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A FORMAL TOTAL SYNTHESIS OF POLYOXIN J USING 4-O-BENZYL-2,3-O-ISOPROPYLIDENE-L-THREOSE AS A COMMON CHIRAL BUILDING BLOCK

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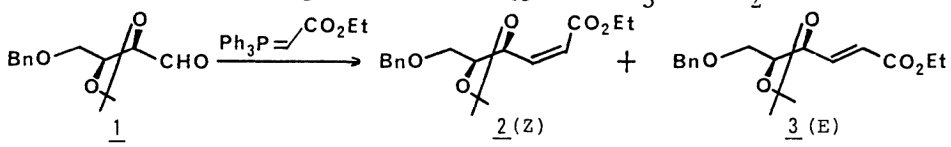
A convergent formal total synthesis of Polyoxin J was achieved. Two fragments, deoxypolyoxin C and 5-O-carbamoylpolyoxamic acid, were synthesized in a highly stereoselective manner from the common chiral building block, 4-O-benzyl-2,3-O-isopropylidene-L-threose, finishing the formal synthesis of Polyoxin J.

The Polyoxin complex is an antifungal antibiotics produced by *Streptomyces cacaoi var. asoensis*,[1] whose pronounced fungicidic activities and unique structure have attracted considerable attention of synthetic chemists. The gross structure of these compounds is devided into two fragments, the nucleoside moiety and the side-chain moiety. In our previous papers,[2] we have demonstrated the high versatility of a new four-carbon chiral building block, 4-O-benzyl-2,3-O-isopropylidene-L-threose 1, in carbohydrate synthesis. In combination with the newly developed stereoselective processes, this aldehyde 1 has a wide potentiality, especially in the synthesis of rare sugars.

In this communication, we wish to describe a formal total synthesis of Polyoxin J where both of the fragments are stereoselectively synthesized from the same starting material 1. First, the synthesis of the nucleoside moiety, deoxypolyoxin C, is described. The Wittig reaction of 1 with $Ph_3P{=}CHCO_2Et$ in MeOH gave mainly the (Z)-olefin, while the usual behavior of the stabilized ylide was observed in dipolar protic solvents (Table 1).[3]

Table 1. Wittig reaction of 1 and $Ph_3P{=}CHCO_2Et$



1 2(Z) 3(E)

Entry	Solvent	Temperature	Yield/%	Z : E[4]
1	DMF	r.t.	77	27 : 73
2	Benzene	reflux	83	30 : 70
3	CH_2Cl_2	"	88	65 : 35
4	MeOH	"	100	80 : 20
5	"	r.t.	88	89 : 11

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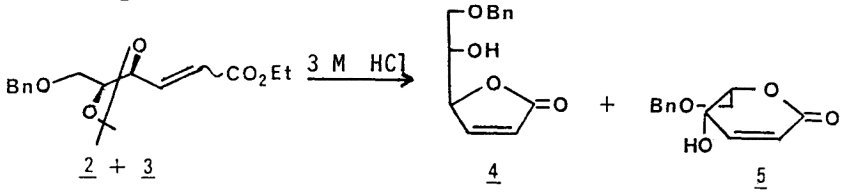
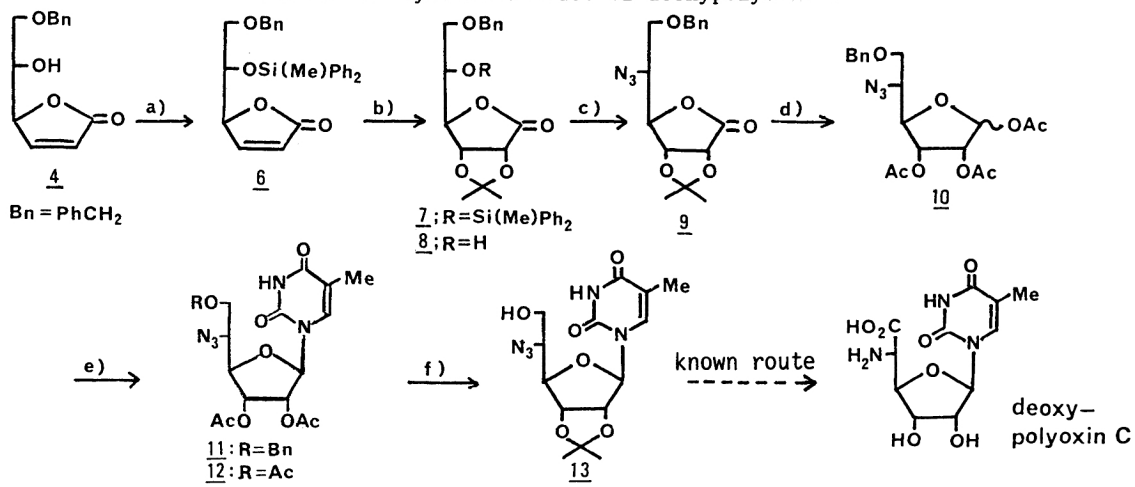
Acid treatment of 2 gave the unsaturated lactones 4 and 5 in the ratio of 7 : 1.[4] After SiO_2 column chromatography, 4[5] was obtained in 78% yield from 1.



