TOTAL SYNTHESES OF (-)-POLYOXIN J AND (-)-POLYOXIN L

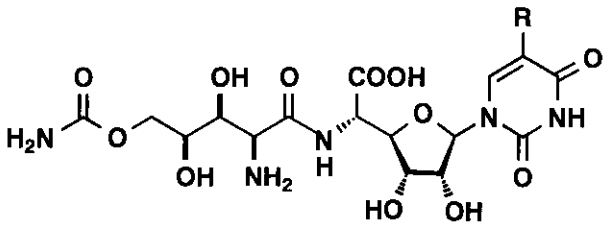
Hiroyuki Akita,* Kimio Uchida, and Keisuke Kato

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

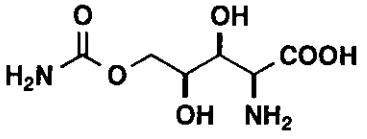
Abstract - A convenient synthesis of the *N*-protected *L*-carbamoylpolyoxamic acid derivative (**7**) from 4-*O*-*tert*-butyldiphenylsilyl-2,3-isopropylidene-*L*-threose (**8**) using vinylmagnesium bromide and its application to the total syntheses of the peptidyl nucleoside antibiotics, polyoxins J (**1**) and L (**2**), are described.

Polyoxins J (**1**) and L (**2**) are an important class of peptidyl nucleoside antibiotics isolated from the culture broths of *Streptomyces cacaoi* var. *asoensis*, which are attracting increasing interest as antifungal compounds because of their ability to inhibit chitin synthetase of a variety of phytopathogenic fungi.[1] In the preceeding paper, we reported a short path synthesis of α-hydroxy ester from methyl 2,3-*O*-isopropylidene-dialdo-*D*-ribofuranoside using 1-ethoxyvinyllithium and its application to the total syntheses of thymine polyoxin C (**3**) and uracil polyoxin C (**4**).[2] Three total syntheses[3] of **1** have been reported, these methods involving coupling of the congener of polyoxamic acid (**5**) with thymine polyoxin C (**3**).[3] A variety of chemical syntheses of 5-*O*-carbamoylpolyoxamic acid derivatives have been reported over years,[4] one of the most important intermediate for the general synthesis of them appeared to be (*R*)-α-hydroxy ester such as **6**. We now describe a convenient synthesis of the *N*-protected *L*-carbamoylpolyoxamic acid derivative (**7**) from 4-*O*-*tert*-butyldiphenylsilyl-2,3-isopropylidene-*L*-threose (**8**) derived from dimethyl *L*-tartrate by employing an addition of vinylmagnesium bromide and its application to the total syntheses of polyoxins J (**1**) and L (**2**).

In seeking a practical route to **7**, use of dimethyl *L*-tartrate with its inherent C-2 axis symmetry appeared to be the most promising. A useful synthesis of **5** also utilizing *L*-tartaric acid has been described by Mukaiyama *et* al.,[4f] the crucial step in which was stereoselective addition of titanium silylacetylide species to the 4-*O*-benzyl-2,3-isopropylidene-*L*-threose (**9**). Our own strategy for the introduction of the α-hydroxy ester functionality involved an addition of vinylmagnesium bromide to 4-*O*-*tert*-butyldiphenylsilyl-2,3-isopropylidene-*L*-threose (**8**) followed by oxidative cleavage of the terminal double bond as key steps. Reduction of an acetonide (**10**) with $NaBH_4$ gave a diol (**11**)(92%), which was treated with $^tBuPh_2SiCl$ (TBDPSCl) in the presence of NaH[5] to afford a monosilyl ether (**12**)(95%). Swern oxidation of **12** provided an aldehyde (**8**)(96%) which reacted with vinylmagnesium bromide followed by acetylation to give the 53:47 diastereomeric mixture of an α-acetoxy esters (**13**) in 73% overall yield. Ozonolysis of **13**



