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SYNTHESES OF PEPTIDYL NUCLEOSIDE ANTIBIOTICS

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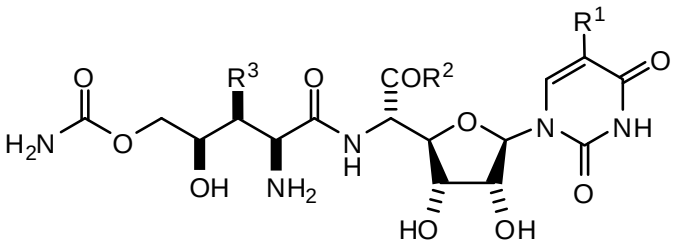
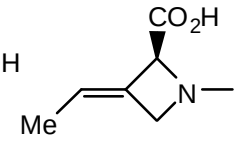
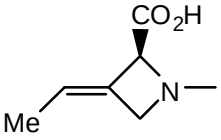
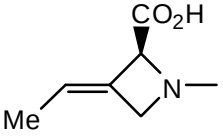
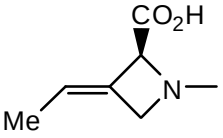
Abstract — Polyoxins and nikkomycins are an important class of peptidyl nucleoside antibiotics isolated from the culture broths of *Streptomyces cacaoi* var. *asoensis* and *Streptomyces tendae*. For the syntheses of these antibiotics, efficient syntheses of 1-(5-amino-5-deoxy-β-D-allofurano-uronosyl)pyrimidines 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 nucleophic 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.

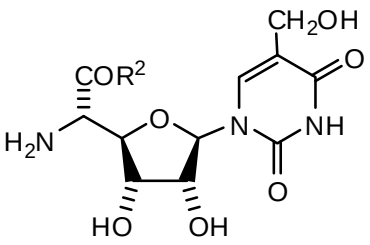
1. INTRODUCTION

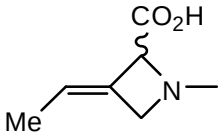
Polyoxins are an important class of peptidyl nucleoside antibiotics isolated from the culture broths of *Streptomyces cacaoi* var. *asoensis*, which are potent competitive inhibitors of chitin synthetase of a variety of phytopathogenic fungi or *Candida albicans*, a medically important human fungal pathogen.[1] 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**).

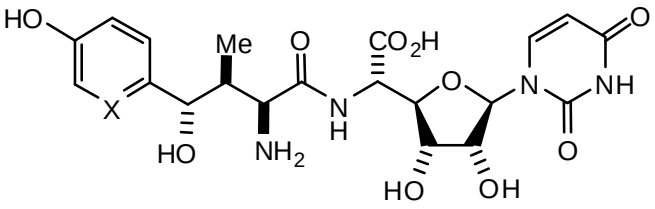
This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.



Polyoxin	R^1	R^2	R^3
A (**1**)	CH_2OH		OH
B (**2**)	CH_2OH	OH	OH
D (**3**)	CO_2H	OH	OH
E (**4**)	CO_2H	OH	H
F (**5**)	CO_2H		OH
G (**6**)	CH_2OH	OH	H
H (**7**)	Me		OH
J (**8**)	Me	OH	OH
K (**9**)	H		OH
L (**10**)	H	OH	OH
M (**11**)	H	OH	H



Polyoxin	R^2
C (**12**)	OH
I (**13**)	



