

HETEROCYCLES, Vol. 95, No. 2, 2017, pp. 662-693. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 8th September, 2016, Accepted, 24th October, 2016, Published online, 16th January, 2017
DOI: 10.3987/REV-16-SR(S)5

SYNTHESIS OF CAPRAZAMYCINS AND RELATED NATURAL PRODUCTS

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Abstract – Caprazamycins are the lead compound for CPZEN-45, which exhibits activity against extensively drug resistant tuberculosis (XDR-TB) and is currently under preclinical studies. The development of an efficient synthetic route to caprazamycins and related compounds is expected to facilitate structure-activity relationship studies on anti-TB agents. This review summarizes current synthetic strategies for caprazamycins, liposidomycins, caprazol, and CPZEN-45, with a particular focus on stereocontrol and diazepanone ring formation.

CONTENTS

1. Introduction
2. Synthesis of CPZEN-45 from caprazamycins
3. Synthetic studies on liposidomycins and caprazamycins
 - 3-1. Synthesis of the uridyl diazepanone core and the side-chain moiety by Kim
 - 3-2. Synthesis of the degradation product of liposidomycins by Knapp
 - 3-3. Synthesis of diazepanone derivatives by Nakajima and Ubukata
 - 3-4. Synthesis of the diazepanone core by Le Merrer and Gravier-Pelletier
 - 3-5. Synthetic studies by Greck, Sarabia, and Miyaoka
4. Total synthesis of caprazol by Matsuda and Ichikawa
5. Total synthesis of caprazamycin A, caprazol, and CPZEN-45 by Takemoto
6. Catalytic asymmetric synthesis of caprazol, caprazamycin B, and CPZEN-45 by Shibasaki and Watanabe
7. Conclusion

This review article is dedicated to Prof. Dr. Masakatsu Shibasaki on occasion of his 70th birthday.

1. INTRODUCTION

Natural products are a rich source of pharmaceuticals. In particular, second metabolites of microorganisms have long been applied as pharmaceuticals, either as is or after synthetic derivatization, to combat infectious diseases. One highly successful example of this is the antiparasitic ivermectin developed from the natural product of a microorganism by Ōmura, who received the Nobel Prize in Physiology or Medicine for his discovery in 2015.¹ The broad spectrum of biological activity exhibited by second metabolites is due to their tremendous structural diversity, and many natural products of this class are considered promising drug leads.

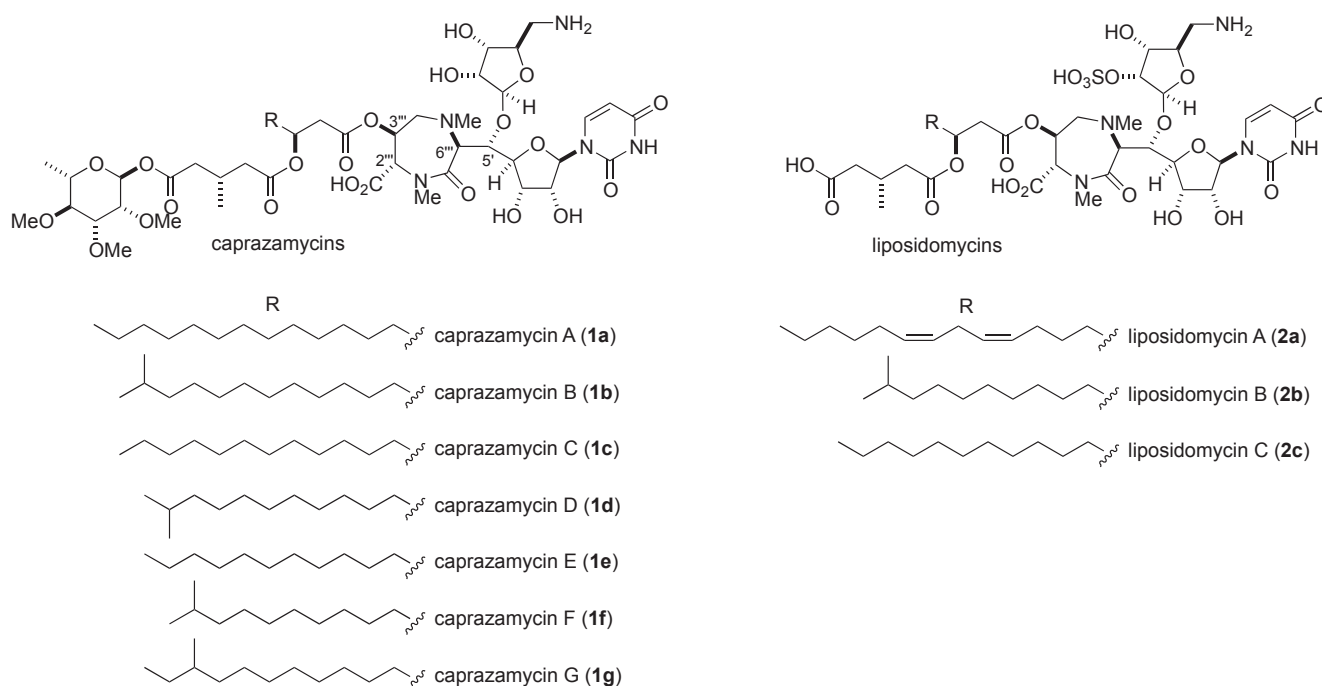


Figure 1. Structure of caprazamycins and liposidomycins

Liponucleoside antibiotics, whose structures are characterized by a nucleoside moiety connected with a lipophilic side-chain portion, are also categorized as second metabolites of microorganisms with a variety of biological activities. Recently, caprazamycins (**1**, Figure 1), which are members of the liponucleoside antibiotic family, have attracted the attention of researchers in the field of medicinal chemistry; a novel anti-tuberculosis (TB) candidate was developed from caprazamycins and is now under preclinical study (*vide infra*). Caprazamycins, produced by the actinomycete *Streptomyces* sp. MK730-62F, were discovered to function as anti-TB antibiotics by Igarashi and co-workers in 2003,² followed by structural elucidation based on degradation studies and extensive NMR analyses.³ Caprazamycins comprise seven congeners with an identical core structure (caprazol core, *vide infra*) attached to a lipophilic side-chain of various lengths and branching patterns, caprazamycins A-G (**1a-1g**). Among them, caprazamycin B (**1b**)

exhibits the most potent anti-TB activity toward *Mycobacterium tuberculosis* (*M. tuberculosis*) H37Rv strain with a MIC value of 3.13 $\mu\text{g/mL}$, as well as against drug-sensitive strains (DS-TB, MIC ranging from 6.25 - 12.5 $\mu\text{g/mL}$). The core structure comprises a uridine portion connected with the characteristic 7-membered lactam, diazepanone ring system, and aminoribose moiety. The structure of caprazamycins resembles that of liposidomycins (**2a-2c**) reported by Isono and co-workers in 1985,⁴ which exhibit antimicrobial activity by the inhibition of MraY,⁵ a key enzyme in the bacterial peptidoglycan biosynthetic pathway. Based on their complex structural features^{6,7} and intriguing biological activity as leads of clinical medicines, caprazamycin-related natural products are widely researched targets in the synthetic community.

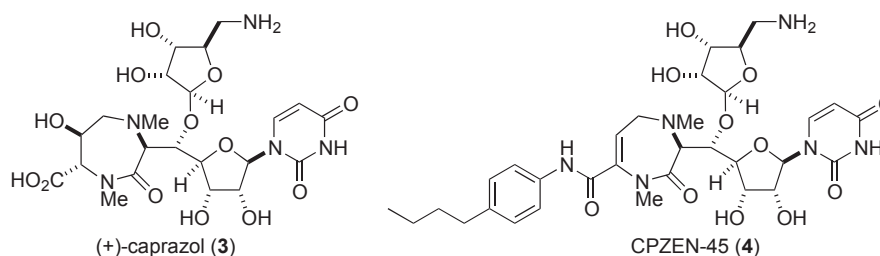


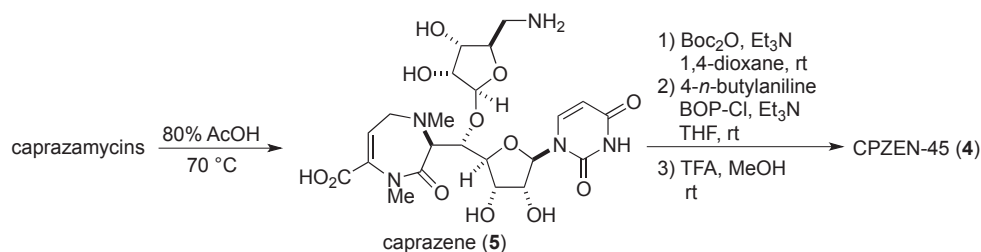
Figure 2. Structure of (+)-caprazol and CPZEN-45

The compound with the simplest structure among this type of natural products is (+)-caprazol (**3**, Figure 2), which is a core structure of caprazamycins and liposidomycins comprising uridine, diazepanone, and aminoribose moieties, but lacking a lipophilic side-chain substructure. Many early studies on the syntheses of liposidomycins focused on the construction of the diazepanone ring system or uridyl diazepanone structure. In 2005, Matsuda, Ichikawa, and co-workers disclosed the first total synthesis of a caprazamycin-related natural product, (+)-caprazol.⁸ This pioneering triumph facilitated the development of synthetic methods for caprazamycins established by Takemoto's group and Shibasaki and Watanabe's group. Notably, caprazamycins were semisynthetically derived into analogs, including CPZEN-45 (**4**, Figure 2), which exhibits anti-TB activity against extensively drug resistant TB (XDR-TB) strains.⁹ Interestingly, a molecular target of CPZEN-45 was revealed to be WecA,¹⁰ a key enzyme in the biosynthesis of mycolyl arabinogalactan, which is essential for the viability of *M. tuberculosis* and yet has never been a molecular target of clinical anti-TB drugs; this mechanism could underlie the anti-multidrug-resistant-TB activity of CPZEN-45. Currently, CPZEN-45 is under preclinical studies and clinical trials are expected to follow soon. The total syntheses of caprazol prompted the establishment of de novo syntheses of CPZEN-45; indeed, caprazol and CPZEN-45 have almost the same structural complexity. This review article summarizes the synthetic efforts toward caprazamycin-related compounds disclosed to date, with a particular focus on the installation of requisite stereochemistries and strategies to

construct the diazepanone ring system. The requisite stereochemistries include the β -hydroxy- α -amino acid portions found between the uridine and diazepanone and within the diazepanone ring, as well as the β -hydroxyester- and unsymmetrically esterified glutaric acid moieties in the side-chain part. It should be also noted that structure-activity relationship (SAR) studies and synthetic study on derivatives of caprazamycin and liposidomycin were carried out by many research groups,^{11,12} while they are beyond the scope of this review article.

2. SYNTHESIS OF CPZEN-45 FROM CAPRAZAMYCINS

Before discussing the total synthesis approach, we describe the preparative method of one of the most important semisynthetic derivatives, CPZEN-45. The development of this analog with outstanding biological activity has provided valuable information regarding the stability of caprazamycins.



Scheme 1. Preparation of CPZEN-45 from caprazamycins

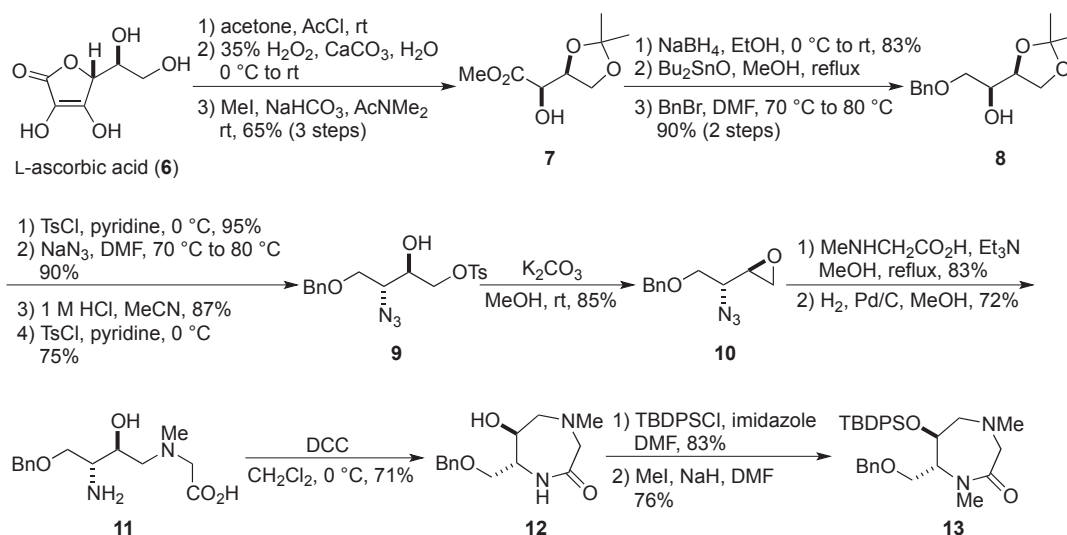
Synthesis of CPZEN-45 was accomplished via caprazene (**5**), which was obtained by elimination of the side-chain moiety of caprazamycins with 80% AcOH at 70 °C for 3 h (Scheme 1).⁹ Caprazene is a useful platform for further derivatization by amidation and esterification to produce CPZEN-45. This SAR study was based on a degradation study³ performed during structure determination showing that weak alkaline conditions resulted in simple hydrolysis of the side-chain moiety to produce caprazol (**3**). Further, treatment of caprazamycins with 80% TFA in MeOH removed the rhamnose component. These outcomes suggested that acidic and basic conditions are incompatible with the final stage of the total synthesis of caprazamycins.

