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DEVELOPMENT OF A GLYCOSYLATION REACTION: A KEY TO ACCESSING STRUCTURALLY UNIQUE NUCLEOSIDES

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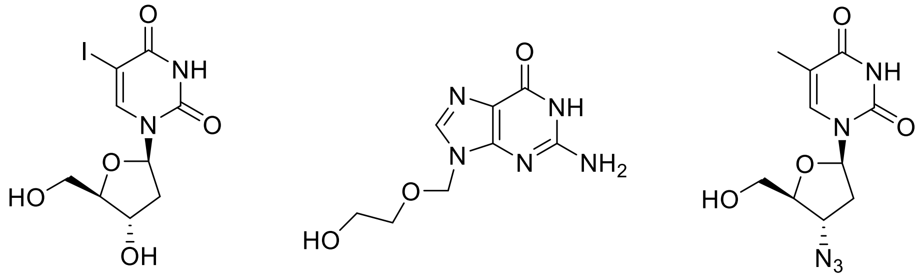
Abstract – Nucleosides are potential drug candidates for antitumor and antiviral chemotherapies. Thus, the synthesis of structurally diverse nucleosides would contribute to the search for new antitumor and antiviral agents. The use of the glycosylation reaction to synthesize nucleoside derivatives would be a practical way to prepare nucleosides with unnatural sugar moieties. Therefore, we synthesized many nucleoside derivatives by using new glycosylation reactions categorized into three types: 1) a Pummerer-type glycosylation reaction used for constructing 4’-thionucleoside skeletons, 2) a sulfur-assisted Mitsunobu reaction used for isonucleoside syntheses, and 3) an oxidative coupling reaction catalyzed by hypervalent iodine for carbocyclic nucleosides and in the syntheses of dihydropyranonucleosides. In this review, we describe the development of the glycosylation reactions and their application to the synthesis of various structurally unique nucleoside derivatives.

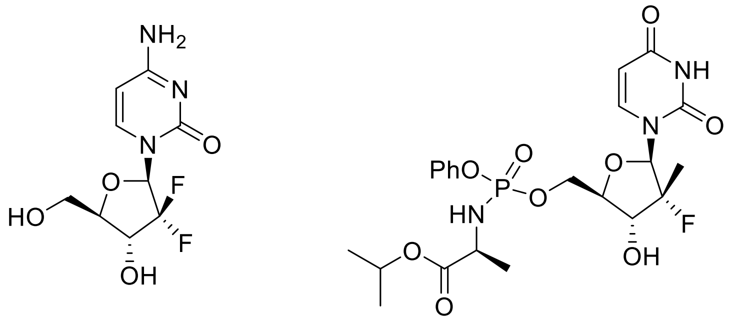
CONTENTS

1. INTRODUCTION

Nucleoside derivatives constitute an important class of compounds because they show antitumor and antiviral activities.[1] To date, many nucleoside antimetabolites have been used as clinical drugs in chemotherapies against cancer and viruses. Idoxuridine, which is a 5-iodo-2'-deoxy derivative of uridine, was the first antiviral agent approved for herpes treatment.[2] Aciclovir, which is the most popular antiherpes drug developed by Welcome, is a 2',3'-nor derivative of guanosine.[3] The first anti-HIV (Human Immunodeficiency Virus) drug approved for the treatment of AIDS (Acquired Immune Deficiency Syndrome), 3'-azido-3'-deoxythymidine (Zidovudine, AZT), still plays a significant role in AIDS treatment.[4] Gemcitabine, 2'-deoxy-2'-difluorocytidine, developed by Eli Lilly, is an anticancer drug approved for the treatment of pancreatic cancer and now is being used in chemotherapies against various tumors, including lung cancer.[5] Sofosbuvir, developed by Pharmasset (Gilead), has had recent success in the treatment of hepatitis C (Figure 1).[6] These drugs show the importance of studying the synthesis of nucleoside derivatives.



Idoxuridine Aciclovir Zidovudine (AZT)



Gemcitabine Sofosbuvir

Figure 1. Structures of nucleoside derivatives approved as drugs

Thus, it is necessary to synthesize nucleoside derivatives with structural diversity for discovering new antitumor and antiviral agents. In general, there are three methods used for synthesizing nucleoside derivatives: 1) synthesis starting from a natural nucleoside,[7] 2) constructing a base moiety on an appropriate sugar portion,[8] and 3) connecting base and sugar moieties by using glycosylation reactions.[9] In particular, the third method using a glycosylation reaction is advantageous because various nucleoside derivatives having different base moieties can be synthesized from one sugar intermediate. To date, we have synthesized many nucleoside derivatives by developing new glycosylation reactions. In this paper, we describe three different glycosylation reactions developed by us: 1) a Pummerer-type glycosylation reaction used for constructing 4’-thionucleoside skeletons, 2) a sulfur-assisted Mitsunobu reaction used for isonucleoside synthesis, and 3) a hypervalent iodine-catalyzed reaction for connecting bases and pseudosugars of carbocyclic nucleosides. In addition, we review the synthesis of nucleoside derivatives with potential biological activities and new structures.

2. DEVELOPMENT OF A PUMMERER-TYPE GLYCOSYLATION REACTION TOWARD THE SYNTHESIS OF 4’-THIONUCLEOSIDES

When we started a new project to explore antitumor and antiviral nucleosides, Walker[10] and Secrist[11] independently reported that 2’-deoxy-4’-thionucleosides, in which the ring oxygen of the 2-deoxyribose moiety of 2’-deoxynucleosides was replaced with sulfur, had potent anti-herpesvirus activity and that some of the derivatives had cytotoxicity. Together with their reports, 2’-substituted cytidine derivatives, such as DMDC (**2**)[12] and gemcitabine,[5] are known to have potent antitumor activity. From these results, we designed 2’-substituted 4’-thiocytidines, 4’-thioDMDC (**3**) and 4’-thiogemcitabine (**4**), as potential antitumor agents (Figure 2). In the synthesis of the target nucleoside derivatives, there were several problems. At the time we started the project, the only 4’-thionucleosides reported were 4’-thioribonucleosides,[13] 4’-thioarabinonucleosides[14] and 2’-deoxy-4’-thionucleosides.[10,11] Therefore, we needed to develop a strategy to synthesize 4’-thionucleosides which was also applicable to the synthesis of 2’-substituted derivatives. From structure-activity relationship (SAR) studies, we thought that a synthetic strategy employing a glycosylation reaction with 4-thiosugars was ideal, as mentioned above, since we had obtained various base-modified analogues from one 4-thiosugar intermediate. Thus, the first problem to overcome was the need for a new synthetic route to prepare 4-thiosugars, which can be used to synthesize 2-substituted derivatives.

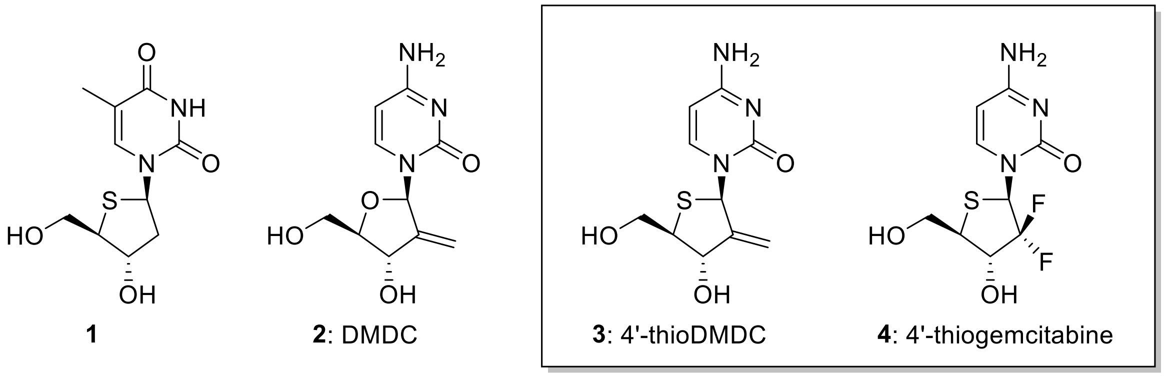
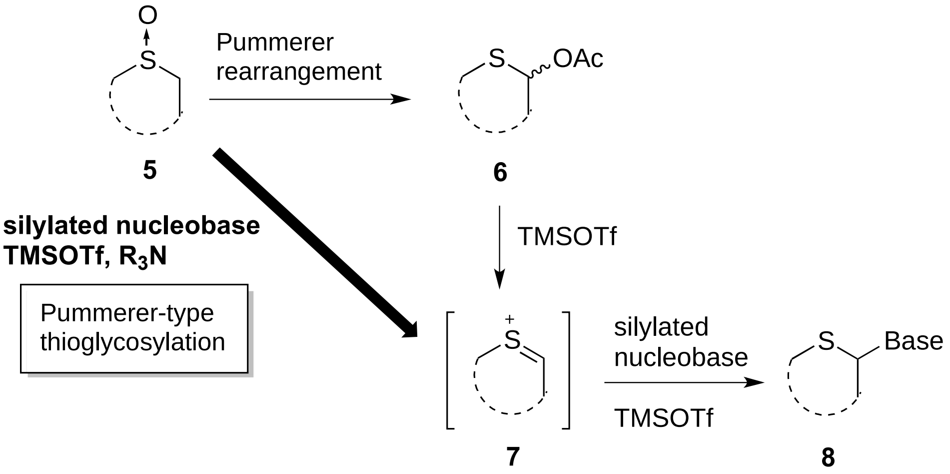