Nikkomycin	X
B (**14**)	CH
Z (**15**)	N

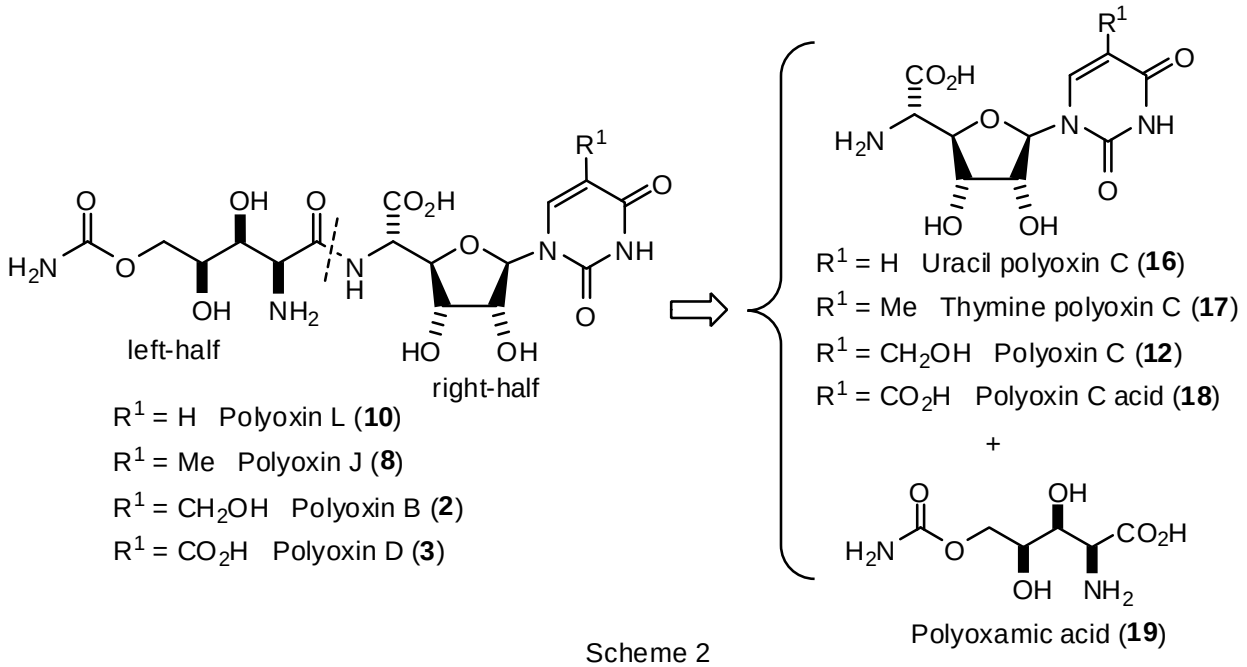
Scheme 1

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

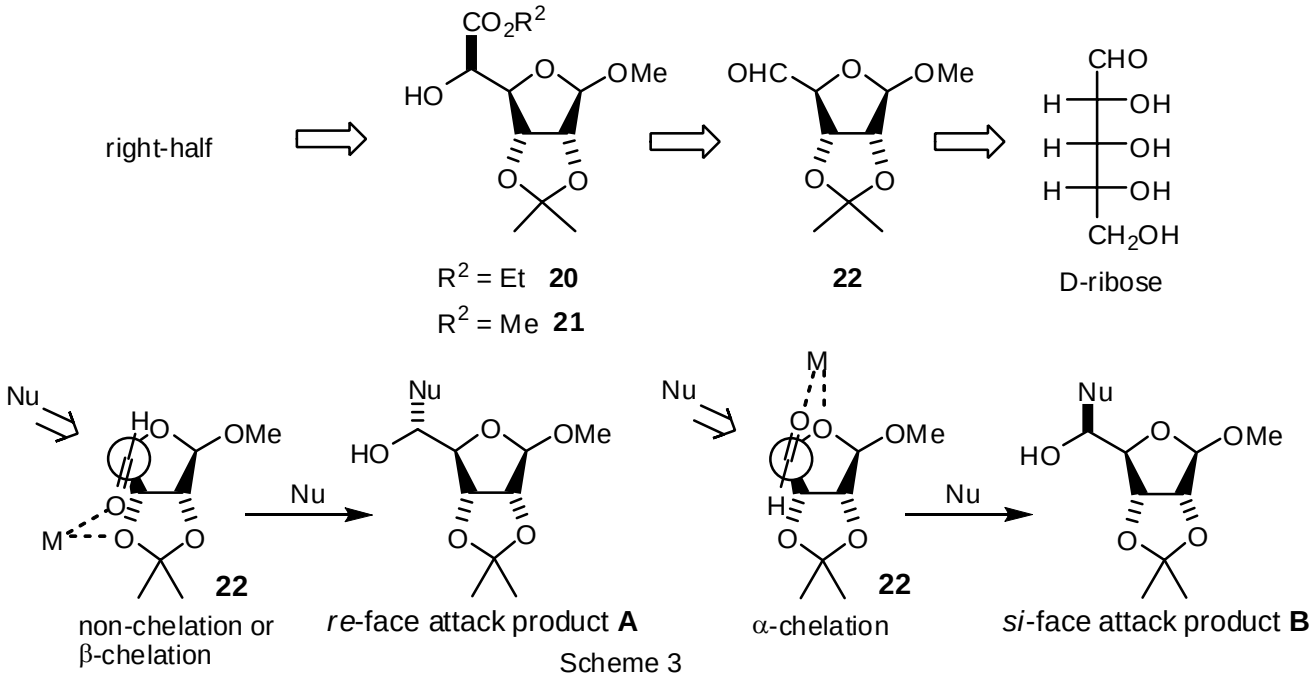
Retrosynthetically, the synthesis of polyoxins L (**10**), J (**8**), B (**2**) and D (**3**) can be achieved by amide formation between the 1-(5-amino-5-deoxy-β-D-allofuranouronosyl)pyrimidines derivatives {uracil polyoxin C (**16**), thymine polyoxin C (**17**), polyoxin C (**12**) and polyoxin C acid (**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**)

