

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

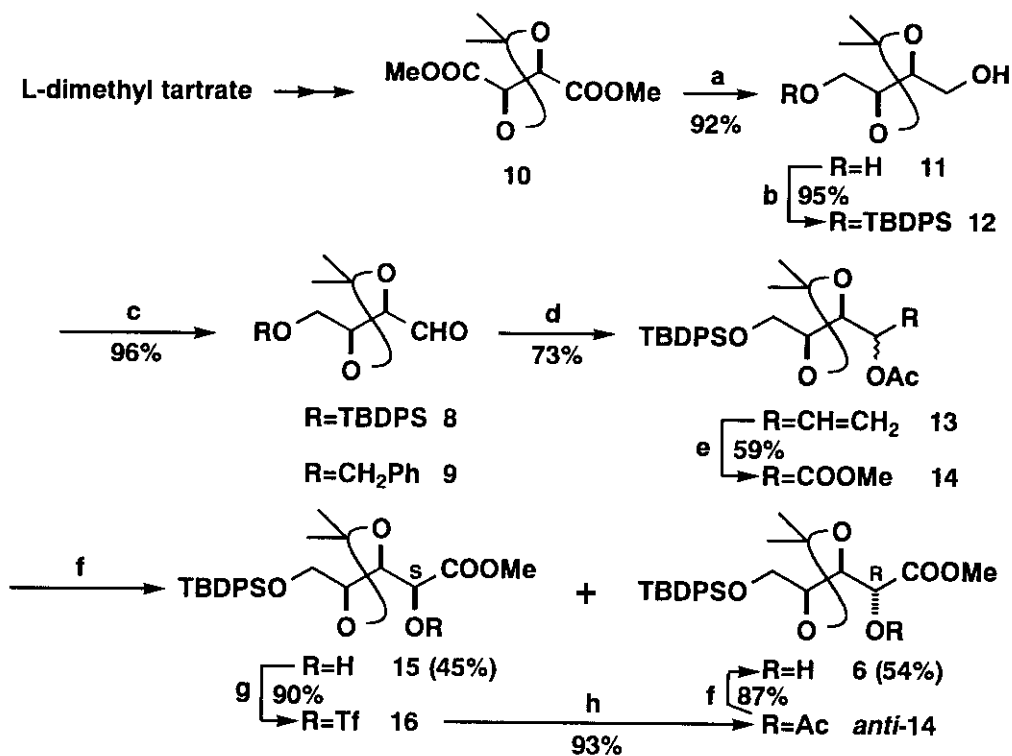
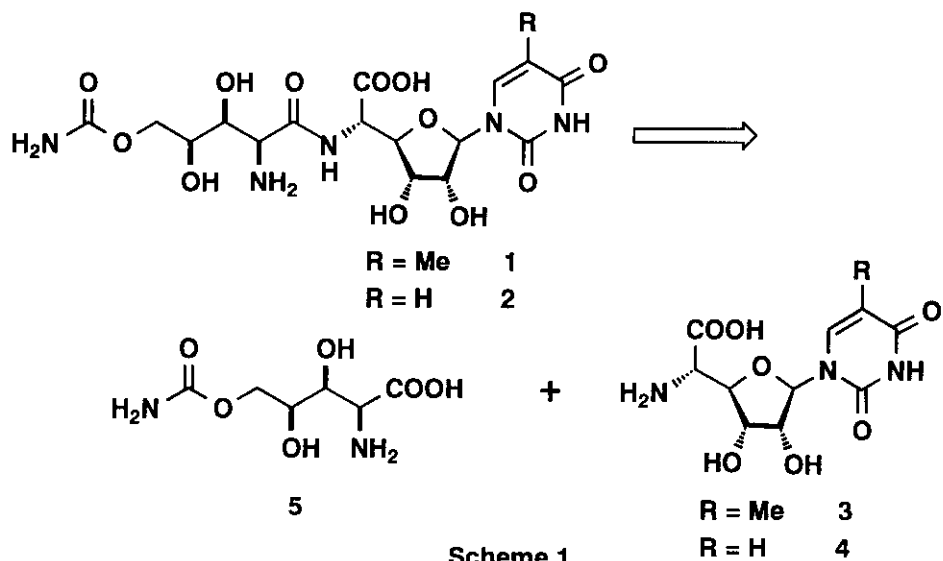
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Abstract - A convenient synthesis of the *N*-protected *L*-carbamoyl-polyoxamic acid derivative (**7**) from 4-*O*-*tert*-butyldiphenylsilyl-2,3-isopropylidene-*L*-threose (**8**) using vinylmagnesium bromide and its application to the total syntheses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