3. SYNTHETIC STUDIES ON LIPOSIDOMYCINS AND CAPRAZAMYCINS

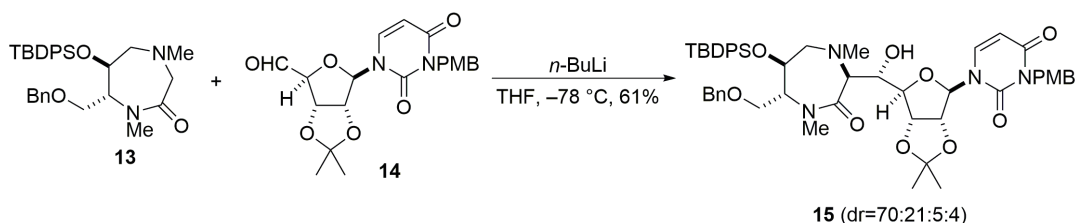
3-1. Synthesis of the uridyl diazepanone core and the side-chain moiety by Kim

Synthesis of the diazepanone core¹³ began with the preparation of a protected triol **7**¹⁴; the stereochemistry was preinstalled onto the starting material, L-ascorbic acid (**6**), in an attempt to furnish the amino- and hydroxy groups of the intermediate **11** in a stereospecific manner (Scheme 2). Indeed, **7** was converted into protected tetraol **8** with one hydroxy group remaining unmasked, with which the

substitution reaction was carried out with NaN₃ as the nucleophile. The nitrogen constituting the diazepanone system was introduced through the opening of epoxide **10** obtained by tosylate **9** to give **11** after reduction of the azide group. Lactamization with DCC then afforded **12** to construct the diazepanonesystem, followed by silylation to give the substrate of the subsequent aldol reaction, **13**.¹⁵



Scheme 2. Synthesis of the diazepanone core by Kim

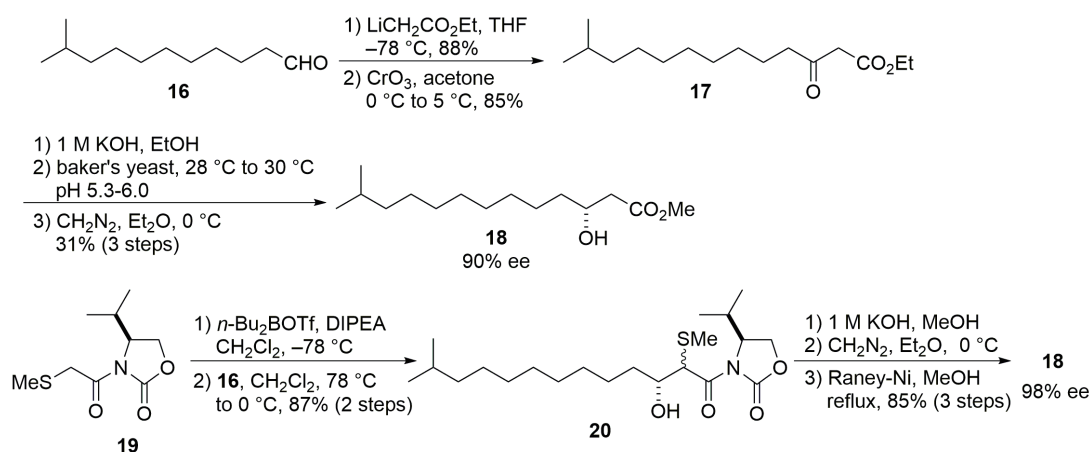


Scheme 3. Aldol reaction to construct the ribosyl uridine structure by Kim

While the aldol approach to connect the uridine- and diazepinone parts of caprazamycins and liposidomycins seems to be a promising tactic, only limited examples using this strategy are reported to date. The result demonstrated in Scheme 3 is one example; the pre-nucleophile **13** was treated with *n*-BuLi for 30 min at -78 °C, and then an aldehyde **14**, which can be prepared from uridine by reported procedures, was added and the reaction was continued for 1.5 h at the same temperature to afford the corresponding adduct **15** in moderate yield and with moderate diastereoselectivity. Kim and co-workers speculated that the predominance of the desired isomer was caused by chelation of the lithium cation to the ring oxygen of the ribose and the carbonyl oxygen of the formyl group. Despite extensive studies,¹⁶ glycosylation and completion of the synthesis of caprazol core have not yet been reported.

Kim and co-workers successfully prepared the side-chain part of liposidomycin B with excellent enantioselectivity (Scheme 4).¹⁷ They used two approaches to furnish the β -hydroxyester moiety of **18**:

one approach was enzymatic reduction of the corresponding ketone **17** prepared from **16**, and the other was a chiral auxiliary-based diastereoselective aldol reaction reported by Evans and co-workers.¹⁸ While the former approach produced an unsatisfactory enantiomeric excess, the latter gave **18** with 98% ee by the reaction of **19** and **16** to afford the adduct **20** following the removal of the auxiliary and sulfur functionality.



Scheme 4. Synthesis of the side-chain substructure by Kim

3-2. Synthesis of degradation product of liposidomycins by Knapp

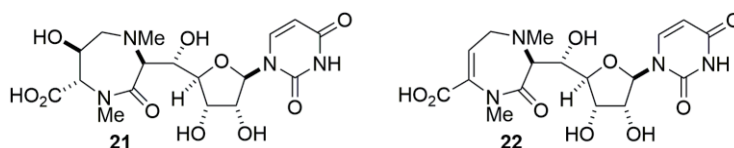
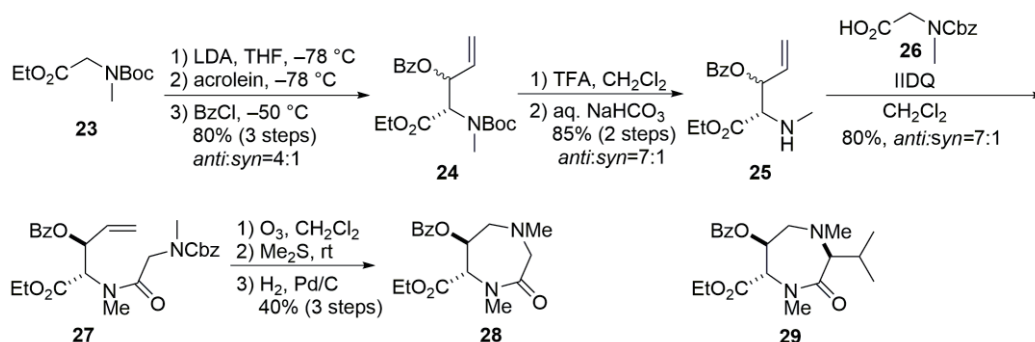


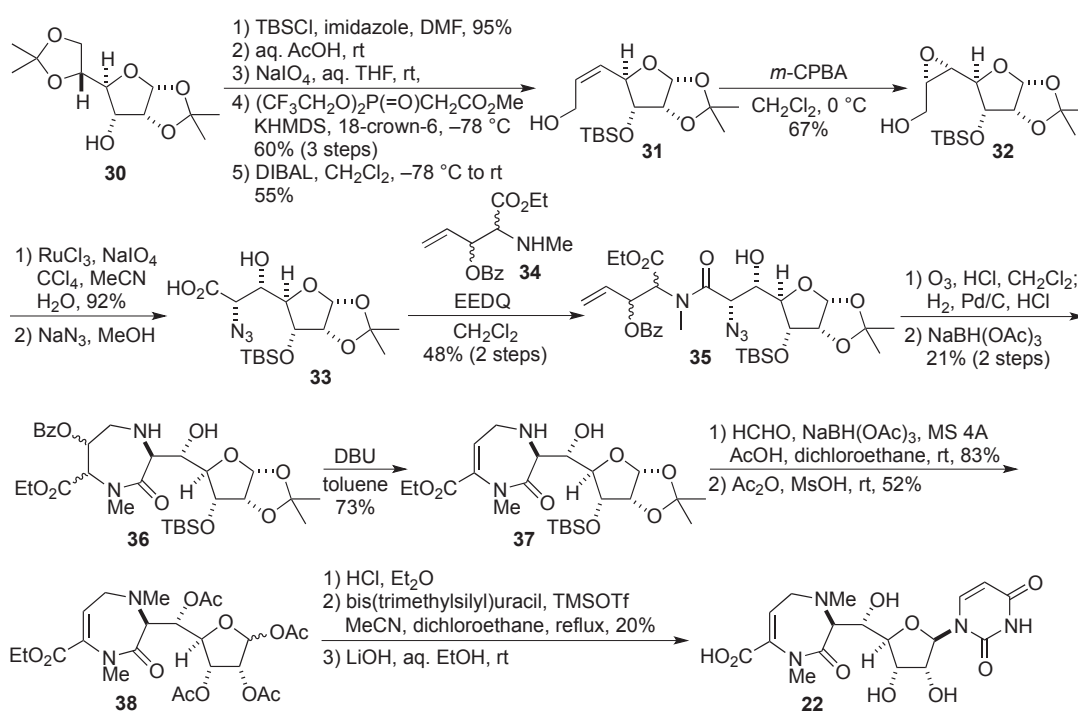
Figure 3. Degradation products of liposidomycins

In the early synthetic studies of liposidomycins, their degradation products maintaining a uridyldiazepinone structure, such as **21**⁷ and **22**⁶ (Figure 3) were frequently set as subgoals. Some of the studies synthesized the stereoisomer of these degradation products because of a lack of information regarding the stereochemistry, even the relative stereochemistry.



Scheme 5. Synthesis of the diazepanone core by Knapp

In 1992, Knapp and co-workers reported the racemic synthesis of diazepamone derivative **28** using two differently protected sarcosine derivatives, **23** and **26** (Scheme 5).¹⁹ An aldol reaction was achieved with **23** and acrolein under standard deprotonation conditions, resulting in **24** after protection of the secondary hydroxy group at a diastereomeric ratio of 4:1. A mixture of diastereomers was used for the subsequent deprotection reaction to afford **25** with a diastereomeric ratio of up to 7:1. Again, the diastereomeric mixture of **25** was applied to the coupling reaction⁵ with the other sarcosine unit **26** to give **27** (70% isolated yield based on the isomeric mixture) and its diastereomer. Hereafter in this section, the description is focused on **27** with the correct relative stereochemistry. The olefin is a masked formyl group; ozonolysis gave aldehyde with spontaneous condensation to cyclic imine, which was hydrogenated to successfully afford the diazepamone ring. Substitution of the second sarcosine derivative with a protected leucine led to the synthesis of additionally functionalized derivative **29**, unequivocally revealing the stereochemistry of the diazepamone substructure.²⁰

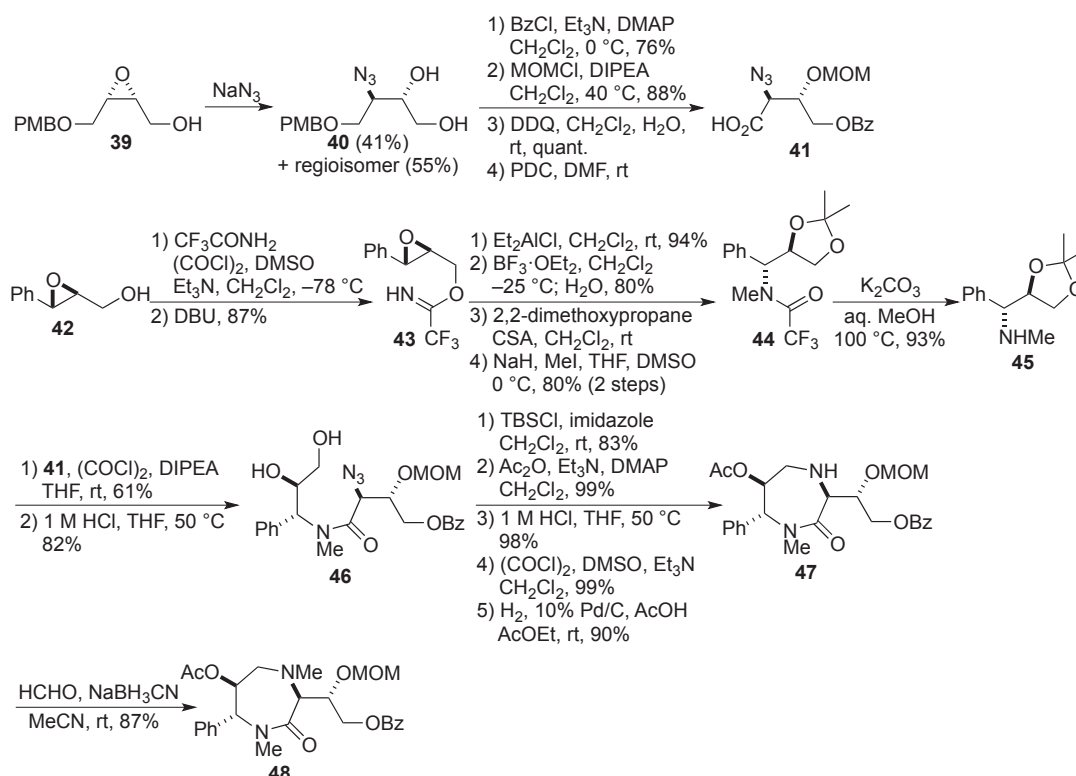


Scheme 6. Synthesis of the degradation product of liposidomycin **22** by Knapp

In further studies aimed at the synthesis of liposidomycin degradation product **22** (Scheme 6),²¹ an allylic alcohol installed onto a ribose core, **31**, was prepared from the commercially available ribose derivative **30**. The correct stereochemistry of the β -hydroxy- α -amino acid structure between the uridine and diazepamone was set by Sharpless epoxidation of **31**, opening of the resultant epoxide **32**, and successive oxidation to the corresponding carboxylic acid. With the azidation product **33** in hand, secondary amine **34** was coupled to make amide **35**, and the reductive amination strategy was again applied as in the

synthesis of **28** to give ribosyl diazepanone derivative **36**. The diazepanone ring was transformed into the diazepanone system by base-promoted elimination to afford **37**, which could be further converted to the glycosyl donor **38**. Introduction of a uracil core was achieved by Lewis acid-mediated glycosylation with an acyl sugar as the donor. Final hydrolysis of all the acetyl groups achieved the synthesis of **22**.

