Review

Fine Synthetic Nucleoside Chemistry Based on Nucleoside Natural Products Synthesis

Satoshi ICHIKAWA

Graduate School of Pharmaceutical Sciences, Hokkaido University; Kita 12, Nishi 6, Kita-ku, Sapporo 060–0812, Japan.

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Synthetic nucleoside chemistry based on nucleoside natural products synthesis were described. First, a samarium diiodide (SmI_2)-promoted aldol reaction with the use of α-phenylthioketone as an enolate was developed. The characteristics of this reaction are that the enolate can be regioselectively generated and the aldol reaction proceeds under near neutral condition. This reaction is proved to be a powerful reaction for the synthesis of complex nucleoside natural products, and herbicidin B and fully protected tunicaminyluracil, which were undecose nucleoside natural products, were synthesized. Next, the synthetic methodology of the caprazamycins, which are promising antibacterial nucleoside natural products, was also developed by the strategy including β-selective ribosylation without using a neighboring group participation. Our synthetic route provided a range of key analogues with partial structures to define the pharmacophore. Simplification of the caprazamycins was further pursued to develop diketopiperazine analogs.

Key words nucleoside natural product; aldol reaction; ribosylation; structure–activity relationship; anti-tuberculosis; antibacterial

Introduction

Nucleosides and nucleotides are one of the most important elements for cells. In adition to that they are a component of DNAs and RNAs, and they play important and various roles in most fundamental cellular metabolic pathways such as metabolite carriers, energy donors, second messengers, cofactors for various enzymes, and carriers for post-translational modifications such as methylation and glycosylation. Therefore, there exists a rich source in drug discovery targeting nucleosides and nucleotides. Nucleoside natural products are found as diverse groups of secondary metabolites of microbial organism.[1—6] They include a variety of structural modifications of nucleosides and nucleotides, often leading to complex structure. Reflecting the inherent manifold roles of nucleosides and nucleotides, biological activities of nucleoside natural products are also wide ranging, including antibacterial, antifungal, antitumor, antiviral, herbicidal, and insecticidal properties. Thus, they are promising leads for drug development.

Some of nucleoside natural products include sensitive functionality as well as complex structures and they are also challenging synthetic targets for organic chemists.[7] In order to exploit nucleoside antibiotics as drug candidates development of the efficient synthetic method should be neccesary to provide a range of analogs to pursue a structure–activity relationship and simplification of the parent molecules. In many cases, these nucleoside natural products contain modified sugar moiety. There are two methodologies to synthesize modified sugar nucleosides: (1) preparation of a modified sugar followed by introduction of a nucleobase *via* glycosidation and (2) direct modification of nucleosides. Because the preparation of the modified sugars requires many reaction steps and the stereoselective introduction or construction of the nucleobase is tedious, it is natural that the latter method is more efficient. However, nucleobases, which inherently have a Lewis basic character, sometime limit the use of reagent, and the intermediate nucleoside such as the 2′ or 3′-keto or 5′-aldehyde derivative are less stable under conditions where the corresponding sugar derivatives are stable enough to be utilized as a reaction substrate. Thus, it is very important to develop reactions and methods, by which the highly coordinating and labile nucleoside intermediates can be used. With these in mind, we have been working on synthetic nucleoside chemistry based on nucleoside natural products, which is described in this review.

1. Synthesis of Branched-Sugar Nucleosides by Samarium Diiodide (SmI_2) Chemistry

1.1. Synthesis of 3′-β-Branched-Sugar Nucleoside Derivatives[8,9] Considerable attention has been focused on branched chain sugar nucleosides because of their biological importance. During the course of synthetic studies aiming to develop antitumor agents, our group has found that branched-chain sugar nucleosides[10—16] are promising antitumor drug candidates[17] such as 1-(2-deoxy-2-methylene-β-D-*erythro*-pentofuranosyl)cytosine[18—21] (DMDC, Fig. 1, **1**) and 1-(2-*C*-cyano-2-deoxy-β-D-*arabino*-pentofuranosyl)cytosine[22—27] (CNDAC, **2**). Among them, 3′-β-branched chain sugar nucleoside 1-(3-*C*-ethynyl-β-D-*ribo*-pentofuranosyl)-uracil (ECyd, **3**) has a remarkable antitumor activity both *in vitro* and *in vivo* and is under phase I clinical trial.[28—32] Although there have also been several studies on 3′-β-branched

e-mail: ichikawa@pharm.hokudai.ac.jp

chain sugar nucleosides,[33—43] only a few 3′-β-branched ribonucleoside analogs, with both a hydroxyl group at the 3′-α-position and a carbon-substituent at the 3′-β-position, have been reported, and their biological activities have not been investigated in detail. This may be because efficient synthetic methods for preparing these 3′-β-branched ribonucleoside analogs have not been developed. Therefore, to examine the biological effects of various 3′-β-branched ribonucleoside analogs, the development of more straightforward methods for their preparation is needed. It has been recognized that addition of carbon nucleophiles to 3′-ketonucleosides proceed with high stereoselectivity from the Re-face to give the corresponding 3′-β-branched xylonucleoside analogs.[35,37] 3′-Ketonucleosides are also known to be unstable, especially under basic conditions. Over the past decade, it has been shown that samarium diiodide (SmI_2) can be used as an efficient electron-transfer reagent in a variety of transformations in organic chemistry due to its functional- and stereoselectivity.[44—52] The reaction conditions using SmI_2 are very mild, and it is suitable for the reactions using unstable 3′-ketonucleosides as a substrate. These prompted us to explore a new method for producing 3′-β-branched ribonucleoside analogs (Fig. 2, **4**—**7**) *via* the SmI_2-promoted intramolecular Reformatsky-type reaction of 3′-ketonucleoside derivatives (Chart 1, **9a** or **9b**).

Synthesis of the target 3′-β-branched ribonucleoside analogs is shown in Chart 1. The 3′-ketonucleoside derivatives (**9a**, **9b**), substrates for the intramolecular Reformatsky-type reaction, was prepared from uridine in 4 or 5 steps in good yields. First, 5′-*O*-bromoacetyl-3′-ketouridine derivative **9b**, which is protected with benzyloxymethyl (BOM) group at the *N*-3 position, was treated with 2.0 eq of SmI_2 in THF at room temperature, and the Reformatsky-type reaction proceeded effectively to give the desired lactone **10b** in 71% yield (Table 1, entry 1). On the other hand, reaction of **9b** with zinc as a reductant in toluene did not give **10b**. When **9b** was treated with 2.0 eq of SmI_2 at −78 °C in THF, the reaction proceeded cleanly to give the lactone **10b** in 85% yield (Table 1, entry 2). We also examined the intramolecular Reformatsky-type reaction of base moiety-unprotected uridine derivative **9a**. Treatment of **9a** with 2.0 eq of SmI_2 at −78 °C in THF gave lactone **10a** in 65% yield and the reduced product, 5′-*O*-acetyl derivative **16**, was also obtained in 18% yield (Table 1, entry 3). Lactone **10a** was obtained in

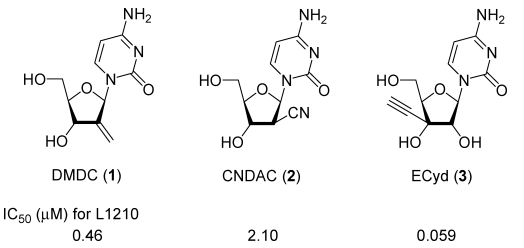


Fig. 1. Structures of Branched-Chain Nucleosides Exhibiting Antitumor Activity

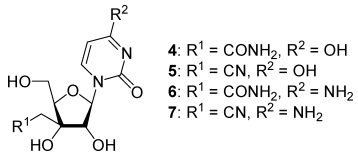
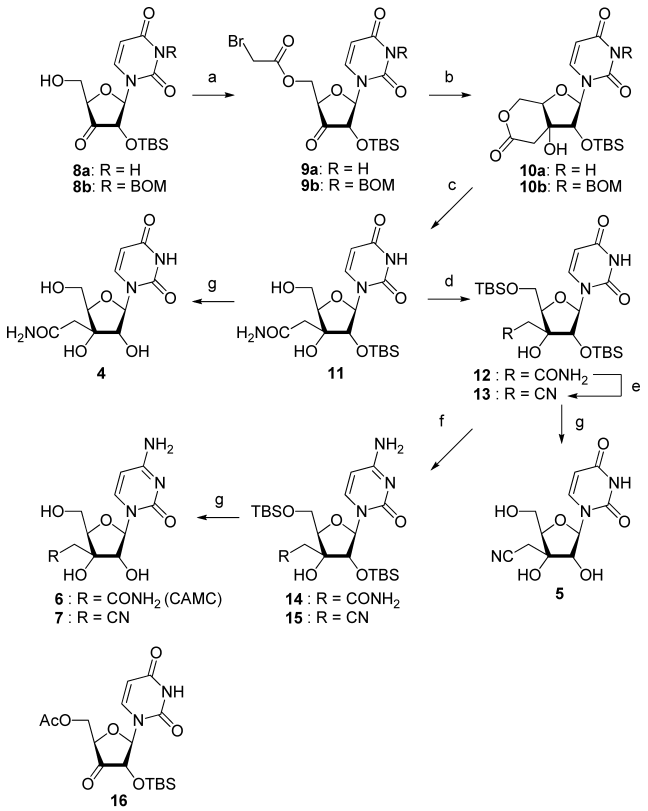


Fig. 2. Structures of Target 3′-β-Branched Ribonucleosides



Reagents and conditions: (a) $BrCH_2COBr$, CH_2Cl_2 -78 °C (70%); (b) see table 1; (c) NH_3/MeOH, −70 °C (98%); (d) TBSCl, imidazole, DMF, room temperature (99%); (e) TsCl, pyridine, reflux (81%); (f) TPSCl, DMAP, Et_3N, MeCN, room temperature, then NH_4OH (76% for **14**, 99% for **15**); (g) NH_4F, MeOH (99% for **4**, 99% for **5**, 79% for **6**, 99% for **7**).

