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Anomeric Configuration-Directed Diastereoselective C–C Bond Formation in Vinyl Sulfone-Modified Carbohydrates: A General Route to Branched-Chain Sugars

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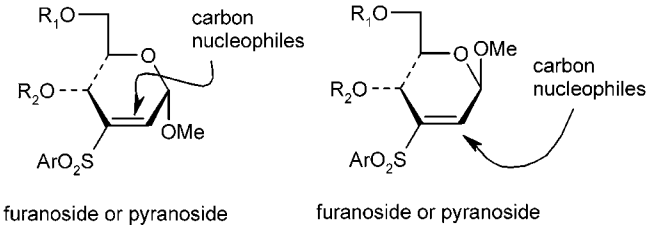
ABSTRACT



This is the first report on the diastereoselective addition of carbon nucleophiles to vinyl sulfone-modified hex-2-enopyranosides and pent-2-enofuranosides. Nucleophiles add to the C-2 position from a direction opposite to that of the disposition of the anomeric methoxy group. This novel concept of anomeric configuration-directed stereocontrolled carbon–carbon bond formation in vinyl sulfone-modified carbohydrates is general in nature and has been implemented in the synthesis of new hexopyranosyl and pentofuranosyl branched-chain sugars and densely functionalized carbohydrates.

Branched-chain sugars, having carbon substituents at the nonterminal carbon atoms of the chains, are components of many natural products, especially antibiotics.[1,2] Branched-chain sugars also constitute an important class of functionalized intermediates, useful for further transformations.[2−4]

The most common methods for the syntheses of branched-chain sugars in general and branched-chain sugars having no substituent at the branching carbon atoms in particular involve the reduction of alkylidene glycosides, opening of sugar-derived oxiranes by carbon nucleophiles, or Michael-type addition of carbon nucleophiles to nitro-alkene sugars and hex-2-enopyranosid-4- or hex-3-enopyranosid-2-uloses.[1,2] The usefulness of nitro-alkene sugars[5] and hexenopyranoside uloses[6] in the synthesis of branched-chain sugars is limited only to pyranose systems and therefore cannot be considered as being of general utility. The carbohydrate oxiranes often

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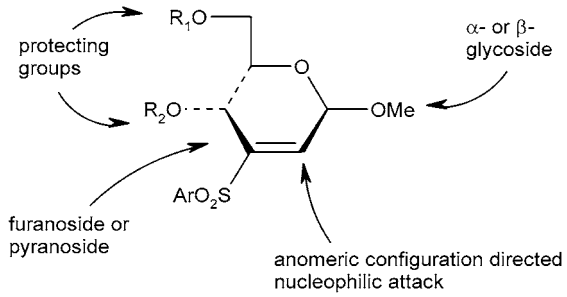
produce a mixture of regioisomers depending on several factors.[7] On the other hand, it is not clear from the available literature whether the reduction of C-2 alkylidene glycosides is influenced by the 3-OH protecting group lowering the stereoselectivity of these reactions as is known for 2-keto sugars.[8] It is therefore obvious that there is a great need for new and general methodologies for the stereocontrolled construction of carbon−carbon bonds in carbohydrates.

Michael-type addition reaction of carbon nucleophiles to vinyl sulfone-modified carbohydrates should be considered as an efficient route for the synthesis of branched-chain sugars mainly because almost all carbohydrates, either in pyranose or furanose form, could be converted to their vinyl sulfone derivatives very easily.[9−11] Moreover, the product of the reaction carrying a sulfone functionality has the potential to undergo a wide variety of transformations.[12,13] We observed that a nucleophile attacked the C-2′ position of the 2′-enesulfone nucleoside exclusively from the α-face of the pent-2′-enofuranosyl moiety of a *β*-nucleoside.[14] This observation led us to investigate the effect of the anomeric configuration on the stereochemical outcome of the addition of nucleophiles to vinyl sulfone-modified carbohydrates (Scheme 1).

