STEREOSELECTIVE *C*-GLYCOSYLATION OF 2,3-DIDEOXYRIBOFURANOSIDES CONTROLLED BY THE METHYLENEPHOSPHONOTHIOATE FUNCTIONAL GROUPS AT THE 3-POSITION¶

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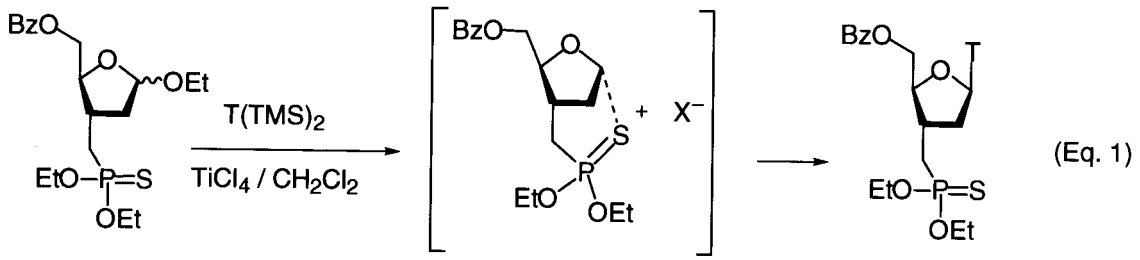
Abstract—*C*-Glycosylation of 2,3-dideoxyribofuranoside (**3**) having a methylenephosphonothioate functional group at the 3-position with allylic carbon-nucleophiles was examined in the presence of a variety of Lewis acids. Good β-selectivity with high chemical yield was observed upon using allyltrimethylsilane 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 2α-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 2α-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 2α-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 methylenephosphonothioate 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 methylenephosphonothioate functionality as a directing group for stereocontrolled *C*-glycosylation of 2,3-dideoxyribofuranosides.[8]

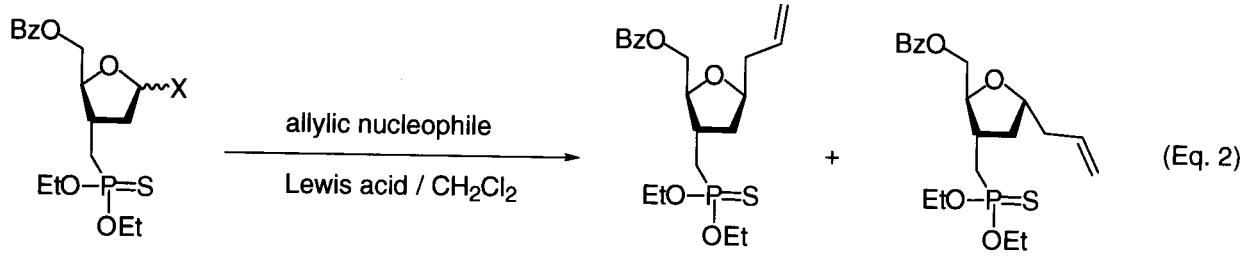
¶ Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday.



1 T=thymine 2 82% (92% *de*)

Initially, *C*-glycosylation reactions of the glycosyl donor (**1**)[7] with representative *C*-nucleophiles such as 1-trimethysiloxy-1-phenylethylene [CH_2=C(OTMS)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**, β/α = *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-trimethysiloxy-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 allytributyltin (**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, $CDCl_3$).



1 X=OEt, **3** X=OAc ⇄ 1) conc. HCl / AcOH, 2) Ac_2O / Py

6 **7**

Next, several representative Lewis acids were examined to clarify their influence on the diastereselectivity 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, BF_3•Et_2O, 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 allytrimethylsilane (**5**) under the influence of these Lewis acids instead of $TiCl_4$ (Entries 6-10). A marked