Chart 1

Satoshi Ichikawa was born in 1971 in Hokkaido. He received his BSc. (1994), M.Sc. (1996), and Ph.D. (1999) degrees from the Faculty of Pharmaceutical Sciences at Hokkaido University, Japan, under the direction of Professor A. Matsuda. He spent 2 years (1999—2001) undertaking postdoctoral studies at The Scripps Research Institute, California, U.S.A. under the direction of Professor Dale L. Boger. Since 2001, he has been as an assistant professor at the Graduate School of Pharmaceutical Sciences, Hokkaido University, Japan. He received the Pharmaceutical Society of Japan Award for a Young Chemist in 2008. His current research interests include synthetic organic chemistry and medicinal chemistry.

Satoshi Ichikawa

Table 1. Intramolecular Reformatsky-Type Reaction of **9** Promoted by SmI_2

Entry	Substrate	Temp. (°C)	Products (yield, %)
1	**9b**	rt	**10b** (71%)
2	**9b**	−78	**10b** (85%)
3[a)]	**9a**	−78	**10a** (65%), **16** (18%)
4[b)]	**9a**	−78	**10a** (85%), **16** (trace)

a) A solution of SmI_2 in THF was added to a solution of **9a** in THF. *b*) A solution of **9a** in THF was added to a solution of SmI_2 in THF. rt: room temperature.

Table 2. Growth Inhibitory Effects of 3′-β-Branched Nucleosides against L1210 and KB Cells[a)]

	IC_{50} (mM)	
	L1210	KB
4	>100	>100
5	>100	>100
6 (CAMC)	0.33	5.61
7	74	>100
14	43	>100

a) IC_{50} (μM) was given as a concentration of 50% inhibiton of cell growth.

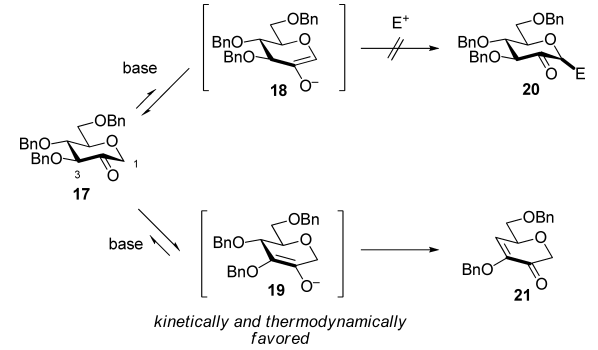


Chart 2

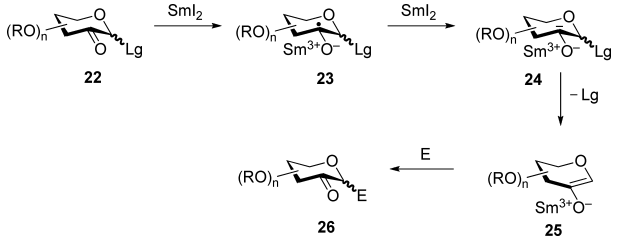


Chart 3

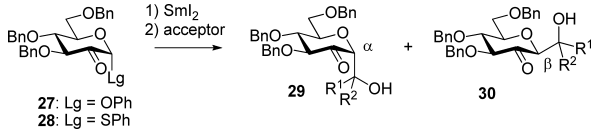


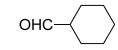
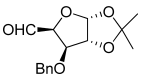
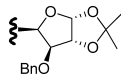
Chart 4

85% yield as a sole product when a solution of **9a** in THF was added slowly to a SmI_2 solution in THF at −78 °C (entry 4). To our knowledge, this is the first example of the efficient use of a SmI_2-mediated *C–C* bond formation reaction in nucleoside chemistry.[8)] This method enabled us to prepare a range of analogs **4**—**7** according to Chart 1, and 3′-β-carbamoylmethylcytidine (CAMC, **6**) was found to exhibit potent cytotoxicity against various human tumor cell lines (Table 2). Most of the nucleoside antitumor agents have to be phosphorylated at the 5′-hydroxyl group by a nucleoside kinase to show cytotoxic activity. Interestingly, the tumor cell growth inhibitory activity of CAMC (**6**) was not reduced in the presence of the nucleosides, including cytidine. Since the phosphorylation of these natural nucleosides by certain nucleoside and/or nucleotide kinases would be competitive with that of CAMC (**6**), the cytotoxicity should be largely reduced if CAMC (**6**) required phosphorylation to show cytotoxicity. This suggests that CAMC possesses a unique property to exhibit growth inhibitory activity without phosphorylation of the 5′-hydroxyl group. This study provides a novel strategy for the development of a new type of antitumor nucleoside.[9)]

1.2. Development of SmI_2-Promoted Aldol Reaction[53)] Since we realized that SmI_2 is a suitable reagent for the *C–C* bond formation in nucleoside chemistry, we pursued to develop the SmI_2-promoted *C*-glycosidation, which can be applicable to the synthesis of nucleoside antibiotics. Aldol-type reactions, which are some of the most effective methods for forming *C–C* bonds, have also been investigated for the formation of a *C*-glycosidic linkage; in these cases, 1-deoxygluco-2-uloses or 2-ulosyl-l-bromides[54,55)] were used as precursors for generating 1-enolates.[56—58)] However, the yields of *C*-glycosides were insufficient, and problems remained; as shown in Chart 2, the former gave undesirable enolization at the 3-position of uloses to give **19**, and in the latter case the precursors were significantly unstable. SmI_2 can reduce functional groups such as hydroxy, acetoxy, and alkoxy groups when a carbonyl group is present at the α-position of these functional groups, and the generation of samarium enolates as intermediates is presumed to occur during the reaction course.[59,60)] Accordingly, an aldol-type reaction may proceed if an electrophile is present in the reaction system (Chart 3). Therefore, we expected that a 1-enolate **25** would be generated regioselectively if 1-*O*- or 1-*S*-glycoside of 2-ulose **22** was treated with SmI_2, and that this could be added to a carbonyl group of ketones or aldehydes to give the corresponding *C*-glycoside **26**.

First, the reaction was carried out with cyclohexanone as an electrophilic acceptor (Chart 4). A solution of the substrate **27** or **28**, in THF was added dropwise to a stirred solution of SmI_2 (2.0 eq) in THF at room temperature. Cyclohexanone (1.1 eq) was then added, and the mixture was stirred at room temperature. *O*-Glycoside **27** did not react at all with cyclohexanone under these reaction conditions (Table 3, entry 1). On the other hand, *S*-glycoside **28** reacted rapidly to give the desired *C*-glycosides **29** and **30** in 19% yield as an anomeric mixture (entry 2, α/β=55/45). When the reaction with **28** was performed at −78 °C, the yield of *C*-glycosides **29** and **30** significantly increased to 87% (entry 3). Under these conditions, the stereoselectivity also improved (α/β=79/21); the axial approach of cyclohexanone to the α-face of the Sm(III) enolate may be favored by a stereoelectronic effect due to the pyranose ring oxygen. Reactions with **28** were also performed in the presence of an additive such as HMPA or TMEDA, which should enhance the ability of SmI_2 to transfer electrons. However, these reactions did not give the *C*-glycosides at all, and homocoupling product was obtained as a sole product in both cases. We also exam-

Table 3. Aldol Reaction Promoted by SmI_2

Entry	Substrate	Temp. (°C)	Acceptor	R^1	R^2	Yield (%)	Ratio (**29**/**30**)
1	**27**	rt				—	—
2	**28**	rt				19	55/45
3	**28**	−78				87	79/21
4	**28**	−78		Et	Et	88	>90/10
5	**28**	−78		H		76	>90/10
6	**28**	−78		H		73	>90/10

ined the reaction with several other carbonyl compounds as electrophilic acceptors including 5-aldehyde derivative of xylofuranose (entries 4—6). All of the reactions proceeded effectively and gave the corresponding α-*C*-glycoside selectively. These α-*C*-glycosides are the single diastereomer. Characteristics of this reaction are 1) a precursor for the ulose-1-enolate is stable and easily prepared, 2) the ulose-1-enolate is regioselectively generated, and 3) the reaction proceeds under mild conditions, which are suitable for the use of the sensitive intermediate nucleoside such as the 2′ or 3′-keto or 5′-aldehyde derivative as a reaction substrate.