Scheme 1

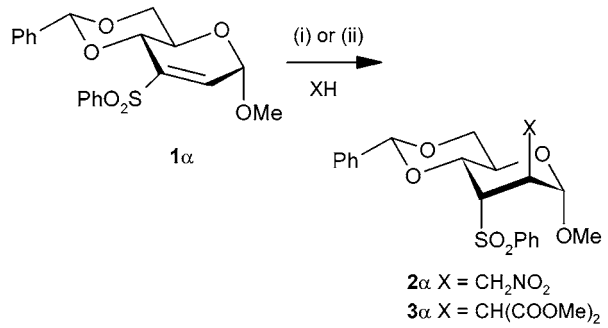


Although amines added in diastereoselective fashion to **1α** and **1*β***, the directing effect of the anomeric configuration on the stereochemical outcome of the reactions was not obvious. The addition of primary amines to **1α** and **1*β*** exclusively produced C-2 equatorial (*gluco*) products. Secondary amines, on reactions with **1*β***, produced only *gluco* derivatives but, with **1α**, produced a mixture in which *gluco* was still the predominant isomer.[11b] On the other hand, sterically bulky *tert*butylamine reacted only with **1*β*** (and not **1α**) at elevated temperatures to produce the *gluco* derivative in high yield.[15]

We report here for the first time that in contrast to our earlier observation,[11b,15] **1α** and **1*β*** on reaction with carbon nucleophiles generated products that manifested fully the directing effect of the anomeric configurations. In both cases, the carbanion added to the planar olefinic systems of **1α** and **1*β*** from a direction opposite to that of the disposition of the anomeric methoxy group.

Thus, the nucleophile generated from CH_3NO_2 and NaOMe reacted with **1α** to produce a single isomer **2α** (60%). Similarly, the nucleophile generated from dimethylmalonate and sodium hydride produced exclusively **3α** (82%) (Scheme 2). It should be noted that in contrast to the α-D-*manno* configuration of the product obtained from the reaction of carbon nucleophiles with 2,3-dideoxy-3-*C*-nitro-α-D-*erythro*-hex-2-enopyranoside,[16] **1α** produced **2α** having three axially disposed functional groups on three consecutive carbon atoms (α-D-*altro* configuration) of a six-membered system.

Scheme 2



(i) CH_3NO_2, NaOMe, MeOH, rt., 36 h, 60%;
(ii) $CH_2(COOMe)_2$, NaH, THF, rt., 1.5 h, 82%.

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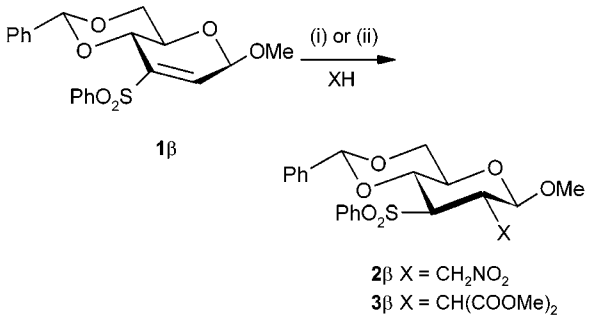
Scheme 3



(i) CH_3NO_2, NaOMe, MeOH, rt., 2 h, 56%;
(ii) $CH_2(COOMe)_2$, NaH, THF, rt., 2 h, 98%.

The nucleophile generated from CH_3NO_2 and NaOMe reacted with **1*β*** to produce a single isomer **2*β*** (56%). Similarly, the nucleophile generated from dimethylmalonate and sodium hydride produced **3*β*** (98%) (Scheme 3). Compound **1*β*** produced the expected[11b,15] *β*-D-gluco analogues **2*β*** and **3*β***. Elucidation of crystal structures of **2α**/**3α** and **2*β***/**3*β*** unambiguously established the configurations at positions C-2 and C-3 of these compounds (Figures 1 and 2).[17,18]

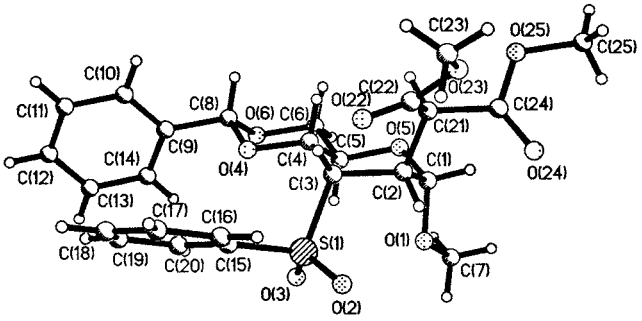


Figure 1. X-ray structure of **3α**.

