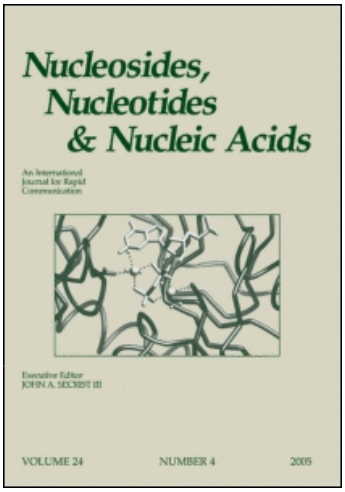

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SYNTHESIS OF COMPLEX NUCLEOSIDE ANTIBIOTICS

Satoshi Ichikawa and A. Matsuda ▫ *Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan*

▫ *Herbicidin B and fully protected tunicaminyluracil, which were undecose nucleoside antibiotics, were synthesized using a samarium diiodide (SmI_2) mediated aldol reaction with the use of α-phenylthioketone as an enolate. The characteristics of the SmI_2-mediated aldol 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 antibiotics. The synthesis of caprazol, the core structure of caprazamycins, was conducted by the strategy including β-selective ribosylation without using a neighboring group participation and the construction of a diazepanone by a modified reductive amination. Our synthetic route would provide a range of key analogues with partial structures to define the pharmacophore, which can be a lead for the development of more effective anti-bacterial agents.*

Keywords Nucleoside Antibiotics, Samarium Diiodide, Aldol Reaction, Herbicidins, Tunicaminyluracil, Caprazol

INTRODUCTION

Some of nucleoside antibiotics include complex structures as well as sensitive functionality, which are challenging targets for organic chemists.[1] Among complex nucleoside antibiotics, there are also good drug candidates because they possess a variety of interesting biological properties. Here we describe the synthesis of complex nucleoside antibiotics, including herbicidin B, protected tumicaminyluracil, and caprazol.

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RESULTS AND DISCUSSION

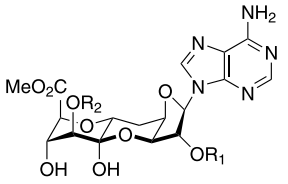
Synthesis of Undecose Nucleosides via SmI_2 Mediated Aldol Reaction

Total Synthesis of Herbicidin B2

Herbicidins (Figure 1, **1**) were isolated from *Streptomyces saganonensis* in 1976.[3] 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 positions. Because of their unique and complex structures, considerable efforts has been devoted to the total synthesis; however, none of these attempts had been yet successful.

Our retrosynthetic analysis of herbicidin B is shown in Scheme 1. This molecule is equivalent to a xlyoadenosine derivative **A**. Compound **B** would be simply obtained by aldol condensation between a xyloadenosine 5'-aldehyde derivative **C** and a sugar enolate **D**. Other group reported that the enolate addition to adenosine 5'-aldehyde derivative failed to occur because of the sensitivity of the aldehyde. In addition to this sensitivity of nucleoside part, regioselective generation of 1-enolate from 2-urose also has a drawback in the regioselectivity. We have developed SmI_2 mediated aldol reaction with 1-phenylthio-2-urose (Scheme 2, **E**) as an enolate source to generate 1-enolate **F** selectively.[4] Since this reaction proceeds under neutral condition, it was expected to be suitable for the use of the sensitive substrates (Scheme 2).

