

HETEROCYCLES, Vol. 77, No. 1, 2009, pp. 67 – 83. © The Japan Institute of Heterocyclic Chemistry
Received, 4th April, 2008, Accepted, 27th May, 2008, Published online, 2nd June, 2008.
DOI: 10.3987/REV-08-SR(F)1

SYNTHESES OF PEPTIDYL NUCLEOSIDE ANTIBIOTICS

Hiroyuki Akita*

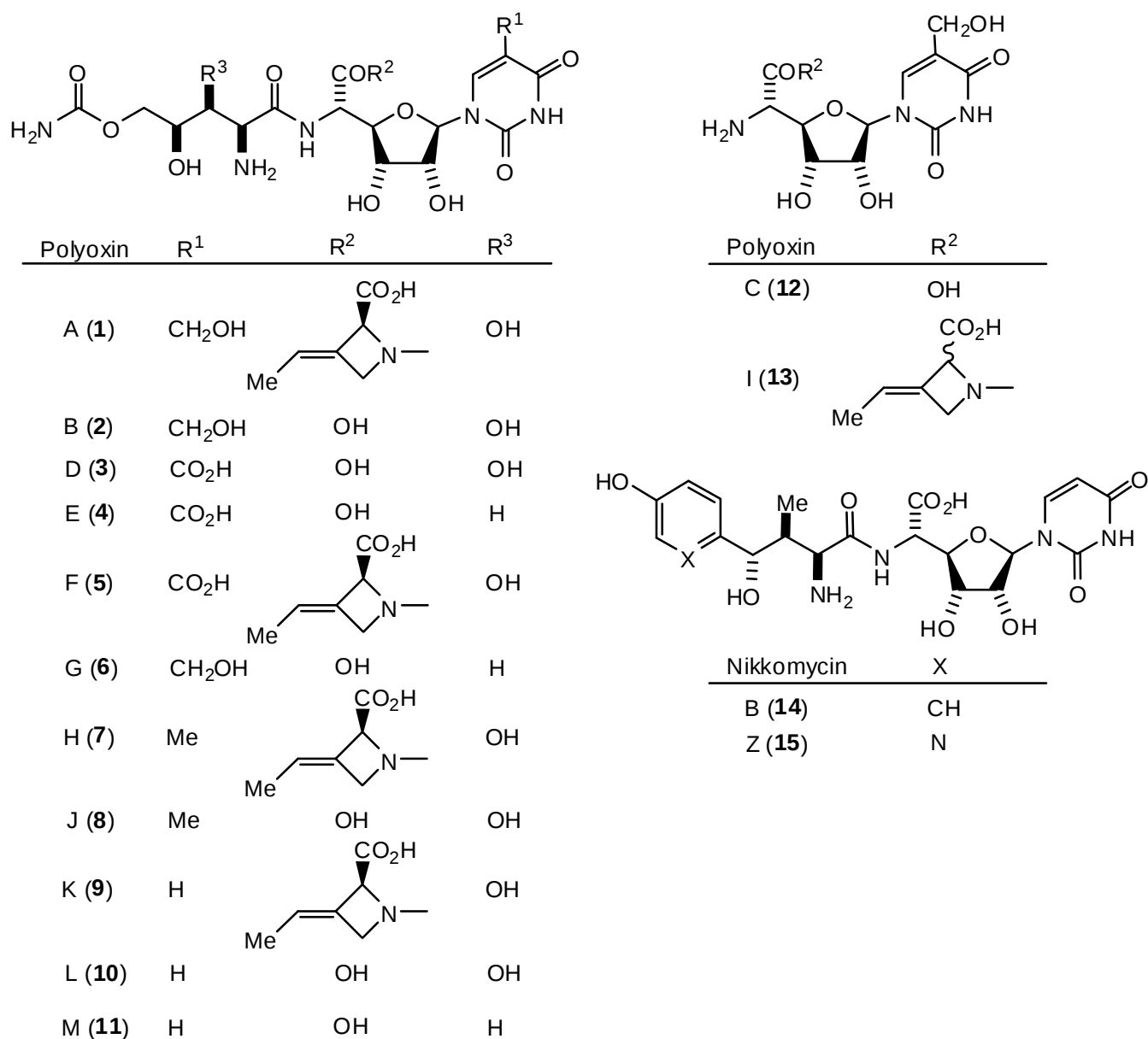
Faculty of Pharmaceutical Science, Toho University, 2-2-1 Miyama, Funabashi,
Chiba 274-8510, Japan

Abstract — Polyoxins and nikkomycins are an important class of peptidyl nucleoside antibiotics isolated from the culture broths of *Streptomyces cacaoi* var. *asoensis* and *Streptomyces tendae*. For the syntheses of these antibiotics, efficient syntheses of 1-(5-amino-5-deoxy- β -D-allofurano-uronosyl)pyrimidines such as thymine polyoxin C, uracil polyoxin C and their congeners as a basic component corresponding to the right half were achieved based on the nucleophilic 1,2-addition to methyl 2,3-*O*-isopropylidene- β -D-ribopentodialdo-1,4-furanoside. Then the syntheses of polyoxamic acid derivatives and their congeners corresponding to the left acid part were carried out based on 1,2-addition of carbon nucleophile to 4-*O*-protected-2,3-*O*-isopropylidene-L-threose. Coupling reaction of the activated ester derived from the left half acid part and amine part derived from the right half gave the *N,O*-protected peptidyl nucleoside congeners which were subjected to deprotection to afford polyoxins B, D, J, L, M, C and nikkomycin B.

1. INTRODUCTION

Polyoxins are an important class of peptidyl nucleoside antibiotics isolated from the culture broths of *Streptomyces cacaoi* var. *asoensis*, which are potent competitive inhibitors of chitin synthetase of a variety of phytopathogenic fungi or *Candida albicans*, a medically important human fungal pathogen.¹ Nikkomycins, peculiar peptidyl nucleoside antibiotics isolated from the culture broths *Streptomyces tendae* and *Streptomyces cacaoi* subsp. *Asoensis* exhibit fungicide and insecticide activities due to an inhibition of cell wall chitin biosynthesis.^{2,3} From the point of view of fungal infections, chitin synthetase inhibition seems to be a useful approach for the sake of safer antifungal agents and much effort has been devoted to the total synthesis of these antibiotics. For convenience, established structures of the polyoxins A (1)–I (13) and nikkomycins B (14) and Z (15) are shown in Scheme 1. Among them, the total syntheses of polyoxin J (8) starting from D-glucose^{4a} or myo-inositol^{4b} were reported and were achieved based on the stereoselective addition of 2-lithiofuran to the sugar nitrone.^{4c,d} In this review, we summarize the syntheses of polyoxins B (2), D (3), J (8), L (10), M (11), C (12), and nikkomycin B (14).

This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.