To establish the general pattern of the directing effect of the anomeric configurations, anomerically pure pentofuranoses **4α** and **4*β*** were synthesized in multisteps from D-xylose.[19] Compounds **4α** and **4*β***, on reaction with carbanions generated from CH_3NO_2/NaOMe and CH_3NO_2/$^tBuO^-K^+$, produced branched-chain sugars **5α** (73%) and

(17) Crystal data. Compound **3α**: $C_{25}H_{28}O_{10}S$, $M = 520.53$, orthorhombic, $a = 12.130(8)$, $b = 14.187(9)$, $c = 14.515(9)$ Å, $U = 2498(3)$ Å^3, $T = 295(2)$ K, space group $P2_12_12_1$ (no. 19), $Z = 4$, μ(Mo Kα) = 0.186 mm^{-1}, 14 406 reflections measured, 5551 unique ($R_{int} = 0.066$), which were used in all calculations. The final w$R(F^2)$ was 0.112 (all data). Compound **3*β***: $C_{25}H_{28}O_{10}S$, $M = 520.53$, monoclinic, $a = 5.6780(5)$, $b = 16.5197(15)$, $c = 13.5563(12)$ Å, $\beta = 95.212(2)°$, $U = 1266.3(2)$ Å^3, $T = 295(2)$ K, space group $P2_1$ (no. 4), $Z = 2$, μ(Mo Kα) = 0.184 mm^{-1}, 7436 reflections measured, 4949 unique ($R_{int} = 0.015$), which were used in all calculations. The final w$R(F^2)$ was 0.0943 (all data).

(18) All these data will be reported and discussed in detail in a full paper.

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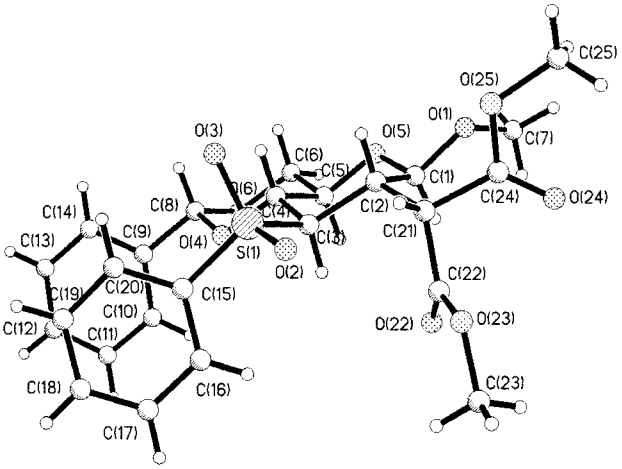
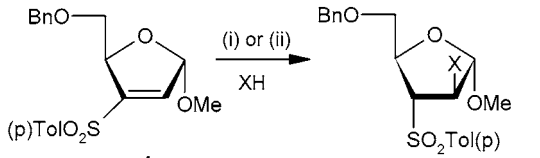


Figure 2. X-ray structure of **3*β***.

5*β* (55%), respectively. Dimethylmalonate adducts **6α** (74%) and **6*β*** (87%) were also synthesized in a diastereoselective fashion (Schemes 4 and 5).

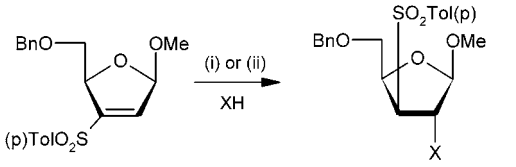
Scheme 4



(i) CH_3NO_2, NaOMe, MeOH, rt., 3 h, 73%;
(ii) $CH_2(COOMe)_2$, NaH, THF, rt., 2.5 h, 74%.