1.3. Total Synthesis of Herbicidin B[61,62] Herbicidins (Fig. 3, **31**) were isolated from *Streptomyces Saganonensis* in 1976.[63—67] They inhibit the growth of *Xanthomonas oryzae*, which causes rice leaf blight. These compounds have some interesting structural features; the sugar moeiety is an unusual undecose constructing a tricyclic structure including the internal hemiketal linkage and all the substituents on it are installed in axial orientations. Because of their unique and complex structures, considerable efforts have been devoted to the total synthesis, however, none of these attempts had been yet successful.[68—75] Having established the SmI_2-promoted aldol reaction, we planned to synthesize herbicidin B by the aldol reaction between 1-phenylthio-2-urose derivative **32** and xyloadenosine-5′-aldehyde derivative **34** (Chart 5). Since this reaction proceeds under neutral condition, it was expected to be suitable for the use of the sensitive substrates such as **34**.

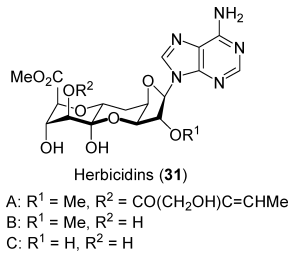
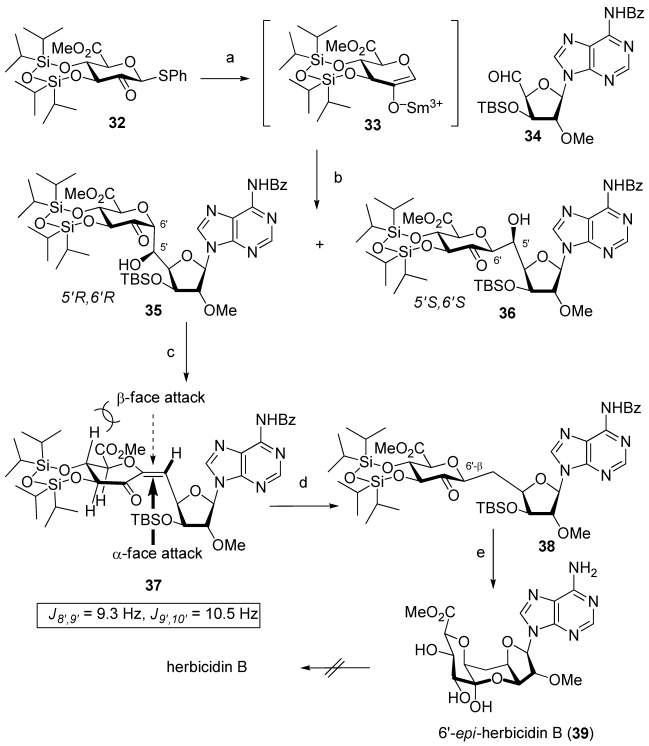


Fig. 3. Structure of Herbicidins



Reagents and conditions: (a) SmI_2, THF, −78 °C, then **34** (75%, **35**/**36** = 79/21); (b) Bergess salt, toluene (49%); (c) H_2, Pd/C, AcOEt (quant); (d) Sm I_2, MeOH (47%); (e) TBAF, THF (71%).

Chart 5

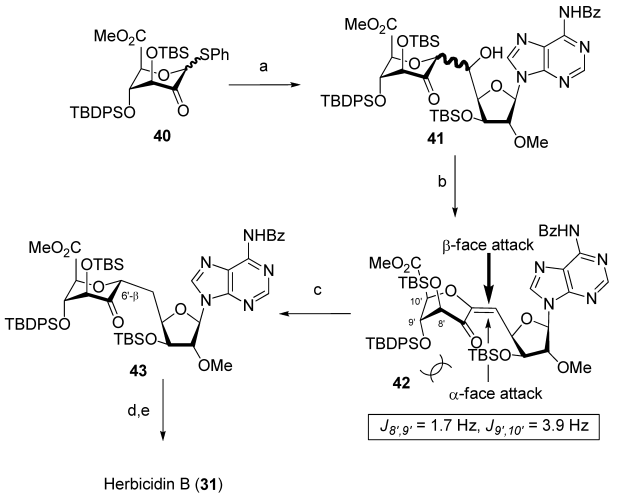
1-Phenylthio-2-urose protected with TIPDS group **32** was prepared from D-glucuronolactone for 10 steps. This compound was treated with 2 eq of SmI_2 in THF at −78 °C, which was followed by the addition of a xyloadenosine 5′-aldehyde derivative **34**. The aldol products **35** and **36** were successufully obtained in 75% yield as a mixture of products, among which the desired 6′*S* product **35** was the major diastereomer. Dehydration of aldol product **35** with Bergess salt[76] followed by catalytic hydrogenation provided 6′-β-compound **38**. Deprotection of the benzoyl group and silyl groups resulted in spotaneous cyclization to afford tricyclic nucleoside **39**. However, only the epimer at the 6′-position of herbicidin B was obtained. All our attempts to epimerize to herbicidin B were unsuccessful. ^{1}H-NMR analysis suggested that the conformation of the enone **37** preferentially adopts a half-boat conformation ($J_{8',9'}$=9.3 Hz, $J_{9',10'}$=10.5 Hz). Since hydrogenation from β-face of the alkenly bond would be disfavored due to the steric repulsion for the 9′-axial proton, α-face attack proceeded to give the undesired diastereomer **37**. We recognized that it would be essential to provide the 6′-α-stereochemistry before the cyclization.

We planned to apply the conformation flip strategy[77,78] to reverse the stereoselectivity of the hydrogenation. Namely,

hygrogenation of the substrate preferetially with a flipped conformation such as **42** might proceed from the β-face, due to the steric repulsion for the axial substituent at 9′-position when the hydrogenation proceeds from the α-face (Chart 6). Thus, we made a screening of enones protected with bulky silyl groups at 8′ and 9′-hydroxyl groups. Small coupling constants between H-8′,9′ and H-9′,10′ in the ^{1}H-NMR spectra ($J_{8',9'}=1.7$ Hz, $J_{9',10'}=3.9$ Hz) indicated that enone **42** preferentially adoped flipped conformation. Hydrogenation of **42** afforded the desired 6′-α-product **43**, a two step-deprotection sequences of which successfully afforded herbicidin B (**31**). This was the first total synthesis of herbicidin B.[61]

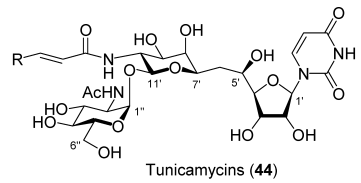
1.4. Tunicaminyluracil[62,79] Tunicamycins (Fig. 4, **44**) were isolated from the fermentation broths of *Streptomyces lysosuperficus* in 1971.[80—82] These are nucleoside natural products composed of uridine, *N*-acetylglucosamine (GlcNAc), an aminoundecose which is a unique higher carbon sugar called tunicamine, and an amide-linked fatty acyl side chain. They exhibit a variety of biological properties including antibacterial and antitumor activities.[83] Much attentions have been focused on the synthesis of tunicamycins because of their unique structure.[84—91] We thought that SmI_2-promoted aldol reaction can also be applied to the synthesis of tunicaminyluracil, a core structure of tunicamycins (Chart 7). Namely, aldol reaction between a phenylthioketone derivative **45** and a uridine 5′-aldehyde derivative **46** would provide an aldol product **47**. As for the construction of hexapyranosyl moiety, we planned to utilize an intramolecular Pummerer reaction between 7′-oxygen and 11′-carbon by installing the phenylthio group at 11′-position of either **48** or **49**.