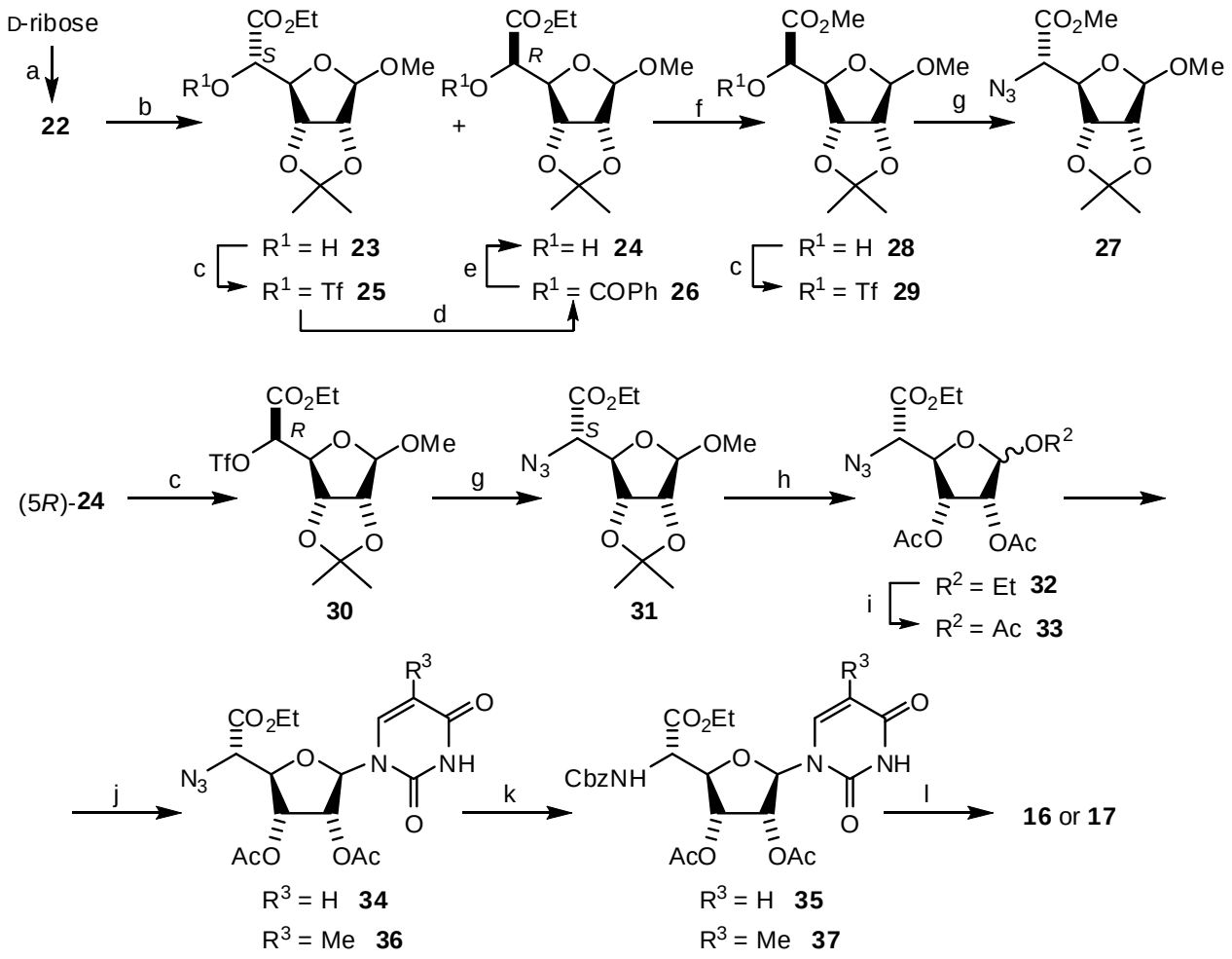


Scheme 2



Scheme 3

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 C_4-C_5 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°C. b; 1) Ethyl vinyl ether / *t*-BuLi / THF, -78°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 / $Ti(O\text{-}iPr)_4$ / 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-$BaSO_4$ / MeOH, 2) CbzCl / 7% $NaHCO_3$ aq. / dioxane. k; for **37**: 1) H_2 / 20% $Pd(OH)_2$-C / MeOH, 2) CbzCl / 7% $NaHCO_3$ aq. / dioxane. l; 1) $LiOH{\cdot}H_2O$ / THF, 2) 0.1 M HCl, 3) H_2 / 10% Pd-C / MeOH.