It should be noted that the Michael addition of various nucleophiles to related furanose systems such as 1-(5-*O*-trityl-2,3-dideoxy-3-toluenesulfonyl-*β*-D-glyceropent-2-enofuranosyl) uracil and the corresponding adenine derivative generated trans-(*xylo*) products exclusively in most cases; a few of these reactions have produced a mixture of cis-(*ribo*) and trans-

Scheme 5



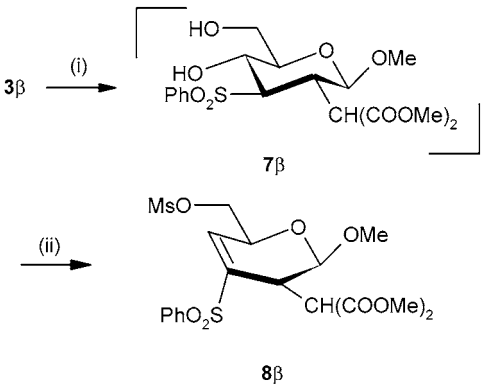
(i) CH_3NO_2, ^tBuOK, THF, rt., 2 h, 55%;
(ii) $CH_2(COOMe)_2$, NaH, THF, rt., 2.5 h, 87%.

(*xylo*) products, although the latter were overwhelmingly the major components. The stereoselectivity of protonation at C-3 after the addition of nucleophiles to C-2 of vinyl sufone modified furanosides can be attributed to steric interactions between the nucleophiles attached at C-2 and the toluenesulfonyl group at C-3.[14a] From the steric consideration, it is therefore expected that **4α** and **4*β***, on reaction with nucleophiles, will produce *arabino* and *xylo* derivatives, respectively. In fact, the structures of **5α** (Scheme 4) and **5*β*** (Scheme 5) have been established unambiguously with the help of X-ray diffraction of single crystals and were found to be in line with the expected configurations at C-2 and C-3.[18]

Although the structures of compounds **2α**/**3α**, **2*β***/**3*β***, and **5α**/**5*β*** have been established unambiguously with the help of X-ray diffraction of single crystals,[18] the multiplicities of the anomeric protons[20] of these products are to a great extent indicative of the configurations at positions C-2 and C-3 as well. For example, the H-1/H-2 coupling constant ($J_{1,2}$) values of authentic methyl α-D-*arabino*furanosides range between 0 and 3.0 Hz.[19,21a,b] Those of authentic methyl α-D-*ribo*furanosides[19,21a,c] range between 4 and 4.9 Hz, and those for methyl α-D-*xylo*furanosides,[19,21a,b,d−f] on the other hand, always range between 4 and 4.7 Hz. Excluding the possibility of any *lyxo* derivative formation for steric reasons,[14a] the $J_{1,2}$ values of **5α** (0.0 Hz) and **6α** (0.0 Hz) surely indicated the presence of an *arabino* configuration in these molecules. On the other hand, it is evident from the available data that the $J_{1,2}$ values of authentic methyl *β*-D-*xylo*furanosides[19,21a,d,f,g] range between 0 and 2.3 Hz and those of methyl *β*-D-*ribo*furanosides[19,21a,c] are close to 0.0 Hz. Although the $J_{1,2}$ values of **5*β*** (3.5 Hz) and **6*β*** (3.9 Hz) were higher than those of the authentic *xylo*furanosides, these values were surely indicative of the absence of a *ribo* configuration in these compounds. On the other hand, the configurations at C-2 and C-3 of many of the pyranosides reported by us earlier[11b,12] as well as **2α**/**3α** and **2*β***/**3*β*** (Schemes 2 and 3) can be predicted to a great extent by comparing the spectral data of our compounds with those of the products obtained from the addition of nucleophiles to nitro-alkene pyranosides.[5,16]

To highlight the usefulness of the branched-chain sugars generated so far with the help of our method, **3*β*** was deprotected under acidic conditions to **7*β*** in high yield. Mesylation of the crude dihydroxy compound **7*β*** furnished a densely functionalized branched-chain sugar **8*β*** (Anal. Calcd for $C_{19}H_{24}O_{11}S_2$: C, 46.33; H, 4.90. Found: C, 46.33; H, 5.07) (Scheme 6). This novel Michael acceptor **8*β*** is a ready intermediate for nucleophilic attack at C-4 as well as C-6 by external nucleophiles for the synthesis of extensively modified carbohydrates.

Scheme 6



(i) conc. HCl, EtOH, rt., 2.5 h, 84%;
(ii) MsCl, Py., 0 to +4 °C, 24 h, 92%.