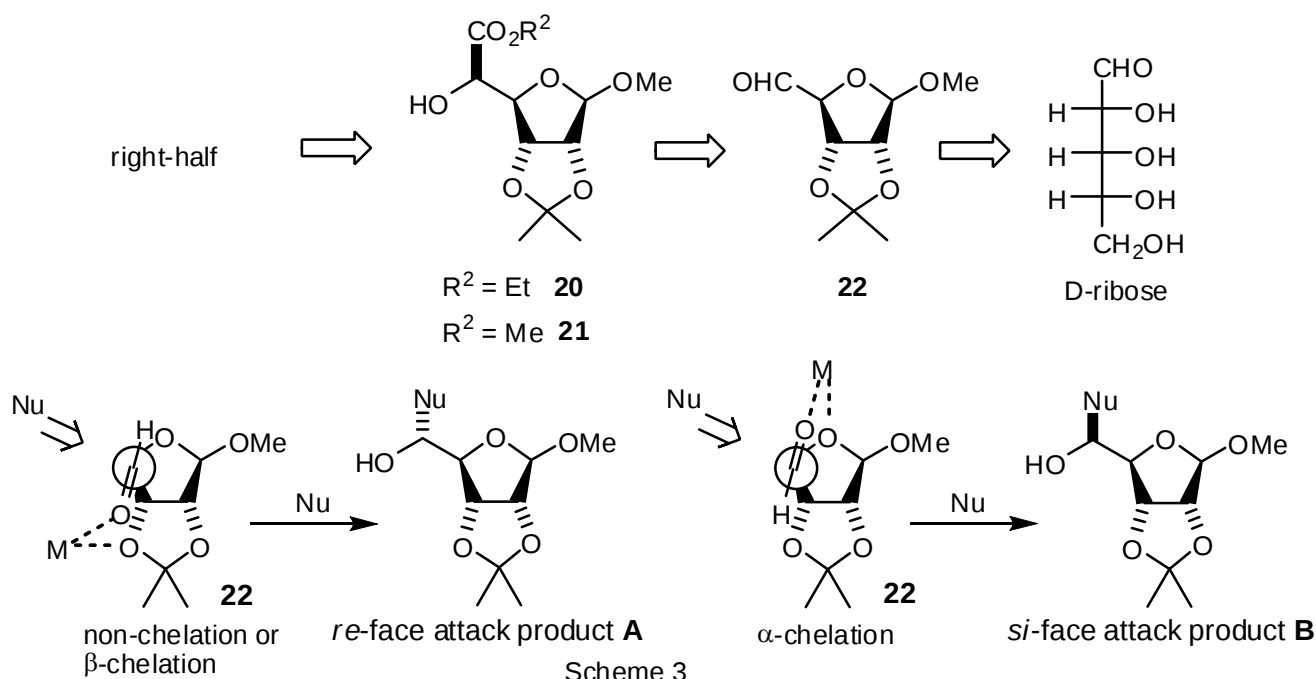
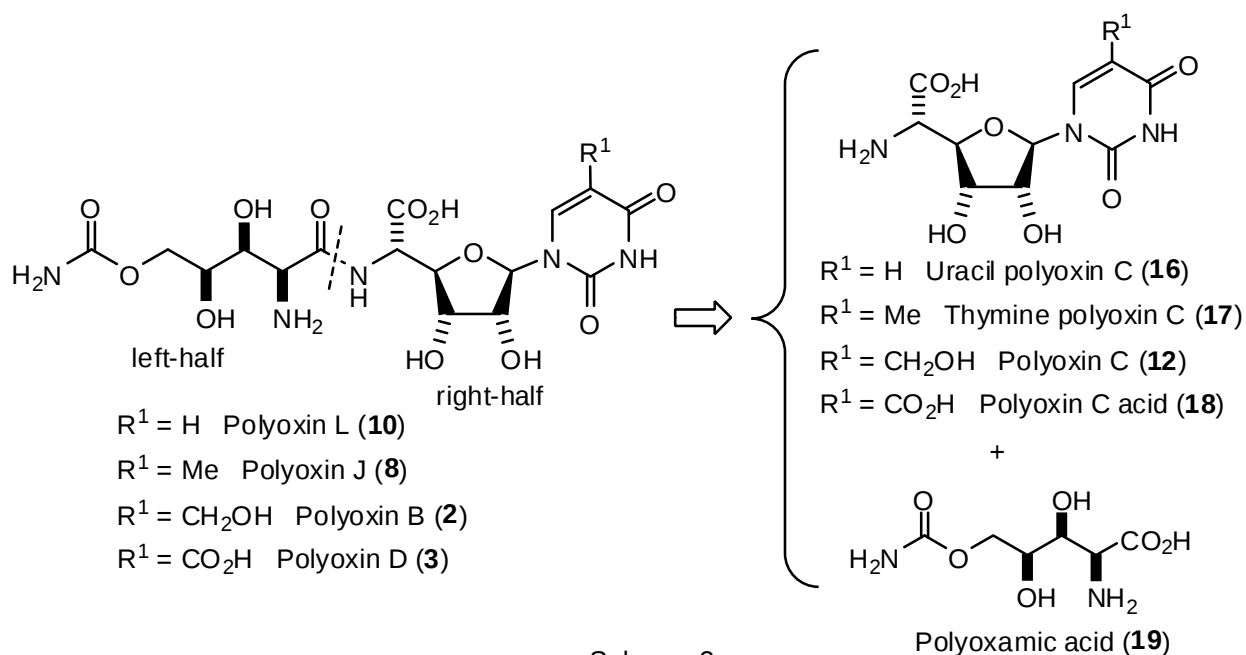
Scheme 1

2. Syntheses of polyoxins L (10), J (8), B (2) and D (3)

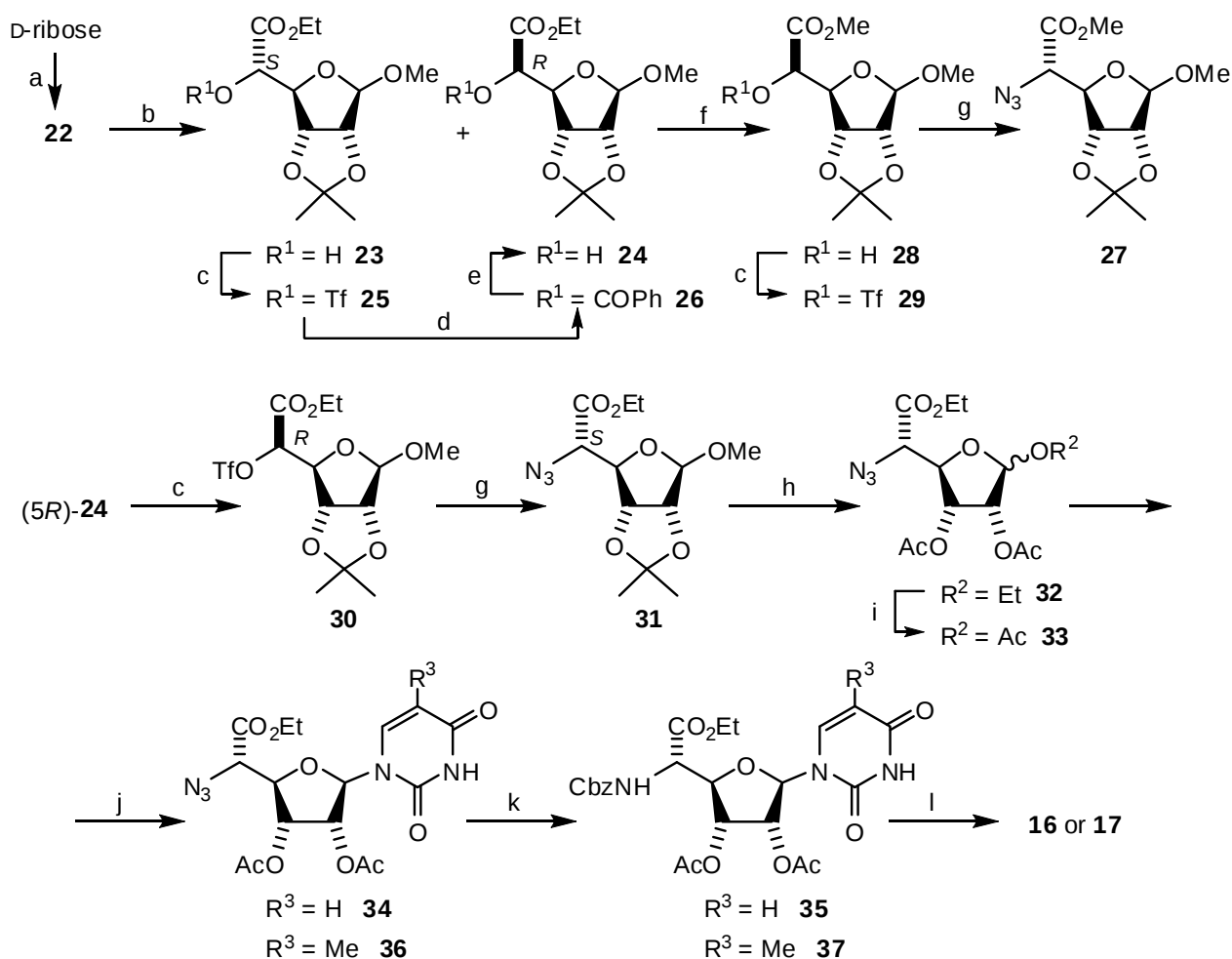
Retrosynthetically, the synthesis of polyoxins L (10), J (8), B (2) and D (3) can be achieved by amide formation between the 1-(5-amino-5-deoxy-β-D-allofuranouronosyl)pyrimidines derivatives {uracil polyoxin C (16), thymine polyoxin C (17), polyoxin C (12) and polyoxin C acid (18)} corresponding to the right-half and the polyoxamic acid (19) congener corresponding to the left-half as shown in Scheme 2.

2.1. Synthesis of right-half {Syntheses of uracil polyoxin C (16) and thymine polyoxin C (17)}^{5a,b}

A variety of chemical syntheses of amino acid nucleosides (16 and 17) have been reported over the years.^{5c-f} One of the most important intermediate for the general synthesis of them appeared to be (*R*)-α-hydroxy esters (20 or 21). The synthesis of 20 or 21 could be achieved based on the nucleophilic addition of carbon-nucleophile to methyl 2,3-*O*-isopropylidene-β-D-ribo-pentodialdo-1,4-furanoside (22)



derived from D-ribose. Nucleophilic 1,2-addition of allyl organometallics to **22** has been reported to give a preferential product **A**, as a result of *re*-face attack on the unchelated aldehyde (non-chelation) a preferential product **A**, as a result of *re*-face attack on the unchelated aldehyde (non-chelation) with a C₄-C₅ conformation depicted in the structure of **22**.⁶ Taking into account the effect of coexisting metal halides, the β -chelation of the metal ion may give the *re*-face attack product **A** as a major component, while the α -chelation of the metal ion would afford the *si*-face attack product **B** as a major product (Scheme 3). The synthesis of uracil polyoxin C (**16**) and thymine polyoxin C (**17**) were shown in Scheme 4. Treatment of D-ribose with acetone in the presence of conc. HCl and MeOH followed by