R = Me 1
R = H 2



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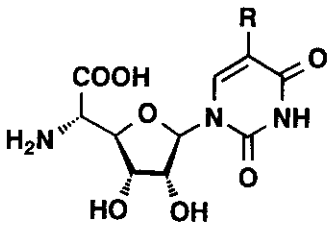
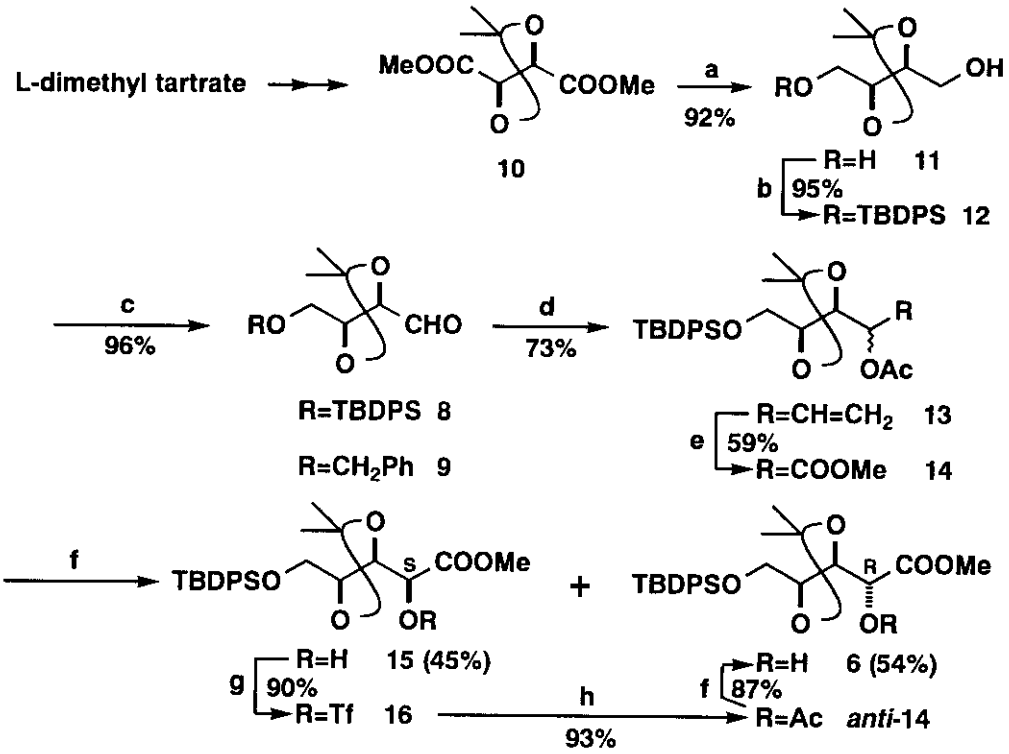


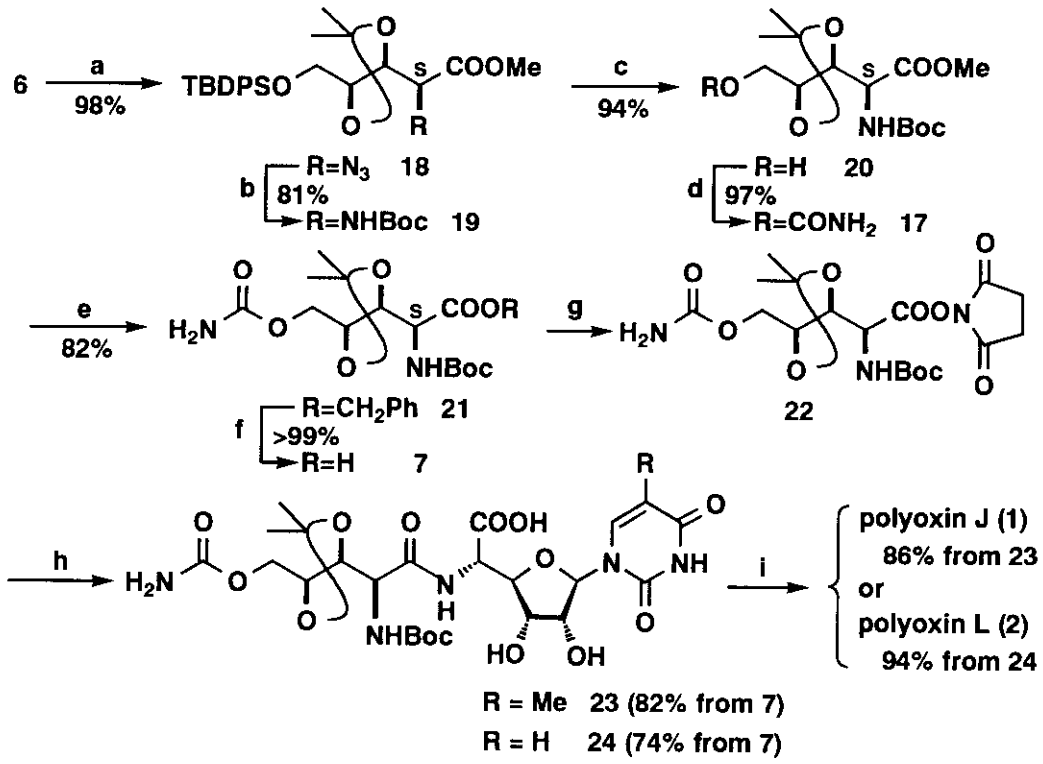
R = Me 3
R = H 4

Scheme 1



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) vinylmagnesium bromide
2) Ac_2O / pyridine e; 1) O_3, CH_2Cl_2, -78°C 2) Me_2S 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