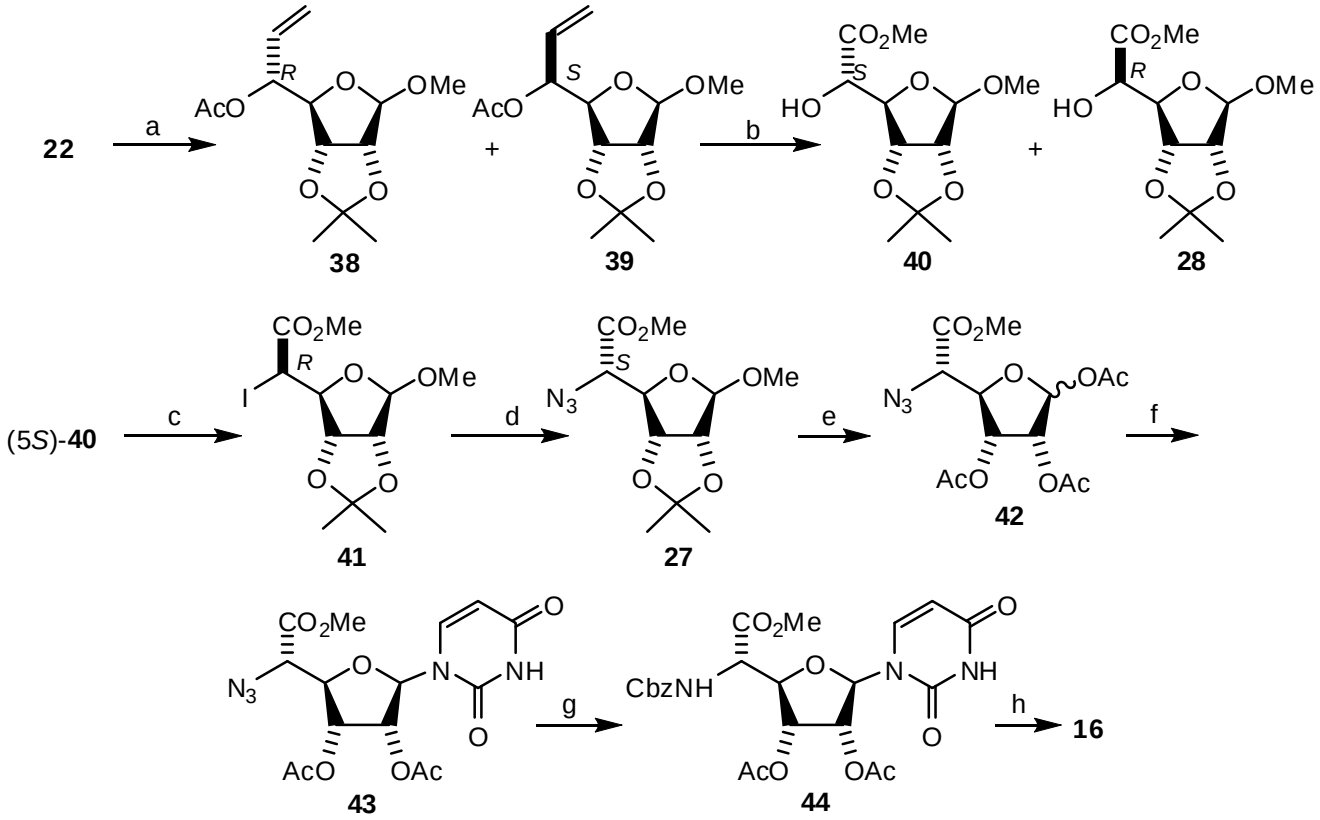
Scheme 4

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 Ti(O-*i*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 (5*S*)-**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), $ClCH_2CH_2Cl$, 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 (5*S*)-**35** (74%). Alkaline hydrolysis of **35** followed by hydrogenation afforded uracil polyoxin C (**16**) (72%). Likewisw, 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% $Pd(OH)_2$-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 (5*S*)-**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 (5*S*)-**23** and (5*R*)-**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 (5*S*)-**23** and (5*R*)-**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 (5*S*)-**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 gave a 3.7:1 diastereomeric mixture of acetoxy 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 (5*S*)-**40** (64% overall yield) and the less polar (5*R*)-**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



a; 1) CH_2=CHMgBr, 2) Ac_2O / pyridine. b; 1) $RuCl_3$ / $NaIO_4$, 2) CH_2N_2, 3) K_2CO_3 / MeOH. c; I_2 / Ph_3P / imidazole. d; NaN_3 / DMF. e; 1) Dowex 50W H^+ / EtOH, reflux, 2) Ac_2O / pyridine, 3) Ac_2O / AcOH / *conc*. H_2SO_4 / CH_2Cl_2. f; 2,4-bis(trimethylsilyloxy)pyrimidine / TMSOTf / $ClCH_2CH_2Cl$, reflux. g; 1) H_2 / 10% Pd-C, 2) CbzCl / 7% $NaHCO_3$. h; 1) $LiOH{\cdot}H_2O$ / THF, 2) 1M HCl, 3) H_2 / 10% Pd-C / MeOH.

Scheme 5

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

22 —(1) CH_2=CHMgBr, additive in THF; (2) Ac_2O / pyridine)→ **38** + **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

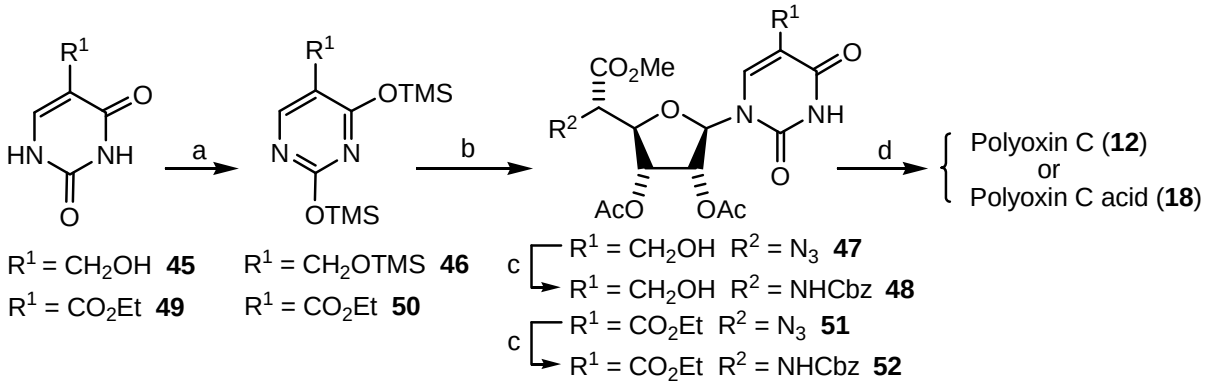
afford the α-azido ester (**27**) (98%). Thus overall yield of the desired **27** from **22** was totally improved to 55% in comparison with the previous case (13%) or the reported procedure (38%) by Barrett *et al.*[7]

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 (5*S*)-**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, $ClCH_2CH_2Cl$, 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**.

