocally identified as the diazidoderivative **12** (16% yield) by its transformation into the 1,2,3-triazole derivatives **13** and **14**. Thus reaction of **12** with dimethylacetylene dicarboxylate (DMAD) in CH_2Cl_2 at room temperature afforded the triazole derivative **13** (41% yield). Further treatment of **13** with DMAD in refluxing toluene gave the cycloaddition product **14** (57% yield).

The stereochemistry at *C*-3 for the diazido derivative **12** was assigned as *xylo* by NOE difference experiments upon irradiation of each of the doublets of the AB system centered at 3.74 ppm corresponding to the 3-CH_2N_3 substituent. Thus, irradiation of the protons of the methylene group induced NOE at the signal corresponding to H-4 this indicated that protons CH_2N_3 and H-4, are in the lower face of the furanose ring (α-face), and thus, the structure of **12** is *xylo*.

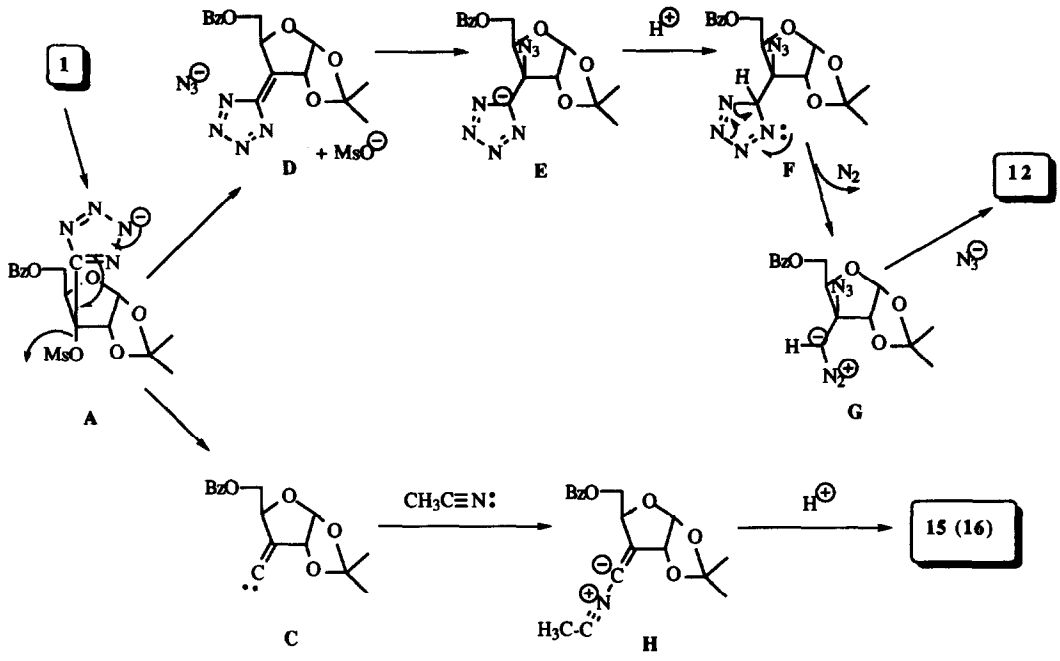
Formation of **12** by addition of azide ion to the double bond of vinylazides **3** or **4** can be discarded because, when these compounds were treated with sodium azide in nitromethane, did not gave compound **12**. The vinylazido isomers (**3** and **4**) were recovered unchanged from the reaction mixture. When the reaction of α-mesyloxynitrile **1** with NaN_3 in nitromethane was followed by HPLC, the relative ratio vinylazides/diazido derivative remained constant in time, indicating that there is no interconversion between these derivatives.



