

**A SHORT PATH SYNTHESIS OF  $\alpha$ -HYDROXY  
ESTER FROM ALDEHYDE USING  
(1-ETHOXYVINYL)LITHIUM AND ITS  
APPLICATION TO THE SYNTHESSES OF THYMINE  
POLYOXIN C AND URACIL POLYOXIN C**

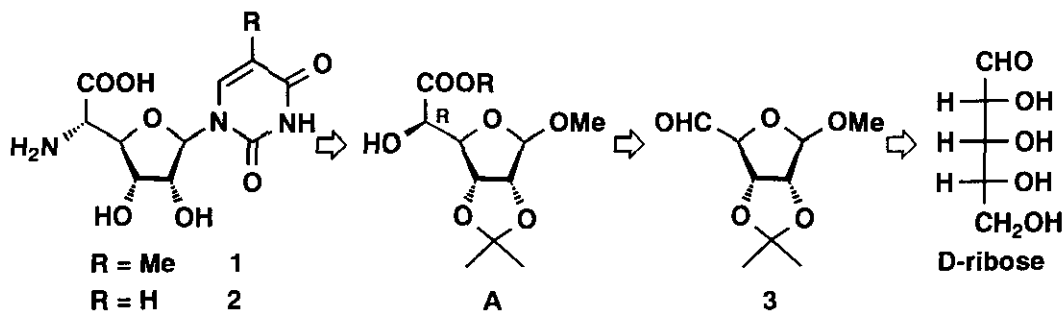
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**Abstract** -A short path synthesis of the  $\alpha$ -hydroxy esters (4 and 5) from the aldehyde (3) using (1-ethoxyvinyl)lithium and its application to the total syntheses of the pyrimidine nucleoside, thymine polyoxin C (1) and uracil polyoxin C (2), are described.

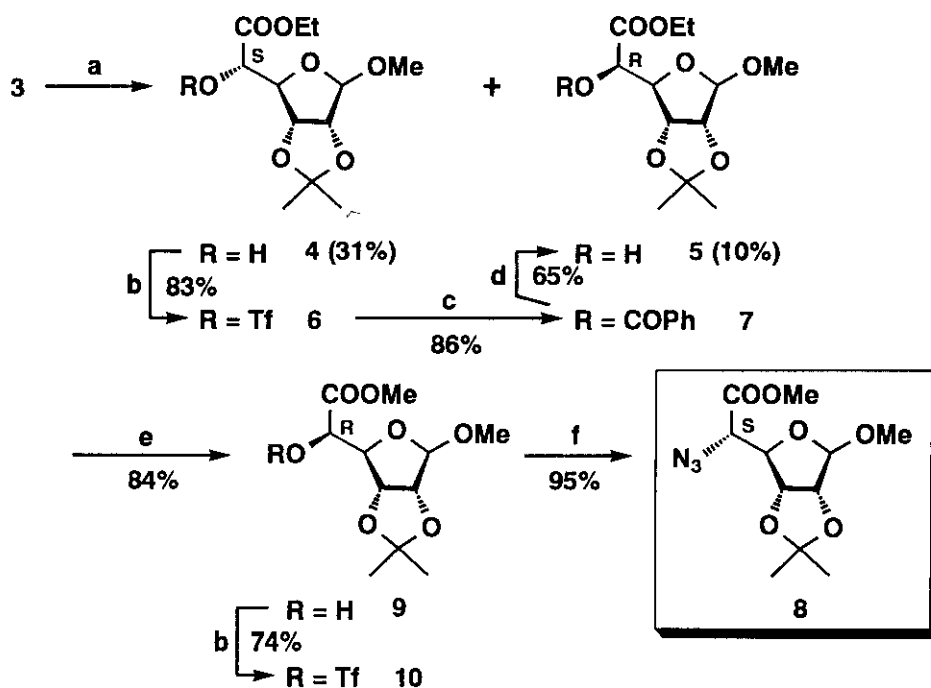
Polyoxins are an important class of peptidyl nucleoside antibiotics isolated from the culture broths of *Streptomyces cacaoi* var. *asoensis*, which are potent competitive inhibitors of chitin synthetase of a variety of phytopathogenic fungi.<sup>1</sup> According to recent studies, polyoxins are also reported to inhibit chitin synthetase of *Candida albicans*, a medically important human fungal pathogen.<sup>2</sup> All members of the polyoxin family bear the 1-(5-amino-5-deoxy- $\beta$ -D-allofuranuronosyl)pyrimidines such as thymine polyoxin C (1) and uracil polyoxin C (2) as a basic component.