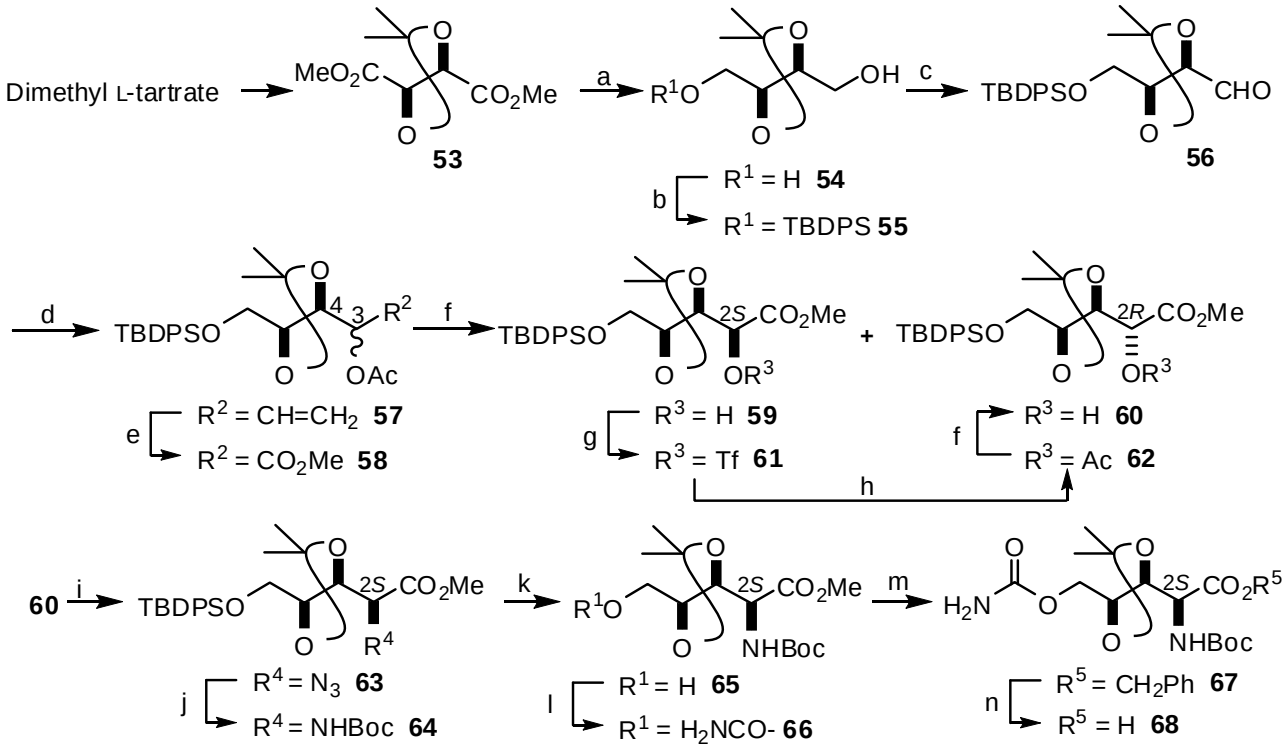


a; $(Me_3Si)_3NH$ / Me_3SiCl. b; **42** / TMSOTf / MeCN. c; 1) H_2 / 10% Pd-C, 2) CbzCl. d; 1) $LiOH·H_2O$ / THF, 2) 1M HCl, 3) H_2 / 10% Pd-C / MeOH.

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-



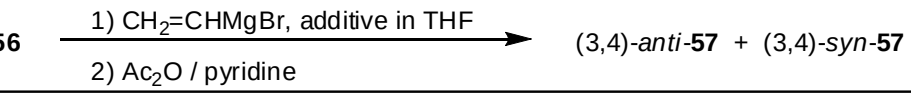
a; $NaBH_4$ / MeOH, 0°C. b; TBDPSCl / NaH / THF, 0°C. c; 1) DMSO / $(COCl)_2$ / CH_2Cl_2, -78°C, 2) Et_3N. d; 1) CH_2=CHMgBr, 2) Ac_2O / pyridine. e; 1) O_3 / CH_2Cl_2. 2) Me_2S / CH_2Cl_2, 3) CrO_3 / H_2SO_4. 4) CH_2N_2. f; K_2CO_3 / MeOH. g; Tf_2O / pyridine / CH_2Cl_2. h; AcOCs / DMF. i; 1) Tf_2O / pyridine / CH_2Cl_2. 2) NaN_3 / DMF. j; 1) H_2 / 20% $Pd(OH)_2$-C / MeOH, 2) Boc_2O/ Et_3N / dioxane. k; HF / pyridine. l; 1) ClCOO-Ph-NO_2(*p*) / pyridine / Et_3N / THF, 0°C, 2) NH_3 / MeOH, 0°C. m; $PhCH_2OH$ / $Ti(O\text{-}iPr)_4$ / 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 (2*S*)-**59** (45%) and the more polar one (2*R*)-**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 NaN_3 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 procedure[15] 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



Entry	Additive	Conditions	Yield **57** (%)	Ratio (*anti*/*syn*)
1	none	0 °C, 2 h	73	53 : 47
2	Et_2AlCl	-40 to 0 °C, 3 h	50	2 : 1
3	$TiCl_4/Ti(O\text{-}iPr)_4$	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