The synthesis of tunicaminyluracil derivative **53** was shown in Chart 7. Treatment of **45**, which was prepared from D-galactose, with 2.2 eq of SmI_2 followed by addition of 1.0 eq of uridine 5′-aldehyde derivative **46** at −78 °C gave the desired aldol product **47** in only 13% yield. The large amount of **45** was observed in the reaction mixture and it was indicated that the α-phenylthio ketone without a hetero atom at this position is less reactive to the two-electron reduction than that with an oxygen atom, which was the case in the herbicidin synthesis. The treatment of **45** with SmI_2 at −40 °C gave complete consumption of **45** and the addition of **46** at −78 °C provided the aldol products **47** in 71% and the ratio was 5′*R*/5′*S*=66/34. These diastereomers were easily separated by silica gel colomun chromatography. Intramolecular hydride delivery from $NaBH(OAc)_3$ to 5′*R*-**48** *via* a 6-membered transition state selectively afforded the desired *anti*-diol **48**. With **48** in hand, an intramolecular Pummerer reaction was examined. There are several methods available to promote the Pummerer reaction including the direct activation of a sulfide or of the corresponding sulfoxide.[92] Direct activation of the sulfide **48** by treatment with NIS in the presence of a catalytic amount of TfOH resulted in the iodoetherification product **50** between the 5′-hydroxyl group and the 5,6-double bond within the uracil base, and the desired cyclization failed to occur. Next, the activation of the corresponding sulfoxide **49** was examined. Oxidation of **48** with *m*CPBA provided the corresponding sulfoxide **49**. Treatment of **49** with Tf_2O in the presence of pyridine at −15 °C provided the desired product **51** in 53% yield. It should be noted



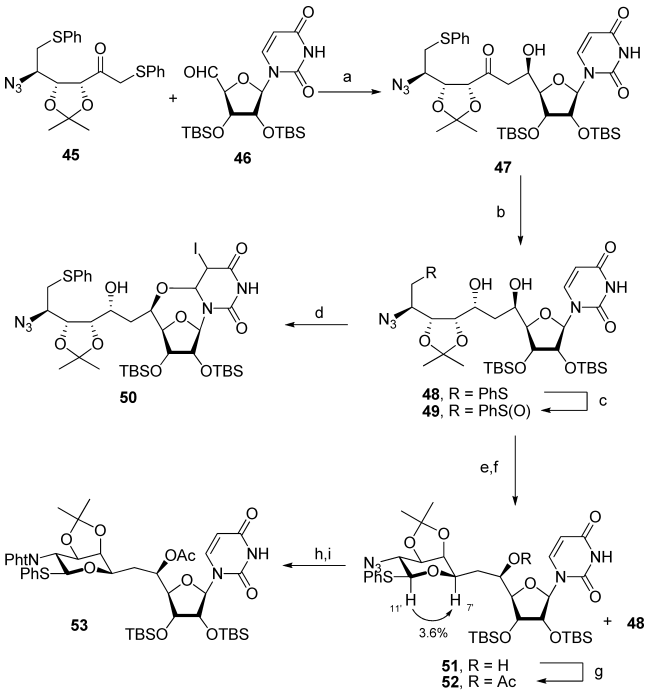
***Reagents and conditions*:** (a) SmI_2, THF, –40 °C, then **34** (71%); (b) Bergess salt, toluene (79%); (c) HCO_2NH_4, Pd/C, MeOH; (d) Sm, I_2, MeOH; (e) TBAF, THF (31%, 3 steps).

Chart 6



I: R = $(CH_2)_7CH(CH_3)_2$
II: R = $(CH_2)_8CH(CH_3)_2$
III: R = $(CH_2)_{10}CH_3$
IV: R = $C_{12}H_{25}$
V: R = $(CH_2)_8CH(CH_3)_2$
VI: R = $(CH_2)_{11}CH(CH_3)_2$
VII: R = $(CH_2)_{10}CH(CH_3)_2$
VIII: R = $(CH_2)_{12}CH_3$

Fig. 4. Structure of Tunicamycins



Reagents and conditions: (a) SmI_2, THF, –40 °C (62%); (b) $NaBH_4$, AcOH–CH_2Cl_2 (92%); (c) *m*CPBA, CH_2Cl_2 (96%); (d) for **48**. NIS, TfOH, CH_2Cl_2. (e) Tf_2O, pyridine, CH_2Cl_2; (f) $NaBH_4$, AcOH–CH_2Cl_2 (53% for **51**, 36% for **48**); (g) Ac_2O, DMAP, CH_2Cl_2 (96%); (h) PhSeH, Et_3N; (i) phthaloyl dichloride, DBU, toluene (92%, 2 steps).

Chart 7

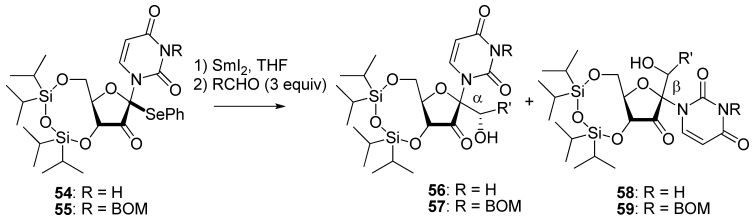


Chart 8

that the ketone **48** was also obtained, probably *via* the intramolecular oxidation of hydroxyl group. Finally, the protecting group manipulations afforded a fully protected tunicaminyluracil **53**.[62]

The characteristics of the SmI_2-promoted aldol reaction with the use of α-phenylthioketone as an enolate are that the enolate can be regioselectively generated and the aldol reaction proceeds under near neutral condition. This reaction is proved to be a powerful reaction for the synthesis of complex nucleoside natural products because it is suitable for the introduction of variety of complex units at a time to the sensitive nucleoside derivatives.

1.5. Synthesis of 1′-α-Branched Nucleoside Derivatives[10] Despite their biological importance, syntheses of nucleoside analogues branched at the anomeric 1′-position are not as common as syntheses of nucleoside derivatives branched at the 2′- and 3′-positions. Most 1′-branched nucleosides are prepared from the corresponding ribose derivatives branched at the 1′-position *via* glycosidation or nucleobase construction. These methods are not very practical and have drawbacks: (1) the preparation of the 1′-branched sugars requires many reaction steps and the overall yields are low and (2) the stereoselective introduction or construction of the nucleobase is tedious.[93—96] We thought that the SmI_2-promoted aldol reaction could be applicable to the synthesis of 1′-branched nucleosides. Namely, 1′-phenylseleno-2′-ketouridine derivative **54** or **55**[95,96] was chosen as a precursor to the SmI_2-promoted aldol reaction. First, the SmI_2-promoted generation of the 1′-enolate was examined (Chart 8). When **54** was treated with 2.5 eq of SmI_2 at −78 °C in THF followed by aqueous NH_4Cl, the de-phenylselenated product was obtained in about 90% yield as a mixture of anomers. These results showed that SmI_2-promoted reductive removal of the phenylseleno group occurred to generate the desired 1′-enolates. The aldol reaction was subsequently investigated. When the samarium enolate solution in THF prepared with 2.1 eq of SmI_2 at −78 °C was treated with an aldehyde as the electrophile, the reaction of the *N*-3-unprotected 2′-keto nucleoside **54** with PhCHO (3 eq) at −78 °C in THF gave the corresponding 1′-branched uridine derivatives **56** and **58** in 89% yield, however it was nonstereoselective and a mixture of the four diastereomers at the 1′- and 1″-positions was obtained. When the *N*-3-BOM substrate **55** was used, the reaction with a variety of aldehydes was stereocontrolled at the 1″-position to produce the 1″*S*-product (Table 4). The highly selective formation of the 1′*R*-branched products may be explained by the steric repulsion due to the tetrahedral 5′-methylene moiety when the aldehyde approaches from the α-face (Fig. 5). The highly selective 1″*S*-stereochemical results suggest that the aldol reaction proceeds *via* the chelation-controlled pathway. In contrast to these results, the aldol reaction between the lithium 1′-enolate **64** (Fig. 6) and PhCHO or Mukaiyama aldol reaction with 2-*O*-TMS-enol ether **65** as the substrate gave unsatisfactory results including low yield or decomposition by β-elimination to give **66**. These experiments clearly demonstrate the usefulness of the SmI_2-promoted aldol reaction with the 1′-phenylseleno-2′-ketouridine derivative **55** as the substrate.

Table 4. SmI_2-Promoted Aldol Reaction between **55** and Aldehydes

Entry	Electrophile	Temp. (°C)	Products (yield, %)	α/β
1	PhCHO	−78	**57** (76%), **59** (10%)	7.6 : 1
2	MeCHO	−78	**57** (29%)	β only
3	*i*-PrCHO	−78	**57** (48%)	β only
4	*t*-BuCHO	−78→rt	—	—
5	$(CHO)_n$	−78→0	**57** (57%), **59** (12%)	4.8 : 1

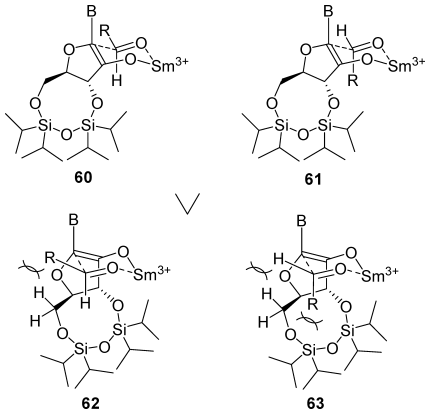


Fig. 5. A Possible Chelation-Controlled Reaction Pathway of the SmI_2-Promoted Aldol Reaction