1 **2**: DMDC **3**: 4'-thioDMDC **4**: 4'-thiogemcitabine

Figure 2. Desired cytotoxic 2’-substituted 4’-thionucleosides

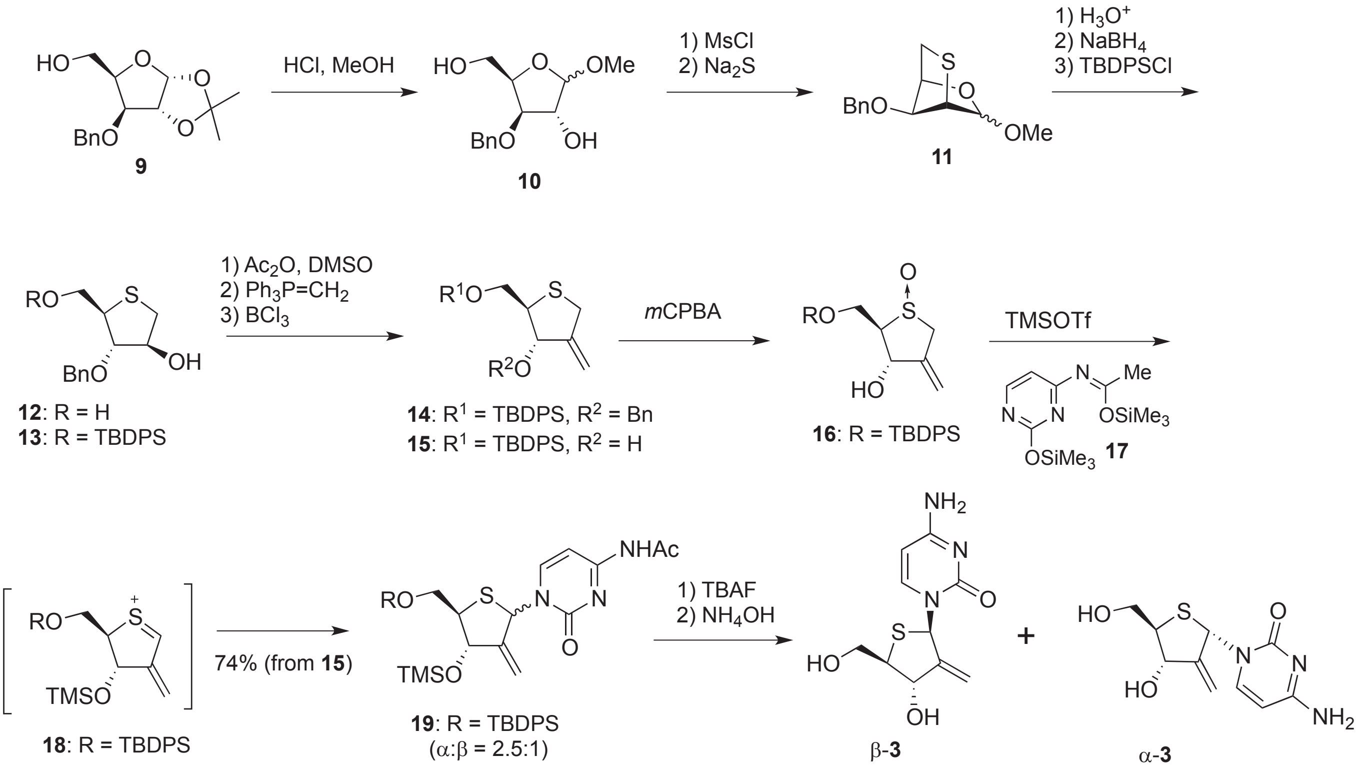
To construct a glycosidic linkage between the base and sugar moiety of nucleoside skeleton **8**, a Vorbrüggen reaction[15] is generally used. As shown by past results,[16] the reaction could be used in the synthesis of 4'-thionucleosides as well as normal "4'-oxy" nucleosides. In addition, we could use original chemistry for sulfur-containing compounds: 1-acetoxy-4-thiosugar **6**, a good substrate for the Vorbrüggen reaction, was easily obtained from the corresponding sulfoxide **5** by using a classical Pummerer rearrangement. Although the scheme mentioned above seemed promising, we introduced an additional synthetic idea. The reaction intermediate of the Vorbrüggen reaction[15] is sulfenium ion **7** which can also be obtained by using a sila-Pummerer reaction, developed by Kita,[17] involving sulfoxide **5**. This new glycosylation reaction is attractive since it skips a step and directly accesses sulfenium ion **7** from sulfoxide **5** (Scheme 1). Thus, our second task for synthesizing 4'-thionucleosides was to develop a Pummerer-type glycosylation reaction.



Scheme 1. Concept for the Pummerer-type glycosylation reaction

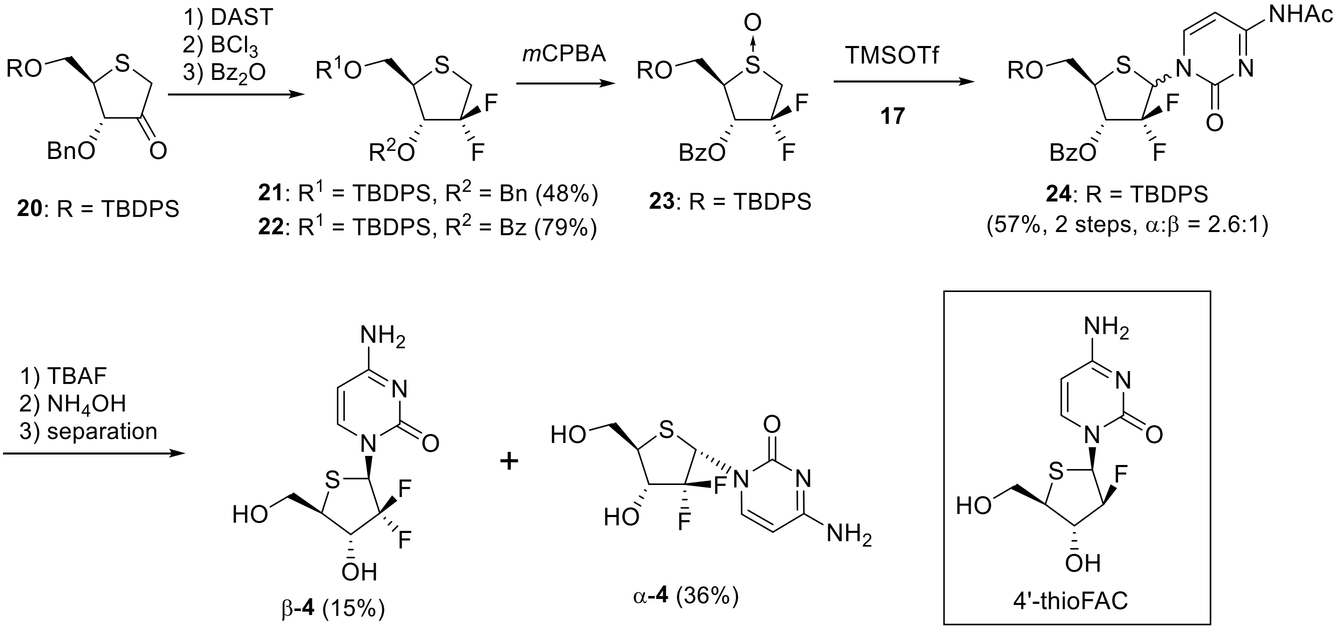
First, we developed a synthetic route involving bicyclic intermediate **11** starting from xylose derivative **9**,[18] as shown in Scheme 2. Formation of **11** was performed by consecutive inter-/intramolecular S_N2 reactions of the dimesylate compound obtained from 3-benzylxylose **10**. After acetal hydrolysis of **11**, followed by hydride reduction, 4-thioarabinose derivative **12** was obtained. Through cyclic intermediate **9**, the chiralities of the 2, 3, and 4 positions of the xylose were transferred to the 4, 3, and 2 positions of 4-thioarabinose derivative **12**, respectively. Compound **13**, which was protected at the primary hydroxyl group, was converted to a ketone, and the resulting ketone was subjected to a Wittig reaction to give 3-benzyl-2-methylene derivative **14**. Deprotection of the benzyl group of **14** gave 2-methylene derivative **15**.

Next, we tried the Pummerer-type glycosylation of *N*⁴-acetylcytosine with sulfoxide **16**, obtained by treatment of **15** with *m*CPBA. We found that simple treatment of **15** with excess persilylated *N*⁴-acetylcytosine in the presence of TMSOTf afforded an anomeric mixture of 4'-thioDMDC derivatives **19** via the formation of sulfenium ion **18** in good yield. Although the ratio of α- and β-anomers was unsatisfactory, the Pummerer-type glycosylation was effective for the formation of the glycoside bond of 4'-thionucleosides. Deprotection of **19** and separation of the anomers afforded 4'-thioDMDC (β-**3**) and its anomer α-**3** (Scheme 2).[19]



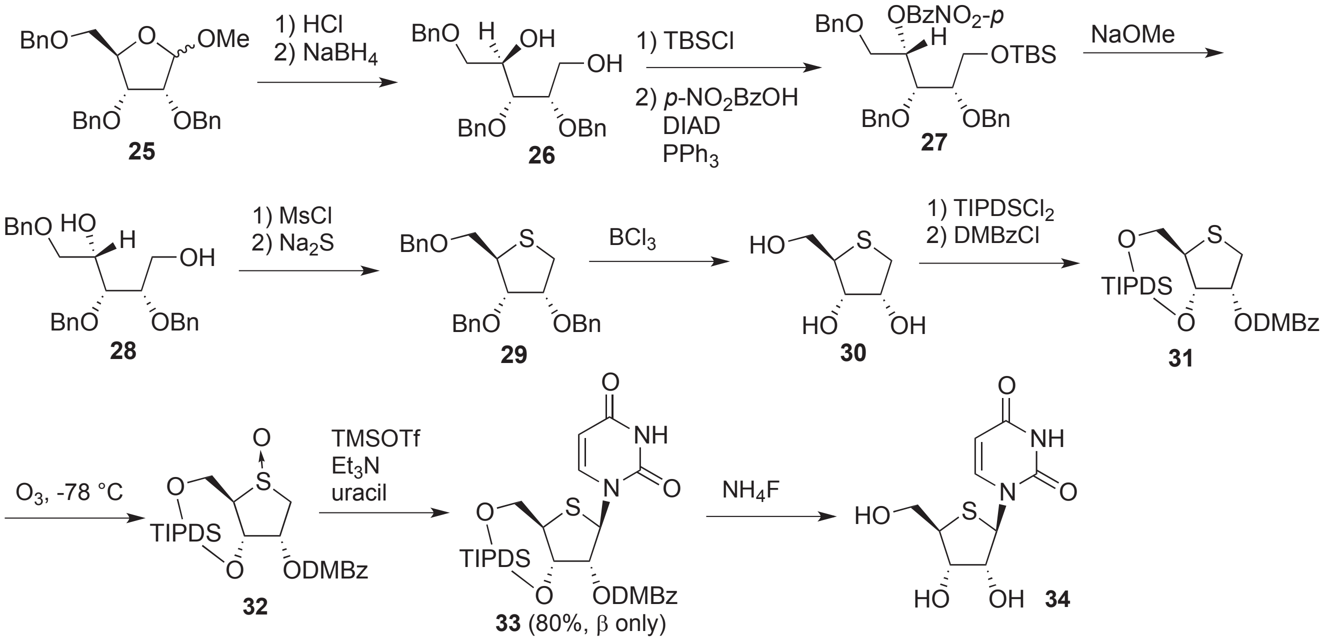
Scheme 2. Synthesis of 4'-thioDMDC

From the common intermediate **20**, described above, we synthesized 4'-thiogemicitabine. The ketone **20** was treated with DAST to give geminal difluoro derivative **21**, which was oxidized to the corresponding sulfoxide to give **23** after conversion of the protecting group. The sulfoxide **23** was subjected to Pummerer-type glycosylation conditions, as in the case of **16**, to give desired 4'-thiogemcitabine derivatives **24** in moderate yield. It is known that 2-fluorosugar derivatives are resistant to hydrolysis and glycosylation due to destabilization of the cationic intermediate by a strong electron-withdrawing fluoro substituent close to the reaction site.[20] Thus, the Pummerer-type glycosylation with **23** having difluoro substituents at the 2-position is a suitable method for obtaining the desired nucleoside derivative since the reaction could avoid C-O bond scission at the anomeric center. Deprotection and the subsequent separation of anomers gave α- and β-anomers of 4'-thiogemcitabine[19] (α- and β-**4**, Scheme 3). Among the synthesized analogues, β-4'-thioDMDC (β-**3**) exhibited potent antitumor activity in comparison to 4'-thiogemcitabine (β-**4**), which showed only moderate activity.[19,21] On the other hand, the most active 4'-thionucleoside we synthesized was the mono-fluorinated derivative 4'-thioFAC.[19,22] 4'-ThioFAC showed potent antitumor activity against various tumor cell lines and was active in in vivo assays using nude mouse model-implanted human tumor.[23] Furthermore, we found that a series of 4'-thioFAC analogues had potent antiherpes virus activity.[24]