Silylation of 4 with $Ph_2(Me)SiCl$ gave butenolide 6. As we reported previously,[6] *vicinal* dihydroxylation of 6 with $KMnO_4$-crown ether proceeded in a highly stereoselective manner ($\alpha : \beta = >30 : 1$).[7] The diol was converted in a usual manner to the alcohol 8,[8] which was further transformed to the azide 9 with a complete inversion of configuration by the method reported by our laboratory.[9] Partial reduction of the lactone 9 furnished the corresponding lactol, which was further hydrolyzed and acetylated to afford 10 as an anomeric mixture. Nucleoside formation was effected by the treatment of 10 with bissilylated thymine[10] in the presence of Me_3SiOTf[11] to give 11. Removal of the benzyl group without reduction of the azide group, and subsequent acetylation furnished 12. Treatment of 12 with excess NH_3 in MeOH gave 1-(5-azido-5-deoxy-β-D-allofuranosyl)thymine, whose structure was confirmed as the acetonide derivative 13,[12] mp 157-158 °C, $[\alpha]_D^{25}$ -13.4° (c 1.0, Pyr.) [lit,[13] mp 158-159 °C, $[\alpha]_D^{25}$ -13.1° (c 0.24, Pyr.)]. Total yield of 13 from 1 was 29%. Since elaboration of 13 to deoxypolyoxin C, the nucleoside moiety of Polyoxin J, has already been established,[13] the synthetic route mentioned above presents a short step access to the molecule.

Scheme 1. Synthetic route of deoxypolyoxin C[14]

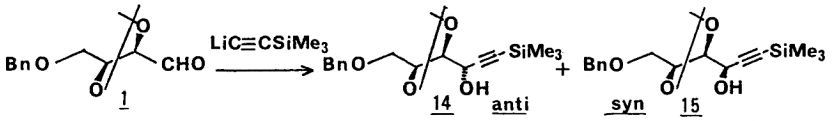


a) $Ph_2(Me)SiCl$, 2,6-lutidine/CH_2Cl_2, r.t.; 91% b)i) $KMnO_4$, dicyclohexano-18-crown-6/CH_2Cl_2, -42 °C ii) $Me_2C(OMe)_2$, cat. p-TsOH/CH_2Cl_2, r.t. iii) KF, cat. $n\text{-}Bu_4N^+HSO_4^-$/CH_2Cl_2-H_2O; 75% d)i) 1-methyl-2-fluoropyridinium tosylate, Et_3N, r.t. ii) LiN_3/HMPA, 80 °C; 71% d)i) DIBAH/PhMe, -78 °C ii) 70% AcOH/80 °C iii) Ac_2O/Pyr., 0 °C; 97% e)i) 2,4-bis(trimethylsiloxy)-5-methylpyrimidine, TMSOTf/$CHCl_3$, reflux; 98% ii) BBr_3/CH_2Cl_2, -42 °C iii) Ac_2O/Pyr., 0 °C; 83% f)i) excess NH_3/MeOH, r.t. ii) $Me_2C(OMe)_2$, cat. p-TsOH/Me_2CO, r.t.; 97%.