15 **16**

Figure 1

Finally, when the reaction between the α-mesyloxynitrile **1** and NaN_3 was performed in acetonitrile, besides the above mentioned **3**, **4** and **12** derivatives two new products were isolated, that were identified as the tetrazole isomers **15** (12%) and **16** (16% yield). The stereochemistry of the double bond of **15** and **16** as *E* and *Z*, respectively, and the substitution at the tetrazole ring (as 1,5), were unequivocally determined by NOE difference experiments. As shown in figure 1 irradiation of the vinylic proton of **15** caused enhancements of the signals for H-2 and the CH_3 of the tetrazole moiety, irradiation of the CH_3 of the tetrazole induced NOE to the signal of the vinylic proton. The NOEs observed indicated that the stereochemistry of the double bond was *E* and



Scheme 4

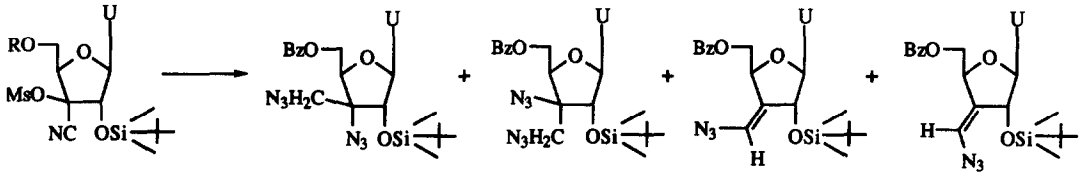
that the methyl group was adjacent to the substituted nitrogen and thus, the tetrazole moiety was 1,5-disubstituted. A similar NOE experiment with compound **16** indicated a *Z* stereochemistry of the double bond and also a 1,5-disubstitution in the tetrazole moiety.

The tetrazole isomers **15** and **16** could be, initially, formed from vinylazides **3** and **4**, by cycloaddition of the azide group with the acetonitrile, this reaction would lead either to the 1,5- or to the 2,5-disubstituted tetrazoles. However, when **3** and **4** were treated with acetonitrile for 15 days, no cycloaddition products were detected. This result together with the fact that in the reaction of **1** with with NaN_3/acetonitrile only the 1,5-disubstituted tetrazoles were formed, suggests a possible interaction of the acetonitrile and the azide ion with the alkylidenecarbene or a precursor of it prior to the formation of the vinylazides.

A possible rational for the formation of **12** and **15** (**16**) is shown in scheme 4. The tetrazolate **A**, resulting from the attack of the azide ion to the cyano group of **1**, would generate, by charge reajustment and loss of N_2 and MsO^-, intermediate **C** (see scheme 2), or by charge reajustment and loss of MsO^-, intermediate **D**. Attack of the azide ion at C-3 of intermediate **D** leads to intermediate **E**. The approach of the azide ion to this intermediate would occur from the less hindered β face of the furanose ring, opposite to the 1,2-*O*-isopropylidene group. Intermediate **E**, after protonation and loss of N_2 makes diazocompound **G**. Then, either desplacement of protonated diazocompound by azide ion, or cycloaddition of azide to diazocompound followed by N_2 loss, would lead to the diazidoderivative **12** . On the other hand, reaction of alkylidene carbene **C** with acetonitrile followed by cycloaddition with azide, would lead to compounds **15** and **16**.

From the results above mentioned, it seems that formation of the diazido derivative **12** is favoured in polar solvents (acetonitrile, nitromethane) whereas in dichloromethane the vinylazides **3** and **4** were obtained exclusively. Conversion of vinylazides to diazidoderivatives was not observed. The relative ratio of vinylazides/diazidoderivatives does not depend on the equivalents of sodium azide used.

In an extension of this work, we decided to study whether the intermediacy of an alkylidene carbene would be applicable to the reaction of α-mesyloxynitriles of nucleosides with sodium azide. These alkylidene carbenes would be useful intermediates for the synthesis of branched-chain nucleosides functionalized with azido groups.