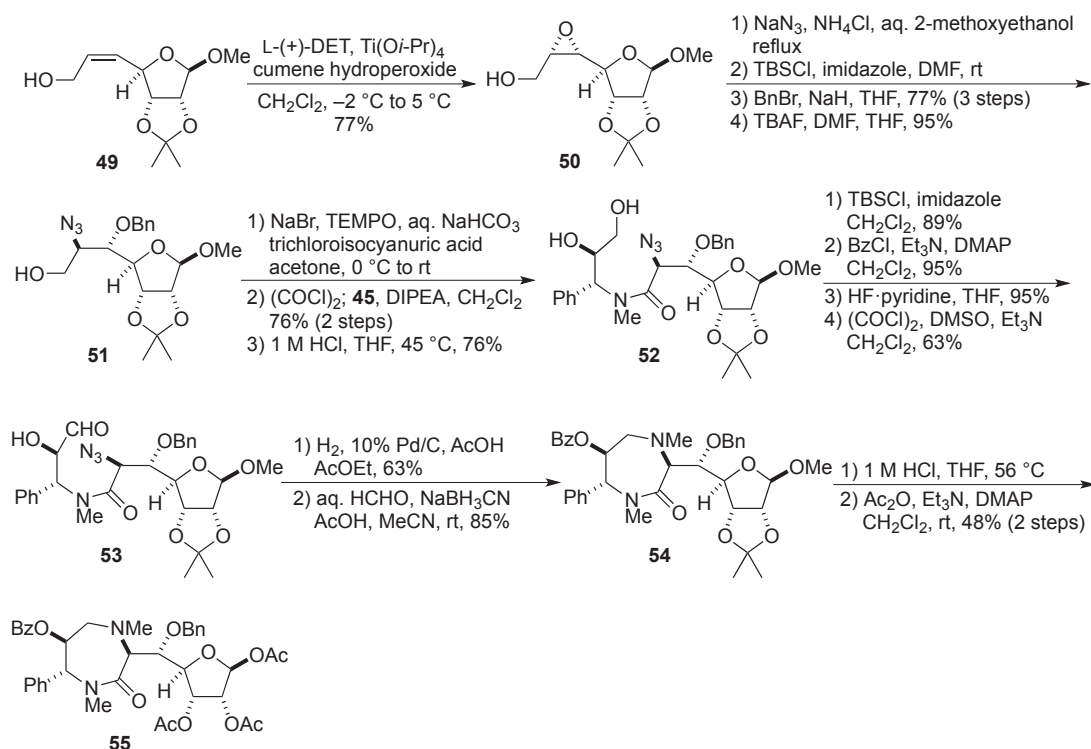
3-3. Synthesis of diazepanone derivatives by Nakajima and Ubukata



Scheme 7. Synthesis of the diazepanone derivative by Nakajima and Ubukata

Nakajima, Ubukata and co-workers also attempted to synthesize liposidomycin degradation products and established a route to diazepinone derivatives with the correct stereochemistry embedded (Scheme 7 and Scheme 8).²² The synthesis commenced with opening of (2*S*,3*S*)-3-phenylglycidol **39** by an azide anion to afford diol **40**, albeit with low regioselectivity. Then, manipulation of the protecting groups and chromium-promoted oxidation led to carboxylic acid **41**. In parallel, a literature-known chiral epoxide **42**²³ was transformed into its trifluoroacetimidate **43** via in situ generation of trifluoroacetonitrile.²⁴ A two-step rearrangement sequence gave rise to **45** via **44**. At this stage, acid chloride was prepared from **41**, which was used in the acylation of **45** to give diol **46** after acid hydrolysis.²⁵ Three-step protection of the secondary hydroxy group of the diol and oxidation to aldehyde led to the diazepinone system of **47** by reductive amination. Methylation of the secondary amine on the ring completed the synthesis of **48**. This

synthesis shares strategies with the synthesis by Knapp; both took advantage of optically active epoxides to furnish a key stereoelement and a reductive amination protocol for ring closure.



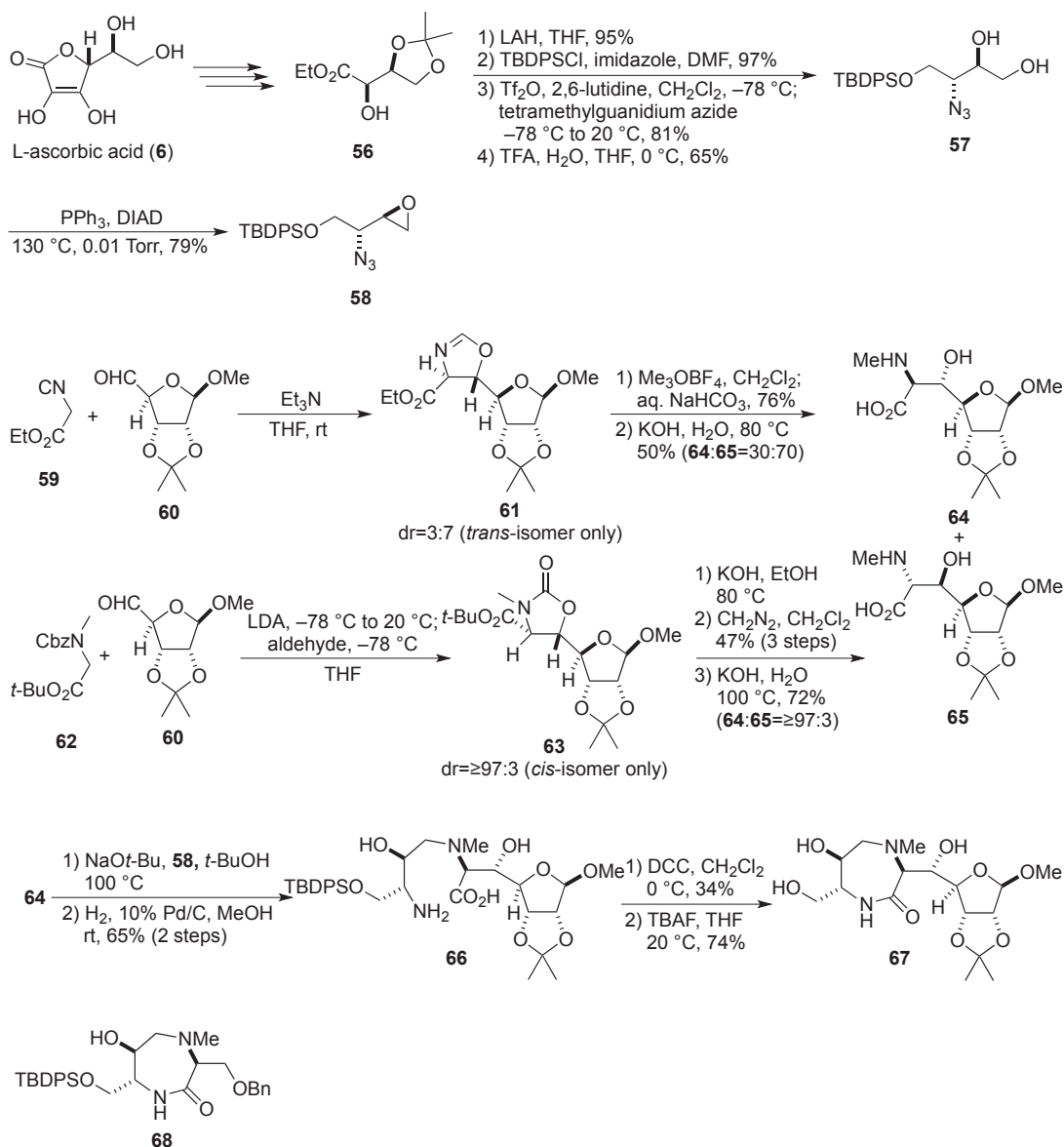
Scheme 8. Synthesis of the ribosyl diazepanone by Nakajima

The synthesis of ribosyl diazepinone derivative **55** (Scheme 8)²⁶ began with a strategy similar to that used for the diazepinone congener by Knapp (Scheme 6); diastereoselective epoxidation of ribose-derived allylic alcohol **49**, and opening of the epoxy moiety of **50** by an azide anion.²⁷ As seen in the synthesis of simpler diazepanone derivative **48**, amidation of the carboxylic acid derived from **51** was achieved, and protecting group manipulation and interconversion of the functional groups afforded **53**, a precursor of diazepanone derivative **54**, via diol **52**. Reductive amination and a change in the protecting groups gave **55**, to which the uracil core²⁸ could not be introduced.

3-4. Synthesis of the diazepanone core by Le Merrer and Gravier-Pelletier

The synthesis of ribosyl diazepanone derivative **67** by Le Merrer can be characterized by the aldol approach to connect the uridine- and diazepinone parts, as demonstrated in Scheme 9.²⁹ A stereodefined fragment of the diazepanone system, **58**, was prepared by a strategy similar to that of Kim starting from ascorbic acid via **56**³⁰ and **57**. Then, to make the β -hydroxy- α -amino acid substructure attaching the uridine- and diazepanone moieties, two types of aldol reactions were examined: an isocyanoacetate aldol reaction of **59** and **60**, and an aldol reaction using sarcosine derivative **62**. In the isocyanoacetate aldol

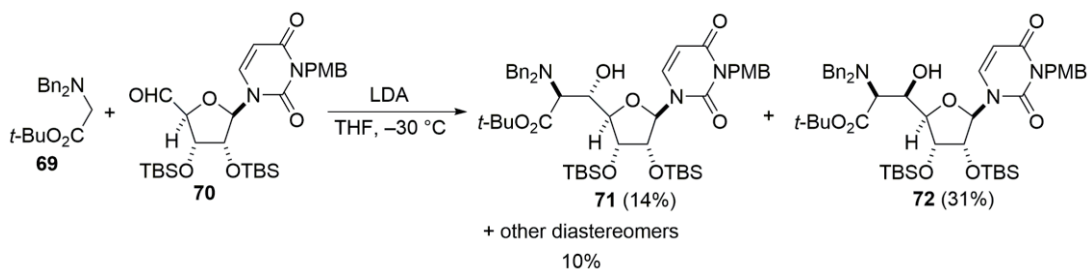
reaction, triethylamine was added to the mixture of the substrates to give the *trans*-oxazoline adduct exclusively (the desired isomer **61** is shown in the scheme), although the undesired diastereomer within the *trans*-product predominated (30:70).



Scheme 9. Synthesis of the ribosyl diazepanone derivative by Le Merrer and Gravier-Pelletier

On the other hand, the approach using sarcosine gave *cis*-oxazolidinone **63** exclusively. The products of both of the reactions could be transformed into the free β -hydroxy- α -amino acid derivatives without difficulty. It is important to point out that the stereochemistry at the α -position of the ester of the oxazolidinone product in the latter reaction condition **63** could be corrected by epimerization, thus achieving indirect but perfect stereocontrol using the aldol approach. To construct the ring system by lactamization from **66** to **67** with DCC, **58** and **64** were assembled by opening the epoxide by the

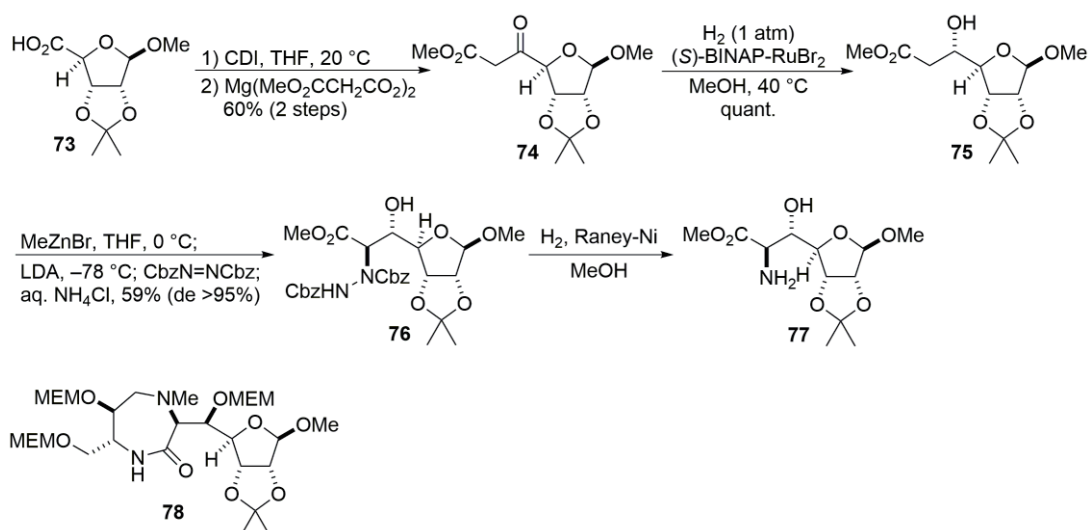
secondary amine to create the whole framework of **66**. Le Merrer and co-workers also reported the synthesis of the simpler diazepanone derivative **68**³¹ and model reaction of aminoribose introduction.³²



Scheme 10. Another aldol approach by Yamashita in the synthesis of muraymycin derivatives

