

STEREOSELECTIVE C-GLYCOSYLATION OF 2,3-DIDEOXYRIBOFURANOSIDES CONTROLLED BY THE METHYLENEDIPHOSPHONOTHIOATE FUNCTIONAL GROUPS AT THE 3-POSITION[†]

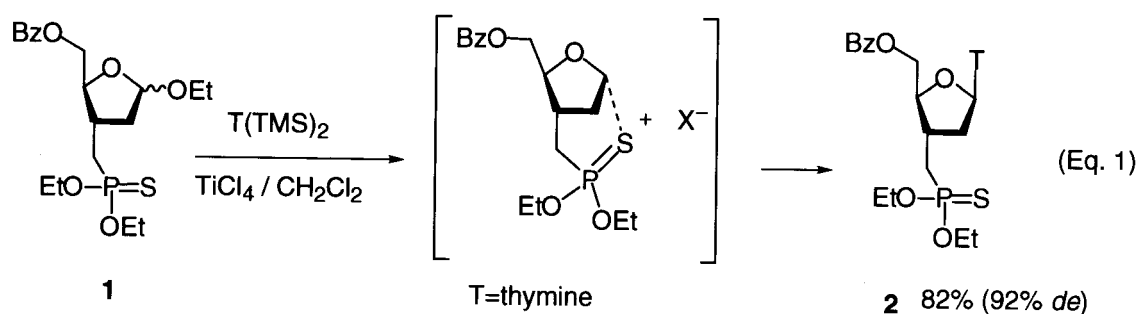
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Abstract—C-Glycosylation of 2,3-dideoxyribofuranoside (**3**) having a methylenediphosphonothioate functional group at the 3-position with allylic carbon-nucleophiles was examined in the presence of a variety of Lewis acids. Good β -selectivity with high chemical yield was observed upon using allyltrimethylsilane as a carbon nucleophile.

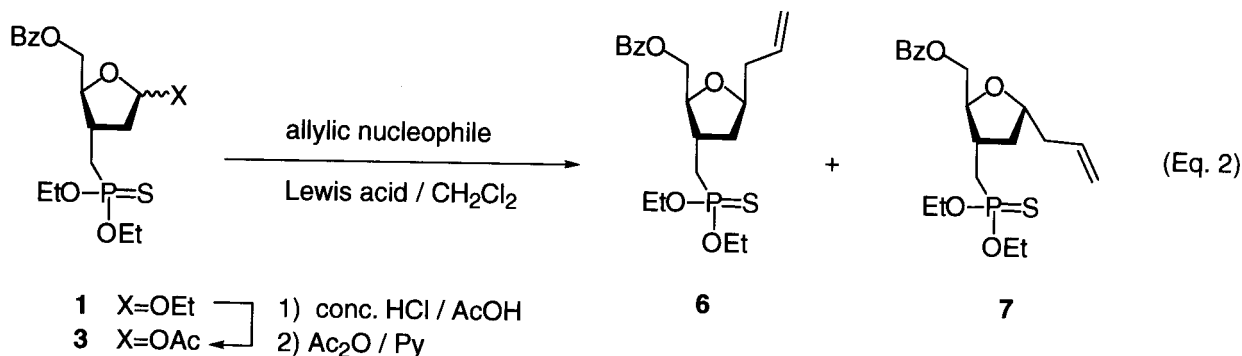
Since the discovery of certain sugar-modified nucleosides having potential antiviral and antitumor effects, reports describing synthesis of analogous compounds for naturally occurring nucleosides and nucleotides have been recently accumulating.¹ Many natural and unnatural ribonucleosides were synthesized stereoselectively by the participation of the neighboring groups such as a 2 α -acyloxy group under the Vorbrüggen glycosylation of ribofuranosides.² However, this synthetic process is much less useful for stereoselective synthesis of 2'-deoxy- and 2',3'-dideoxynucleosides, since approximately 1:1 mixtures of α - and β -anomers are usually formed with substrates lacking a 2 α -acyloxy group.³ As a solution to this problem, intramolecular versions of Vorbrüggen glycosylation and the related reactions have been developed.^{4,5} An alternative strategy to achieve highly β -selective glycosylation with substrates lacking a 2 α -acyloxy group involves neighboring group participation directed by a C3-substituent of the furanosides.⁶ In the course of the investigation for stereoselective synthesis of a metabolically stable analogue of thymidine 3'-phosphate, we have observed a remarkable neighboring group participation of the methylenediphosphonothioate functionality in favor of β -N-glycosylation of 2,3-dideoxyfuranoside (**1**) under Vorbrüggen conditions (Eq. 1).⁷ We have now extended these studies to explore further utility of the methylenediphosphonothioate functionality as a directing group for stereocontrolled C-glycosylation of 2,3-dideoxyribofuranosides.⁸

[†] Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday.