17a,b,c **18** **19** **20** **21**

a; R=Si(Me)$_2$*t*-Bu
b; R=H
c; R=Bz

Scheme 5

Reaction of the 2',5'-bis-*O*-silylated-3'-α-mesyloxynitrile of uracil **17a**[22] (scheme 5) with NaN_3 in nitromethane and in the presence of tetrabutylammonium hydrogensulfate, gave a complex reaction mixture from which only the undesired 5'-*O*-deprotected nucleoside **17b** could be isolated. This 5'-*O*-deprotection was avoided when 5'-*O*-silyl group of **17a** was replaced by a benzoyl group. Thus, treatment of **17a** with 1N-HCl followed by benzoylation with benzoyl chloride in pyridine afforded **17c** in 90% yield. **17c** Was then reacted with sodium azide in nitromethane, in the presence of tetrabutylammonium hydrogensulfate, to afford after laborious chromatographic purifications, a mixture of the diazido nucleosides **18** and **19** (18% and 11% yield, respectively), and the vinylazidonucleosides **20** and **21** (15% yield). The *xylo* and *ribo* stereochemistry of the diazido derivatives **18** and **19**, respectively, was established by NOE difference experiments upon irradiation of the 3'-methylene protons as described for the sugar diazido derivative **12**.

When the reaction of **17c** with NaN_3 was carried out in CH_2Cl_2, solvent that with the sugar derivative (**1**) afforded exclusively, the vinyl azides **3** and **4**, not only the vinylazido nucleosides **20** and **21** were obtained as the major compounds (33%), but also the diazido nucleosides **18** and **19** were isolated in 16% and 6% yield, respectively. The relative ratio of vinylazides (**20, 21**)/diazidoderivatives (**18, 19**) does not vary with number of equivalents of NaN_3.

It can be concluded that an alkylidenecarbene or carbenoid intermediate is involved in the reaction of α-mesyloxynitriles of sugars and nucleosides with sodium azide. The high reactivity of the carbene intermediate formed in this reaction makes very important the choice of the right solvent, otherwise products derived from interaction of the carbene with the solvent would be the major ones obtained.

To the best of our knowldge, this is the first time that the intermediary of an alkylidenecarbene has been demonstrated in the chemistry of carbohydrates and used in the chemistry of nucleosides. The overall result of the process described in this paper is the transformation of a cyanide group to a functionalized olefin. The α-mesyloxynitriles of sugars and nucleosides, used as precursors of the alkylidene carbenes, are easily available from the corresponding uloses, and have not, so far, been employed to generate alkylidene carbenes. These reactive intermediates open new possibilities of functionalization in C-branched-chain sugars and nucleosides. Thus, we have obtained a variety of highly functionalized branched-chain sugars and nucleosides such as vinylazides (**3** ,**4**, **20** and **21**), vicinal diazido derivatives (**12**, **18** and **19**), vinylsilanes (**6** and **7**) or vinylethers (**8** and **9**). Vinylazides have been the subject of considerable interest and the procedures for their preparation are rather limited.[23] On the other hand, vicinal diazido derivatives are rather scarce in the literature,[24] and have the additional interest of being transformed into 1,2-diamines.[25] Finally, vinylsilanes[26] and vinylethers,[27] are, in general, important reactive intermediates that can be furher used for the synthesis of new branched-chain sugar and nucleoside derivatives.

Table 2. Selected ^{1}H NMR Spectral Data of Nucleosides: Chemical Shifts (ppm), Multiplicity and Coupling Constants (Hz)[a]

Compd.	H-1' ($J_{1',2'}$)	H-2'	H-4' ($J_{4',5'}$)	H-5	H-Vinylic (J)	H-5 ($J_{5,6}$)	H-6	Others
18	5.92 d (6.8)	4.57 d	4.26 t (4.5)	4.6 m	—	5.55 dd (8.0)	b	3.84 d, 3.67 d (AB system, J=13.2, CH_2N_3-3), 8.57 bs (NH-3)
19	5.67 d (0.7)	4.49 d	4.41 dd (4.2, 5.9)	4.69 dd, 4.59 dd	—	5.77 dd (8.3)	c	4.01 d, 3.79 d (AB system, J=12.6, CH_2N_3-3), 9.10 bs (NH-3)
20[d]	5.80 d (6.8)	4.65 m	5.05 m	4.69-4.58 m	6.32 t (2.22)	5.58 dd (8.2)	e	8.80 bs (NH-3)
21[d]	5.83 d (1.3)	4.72 m	5.10 m	4.69-4.58 m	6.45 dd (1.1, 1.2)	5.48 dd (8.2)	e	8.90 bs (NH-3)

[a] $CDCl_3$ at 300 MHz. [b] With the aromatics at 7.27-8.02 ppm. [c] With the aromatics at 7.46-8.09 ppm. [d] Fron the spectrum of the mixture. [e] With the aromatics at 7.35-8.02.