Interestingly, the outcome of the latter approach is highly influenced by the substrate structure; the combination of bisbenzyl-protected glycine **69** and uridine-derived aldehyde **70** protected with TBS groups increased the proportion of the desired diastereomer **71**, although the undesired isomers **72** predominated (Scheme 10).³³

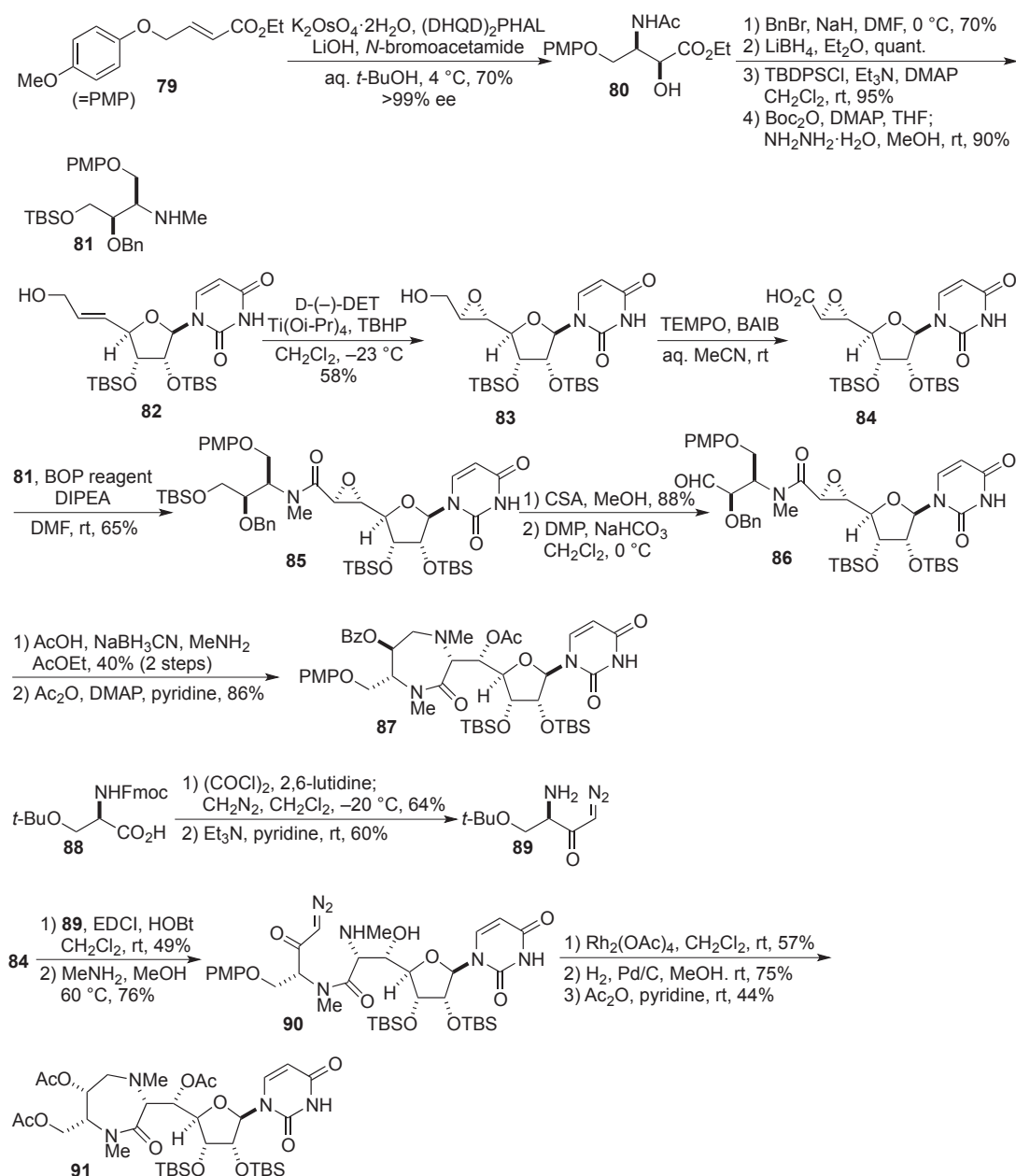
3-5. Synthetic studies by Greck, Sarabia, and Miyaoka



Scheme 11. Synthesis of the ribosyl diazepanone derivative by Greck

In this section, three more interesting approaches are described. Scheme 11 summarizes the synthesis of ribosyl diazepanone **78** by Greck and co-workers, although it is epimeric to the requisite configuration.³⁴ They installed the correct stereochemistry for the β -hydroxy- α -amino acid substructure at the junction of uridine and the diazepanone by a Noyori reduction of β -ketoester **74** prepared from **73** in two steps (dr=95:5), and electrophilic amination of the zinc enolate prepared from **75** in excellent diastereoselectivity (over 95% de). The bond between the two nitrogens of **76** was abolished by Raney-Ni

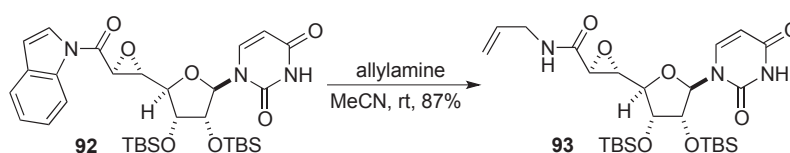
with concomitant removal of the Cbz group to afford **77**. In the same manner, the 5'-*epi*-derivative (caprazamycin numbering) could be synthesized, from which **78** was obtained by reductive amination to construct the diazepanone ring.³⁵



Scheme 12. Synthesis of the uridyl diazepanone derivatives by Sarabia

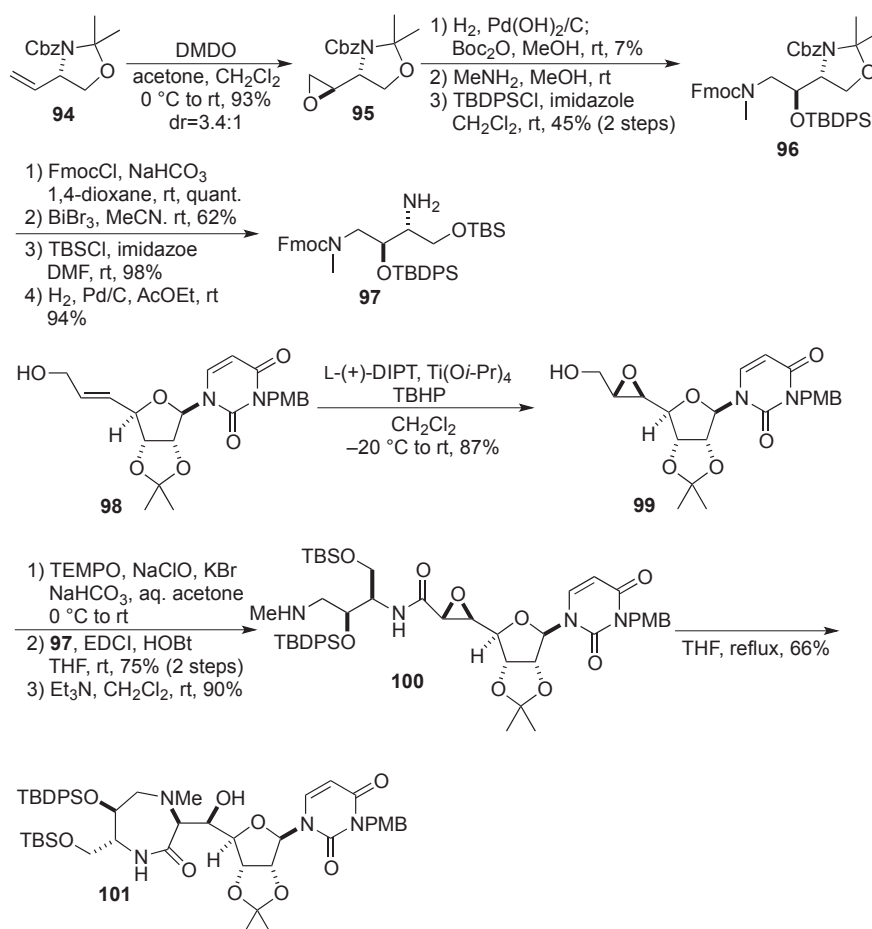
Sarabia and co-workers synthesized a 6''''-*epi*-uridyl diazepinone derivative (caprazamycin numbering) **87** as demonstrated in Scheme 12.³⁶ Stereocontrol of one hydroxy group was accomplished by the opening of epoxide **86**; it is distinct from the previous report in which the opening reaction was set at the final stage where a 7-membered ring was closed by nucleophilic attack of the methylamino group introduced by the reductive amination of **86**. The correct stereochemistry of the β -hydroxy- α -amino acid substructure found

in the diazepanone system was furnished by the Sharpless aminohydroxylation reaction using **79** as the substrate to give **80**, which was further transformed into **81** by standard reactions.³⁷ Next, configuration of the epoxide **83** was defined by Sharpless epoxidation of **82**, and oxidation was carried out to give carboxylic acid **84**. Carboxylic acid **84** was connected with **81** to afford **85**, the precursor of **86**, by the standard amidation reaction. They also tried a unique approach to an intramolecular cross-coupling reaction³⁸ of **90** (prepared from **89**), taking advantage of its diazo moiety and the secondary amine to cyclize a 7-membered ring in the synthesis of **91** with an unnatural configuration at the two carbons.



Scheme 13. Preparation of uridyl amide

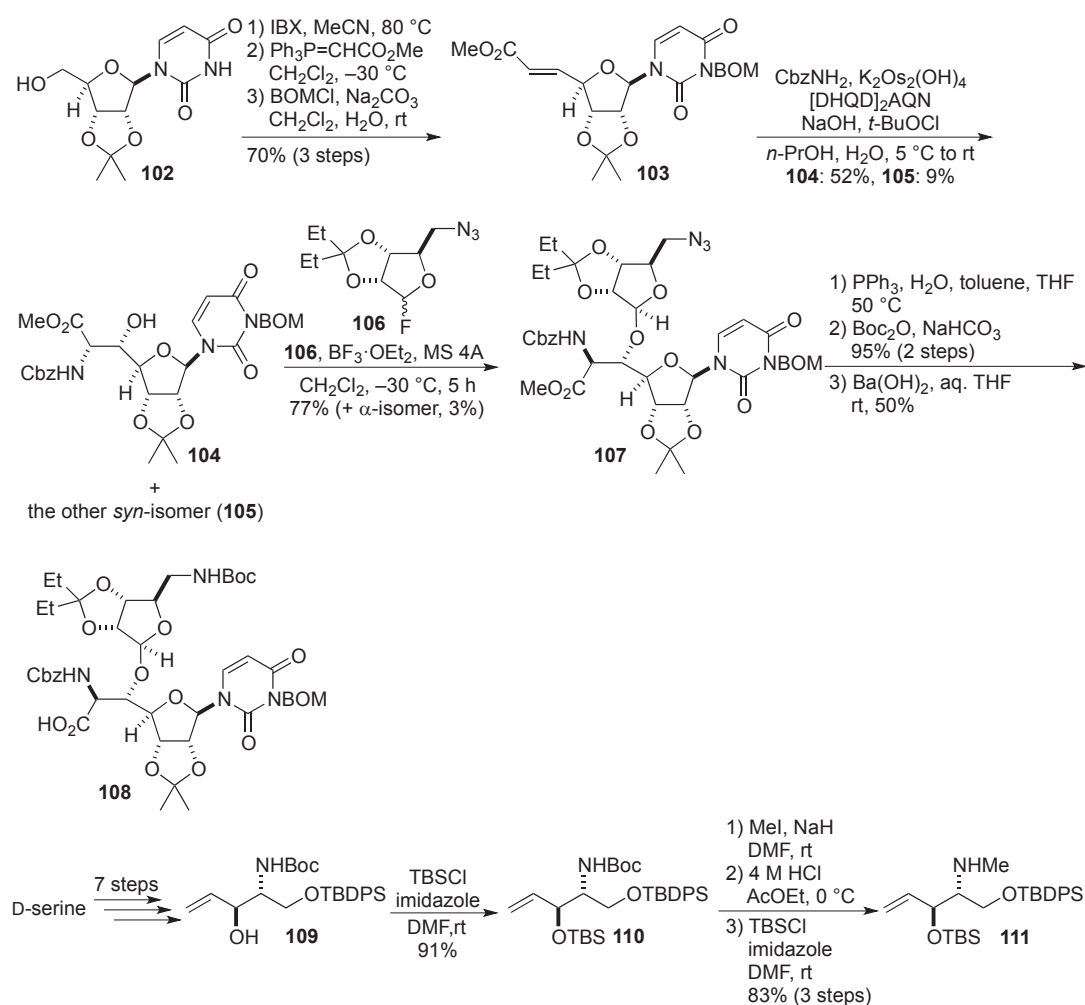
Additionally, Sarabia and co-workers established an efficient protocol to prepare uridyl amides such as **93** (Scheme 13) by amide-interconversion from **92**; mixing with an external amine effectively achieved this transformation.³⁹



Scheme 14. Synthesis of 5'-*epi*-uridyl diazepanone derivatives by Miyaoaka

Miyaoka and co-workers also reported the synthesis of 5'-*epi*-uridyl diazepanone derivative **101** (Scheme 14) using a strategy similar to that of Sarabia.⁴⁰ They also took advantage of the epoxide opening of **100** for the final cyclization leading to the diazepanone system; **100** was prepared by Sharpless epoxidation of **98** and embellishment of the resultant epoxide **99**. Another requisite fragment corresponding to a part of the diazepanone ring, **97**, was synthesized starting from known chiral building block **94**⁴¹ via **95** and **96**.

