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Highly β-Selective C-Allylation of a Ribofuranoside Controlling Steric Hindrance in the Transition State

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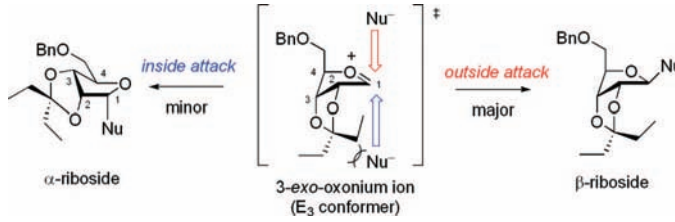
ABSTRACT



A highly β-selective C-allylation of 2,3-*O*-(3-pentylidene)-D-ribofuranosyl fluoride is described. This strategy will provide a new concept for synthesizing β-*C*-ribosides by controlling the effect of steric hindrance in the transition state.

Stereoselective C-ribosylation is an important reaction that is often employed to obtain biologically relevant molecules such as saccharides, nucleosides, and natural products containing the tetrahydrofuran moiety and is of great interest in stereocontrolled synthesis.[1−5] Since Lewis acid-promoted nucleophilic substitution of ribosyl donors is generally believed to proceed via an oxocarbenium ion intermediate,[6] an understanding of the stereoselective reactions of oxocarbenium ions would imply consideration of the preferred conformation of the charged intermediate.[7,8] Some C-ribosylations, e.g., allylation of 2,3,5-tri-*O*-benzyl-D-ribofuranosyl donors, are known to give α-*C*-ribosides in a highly stereoselective manner.[9] Among the arguments for stereochemical control,[9a,10−12] Woerpel et al. in extensive studies elegantly explained that the stereoselectivity of C-glycosylation reactions, including that of pentofuranoside cases, is also largely governed by a stereoelectronic effect.[13] Thus, a stereoelectronically preferred inside attack on the lowest

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(2) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: Boca Raton, FL, 1995.

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energy E_3 conformer in an oxocarbenium ion of D-furanosides with a 3-*C*-alkoxy substituent gives predominantly α-*C*-furanosides. Since, unlike O-ribosylation, neighboring group participation[14] is not usually effective in C-ribosylation reactions,[15,16] it is quite difficult to synthesize *β*-*C*-ribosides by a Lewis acid-promoted direct alkylation of ribosyl donors.[17−19] We recently developed highly *β*-selective O-ribosylation by using a cyclic ketal protecting group at the 2,3-hydroxyl groups. Density functional theory (DFT) quantum mechanical calculations at the B3LYP/6-31G** level suggested that the lowest-energy conformation of intermediated oxocarbenium ions protected with the cyclic ketal is the E_3 conformer, which is ca. 11 kcal/mol more stable than the corresponding ^{3}E conformer. Inside attack of the nucleophile would suffer significant steric interactions from one of the alkyl groups of the cyclic ketal moiety in its transition state. Increasing the size of the alkyl substituents such as ethyl groups in the 3-pentylidene group would result in severe steric repulsion on the α-face, leading to outside attack with complete reversal of stereoselectivity to give *β*-ribosides (Figure 1).[20,21] A cyclic ketal group is removed

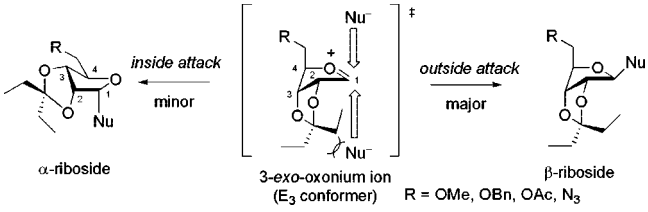
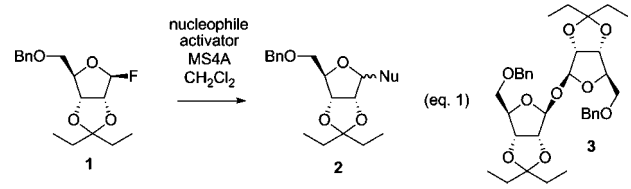


