N-GLYCOSYLATION WITH GLYCOSYL DIETHYL PHOSPHITES: A HIGHLY STEREOSELECTIVE SYNTHESIS OF 2'-DEOXY-β-RIBONUCLEOSIDES†

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Abstract – A facile and direct method for the construction of 2'-deoxy-β-*N*-glycosidic linkages in 2'-deoxyribonucleoside synthesis has been developed by using 3-(3,4,5-trimethoxybenzoyl)-protected 2-deoxyribofuranosyl diethyl phosphites as a glycosyl donor in the presence of trimethylsilyl triflate, wherein coupling reactions with silylated pyrimidine bases have been found to exhibit β-selectivities up to 96%.

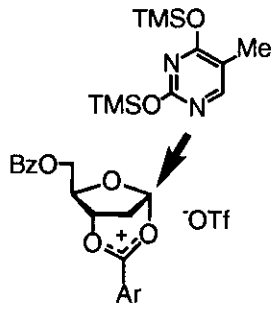
Synthetic nucleosides have occupied a central role in medicinal chemistry with the observation of their activity as antiviral and anticancer agents.[1] The Vorbrüggen glycosidation[2] and its variations involving the reaction of silylated bases with glycosyl donors under Lewis acid conditions have been used to prepare many modified nucleosides. This method is particularly useful when there is an α-acyloxy group at C-2 of the glycosyl donor, producing β-nucleosides in a stereocontrolled manner because of the neighboring group participation of the acyl group. In the case of 2'-deoxynucleosides, on the other hand, no such participation can be applied; thus, varying ratios of an anomeric mixture result which are often difficult to separate. Since only the β-anomers generally exhibit useful biological activity, the need for β-selective glycosidation methodology is apparent. This problem has recently been addressed in several ways.[3,4] With regard to the stereoselective construction of the 2',3'-dideoxy- and 2',3'-didehydro-2',3'-dideoxy-β-*N*-glycosidic linkages,[5-10] the most dominant concept hinges on 1,2-*trans*-glycosidation with the neighboring group participation of temporarily installed 2α-substituents such as phenylthio,[6] phenylseleno,[7,8] or iodo[9] groups followed by a removal of such groups *via* reduction or elimination. Despite an enormous amount of effort, however, the synthetically useful levels of β-selectivity with 2-deoxyribofuranosyl donors have not been attained by a similar strategy capitalizing on the neighboring group participation of 3α-substituents,[11-14] until the advent of recent felicitous methods of Young[15] and

†Dedicated to the memory of the late Dr. Shun-ichi Yamada, Professor Emeritus of University of Tokyo.

Mukaiyama[16] exploiting *N*-benzoylcarbamate and *N,N*-diethylthiocarbamate groups as a stereodirecting group, respectively.[17,18] As part of a program to extend the recently developed glycosidation method capitalizing on diethyl phosphite as a leaving group,[19] we herein wish to report a stereocontrolled construction of 2'-deoxy-β-*N*-glycosidic linkages in 2'-deoxyribonucleoside synthesis by employing 3-(3,4,5-trimethoxybenzoyl)-protected 2-deoxyribofuranosyl diethyl phosphites as a glycosyl donor in the presence of trimethylsilyl triflate (TMSOTf), wherein coupling reactions with silylated pyrimidine bases have been found to exhibit β-selectivities up to 96%.

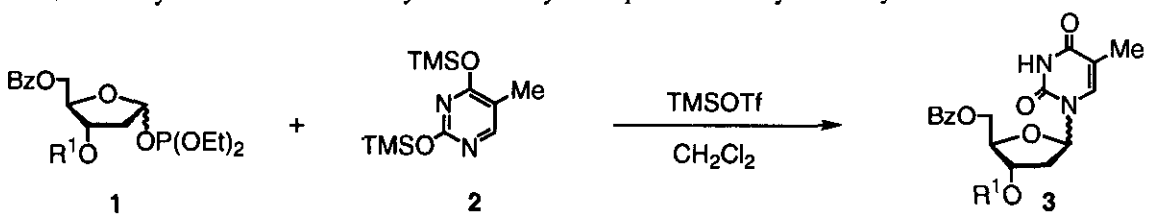
The initial phase of our study was focused on glycosidations of 5-*O*-benzoyl-2-deoxy-D-ribofuranosyl diethyl phosphites (**1a-i**) bearing different protective groups at *O*-3, which were readily prepared by condensation of the corresponding 2-deoxy-D-ribofuranoses with diethyl phosphorochloridite (1.2 equiv) in the presence of triethylamine (2.5 equiv) (CH_2Cl_2, -78 °C, 1 h). These donors could be stored in the freezer (at -30 °C) for several months without any decomposition.