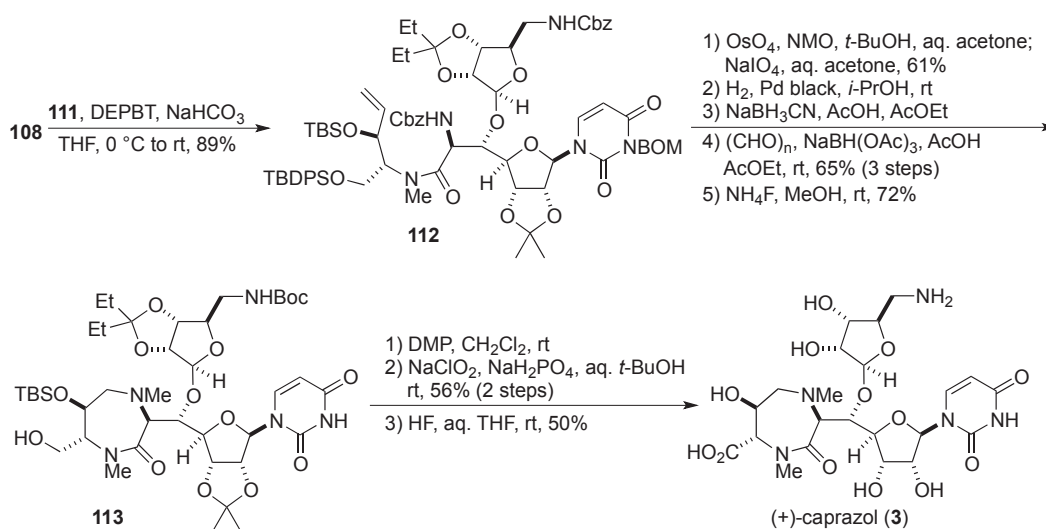
4. TOTAL SYNTHESIS OF (+)-CAPRAZOL BY MATSUDA AND ICHIKAWA



Scheme 15. Total synthesis of (+)-caprazol by Matsuda and Ichikawa: stereoselective segment synthesis

The first total synthesis of a caprazamycin-related natural product was accomplished by Matsuda, Ichikawa and co-workers in 2005 (Scheme 15),^{8,42} who developed the glycosylation procedure to set up the aminoribose moiety. In the initial step, uridine derivative **102** was oxidized to an aldehyde with a uracil core protected by a benzyloxymethyl (BOM) group, with which a Horner-Wadsworth-Emmons reaction was applied to afford α,β -unsaturated ester **103**. The first key stereoselective transformation in this synthesis was Sharpless asymmetric aminohydroxylation to give *syn*-aminoalcohol protected as the

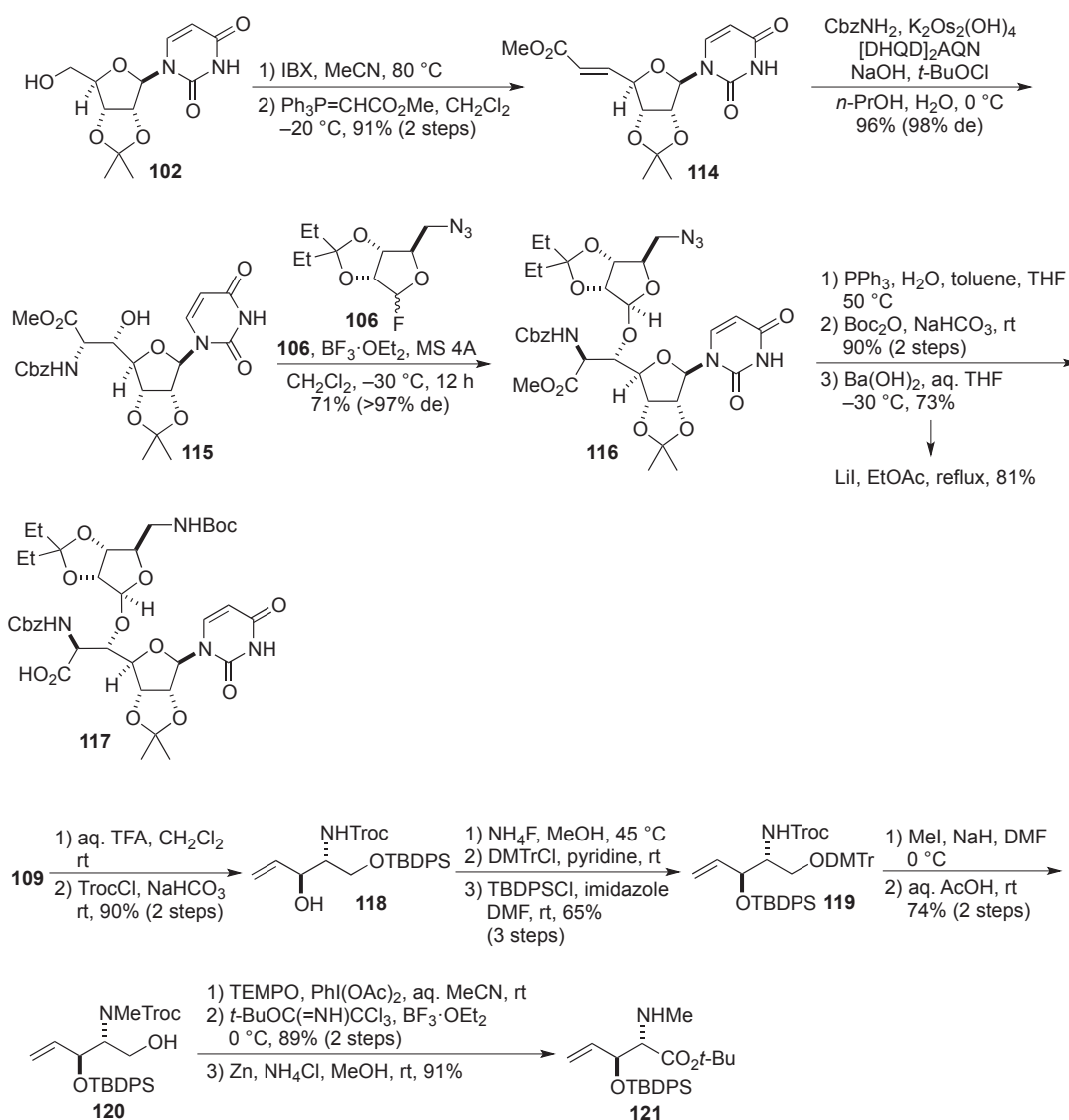
Cbz carbamate **104**; the desired isomer was obtained in 52% yield, whereas the *syn*-isomer **105** was observed in 9%. Next, the glycosylation conditions were screened. To obtain β -riboside with high selectivity, fluorosugar (**106**) was used as the glycosyl donor and the 2,3-dihydroxy moiety was protected by a 3-pentylidene group, which is bulkier than the more commonly used isopropylidene group; production of the dominant conformer was speculated based on calculations to rationalize the β -selectivity. Under the optimized conditions at $-30\text{ }^{\circ}\text{C}$ with $\text{BF}_3\cdot\text{OEt}_2$ as the promoter in CH_2Cl_2 ,⁴³ β -glycoside was obtained in an amount almost 26 times greater than that of α -glycoside. Use of a silver salt/Lewis acid combination such as $\text{AgOTf}/\text{Cp}_2\text{HfCl}_2$,⁴⁴ $\text{AgOTf}/\text{SnCl}_2$ ⁴⁵ and $\text{AgClO}_4/\text{SnCl}_2$ resulted in less satisfactory selectivity, and TMSOTf was not converted. This condition has a general substrate scope; examples of six different primary or secondary alcohols other than **104** showed a reasonable isolated yield and selectivity (β : α ratio ranging from 81:19 to 97:3), and a change of the azide group of **104** to methoxy-, benzyloxy-, and acetoxy groups was also tolerated. Manipulation of the functional group and protecting group gave carboxylic acid intermediate **108**. In parallel, another segment, **111**, corresponding to a part of the diazepamone framework was synthesized by an array of standard reactions from **109**, which can be prepared from D-serine according to the published procedure,⁴⁶ in a four-step protocol via **110**.



Scheme 16. Total synthesis of (+)-caprazol by Matsuda and Ichikawa

A coupling reaction of two segments, **108** and **111**, was accomplished by taking advantage of DEPBT⁴⁷ as the coupling reagent to give **112** (Scheme 16). Then, a hidden formyl group was unveiled by dihydroxylation and the subsequent oxidative cleavage of the olefin moiety, which was subsequently exposed to hydrogenolysis conditions to remove Cbz. The deprotection was followed by spontaneous formation of cyclic imine, and further hydrogenation did not occur under these conditions. At the same

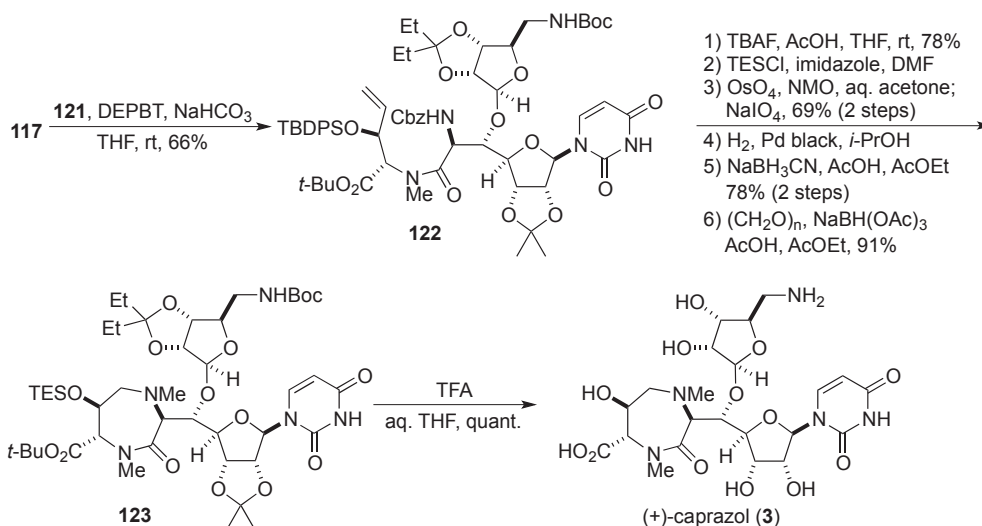
time, the BOM group was removed to expel formaldehyde, which contributed to the partial methylation of the secondary amine during subsequent hydride reduction of the imine. For this reductive amination, the proper choice of solvent and reductant are crucial; *i*-PrOH and NaBH(OAc)₃ are more suitable than MeOH or EtOH, and NaBH₃CN, respectively. The unreacted secondary amine was further methylated by reductive amination with paraformaldehyde, and selective desilylation of the primary silyl ether gave **113** to construct the skeleton of (+)-caprazol. Finally, oxidation of the primary alcohol to carboxylic acid and total deprotection with hydrofluoric acid completed the first total synthesis of (+)-caprazol.



Scheme 17. Improved synthesis of (+)-caprazol by Matsuda and Ichikawa: segment synthesis

Soon after the first total synthesis was reported, Matsuda and Ichikawa made improvements to the synthetic route (Scheme 17).⁴⁸ First, BOM protection of the uracil core was unnecessary; almost perfect diastereoselectivity (98%) was achieved by aminohydroxylation of **114** to give **115**, and glycosylation to

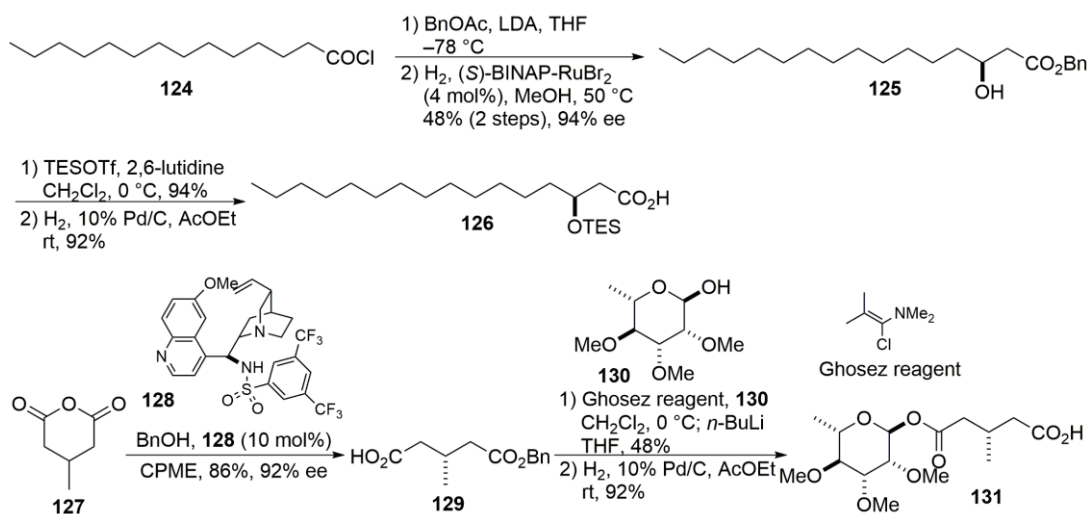
afford **116** (>97% de). The carboxylic acid segment could be synthesized in the same manner as shown in Scheme 15, but the hydrolysis condition using Ba(OH)₂ was updated to a more reproducible method (LiI, AcOEt, reflux).⁴⁹ Another fragment, **121**, which has an oxidation state of ester, was prepared from **109** in 10 steps via **118**, **119**, and **120**.