Next, the synthesis of 5-O-carbamoylpolyoxamic acid, the side-chain moiety of Polyoxin J, was investigated. The key feature of the synthesis is the stereo-

selective introduction of the α-amino acid functionality, and we chose the following two-step operations i) stereoselective introduction of carboxyl anion equivalent ($^{-}CO_2H$) to 1, and ii) introduction of amino functionality. As for the stage i), the stereoselectivity of the addition of acetylide to the aldehyde 1 was investigated.

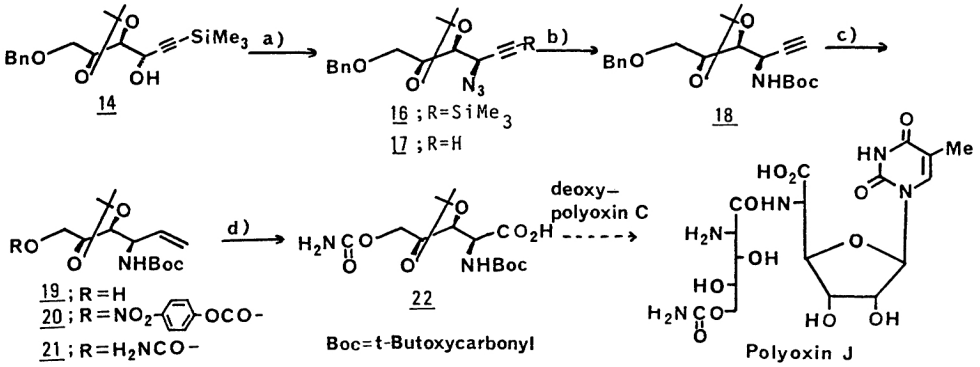
Table 2. Addition of TMS-acetylene to 1



Entry	Additive	Yield/%	anti : syn[4]
1	—	97	68 : 32
2	Cp_2TiCl_2	47	83 : 17
3	$Cl_2Ti(O\text{-}i\text{-}Pr)_2$	22	76 : 24
4	$ClTi(O\text{-}i\text{-}Pr)_3$	27	98 : 2
5	$TiCl_4$-$Ti(O\text{-}i\text{-}Pr)_4$(1:1)	83	98 : 2

As shown in Table 2, the titanium acetylide derivative, prepared from $Me_3SiC \equiv CLi$ and 1:1 $TiCl_4$-$Ti(O\text{-}i\text{-}Pr)_4$, gave the best result and essentially pure *anti*-14[15] was obtained. This stereochemical feature of the addition could be explained in terms of the Felkin's model as stated in the previous papers.[2] The acetylenic alcohol 13, was transformed to polyoxamic acid by the following sequence: The alcohol 14 was converted to the azide 16 *via* the tosylate. The azide 16 was de-silylated under phase-transfer conditions to give 17 which was reduced and N-protected to afford 18. The benzyl group of 18 was removed by the Birch reduction conditions, while a concomitant reduction of alkynyl group to alkenyl group took place to give 19.[16] After carbamoylation to 21 *via* 20, the terminal olefin was oxidized by $KMnO_4$ to yield the corresponding carboxyl group,[17] whose structure 21 was identified as Polyoxamic acid after hydrolysis (3 M HCl/Et_2O); mp 167-170 °C (decomp.) [lit,[1] mp 170-171 °C (decomp.)].

Scheme 2. Synthetic route of polyoxamic acid[14]



a)i) TsCl/Pyr., 0 °C; 84% ii) LiN_3/HMPA, 0 °C; 85% iii) NH_4F, cat. $n\text{-}Bu_4N^+ HSO_4^-$, r.t.; quant b)i) 2.6 eq. $LiAlH_4/Et_2O$, 0 °C ii) t-butyl S-4.6-dimethylpyrimid-2-ylthiocarbonate (Boc-S reagent), Et_3N/dioxane-H_2O, r.t.; 76% c)i) Na/liq. NH_3, -33 °C; quant. ii) p-nitrophenyl chloroformate/Pyr., 0 °C; 86% iii) NH_3/MeOH, r.t.; 80% d) $KMnO_4$/aq. Me_2CO, 0 °C; 88%.