a; 1) MeOH / acetone / *conc.* HCl, 2) DMSO / $(COCl)_2$ / Et_3N , $-78^\circ C$. b; 1) Ethyl vinyl ether / *t*-BuLi / THF, $-78^\circ C$, 2) O_3 / CH_2Cl_2 , 3) Me_2S / CH_2Cl_2 . c; Tf_2O / pyridine / CH_2Cl_2 . d; $PhCO_2H$ / CsF / DMF. e; EtONa / EtOH. f; MeOH / $Ti(O-iPr)_4$ / benzene, reflux. g; NaN_3 / DMF. h; 1) Dowex 50W H^+ / EtOH, reflux, 2) Ac_2O / pyridine. i; Ac_2O / AcOH / *conc.* H_2SO_4 / CH_2Cl_2 . j; for **34**: 2,4-bis(trimethylsilyloxy)pyrimidine / TMSOTf / $ClCH_2CH_2Cl$, reflux. for **36**: 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine / TMSOTf / $ClCH_2CH_2Cl$, reflux. k; for **35**: 1) H_2 / 5% Pd-BaSO₄ / MeOH, 2) CbzCl / 7% NaHCO₃ aq. / dioxane. k; for **37**: 1) H_2 / 20% Pd(OH)₂-C / MeOH, 2) CbzCl / 7% NaHCO₃ aq. / dioxane. l; 1) LiOH·H₂O / THF, 2) 0.1 M HCl, 3) H_2 / 10% Pd-C / MeOH.

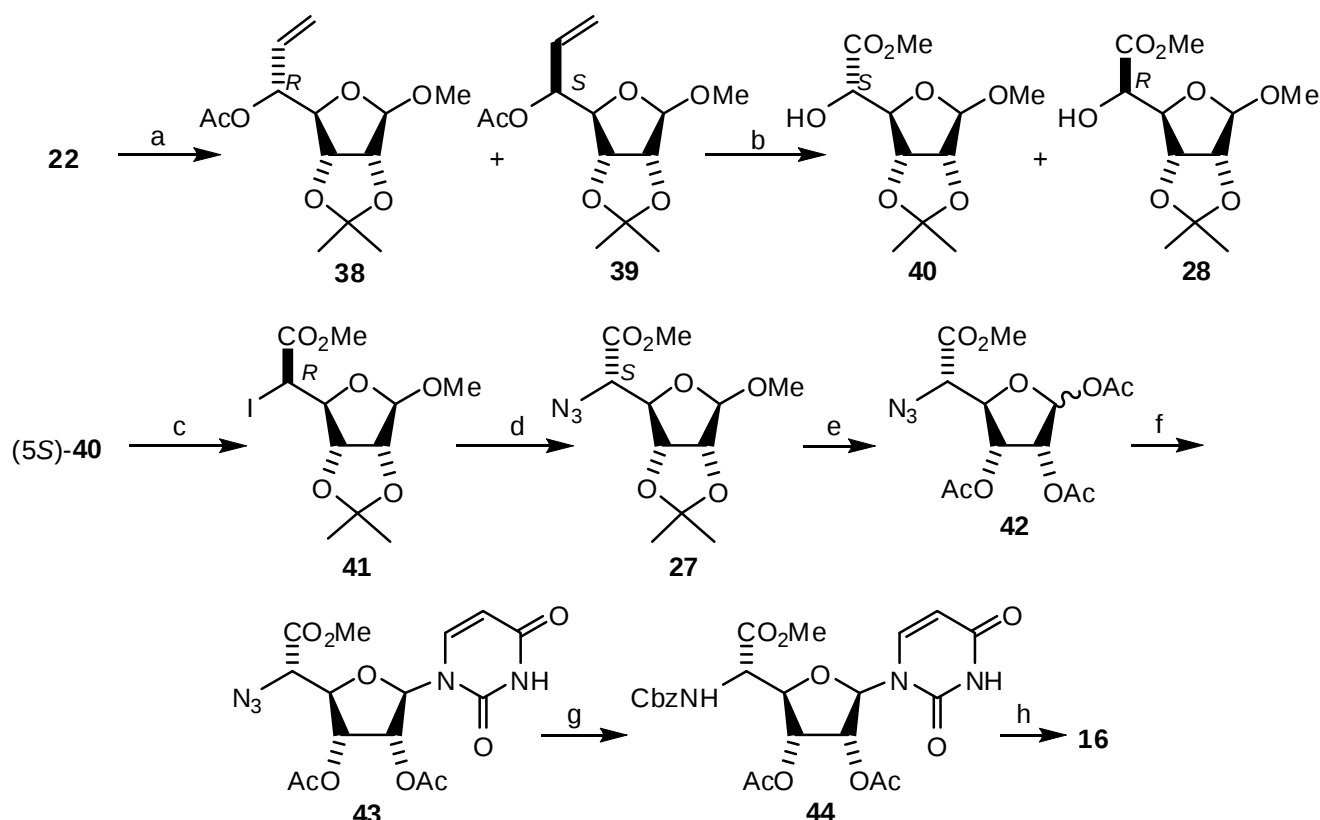
Scheme 4

Swern oxidation gave the 5-aldehyde (**22**) (60%). The reaction of **22** with (1-ethoxyvinyl)lithium followed by ozonolysis and subsequent treatment with dimethylsulfide gave a diastereomeric mixture of α -hydroxy esters, which were separated into the major α -hydroxy ester (**23**) (31% from **22**) and the minor one (**24**) (10%). For the purpose of conversion of **23** into **24**, treatment of **23** with trifluoromethanesulfonic anhydride (Tf_2O) afforded the triflate (**25**) (83%), which was treated with benzoic acid in the presence of CsF to provide the α -benzoyloxy ester (**26**) (86%). Alcoholysis of **26** gave the C-5 inverted isomer (**24**) (65%) which was consistent with the minor component of α -hydroxy esters. In order to determine the stereochemistry of **24**, the α -hydroxy ethyl ester **24** was converted to the reported (5*S*)-azide methyl ester **27**.⁷ Transesterification of **24** with MeOH into the methyl ester (**28**)

in the presence of $\text{Ti}(\text{O}-i\text{Pr})_4$ was achieved in 84% yield. Triflation of **28** followed by treatment of the triflate (**29**) (74%) with NaN_3 afforded the diastereomerically pure α -azide ester **27** (95%) whose spectral data were identical with those of the reported (5S)-**27**. Thus, the stereochemistry due to the C-5 position of α -hydroxy ethyl esters **23** and **24** was found to be (S)- and (R)-configurations, respectively. For the total synthesis of the target molecules **16** and **17**, conversion of the ethyl ester group into the methyl ester group is not always essential process. The (R)- α -hydroxy ethyl ester (**24**) was converted to the (S)- α -azide ethyl ester (**31**) (55% from **24**) via the triflate (**30**) (64%) by the same way as in the case of conversion of **29** to **27**. Deisopropylidenation of **31** (Dowex 50W H^+ , EtOH, reflux) afforded the diol, which was acetylated directly (Ac_2O , pyridine) to yield the diacetate (**32**) (87%). Anomeric acetolysis smoothly gave the triacetate (**33**) (88%) in which no C-5 epimerization could be detected. Reaction of the key triacetate (**33**) with 2,4-bis(trimethylsilyloxy)pyrimidine under the conditions reported by Vorbrüggen {trimethylsilyl trifluoromethanesulfate (TMSOTf), $\text{ClCH}_2\text{CH}_2\text{Cl}$, reflux}⁸ afforded exclusively the β -nucleoside (**34**) (84%). Hydrogenation of the azide (**34**) in the presence of 5% Pd-BaSO_4 followed by protection of the amino group with CbzCl in the presence of 7% aqueous NaHCO_3 gave the (5S)-**35** (74%). Alkaline hydrolysis of **35** followed by hydrogenation afforded uracil polyoxin C (**16**) (72%). Likewise, reaction of **33** with 5-methyl-2,4-bis(trimethylsilyloxy) pyrimidine under similar conditions afforded exclusively the β -nucleoside (**36**) (84%). Hydrogenation of the azide (**36**) in the presence of 20% $\text{Pd}(\text{OH})_2\text{-C}$ afforded the α -amino acid ester which was treated with benzyl chloroformate (CbzCl) in the presence of 7% aqueous NaHCO_3 to provide the (5S)-**37** (90%). Alkaline hydrolysis of **37** followed by hydrogenation gave thymine polyoxin C (**17**) (75%). The physical data of the synthetic material (**17**) were identical with those of authentic material (**17**).^{9a,b} The synthesis described herein demonstrates the utility of (1-ethoxyvinyl)lithium for the short path synthesis of the α -hydroxy esters (**23** and **24**) from the aldehyde (**22**), which contributed to the total syntheses of uracil polyoxin C (**16**) and thymine polyoxin C (**17**).