After some optimization of the reaction conditions, addition of the phosphites (**1a-i**) (1.0 equiv) in CH_2Cl_2 over 5 min to a premixed solution of TMSOTf (1.1 equiv) and 2,4-bis(trimethylsilyl)thymine (**2**) (1.5 equiv) in CH_2Cl_2 at -50 °C or -60 °C was found to lead to the formation of the 2'-deoxythymidine derivatives (**3a-i**) in good to high yields (Table 1). On the other hand, our standard procedure in the previous studies typified by addition of TMSOTf to a mixture of the phosphite (**1a**) and the thymine base resulted in less satisfactory yield because of the production of the ribofuranosyl phosphonates (22% yield).[20] As is apparent from the poor stereoselectivity with **1h,i** bearing benzyl or *tert*-butyldiphenylsilyl ether protection (entries 1-7 *vs* 8 and 9), the β-selectivities observed here might be ascribed to the anchimeric assistance by *O*-3 acyl groups.[21, 22] In this respect, it is well documented that participating effects of *O*-3 acyl groups such as benzoyl or toluoyl groups on the anomeric ratio are generally modest with *N*-glycosidations of 2-deoxyribofuranosyl donors.[11,14,16] Thus, it is worthy of note that the phosphite method has advantage of allowing a coupling temperature lower than usual so as to make the participating effects of *O*-3 acyl groups more powerful.[23] It is of particular interest that the use of 3,4,5-trimethoxybenzoyl group originally developed by Ikegami and Iimori[14] exhibited the superior β-selectivity (α:β=8:92) over any other acyl groups screened (entry 7). While the beneficial effects of this directing group other than the neighboring group effect remain presently unclear, it is worthy of note that the highest β-selectivity observed here exceeds or matches those reported by Young[15] and Mukaiyama,[16] respectively.



With the effectiveness of 3,4,5-trimethoxybenzoyl group as a stereodirecting group identified, we next turned our attention to the effects of *O*-5 protective groups of the donor as well as 5-substituents of the pyrimidine base (Table 2). As seen from the Table, the present protocol was found to allow for

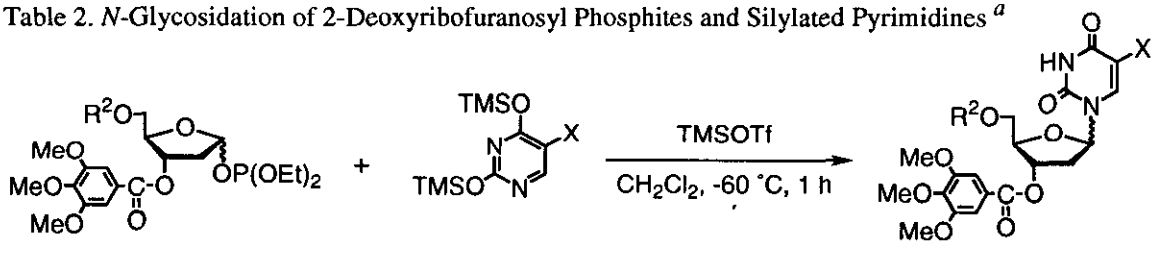
Table 1. *N*-Glycosidation of 2-Deoxyribofuranosyl Phosphites and Silylated Thymine [a]



entry	phosphite [b]		conditions		2'-deoxyribonucleoside		
		R^1	temp, °C	time, h		yield,[c] %	α : β [d]
1	**1a**	Bz	-50	0.5	**3a**	83	19 : 81
2	**1b**	Ac	-50	0.5	**3b**	87	20 : 80
3	**1c**	1-Naphthoyl	-50	1	**3c**	84	18 : 82
4	**1d**	4-$CF_3C_6H_4CO$	-50	1	**3d**	86	16 : 84
5	**1e**	4-$MeOC_6H_4CO$	-60	1	**3e**	82	17 : 83
6	**1f**	2,4,6-$Me_3C_6H_2CO$	-50	1	**3f**	88	23 : 77
7	**1g**	3,4,5-$(MeO)_3C_6H_2CO$	-60	1	**3g**	86	8 : 92
8	**1h**	Bn	-60	1	**3h**	77	42 : 58
9	**1i**	TBDPS	-60	1	**3i**	91	43 : 57

[a] The reaction was carried out in dichloromethane on 0.1 mmol scale. Donor/acceptor/promoter molar ratio = 1.0/1.1/1.5. [b] The anomeric ratio of the phosphites: **1a**, 66:34; **1b**, 57:43; **1c**, 61:39; **1d**, 36:64; **1e**, 61:39; **1f**, 57:43; **1g**, 56:44; **1h**, 56:44; **1i**, 45:55. [c] Isolated total yield. [d] The ratio was determined by integration of the anomeric protons in 500 MHz ^{1}H NMR.