EXPERIMENTAL SECTION

Chemical Procedures. Microanalyses were obtained with a Heraeus CHN-O-RAPID instrument. ^{1}H NMR spectra were recorded with a Varian EM-390, a Varian XL-300 and a Bruker AM-200 spectrometer operating at 300 and 200 MHz, and ^{13}C NMR spectra with a Bruker AM-200 spectrometer and a Bruker WP-80-SY operating at 50 and at 20 MHz, with Me_4Si as internal standard. IR spectra were recorded with a Shimadzu IR-435 spectrometer. Analytical TLC was performed on silica gel 60 F_{254} (Merck). Separations on silica gel were performed by preparative centrifugal circular thin layer chromatography (CCTLC) on a Chromatotron^R (Kiesegel

60 PF 254 gipshaltig (Merck)), layer thickness (1mm), flow rate (5 mL/min), or by flash column chromatography performed with silica gel 60 (230-400 mesh) (Merck). Proximities were established conventionally on the basis of using NOE. For the NOE difference spectra the signals were irradiated during 3 s with γB_2=20 Hz of decoupling power. An analytical sample of the compounds was prepared by chromatographing a portion, of the corresponding purified reaction mixtures, on CCTLC on chromatotron using chloroform/ethyl acetate (15:1) as eluent.

General Procedure for the Reaction of 5-*O*-Benzoyl-3-*C*-cyano-1,2-*O*-isopropylidene-3-*O*-mesyl-α-D-ribofuranose (1)[13] with Sodium Azide in different solvents. To a solution of **1**[13] (400 mg, 1.0 mmol) in the solvents indicated below (8 mL), tetrabutylammonium hydrogensulfate (339 mg, 1.0 mmol) and NaN_3 (260 mg, 4.0 mmol) were added. The resulting mixture was stirred at room temperature for 1-5 days. The solvent was evaporated to dryness and the residue, thus obtained, was treated with CH_2Cl_2 (50 mL) and water (25 mL). The organic phase was separated, washed twice with brine (25 mL), dried (Na_2SO_4), filtered and evaporated to dryness. The residue was purified by flash-column chromatography. **CAUTION** should be taken with the reactions involving NaN_3 (see ref. 28).

a) Reaction in Dichloromethane. The general procedure was followed. Chromatography with hexane/ethyl acetate (10:1) afforded 100 mg (30% yield) of a (2:3) mixture of **(*E*)- and (*Z*)-3-*C*-azidomethylene-5-*O*-benzoyl-3-deoxy-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (3** and **4)** as a syrup. IR (film): 2100 (N_3), 1715 (CO), 1670 cm^{-1} (C=C-N); ^{13}C NMR ($CDCl_3$, 50 MHz) d: 27.12, 27.32, 27.52, 27.73 (CH_3-isopropyl), 65.16, 65.56 (2 C-5), 76.12, 80.20 (C-2, C-4), 104.95, 105.51 (2 C-1), 113.06, 112.70 (C-isopropyl), 124.76, 125.36 (2 C=*C*H), 126.26, 126.55 (2 C-3), 166.08 (C=O). Anal. Calcd. for $C_{16}H_{17}O_5N_3$: C, 58.00; H, 5.17; N, 12.68. Found: C, 58.01; H, 5.16; N, 12.95.