A variety of chemical syntheses of amino acid nucleosides (1 and 2) have been reported over the years,<sup>3</sup> one of the most important intermediate for the general synthesis of them appeared to be (*R*)- $\alpha$ -hydroxy ester (A). We now report the short path synthesis of A from the readily available methyl 2,3-*O*-isopropylidene-dialdo-D-ribofuranoside (3)<sup>3i</sup> derived from D-ribose by employing an addition of (1-ethoxyvinyl)lithium and its application to the total syntheses of thymine polyoxin C (1) and uracil polyoxin C (2).



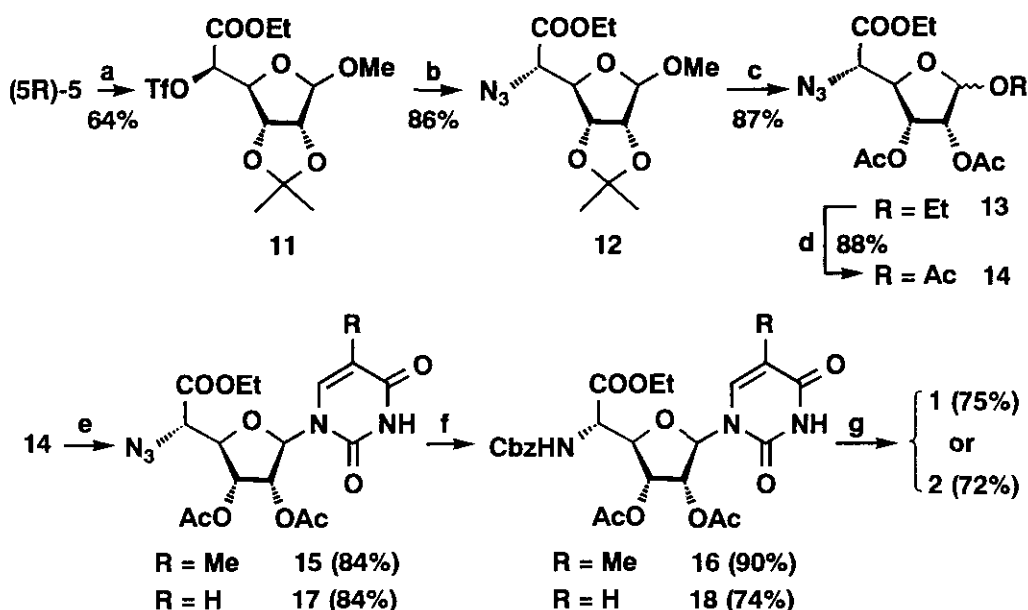
Scheme 1

The reaction of the aldehyde (**3**) with (1-ethoxyvinyl)lithium<sup>4</sup> followed by ozonolysis and subsequent treatment with Me<sub>2</sub>S gave the diastereomeric mixture of  $\alpha$ -hydroxy esters which were separated into the major  $\alpha$ -hydroxy ester (**4**)<sup>5</sup> {31% from **3**, [ $\alpha$ ]<sub>D</sub> -52.3° (c=1.00, CHCl<sub>3</sub>)} and the minor one (**5**) {10% from **3**, [ $\alpha$ ]<sub>D</sub> -44.2° (c=1.46, CHCl<sub>3</sub>)}. The low diastereoselectivity (2:1) against **3** using vinyl magnesium bromide is also reported.<sup>6</sup> An improvement of the diastereoselectivity of **4** and **5** is being undertaken. For the purpose of conversion of **4** into **5**, treatment of **4** with trifluoromethanesulfonic anhydride (Tf<sub>2</sub>O) afforded the triflate (**6**) (83%) which was treated with PhCOOH in the presence of CsF<sup>7</sup> to provide the  $\alpha$ -benzoyloxy ester (**7**) (86%). Alcoholysis of **7** gave the inverted  $\alpha$ -hydroxy ester (**5**) (65%) which is consistent with the minor one (**5**). In order to determine the stereochemistry of **5**, the  $\alpha$ -hydroxy ethyl ester (**5**) was converted to the reported (*S*S)-azide methyl ester (**8**).<sup>3i</sup> Transesterification of **5** with MeOH into the methyl ester (**9**) in the presence of Ti(O-*i*Pr)<sub>4</sub> was achieved in 84% yield. Triflation of **9** followed by treatment of the triflate (**10**) (74%) with NaN<sub>3</sub> afforded the diastereomerically pure  $\alpha$ -azide ester (**8**) {95%, [ $\alpha$ ]<sub>D</sub> -53.3° (c=1.41, CHCl<sub>3</sub>)} whose spectral data were identical with those { [ $\alpha$ ]<sub>D</sub> -55.3° (c=0.89, CHCl<sub>3</sub>), <sup>1</sup>H-NMR } of the reported (*S*S)-**8**.<sup>3i</sup> Thus, the stereochemistry due to the C-5 position of  $\alpha$ -hydroxy ethyl esters (**4**) and (**5**) was found to be *S*- and *R*-configurations, respectively. For the total synthesis of the target molecules (**1**) and (**2**), conversion of ethyl ester group into the methyl ester group is not always essential process. The (*R*)- $\alpha$ -hydroxy ethyl ester (**5**) was converted to the (*S*)- $\alpha$ -azide ethyl ester (**12**) {55% overall yield from **5**, [ $\alpha$ ]<sub>D</sub> -49.1° (c=1.17, CHCl<sub>3</sub>)} via the triflate (**11**) (64%) by the