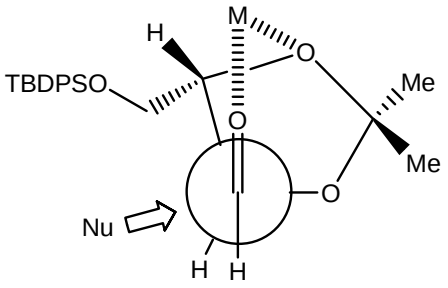


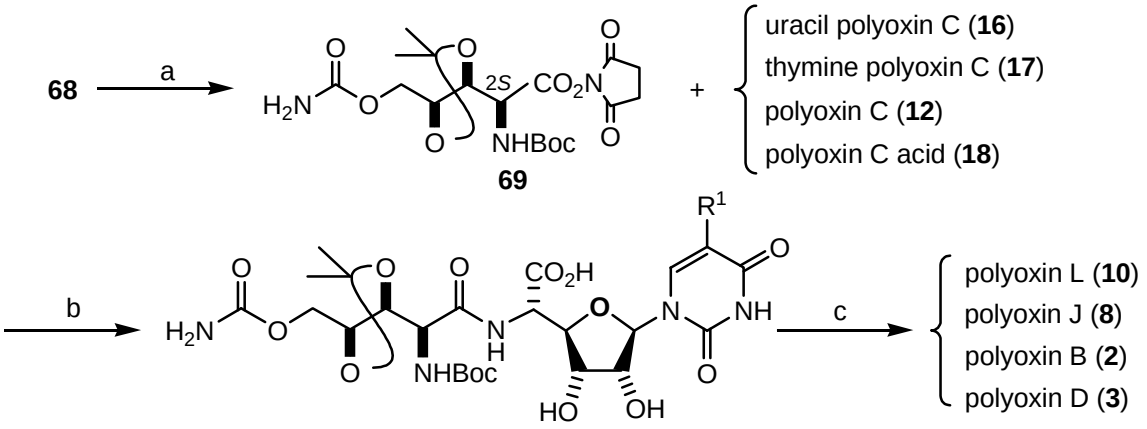
Figure 1

The *anti*-selective addition of nucleophile to **56** is explainable by the Felkin-Anh model[16] 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 $TBDPSOCH_2$-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 $ZnBr_2$ 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 °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 $Ti(O\text{-}i\text{-}Pr)_4$ 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] ($[\alpha]_D$ 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 180-183 °C (decomp), ($[\alpha]_D$ +35.0° (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] {$[\alpha]_D$ +34.4° (c=1, H_2O) }.



R^1 = H **70**, R^1 = Me **71**, R^1 = CH_2OH **72**, R^1 = CO_2H **73**

a; DCC / HOSu / AcOEt, 0°C. b; $(i\text{-}Pr)_2NEt$ / DMSO. c; CF_3CO_2H / MeOH-H_2O (2:1).