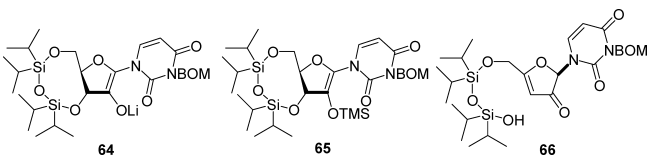


Fig. 6

2. Synthetic Study of Antibacterial Nucleoside Antibiotics

2.1. MraY as a Novel Target for the Development of Antibacterial Agents Tuberculosis (TB) is a disease primarily of the respiratory system from which two million people die each year.[97] With resistant strains continuing to emerge,[98—100] the need for better anti-TB agents possessing new mechanisms of action remains critical.[101,102] To keep pace with the serious public health problem due to multian-

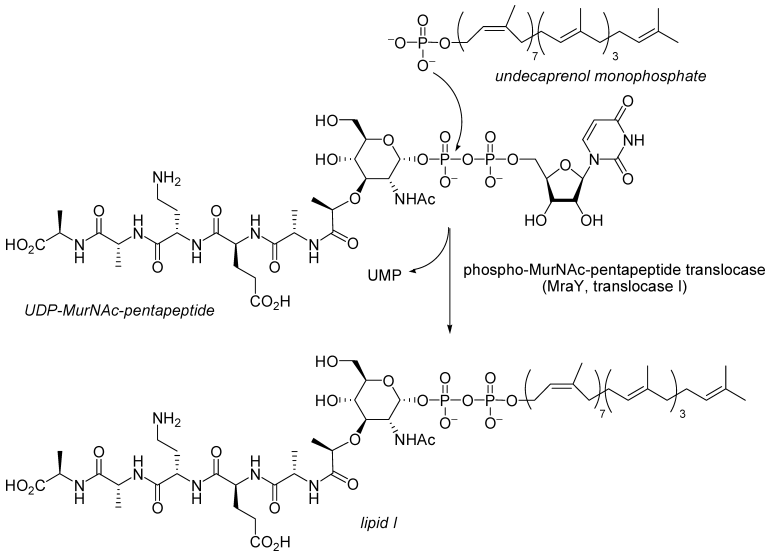


Fig. 7. Formation of Lipid I Catalyzed by MraY (Translocase I)

tibiotic resistant bacterial pathogens arising from the extensive use of antibiotics, new antibiotics to treat multidrug resistant *Mycobacterium tuberculosis*, methyciline-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE) and vancomycin-resistant *Staphylococcus aureus* (VRSA) are also urgently needed. Peptide glycan biosynthesis consists of three stages, including the formation of uridine diphosphate *N*-acetylmuraminylpentapeptide (UDP-MurNAc-pentapeptide) in cytoplasm, the membrane-anchored synthesis of lipid I and lipid II, a precursor to the peptide glycan, and polymerization of the resulting lipid II by transpeptidation and transglycosidation. The second and the third stages are involved in a lipid cycle, and the MraY catalyzes the first step of the lipid-linked cycle of the reactions, where UDP-MurNAc-pentapeptide is attacked by the undecaprenol monophosphate in the bacterial cell membrane providing lipid I (Fig. 7). Lipid I anchored to the cell membrane is further glycosylated by *N*-acetylglucosamine to afford lipid II. Since MraY is an essential enzyme among bacteria, it is potentially a target for the development of anti-TB agents as well as general antibacterial agents.[103—105] Therefore, MraY inhibitors are promising leads for novel antibacterial agents.

2.2. Caprazamycins[106—110] Caprazamycins (CPZs, Fig. 8, **67**) were isolated from a culture broth of the Actinomycete strain *Streptomyces* sp. MK730-62F2 in 2003[111—114] and represent the newest members of a class of naturally occurring 6′-*N*-alkyl-5′-*β*-*O*-aminoribosyl-glycyluridine antibiotics including liposidomycins[115—122] (LPMs, **68**), which have been shown to exhibit excellent antimicrobial activity against Gram-positive bacteria. In particular, the CPZs have shown excellent anti-mycobacterial activity *in vitro* against drug-susceptible (MIC=3.13 μg/ml) and multi drug-resistant *Mycobacterium tuberculosis* strains (MIC=3.13 μg/ml), and exhibit no significant toxicity in mice. With such excellent biological properties, CPZs are expected to become promising leads for the development of anti-tuberculosis agents with a novel mode of action. A biological target of the 6′-*N*-alkyl-5′-*β*-*O*-aminoribosyl-glycyluridine class of antibiotics is believed to be the phospho-MurNAc-pentapeptide translocase (MraY, translocase I, Fig. 7), and it is known that this class of antibiotics strongly inhibits MraY (*E. coli* translocase, IC_{50}=0.05 μg/ml for LPMs). Because of their complex structural and biological similarities, it has been suggested that the CPZs may possess the same mode of action as the LPMs.

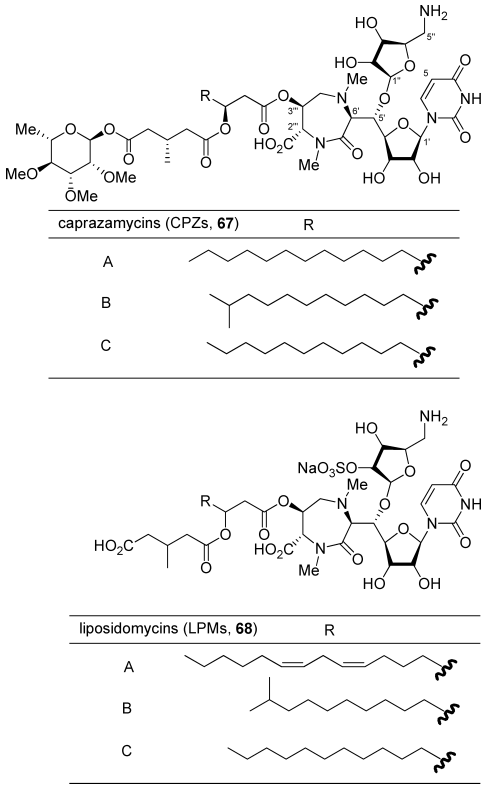
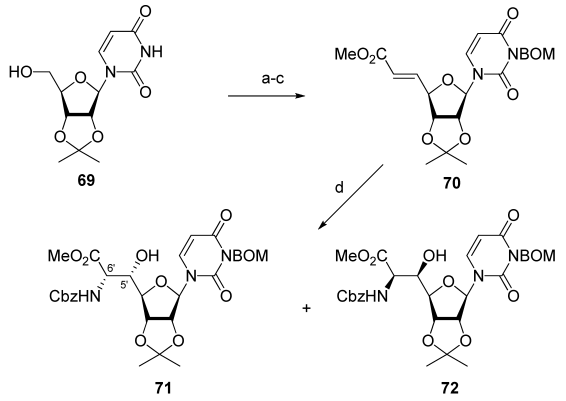


Fig. 8. Structures of Nucleoside Antibiotics Possessing the 6′-*N*-Alkyl-5′-*O*-aminoribosyl-5′-*C*-glycyluridine

The structure of LPMs and CPZs contain uridine, ribose, and fatty acyl moieties and a class of one of the most complex nucleoside antibiotics. Very recently, the absolute stereochemistry of the deacylated compound, named caprazole (**86**), was determined by X-ray crystal structure analysis. We



Reagents and conditions: (a) IBX, MeCN, 80 °C; (b) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, –30 °C; (c) BOMCl, Na_2CO_3, Bu_4NI, CH_2Cl_2–H_2O, room temperature (70%, 3 steps); (d) $CbzNH_2$, $K_2OsO_2(OH)_4$, $(DHQD)_2AQN$, NaOH, *t*-BuOCl, *n*-PrOH–H_2O, 5 °C–room temperature (52% for **71**, 9% for **72**).

Chart 9

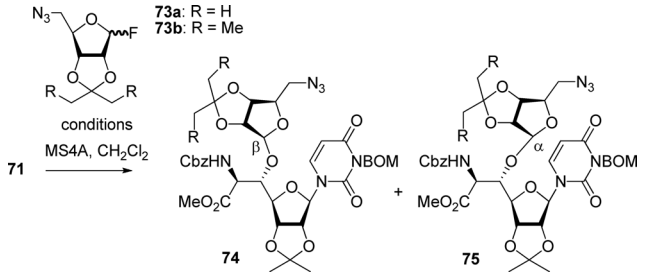


Chart 10

Table 5. Ribosylation Reactions of 5′-*C*-Glycyluridine **71**

Entry	Donor	Activator (eq)	Temp. (°C)	Yield (%)	Ratio (**74**/**75**)
1	**73a**	$BF_3{\cdot}OEt_2$ (1.5)	0	72	2.8/1
2	**73a**	$BF_3{\cdot}OEt_2$ (1.2)	−30	78	2.7/1
3	**73a**	TMSOTf (1.0)	0	Trace	—
4	**73a**	AgOTf (1.5)/Cp_2HfCl_2 (1.5)	−40	Quant.	1.2/1
5	**73a**	AgOTf (1.5)/$SnCl_2$ (1.5)	0	60	2.0/1
6	**73a**	$AgClO_4$ (1.5)/$SnCl_2$ (1.5)	0	40	2.6/1
7	**73b**	$BF_3{\cdot}OEt_2$ (1.5)	0	80	24.0/1