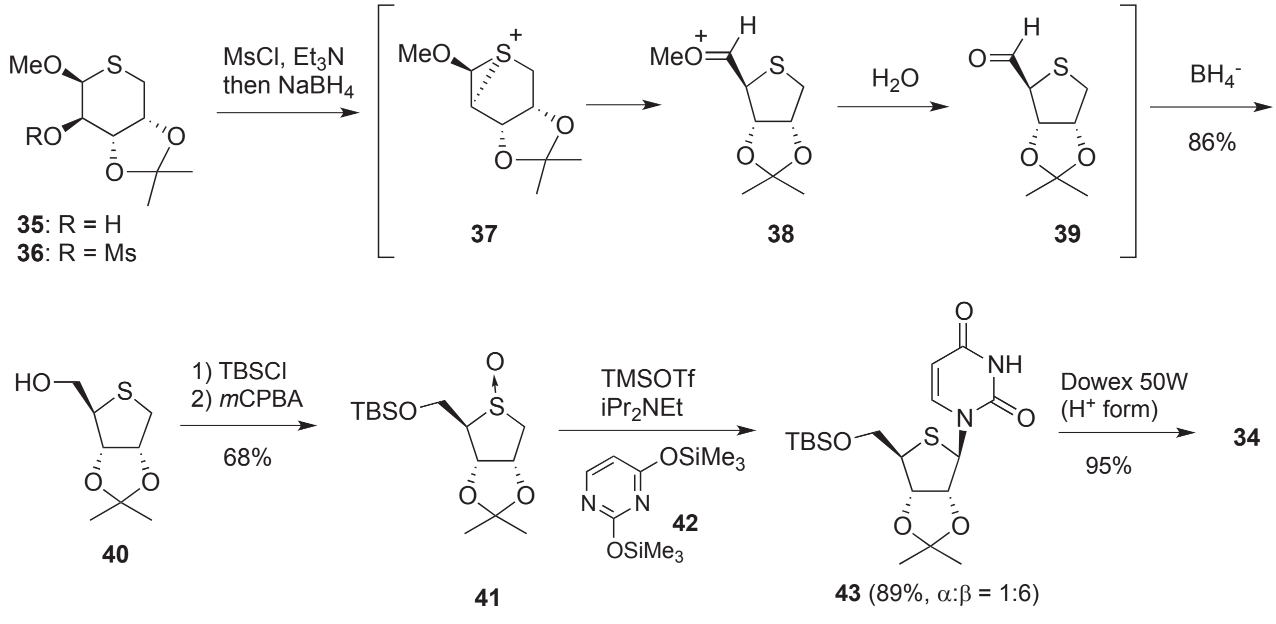


Scheme 3. Synthesis of 4'-thiogemcitabine

After the synthesis of 4'-thioDMDC and 4'-thiogemcitabine using the Pummerer-type glycosylation reaction was reported by us, many other groups reported various 4'-thionucleoside derivatives. Matsuda and co-workers applied the reaction to the syntheses of 4'-thioribonucleosides.[25] Diol **26** was synthesized from tri-*O*-benzylated ribose **25**, of which the primary hydroxyl group was protected by the TBS group, and then subjected to the Mitsunobu reaction to give *p*-nitrobenzoate **27**. After deprotection of the *p*-nitrobenzoate moiety, epimerized diol **28** was converted to a 4-thioribose derivative, as in the case of 4'-thioDMDC shown above, to give 4-thioribose derivative **29**. Deprotection of **29** and protection of the 3- and 5-hydroxyl groups by using 1,1,3,3-tetraisopropyl-1,3-dichlorodisiloxane-1,3-diyl (TIPDS), followed by acylation at the 2-position with dimethoxybenzoyl group (DMBz), gave 2-dimethoxybenzoate **31**. Introduction of DMBz at the 2-position and diastereselective formation of sulfoxide **32**, favored in Pummerer-type glycosylation reactions, were key tactics in Matsuda's synthesis. Under optimized conditions for **32**, the desired 4'-thiouridine derivative was obtained as the sole product in excellent yield (Scheme 4).[25]

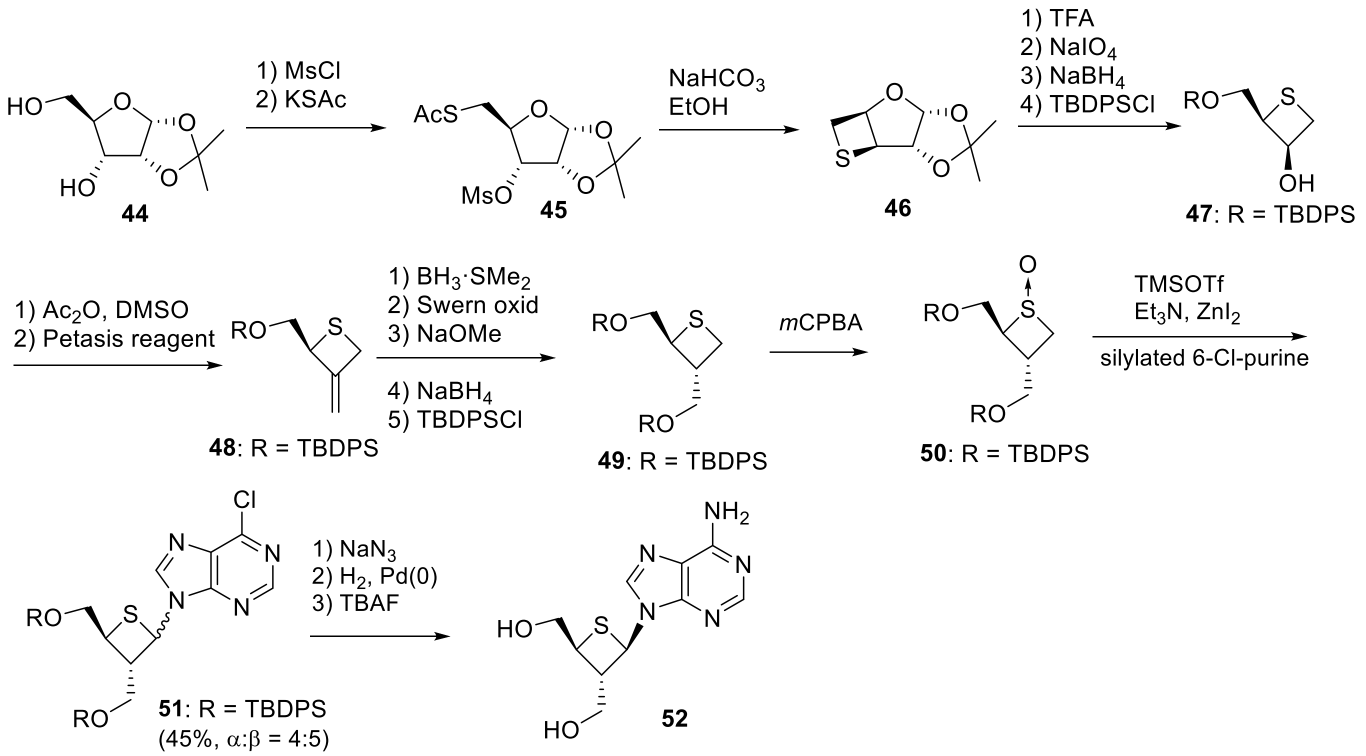


Scheme 4. Synthesis of 4'-thioribonucleoside by Matsuda's group



Scheme 5. Synthesis of 4'-thioribonucleoside by our group

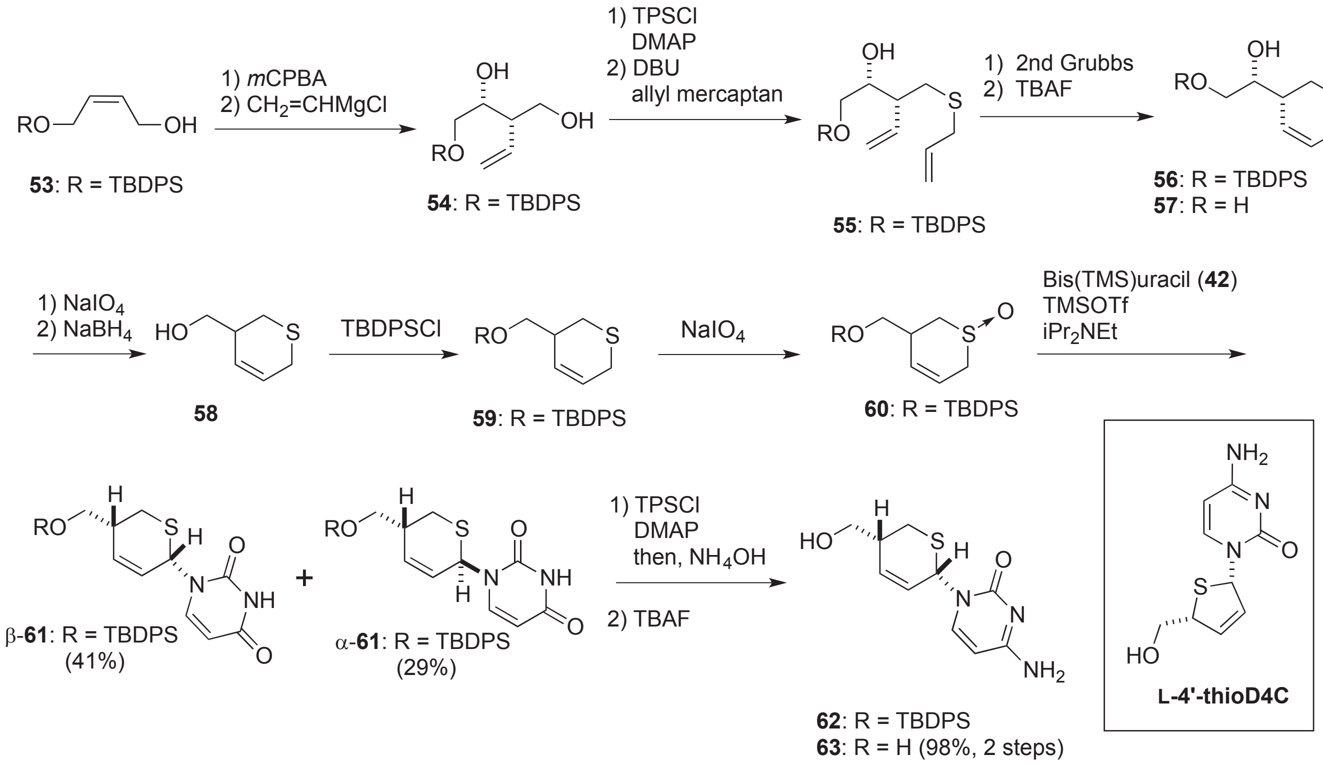
We synthesized 4'-thioribonucleosides by using a different synthetic method.[26] The skeleton of the 4-thioribose was constructed via a ring-contraction reaction under reductive conditions. 2-Mesylate **36**, obtained from **35**, was used without any purification due to its instability. The reaction mixture containing **36** was treated with $NaBH_4$ in aqueous EtOH to give the ring contracted product **40** in good yield. As shown in Scheme 5, the reaction proceeded via the following three steps: 1) intramolecular nucleophilic attack of sulfur at the 5-position and the formation of episulfonium ion **37**, 2) ring contraction and generation of 5-aldehyde **39**, and 3) hydride reduction of **39**. 5-*O*-Silylated sulfoxide **41**, prepared from **40**, was subjected to the Pummerer-type glycosylation reaction by treatment with persilylated uracil **42** and excess diisopropylethylamine (DIPEA) in the presence of TMSOTf to give 4'-thiouridine derivative **43** stereoselectively (Scheme 5).[26]