2. 2. Improved synthesis of uracil polyoxin C (**16**)¹⁰

The α -hydroxy esters (5S)-**23** and (5R)-**24** are obtained from the reaction of **22** and 1-ethoxyvinyl lithium followed by ozonolysis and subsequent reductive treatment in overall yield of 31% and 10%, respectively. Although both (5S)-**23** and (5R)-**24** were converted to the desired α -azide ester (**31**), overall yield of **31** from **22** is quite low (13%). We report the improved synthesis of α -azido ester (5S)-**27** from **22** and its application to the total synthesis of uracil polyoxin C (**16**) as shown in Scheme 5. The reaction of **22** with vinylmagnesium bromide was carried out and the reaction mixture was subjected to acetylation to give a 3.7:1 diastereomeric mixture of acetoxymethyl compounds **38** and **39** in 71% overall yield. Oxidative treatment of this mixture with RuCl_4 and NaIO_4 followed by consecutive esterification and hydrolysis afforded a mixture of α -hydroxy esters, which were separated to the more polar (5S)-**40** (64% overall yield) and the less polar (5R)-**28** (22% overall yield). Treatment of **40** with iodine and triphenylphosphine in the presence of imidazole gave the inverted α -iodo ester (**41**) (92%) which was treated with NaN_3 to



Scheme 5

Table 1. Reaction of **22** and vinylmagnesium bromide in the presence of additives

$\text{22} \xrightarrow[2) \text{Ac}_2\text{O} / \text{pyridine}]{1) \text{CH}_2=\text{CHMgBr}, \text{additive in THF}} \text{38} + \text{39}$				
Entry	Additive	Conditions	Yield (38 + 39) (%)	Ratio (38/39)
1	none	-78 °C ~ -20 °C, 1.5 h	71	3.7 : 1
2	CeCl_3	-78 °C, 1.5 h	53	4.4 : 1
3	ZnBr_2	0 °C, 1.5 h	52	1.7 : 1

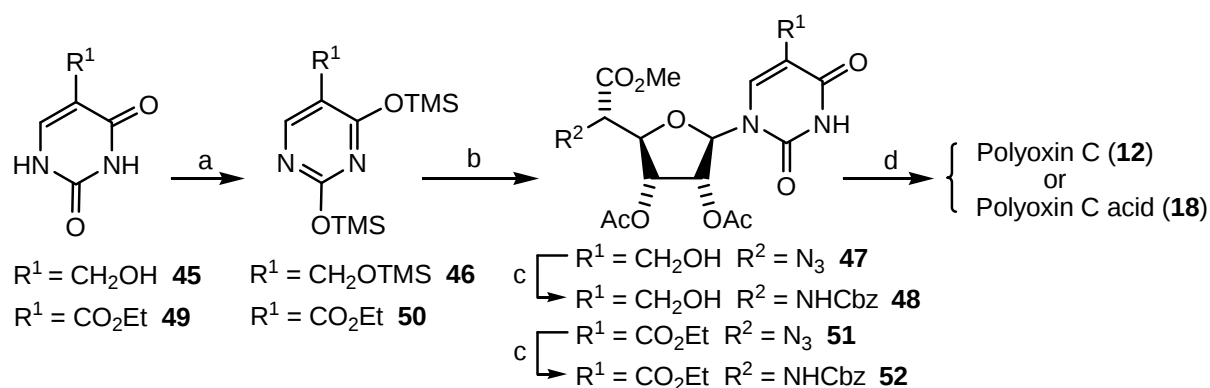
afford the α -azido ester (**27**) (98%). Thus overall yield of the desired **27** from **22** was totally improved to 55% in comparison with the previous case (13%) or the reported procedure (38%) by Barrett *et al.*⁷

For the purpose of the improvement of the diastereoselectivity, effect of coexisting metal halide in addition to **22** was examined and the results are shown in Table 1. In comparison with no additive (entry 1), addition of metal ion (entries 2 and 3) decrease the overall yield of products (**38** and **39**) and additive CeCl_3 (entry 2) may enhance the β -chelation effect. In every case, improvement of selectivity was not found. Thus obtained (5S)-**27** was subjected to consecutive treatment with Dowex 50W H^+ resin in MeOH and Ac_2O in pyridine to afford the triacetate **42** (69% overall yield from **40**) in which no C-5

epimerization could be detected. Reaction of the triacetate (**42**) with 2,4-bis(trimethylsilyloxy)-pyrimidine under the conditions reported by Vorbrüggen (TMSOTf, $\text{ClCH}_2\text{CH}_2\text{Cl}$, reflux) gave exclusively the β -nucleoside (**43**) (89%). Hydrogenation of the azide (**43**) in the presence of 10% Pd-C afforded the α -amino acid ester which was treated with CbzCl in the presence of 7% aqueous NaHCO_3 to provide the (5*S*)-**44** (66%). Alkaline hydrolysis of **44** followed by hydrogenation gave uracil polyoxin C (**16**) (53%).

2. 3. Synthesis of polyoxin C (**12**) and polyoxin C acid (**18**)

By applying the Vorbrüggen procedure,⁸ the commercially available 5-hydroxymethyl uracil (**45**) was treated with 1,1,1,3,3,3-hexamethyldisilazane and trimethylsilyl chloride to give the 5-trimethylsiloxymethyl-2,4-bis(trimethylsiloxy)pyrimidine (**46**) which was reacted with the triacetate (**42**) in the presence of TMSOTf to afford exclusively the β -nucleoside (**47**) in 62% overall yield. Hydrogenation of the azide (**47**) in the presence of 10% Pd-C gave the α -amino acid ester which was treated with CbzCl in the presence of 7% NaHCO_3 to provide the 5-amino-*N*-Cbz-derivative (**48**) in 61% overall yield. Alkaline hydrolysis of **48** followed by hydrogenation gave polyoxin C (**12**) in 40% overall yield, which was consistent with the reported **12**.^{1b} Likewise, ethyl uracil 5-carboxylate (**49**)¹¹ was converted to the 2,4-bis(trimethylsiloxy) pyrimidine (**50**) which was condensed with the triacetate (**42**) to yield exclusively the β -nucleoside (**51**) in 98% overall yield. Conversion of **51** into the polyoxin C acid (**18**) via the Cbz-derivative (**52**) was achieved in 44% overall yield by the same way as for the preparation of **12** from **48**.

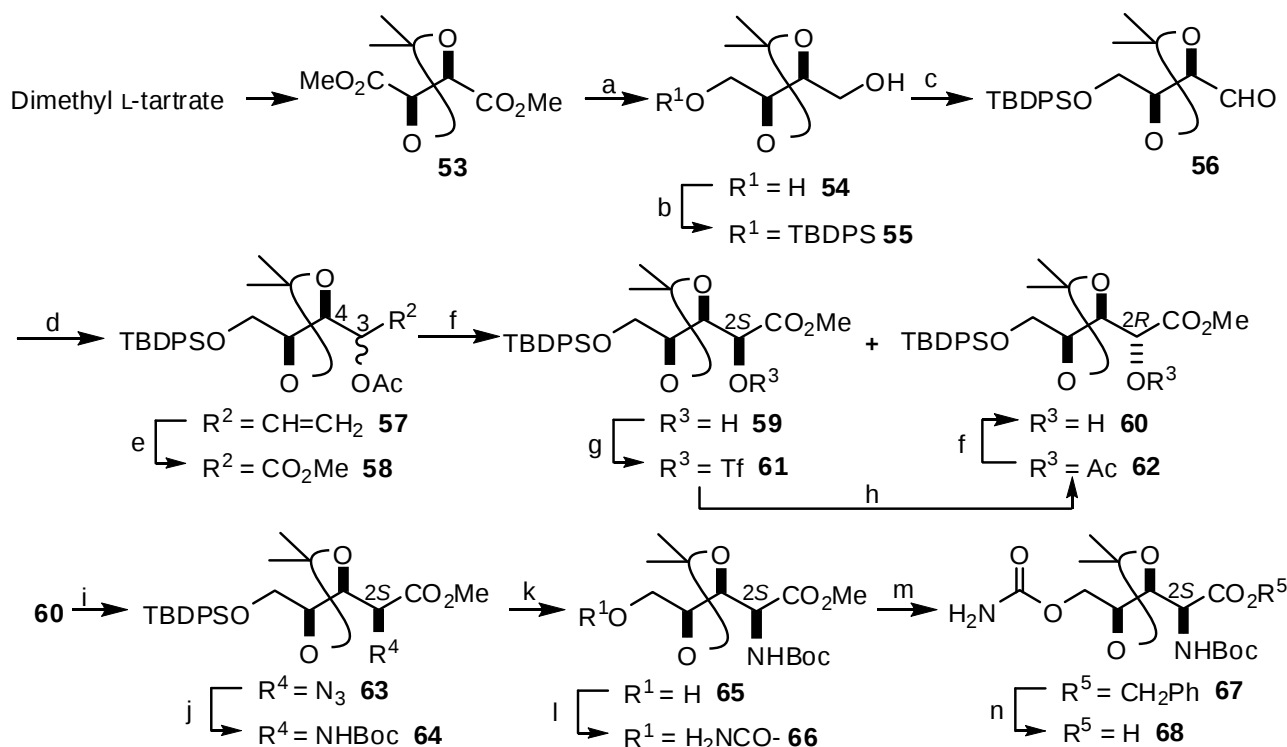


a; $(\text{Me}_3\text{Si})_3\text{NH} / \text{Me}_3\text{SiCl}$. b; **42** / TMSOTf / MeCN. c; 1) H_2 / 10% Pd-C, 2) CbzCl. d; 1) $\text{LiOH} \cdot \text{H}_2\text{O} / \text{THF}$, 2) 1M HCl, 3) H_2 / 10% Pd-C / MeOH.