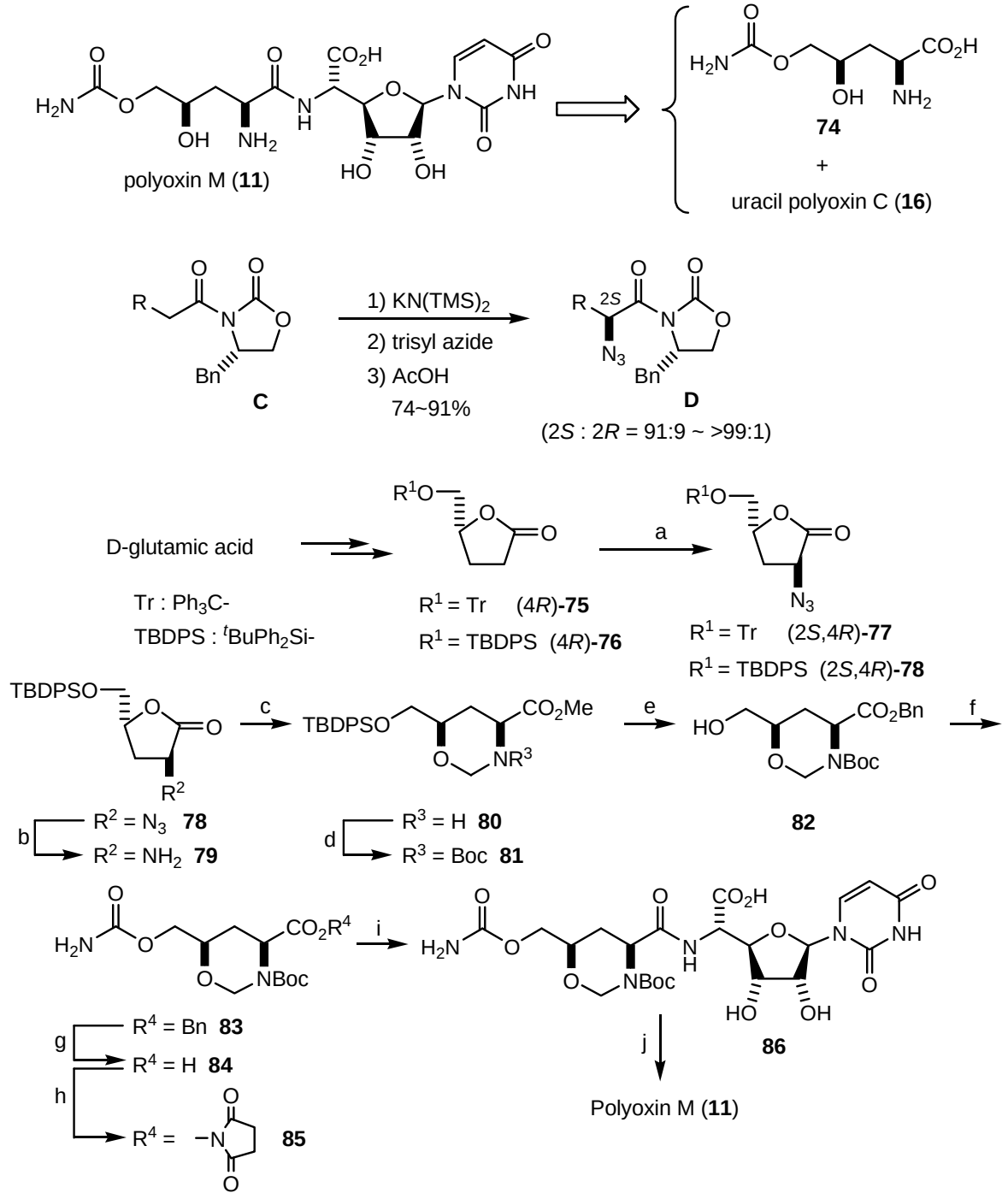
Scheme 8

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 195-200°C (decomp), ($[\alpha]_D$ +35.7° (c=0.68,

H_2O) } 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° (c=0.8, H_2O)[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° (c=0.52, H_2O), 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° (c=1, H_2O)).[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° (c=0.16, H_2O), mp 173-175 °C (dec.)) in 90% yield. The physical properties ($[\alpha]_D$, ^{1}H-NMR and ^{13}C-NMR) of the present **3** were identical with those {$[\alpha]_D$ +30° (c=1, H_2O),[1b] ^{1}H-NMR and ^{13}C-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 diastereoselectivity[21] 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 hexamethyldisilyazide (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



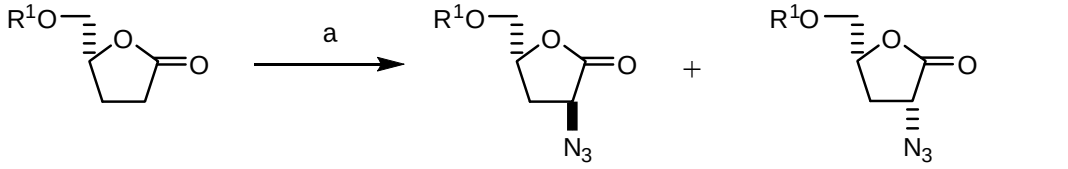
a; 1) LiHMDS / THF, 2) trisyl azide / AcOH or 1) LiHMDS / THF, 2) trisyl azide / TMSCl. b; 1) Ph_3P, 2) H_2O. c; 1) NaOH aq., / THF, 2) HCHO aq., 3) H^+, 4) CH_2N_2. d; $(Boc)_2O$ / dioxane. e; 1) BnOH / Ti(O-*i*Pr)$_4$ / PhH, 2) $Bu_4N^+F^-$ / THF. f; 1) 4-nitrophenylchloroformate / pyridine / Et_3N / THF, 2) NH_3 / MeOH. g; H_2 / 10%Pd-C / MeOH. h; HOSu /DCC / AcOEt. i; **16** / (*i*-Pr)$_2$NEt / DMSO. j; CF_3CO_2H / MeOH / H_2O.

Scheme 9

NOE experiment. Then conversion of (2*S*,4*R*)-**78** to the left-half congener (**85**) corresponding to **74** was carried out. Reduction of (2*S*,4*R*)-**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-oxadinane 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 $(i\text{-Pr})_2$NEt 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° (*c* 0.29, H_2O), mp 215–220 °C (dec) } in 47% yield. The specific rotation of synthetic **11** was in good agreement with that {$[\alpha]_D$ +49.9° (H_2O) } of the reported natural product (**11**)[1b] (Scheme 9).

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



R^1 =Tr **75**
R^1 =TBDPS **76**

R^1 =Tr (2*S*,4*R*)-**77**
R^1 =TBDPS (2*S*,4*R*)-**78**

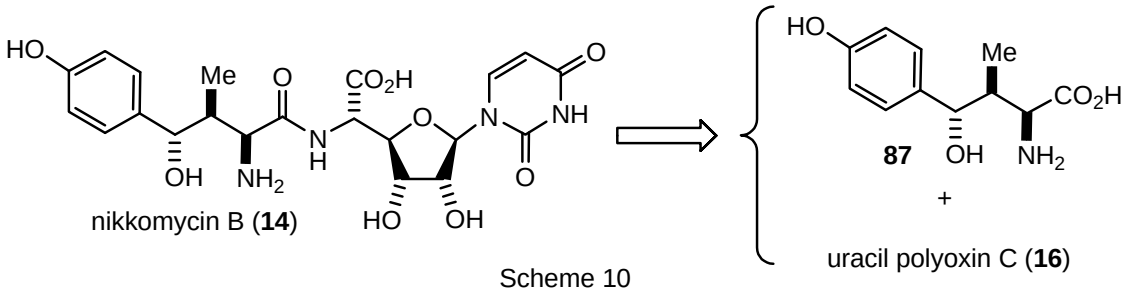
R^1 =Tr (2*R*,4*R*)-**77**
R^1 =TBDPS (2*R*,4*R*)-**78**