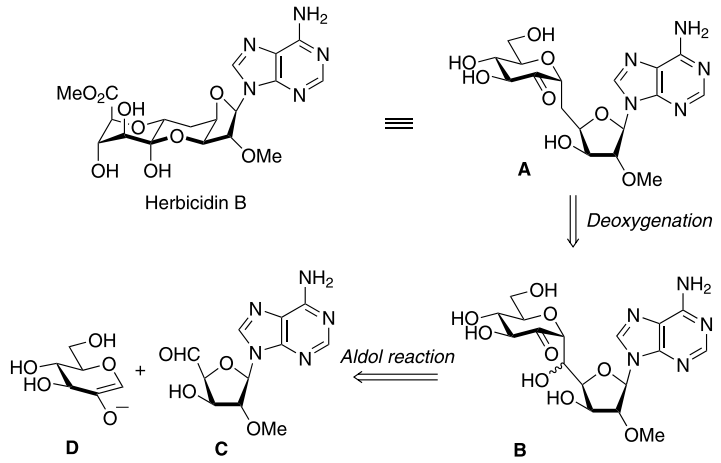
1-Phenylthio-2-urose protected with TIPDS group **2** was prepared from D-glucuronolactone for 10 steps. This compound was treated with 2 equiv. of SmI_2 in THF at $-78°C$, which was followed by the addition of a xyloadenosine 5'-aldehyde derivative **3**. The aldol products **4** and **5** were obtained in 75% yield as a mixture of products, among which the desired 6'*S* product **4** was the major diastereomer. Dehydration of aldol product **4** followed by catalytic hydrogenation provided 6'-β-compound **7**. Deprotection of the benzoyl group and silyl groups resulted in spotaneus cyclization to afford tricyclic nucleoside **8**. However, only the



Herbicidins (**1**)

A: R^1 = Me, R^2 = $CO(CH_2OH)C{=}CHMe$
B: R^1 = Me, R^2 = H
C: R^1 = H, R^2 = H

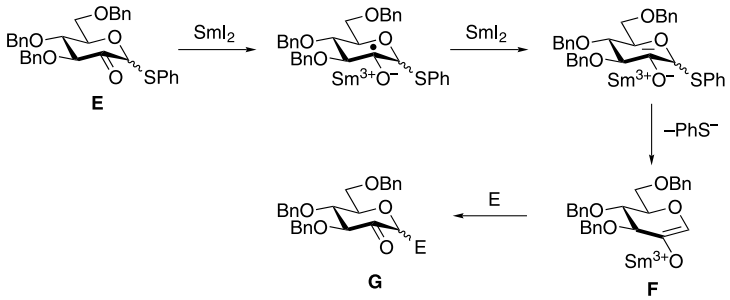
FIGURE 1 Structure of herbicidins.



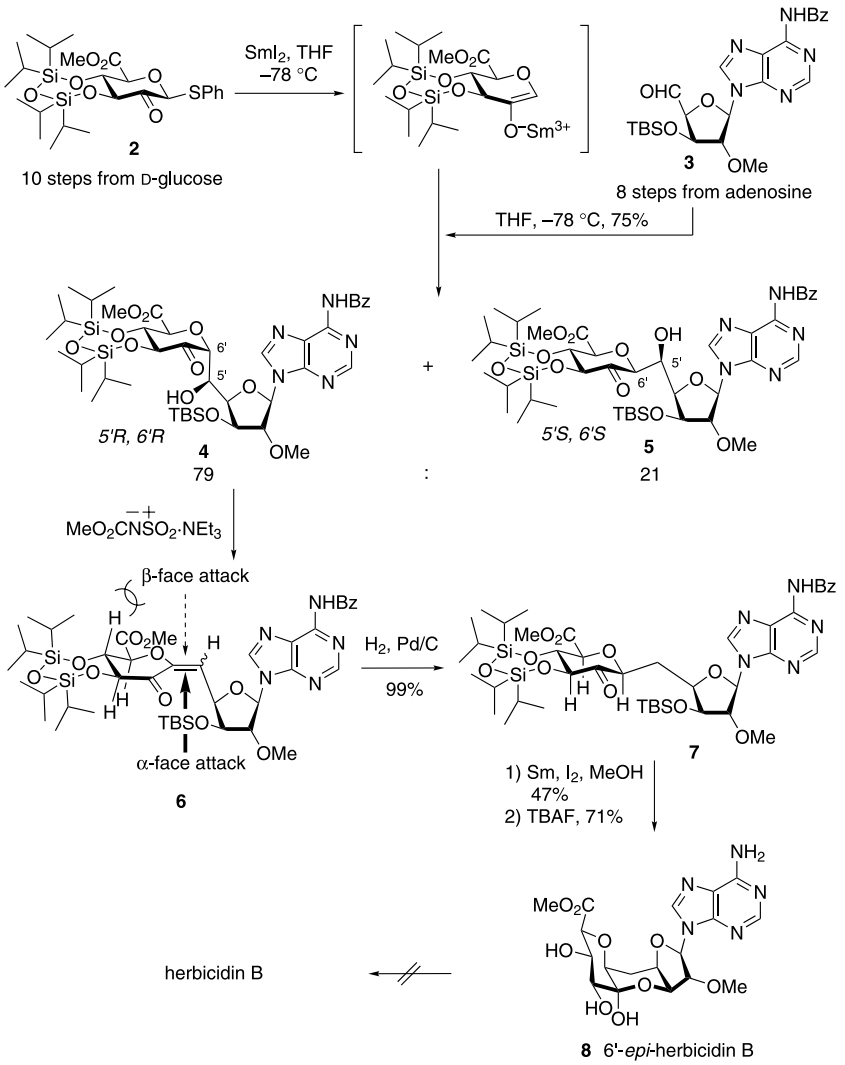
SCHEME 1 Retrosynthetic analysis of herbicidin B.