Scheme 6

2.4. Synthesis of left-half {Synthesis of polyoxamic acid congener (**68**)}¹²

A variety of chemical syntheses of 5-*O*-carbamoyl-polyoxamic acid derivatives have been reported over the years,^{4d, 13} one of the most important intermediate for the general synthesis of them appeared to be a (2*R*)-hydroxy ester such as **60** as shown in Scheme 7. We describe a convenient synthesis of the *N*-protected 5-*O*-carbamoyl-L-polyoxamic acid derivative (**68**) via **60** from 4-*O*-*tert*-butyldiphenylsilyl-



a; NaBH_4 / MeOH , 0°C . b; TBDPSCI / NaH / THF , 0°C . c; 1) DMSO / $(\text{COCl})_2$ / CH_2Cl_2 , -78°C , 2) Et_3N . d; 1) $\text{CH}_2=\text{CHMgBr}$, 2) Ac_2O / pyridine. e; 1) O_3 / CH_2Cl_2 . 2) Me_2S / CH_2Cl_2 , 3) CrO_3 / H_2SO_4 . 4) CH_2N_2 . f; K_2CO_3 / MeOH . g; Tf_2O / pyridine / CH_2Cl_2 . h; AcOCs / DMF . i; 1) Tf_2O / pyridine / CH_2Cl_2 . 2) NaN_3 / DMF . j; 1) H_2 / 20% $\text{Pd}(\text{OH})_2\text{-C}$ / MeOH , 2) Boc_2O / Et_3N / dioxane. k; HF / pyridine. l; 1) $\text{ClCOO-Ph-NO}_2(p)$ / pyridine / Et_3N / THF , 0°C , 2) NH_3 / MeOH , 0°C . m; PhCH_2OH / $\text{Ti}(\text{O-}i\text{Pr})_4$ / benzene, reflux, n; H_2 / 10% Pd-C / MeOH .

Scheme 7

2,3-O-isopropylidene-L-threose (**56**) derived from dimethyl L-tartrate by employing an addition of vinylmagnesium bromide (Scheme 7). In seeking a practical route to **68**, use of dimethyl L-tartrate with its inherent C-2 axis symmetry appeared to be the most promising. A useful synthesis of **19** utilizing L-tartaric acid has been described by Mukaiyama *et al.*,^{13f} the crucial step in which was stereoselective addition of titanium silylacetylide species to the 4-O-benzyl-2,3-isopropylidene-L-threose. Our own strategy for the introduction of the α -hydroxy ester functionality involved an addition of vinylmagnesium bromide to **56** followed by oxidative cleavage of the terminal double bond as key steps. Reduction of the commercially available acetonide (**53**) with NaBH_4 gave the diol (**54**) (92%), which was treated with *tert*-butyldipheylsilyl (TBDPS) chloride in the presence of NaH^{14} to afford the monosilyl ether (**55**) (95%). Swern oxidation of **55** provided the L-threose derivative (**56**) (96%) which reacted with vinylmagnesium bromide followed by acetylation to give a 53:47 diastereomeric mixture of the acetates (**57**) in 73% overall yield. Ozonolysis of **57** followed by treatment with Jones reagent and diazomethane afforded a diastereomeric mixture of the α -acetoxy esters (**58**) in 59% overall yield. This mixture was hydrolysed to a diastereomeric mixture of the α -hydroxy esters, which were separated to the less polar alcohol (2S)-**59** (45%) and the more polar one (2R)-**60** (54%). For the purpose of conversion of **59** into **60**, treatment of **59** with trifluoromethanesulfonic anhydride afforded the triflate (**61**) (90%) which was

treated with cesium acetate to provide the (2*R*)-acetoxy ester (**62**) (93%). Alcoholysis of (2*R*)-**62** gave the inverted (2*R*)-hydroxy ester (**60**) (87%). Triflation of **60** followed by treatment with NaN₃ afforded the diastereomerically pure (2*S*)-azide ester (**63**) (98% overall yield) which was subjected to hydrogenation and subsequent *N*-Boc derivation to provide the (2*S*)-*N*-Boc ester (**64**) (81% overall yield). Treatment of **64** with HF in pyridine gave the desilylated alcohol (**65**) (94%) which was subjected to carbamoylation by the reported procedure¹⁵ to furnish the ultimately desired *N*-protected 5-*O*-carbamoyl-*L*-polyoxamic acid ester (**66**) (97%). Physical data ($[\alpha]_D$ and NMR) of the present **66** were identical with those ($[\alpha]_D$ and NMR) of the reported (2*S*,3*S*,4*S*)-**66**.^{13c} Thus, the configurations of the newly generated chiral centers of α -hydroxy esters **60** and **59** were found to be (*R*)- and (*S*)-configuration, respectively. In the nucleophilic addition of vinylmagnesium bromide to the aldehyde **56**, the low diastereoselectivity (53:47) was observed. For the purpose of the improvement of the diastereoselectivity, effect of coexisting metal halides in addition to **56** was examined and the results are shown in Table 2.

Table 2. Reaction of **56** and vinylmagnesium bromide in the presence of additives

$\text{56} \xrightarrow[\text{2) Ac}_2\text{O / pyridine}]{\text{1) CH}_2=\text{CHMgBr, additive in THF}} (3,4)\text{-anti-57} + (3,4)\text{-syn-57}$				
Entry	Additive	Conditions	Yield 57 (%)	Ratio (<i>anti</i> / <i>syn</i>)
1	none	0 °C, 2 h	73	53 : 47
2	Et ₂ AlCl	-40 to 0 °C, 3 h	50	2 : 1
3	TiCl ₄ /Ti(<i>O</i> - <i>i</i> Pr) ₄	0 °C, 2 h	69	4 : 3
4	ZnBr ₂	-40 to 0 °C, 2 h	80	5 : 1
5	ZnBr ₂	-78 to 0 °C, 2 h	50	8 : 1
6	ZnBr ₂	-78 to 0 °C, 4 h	70	5 : 1

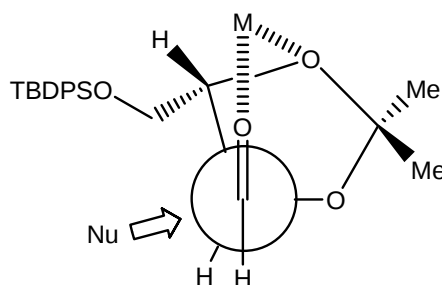


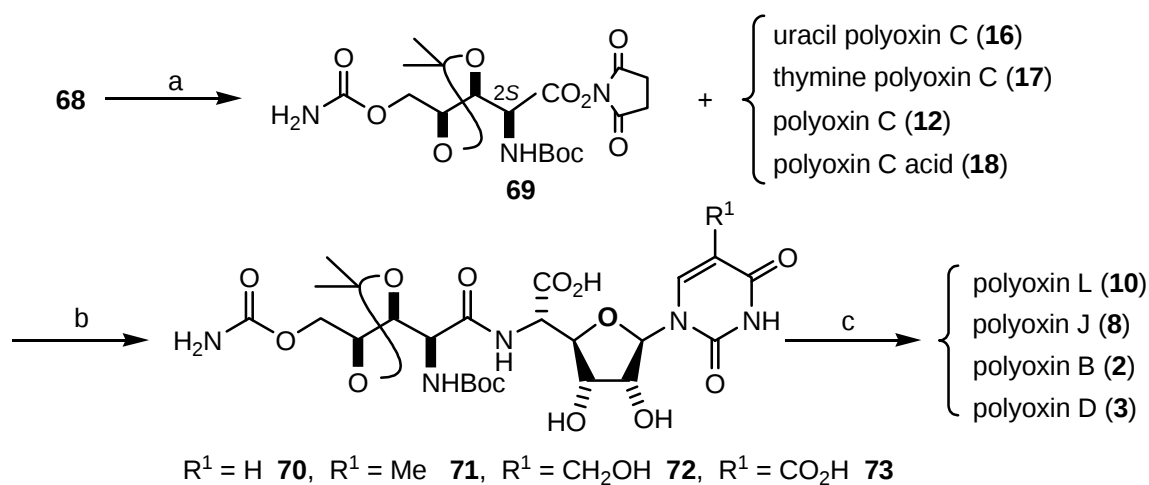
Figure 1

The *anti*-selective addition of nucleophile to **56** is explainable by the Felkin-Anh model¹⁶ as depicted in Figure 1. The β -chelation of metal ion enhances the Felkin selectivity. The addition of nucleophile to **56** may be controlled by the above mentioned reason since the TBDPSOCH₂-group is located *trans* to the reacting formyl group on the dioxolane ring. The addition of vinyl magnesium bromide to **56** in the presence of ZnBr₂ followed by acetylation raised *anti*-selective and afforded (3,4)-*anti*-**57** (entries 4-6) as