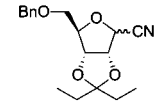
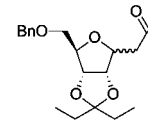
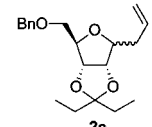
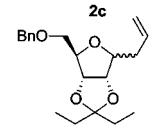
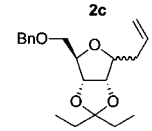
Figure 1. Schematic representation of the *β*-stereoselectivity of the nucleophilic attack to oxocarbenium ions of 3-pentylidene-protected ribofuranoside.

by acidic conditions; this enabled us to synthesize the base-sensitive nucleoside natural products, caprazol and FR-900493.[22,23] If this reaction could be extended to carbon nucleophiles, as we expected, then our stereoselective ribosylation reaction would be applicable to *β*-*C*-ribosides. Herein, we describe the highly *β*-selective direct C-allylation of D-ribofuranosides.

As a preliminary study, some reactions were examined with different types of nucleophiles. Initially, the cyanation of 5-*O*-benzyl-2,3-*O*-(3-pentylidene)-D-ribofuranosyl fluoride **1**[21] was carried out.[24] Treatment of **1** with TMSCN (2.0 equiv) and BF_3·OEt_2 (0.5 equiv) and molecular sieves 4 Å (MS4Å) in CH_2Cl_2 at 0 °C resulted in the rapid formation of the corresponding cyano derivative **2a** in 71% yield (Table 1, entry 1). ^{1}H NMR (500 MHz) analysis of the product

Table 1. C-Ribosylation of 3-Pentylidene-Protected Ribosyl Fluoride



entry	nucleophile	activator	products	yield (%)[a]	ratio (β/α)[b]
1	TMSCN	BF_3·OEt_2	 **2a**	71	97/3
2		BF_3·OEt_2	 **2b**	94	97/3
3		BF_3·OEt_2	 **2c**	86	>98/2
4		$SnCl_4$	 **2c**	57	97/3
5		$TiCl_4$	 **2c**	48	>98/2

[a] Combined isolated yields after column chromatography. [b] Anomeric ratio determined from ^{1}H NMR integration values of selected protons.

revealed a *β*/α ratio of 97/3 and good *β*-selectivity as expected. A Mukaiyama−aldol-type reaction using a silyl enol ether of acetophenone also proceeded well, and the desired **2b** was obtained in 94% yield with good *β*-selectivity (*β*/α = 97/3, entry 2). Next, a Sakurai−Hosomi-type

(14) Jung, K.; Muller, M.; Schmidt, R. *Chem. Rev.* **2000**, *100*, 4423–4442.
(15) Kozikowski, A. P.; Sorgi, K. L. *Tetrahedronn Lett.* **1983**, *24*, 1563–1566.
(16) McDevitt, J. P.; Lansbury, P. T. *J. Am. Chem. Soc.* **1996**, *118*, 3818–3828.
(17) Alternatively, *β*-*C*-furanosides can be stereoselectively prepared by a two-step sequence involving nucleophilic addition of a suitably protected ribonic *γ*-lactone followed by Lewis acid-promoted silane reduction. For examples, see: (a) Gudmundsson, K. S.; Drach, J. C.; Townsend, L. B. *J. Org. Chem.* **1997**, *62*, 3453–3459. (b) Calzada, E.; Clarke, C. A.; Roussin-Bouchard, C.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 517–518.
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(23) Hirano, S.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **2008**, *73*, 569–577.
(24) *β*-Fluoride was used in this study to clarify the reaction conditions. The reaction with the corresponding α-fluoride gave the similar results although not optimized.

allylation[9,15,16,25] was conducted. The reaction of **1** with allyltrimethylsilane (2.0 equiv) in the presence of BF_3•OEt_2 (0.5 equiv) and MS 4Å in CH_2Cl_2 at 0 °C gave **2c**. The reaction proceeded smoothly within 10 min, and the desired *C*-allylriboside **2c** was obtained in 86% yield with excellent β-selectivity (β/α > 98/2, entry 3). The stereochemistry at the 1-position was determined by 500 MHz NOE experiments, as shown in Figure 2. In addition, the coupling