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 the conformation of the enone **6** preferentially adopts a half-boat conformation. 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 **7**. We recognized that it would be essential to provide the 6'-α-stereochemistry before the cyclization (Scheme 3).

We planned to apply this conformation flip to reverse the stereoselectivity of the hydrogenation. Namely, hygrogenation of the substrate preferentially with a flipped conformation such as **11** 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. Thus, we made a screening of enones protected with bulky silyl groups at 8' and 9'-hydroxyl groups (Scheme 4). Small coupling constants between H-8',9' and H-9',10' in the ^{1}H NMR spectra, indicated that enone **11** preferentially adoped fliped conformation. Hydrogenation of **11** followed by a two-step



SCHEME 2 SmI_2-mediated aldol-type C-glycosidation.

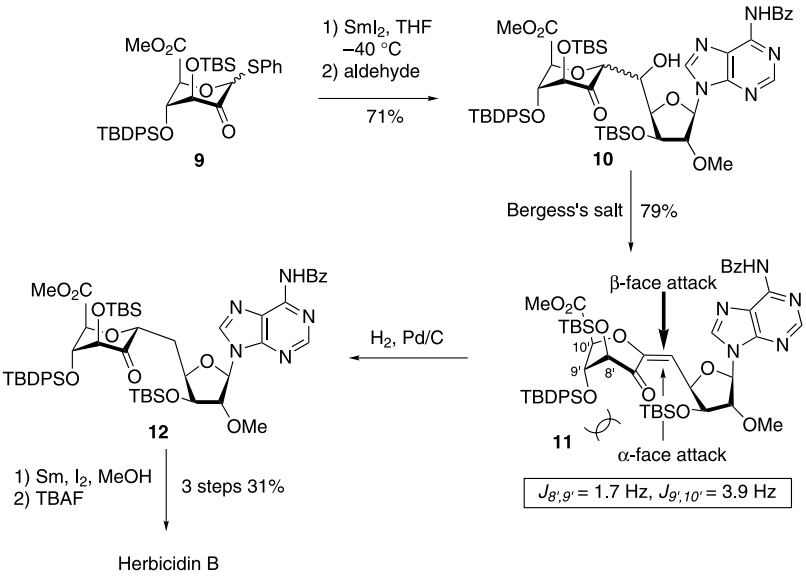


SCHEME 3 Synthesis of 6′-epi-herbicidin B.

deprotection sequence successfully afforded herbicidin B. This was the first total synthesis of herbicidin.[2]

Synthesis of Fully Protected Tunicaminyluracil

Tunicamycins (Figure 2, **13**) were isolated from the fermentation broths of *Streptomyces glysosuperficus* in 1971.[5,6] These are nucleoside antibiotics 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.



SCHEME 4 Total synthesis of herbicidin B.

We thought that SmI_2-mediated aldol reaction can also be applied to the synthesis of tunicaminyluracil (Scheme 5). Namely, aldol reaction between a phenylthioketone **K** and a uridine 5'-aldehyde **J** would provide an aldo product **I**. 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 **H**.