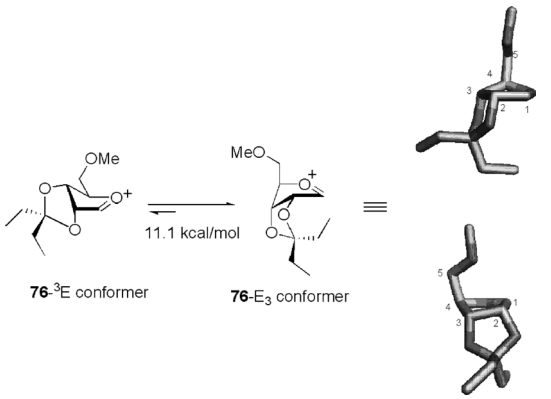


Fig. 9. Optimized Geometries (B3LYP/6-31G**) of the E_3 Conformers of the Oxocarbenium Ions of 2,3-*O*-3-Pentylidene-5-*O*-methyl-D-ribofuranose

are interested in the biological activity of this class of natural products as well as structural complexity and started the synthetic study of CPZs. More than 8 groups have studied the total synthesis of LPMs.[123—140] Difficulty in the synthesis of this class of molecules may lie with the introduction of 5-aminoribose moiety found in CPZs and LPMs after construction of a uridyldiazepanone moiety because the tertiary amine contained in the diazepanone structure inhibited the usual ribosylation promoted by Lewis acid. In addition, CPZs and LPMs would be sensitive to basic conditions because they contain a β-heterosubstituted carboxyl moiety. There is a general method for the construction of β-glycosides to use a glycosyl donor protected with a 2-*O*-acyl group, *via* a neighboring group participation, which is usually deprotected under basic conditions. We planned to introduce an aminoribose protected with an acid labile protecting group at an early stage of the synthesis and control β-selective introduction *via* a steric hindrance installed at the α-face of the ribofuranosyl donor. Compound **71**, which was the ribosyl acceptor, was prepared as shown in Chart 9. Oxidation of 2′,3′-*O*-isopropylideneuridine **69** by iodoxybenzoic acid[141] (IBX) followed by 2-carbon elongation by Wittig reaction and protection of 3-position with BOM group gave the unsaturated ester **70**. Then, the Sharpless aminohydroxylation[142] was conducted with the use of $[DHQD]_2AQN$ ligand, the (*5′S,6′S*)-aminoalcohol **71** was obtained as a major diastereomer. Then, the ribosylation was investigated as shown in Chart 10. First, the reaction was examined with the ribosyl fluoride protected with 2,3-*O*-isopropylidene group **73a** as a ribosyl donor. When **73a** was activated with $BF_3{\cdot}OEt_2$[142] at 0 °C, the ribosides **74** and **75** were obtained in 72% yield with moderate stereoselectivity at the anomeric position (**74**/**75**=2.8/1, Table 5, entry 1). Lower temperature did not affect the selectivity (entry 2). When other activators, including AgOTf/Cp_2HfCl_2,[144] AgOTf/$SnCl_2$[145] or $AgClO_4$/$SnCl_2$ were used, the stereoselectivity did not improve (entries 4—6). Further exploration using the ribosyl fluoride **73b** possessing a more sterically hindered 3-pentylidene group afforded the desired **74** with excellent β-selectivity (**74**/**74**= 24.0/1) when activation was conducted with $BF_3{\cdot}OEt_2$ at 0 °C (entry 7). In order to obtain more insight into the factors responsible for the high β-selectivity with the 2,3-pentylidene protected ribosyl donors, we optimized these conformers for the 3-pentylidene protected 5-*O*-methylribofuranosyl oxocarbenium ions (Fig. 9, **76**) by density functional theory (DFT) quantum mechanical calculations at the BL3LYP/6-31G** level.[146—148] From these results, we calculated the E_3 conformer, where the 3-oxy group was orientated in the pseudoaxial position, to be lower in energy than the ^3E conformer.[149—153] Two potentially favorable modes of nucleophilic attack are possible for the oxocarbenium ions, and these modes are governed by both ground-state effects and transition-state effects, issues which have been extensively studied by Woerpel *et al.*[153] For the oxocarbenium ion in the E_3 conformer, nucleophilic attack from the α-face is favored by inside attack in the ground state to give the α-riboside (Fig. 10). However, nucleophilic attack from the α-face 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

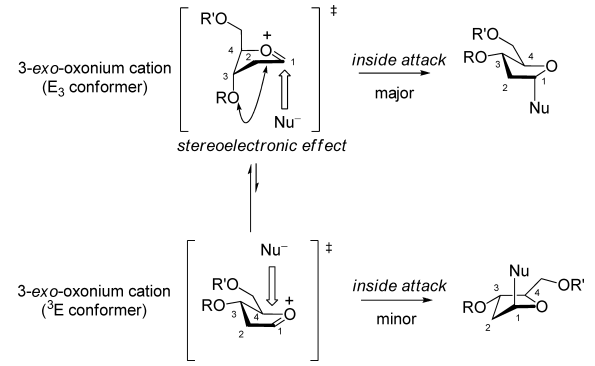


Fig. 10. Schematic Representation of the Stereoselectivity of the Nucleophilic Attack to Oxocarbenium Ions of *C*-3-Alkoxyfuranosides

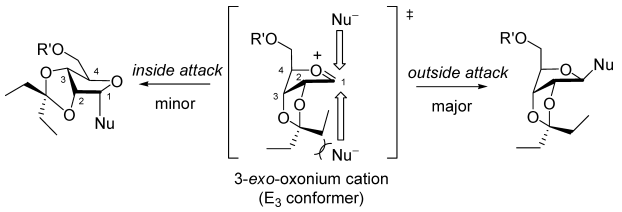
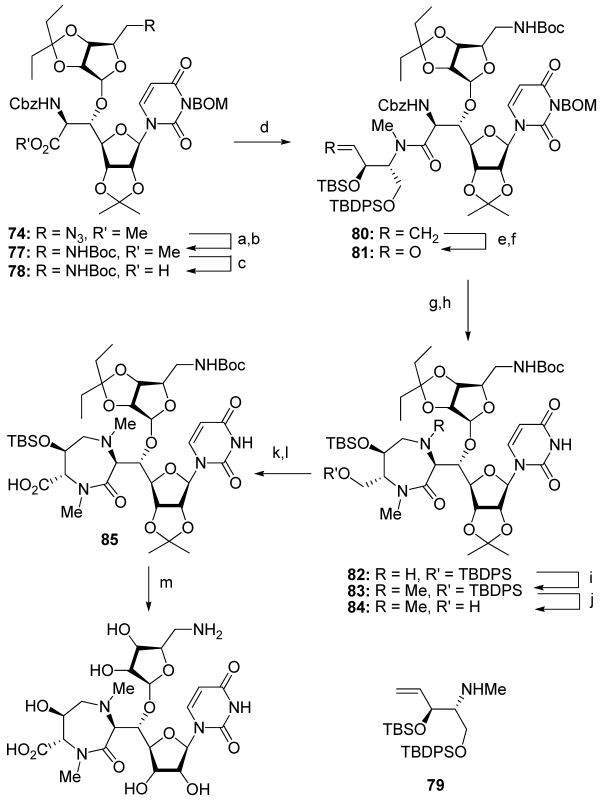


Fig. 11. Schematic Representation of the β-Stereoselectivity of the Nucleophilic Attack to Oxocarbenium Ions of 3-Pentylidene Protected Ribofuranoside

complete reversal of stereoselectivity (Fig. 11). Because of the inherent nature of the E_3 conformation, the terminal methyl substituent of the 3-pentylidene group on the α-face is oriented toward the anomeric carbon atom and not toward the C-4 carbon atom, an orientation that would also help to prevent the approach of the nucleophile from the α-face of **76** (Fig. 9). This could be a possible explanation for the large disparity in the anomeric selectivity observed between the isopropylidene and the 3-pentylidene protected ribofuranosides.