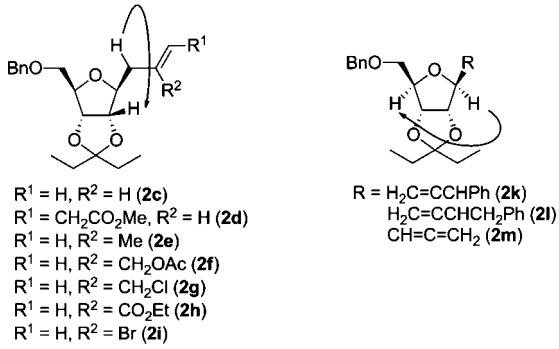
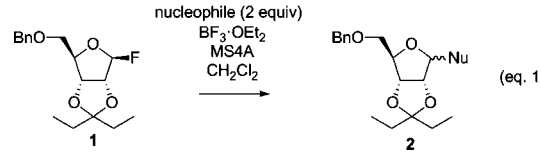


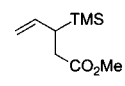
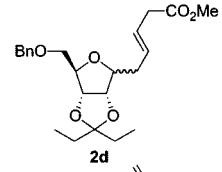
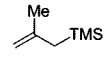
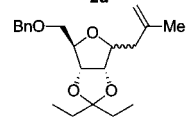
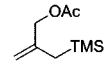
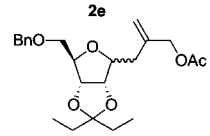
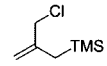
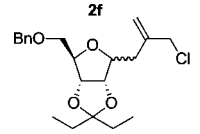
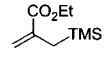
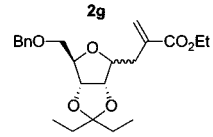
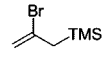
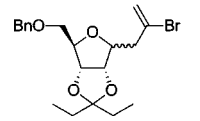
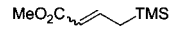
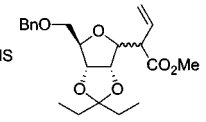
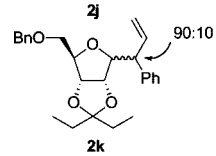
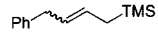
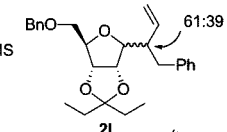
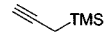
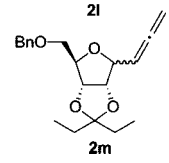
Figure 2. Key NOE correlations of the β-*C*-allylribosides.

constants of H-2, for all the *C*-allylribosides obtained in this study, were 4.6 and 6.9 Hz, indicative that they had the same stereochemistry at the anomeric position. The stereoselectivity was not influenced by other activators such as $SnCl_4$ or $TiCl_4$, although the yield of **2c** was reduced (entries 4 and 5). As for the cyanation and Mukaiyama−aldol-type reactions, it cannot be completely excluded that the α-anomers undergo epimerization to give the β-anomers, in equilibrium. However, the products never interconvert in the Sakurai−Hosomi-type allylation, and so the β-riboside must be the kinetically controlled product. In the absence of MS 4Å, a large amount of 1-*O*-(β-D-ribofuranosyl)-β-D-ribofuranoside **3**, which is a *C*-2 symmetric dimer, was obtained as a byproduct. Presumably, the dimer was obtained by ribosylation of 5-*O*-benzyl-2,3-*O*-(3-pentylidene)-D-ribofuranose generated by partial hydrolysis of the fluoride **1**. It is important to note that the stereogenic centers at the anomeric positions of **3** were both in the β-configuration, and the other possible diastereomers were not obtained at all. Namely, β-selective O-ribosylation occurred to produce only the dimer **3** in this case.

With these promising results in hand, we expanded our study of the reaction with various substituted allyltrimethylsilane derivatives (Table 2). Introduction of a substituent at the α-position to the TMS group of allyltrimethylsilane such as methyl 3-trimethylsilyl-4-pentenoate gave the desired

Table 2. C-Allylation of 3-Pentylidene-Protected Ribosyl Fluoride with Various Substituted Allyltrimethylsilanes



entry	nucleophile	products	yield (%)[a]	ratio (β/α)[b]
1		 **2d**	99	98/2
2		 **2e**	72	98/2
3		 **2f**	88	97/3
4		 **2g**	93	>98/2
5[c]		 **2h**	31	>98/2
6		 **2i**	54	95/5
7		 **2j**	–	–
8		 **2k**	92	97/3
9		 **2l**	91	98/2
10		 **2m**	77	97/3

[a] Combined isolated yields after chromatography. [b] Anomeric ratio determined from ^{1}H NMR integration values of selected protons. [c] Reaction time was 1 h.