Since the assembly of the two fragments to construct Polyoxin J has been described by Kuzuhara *et al.*,[18] the synthetic route utilizing the aldehyde 1 is a highly efficient approach not only to Polyoxin J but also to the related molecules of biological interests.

References

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2) T. Mukaiyama, K. Suzuki, and T. Yamada, Chem. Lett., 1982, 929; T. Mukaiyama, Y. Yuki, and K. Suzuki, *ibid.*, 1982, 1169; T. Mukaiyama, T. Yamada, and K. Suzuki, *ibid.*, 1983, 5.
3) J. M. J. Tronchet, B. Gentile, Helv. Chim. Acta, 62, 2091 (1979); N. Minami, S. S. Ko, and Y. Kishi, J. Am. Chem. Soc., 104, 1109 (1982).
4) The ratio was determined by HPLC (Merck LiChrosorb SI 60, hexane - AcOEt).
5) Mp 79-81 °C (AcOEt - hexane); $[\alpha]_D^{21}$ -73.2° (c 1.0, $CHCl_3$); ^1H NMR δ ($CDCl_3$) 2.8 (1H, br. s), 3.4-3.8 (2H, m), 3.9 (1H, unresoluble ddd; J = 4.8 Hz, 5 Hz, 6.5 Hz), 4.5 (2H, s), 5.1 (1H, ddd; J = 5 Hz, 1.9 Hz, 1.6 Hz), 6.1 (1H, dd; J = 5.7 Hz, 1.9 Hz), 7.3 (5H, s), 7.4 (1H, dd; J = 5.7 Hz, 1.6 Hz), IR (KBr) 3590, 3050, 2880, 1760, 1500, 1465 cm^{-1}.
6) T. Mukaiyama, F. Tabusa, and K. Suzuki, Chem. Lett., 1983, 173.
7) The ratio was determined by HPLC (Merck LiChrosorb SI 60, hexane - AcOEt) after acetylation (Ac_2O/Pyr.).
8) Mp 80-83 °C (AcOEt - Et_2O); $[\alpha]_D^{27}$ -10.3° (c 1.0, $CHCl_3$); ^1H NMR δ ($CDCl_3$) 1.3 (3H, s), 1.4 (3H, s), 2.7-3.1 (1H, br. s), 3.45-3.65 (2H, m), 3.7-4.1 (1H, m), 4.5 (3H, s), 4.7 (2H, s), 7.3 (5H, s), IR (KBr) 3420, 2980, 2840, 2900, 2880, 1780, 1635 cm^{-1}.
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12) ^1H NMR δ ($CDCl_3$-CD_3OD) 1.3 (3H, s), 1.5 (3H, s), 1.8 (3H, s), 3.6-4.1 (4H, m), 4.7-5.1 (2H, m), 5.7 (1H, d; J = 1.8 Hz), 7.3 (1H, s); IR (KBr) 3540, 3310, 2140, 2100, 1720, 1710, 1690, 1680, 1670 cm^{-1}.
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14) All new compounds exhibited satisfactory spectral data.
15) $[\alpha]_D^{20}$ -2.7° (c 0.47, CCl_4); ^1H NMR δ (CCl_4) 0.2 (9H, s), 1.4 (6H, s), 2.5-2.7 (1H, br. s), 3.5-3.8 (2H, m), 3.8-4.5 (3H, m), 4.5 (2H, s), 7.3 (5H, s); IR (neat) 3430, 2900, 2170, 1500, 1250 cm^{-1}.
16) $[\alpha]_D^{24}$ -1.98° (c 1.00, acetone); ^1H NMR δ (CCl_4) 1.35 (6H, s), 1.4 (9H, s), 3.15 (1H, br. s), 3.4-4.4 (5H, m), 4.9-5.4 (3H, m), 5.5-6.1 (1H, m); IR (KBr) 3450, 3000, 2950, 1700, 1500 cm^{-1}.
17) Methyl ester of 22:
$[\alpha]_D^{25}$ -5.88° (c 4.2, CH_2Cl_2); ^1H NMR δ ($CDCl_3$) 1.4 (15H, s), 3.65 (3H, s), 3.7-4.2 (5H, m), 4.9-5.3 (3H, m).
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