b) Reaction in THF. The general procedure was followed. Chromatography with hexane/ethyl acetate (8:1) gave 14 mg (4%) of **3** and **4**. Subsequent elution with hexane/ethyl acetate (6:1) afforded 240 mg (60%) of a (1:10) mixture of **(*E*)- and (*Z*)-3-*C*-[(4-azido)butoxymethylene]-5-*O*-benzoyl-3-deoxy-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (10** and **11)** as a syrup. IR (film): 2950, 2900, 2850 (CH-alkyl), 2090 (N_3), 1720 (CO), 1690 cm^{-1} (C=C-O); ^{13}C NMR ($CDCl_3$, 20 MHz) d: 25.18, 26.80 (2 CH_2), 50.89 (CH_2N_3), 65.60 (C-5), 72.65 (CH_2O), 76.05, 77.93 (C-2, C-4), 104.91 (C-1), 112.20, 114.31 (C-isopropyl, C-3), 128.30-133.04 (aromatics), 143.44 (C=*C*H), 166.20 (C=O). Anal. Calcd. for $C_{20}H_{25}O_6N_3$: C, 59.54; H, 6.24; N, 10.41. Found: C, 59.73; H, 6.18; N, 10.20.

c) Reaction in Nitromethane. The general procedure was followed. Chromatography with hexane/ethyl acetate (10:1) gave, from the fastest moving fractions, 58 mg (16%) of **3-azido-3-*C*-(azidomethyl)-5-*O*-benzoyl-3-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (12)** as a syrup. $[\alpha]_D$ +13.2 (c, 1, $CHCl_3$).IR (film): 2100 (N_3), 1720 cm^{-1} (CO); ^{13}C NMR ($CDCl_3$, 50 MHz) d: 26.30, 26.63 (CH_3-isopropyl), 51.79 (CH_2N_3), 62.42 (C-5), 73.12 (C-3), 78.96, 83.13 (C-2, C-4), 104.32 (C-1), 113.16 (C-isopropyl), 128.47, 129.36, 129.69, 133.34 (C_6H_5), 166.03 (CO). Anal. Calcd. for $C_{16}H_{18}O_5N_6$: C, 51.33; H, 4.84; N, 22.45. Found: C, 51.55; H, 4.94; N, 22.10.

The slowest moving fractions gave 60 mg (18%) of a (3:2) mixture of **3** and **4**.

d) Reaction in Acetonitrile. The general procedure was followed. Chromatography with hexane/ethyl acetate (10:1) afforded, from the fastest moving fractions 35 mg (10%) of **12**. The slowest moving fractions gave (30 mg, 9%) of a mixture of **3** and **4**.

Then the column was eluted with chloroform/acetone (8:1). The fastest moving fractions afforded 45 mg (12%) of **(*E*)-5-*O*-benzoyl-3-deoxy-1,2-*O*-isopropylidene-3-*C*-(5-methyl-tetrazol-1-yl) methylen-α-D-*erythro*-pentofuranose (15)** as an amorphous solid. $[\alpha]_D$ +274 (c, 1, $CHCl_3$); IR (film): 1705 (CO), 1655 cm^{-1} (C=C); ^{13}C NMR ($CDCl_3$, 50 MHz) d: 8.95 (CH_3-tetrazole), 27.68, 27.97 (CH_3-isopropyl), 65.68 (C-5), 79.03, 81.36 (C-2, C-4), 104.97 (C-1), 115.75 (C=*C*H), 113.80 (C-isopropyl), 128.50-133.30 (aromatics), 136.06 (C-3), 151.44 (CH_3CN_4), 165.70 (C=O). Anal. Calcd. for $C_{15}H_{20}O_5N_4$: C, 58.06; H, 5.41, N, 15.04. Found: C, 57.95; H, 5.59; N, 15.19.

From the slowest moving fractions 60 mg (16%) of **(*Z*)-5-*O*-benzoyl-3-deoxy-1,2-*O*-isoproylidene-3-*C*-(5-methyl-tetrazol-1-yl) methylen-α-D-erythro-pentofuranose (16)** were isolated as an amorphous solid. $[\alpha]_D$ +132 (c, 1, $CHCl_3$); IR (film): 1715 (CO), 1675 cm^{-1} (C=C); ^{13}C NMR ($CDCl_3$, 50 MHz) d: 8.77 (CH_3-tetrazole), 26.90, 27.20 (CH_3-isopropyl), 64.50 (C-5), 77.08, 78.39 (C-2, C-4), 109.94 (C-1), 113.20 (C-isopropyl), 115.51 (C=*C*H), 128.48-133.46 (aromatics), 136.86 (C-3), 151.72 (CH_3CN_4), 166.09 (C=O). Anal. Calcd. for $C_{18}H_{20}O_5N_4$: C, 58.06; H, 5.41; N, 15.04. Found: C, 57.89; H, 5.51; N, 14.85.