Having been established the highly β-selective ribosylation reaction without using neighboring group participation, the total synthesis of caprazol (**86**) was then undertaken (Chart 11). The azide group of the riboside **74** was reduced to the corresponding amine, which was protected with a Boc group to give **77**. Basic hydrolysis of the methyl ester was troublesome, the desired carboxylic acid **78** was obtained only when it was treated with $Ba(OH)_2$ in aqueous THF. Thus, the basic treatment should be avoided through the synthesis. Coupling the carboxylic acid **78** with the secondary amine **79** using DEPBT[154,155] as a coupling reagent gave the amide **80**. The vinyl group was converted to the aldehyde and the hydrogenolysis of Cbz group in *i*-PrOH followed by the hydride reduction with $NaBH(OAc)_3$ provided the desired diazepanone **82**. Interestingly its *N*-methylated compound **83**, one step advanced compound, was also obtained in 34%. It is supposed that the methyl source in the formation of **83** was the formaldehyde generated in the course of BOM group deprotection. The conversion of the alcohol **83** to carboxylic acid **85** was conducted by the sequential oxidation of the TBDPS deprotected compound **84**. Finally, global deprotection of isopropylidene, pentylidene, Boc, and TBS group with aqueous HF was applied to compound **85**, and successfully provided (+)-caprazol (**86**). This synthetic material was

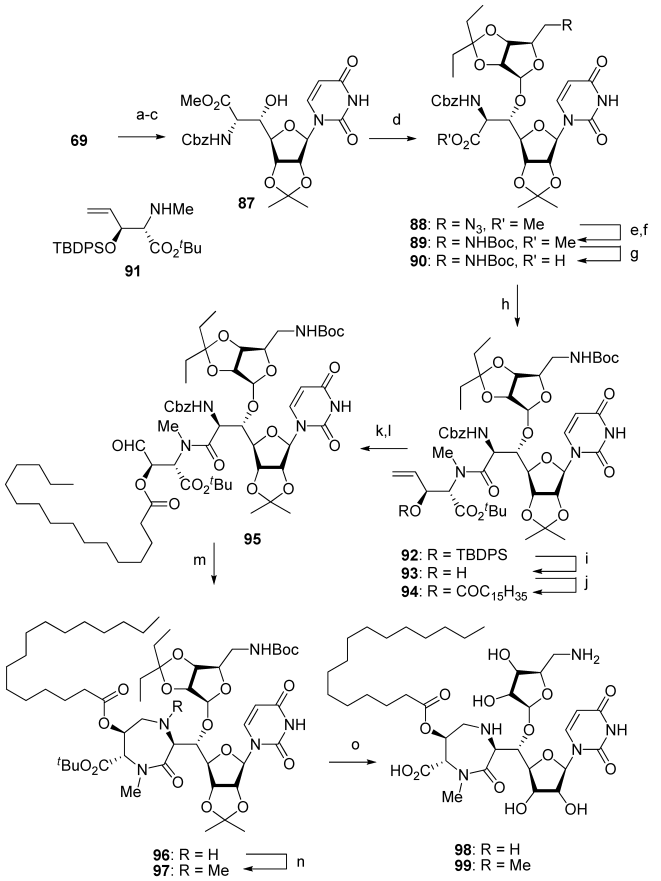


Reagents and conditions: (a) Ph_3P, H_2O, benzene–THF, 50 °C; (b) $(Boc)_2O$ (95%, 2 steps); (c) $Ba(OH)_2$, THF–H_2O, room temperature (50%) (d) **79**, DEPBT, $NaHCO_3$, THF, 0 °C–room temperature (81%); (e) OsO_4, NMO, *t*-BuOH, acetone–H_2O, room temperature; (f) $NaIO_4$, acetone–H_2O, room temperature (61%, 2 steps); (g) H_2, Pd black, *i*-PrOH, room temperature; (h) $NaBH(OAc)_3$, AcOH, AcOEt, room temperature (24% for **82**, 34% for **83**); (i) $(CH_2O)_n$, $NaBH(OAc)_3$, AcOH, AcOEt, room temperature (65%); (j) NH_4F, MeOH, room temperature (60%); (k) Dess-Martin periodinane, CH_2Cl_2, room temperature; (l) NaClO, NaH_2PO_4, *t*-BuOH–H_2O (56%, 2 steps); (m) HF, THF–H_2O (50%).

Chart 11

identical in all respects with the properties for the authentic caprazol.[113,114]

This approach provided a range of key analogues with simpified fatty acyl side chain and partial structures to define the pharmacophore. First, a palmitoyl caprazol (**99**), which possesses a simple fatty acyl side chain at the 3‴-position of the diazepanone moiety, and several truncated analogs were synthesized in a manner similar to the synthesis of caprazol (**86**) (Chart 12) and their antibacterial activity was evaluated. Palmitoyl caprazol (**99**) exhibited antibacterial activity against *Mycobacterium smegmatis* ATCC607 (MIC=6.25 μg/ml) with a potency similar to that of the CPZs (Table 6). Therefore, simplification of the fatty acyl side chain in the CPZs to the palmitoyl group, lacking substituents and stereocenters was tolerated for antibacterial activity. Removal of the methyl group at the $N^{6'}$-position had a relatively high impact on anti-*Mycobacterium* activity, and **98** resulted in a modest 4-fold reduction in potency. Clinically used β-lactams and vancomycin inhibit peptidoglycan biosynthesis; their mode of action is inhibition of the polymerization of the lipid II at the bacterial surface. Since the reaction catalyzed by MraY is located upstream of the lipid II polymerization and is the essential step for the growth of most bacteria, it is expected that MraY inhibitors would exhibit antibacterial ac-



Reagents and conditions: (a) IBX, MeCN, 80 °C; (b) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, –30 °C (90%, 2 steps); (c) $CbzNH_2$, $K_2OsO_2(OH)_4$, $(DHQD)_2AQN$, NaOH, *t*-BuOCl, *n*-PrOH–H_2O, 5 °C–room temperature (96%); (d) **73b**, $BF_3{\cdot}OEt_2$, MS4A, CH_2Cl_2, –30 °C (71%); (e) Ph_3P, H_2O, benzene–THF, 50 °C; (f) $(Boc)_2O$ (90%, 2 steps); (g) $Ba(OH)_2$, THF–H_2O, room temperature (73%) (h) **91**, DEPBT, $NaHCO_3$, THF, 0 °C–room temperature (66%); (i) TBAF, THF (78%); (j) palmitic acid, EDCI, DMAP, CH_2Cl_2; (k) OsO_4, NMO, *t*-BuOH, acetone–H_2O, room temperature; (l) $NaIO_4$, acetone–H_2O, room temperature (83%, 3 steps); (m) H_2, Pd black, *i*-PrOH, room temperature; (n) $NaBH(OAc)_3$, AcOH, AcOEt, room temperature (96%, 2 steps); (o) $(CH_2O)_n$, $NaBH(OAc)_3$, AcOH, AcOEt, room temperature (65%); (o) *aq*. TFA (quant.)

Chart 12

Table 6. Antibacterial Activity of **98** and **99**

Test organisms	MIC (μg/ml)	
	98	**99**
M. smegmatis ATCC607	6.25	25
S. aureus FDA 209P	1.56	1.56
S. aureus MS9610 (MDR)	3.13	3.13
S. aureus MRSA No. 5 (MRSA)	6.25	6.25
S. aureus MRSA No. 17 (MRSA)	6.25	6.25
S. aureus MS16526 (MRSA)	6.25	6.25
S. aureus TY04282 (MRSA)	6.25	12.5
E. faecalis NCTC 12201 (VRE)	12.5	12.5

tivity against drug-resistant strains. As expected, Analogs **98** and **99** also exhibited antibacterial activity against drug-resistant bacteria including MRSA and VRE strains (MIC=3.13—12.5 μg/ml). In order to further simplify CPZs, the structure–activity relationship of **99** was next conducted. Thus, several truncated analogs **100**—**102** including caprazol (**86**) were synthesized and their antibacterial activity was evaluated to see the impact of each the uridine, the aminoribose, the diazepanone, and the fatty acyl side chain on anti-

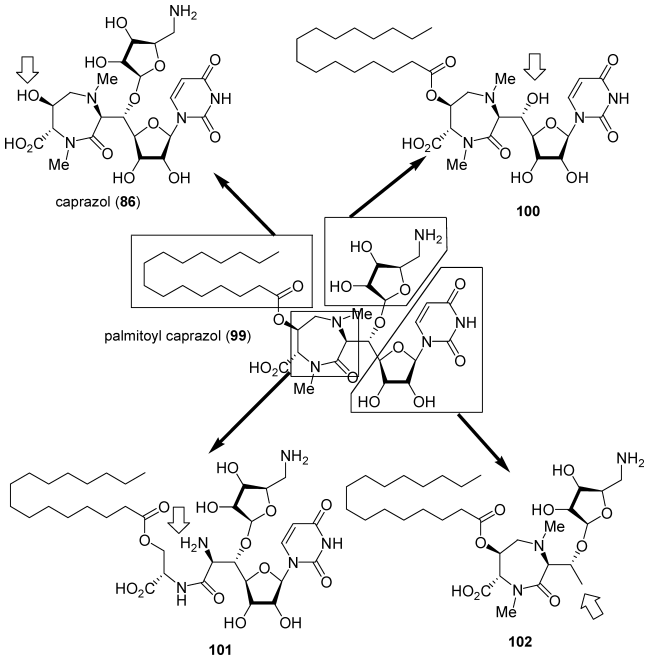


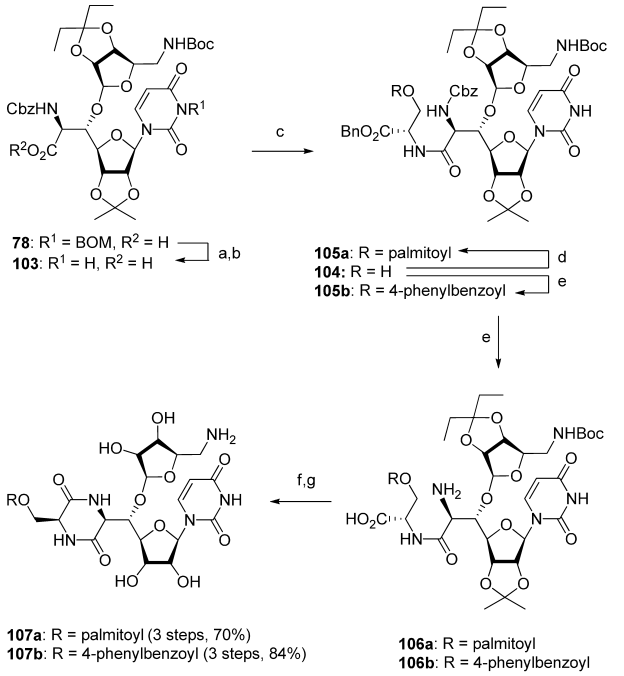
Fig. 12. Structure of Truncated Analogs of CPZs