shown in Table 2. When this reaction was carried out at $-78\text{ }^{\circ}\text{C}$, ratio of *anti/syn* was enhanced up to 8:1. Without ZnBr_2 , on the contrary, the addition was non-selective to give a 53:47 mixture of (3,4)-*anti*- and (3,4)-*syn*-**57** (entry 1). For the purpose of mass production of (2*R*)-**60**, the 5:1 mixture of (3,4)-*anti*-**57** (entry 6) was converted to **60** (52% overall yield from (3,4)-*anti*-**57**) as a main product by the same way as stated above. From viewpoint of synthetic effectiveness (diastereoselectivity and conversion yield), the present synthetic route to the desired α -azide ester (2*S*)-**63** by way of (2*S*)-**59** and (2*R*)-**60** seemed to be useful because both (2*S*)-**59** and (2*R*)-**60** were finally converted to the important intermediate **63** for the synthesis of the *N*-protected (2*S*)-5-*O*-carbamoyl-L-polyoxamic acid derivative (**68**). For the purpose of conversion of ester group in **66** to carboxylic acid under mild conditions, transesterification of **66** with benzyl alcohol into the benzyl ester (**67**) in the presence of $\text{Ti}(\text{O}-i\text{-Pr})_4$ was achieved in 82% yield. Catalytic deprotection of benzyl group in **67** gave the desired **68** in quantitative yield, which is consistent with the reported **68**^{13c} ($[\alpha]_{\text{D}}$ and NMR).

2.5. Syntheses of polyoxins L (**10**), J (**8**), B (**2**) and D (**3**)^{12,17}

Successful coupling of uracil polyoxin C (**16**) with **68** was carried out by the *N,N*-dicyclohexylcarbodiimide-*N*-hydroxysuccinimide (DCC-HOSu) active ester method^{4a} in DMSO and *N,N*-diisopropylethylamine as the base. Treatment of polyoxamic acid derivative (**68**) with DCC-HOSu gave the active ester (**69**) which was condensed with **16** to afford the dipeptide (**70**) (74% from **68**). Removal of the *N*-Boc and *O*-isopropylidene protecting groups by acid hydrolysis provided polyoxin L (**10**) {mp $180\text{--}183\text{ }^{\circ}\text{C}$ (decomp), ($[\alpha]_{\text{D}} +35.0^{\circ}$ ($c=1.215$, H_2O))} in 94% yield. The physical properties of the present **10** were in good agreement with the literature of natural polyoxin L (**10**)¹⁸ { $[\alpha]_{\text{D}} +34.4^{\circ}$ ($c=1$, H_2O)}.



a; DCC / HOSu / AcOEt, 0°C . b; $(i\text{-Pr})_2\text{NEt}$ / DMSO. c; $\text{CF}_3\text{CO}_2\text{H}$ / $\text{MeOH-H}_2\text{O}$ (2:1).

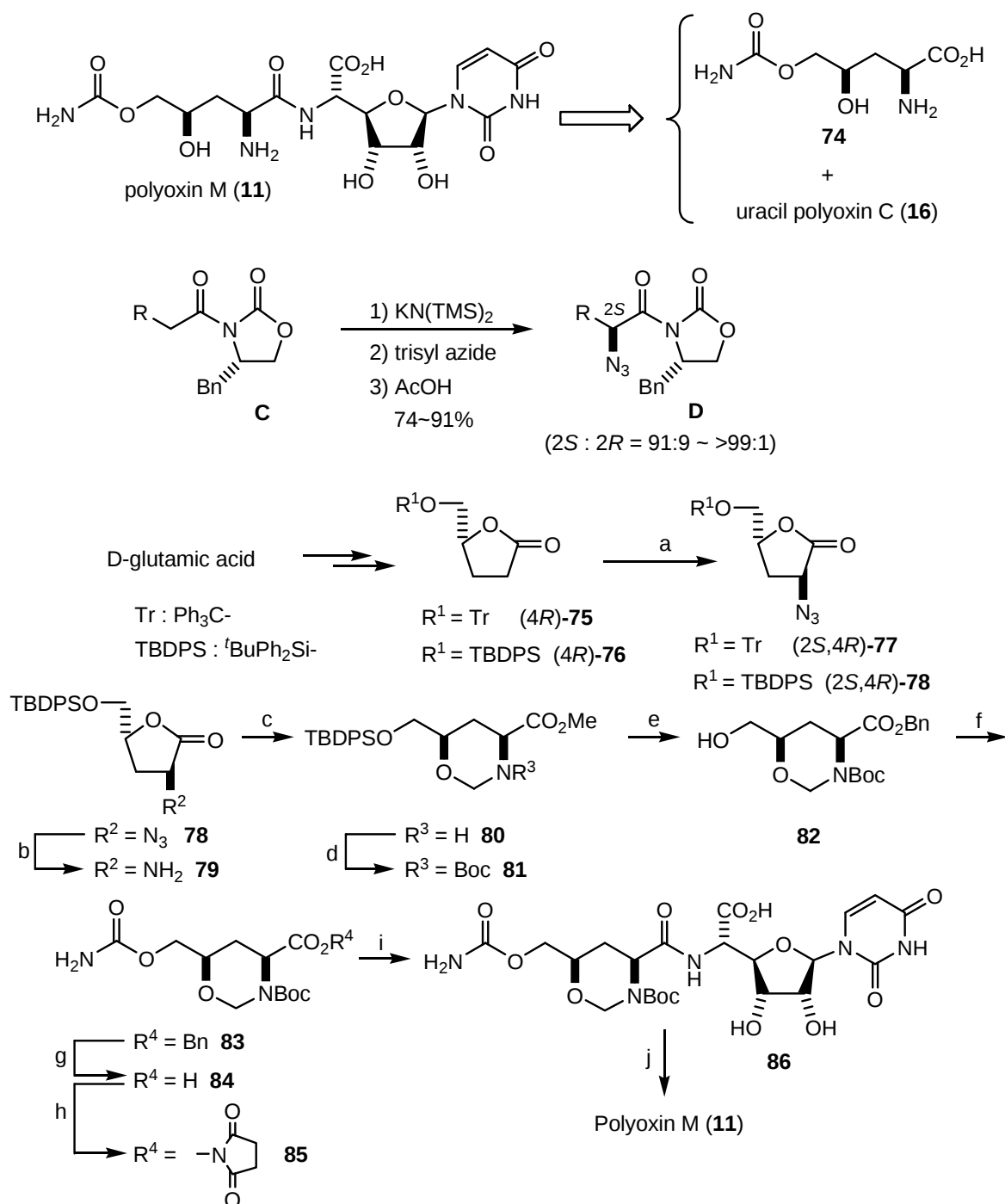
Scheme 8

Likewise, condensation of the active ester (**69**) with thymine polyoxin C (**17**) afforded the dipeptide (**71**) (74% from **68**) which was converted to polyoxin J (**8**) {mp $195\text{--}200^{\circ}\text{C}$ (decomp), ($[\alpha]_{\text{D}} +35.7^{\circ}$ ($c=0.68$,

H₂O) } in 86% yield. The physical properties of the present **8** were in good agreement with the reported polyoxin J (**8**) {mp 200 °C (decomp),^{4c} $[\alpha]_D +35.0^\circ$ (c=0.8, H₂O)^{4b}}. Likewise, condensation of active ester (**69**) with polyoxin C (**12**) afforded the dipeptide **72** (81% from **68**). Removal of the *N*-Boc and *O*-isopropylidene protecting groups by acid hydrolysis provided polyoxin B (**2**) { $[\alpha]_D +36.0^\circ$ (c=0.52, H₂O), mp }150-153 °C (dec.)} in 73% yield. The physical properties of the present **2** were in good agreement with the literature of natural polyoxin B (**2**) ($[\alpha]_D +34.0^\circ$ (c=1, H₂O)).^{1b} Likewise, condensation of the active ester (**69**) with polyoxin C acid (**18**) afforded the dipeptide (**73**) (50% from **68**) which was converted to polyoxin D (**3**) {($[\alpha]_D +30.6^\circ$ (c=0.16, H₂O), mp 173-175 °C (dec.)) in 90% yield. The physical properties ($[\alpha]_D$, ¹H-NMR and ¹³C-NMR) of the present **3** were identical with those { $[\alpha]_D +30^\circ$ (c=1, H₂O),^{1b} ¹H-NMR and ¹³C-NMR } of natural polyoxin D (**3**) given by Dr. H. Osada. The syntheses described herein demonstrate an applicable synthesis of other components of polyoxin families.^{1a}