The synthesis of tunicaminyluracil **21** was shown in Scheme 6. Treatment of **14**, which was prepared from D-galactose, with 2.2 equiv. of SmI_2 followed by addition of 1.0 equiv. of uridine 5'-aldehyde derivative **15** at −78°C gave the desired aldol products **16** and **17** in only 13% yield. The large amount of **14** 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

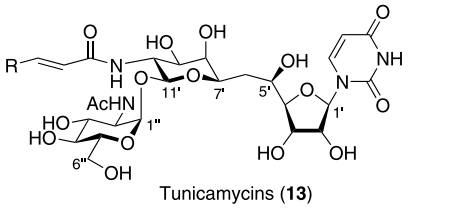
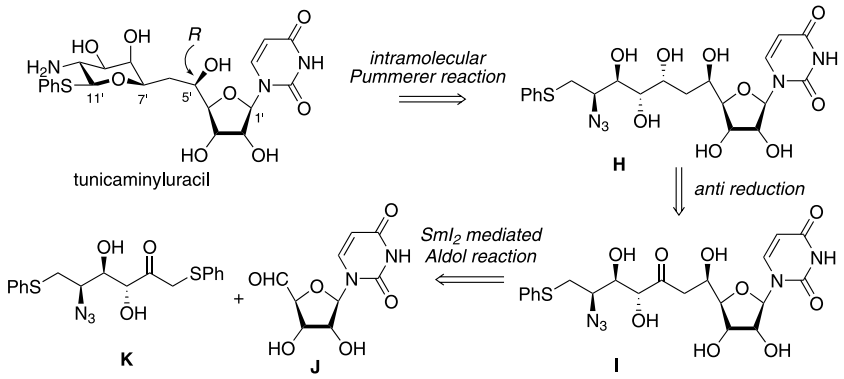


FIGURE 2 Structure of tunicamycins.



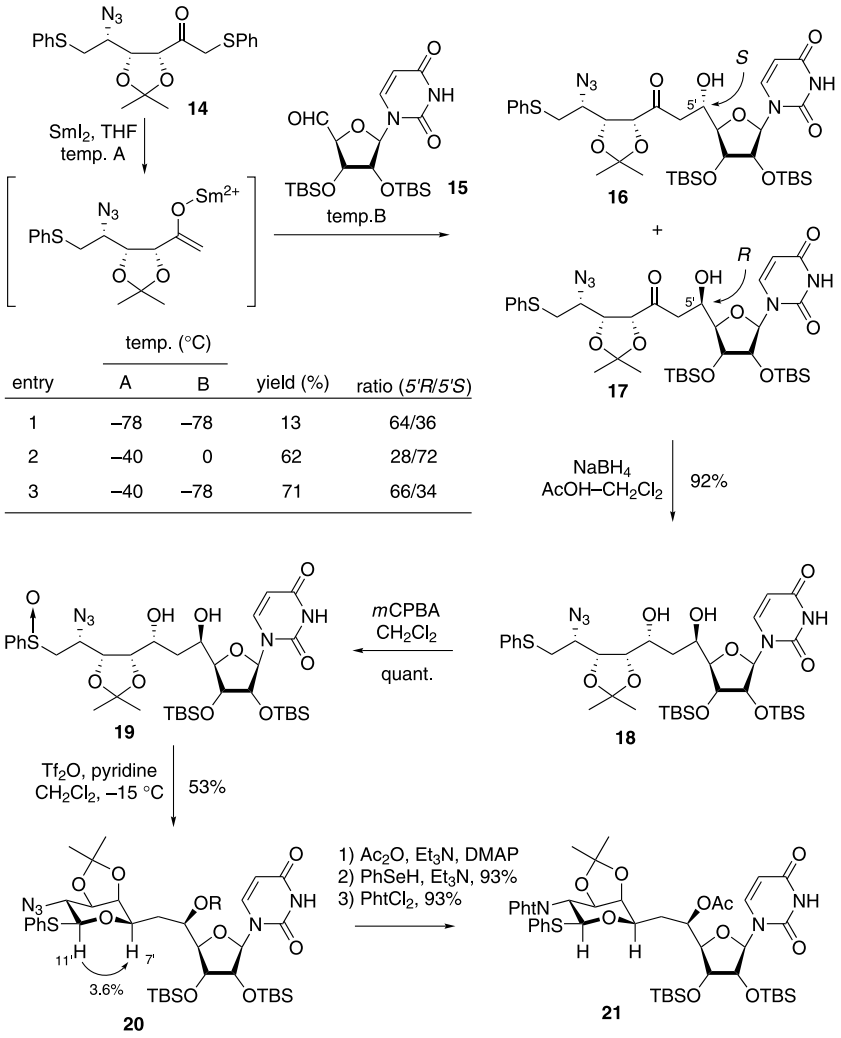
SCHEME 5 Retrosynthetic analysis of tunicaminyluracil.