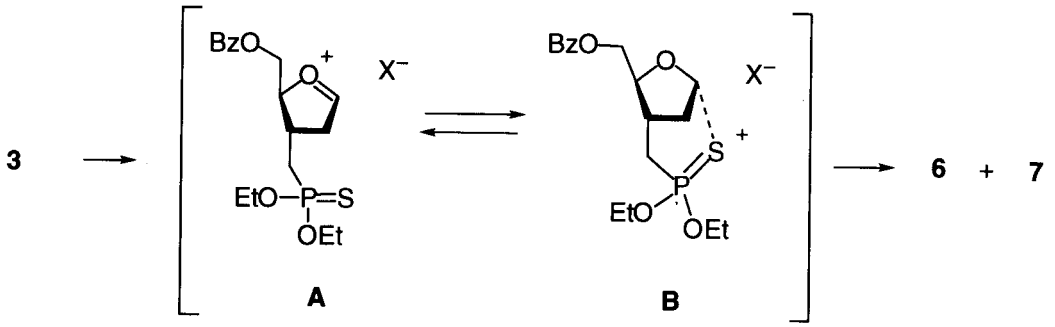
difference in reactivity of **4** and **5** was observed when $EtAlCl_2$ was used as a Lewis acid (Entry 5 *vs* Entry 10). No de-bezoylation products were detected and **6** of 72% *de* was isolated in high yield from the $EtAlCl_2$-induced allylation with **5** (Entry 10). The best results (80% *de* of 100% yield) were obtained with the BF_3•Et_2O-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	$TiCl_4$	*n*-$Bu_3SnCH_2CH{=}CH_2$ (**4**)	3.5	61	81:19
2	$SnCl_4$	**4**	2	16	76:24
3	TMSOTf	**4**	1.5	91	68:32
4	BF_3•Et_2O	**4**	2	87	76:24
5	$EtAlCl_2$	**4**	2.5	(100)[e]	(67:33)[e]
6	$TiCl_4$	$Me_3SiCH_2CH{=}CH_2$ (**5**)	8	87	82:18
7	$SnCl_4$	**5**	3.5	99	87:13
8	TMSOTf	**5**	15	100	89:11
9	BF_3•Et_2O	**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 ^{31}P-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 allytrimethylsilane (**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 ($T(TMS)_2$), 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.

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REFERENCES AND NOTES

1. (a) D. W. Norbeck, *Ann. Rep. Med. Chem.*, 1990, **25**, 149. (b) "Nucleoside & Nucleotides as Antitumor and Antiviral Agents," ed. by C. K. Chu and D. C. Baker, Plenum Press, New York, 1993.
2. H. Vorbrüggen, *Acc. Chem. Res.*, 1995, **28**, 509.
3. H. Vorbrüggen, K. Krolikiewict, and B. Bennya, *Chem. Ber.*, 1981, **114**, 1234.
4. Recent intramolecular *N*-glycosylation of 2-deoxyribofuranosides: (a) M. E. Jung and C. Castro, *J. Org. Chem.*, 1993, **58**, 807. (b) K. Sujino and H. Sugimura, *Chem. Lett.*, 1993, 1187. (c) K. Sujino and H. Sugimura, *Tetrahedron Lett.*, 1994, **35**, 1883 and references cited therein.
5. For an intramolecular approach to stereoselective synthesis of a metabolically stable analogue of thymidine 3′-phosphate: T. Yokomatsu, T. Shimizu, T. Sada, and S. Shibuya, *Heterocycles*, 1999, **50**, 21.
6. (a) T. Oguchi, H. Kubota, and K. Narasaka, *Chem. Lett.*, 1989, 801. (b) J.-F. Lavallee and G. Just, *Tetrahedron Lett.*, 1991, **32**, 3469. (c) T. Mukaiyama, N. Hirano, M. Nishida, and H. Uchiro, *Chem. Lett.*, 1996, 99.
7. T. Yokomatsu, T. Sada, T. Shimizu, and S. Shibuya, *Tetrahedron Lett.*, 1998, **39**, 6299.
8. Reviews for *C*-nucleoside analogues: a) K. A. Watanabe, "The Chemistry of *C*-Nucleosides," in "Chemistry of Nucleoside and Nucleotides," ed. by L.B. Townsend, Plenum Press, New York, 1994, Vol 3, p. 421. b) L. J. S. Knutsen, *Nucleosides & Nucleotides*, 1992, **11**, 961. c) M. H. D. Postema, *Tetrahedron*, 1992, **48**, 8545. d) N. C. Chaudhuri, R. X.-F. Ren, and E. T. Kool, *Synthesis*, 1997, 341.
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, $^3J_{PC}$ = 17.2 Hz), 78.27, 65.72, 62.51 (d, $^2J_{PC}$ = 6.8 Hz), 62.45 (d, $^2J_{PC}$ = 6.8 Hz), 39.58 (d, $^1J_{PC}$ = 146.8 Hz), 37.71 (d, $^3J_{PC}$ = 3.2 Hz), 37.64, 35.78 (d, $^2J_{PC}$ = 3.1 Hz), 16.24 (d, $^3J_{PC}$=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 $C_{20}H_{29}O_5PS$: C, 58.23; H, 7.09. Found: C, 58.68; H, 7.30.
11. For nucleophile-dependent allylation reactions: (a) Y. Yamamoto, S. Nishi, and J. Yamada, *J. Am. Chem. Soc.*, 1986, **108**, 7116. (b) T. Sato, J. Otera, and H. Nozaki, *J. Org. Chem.*, 1990, **55**, 6116.

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