Scheme 6. Synthesis of 3'-thiooxetanocin

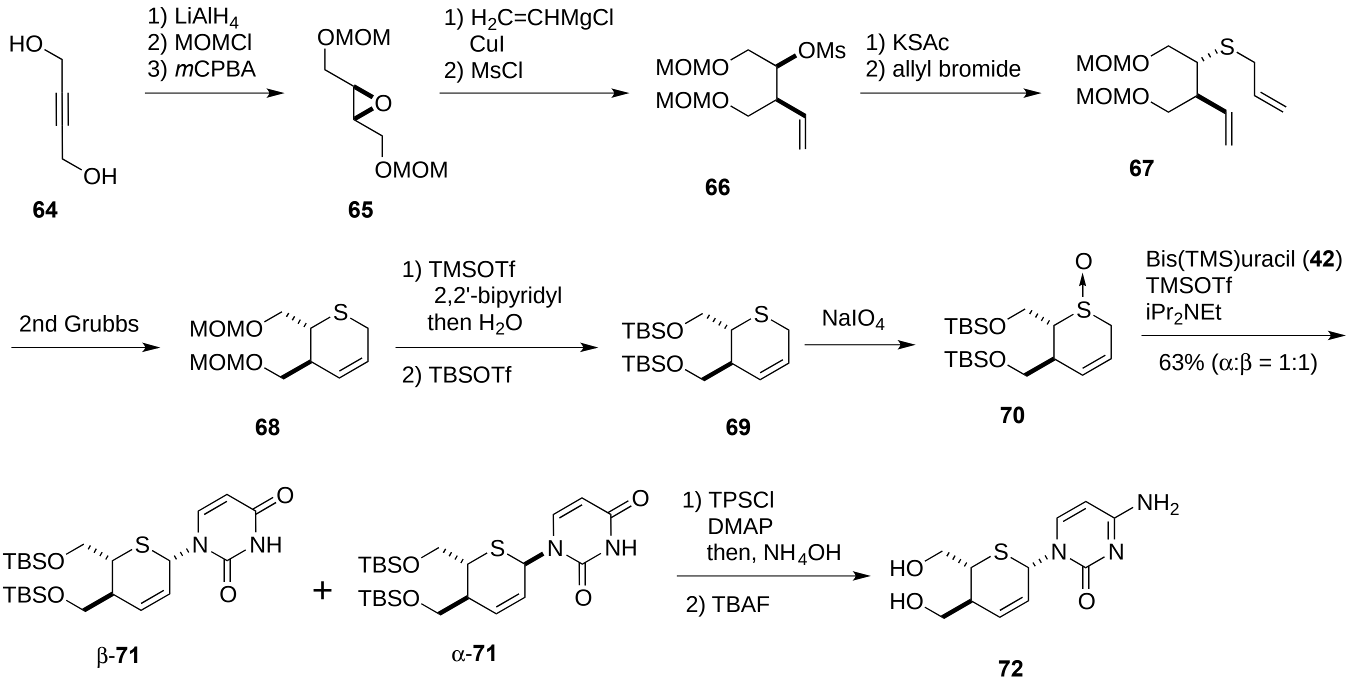
Chu[27] and Matsuda[28] independently studied the synthesis of 3'-thio analogues of oxetanocin A[29] which is a nucleoside antibiotic having oxetanose as a sugar portion, using the Pummerer-type glycosylation as a key step. Chu and his co-workers synthesized thietanose derivative **47** from ribose derivative **44** via a strategy similar to that for 4'-thioDMDC. Thietanose derivative **47** was oxidized, and the resulting ketone was treated with the Petasis reagent[30] to give exo-methylene **48**. Hydroboration of **48**, followed by oxidation with *m*CPBA, gave thietanose sulfoxide **50**, which was subjected to Pummerer-type glycosylation under modified conditions (silylated 6-chloropurine, TMSOTf, Et$_3$N, ZnI$_2$) to give a 4:5 mixture of α- and β-anomers of **51**. Stepwise amination at the 6-position of **51** and desilylation by treatment with TBAF yielded 3'-thiooxetanocin A (**52**) (Scheme 6).[27]

On the basis of the reports of Chu and Matsuda, Pummerer-type glycosylation is effective for preparing thietanose, a 4-membered cyclic thiosugar. We focused on the scope and limitations of the reaction and decided to apply it to a 6-membered ring system with dihydrothiopyranose as a substrate.[31] We designed a ring-expanded analogue of L-4’-thioD4C,[32] which has been reported to possess anti-HIV activity. Since the L-isomer of Lamivudine has more potent anti-HIV activity with lesser cytotoxicity,[33] it has been thought that both the D- and L-isomers of nucleosides should be active against HIV.[34] Therefore, we tried to synthesize the target analogue as a racemate. Monosilylated 2-butene-1,4-diol **53**[35] was converted to the corresponding epoxide, which was treated with vinyl Grignard reagent in the presence of copper iodide to give diol **54**. Selective introduction of a 2,4,6-triisopropylbenzenesulfonyl (TPS) group at the primary alcohol of **54** and nucleophilic substitution by allyl mercaptan gave diene **55**. The ring-closing metathesis (RCM) reaction of **55** using the second generation Grubbs catalyst[36] gave dihydrothiopyran derivative **56** in excellent yield. After one-carbon deletion, protection at the resulting primary hydroxyl group of **58** and oxidation gave sulfoxide **60**. Sulfoxide **60** was subjected to the Pummerer-type glycosylation reaction. Treatment of sulfoxide **60** with bis-$O^{2,4}$-(trimethylsilyl)uracil (**42**), TMSOTf, and DIPEA gave dihydrothiopyranyluracil derivatives β-**61** and α-**61** in 41% and 29% yields, respectively. Finally, conversion of the uracil moiety of β-**61** to cytosine and desilylation afforded dihydrothiopyranyl cytosine **63** (Scheme 7).[31]



Scheme 7. Synthesis of dihydrothiopyranyl cytosine derivative

However, **63** did not show anti-HIV activity. Thus, we prepared an analogue with an extra hydroxymethyl unit at the 4’-position of **63**, which resembles the structure of oxetanocin.[37] Epoxide **65** was prepared from 2-butyne-1,4-diol (**64**) in 3 steps and was treated with vinyl Grignard reagent, as described above, followed by mesylation, to give mesylate **66**. Introduction of an allyl sulfide unit in **66** gave diene **67**, followed by RCM with the second generation Grubbs catalyst,[36] afforded dihydrothiopyran **68**. After transformation of the protecting group from MOM[38] to TBS and oxidation, Pummerer-type glycosylation of the resulting sulfoxide **70** gave a mixture of β-**71** and α-**71** in 63% yield (α:β = 1:1). Using the same procedure as that for **63**, bis(hydroxymethyl)dihydrothiopyranyl cytosine derivative **72** was synthesized and was shown to have anti-HIV activity (Scheme 8).[37]



Scheme 8. Synthesis of bis(hydroxymethyl)dihydrothiopyranyl cytosine derivative

3. DEVELOPMENT OF A SULFUR-ASSISTED MITSUNOBU REACTION TOWARD THE SYNTHESIS OF ISONUCLEOSIDES

During the synthesis of 4'-thioFAC, we confirmed that the reaction of **13** by using DAST gave a fluorinated compound with retention at the reaction site.[22] Marquez reported similar results, suggesting that the reaction proceeded via the neighboring group participation of the ring sulfur to form an episulfonium ion as an intermediate.[39] Thus, we synthesized iso-4'-thio-ddA **75**[40] as a potential anti-HIV agent since iso-ddA **74**[41] was known to have anti-HIV activity comparable to that of ddA, a parental compound of the anti-HIV drug didanosine (**73**).[42]

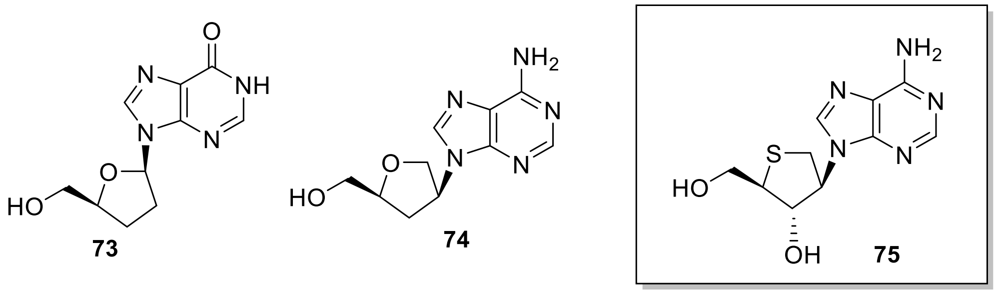
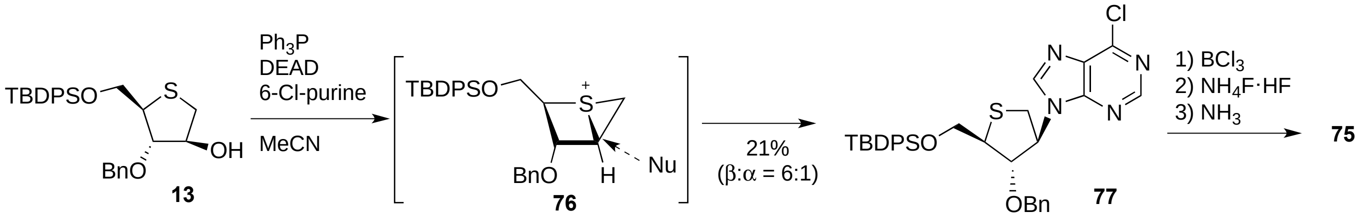