than that with an oxygen atom, which was the case in the herbicidin synthesis. The treatment of **14** with SmI_2 at $-40°C$ gave complete consumption of **14** and the addition of **15** at $-78°C$ provided the aldol products **16** and **17** in 71% and the ratio was 5'*R*/5'*S* = 66/34. Intramolecular hydride delivery from $NaBH(OAc)_3$ via a 6-membered transition state selectively afforded the desired *anti*-diol **18**. Oxidation of **18** with *m*CPBA provided the corresponding sulfoxide **19**. Treatment of **19** with Tf_2O in the presence of pyridine at $-15°C$ provided the desired product **20** in 53% yield. It should be noted that this ketone was also obtained, probably via the intramolecular oxidation of hydroxyl group. Finally, the protecting group manipulations afforded a fully protected tunicaminyluracil **21**.[5]

The characteristics of the SmI_2-mediated 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 antibiotics because it is suitable for the introduction of variety of complex units at a time to the sensitive nucleoside derivatives.

Synthetic Study of Antibacterial Nucleoside Antibiotics: Total Synthesis of Caprazol

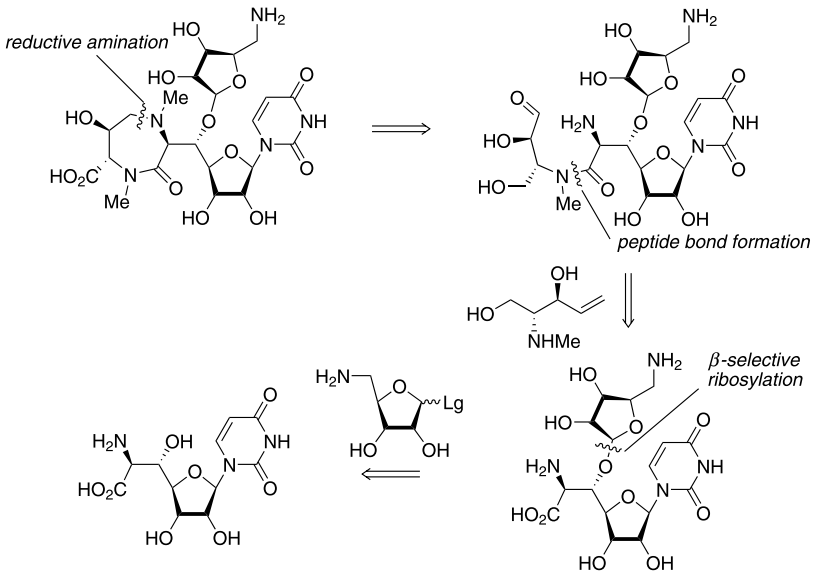
Concerned that the bacteria will acquire resistance to the new drugs, development of new antibacterial drugs has still been necessary for the next defense against the drug-resistant bacteria such as vancomycin-resistant *Staphylococcus aureus* (VRSA).[7] Liposidomycins (LPSs, **22**), isolated from *Streptomyces griseosporeus* in 1985, show antibacterial activity against Gram-positive bacteria including *Mycobacterium* spp.[8] and did not exhibit any significant toxicity in mice. It is reported that LPS strongly inhibit Mra Y, one of the enzymes responsible for peptidoglycan biosynthesis and expected to be a good target for the development of antibacterial agents. Recently isolated caprazamycins (CPZs, **23**) show antibacterial activities against *Mycobacterium*, which cause tuberculosis, and thus



entry	temp. (°C) A	B	yield (%)	ratio (5′*R*/5′*S*)
1	–78	–78	13	64/36
2	–40	0	62	28/72
3	–40	–78	71	66/34