Standard Trapping Reactions. General Procedure. To a solution of **1** (400 mg, 1.0 mmol) in CH_2Cl_2 (5 mL), the trapping reagent (4 mL), NaN_3 (97 mg, 1.5 mmol) and tetrabutylammonium hydrogensulfate (339 mg, 1.0 mmol) were added. The resulting mixture was stirred at room temperature for 48 h. Then, CH_2Cl_2 (20 mL) and water (10 mL) were added. The organic phase was separated, and the aqueous phase was washed with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried (Na_2SO_4) filtered and evaporated to dryness. The residue was purified by flash column chromatography.

a) 5-*O*-Benzoyl-3-(7-bicyclo-[4.1.0]-heptylidene)-3-deoxy-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (5). The general procedure was followed with cyclohexane as trapping reagent. Chromatography with hexane/ethyl acetate (12:1) afforded 120 mg (35%) of a (1:1) mixture of the aducts **5** as a syrup. IR (film): 2900, 2580 (C-H alkyl), 1760 cm^{-1} (C=C). ^1H NMR ($CDCL_3$, 300 MHz) d: 1.36-1.59 (m, 16H, C-isopropyl, C_6H_{10}), 4.24 (m, 1H, H-5a), 4.68 (m, 1H, H-5b), 5.11 (dd, 1H, H-2), 5.15 (m, 1H, H-4), 5.95 (d, 1H, $J_{1,2}$=4.1 Hz, H-1), 7.27-8.03 (m, 5H, aromatics). Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07. Found: C, 71.30; H, 7.14.

b) (*E*)- and (*Z*)-5-*O*-benzoyl-3-deoxy-1,2-*O*-isopropylidene-3-*C*-(triethylsilyl)methylene-α-D-*erythro*-pentofuranose (6 and **7).** The general procedure was followed with triethylsilane (1.5 mL), as trapping reagent. Chromatography with hexane/ethyl acetate (15:1) afforded 240 mg (59%) of a (3:2) mixture of the vinylsilanes **6** and **7**, as a syrup. IR (film): 2930, 2870 (C-H alkyl), 1720 cm^{-1} (C=O). Anal. Calcd. for $C_{22}H_{32}O_5Si$: C, 65.31; H, 7.97. Found: C, 65.08; H, 7.90.

c) (*E*)- and (*Z*)-5-*O*-benzoyl-3-deoxy-1,2-*O*-isopropylidene-3-*C*-methoxymethylene-α-D-*erythro*-pentofuranose (8 and **9).** The general procedure was followed except that MeOH (8 mL) was used

as solvent and trapping reagent, and the reaction mixture was heated at 60°C for 3 days. Chromatography with hexane/ethyl acetate (10:1) afforded 8 mg (2.5%) of a mixture of **3** and **4**. Elution with hexane/ethyl acetate (8:1) gave 180 mg (56%) of a (3:2) mixture of the vinyl ether derivatives **8** and **9** as a syrup. IR (film): 1715 (CO), 1695 cm^{-1} (C=C-O); ^{13}C NMR ($CDCl_3$, 50 MHz) d: 27.11, 27.38, 27.42, 27.75 (CH_3-isopropyl), 60.58, 60.71 (CH_3O), 65.29, 65.98 (2 C-5) 75.04, 81.23 (C-2, C-4), 105.03, 105.45 (2 C-1), 112.30, 114.63 (C-isopropyl, C-3), 127.81-134 (aromatics), 144.89, 145.81 (2 C=*C*H), 166.33, 166.37 (C=O). Anal. Calcd. for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.41; H, 6.08.