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

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

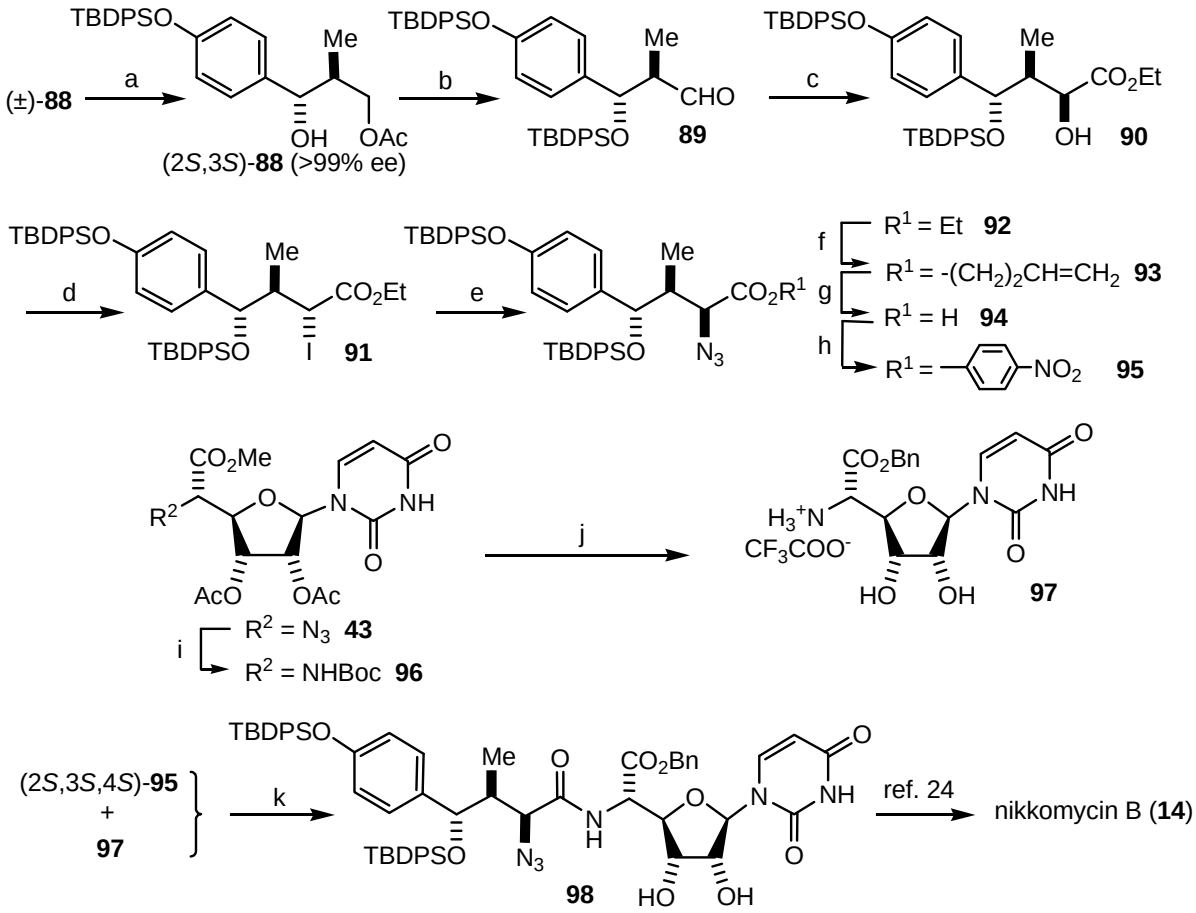
4. Formal synthesis of nikkomycin B (14)[22]

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.



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" / H_2O-saturated diisopropyl ether. b; 1) *t*-$BuPh_2SiCl$ / imidazole / DMF, 2) $HAl(i\text{-}Bu)_2$. 3) $(COCl)_2$ / DMSO / Et_3N / CH_2Cl_2. c; 1) ethyl vinyl ether / *t*-BuLi, 2) O_3, 3) Me_2S. d; I_2 / Ph_3P / imidazole / MeCN / H_2O. e; NaN_3 / DMF. f; CH_2=CH$(CH_2)_2OH$ / Ti(O-*i*Pr)$_4$. g; 1) O_3, 2) Me_2S, 3) DBU, 4) H^+. h; *p*-nitrophenol / DCC. i; H_2 / 10%Pd-C / MeOH, 2) Boc_2O / Et_3N. 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*-Bu_4NBH_4[23] 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 Ti(O-*i*-Pr)$_4$ gave the corresponding ester **93** (90%). Ozonolysis of the butenyl moiety followed by treatment with DBU *in stiu* 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 Ti(O-*i*-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**) {$[\alpha]_D$ -10.9° (c=1.26, $CHCl_3$), 53%}. The spectral data ($[\alpha]_D$, ^{1}H-NMR, ^{13}C-NMR and FAB-MS) of **98** were identical with those {$[\alpha]_D$ -10.2° (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 nucleophic 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**).

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