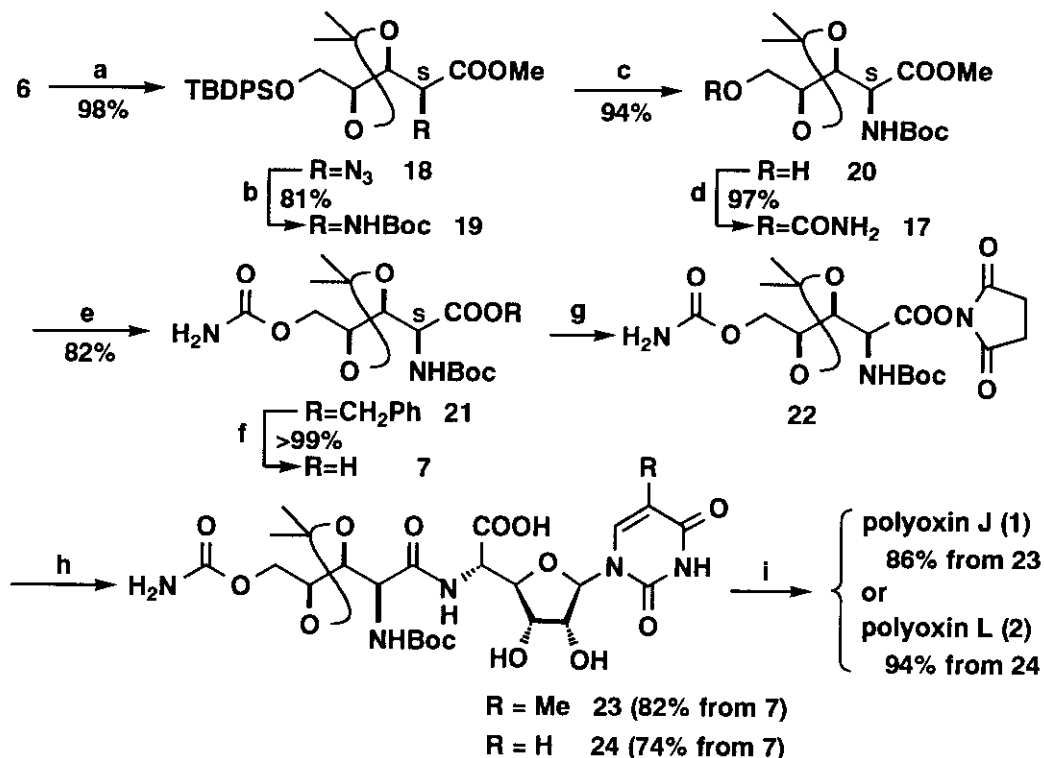
Polyoxins J (**1**) and L (**2**) are an important class of peptidyl nucleoside antibiotics isolated from the culture broths of *Streptomyces cacaoi* var. *asoensis*, which are attracting increasing interest as antifungal compounds because of their ability to inhibit chitin synthetase of a variety of phytopathogenic fungi.¹ In the preceding paper, we reported a short path synthesis of α -hydroxy ester from methyl 2,3-isopropylidene-dialdo-*D*-ribofuranoside using 1-ethoxyvinyl lithium and its application to the total syntheses of thymine polyoxin C (**3**) and uracil polyoxin C (**4**).² Three total syntheses³ 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 NaBH₄ gave a diol (**11**)(92%), which was treated with ^tBuPh₂SiCl (TBDPSCl) in the presence of NaH⁵ 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**



- a; $\text{NaBH}_4 / \text{MeOH}$, 0°C b; $\text{TBDPSCI} / \text{NaH}$, THF , 0°C
 c; 1) $\text{DMSO} / (\text{COCl})_2$, CH_2Cl_2 , -78°C 2) Et_3N d; 1) vinylmagnesium bromide
 2) $\text{Ac}_2\text{O} / \text{pyridine}$ e; 1) O_3 , CH_2Cl_2 , -78°C 2) Me_2S 3) $\text{CrO}_3 / \text{H}_2\text{SO}_4$ 4) CH_2N_2
 f; K_2CO_3 , MeOH g; $\text{Tf}_2\text{O} / \text{pyridine}$, CH_2Cl_2 h; AcOCs , DMF

Scheme 2



- a; 1) Tf₂O / pyridine, CH₂Cl₂, 0°C 2) NaN₃, DMF
 b; 1) H₂ / 20% Pd(OH)₂-C, MeOH 2) Boc₂O / Et₃N, dioxane c; HF / pyridine
 d; 1) ClCOO-Ph-NO₂(*p*) / pyridine / Et₃N, THF, 0°C 2) NH₃ / MeOH, 0°C
 e; PhCH₂OH / Ti(O-*i*-Pr)₄, benzene, reflux f; H₂ / 10% Pd-C, MeOH
 g; dicyclohexylcarbodiimide (DCC) / *N*-hydroxysuccinimide, AcOEt, 0°C
 h; for 23: 3 / (*i*-Pr)₂NEt, DMSO h; for 24: 4 / (*i*-Pr)₂NEt, DMSO
 i; CF₃COOH, MeOH-H₂O (2:1)