3-Azido-5-*O*-benzoyl-3-deoxy-3-*C*-[(4,5-dicarbomethoxy-1,2,3-triazol-1-yl)methyl]-1,2-*O*-isopropylidene-α-D-xylofuranose (13). To a solution of **12** (60 mg, 0.16 mmol) in dry CH_2Cl_2 (4 mL), dimethylacetylene dicarboxylate (DMAD) was added (0.112 mL, 0.8 mmol). The mixture was stirred at room temperature for 7 days. The solvent was evaporated to dryness and the residue was purified by flash-column chromatography with hexane/ethyl acetate (3:1) to afford 40 mg (41%) of a syrup that was identified as **13**. IR (film): 2100 (N_3), 1735, 1725 cm^{-1} (CO); ^{13}C NMR ($CDCl_3$, 50 MHz) d: 26.31, 26.65 (CH_3-isopropyl), 48.03 (CH_2-N), 52.72, 53.42 (CO_2CH_3), 61.91 (C-5), 72.73 (C-3), 79.16, 82.95 (C-2, C-4), 104.20 (C-1), 113.42 (C-isopropyl), 128.54-133.41 (aromatics), 139.75 (=C), 158.98, 160.26 (CO_2Me), 166.05 (C=O). Anal. Calcd. for $C_{22}H_{24}O_9N_6$: C, 51.16; H, 4.68; N, 16.27. Found: C, 50.98; H, 4.55; N, 16.40.

5-*O*-Benzoyl-3-deoxy-3-(4,5-dicarbomethoxy-1,2,3-triazol-1-yl)-3-*C*-[(4,5-dicarbomethoxy-1,2,3-triazol-1-yl)methyl]-1,2-*O*-isopropylidene-α-D-xylofuranose (14). Compound **13** (40 mg, 0.08 mmol) was dissolved in toluene (3 mL) and DMAD was added (0.10 mL, 0.71 mmol). The mixture was refluxed for 12 h, and then, the solvent was evaporated to dryness. Purification by flash-column chromatography with chloroform/ethyl acetate (6:1) afforded 30 mg (57%) of a syrup, that was identified as **14**. IR (film): 1730, 1710 cm^{-1} (CO). Anal. Calcd. for $C_{28}H_{30}O_{13}N_6$: C, 51.07; H, 4.59; N, 12.76. Found: C, 51.00; H, 4.75; N, 12.54.

1-[5'-*O*-Benzoyl-2'-*O*-(*tert*-butyldimethylsilyl)-3'-*C*-cyano-3'-*O*-mesyl-β-D-xylofuranosyl]uracil (17c). A solution of **17a**[22] (500 mg, 0.8 mmol) in 50 mL of 0.1N HCl in MeOH, was stirred at room temperature for 3 h. Then it was neutralized with NaOH-MeOH, and the solvent was evaporated to dryness. The residue was dissolved in pyridine (3 mL) and benzoyl chloride (0.1 mL, 0.87 mmol) was added. The mixture was stirred at room temperature overnight, poured into ice and water and extracted with chloroform (2 x 50 mL). The combined organic extracts were washed, successively, with 1N HCl (30 mL), aqueous sodium hydrogencarbonate (30 mL) and brine (30 mL), dried ($NaSO_4$) and filtered. The solvent was evaporated to dryness, the residue was purified by flash-column chromatography with hexane/ethyl acetate (2:1) to give 440 mg (90%) of **17c** as a foam. ^1H NMR ($CDCl_3$, 90 MHz) d: 0.90 (s, *t*-Bu), 3.22 (s, SO_2CH_3), 4.70-4.98 (m, H-4', 2H-5'), 5.06 (d, $J_{1',2'}$=1-2 Hz, H-2'), 5.74 (d, H-5), 5.91 (d, H-1'), 7.36-8.21 (m, H-6, C_6H_5), 9.25 (br. s, 3-NH); ^{13}C NMR ($CDCl_3$, 50 MHz) d: 17.84 (C-Si), 25.61 [(CH_3)$_3$C-Si], 40.21 (CH_3SO_2), 59.13 (C-5"), 81.06, 82.45 (C-2', C-4'), 81.64 (C-3'), 92.56 (C-1'), 102.59 (C-5), 112.46 (CN), 138.75 (C-6), 150.15 (C-2), 168.38 (C-4), 165.77 (COC_6H_5). Anal. Calcd. for $C_{24}H_{31}N_3O_9SSi$: C, 50.96; H, 5.52; N, 7.42. Found: C, 51.03; H, 5.47; N, 7.17.