Scheme 2



a; 1) Tf_2O / pyridine, CH_2Cl_2, 0°C 2) NaN_3, DMF

b; 1) H_2 / 20% $Pd(OH)_2$-C, MeOH 2) Boc_2O / Et_3N, dioxane c; HF / pyridine

d; 1) ClCOO-Ph-NO_2(*p*) / pyridine / Et_3N, THF,0°C 2) NH_3 / MeOH, 0°C

e; $PhCH_2OH$ / Ti(O-*i*-Pr)$_4$, benzene, reflux f; H_2 / 10% Pd-C, MeOH

g; dicyclohexylcarbodiimide (DCC) / *N*-hydroxysuccinimide, AcOEt, 0°C

h; for 23: 3 / (*i*-Pr)$_2$NEt, DMSO h; for 24: 4 / (*i*-Pr)$_2$NEt, DMSO

i; CF_3COOH, MeOH-H_2O (2:1)

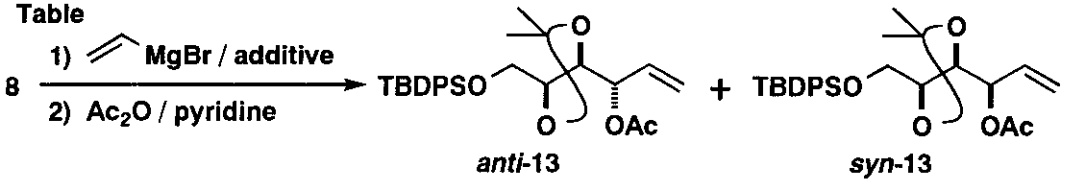
Scheme 3

followed by treatment with Jones reagent and CH_2N_2 afforded the diasteromeric mixture of α-acetoxy esters (**14**) in 59% overall yield. This mixture was hydrolysed to the diastereomeric mixture of α-hydroxy esters (**15** and **6**), which were separated to the less polar alcohol (**15**)[6] {45%, $[\alpha]_D$ +4.0° (c=0.80, CHCl3)} and the more polar one (**6**) {54%, $[\alpha]_D$ -21.3° (c=0.95, CHCl3)}. For the purpose of conversion of **15** into **6**, treatment of **15** with trifluoromethanesulfonic anhydride (Tf_2O) afforded the triflate (**16**) (90%) which was treated with cesium acetate (AcOCs) to provide the α-acetoxy ester *anti*-(**14**) {(93%, $[\alpha]_D$ -15.2° (c=1.34, CHCl3)}. Alcoholysis of *anti*-**14** gave the inverted α-hydroxy ester (**6**) {(87%, $[\alpha]_D$ -21.8° (c=1.25, CHCl3)} which is consistent with the above mentioned α-hydroxy ester (**6**). In order to determine the stereochemistry of **6**, the α-hydroxy ethyl ester (**6**) was converted to the reported *N*-protected 5-*O*-carbamoyl-(2*S*)-polyoxamic acid derivative (**17**).[4c] Triflation of **6** followed by treatment with NaN3 afforded the diastereomerically pure α-azide ester (**18**) {98% overall yield, $[\alpha]_D$ -16.2° (c=1.02, CHCl3)} which was subjected to hydrogenation and subsequent *N*-Boc derivation to provide the