3. Synthesis of polyoxin M (**11**)¹⁹

Retrosynthetically, the synthesis of polyoxin M (**11**) can be achieved by amide formation between the left-half α -amino acid congener **74** and the right-half **16** as shown in Scheme 9. We describe the first synthesis of polyoxin M (**11**) based on the electrophilic azide transfer to chiral enolate (Scheme 9). For the synthesis of **74**, (2*S*,4*R*)-2-azido-(4-protected hydroxymethyl)-4-butanolide congeners (**77**, **78**) are thought to be an important intermediate. These azide compounds (**77**, **78**) could be obtained by the diastereoselective azide transfer to chiral enolate derived from the (4*R*)-(protected hydroxymethyl)-4-butanolides (**75**, **76**), respectively. By applying the reported method,²⁰ the synthesis of (4*R*)-**75** or (4*R*)-**76** was achieved by tritylation or silylation of (4*R*)- γ -hydroxymethyl- γ -butyrolactone derived from D-glutamic acid. On the other hand, treatment of chiral enolate derived from *N*-acyloxazolidone (**C**) with 2,4,6-triisopropylbenzenesulfonyl azide (trisyl azide), followed by addition of AcOH was reported to give (2*S*)-azido carboximides (**D**) with high diastereoselectivity²¹ as shown in Scheme 9. On consideration of this report, our attention was focused only on the electrophilic azide transfer to the (4*R*)-4-butanolides (**75**, **76**) (Table 3). Chiral enolate derived from (4*R*)-**75** with lithium hexamethyldisilylazide (LiHMDS) was treated with trisyl azide, followed by addition of AcOH to give (2*S*,4*R*)-**77** (37%) and (2*R*,4*R*)-**77** (12%) (entry 1). Change of the counter metal cation to sodium or potassium caused decrease of the yield of (2*S*,4*R*)-**77** (entries 2 and 3). Treatment of chiral enolate derived from (4*R*)-**76** with trisyl azide, followed by addition of AcOH provided (2*S*,4*R*)-**78** (33%) and (2*R*,4*R*)-**78** (13%) (entry 4), while change of AcOH to trimethylsilyl chloride (TMSCl) brought about a remarkable increase of the yield of (2*S*,4*R*)-**78** (53%) along with (2*R*,4*R*)-**78** (28%) (entry 5). In the case of the electrophilic azide transfer to an enolate, the quench reagent was found to be an essential ingredient for successful azide transfer.²¹ Surprisingly, AcOH proved to be superior to the silylating agents, TMSCl or TMSOTf, or strong acid, trifluoroacetic acid, while TMSCl was found to be a more effective quench agent in the present case. The structure of (2*S*,4*R*)-**78** was determined by NMR analysis including



a; 1) LiHMDS / THF, 2) trisyl azide / AcOH or 1) LiHMDS / THF, 2) trisyl azide / TMSCl. b; 1) Ph_3P , 2) H_2O .
c; 1) NaOH aq., / THF, 2) HCHO aq., 3) H^+ , 4) CH_2N_2 . d; $(\text{Boc})_2\text{O}$ / dioxane. e; 1) BnOH / $\text{Ti}(\text{O}-i\text{Pr})_4$ / PhH, 2) $\text{Bu}_4\text{N}^+\text{F}^-$ / THF. f; 1) 4-nitrophenylchloroformate / pyridine / Et_3N / THF, 2) NH_3 / MeOH. g; H_2 / 10%Pd-C / MeOH. h; HOSu / DCC / AcOEt. i; **16** / $(i\text{-Pr})_2\text{NEt}$ / DMSO. j; $\text{CF}_3\text{CO}_2\text{H}$ / MeOH / H_2O .

Scheme 9

NOE experiment. Then conversion of (2S,4R)-**78** to the left-half congener (**85**) corresponding to **74** was carried out. Reduction of (2S,4R)-**78** with Ph_3P and H_2O gave the amine (**79**) (97%), which was subjected to consecutive alkaline hydrolysis and acetal formation with formaldehyde to afford the 1,3-oxadiazine derivative (**80**) in 70% overall yield. Protection of the secondary amino group of **80** with a Boc group gave **81** (81%), which was subjected to consecutive trans-esterification and desilylation to afford the

alcohol (**82**) in 86% yield. Conversion of **82** to the carbamoyl compound (**83**) (80%), followed by catalytic hydrogenation yielded the desired carboxylic acid (**84**) in 98% yield. Treatment of **84** with *N*-hydroxysuccinimide in the presence of DCC in DMSO^{4a} provided an active ester (**85**), which was coupled with uracil polyoxin C (**16**) in the presence of (*i*-Pr)₂NEt to give the dipeptide (**86**) in 74% yield from **84**. Removal of the *N*-Boc and *N,O*-acetal protecting groups upon acid hydrolysis provided polyoxin M (**11**) $\{[\alpha]_D^{25} +46.9^\circ$ (c 0.29, H₂O), mp 215–220 °C (dec) $\}$ in 47% yield. The specific rotation of synthetic **11** was in good agreement with that $\{[\alpha]_D +49.9^\circ$ (H₂O) $\}$ of the reported natural product (**11**)^{1b} (Scheme 9).

Table 3. Reaction of **75** or **76** and trisyl azide

$R^1 = \text{Tr}$ **75**
 $R^1 = \text{TBDPS}$ **76**

$R^1 = \text{Tr}$ (2*S*,4*R*)-**77**
 $R^1 = \text{TBDPS}$ (2*S*,4*R*)-**78**

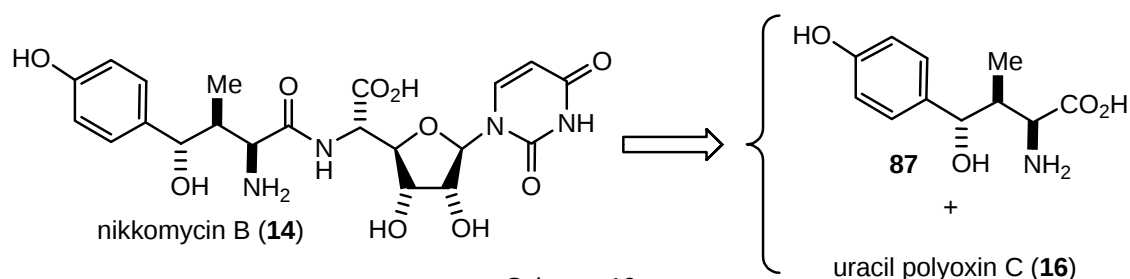
$R^1 = \text{Tr}$ (2*R*,4*R*)-**77**
 $R^1 = \text{TBDPS}$ (2*R*,4*R*)-**78**

a; 1) base / THF 2) trisyl azide 3) acid

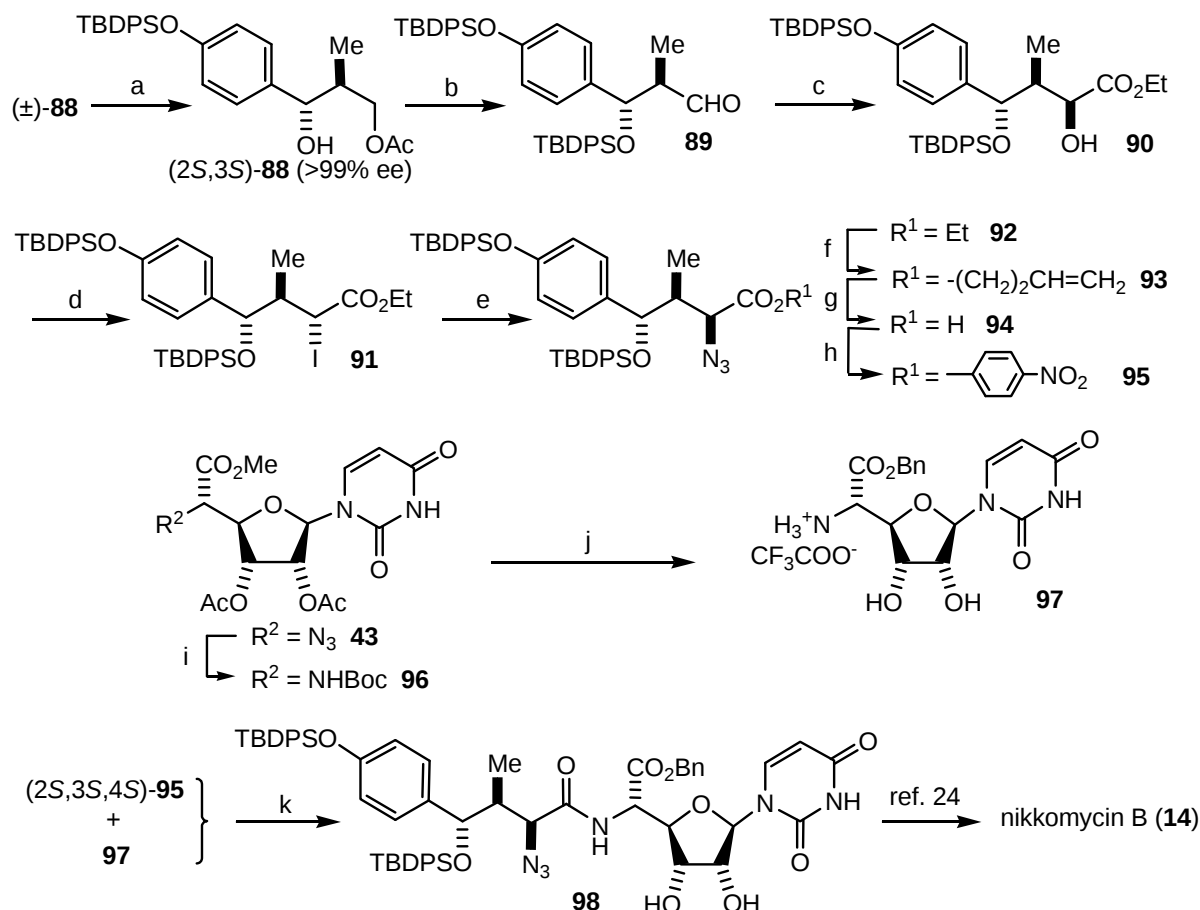
Entry	R ¹	Base	Acid	Product (yield)	
1	Tr	LiHMDS	AcOH	(2 <i>S</i> ,4 <i>R</i>)- 77 (37%)	(2 <i>R</i> ,4 <i>R</i>)- 77 (12%)
2	Tr	NaHMDS	AcOH	(2 <i>S</i> ,4 <i>R</i>)- 77 (25%)	(2 <i>R</i> ,4 <i>R</i>)- 77 (trace)
3	Tr	KHMDS	AcOH	(2 <i>S</i> ,4 <i>R</i>)- 77 (11%)	(2 <i>R</i> ,4 <i>R</i>)- 77 (trace)
4	TBDPS	LiHMDS	AcOH	(2 <i>S</i> ,4 <i>R</i>)- 78 (33%)	(2 <i>R</i> ,4 <i>R</i>)- 78 (13%)
5	TBDPS	LiHMDS	TMSCl	(2 <i>S</i> ,4 <i>R</i>)- 78 (53%)	(2 <i>R</i> ,4 <i>R</i>)- 78 (28%)