Reaction of 17c with NaN_3. Method A. To a solution of **17c** (550 mg, 0.97 mmol) in dry nitromethane (8 mL), tetrabutylamonium hydrogensulfate (328 mg, 1.17 mmol) and NaN_3 (304 mg, 4.6 mmol) were added. The mixture was stirred at room temperature for 3 days. The solvent was evaporated to dryness and the residue was treated with ethyl acetate (50 mL) and water (30 mL). The organic phase was separated and washed with brine (50 mL), dried (Na_2SO_4), filtered and evaporated to dryness. The residue, thus obtained, was purified by flash-column chromatography with hexane/ethyl acetate (7:2). The fastest moving fractions afforded 65 mg (12%) of **1-[3'-azido-3'-*C*-(azidomethyl)-5'-*O*-benzoyl-2-*O*-(*tert*-butyldimethylsilyl)-3'-deoxy-β-D-xylofuranosyl]uracil (18)** as a syrup. IR (film): 2200, 2100 cm^{-1} (N_3). Anal. Calcd. for $C_{23}H_{30}N_8O_6Si$: C, 50.91; H, 5.57; N, 20.65. Found: C, 50.83; H, 5.68; N, 20.51.

From the next moving fractions, mixtures of **18**, **19**, **20** and **21** were obtained. The mixture of the above mentioned compounds was purified by CCTLC on chromatotron with chloroform/ethyl acetate (8:1). The fastest moving band afforded 30 mg (6%) of **18**.

The next moving band yielded 59 mg (11%) of **1-[3'-azido-3'-*C*-(azidomethyl)-5'-*O*-benzoyl-2-*O*-(*tert*-butyldimethylsilyl)-3'-deoxy-β-D-ribofuranosyl]uracil (19)** as a syrup. IR (film): 2100 cm^{-1} (N_3). Anal. Calcd. for $C_{23}H_{30}N_8O_6Si$: C, 50.91; H, 5.57; N, 20.65. Found: C. 50.99, H, 5.65; N, 20.48.

From the slowest moving band a (3:1) mixture of **(*E*)- and (Z)-1-[3'-*C*-(azidomethyl)-5'-*O*-benzoyl-2-*O*-(*tert*-butyldimethylsilyl)-3'-deoxy-β-D-*erythro*-pentofuranosyl]uracil (20** and **21)** was obtained (75 mg, 15%) as a syrup. IR (film): 2100 cm^{-1} (N_3). Anal. Calcd. for $C_{23}H_{29}N_5O_6Si$: C, 55.29; H, 5.85; N, 14.02. Found: C, 54.84; H, 5.55; N, 14.35.

Reaction of 17c with NaN_3. Method B. Method A was followed except that **17c** was dissolved in dry CH_2Cl_2. A similar work-up as described for method A afforded, after purification by flash-column chromatography and CCTLC in chromatotron, compounds **18** (82 mg, 16%), **19** (32 mg, 6%) and a (7:4) mixture of **20** and **21** (158 mg, 33%).

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28. There have been reported azide explosions by combination of sodium azide and halogenated solvents or cosolvents (seeN.P. Peat and P.N. Weintraub, *C&E News* **1993**, April 19, page 4 and V.J. Hruby, L. Boteju and G. Li, *C&E News* **1993**, October 11, page 2). The first group combined sodium azide and sulfuric acid, generating, the very explosive,hydrogen azide. The second report was less explicit, but an explosive more volatile than dichloromethane was involved. These authors strongly urge to all synthetic laboratories to avoid azide reactions in halogenated solvents or cosolvents. However, P.G. Urben, *C&E News*, **1993**, December 13, page 4, postulated that avoiding halogenated solvents will not eliminate the possibility of azide explosions.

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