Table 7. Antibacterial Activity of CPZ Analogs against *Mycobacterium tuberculosis* H37Rv

Test organism	MIC_{50} (μg/ml)				
	86	**99**	**100**	**101**	**102**
Mycobacterium tuberculosis H37Rv	>100	2.50	>100	6.25	>100

TB activity (Fig. 12, Table 7). Caprazol **86** exhibits no antibacterial activity against a range of bacterial strains, and the hydrophobic fatty acyl side chain at the diazepanone moiety therefore plays an important role in antibacterial activity. The aminoribose-truncated analog **100** and the uridine-truncated analog **102** of the CPZs were also inactive, and the aminoribose and uridine moieties of CPZs are also important to exhibit antibacterial activity. On the other hand, the antibacterial activity of the acyclic analog **101**, where the diazepanone ring is broken, was decreased but **101** still retains moderate antibacterial activity (6.25 μg/ml). From these result, it is suggested that the diazepanone ring might play an important role as a scaffold on which to hang the aminoribosyluridine and the fatty acyl moieties thus allowing them to be placed in the right orientation to interact with the target MraY.

With these initial structure–activity relationship in hand, we thought that the diazepanone structure, which constitutes a molecular complexity of this class of natural products, could be replaced by a simpler scaffold. We selected a diketopiperazine structure as a scaffold[156—158] to provide newly designed simple analogs of CPZs and LPMs in order to connect the aminoribosyluridine and the fatty acyl moieties with the simpler scaffold. The analogs were systematically synthesized (Chart 13) and their antibacterial activity was evaluated. As a result, the diketopiperazine analog **107a**, which possessed a palmitoyl side chain, demonstrated moderate antibacterial activity (MIC=12.5—50 μg/ml) against some strains including *Micrococcus* sp. or *Corynebacterium* sp.



Reagents and conditions: (a) H_2, $Pd(OH)_2$/C, MeOH; (b) CbzCl, $NaHCO_3$, *aq*. THF (79%, 2 steps); (c) L-Ser(OBn)·HCl, EDCI, HOBt, DMF; (d) palmitic acid, EDCI, DMAP, CH_2Cl_2 (89%); (d) 4-phenylbenzoic acid, EDCI, DMAP, CH_2Cl_2 (87%); (f) EDCI, HOBt, CH_2Cl_2; (g) 80% *aq*. TFA (3 steps, 70% for **107a**, 84% for **107b**).

Chart 13

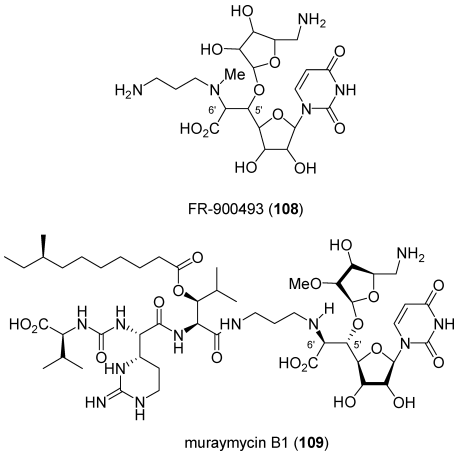


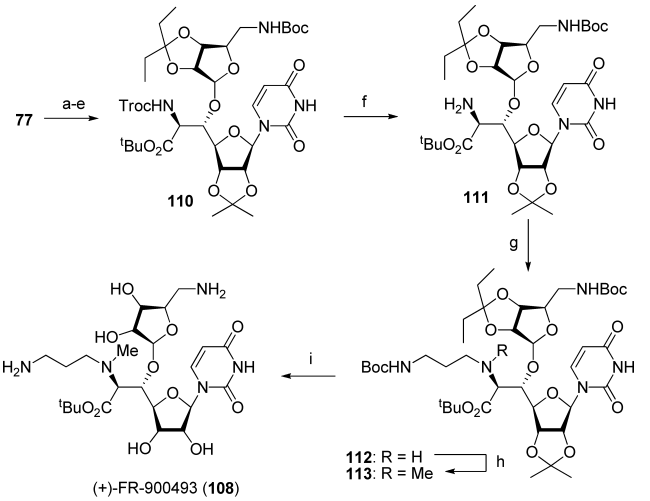
Fig. 13. Structures of FR-900493 and Muraymycin B1

Therefore, this approach would provide ready access to a range of analogs for the development of antibacterial agents although more precise optimization and simplification of the CPZs should be neccesary. These study is in progress.

2.3. FR-900493[159] FR-900493[159—161] (Fig. 13, **108**), which was isolated from the culture broth of *Bacillus cereus* in 1989, belongs to a class of antibacterial nucleoside natural products that are active against both Gram-positive and Gram-negative bacteria. Muraymycins[162] (MRYs, **109**), which are structurally related antibiotics, exhibited more promising antibacterial activity. These nucleoside antibiotics are also believed to be inhibitors of MraY similar to CPZs and LPMs. Utilizing the synthetic methodology toward the CPZs analogs, we have accomplished the first total synthesis of (+)-FR-900493 in 17 steps from uridine by simple protecting group manupilations, alkylation, and deprotection (Chart 14). This study also estabilised its relative and absolute stereochemistry and its absolute stereochemistry to be 1′*R*,2′*R*,3′*R*,4′*S*,5′*S*,6′*S*,1″,2″,3″*R*,4″*R* as shown in Chart 14. This synthetic strategy could be applicable to the synthesis of related nucleoside antibiotics such as MRYs (**109**). This study is currently underway.

Table 8. Antibacterial Activity of Diketopiperazine Analogs

Test organisms	MIC (μg/ml)	
	107a	**107b**
S. aureus SMITH	25	>100
S. aureus MS9610 (MDR)	100	>100
S. aureus MRSA No. 5 (MRSA)	100	>100
Micrococcus luteus FDA16	25	>100
Micrococcus luteus PCI 1001	50	>100
Bacillus subtilis NRRL B-558	25	>100
Corynebacterium bovis 1810	50	>100



Reagents and conditions: (a) $Ba(OH)_2$•$8H_2O$, *aq*. THF; (b) *t*BuOC(NH)CCl_3, BF_3•Et_2O, CH_2Cl_2 (46%, 2 steps); (c) H_2, Pd/C, MeOH; (d) TrocCl, Et_3N, CH_2Cl_2 (79%, 2 steps); (e) H_2, $Pd(OH)_2$/C, TCA, MeOH (92%); (f) activated Zn powder, NH_4Cl, MeOH (95%); (g) $BocHNCH_2CH_2CHO$, $NaBH(OAc)_3$, AcOH, CH_2Cl_2 (80%); (h) $(CH_2O)n$, $NaBH(OAc)_3$, AcOH, AcOEt (70%); (i) *aq*. 80% TFA (quant.).

Chart 14

Conclusion

Nucleosides and nucleotides are a rich source in drug discovery because they are not only a component of DNAs and RNAs, but also they play important and various roles in most fundamental cellular metabolic pathways in cells. Reflecting the inherent manifold roles of nucleosides and nucleotides, biological activities of nucleoside natural products, which include a variety of structural modifications of nucleosides and nucleotides, are also wide ranging. Therefore, nucleoside natural products are promising leads for drug development. By developing reactions suitable for the synthesis of labile and complex nucleoside natural products, herbicidin B, fully protected tunicaminyluracil, caprazol, and FR-900493 were synthesized. Our synthetic route of caprazol provided a range of key analogues to examine a structure–activity relationship. More precise optimization should be neccesary to reduce the size of molecules and stabilize the chemically labile struc-

ture. Although these objectives are not easy to be accomplished, a full chemical synthetic approach of novel agents supported by lesson from the nucleoside natural products and rational drug design should result in the discovery of novel antibacterial drugs. We hope these studies would provide a new strategy to develop novel antibacterial drugs.

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