Figure 3. Structures of isonucleosides

After optimizing the reaction conditions, we found that the Mitsunobu reaction with 6-chloropurine in acetonitrile selectively gave the β-isomer of **77**, although the reaction yield was low. Deprotection and amination at the 6-position of **77** gave desired **75** (Scheme 9).[40]



Scheme 9. Synthesis of iso-4'-thionucleoside

Although **75** did not show anti-HIV activity, the results prompted us to study 4'-substituted isonucleosides. With iso-ddA as an example, isonucleosides are a unique category of nucleoside derivatives and have superior tolerance against acid and enzymatic hydrolysis.[41] On the other hand, since 4'-ethynyl nucleosides, such as **78**,[43] show potent anti-HIV-1 activity, the corresponding D4T derivative **79**, which exhibited anti-HIV activity, was synthesized.[44] From these results, 4'-substituted isonucleosides are attractive target molecules for anti-HIV agents. At that time, only the report on the synthesis of 4'-substituted isonucleosides by Nair was available.[45] The development of a new method to access 4'-substituted isonucleosides was necessary to study the SAR of these analogues. Therefore, we developed a strategy for the synthesis of 4'-hydroxymethylisonucleosides, such as **80**, which could serve as an intermediate for the synthesis of a variety of 4'-substituted isonucleosides (Figure 4).[46,47]

We synthesized **85** from intermediate **84** by desulfurization. From the synthesis of iso-4'-thionucleosides described above, the reaction occurred via a Mitsunobu reaction using a nucleobase accompanied by sulfide migration.[40] On the other hand, by using the sulfide attachment at the 3'-position of **84**, the formation of a thietane ring around the 3'- and 4'-positions would afford bicyclo-isonucleoside **81**, an analogue structurally resembling Lamivudine (Scheme 10).

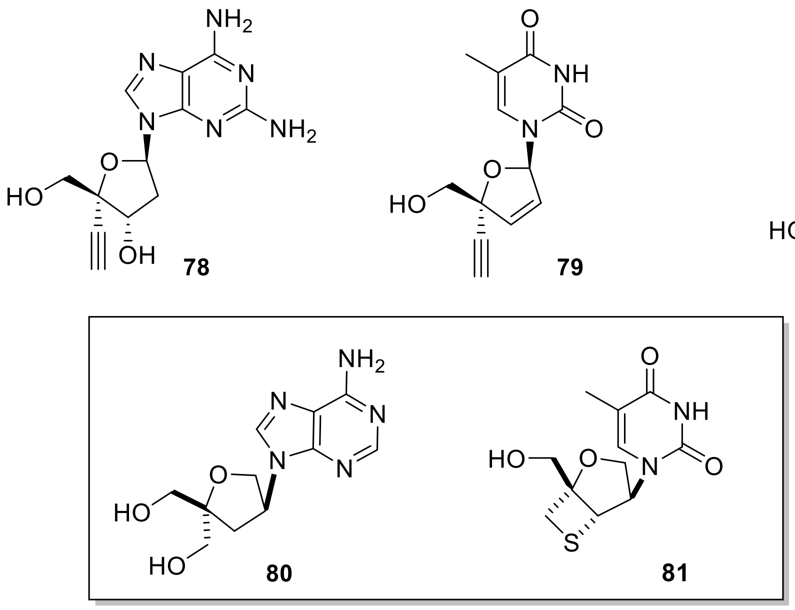
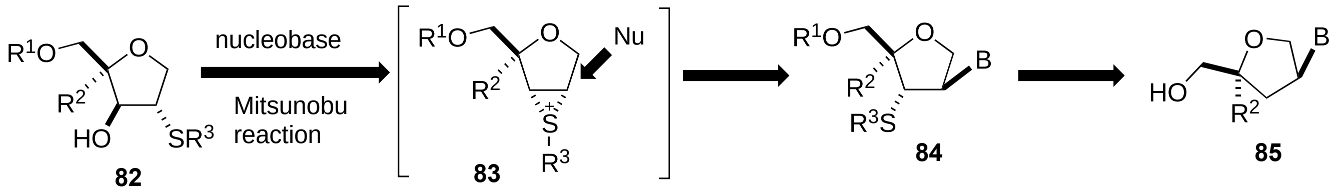
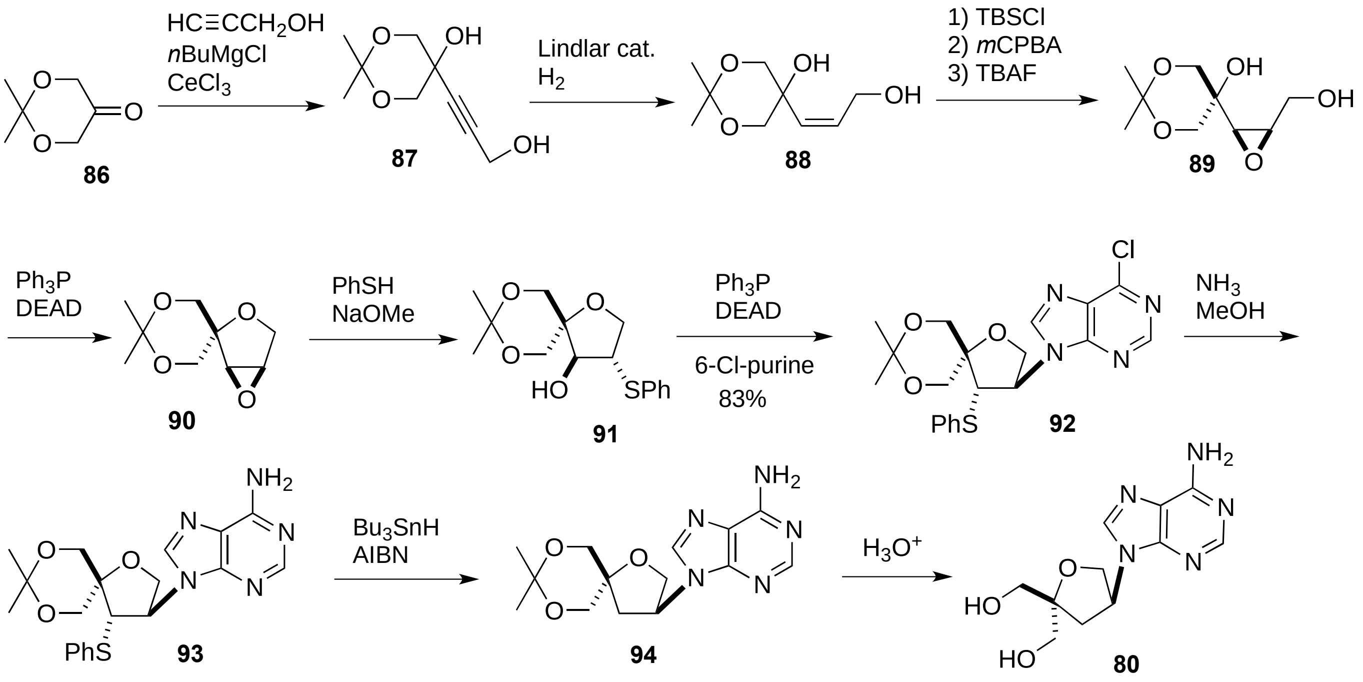


Figure 4. Structures of 4'-substituted nucleosides

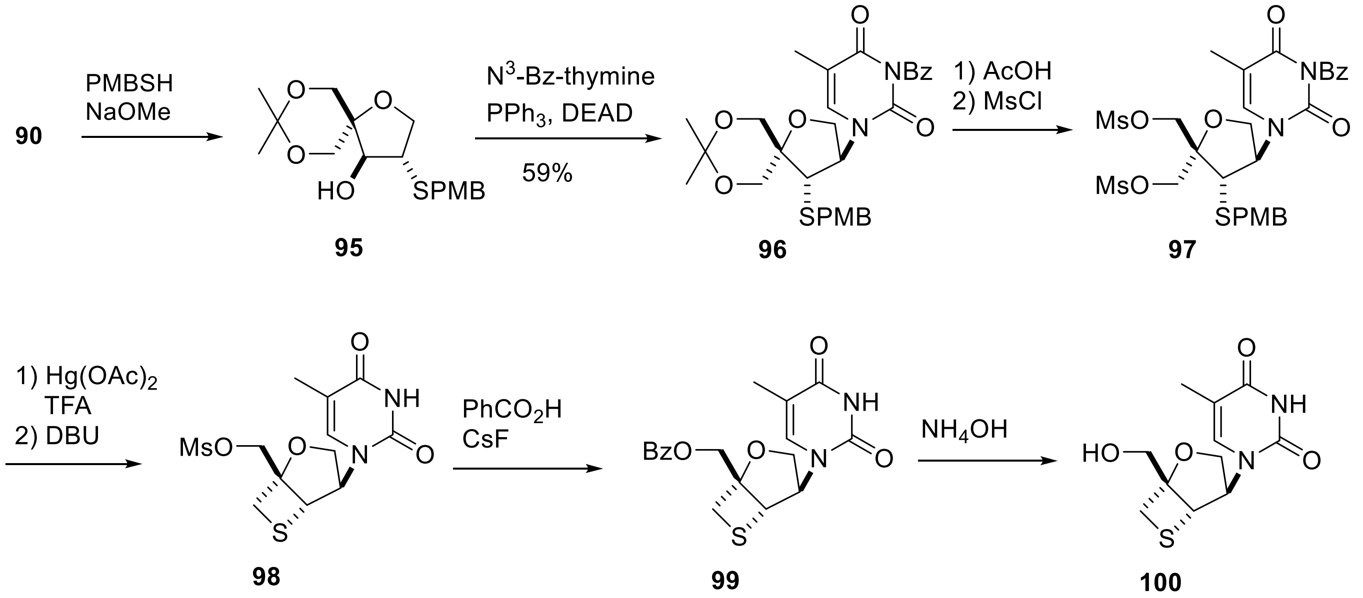


Scheme 10. Strategy for the synthesis of 4'-substituted isonucleosides

The reaction of the dianion of propargyl alcohol and **86** gave diol **87**. Semi-hydrogenation of **87** in the presence of a Lindlar catalyst gave (*Z*)-allyl alcohol derivative **88**. Silylation of the primary alcohol of **88**, followed by treatment with *m*CPBA and desilylation, gave epoxide **89**. Intramolecular etherification of **89** was carried out under Mitsunobu reaction conditions to give the desired dioxabicyclohexane derivative **90**. Cleavage of the epoxide ring of **90** was achieved by treatment with sodium thiophenoxide to give thiophenyl derivative **91** as the sole product. As we expected, the Mitsunobu reaction of **91** with 6-chloropurine in the presence of DEAD and triphenylphosphine proceeded in a regiospecific manner and stereoselectively gave purine isonucleoside derivative **92** in 83% yield. After amination at the 6-position of **92**, desulfurization by radical reduction gave **94**, which was deprotected by acid treatment to give the desired 4'-hydoroxymethyl-iso-ddA **80** (Scheme 11).[46,47]