Scheme 18. Improved synthesis of (+)-caprazol by Matsuda and Ichikawa

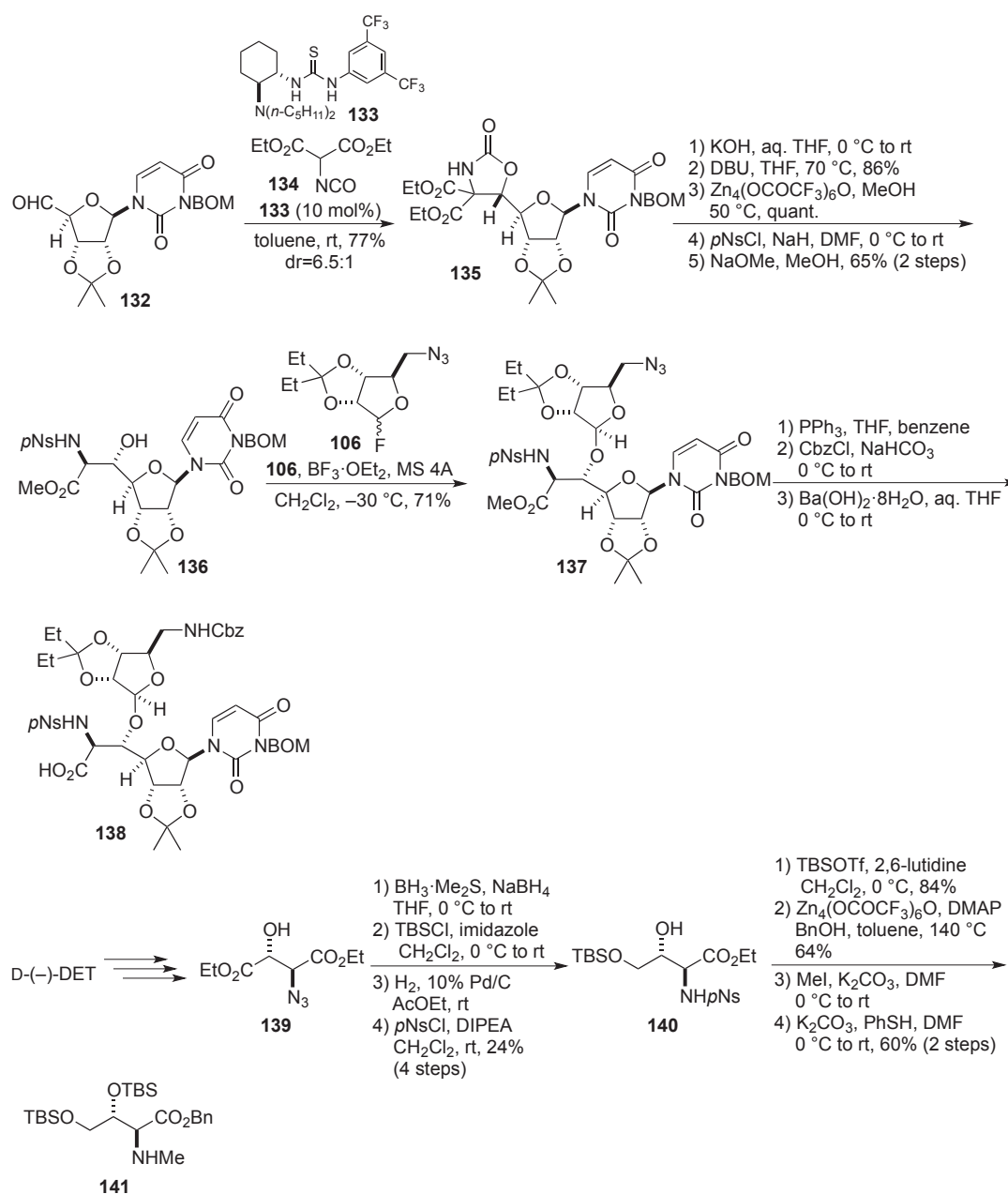
The synthesis of (+)-caprazol via **122** and **123** was completed in principle in the same manner as before except for protecting group manipulation (Scheme 18).

5. TOTAL SYNTHESIS OF CAPRAZAMYCIN A, CAPRAZOL, AND CPZEN-45 BY TAKEMOTO



Scheme 19. Synthesis of the side-chain moiety of caprazamycin A by Takemoto: synthesis of side-chain fragments

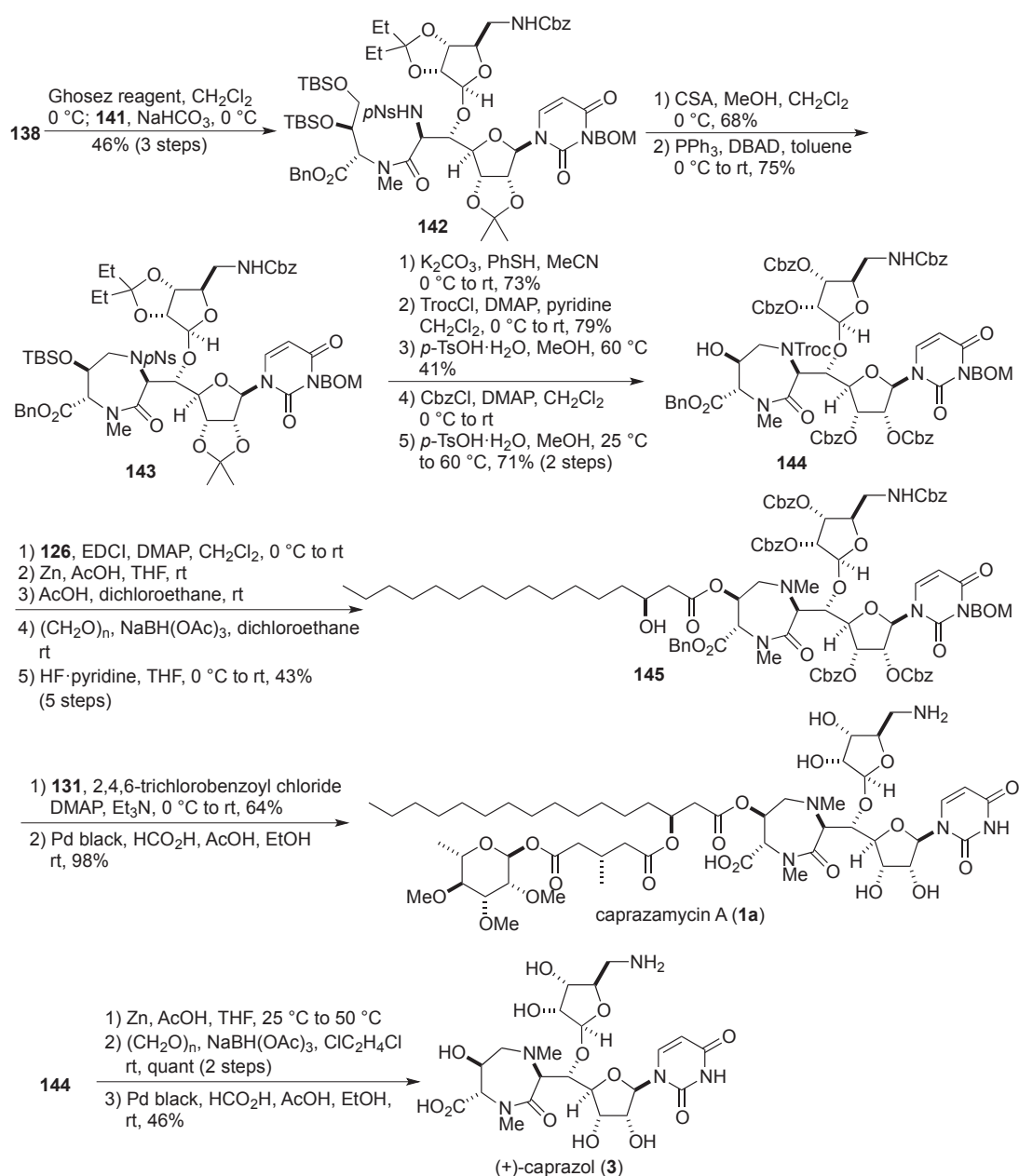
The first total synthesis of caprazamycin was achieved by Takemoto and co-workers setting caprazamycin A as the target.⁵⁰ At the outset, they synthesized the two fragments **126** and **131** as a lipophilic side-chain moiety (Scheme 19). The β -hydroxyester fragment **126** was prepared from the reported acid chloride **124**; lithium enolate generated from benzyl acetate was added to **124** to form β -ketoester, to which Noyori reduction⁵¹ conditions were applied, resulting in (*S*)- β -hydroxyester **125** in 94% ee. A change in the protection pattern led to **126** without difficulty. The chiral half-ester of glutaric acid, **131**, was prepared by catalytic asymmetric alcoholysis of 3-methylglutaric anhydride **127** using



Scheme 20. Total synthesis of caprazamycin A by Takemoto: segment synthesis

cinchona alkaloid-based chiral organocatalyst **128** developed by Song and co-workers⁵² to afford half-ester **129** in 92% ee. The corresponding acid chloride was then formed under neutral conditions with a Ghosez reagent,⁵³ which was reacted with rhamnose derivative **130** to make **131** after removal of the benzyl group.

The segments for the caprazol core were synthesized as shown in Scheme 20. In this synthesis, a bond was formed between the uridine- and diazepanone substructures (**132** and **134**) by a diastereoselective aldol reaction catalyzed by the thiourea catalyst **133** previously developed by Takemoto's group.⁵⁵ Under optimized conditions with 10 mol% of **133**, oxazolidinone adduct **135** was obtained in reasonable diastereoselectivity (6.5:1). The selectivity was not under substrate control; treatment of Et₃N decreased



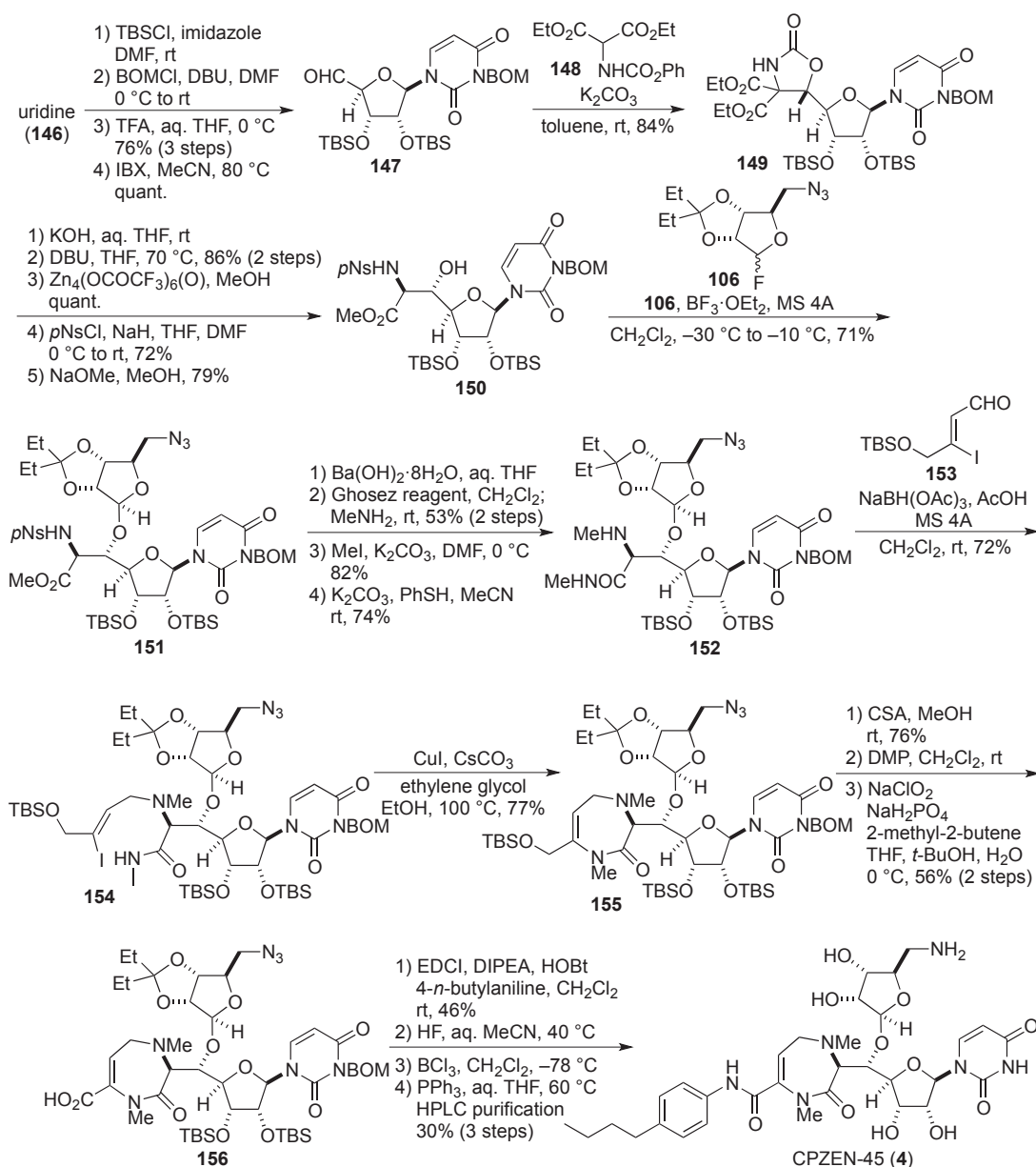
Scheme 21. Total synthesis of caprazamycin A and (+)-caprazol by Takemoto

the selectivity to 1:1.8, and the undesired isomer predominated. Relatively long chains on the nitrogen of the cyclohexyldiamine moiety of **133** were also indispensable; a change to methyl groups decreased the selectivity (3.1:1). The successive decarboxylation was followed by base-promoted equilibrium of the resultant monoester to the more stable *trans*-oxazolidinone. Transesterification,⁵⁶ protection of nitrogen by the *p*Ns group, and decarbonylation then afforded β -hydroxy- α -amino acid **136**. Successive glycosylation was achieved under conditions developed by Matsuda and Ichikawa, leading to **137**, which was subsequently transformed into carboxylic acid **138**. The other fragment, **141**, was prepared by a four-step procedure from known chiral building block **139** prepared from the chiral building block **139** which was synthesized from D-(–)-DET via **140**.