SCHEME 6 Synthesis of fully protected tunicaminyluracil.

they are expected to be potent antitubercrosis agents.[9] The structure of LPSs 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 (**24**), was determined by X-ray crystal structure analysis. We are interested in the biological activity of this class of natural products as well as structural complexity and started the synthesis of LPS core structure, which might be the same as caprazole. More than 6 groups have studied the total synthesis of LPS. Difficulty in the synthesis of this class of molecules may lie with the introduction of 5-aminoribose moiety found in **22–24** after construction of a uridyldiazepanone moiety because the tertiary amine contained in the diazepanone structure inhibited the usual ribosylation promoted by Lewis acid. In



SCHEME 7 Retrosynthetic analysis of caprazol.

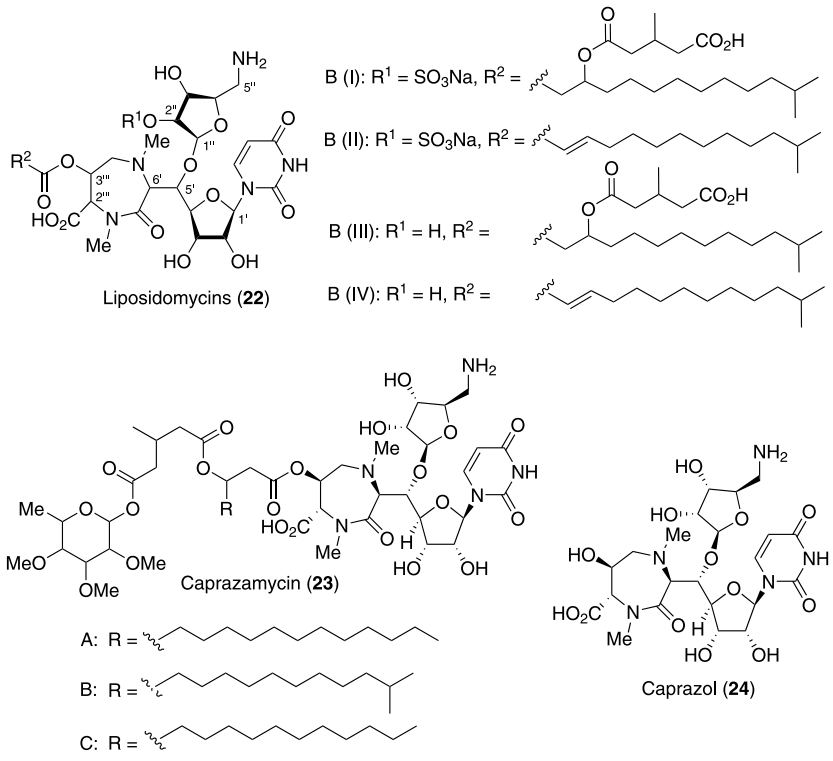
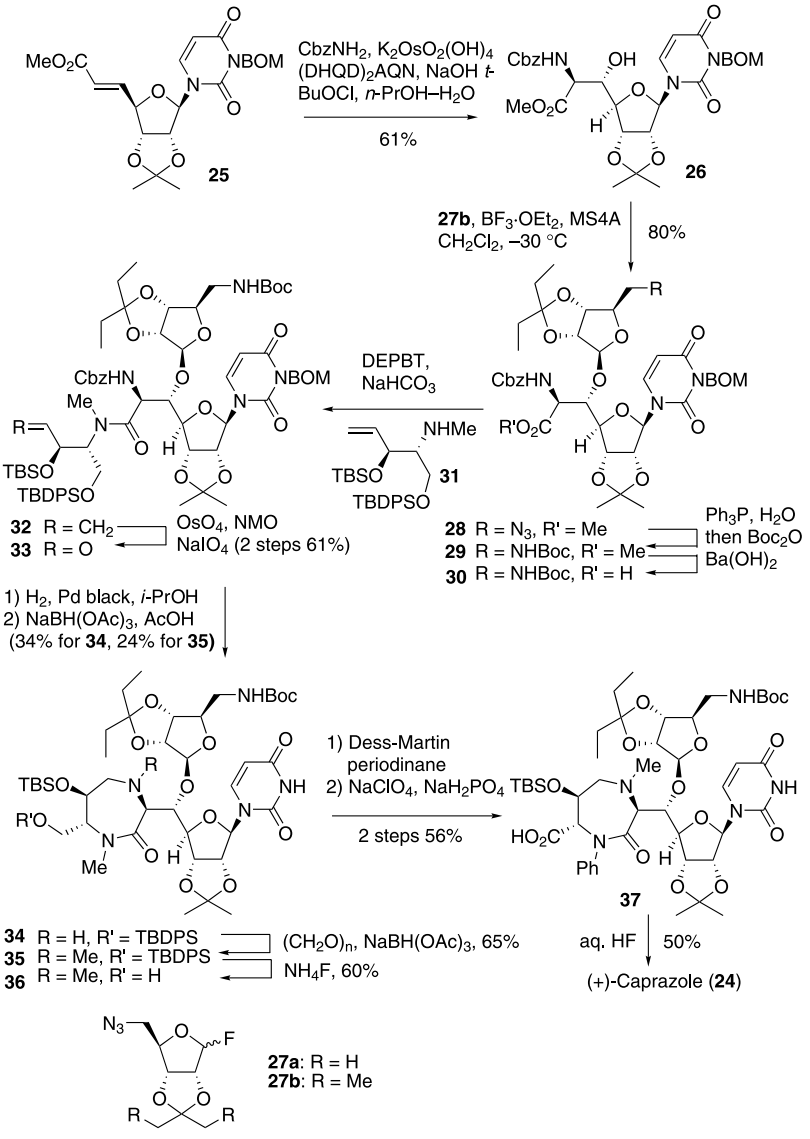