Scheme 11. Synthesis of 4'-hydoroxymethyl-iso-ddA



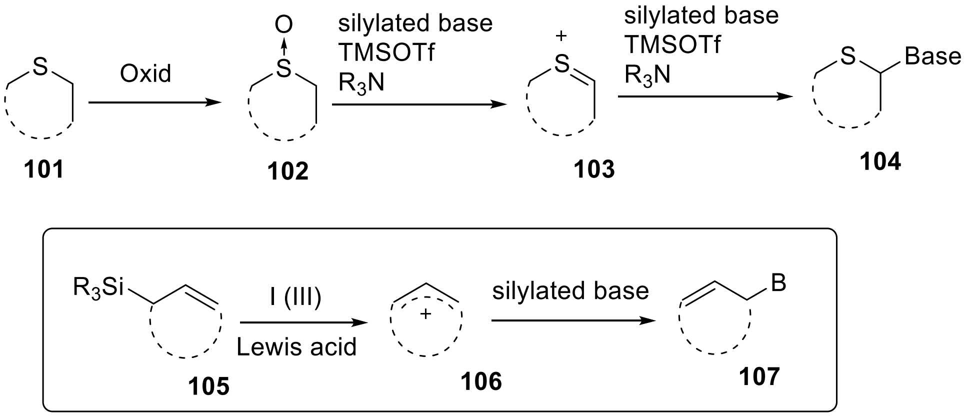
Scheme 12. Synthesis of bicyclo-isonucleoside structurally resembling Lamivudine

Using a similar procedure as that described above, the oxirane ring of **90** was cleaved by treatment with the sodium salt of PMB mercaptan to give PMB sulfide **95** as the sole product. Compound **95** was subjected to the sulfur-assisted Mitsunobu reaction in the presence of *N*^{3}-benzoylthymine to give isothymidine derivative **96** in 59% yield. After removal of the acetal group, followed by mesylation, the PMB group of dimesylate **97** was removed, and the resulting thiol was treated with DBU to give thietane

98. The desired bicylco-isothymidine **100** was synthesized by converting the mesylate moiety to a benzoate moiety via an S_N2 reaction of **98**, followed by treatment with aqueous NH_3 (Scheme 12).[47]

4. DEVELOPEMENT OF AN OXIDATIVE COUPLING REACTION CATALYZED BY HYPAERVALENT IODINE TOWARD THE SYNTHESIS OF CARBOCYCLIC NUCLEOSIDES

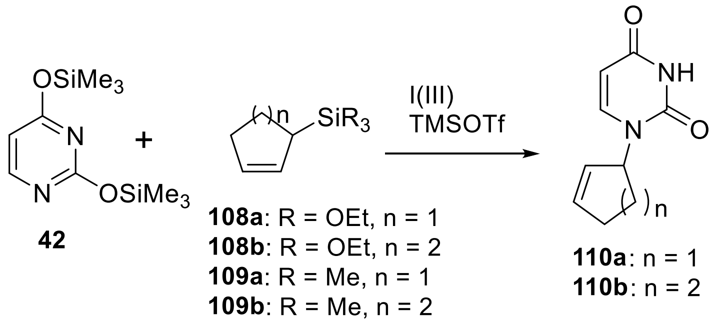
As described above, we developed a Pummerer-type glycosylation reaction, where silylated nucleobases are directly coupled with sulfoxides. Since this glycosylation reaction could be coupled with oxidation, we thought that the reaction was applicable to carbocyclic nucleoside synthesis. In other words, allylsilanes act as a pseudosugar donor for a carbocyclic nucleoside by using a hypervalent iodine reagent.[48] In the Pummerer-type glycosylation, thiosugar donor **101** was oxidized to sulfoxide **102**, the reaction of which was mediated by a Lewis acid (TMSOTf) and a base to give desired thionucleoside **104** via the formation of sulfenium ion **103**. Following the concept of the Pummerer-type glycosylation, the coupling reaction of cyclic allylsilane **105**, a pseudosugar donor for carbocyclic nucleosides **107**, with a persilylated nucleobase was achieved by using hypervalent iodine in the presence of an appropriate Lewis acid (Scheme 13).



Scheme 13. Oxidative coupling reaction for the synthesis of carbocyclic nucleosides

First, model reactions of the oxidative coupling reaction were examined using simple cycloalkenylsilanes **108a,b** and **109a,b**, prepared by hydrosilylation of cyclopentadiene and cyclohexadiene,[49] respectively. The coupling reactions of **108a,b** and **109a,b** with bis(trimethylsilyl)uracil (**42**) in the presence of a hypervalent iodine reagent and TMSOTf were examined, and the results are summarized in Scheme 14 and Table 1. The reactions of allylsilane **108a** and **108b** with **42** in the presence of (diacetoxyiodo)benzene ($PhI(OAc)_2$) gave cycloalkenyluracil **110a** and **110b** in moderate yields (entries 1 and 2, respectively). Treatment of **109a** and **109b** under the same conditions gave **110a** and **110b** in 65%

yield (entries 3 and 4, respectively). The use of [di(trifluoroacetoxy)iodo]benzene ($PhI(O_2CCF_3)_2$ (entry 5) and iodosobenzene (PhIO) (entry 6) slightly decreased the reaction yields. On the other hand, the reaction using [hydroxy(tosyloxy)iodo]benzene (PHI(OH)OTs) gave **110b** in a poor yield (entry 7).[50]

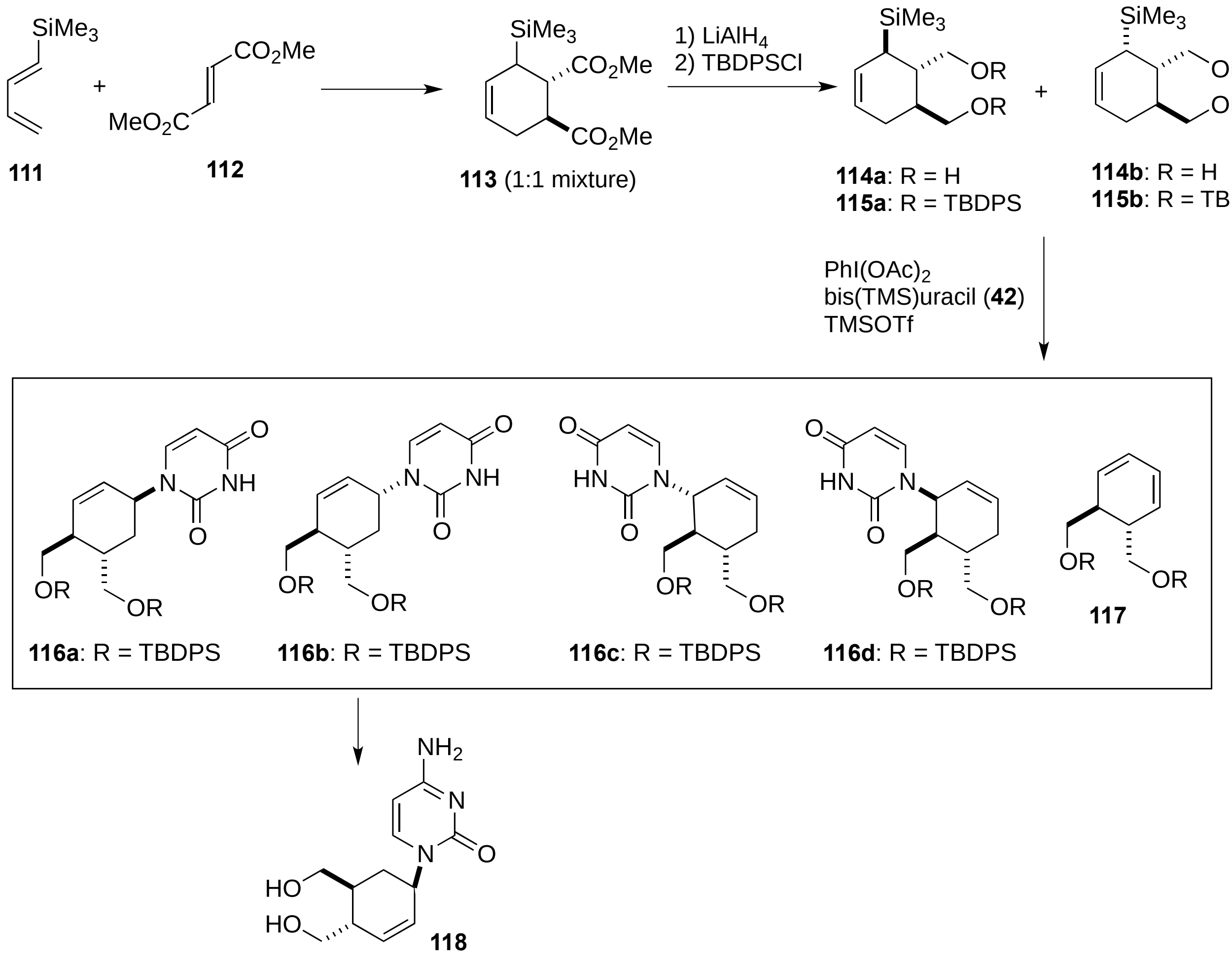


Scheme 14. Oxidative coupling reaction of cyclic allylsilanes and persilylated uracil

Table 1. Summary of the oxidative coupling reaction of cyclic allylsilanes **108** and **109** and persilylated uracil

entry	comp	I(III)	time (h)	yield (%)
1	**108a**	$PhI(OAc)_2$	15	45
2	**108b**	$PhI(OAc)_2$	15	49
3	**109a**	$PhI(OAc)_2$	1	65
4	**109b**	$PhI(OAc)_2$	1	65
5	**109b**	$PhI(O_2CCF_3)_2$	1	55
6	**109b**	PhIO	1	57
7	**109b**	PhI(OH)OTs	1	29

The developed oxidative coupling reaction was applied to the synthesis of new carbocyclic nucleoside derivatives **118**, designed as potential anti-HIV agents. The Diels-Alder reaction of trimethylsilylbutadiene **111** and dimethyl fumarate (**112**) gave cyclohexene diester **113** as a 1:1 mixture.[51] Hydride reduction of **113** and subsequent separation by silica gel column chromatography gave **114a**,**b**, which were protected by the silyl group to give di-*O*-TBDPS derivatives **115a** and **115b**. The coupling reaction of **115a** and **115b** with persilylated uracil **42** was performed by using (diacetoxyiodo)benzene as an oxidant. The results are shown in Table 2. Since the reaction proceeds via an allyl cation, the reaction of **115a** gave an inseparable mixture containing 4 stereoisomers of **116a–d** in a ratio of 6:10:2:1.5, estimated from the ^{1}H NMR spectrum of the reaction mixture, and the reaction of **115b** gave similar results.[50] Cyclohexadiene **117**, obtained in both cases, was consistent with the proposed reaction mechanism shown above and was formed via an E1 elimination of the allyl cation intermediate. The different reactivities of **115a** and **115b** were explained by steric interaction of the substituents on the cyclohexene ring with the approaching nucleobase (Scheme 15 and Table 2).