Initially, *C*-glycosylation reactions of the glycosyl donor (**1**)⁷ with representative *C*-nucleophiles such as 1-trimethylsiloxy-1-phenylethylene [$\text{CH}_2=\text{C}(\text{OTMS})\text{Ph}$], allyltributyltin (**4**), and allyltrimethylsilane (**5**) were examined in CH_2Cl_2 in the presence of TiCl_4 (5.0 equiv.) at various temperatures (-78 to 25°C). However, the glycosyl donor (**1**) was found to be totally inert to this series of reactions and remained unreacted under the conditions.⁹

In an effort to obtain *C*-glycosylation products, reactions of 1-*O*-acetyl-2,3-dideoxyribofuranose (**3**, $\beta/\alpha = ca. 1$), derived from **1** in the usual manner, with the same nucleophiles were examined using TiCl_4 as a Lewis acid. While a complex mixture was formed with 1-trimethylsiloxy-1-phenylethylene, a mixture of the desired *C*-nucleotide analogues (**6** and **7**)¹⁰ was obtained in a ratio of 81:19 in 61% yield on treatment with allyltributyltin (**4**) at room temperature (Eq. 2). The yield increased to 87% without loss of the diastereoselectivity (82:18), when the reaction was conducted with allyltrimethylsilane (**5**) in replacement of **4** under the same conditions. The major product (**6**) was confirmed to be a β -isomer on the basis of a diagnostic correlation between C(5)-protons and the terminal vinyl-protons in the NOESY spectra (400 MHz, CDCl_3).



Next, several representative Lewis acids were examined to clarify their influence on the diastereoselectivity for the allylation reaction of **3** by using both allylic nucleophiles (**4** and **5**). The results are summarized in the Table. When allyltributyltin (**4**) was used as a nucleophile, replacement of TiCl_4 with other Lewis acids such as SnCl_4 , TMSOTf , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, and EtAlCl_2 resulted in a decrease of the diastereoselectivity which varied from 34 to 52% *de* (Entry 1 vs Entries 2-5). A low yield (16%) was observed upon using SnCl_4 (Entry 2). It should be mentioned that the reaction induced by EtAlCl_2 proceeded with concomitant de-benzoylation to give a mixture of the de-benzoylation products of **6** and **7** in excellent yield, whereas the diastereoselectivity was very low (34% *de*) (Entry 5). In contrast to these results, the diastereoselectivities (72-80% *de*) significantly increased when the reactions were carried out in the presence of allyltrimethylsilane (**5**) under the influence of these Lewis acids instead of TiCl_4 (Entries 6-10). A marked

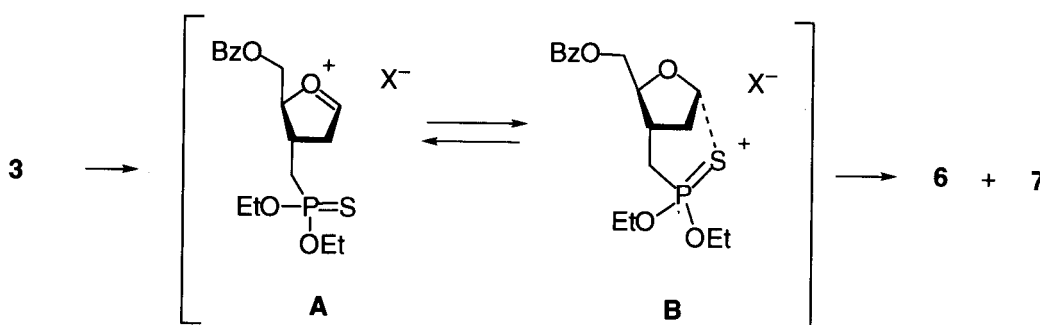
difference in reactivity of **4** and **5** was observed when EtAlCl_2 was used as a Lewis acid (Entry 5 vs Entry 10). No de-benzoylation products were detected and **6** of 72% *de* was isolated in high yield from the EtAlCl_2 -induced allylation with **5** (Entry 10). The best results (80% *de* of 100% yield) were obtained with the $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -induced allylation reaction in the presence of **5** (Entry 9).