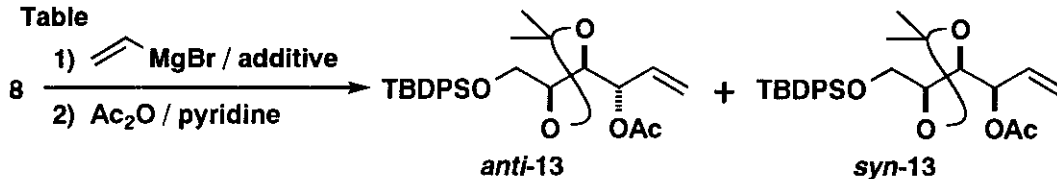
Scheme 3

followed by treatment with Jones reagent and CH₂N₂ afforded the diastereomeric 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%, [α]_D +4.0° (c=0.80, CHCl₃)} and the more polar one (**6**) {54%, [α]_D -21.3° (c=0.95, CHCl₃)}. For the purpose of conversion of **15** into **6**, treatment of **15** with trifluoromethanesulfonic anhydride (Tf₂O) afforded the triflate (**16**) (90%) which was treated with cesium acetate (AcOCs) to provide the α-acetoxy ester *anti*-**14** {(93%, [α]_D -15.2° (c=1.34, CHCl₃)}. Alcoholysis of *anti*-**14** gave the inverted α-hydroxy ester (**6**) {(87%, [α]_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, [α]_D -16.2° (c=1.02, CHCl₃)} which was subjected to hydrogenation and subsequent *N*-Boc derivation to provide the

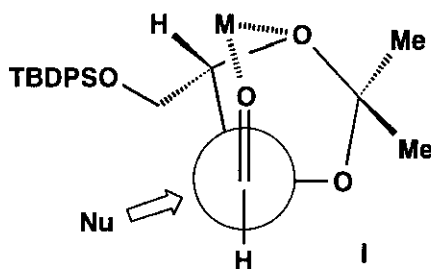
(2*S*)-*N*-Boc ester (**19**) {81% overall yield, $[\alpha]_D +1.4^\circ$ ($c=0.51$, CHCl_3)}. Treatment of **19** with HF in pyridine gave the desilylated ester (**20**) {94%, $[\alpha]_D +15.3^\circ$ ($c=1.0$, CHCl_3)} which was subjected to carbamoylation by the reported procedure⁷ to furnish the ultimately desired *N*-protected carbamoylpolyoxamic acid ester (**17**) {97% overall yield, $[\alpha]_D -2.7^\circ$ ($c=1.05$, CH_2Cl_2)}. Physical data ($[\alpha]_D$ and NMR) of the present **17** were identical with those $\{[\alpha]_D -3.6^\circ$ ($c=1.5$, CH_2Cl_2) and NMR} of the reported (2*S*,3*S*,4*S*)-**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**) $\{[\alpha]_D -16.4^\circ$ ($c=1.01$, CHCl_3)} in the presence of $\text{Ti}(\text{O}-i\text{Pr})_4$ was achieved in 82% yield. Catalytic deprotection of benzyl group in **21** gave the desired *N*-protected (2*S*)-carbamoylpolyoxamic acid derivative (**7**) $\{[\alpha]_D +1.03^\circ$ ($c=0.77$, acetone)} in quantitative yield, which is consistent with the reported (**7**)^{4c} $\{[\alpha]_D +0.3^\circ$ ($c=1.5$, 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*-selective addition of nucleophile to **8** is explainable by the Felkin-Anh model⁸ 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 TBDPSOCH₂-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. ($^\circ\text{C}$)	Yield	<i>anti</i> / <i>syn</i>
1	none	0	73	47 / 53
2	Et_2AlCl	0	24	66 / 34
3	TiCl_4 - $\text{Ti}(\text{O}-i\text{Pr})_4$ (1:1)	-40	27	56 / 44
4	ZnBr_2	-78	43	8 / 1



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), $[\alpha]_D^{+35.7^\circ}$ ($c=0.68$, H₂O)} in 86% yield. The physical properties of the present **1** were identical with those of synthetic polyoxin J (**1**) $\{[\alpha]_D^{+33.0^\circ}$ ($c=0.75$, H₂O),^{1a} mp 200-210°C (decomp),^{1b} $[\alpha]_D^{+35.0^\circ}$ ($c=0.8$, H₂O)^{1b} and NMR,^{1b} mp 200°C (decomp),^{1c} $[\alpha]_D^{+30.3^\circ}$ ($c=0.10$, H₂O)^{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), $[\alpha]_D^{+35.0^\circ}$ ($c=1.21$, H₂O)} in 94% yield. The physical properties of the present **2** were in good agreement with the literature of natural polyoxin L (**2**)⁹ $\{[\alpha]_D^{+34.4^\circ}$ ($c=1$, H₂O)}. 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 nikkomycin¹⁰ families.

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