- a;** 1) Ethyl vinyl ether / *t*-BuLi, THF, -78 °C    2) O<sub>3</sub> / CH<sub>2</sub>Cl<sub>2</sub>    3) Me<sub>2</sub>S / CH<sub>2</sub>Cl<sub>2</sub>  
**b;** Tf<sub>2</sub>O, pyridine / CH<sub>2</sub>Cl<sub>2</sub>    **c;** PhCOOH, CsF / DMF    **d;** EtONa / EtOH  
**e;** MeOH, Ti(O-*i*Pr)<sub>4</sub> / PhH, reflux    **f;** NaN<sub>3</sub> / DMF

Scheme 2



- a;** Tf<sub>2</sub>O, pyridine / CH<sub>2</sub>Cl<sub>2</sub>      **b;** NaN<sub>3</sub> / DMF      **c;** 1) Dowex 50 WH<sup>+</sup> / EtOH, reflux  
 2) Ac<sub>2</sub>O / pyridine      **d;** Ac<sub>2</sub>O, AcOH, *conc.* H<sub>2</sub>SO<sub>4</sub> / CH<sub>2</sub>Cl<sub>2</sub>  
**e;** for 15: 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine, TMSOTf / CH<sub>2</sub>Cl<sub>2</sub>, reflux  
**e;** for 17: 2,4-bis(trimethylsilyloxy)pyrimidine, TMSOTf / CH<sub>2</sub>Cl<sub>2</sub>, reflux  
**f;** for 16: 1) H<sub>2</sub>, 20% Pd(OH)<sub>2</sub>-C / MeOH 2) CbzCl, 7% NaHCO<sub>3</sub> aq. / dioxane  
**f;** for 18: 1) H<sub>2</sub>, 5% Pd-BaSO<sub>4</sub> / MeOH 2) CbzCl, 7% NaHCO<sub>3</sub> aq. / dioxane  
**g;** 1) LiOH·H<sub>2</sub>O / THF 2) 0.1 N HCl 3) H<sub>2</sub>, 10% Pd-C / MeOH

### Scheme 3

same way as in the case of conversion of 9 to 8. Deisopropylidenation (Dowex 50W H<sup>+</sup>, EtOH, reflux) afforded the diol, which was acetylated directly (Ac<sub>2</sub>O, pyridine) to yield the diacetate (13) (87%). Anomeric acetolysis smoothly gave the triacetate (14) (88%) in which no C-5 epimerization could be detected. Reaction of the triacetate (14) with 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine<sup>8</sup> under the conditions reported by Vorbruggen<sup>9</sup> {trimethylsilyl trifluoromethanesulfonate (TMSOTf), ClCH<sub>2</sub>CH<sub>2</sub>Cl, reflux} gave exclusively the β-nucleoside (15)<sup>10</sup> (84%). Hydrogenation of the azide (15) in the presence of 20% Pd(OH)<sub>2</sub>-C afforded the α-amino acid ester which was treated with carbobenzyloxy chloride (CbzCl) in the presence of 7% aqueous NaHCO<sub>3</sub> to provide the (5S)-16 (90%). Alkaline hydrolysis of 16 followed by hydrogenation gave thymine polyoxin C (1) (75%). The synthetic material (1) {[α]<sub>D</sub> +8.5° (c=0.53, H<sub>2</sub>O), mp 190-192 °C, <sup>1</sup>H-NMR} was identical with authentic material {[α]<sub>D</sub> +8.2° (c=0.7, H<sub>2</sub>O),<sup>3a</sup> [α]<sub>D</sub> +8.0° (c=0.37, H<sub>2</sub>O),<sup>3c</sup> mp 190-194 °C,<sup>3c</sup> mp 180-190 °C,<sup>3f</sup> <sup>1</sup>H-NMR<sup>3c,d</sup>}. Likewise, reaction of the key triacetate (14) with 2,4-bis(trimethylsilyloxy)pyrimidine<sup>8</sup> under similar conditions afforded exclusively the β-nucleoside (17)<sup>10</sup> (84%). Hydrogenation of the azide (17) in the presence of 5% Pd-BaSO<sub>4</sub> and followed by protection of amino group with Cbz group, alkaline hydrolysis and deprotection of Cbz group afforded uracil polyoxin C (2) {[α]<sub>D</sub> +15.9° (c=0.58, H<sub>2</sub>O), mp 247-250 °C, <sup>1</sup>H-NMR} which was identical with authentic material (2) {[α]<sub>D</sub> +15.8° (c=0.205, H<sub>2</sub>O),<sup>1a</sup> mp 240-247