4. Formal synthesis of nikkomycin B (**14**)²²

Synthesis of nikkomycin B (**14**) could be achieved by the coupling of two structural units, the N-terminal amino acid (**87**) and the C-terminal nucleoside amino acid, uracil polyoxin C (**16**) as shown in Scheme 10.



The presence of three consecutive stereogenic centers in **87** is the greater synthetic challenge, and several approaches to this amino acid and its congener in either racemic or optically active form,²² have been recently reported. Barrett's intermediate (2*S*,3*S*,4*S*)-**95** corresponding to **87** could be synthesized from chiral (2*S*,3*S*)-monoacetate **88**, while uracil polyoxin C congener **97** corresponding to **16** could be obtained from the above-mentioned **43** as shown in Scheme 11.



a; lipase "Amano P" / H₂O-saturated diisopropyl ether. b; 1) *t*-BuPh₂SiCl / imidazole / DMF, 2) HAl(*i*-Bu)₂.

3) (COCl)₂ / DMSO / Et₃N / CH₂Cl₂. c; 1) ethyl vinyl ether / *t*-BuLi, 2) O₃, 3) Me₂S. d; I₂ / Ph₃P / imidazole / MeCN / H₂O. e; NaN₃ / DMF. f; CH₂=CH(CH₂)₂OH / Ti(O-*i*Pr)₄. g; 1) O₃, 2) Me₂S, 3) DBU, 4) H⁺.

h; *p*-nitrophenol / DCC. i; H₂ / 10%Pd-C / MeOH, 2) Boc₂O / Et₃N. j; 1) BnOH / Ti(O-*i*Pr)₄. 2) TFA / AcOEt.

k; *N*-methylmorpholine / DMF.

Scheme 11

The chiral (2*S*,3*S*)-**88** was obtained by the lipase-assisted enantioselective hydrolysis of racemic **88**, which was obtained by the following procedure. Reformatsky reaction of *p*-silyloxybenzaldehyde derived from *p*-hydroxybenzaldehyde and α-bromopropionate gave α-methyl-β-hydroxy ester which was subjected to Jones oxidation to give the corresponding β-keto ester. Reduction of the β-keto ester with *n*-Bu₄NBH₄²³ gave selectively (±)-*anti*-α-methyl-β-hydroxy ester (*anti/syn* = 15/1), which was subjected to consecutive reduction and monoacetylation to afford (±)-**88**. Thus obtained optically pure (2*S*,3*S*)-**88** was subjected to consecutive silylation, reductive deacetylation and Swern oxidation to provide the aldehyde (**89**). By applying Barrett's procedure,²⁴ **89** was subjected to the Felkin Ahn controlled

addition of lithiated ethyl vinyl ether at -78°C . The generated vinyl ether was directly ozonolyzed and subsequently treated with dimethyl sulfide to yield a 4.3:1 mixture of ethyl α -hydroxy esters, which was separated to **90** (47% overall yield from **88**) and its diastereomer (11% overall yield from **88**). Conversion of **90** to the iodide (**91**) (77%) followed by nucleophilic displacement with NaN_3 provided the desired ethyl (2*S*)- α -azido ester (**92**) (88%) as a single diastereoisomer. Formation of the activated ester **95** was carried out in the same way as Barrett's procedure.²⁴ Transesterification of **92** in the presence of 3-buten-1-ol and $\text{Ti}(\text{O-}i\text{-Pr})_4$ gave the corresponding ester **93** (90%). Ozonolysis of the butenyl moiety followed by treatment with DBU *in situ* afforded the α -azido acid (**94**). Without further purification, treatment of **94** with *p*-nitrophenol in the presence of DCC gave the activated ester (**95**) (43%). On the other hand, uracil polyoxin C congener **97** corresponding to the C-terminal nucleoside amino acid part of nikkomycin B (**14**) was synthesized from **43**. Hydrogenation of the azide (**43**) in the presence of 10% Pd-C afforded the α -amino acid ester which was treated with di-*tert*-butyldicarbonate (Boc_2O) in the presence of triethylamine to provide the N-protected amino acid ester (**96**) (65%). Transesterification of **96** in the presence of benzyl alcohol and $\text{Ti}(\text{O-}i\text{-Pr})_4$ provided the corresponding benzyl ester (47%) along with the selective deacetylation. Benzyl ester was treated with trifluoroacetic acid to give the corresponding ammonium trifluoroacetate (**97**) which was directly subjected to the amide formation reaction with the activated ester **95** using *N*-methylmorpholine in DMF to afford the amide (**98**) $\{[\alpha]_{\text{D}} -10.9^{\circ}$ ($c=1.26$, CHCl_3), 53%}. The spectral data ($[\alpha]_{\text{D}}$, $^1\text{H-NMR}$, $^{13}\text{C-NMR}$ and FAB-MS) of **98** were identical with those $\{[\alpha]_{\text{D}} -10.2^{\circ}$ ($c=0.98$, CHCl_3) } of authentic **98** reported by Barrett.²⁴ The total synthesis of nikkomycin B (**14**) from **98** has already been achieved by Barrett.²⁴

5. Conclusion

Total syntheses of polyoxins B (**2**), D (**3**), J (**8**), L (**10**), M (**11**), C (**12**) and formal synthesis of nikkomycin B (**14**) were summarized in this review. The efficient syntheses of 1-(5-amino-5-deoxy- β -D-allofurano-uronosyl) pyrimidines such as thymine polyoxin C (**16**), uracil polyoxin C (**17**) and polyoxin C acid (**61**) corresponding to the right half were achieved based on the nucleophilic 1,2-addition of 1-ethoxyvinyl lithium or vinylmagnesium bromide to methyl 2,3-*O*-isopropylidene- β -D-ribopentodialdo-1,4-furanoside. Then the syntheses of polyoxamic acid derivatives and their congeners corresponding to the left acid part were carried out based on 1,2-addition of vinylmagnesium bromide to 4-*O*-protected-2,3-*O*-isopropylidene-L-threose. The left half acid parts were led to the corresponding activated esters, which were coupled with amine part derived from the right half to give the *N,O*-protected peptidyl nucleoside congeners. Deprotection of the coupled compounds afforded polyoxins B (**2**), D (**3**), J (**8**), L (**10**), M (**11**) and nikkomycin B (**14**).

ACKNOWLEDGMENT

I am grateful to Assoc. Prof. K. Kato, Dr. M. Fujii, Dr. C. Y. Chen, M.S(c). K. Uchida and M.S(c). Y. Shiro for their supporting the present works.

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Hiroyuki Akita, born in 1944 in Kagoshima prefecture(Japan), obtained an M.S. degree in 1970 from Kyushu University and in the same year joined the Riken Institute (The Institute of Physical and Chemical Research), where he worked with the late Dr. Akira Tahara. He received his Ph.D. degree from Kyushu University (Prof. Masatomo Hamana) in 1975. From 1978 he spent two years as a postdoctoral fellow at Department of Chemistry, Columbia University, with Professor Koji Nakanishi. He was a scientist from 1975 to 1991 under the direction of Dr. Takeshi Oishi at Riken Institute and then moved to the School of Pharmaceutical Sciences, Toho University, as professor of organic chemistry in 1991. His research interests are the use of biocatalyst in organic synthesis and application of the chiral compounds obtained by means of biocatalyst to the synthesis of biologically active natural products. He received “The PSJ Award for Young Scientists” from the Pharmaceutical Society of Japan In 1990.