Scheme 15. Synthesis of carbocyclic nucleosides using oxidative coupling reaction

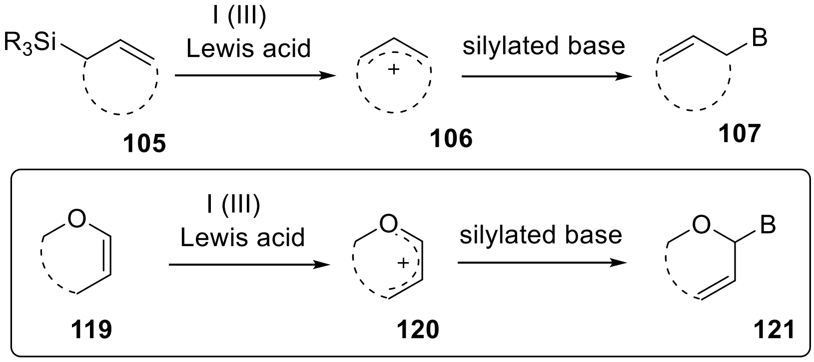
Table 2. Summary of the oxidative coupling reaction of cyclic cyclohexenylsilanes **115a**,**b** and uracil

comp	time (h)	yield (%)			ratio
		116a-d	**117**	recov.	**116a**:**116b**:**116c**:**116d**
115a	1	60	18	0	6:10:2.0:1.5
115b	24	50	11	20	3:10:2.5:0.5

During the conversion of **116a–d** to cytosine analogues by the same procedure described above, all the stereoisomers were separated. Among them, cytosine derivative **118** only showed weak anti-HIV activity.[50]

5. APPLICATION OF HYPERVALENT IODINE CHEMISTRY TO THE SYNTHESIS OF DIHYDROPYRANONUCLEOSIDES

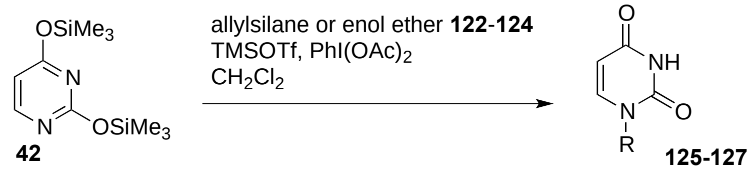
We developed a hypervalent iodine-catalyzed reaction for condensing bases and pseudosugars to form the skeleton of carbocyclic nucleosides. The success of the oxidative coupling reaction led us to develop a glycosylation reaction applicable to another sugar donor, i.e., a glycal. The direct coupling of glycals with nucleobases is challenging since it is formally a C-N bond forming reaction with cleavage of an inactive C-H bond. Similar C-N bond forming reactions have been extensively studied in the field of hypervalent iodine chemistry.[52] The hypervalent iodine-catalyzed coupling reaction occurs via two steps: 1) the generation of carbocation **106** by the oxidative reaction of allylsilane **105** with $PhI(OAc)_2$ and TMSOTf, followed by 2) the addition of a persilylated base, as shown in Scheme 16. We thought that the reaction of electron-rich glycal **119** under the oxidation conditions described above generated oxocarbenium ion **120**, which would serve as an intermediate to give nucleoside **121** (Scheme 16).



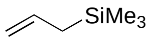
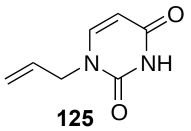
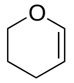
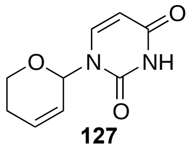
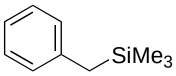
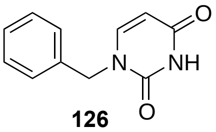
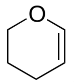
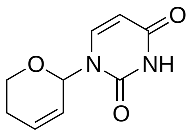
Scheme 16. Oxidative coupling reaction of glycals using hypervalent iodine

First, we performed model reactions of the oxidative coupling of an allylsilane or enol ether using the $TMSOTf/PhI(OAc)_2$ system. The reaction of allyltrimethylsilane **122** gave 1-allyluracil **125** in 69% yield by treatment with 1 equiv of $PhI(OAc)_2$, TMSOTf, and **42** in dichloromethane (entry 1 in Table 3). Although the same reaction was applied to benzyltrimethylsilane **123**, the desired product **126** did not form (entry 2). Next, we tried the reaction with 3,4-dihydro-2*H*-pyran (**124**). The conditions for the reaction involving **124** needed to be optimized. After several attempts, it was found that dihydropyranyluracil derivative **127** was obtained in 31% yield when **124** was treated under the conditions labeled method A (entry 3). $Cu(OTf)_2$ could also catalyze the reaction, and the reaction of **124** with 0.2 equiv of $Cu(OTf)_2$ at room temperature (method B) gave **127** in 24% yield (entry 4).[53]

Table 3. Summary of the oxidative coupling of bis(TMS)uracil **42** with allylsilanes and enol ethers



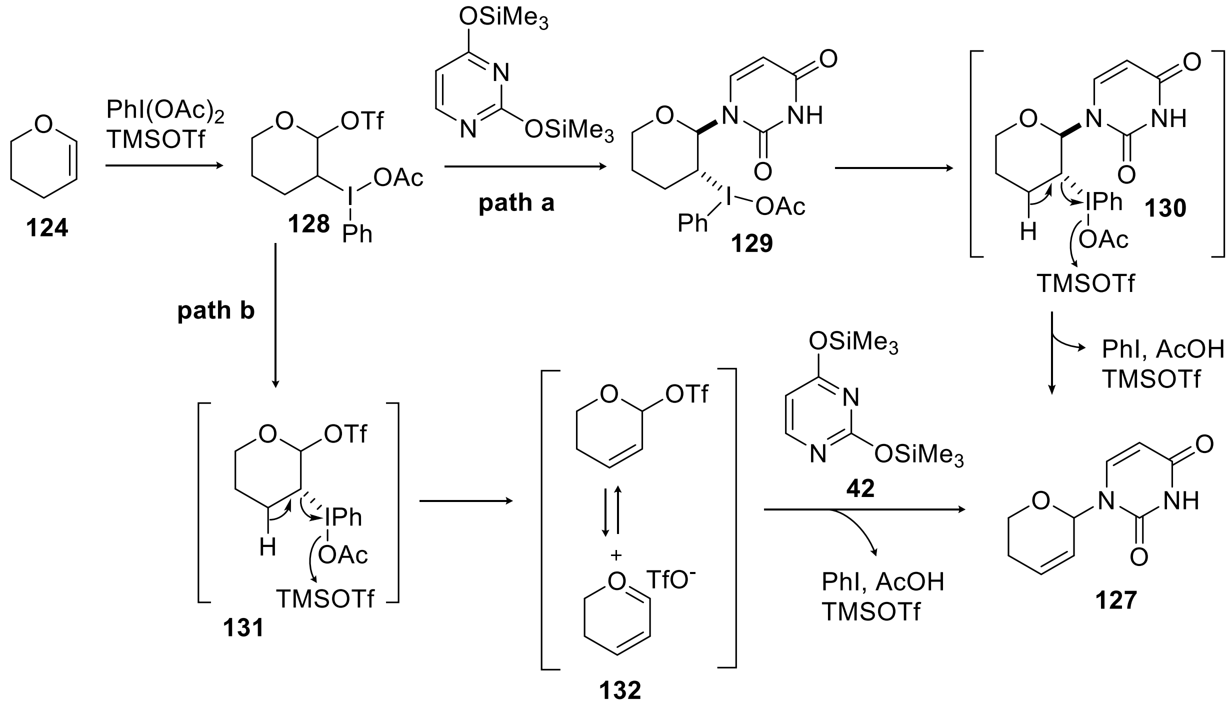
42 **125-127**

entry	comp	product	yield	entry	comp	product	yield
1	 **122**	 **125**	69%	3	 **124**	 **127**	31% (method A)
2	 **123**	 **126**	ND	4	 **124**	 **127**	24% (method B)

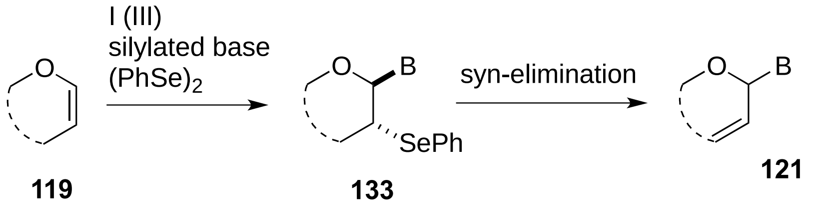
Method A: PhI(OAc)$_2$ (1.5 equiv), TMSOTf (0.4 equiv), and **2** (2.0 equiv) from −40 °C to rt.
Method B: PhI(OAc)$_2$ (1.5 equiv), Cu(OTf)$_2$ (0.2 equiv), and **2** (2.0 equiv) at rt.

A possible reaction mechanism for the oxidative coupling reaction is shown in Scheme 17. When dihydropyran **124** was reacted with PhI(OAc)$_2$, acetoxyiodobenzene derivative **128** formed first upon reaction with TMSOTf. There are two plausible reaction paths from intermediate **128** to the *N*^{1}-substituted uracil **127**: nucleophilic attack of bis(TMS)uracil **42** occurs prior to elimination (path a), and an allylic carbocation **132** formed from **131** reacts with **42** (path b). In the reaction with dihydrofuran, side products generated from intermediate **130** were isolated (data not shown). The results strongly suggest that path a occurs more than path b does (Scheme 17).