Table 2. *N*-Glycosidation of 2-Deoxyribofuranosyl Phosphites and Silylated Pyrimidines [a]



entry	phosphite [b]		silylated base		2'-deoxyribonucleoside			
		R^2		X		yield,[c] %	α : β [d]	δ ^{1}H [e]
1	**1g**	Bz	**2**	Me	**3g**	86	8 : 92	6.40 (6.26)
2	**4**	Bn	**2**	Me	**10**	77	6 : 94	6.55 (6.33)
3	**5**	TBDPS	**2**	Me	**11**	81	4 : 96	6.45 (6.28)
4	**5**	TBDPS	**6**	H	**12**	86	8 : 92	6.41 (6.23)
5	**5**	TBDPS	**7**	I	**13**	82	10 : 90	6.32 (6.22)
6	**5**	TBDPS	**8**	F	**14**	81	12 : 88	6.35 (6.28)
7	**5**	TBDPS	**9**	CF_3	**15**	84	8 : 92	6.21 [f]

[a] The reaction was carried out in dichloromethane on 0.1 mmol scale. Donor/acceptor/promoter molar ratio = 1.0/1.1/1.5. [b] The anomeric ratio of the phosphites: **4**, 55:45; **5**, 56:44. [c] Isolated total yield. [d] The ratio was determined by integration of the anomeric protons in 500 MHz ^{1}H NMR. [e] Chemical shifts for the anomeric protons of 2'-deoxy-β-ribonucleosides. Values in parentheses correspond to those of 2'-deoxy-α-ribonucleosides. [f] Chemical shifts for the α- and β-anomeric protons were identical so that the α:β ratio was determined by integration of H-2'α (α: δ 2.45, β: δ 2.27).

considerable variation in *O*-5 protective group patterns of the donor and 5-substituents of the pyrimidine base, wherein coupling of **5** bearing *O*-5 *tert*-butyldiphenylsilyl group with **2** attained to the highest β-selectivity of 96% (entry 3). It is also noteworthy that the precursors (**14** and **15**) to the anticancer nucleosides 5-fluoro-2'-deoxyuridine and 5-trifluoromethyl-2'-deoxyuridine could be synthesized in a highly stereoselective manner (entries 6 and 7).[24]

In conclusion, we have developed a facile and direct method for the synthesis of 2'-deoxy-β-ribonucleosides, wherein the combinational use of diethyl phosphite as a leaving group of glycosyl donors and 3,4,5-trimethoxybenzoyl group as *O*-3 stereodirecting group is crucial for a high order of β-selectivity. We are currently investigating the applicability of our protocol to the synthesis of 2'-deoxy-β-ribonucleosides bearing purine bases.

ACKNOWLEDGMENT

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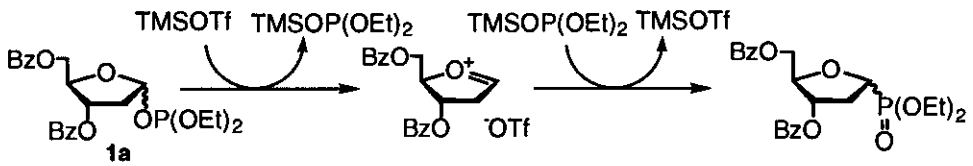
20. Since the phosphite (**1a**) was readily converted into the corresponding phosphonate (α:β=ca. 1:1) with the aid of TMSOTf at -50 °C (eq. 1), this result could be accounted for by the competitive complexation of TMSOTf to the oxygen atom of the phosphite and the nitrogen atom of the silylated thymine. Thus, the precomplexation of TMSOTf and thymine base was crucial for the chemoselectivity in this reaction.



(1)

21. In the present reaction, effects of the anomeric configuration of the donor on the stereochemical outcome could not be explored, because the donor with different anomeric ratios could not be prepared. However, the stereoselectivities observed here are assumed to be independent of the anomeric composition of the donor by analogy with those in the previous studies.[19]
22. For the coupling of **1a** with **2** at -50 °C, the use of propionitrile, ether, and toluene gave rise to nearly the same yields and α:β ratios as those obtained in CH_2Cl_2.
23. The stereoselectivity was found to be largely influenced by a coupling temperature; the lower the temperature, the higher was β-selectivity (α:β ratio with **1a**: 24:76 at -23 °C; 34:66 at 0 °C).
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