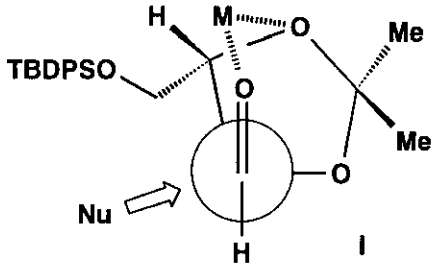
(2*S*)-*N*-Boc ester (**19**) {81% overall yield, $[\alpha]_D$ +1.4° (c=0.51, $CHCl_3$)}. Treatment of **19** with HF in pyridine gave the desilylated ester (**20**) {94%, $[\alpha]_D$ +15.3° (c=1.0, $CHCl_3$)} which was subjected to carbamoylation by the reported procedure[7] to furnish the ultimately desired *N*-protected carbamoylpolyoxamic acid ester (**17**) {97% overall yield, $[\alpha]_D$ -2.7° (c=1.05, CH_2Cl_2)}. Physical data ($[\alpha]_D$ and NMR) of the present **17** were identical with those {$[\alpha]_D$ -3.6° (c=1.5, CH_2Cl_2) and NMR} of the reported (2S,3S,4S)-**17**.[4c] Thus, the stereochemistry due to the C-2 position of α-hydroxy esters (**6**) and (**15**) was found to be R- and S-configurations, respectively. For the purpose of conversion of ester group in **17** to carboxylic acid under mild conditions, transesterification of **17** with benzyl alcohol into the benzyl ester (**21**) {$[\alpha]_D$ -16.4° (c=1.01, $CHCl_3$)} in the presence of Ti(O-*i*Pr)4 was achieved in 82% yield. Catalytic deprotection of benzyl group in **21** gave the desired *N*-protected (2*S*)-carbamoylpolyoxamic acid derivative (**7**) {$[\alpha]_D$ +1.03° (c=0.77, acetone)} in quantitative yield, which is consistent with the reported (**7**)[4c] {$[\alpha]_D$ +0.3° (c=1.5, acetone) and NMR}.

In the nucleophilic addition of vinylmagnesium bromide to the aldehyde (**8**) , the low diastereoselectivity (53:47) was observed. For the purpose of the improvement of the diastereoselectivity, effect of coexisting metal halides in addition to **8** was examined and the results are shown in Table. The *anti*-selectivie addition of nucleophile to **8** is explainable by the Felkin-Anh model[8] as depicted in I. The β-chelation of metal ion enhances the Felkin selectivity. The addition of nucleophile to **8** 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 vinylmagnesium bromide to **8** in the presence of $ZnBr_2$ followed by acetylation is highly *anti*-selective (Run 4) to afford *anti*-**13**. Without $ZnBr_2$, on the contrary, the addition was non-selective to give a 53:47 mixture of *syn*- and *anti*-**13** (Run 1). The 8:1 mixture of *anti*-**13** (Run 4) was converted to the (2*R*)-α-hydroxy ester (**6**) as a main product by the same way as stated above.

Table



Run	Additive	Temp. (°C)	Yield	*anti* / *syn*
1	none	0	73	47 / 53
2	Et_2AlCl	0	24	66 / 34
3	$TiCl_4$-Ti(O-*i*-Pr)$_4$ (1:1)	-40	27	56 / 44
4	$ZnBr_2$	-78	43	8 / 1



I

Successful coupling of thymine polyoxin C (**3**) with the desired *N*-protected (2*S*)-**7** was carried out by the *N*,*N*-dicyclohexylcarbodiimide-*N*-hydroxysuccinimide (DCC-HOSu) active ester method[3a] in DMSO and *N*,*N*-diisopropylethylamine as the base. Thus, the treatment of polyoxamic acid derivative (**7**) with DCC-HOSu gave the active ester (**22**) which was condensed with **3** to afford the dipeptide (**23**) (82% from **7**). Removal of the *N*-Boc and *O*-isopropylidene protecting groups upon acid hydrolysis provided polyoxin J (**1**) {mp 195-200°C (decomp), $[\alpha]_D$ +35.7° (c=0.68, H_2O)} in 86% yield. The physical properties of the present **1** were identical with those of synthetic polyoxin J (**1**) {$[\alpha]_D$ +33.0° (c=0.75, H_2O),[1a] mp 200-210°C (decomp),[1b] $[\alpha]_D$ +35.0° (c=0.8, H_2O)[1b] and NMR,[1b] mp 200°C (decomp),[1c] $[\alpha]_D$ +30.3° (c=0.10, H_2O)[1c]}. Likewise, condensation of the active ester (**22**) with uracil polyoxin C (**4**) afforded the dipeptide (**24**) (74% from **7**) which was converted to polyoxin L (**2**) {mp 180-183° (decomp), $[\alpha]_D$ +35.0° (c=1.21, H_2O)} in 94% yield. The physical properties of the present **2** were in good agreement with the literature of natural polyoxin L (**2**)[9] {$[\alpha]_D$ +34.4° (c=1, H_2O)}. The present latter synthesis means the first total synthesis of polyoxin L (**2**). The syntheses described herein demonstrate an applicable synthesis of other components of the polyoxin[1a] and nikkomycin[10] families.

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