In summary, a facile route for the synthesis of new branched chain sugars has been designed by utilizing the directing effects of the anomeric configuration of easily accessible vinyl sulfone-modified carbohydrates for the first time. Studies on the further functionalization of the branched chain sugars and the application of this methodology in the synthesis of higher sugars, unnaturally linked oligosaccharides, and acyclic synthons are currently in progress.[22]

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(20) Selected analytical data. Compound **2α**: mp 188−189 °C; $[\alpha]_D^{25.5}$ +26.4 (*c* 0.880, $CHCl_3$); ^{1}H NMR *δ* 4.66 (s, 1 H, H-1), 5.40 (s, 1 H, PhCH). Anal. Calcd for $C_{21}H_{23}O_8NS$: C, 56.11; H, 5.15; N, 3.11. Found: C, 56.31; H, 4.96; N, 3.27. Compound **2*β***: mp 149−150 °C; $[\alpha]_D^{25.5}$ −64.4 (*c* 0.977, $CHCl_3$); ^{1}H NMR *δ* 4.69 (d, J = 8.3 Hz, 1 H, H-1), 5.31 (s, 1 H, PhCH). Anal. Calcd for $C_{21}H_{23}O_8NS$: C, 56.11; H, 5.15; N, 3.11. Found: C, 56.29; H, 5.20; N, 3.21. Compound **3α**: mp 239−240 °C; $[\alpha]_D^{27.5}$ +18.3 (*c* 1.00, $CHCl_3$); IR (Nujol, cm^{-1}); ^{1}H NMR *δ* 4.58 (s, 1 H, H-1), 5.38 (s, 1 H, PhCH). Anal. Calcd for $C_{25}H_{28}O_{10}S$: C, 57.68; H, 5.41. Found: C, 57.64; H, 5.27. Compound **3*β***: mp 98−99 °C; $[\alpha]_D^{27.5}$ −98.2 (*c* 0.9, $CHCl_3$); ^{1}H NMR *δ* 5.17 (d, J = 7.8 Hz, 1 H, H-1), 5.21 (s, 1 H, PhCH). Anal. Calcd for $C_{25}H_{28}O_{10}S$: C, 57.68; H, 5.41. Found: C, 57.63; H, 5.04. Compound **5α**: mp 88−89 °C; $[\alpha]_D^{26.5}$ +58.8 (*c* 1.01, $CHCl_3$); ^{1}H NMR *δ* 4.91 (s, 1 H, H-1). Anal. Calcd for $C_{21}H_{25}O_7NS$: C, 57.91; H, 5.78; N, 3.21; S, 7.36. Found: C, 57.89; H, 5.67; N, 3.01; S, 7.57. Compound **5*β***: mp 125−126 °C; $[\alpha]_D^{26.5}$ +14.3 (*c* 1.017, $CHCl_3$); ^{1}H NMR *δ* 5.02 (d, J = 3.5 Hz, 1 H, H-1). Anal. Calcd for $C_{21}H_{25}O_7NS$: C, 57.91; H, 5.78; N, 3.21; S, 7.36. Found: C, 58.03; H, 5.91; N, 3.14; S, 7.56. Compound **6α**: mp 91−92 °C; $[\alpha]_D^{27.5}$ +51.4 (*c* 0.90, $CHCl_3$); ^{1}H NMR *δ* 4.96 (s, 1 H, H-1). Anal. Calcd for $C_{25}H_{30}O_9S$: C, 59.27; H, 5.96; S, 6.33. Found: C, 59.16; H, 6.64; S, 6.43. Compound **6*β***: mp 99−100 °C; $[\alpha]^{27.5}$ +9.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR *δ* 5.16 (d, J = 3.9 Hz, 1 H, H-1). Anal. Cald for $C_{25}H_{30}O_9S$: C, 59.27; H, 5.96. Found: C, 59.04; H, 5.94.

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(22) It is not clear at present whether the difference in mode of addition of amines and carbon nucleophiles to **1α** is a result of thermodynamic versus kinetic control alone. In general, any discussion on the diastereoselectivity of addition of nucleophiles to complicated systems such as **1α**/**1*β*** or **4α**/**4*β*** should also take into account other factors such as, electrostatic interactions, stereoelectronic control, steric hindrance, and hydrogen bonding.