It was impossible to optimize the oxidative coupling reaction further. To improve the reaction yield of the oxidative coupling reaction, we examined the use of a co-catalyst. The proposed reaction mechanism described above suggested that the instability of intermediate **128** caused the low yield. Therefore, we used (PhSe)$_2$ as a co-catalyst, which should prevent the formation of unstable **128**, to obtain **121** in one step (Scheme 18).



Scheme 17. A proposed reaction mechanism for the oxidative coupling of 3,4-dihydro-2*H*-pyran **124** with TMSOTf/PhI(OAc)$_2$

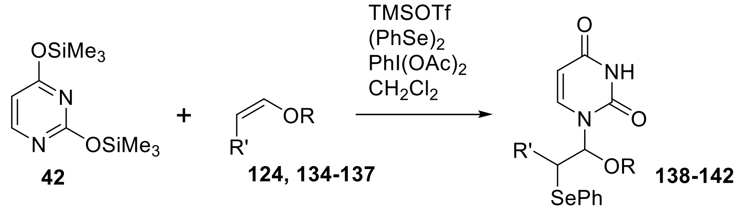


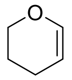
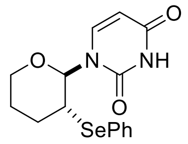
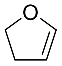
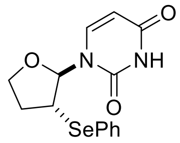
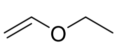
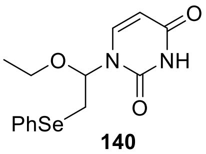
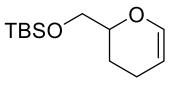
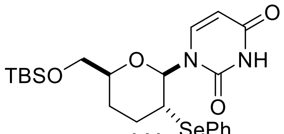
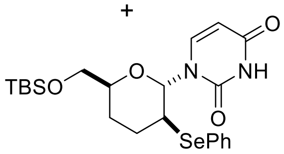
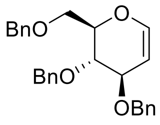
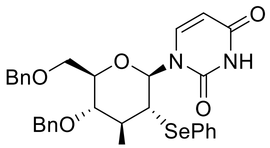
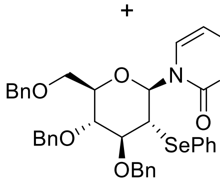
Scheme 18. Synthesis of 1-(3-phenylselanyltetrahydropyran-2-yl)uracil **121** using a co-catalyst

When **124** and **42** were treated with PhI(OAc)$_2$ and (PhSe)$_2$ in the presence of catalytic amounts of TMSOTf, the trans-isomer of 1-(3-phenylselanyltetrahydropyran-2-yl)uracil **138** was selectively obtained, as depicted in entry 1 of Table 4. Although the results were different from those expected, they suggested that the reaction could be used to obtain 2'-deoxynucleosides as well as dideoxydidehydronucleosides. Moreover, by using the conditions mentioned above, we avoided the use of an unstable reagent, like PhSeBr, to obtain 2'-phenylselanyl nucleoside derivatives.

The oxidative coupling reaction of **42** with enol ethers and glycals using the TMSOTf/PhI(OAc)$_2$/(PhSe)$_2$ system were performed, and the results are summarized in Table 4.

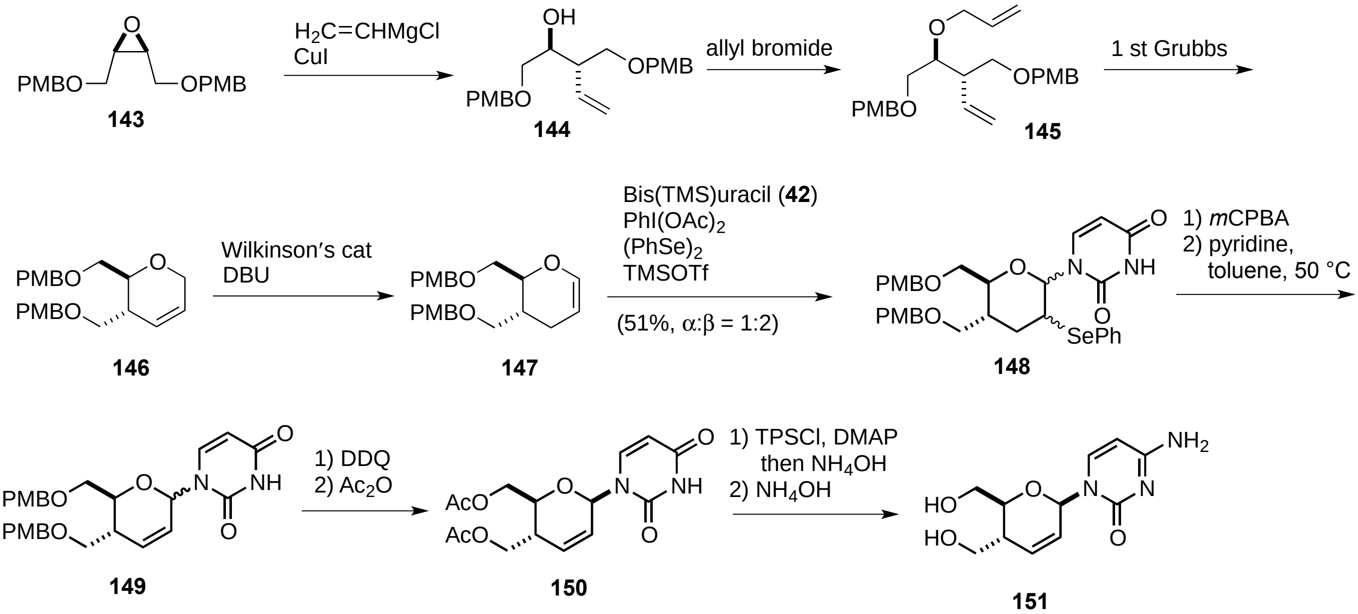
Table 4. Summary of the oxidative coupling reaction of bis(TMS)uracil **42** with enol ethers using the TMSOTf/PhI(OAc)$_2$/(PhSe)$_2$ system



entry	enol ether	product	yield
1	 **124**	 **138**	73%
2	 **134**	 **139**	31%
3	 **135**	 **140**	69%
4	 **136**	 β-**141** +  α-**141**	80% (α:β = 1:2)
5	 **137**	 β-**142** +  α-**142**	64% (α:β = 1:1)

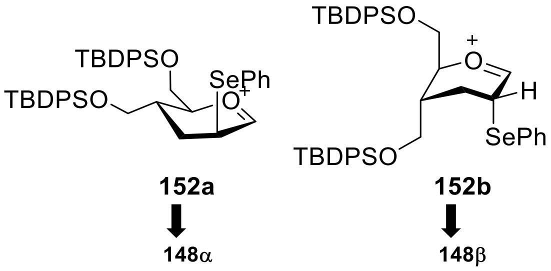
The reaction with **134** afforded 1-(3-phenylselanyltetrahydrofuran-2-yl)uracil **139** in 31% yield (entry 2). The reaction of **135** with **42** at −5 °C afforded **140** in 69% yield (entry 3). The reaction involving **136** gave α-**141** and β-**141** in 80% yield with the β-nucleoside as the major product (entry 4). On the other hand, the oxidative glycosylation reaction of D-glucal **137** gave a mixture of α-**142** and β-**142** in 64% yield without stereoselectivity (entry 5). The oxidative coupling reaction of glycal derivatives, like **136** and **137**, is a new glycosylation reaction, by which 2'-deoxy- and 2',3'-dideoxydidehydronucleosides can be accessed (Table 4).[53]

As part of our studies on SAR of nucleoside derivatives constructed on a 6-membered pseudosugar, like dihydrothiophenonucleoside **72** and carbocyclic nucleoside **118**, we designed the synthesis of a dihydropyranonucleoside by using the oxidative coupling reaction described above.[54] PMB-protected epoxide **143** was treated with vinylmagnesium chloride to give homoallyl alcohol derivative **144**, the hydroxyl group of which was then allylated to give diene **145**. To construct the dihydropyran ring, RCM of **145** catalyzed with the first generation Grubbs catalyst[55] was performed to give dihydropyran derivative **146**. Isomerization of the double bond in **146** was achieved by treatment with a Wilkinson catalyst under basic conditions[56] to afford glycal **147** (Scheme 19).



Scheme 19. Synthesis of dihydropyranonucleoside

Oxidative glycosylation of bis(trimethylsilyl)uracil (**42**) and glycal **147** gave an inseparable mixture of α- and β-anomers of **148** (α:β = 1:2) in 51% yield. Steric repulsion and dipole interactions between two siloxymethyl substituents should favor the formation of the all axial-substituted carbocation intermediate **152b** having a structure similar to the carbocation generated from conformationally "super armed glycosyl donor".[57] As a result, the β-anomer **148β** should predominantly form (Scheme 20).



Scheme 20. Possible carbocation intermediates **152a** and **152b**

Compound **148** was oxidized by treatment with *m*CPBA to give the corresponding selenoxides. An elimination reaction of the resulting selenoxides without any purification gave **149**. Then the PMB group of **149** was deprotected by treatment with DDQ to give a mixture of free nucleosides. After acetylation of the products, an anomeric mixture of diacetates **150** was separated by using simple silica gel column chromatography. The major β-anomer of **150** was converted into a cytosine derivative, followed by deprotection, to give the desired dihydropyranylcytosine derivative **151**.[54] Antiviral evaluations of the final compound revealed that **151** did not show any activity against HIV though its 5'-thio counterpart **72** showed anti-HIV activity (Scheme 19).[54]

6. CONCLUSION

We synthesized many structurally unique nucleoside derivatives by using new glycosylation reactions. Our early products were 4'-thioDMDC and 4'-thioisonucleoside, for which we developed the Pummerer-type glycosylation. In the case of isonucleosides, a sulfur-assisted Mitsunobu reaction was developed and applied to construct the glycosidic bond of bicyclic isonucleosides, which have structures similar to that of Lamivudine. The Pummerer-type glycosylation, on the other hand, was efficiently applied to synthesize dihydrothiopyranonucleosides. As can be seen, the Pummerer-type glycosylation included oxidation of a sulfide to the corresponding sulfoxide, followed by a TMSOTf-mediated coupling reaction. Considering the Pummerer-type glycosylation, a new glycosylation reaction for carbocyclic nucleosides using allylsilane derivatives and hypervalent iodine was developed to synthesize cyclohexenylnucleosides. In the glycosylation reaction, hypervalent iodine chemistry was applied to build a glycosyl bond between nucleobases and glycal derivatives. This new method was employed for the synthesis of dihydropyranonucleosides. From our synthetic studies on nucleoside derivatives, we found many biologically interesting nucleosides active against tumors as well as viruses. The results prove the power of glycoside bond forming reactions toward the synthesis of and search for biologically active nucleoside derivatives.

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