Table. Lewis acid-mediated C-glycosylation of 2,3-dideoxyribofuranoside (**3**) with allylic nucleophiles (**4** and **5**)^a

Entry	Lewis Acid ^b	Nucleophile ^b	Reaction Time (h)	Yield ^c (%)	Ratio ^d of 6 : 7
1	TiCl_4	<i>n</i> - $\text{Bu}_3\text{SnCH}_2\text{CH}=\text{CH}_2$ (4)	3.5	61	81:19
2	SnCl_4	4	2	16	76:24
3	TMSOTf	4	1.5	91	68:32
4	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	4	2	87	76:24
5	EtAlCl_2	4	2.5	(100) ^e	(67:33) ^e
6	TiCl_4	$\text{Me}_3\text{SiCH}_2\text{CH}=\text{CH}_2$ (5)	8	87	82:18
7	SnCl_4	5	3.5	99	87:13
8	TMSOTf	5	15	100	89:11
9	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	5	2.5	100	90:10
10	EtAlCl_2	5	1.5	97	86:14

^a All reactions were carried out at 25 °C in the presence of molecular sieves 4A. ^b 5.0 Equivalents of the Lewis acid and 4.0 equivalents of the nucleophile were used. ^c Combined yield of **6** and **7**. ^d Determined by ³¹P-NMR (162 MHz) analysis of crude materials. ^e For the data of de-benzoyl derivatives of **6** and **7**.

Marked differences in the diastereoselectivity associated with the Lewis acid-mediated allylation reaction of 1-*O*-acetyl-2,3-dideoxyribofuranose (**3**) with allyltributyltin (**4**) and allyltrimethylsilane (**5**) might be attributed in part to the good leaving character of the acetyloxy functionality of **3** and the difference in nucleophilicity of **4** and **5**,¹¹ respectively. It would be anticipated that exposure of **3** having a good leaving group to the Lewis acids forms rapidly an oxocarbenium ion (**A**) which then exists in equilibrium with a bicyclic cationic intermediate (**B**) by the participation of the methylenephosphonothioate functional group.



Capture of the intermediate (**A**) with the nucleophiles would result in low diastereoselectivity. The process of capturing the intermediate (**A**) with allyltributyltin (**4**) may be more easier than with allyltrimethylsilane (**5**), since the nucleophilicity of **4** is rather stronger than that of **5**.¹¹ Consequently, the reaction between **3** and **4** proceeded with low diastereoselectivity. While a clear understanding of the nucleophile-dependent

variations of the diastereoselectivity must await further experimentation, very low diastereoselectivity was also observed with TiCl_4 -mediated *N*-glycosylation of **3** with bis-trimethylsilylthymine ($\text{T}(\text{TMS})_2$), a stronger nucleophile than **4** and **5**, at 25 °C. This reaction gave the thymidine analogue (**2**) of 26% *de* in 92% yield.

In conclusion, we have demonstrated the usefulness of neighboring participation of the methylenephosphonothioate functional group for stereocontrolled C-glycosyl bond-formations. During the study, nucleophile-dependent variations of the diastereoselectivity were observed.

ACKNOWLEDGMENT

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9. An epimerization of the anomeric center of the substrate was observed when the β -anomer of **1** was used as a glycosyl donor.
10. Spectroscopic data of **6**: $[\alpha]_D^{25} +24.8$ (c 1.04, CHCl_3) for a sample of 83% *de*; ^1H NMR (400 MHz, CDCl_3) δ 8.08-8.06 (2H, m), 7.58-7.54 (1H, m), 7.46-7.42 (2H, m), 5.83-5.76 (1H, m), 5.10-5.04 (2H, m), 4.46 (1H, dd, $J = 3.8, 11.7$ Hz), 4.36 (1H, dd, $J = 5.4, 11.7$ Hz), 4.20-4.00 (5H, m), 3.96-3.92 (1H, m), 2.62-2.50 (1H, m), 2.40-2.33 (1H, m), 2.29-2.18 (2H, m), 2.08-1.98 (1H, m), 1.29 (3H, t, $J = 7.1$ Hz), 1.26 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 166.51, 134.41, 133.08, 130.08, 129.78, 128.40, 117.36, 82.70 (d, $^3J_{\text{PC}} = 17.2$ Hz), 78.27, 65.72, 62.51 (d, $^2J_{\text{PC}} = 6.8$ Hz), 62.45 (d, $^2J_{\text{PC}} = 6.8$ Hz), 39.58 (d, $^1J_{\text{PC}} = 146.8$ Hz), 37.71 (d, $^3J_{\text{PC}} = 3.2$ Hz), 37.64, 35.78 (d, $^2J_{\text{PC}} = 3.1$ Hz), 16.24 (d, $^3J_{\text{PC}} = 6.8$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ 96.41 (for the major isomer), 96.13 (for the minor isomer); IR (neat) 1722, 1273, 1025 cm^{-1} ; FABMS m/z 413 (MH^+). Anal. Calcd for $\text{C}_{20}\text{H}_{29}\text{O}_5\text{PS}$: C, 58.23; H, 7.09. Found: C, 58.68; H, 7.30.
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