The two segments **138** and **141** were connected after generation of the corresponding acid chloride of **138**, followed by selective removal of the TBS group on the primary hydroxy group of **142** (Scheme 21). The stage was then set for a Mitsunobu reaction to construct the diazepanone ring of **143**, for which protection of the amino group by the *p*Ns group was needed. Manipulation of the protecting group gave (Cbz)₄-caprazol derivative **144**, which is reasonable selection for the protecting group because neither acidic nor basic conditions are applicable for the final deprotection of the synthesis of caprazamycin, as discussed in section 2. The unprotected secondary hydroxy group of **144** was acylated with **126** with EDCI, and the Troc group was removed under mild conditions that did not affect the unstable β -acyloxy moiety on the diazepanone ring. A methyl group was introduced by reductive amination, and a TES group was subsequently removed to afford **145**. Acylation with **131** was successful under the Yamaguchi protocol to install the whole framework of caprazamycin A. Finally, global deprotection under hydrogenolysis conditions completed the first total synthesis of caprazamycin A. Moreover, (+)-caprazol was also synthesized from intermediate **144**.

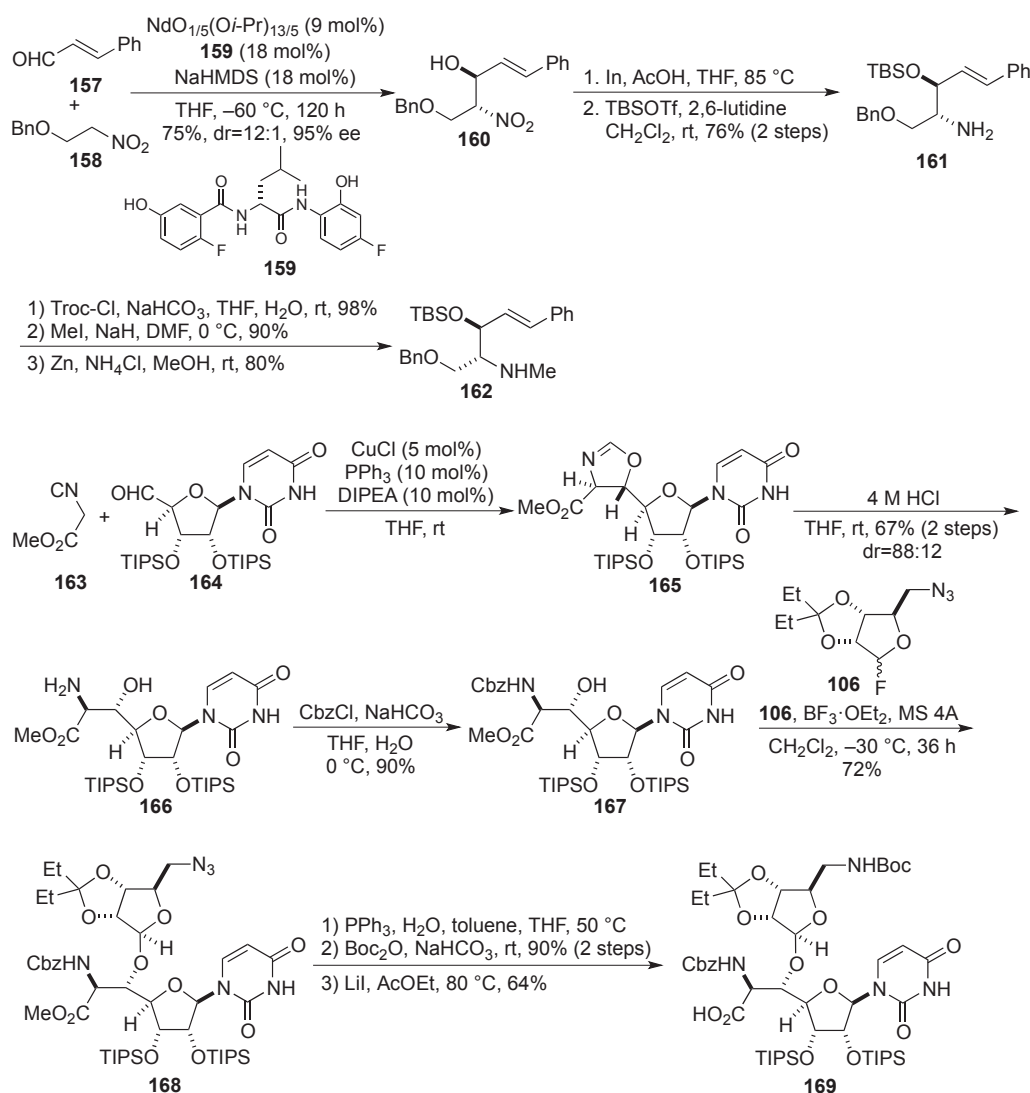
Very recently, Takemoto and co-workers accomplished an efficient synthesis of CPZEN-45, as shown in Scheme 22.⁵⁷ The synthesis used the uridine (**146**)-derived aldehyde **147** protected by TBS groups instead of an isopropylidene group. In the succeeding aldol reaction, more stable malonate derivative **148** compared to **134** in Scheme 20 was utilized in the presence of K₂CO₃ to give the cyclized adduct **149** in good yield, even without a chiral catalyst such as **133**. Then, the β -hydroxy- α -amino acid derivative **150** was obtained according to the same protocol as before, followed by glycosylation to afford **151**. In this synthesis, the diazepinone ring⁵⁸ was formed by intramolecular vinyl halide-amide coupling⁵⁹ promoted (or even catalyzed) by CuI (from **154** to **155**). For this purpose, secondary amide **152** was constructed using general procedures, and the vinyl halide substructure was introduced by reductive amination using **152** and **153** as substrates. In the key cyclization reaction, Takemoto and colleagues speculated that copper should coordinate to amide- and tertiary amine nitrogen atoms in a bidentate manner in the

presence of an external base, which are believed to suppress a side reaction – reduction of vinyl iodide.^{60,61} In addition, an additive effect of ethylene glycol was also reported,⁶⁰ which avoids the elimination side-reaction to give alkyne. In the stoichiometric condition, cyclized product **155** was isolated in 77% yield, and notably, a catalytic amount of CuI and ethylene glycol (20 mol% each) also afforded the desired product in 63% yield. Functional group interconversions and protective group manipulations accomplished the synthesis of CPZEN-45 via **156**.



Scheme 22. Total synthesis of CPZEN-45 by Takemoto

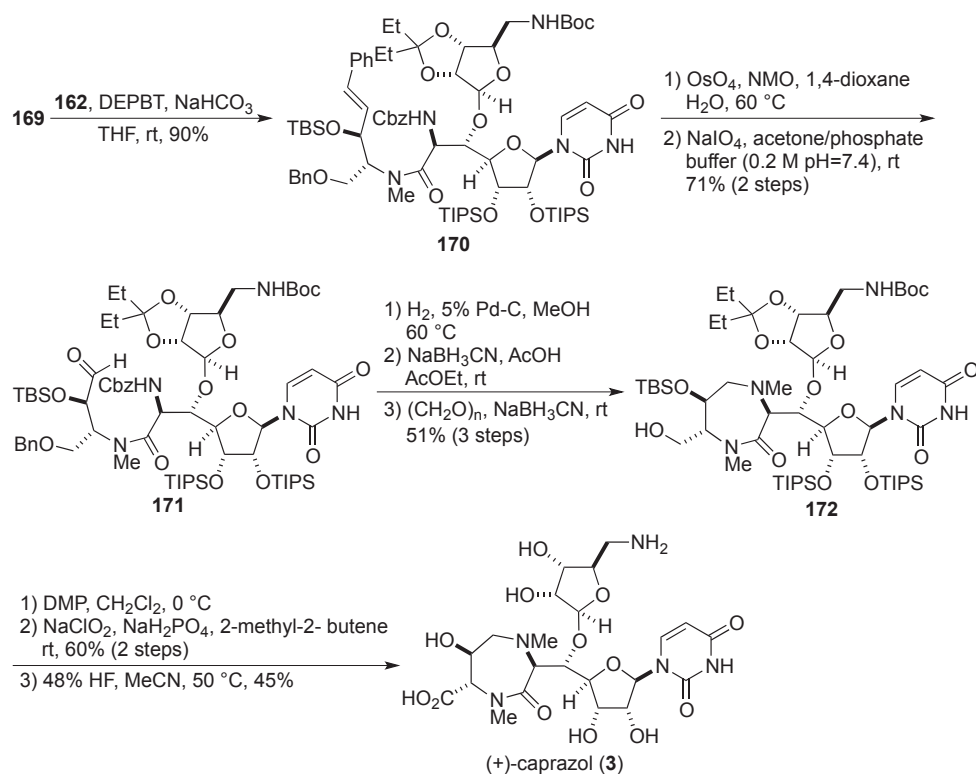
6. CATALYTIC ASYMMETRIC SYNTHESIS OF CAPRAZAMYCIN A, CAPRAZOL, AND CPZEN-45 BY SHIBASAKI AND WATANABE



Scheme 23. Total synthesis of (+)-caprazol by Shibasaki and Watanabe: segment synthesis

In the synthesis of caprazamycin B and (+)-caprazol,⁶² Shibasaki, Watanabe and co-workers planned to use catalytic asymmetric reactions for key stereocontrolled transformations, especially the formation of C-C bonds, simultaneously enabling construction of the molecular framework and installation of the requisite configuration, which would render the whole synthetic process more efficient. The first reaction fulfilling this criterion is the catalytic asymmetric *anti*-selective nitroaldol reaction developed by Shibasaki and Kumagai (Scheme 23).⁶³ The reaction takes advantage of the catalyst comprising chiral amide ligand **159** and two metals: Na and Nd. The catalyst promotes nitroaldol reactions with a broad substrate scope, which could be used as the key reaction in the total synthesis of biological active compound.⁶⁴ Recently, the practicality of the reaction was greatly improved by development of the

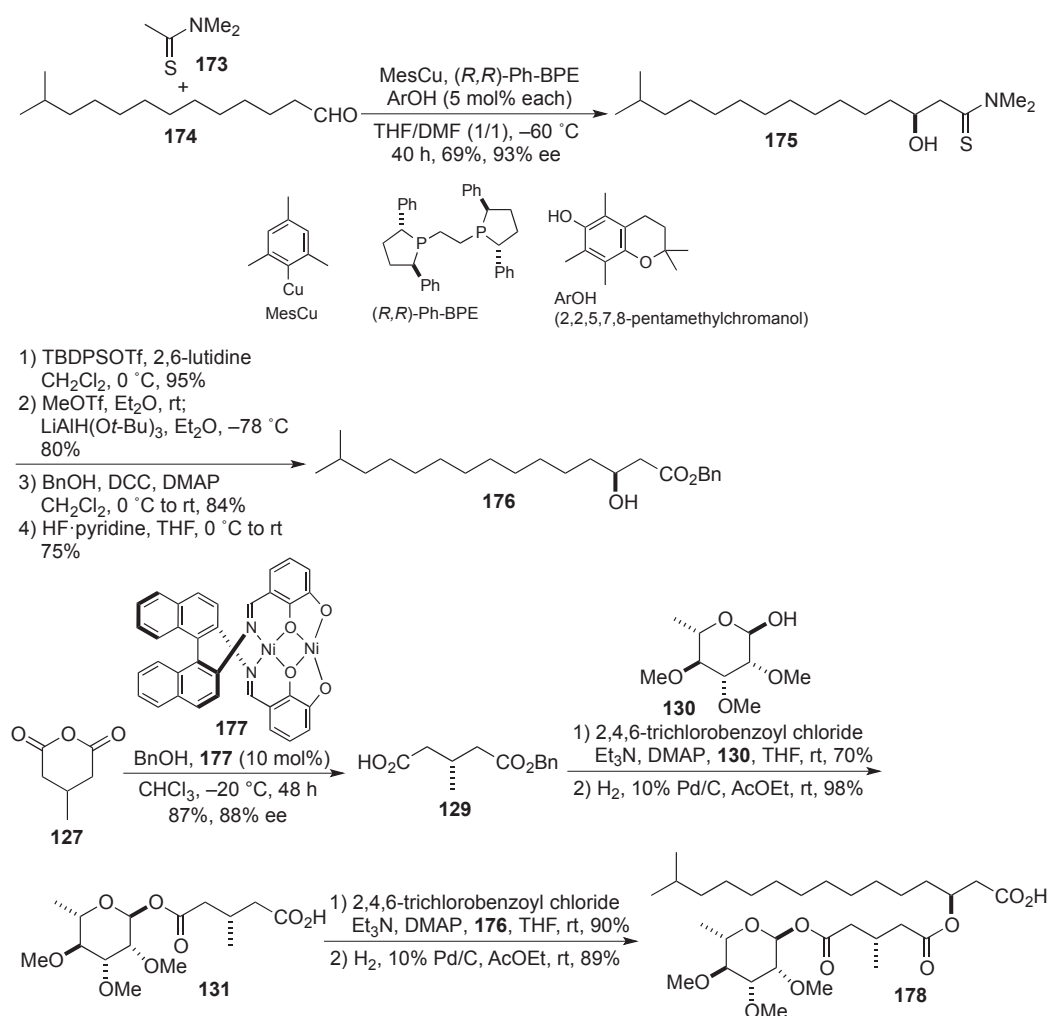
catalyst confined in a carbon nanotube,⁶⁵ application to a flow system,⁶⁶ and a simpler preparative method of the catalyst.⁶⁷ For the present synthesis, cinnamaldehyde **157** and 2-benzyloxynitroethane **158** were converted to the adduct **160** in the presence of a catalytic amount of the complex. Albeit with a relatively long reaction time (120 h), anti-product **160** was produced almost exclusively (12:1) with excellent enantioselectivity (95% ee). Notably, **160** could not be obtained under acid- or base-promoted standard conditions in good yield and reasonable purity as it suffers from over-reactions of the product. After reduction of the nitro group to an amino group by an In-mediated procedure, manipulation of protecting groups and methylation of the nitrogen atom afforded secondary amine intermediate **162** via **161**. Synthesis of another segment **169** commenced with a diastereoselective isocyanoacetate aldol reaction of **163** and **164** inspired by the report of Le Merrer and co-workers²⁹ (Scheme 9). Although the diastereoselectivity of the precedent was not satisfactory (30:70), we further screened reaction conditions and substrate structures to improve the outcome. In fact, Cu-catalyzed conditions reported by Kirchner⁶⁸ afforded the *trans*-oxazoline exclusively (**165**, main isomer within *trans*-oxazoline). After unveiling the aminoalcohol moiety (**166**) by acidic hydrolysis, the diastereomeric ratio of the isocyanoacetate aldol reaction was determined to be 88:12. Proper selection of the protecting group on a diol unit on ribose is crucial for the success of the reaction; isopropylidene acetal instead of TIPS groups decreased the selectivity to 40:60 under the same reaction conditions, whereas treatment of the TIPS-protected substrate with stoichiometric amounts of triethylamine resulted in a diastereomeric ratio of 55:45. After protection