(25) Wilcox, C. S.; Otoski, R. M. *Tetrahedron Lett.* **1986**, *27*, 1011–1014.

(26) Hosomi, A.; Hashimoto, H.; Sakurai, H. *Tetrahedron Lett.* **1980**, *21*, 951–954.

(27) This was prepared by a cross-metathesis reaction of methyl acrylate and allyltrimethylsilane in a manner similar to the procedure previouly reported.[29]

(28) Evans, D. A.; Aye, Y.; Wu, J. *Org. Lett.* **2006**, *8*, 2071–2073.

(29) Blanco, O. M.; Castedo, L. *Synlett* **1999**, *5*, 557–558.

C-allylriboside **2d** in high yield and with excellent selectivity (entry 1). Next, the reaction with β-substituted allytrimethylsilanes was examined. The reaction with methallyltrimethylsilane gave **2e** in a highly β-stereoselective manner (entry 2). Acetoxymethyl and chloromethyl substitutions had no influence on either the yield or the stereoselectivity, and the corresponding *C*-allylribosides **2f** and **2g** were obtained in a β-selective manner ($\beta/\alpha = 97/3$ for **2f**, $>98/2$ for **2g**) in 88% and 93% yields (entries 3 and 4), respectively. However, the presence of an electron-withdrawing substituent such as an ester or a halogen at the β-position to the TMS group required a long reaction time,[26] and the yields of the corresponding *C*-allylribosides **2h** and **2i** were decreased, although the same high level of stereoselectivity remained (entries 5 and 6).

The effect of the substituent at the γ position to the TMS group was also examined. Reaction of **1** with methyl 4-trimethylsilyl-2-butenoate[27] did not proceed at all because the electron-withdrawing nature of the ester at the γ position strongly reduced the electron density at the nucleophilic γ position of the allyltrimethylsilane (entry 7). An allyltrimethylsilane with a phenyl[28] or a benzyl group[29] at the γ-position smoothly reacted with **1** to provide the corresponding branched *C*-allylribosides **2k** and **2l** in good yields as a mixture of diastereomers at the additionally formed stereocenter (entries 8 and 9). Furthermore, reaction with propargyltrimethylsilane gave the corresponding allene derivative **2m** in an excellent β-selective manner ($\beta/\alpha = 97/3$, entry 10).

As previously reported,[21] high β-selectivity in a ribosylation reaction could be explained by steric hindrance in the transition state. Compared to our previous studies where alcohols were employed as the nucleophiles ($\beta/\alpha = 82/18-97/3$), nearly complete β-selectivity was observed when carbon nucleophiles were used. Because of the inherently weaker nucleophilic character of carbon nucleophiles versus heteroatom nucleophiles, the reaction generally tends to proceed by addition to the activated sp^2 center or stabilized carbocation via an S_N1 mechanism. Therefore, it is presumed that the reaction pathways, including a direct S_N2 substitution of the fluoride **1** or its contact ion pair, might be suppressed, and the reaction via the oxocarbenium ion is much more dominant. This could partially account for the increased β-selectivity in this study. The steric effect in the transition state would contribute significantly to afford excellent β-selectivity resulting in an unusual outside attack with complete reversal of the stereoselectivity compared to a general inside attack mechanism (Figure 1). This strategy provides a new concept for the synthesis of β-*C*-ribosides, where controlled steric hindrance in the transition state determines the stereochemistry of C-glycosylation.

In conclusion, we report herein a highly β-selective access to *C*-allylribosides from 2,3-*O*-(3-pentylidene)-D-ribofuranosyl fluoride. The influence of this type of reaction in synthetic and biological chemistry has been limited due to the tendency for α-selective substitutions of ribosyl donors promoted by Lewis acids. Our method now allows for the convenient synthesis of biologically relevant molecules such as *C*-nucleosides or natural products.

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Supporting Information Available: Experimental procedures, ^1H NMR, and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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