FIGURE 3 Structures of liposidomycins, caprazamycins, and caprazol.

addition, **22–24** 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 the aminoribose protected with an acid labile protecting group at an early stage of the synthesis as shown in Scheme 7 and control β-selective introduction via a steric hindrance installed at the α-face of the ribofuranosyl donor (Figure 3).



SCHEME 8 Total synthesis of caprazol.

Compound **25** was prepared by the IBX oxidation of 2',3'-*O*-isopropylideneuridine followed by 2-carbon elongation by Wittig reaction and protection of 3-position with BOM group. Then, the Sharpless' aminohydroxylation was conducted with the use of $[DHQD]_2AQN$ ligand, the (5'*S*,6'*S*)-aminoalcohol **26** was obtained as a major diastereomer. When the ribosyl fluoride **27a** was activated with $BF_3 \cdot Et_2O$ at $-30°C$, the stereoselectivity was observed up to $\alpha/\beta = 27/73$. We thought the stereoselectivity was enhanced by introducing the more sterically hindered protecting group at the α-face of ribose. When the pentylidene protected ribosyl fluorides **27b** was activated with $BF_3 \cdot Et_2O$ at $-30°C$, the stereoselectivity was dramatically increased and the ratio of the anomer was $\alpha/\beta = 4/96$. Since our method is simple and quite effective, it would be an alternative entry to construct β-ribosides without using a neighboring group participation.

The azide group of the riboside **28** was reduced to the corresponding amine, which was protected with a Boc group to give **29**. Basic hydrolysis of the methyl ester was troublesome, the desired carboxylic acid **30** 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 **30** with the secondary amine **31** using DEPBT as a coupling reagent gave the amide **32**. 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 **34**. Interestingly, its *N*-methylated compound **35**, one step advanced compound, was also obtained in 34%. It is supposed that the methyl source in the formation of **35** was the formaldehyde generated in the course of BOM group deprotection. The conversion of the alcohol **36** to carboxylic acid **37** was conducted by the sequential oxidation of the TBDPS deprotected compound. Finally, global deprotection of isopropylidene, pentylidene, Boc, and TBS group with aqueous HF was applied to compound **37**, and successfully provided **24**. This synthetic material was identical in all respects with the properties for the authentic caprazol (Scheme 8).

This approach would provide a range of key analogues with partial structures to define the pharmacophore, which can be a lead for the development of more effective antibacterial agents.

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