Scheme 24. Total synthesis of (+)-caprazol by Shibasaki and Watanabe

of the amino group as Cbz carbamate **167**, glycosylation smoothly proceeded (**168**), from which carboxylic acid intermediate **169** was synthesized uneventfully.

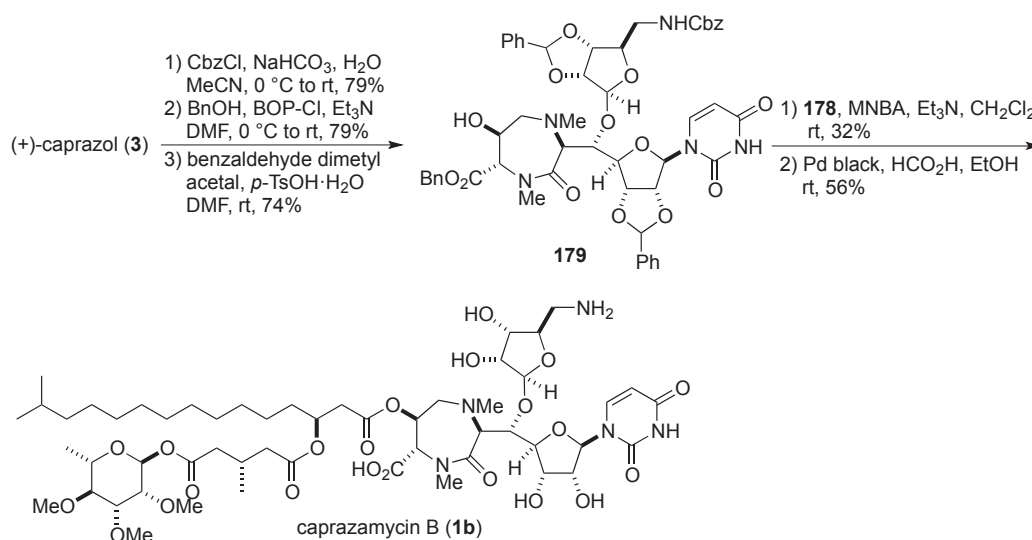
An amide bond was formed between the two segments **162** and **169**, and the olefin in **170** was utilized as the hidden formyl group, which was exposed (**171**) by a two-step oxidation protocol. The diazepanone ring formation was achieved by reductive amination, followed by methylation of the secondary amine to give **172**. Oxidation and final global deprotection achieved the catalytic asymmetric total synthesis of (+)-caprazol (Scheme 24).



Scheme 25. Synthesis of the side-chain moiety of caprazamycin B by Shibasaki and Watanabe

The side-chain part of caprazamycin B was synthesized⁶⁹ (Scheme 25) in a highly enantioselective manner using a different strategy from that of Takemoto and co-workers. The (*S*)- β -hydroxyester **176** was prepared by taking advantage of the catalytic asymmetric thioamide aldol reaction developed by Shibasaki and Kumagai.⁷⁰ The reaction proceeded with acetate-derived thioamide **173** and aldehyde with

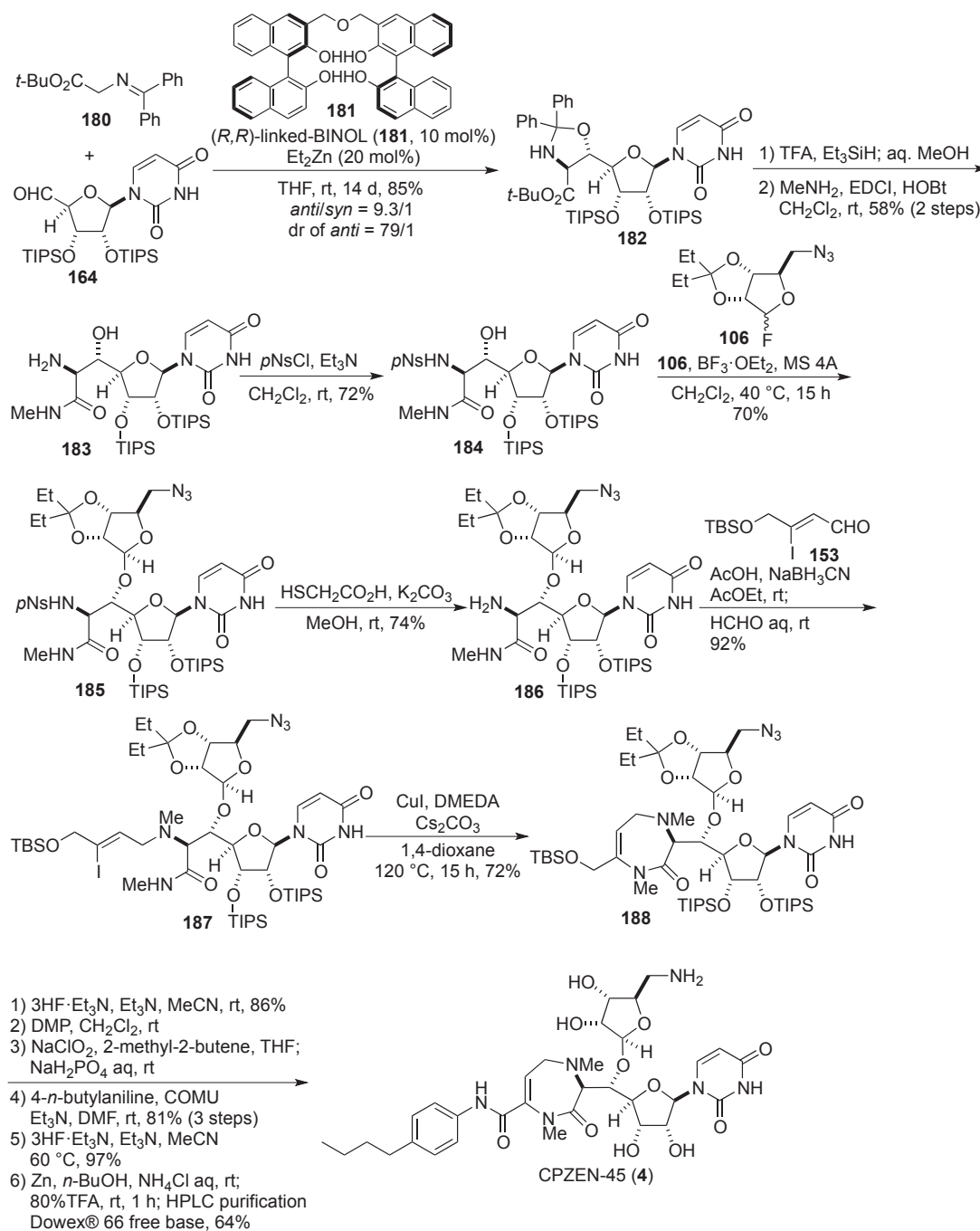
long aliphatic side-chain **174** in the presence of a catalyst comprising copper, a chiral bidentate ligand, and a phenolic additive. The copper complex, a soft Lewis acid, should selectively coordinate to the thioamide, a soft functionality, to activate **173** for deprotonation at the α -position even in the presence of an aldehyde having a more acidic α -proton. The whole process is accompanied only by proton migration, meaning that the reaction is atom economical. In the case of this particular synthesis, the choice of the solvent system was important, and it was found that a mixed system of THF/DMF was effective. The thioamide aldol adduct **175** in 93% ee was transformed into (*S*)- β -hydroxyester **176** following a series of standard reactions. Next, we newly developed a catalytic asymmetric desymmetrization reaction to obtain half-ester **129** from the corresponding anhydride **127**. Screening catalyst systems developed by Shibasaki's group revealed that dinickel-chiral Schiff base complex **177** developed by Shibasaki and Matsunaga⁷¹ was effective.⁷² Benzyl alcohol and 3-methylglutaric anhydride **127** were reacted under the influence of **177**, resulting in 88% ee of **129**. The reaction has a good scope for acid anhydrides with a relatively small substituent at the 3-position, and some extent of aromatic substituents is also tolerable. Difficulties may be encountered when using the currently oft-used cinchona alkaloid-based chiral organocatalysts^{52,73} to construct the enantiomeric product because the pseudoenantiomer of the catalyst must be used and the same degree of enantioselectivity is not always guaranteed. Therefore, metal-based catalysts can be complementary to organocatalysts in this type of reaction. After preparation of **131** as shown above, an ester linkage was formed to synthesize a side-chain segment.



Scheme 26. Synthesis of caprazamycin B by Shibasaki and Watanabe

Finally, properly protected caprazol **179** was acylated with **178** under Shiina's protocol⁷⁴ with moderate yield (32%). It should be noted that Takemoto reported that direct introduction of the whole side-chain segment to caprazol derivatives is extremely troublesome; β -elimination of the β -hydroxyester moiety of

the side-chain and diazepanone system occurs, and the latter may also undergo a retro-aldol reaction. Final total deprotection completed the synthesis of caprazamycin B (Scheme 26).⁷⁵



Scheme 27. Catalytic asymmetric synthesis of CPZEN-45 by Shibasaki and Watanabe

This year, Shibasaki, Watanabe and co-workers also reported the catalytic asymmetric synthesis of CPZEN-45 (Scheme 27).⁷⁶ They initially attempted to update the first step, the diastereoselective aldol reaction, to construct a β -hydroxy- α -amino acid between the uridine- and diazepinone parts. In fact, a Zn-linked-BINOL (**181**) complex catalyzed the aldol reaction⁷⁷ using glycine-derived Schiff base **180** and

TIPS-protected uridine-derived aldehyde **164** afforded the adduct **182** with excellent *anti*-selectivity (9.3:1) and perfect diastereoselectivity (79:1) within the *anti*-product. In the original report, these reaction conditions were only applicable to the aldol process with α -hydroxyketone as a pre-nucleophile; this synthesis has expanded the scope of the reaction. Unveiling of the aminoalcohol substructure (**183**), protection (**184**), glycosylation (**185**), and removal of the *p*Ns group (**186**) were achieved by standard reactions. In the present synthesis, the diazepinone ring was cyclized by vinyl halide-amide coupling of **187**,⁷⁸ which could be synthesized from **186** and **153** by reductive amination. The thus-prepared diazepinone derivative **188** was uneventfully transformed into CPZEN-45 in a six-step procedure.

7. CONCLUSION

This review describes how advances in stereoselective transformation have altered the synthetic strategy for complex molecules such as caprazamycins, liposidomycins, caprazol, and CPZEN-45. In earlier works, key stereochemical elements were installed utilizing chiral pools, such as amino acid and ascorbic acid, as starting materials, or by auxiliary-based diastereoselective reaction. Well-established asymmetric processes such as Sharpless' epoxidation and aminohydroxylation and Noyori reduction were also applied. Catalytic asymmetric C-C bond-forming reactions were recently added as key stereoselective transformations for the synthesis of natural products in this family, and contribute to the total synthesis, demonstrating the practicality of these processes. It should be emphasized that the established synthetic methods of caprazamycin-related natural products are currently under SAR studies to facilitate the search for novel clinical medicines to combat infectious diseases. I expect that new catalytic asymmetric reaction methodologies will be applied to synthetic studies of biologically active compounds to expand accessibility to unknown chemical entities, which in turn will contribute to improve public health by enhancing the development of novel drug leads.

ACKNOWLEDGMENT

The author thanks to Prof. Dr. Masakatsu Shibasaki for his helpful discussion, precious suggestions, and encouragement for the part of works in this review (section 6). The author is grateful to Drs. P. Gopinath, T. Takeuchi, L. Wang, G. Ravi, T. Masuda, and Mr. H. Abe (BIKAKEN) for their vigorous research activities for the work in section 6, and thankful to KAKENHI (No. 23590037 and No. 26460168), JST (ACT-C), The Uehara Memorial Foundation, Takeda Science Foundation, NOVARTIS Foundation for the Promotion of Science, JSPS for Postdoctoral Fellowship for Foreign Researcher for financial support.

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