$^{\circ}\text{C}$ ,  $1\alpha$   $^1\text{H-NMR}^3\text{i}$ ). The syntheses described herein demonstrate the utility of (1-ethoxyvinyl)lithium for the short path synthesis of the  $\alpha$ -hydroxy esters (**4** and **5**) from the aldehyde (**3**), which contribute to the total syntheses of thymine polyoxin C (**1**) and uracil polyoxin C (**2**).

## ACKNOWLEDGEMENTS

The authors are grateful to Dr. Akio Kinumaki of Tanabe Seiyaku Co. LTD., Japan for measurement of mass spectra (FAB-MS) of synthetic thymine polyoxin C (**1**) and uracil polyoxin C (**2**). This work was supported by a grant for the "Biodesign Research Program" from Riken (The Institute of Physical and Chemical Research) to H.A.

## REFERENCES AND NOTES

1. a) K. Isono, K. Asahi, and S. Suzuki, *J. Am. Chem. Soc.*, 1969, **91**, 7490. b) K. Isono and S. Suzuki, *Heterocycles*, 1979, **13**, 333.
2. J. M. Becker, N. L. Covert, P. S. Shenbagamurthi, A. Steinfeld, and F. Naider, *Antimicrob. Agents Chemother.*, 1983, **23**, 926.
3. Syntheses of thymine polyoxin; a) H. Ohri, H. Kuzuhara, and S. Emoto, *Tetrahedron Lett.*, **1971**, 4267. b) P. Garner and J. M. Park, *Tetrahedron Lett.*, 1989, **30**, 5065. c) P. Garner and J. M. Park, *J. Org. Chem.*, 1990, **55**, 3772. d) Y. Auberson and P. Vogel, *Tetrahedron*, 1990, **46**, 7019. e) A. Chen, I. Savage, E. J. Thomas, and P. D. Wilson, *Tetrahedron Lett.*, 1993, **34**, 6769. f) A. Dondoni, F. Junquera, F. L. Merchan, P. Merino, and T. Tejero, *Tetrahedron Lett.*, 1994, **35**, 9439. g) N. Chida, K. Koizumi, Y. Kitada, C. Yokoyama, and S. Ogawa, *J. Chem. Soc., Chem. Commun.*, **1994**, 111. Syntheses of uracil polyoxin; h) N. P. Damodaran, G. H. Jones, and J. G. Moffatt, *J. Am. Chem. Soc.*, 1971, **93**, 3812. i) A. G. M. Barrett and S. A. Lebold, *J. Org. Chem.*, 1990, **55**, 3853.
4. J. E. Baldwin, G. A. Hofle, and O. W. Jr. Lever, *J. Am. Chem. Soc.*, 1974, **96**, 7125.
5. Satisfactory analytical data were obtained for all new compounds.
6. S. J. Danishefsky, M. P. DeNinno, G. B. Phillips, R. E. Zelle, and P. A. Lartey, *Tetrahedron*, 1986, **42**, 2809.
7. T. Sato and J. Otera, *Synlett*, **1995**, 336.
8. T. Nishimura and I. Iwai, *Chem. Pharm. Bull.*, 1964, **12**, 352.
9. H. Vorbruggen, K. Krolkiewicz, and B. Bennua, *Chem. Ber.*, 1981, **114**, 1234.
10. **15**; colorless oil,  $[\alpha]_{\text{D}}^{-66.9^{\circ}}$  ( $c=1.12$ ,  $\text{CHCl}_3$ ), IR(neat) 2116, 1749, 1693  $\text{cm}^{-1}$ , HRMS (FAB-MS) Calcd for  $\text{C}_{17}\text{H}_{22}\text{N}_5\text{O}_9$  (M+H); 440.1418. Found; 440.1422. NMR( $\text{CDCl}_3$ )  $\delta$  9.28 (br, 1H, NH), 7.32 (d,  $J=1$  Hz, 1H, 6-H), 6.21 (d,  $J=7$  Hz, 1H, 1'-H), 5.42 (dd,  $J=6$ , 3 Hz, 1H, 3'-H), 5.33 (dd,  $J=7$ , 6 Hz, 1H, 2'-H), 4.50 (d,  $J=3$  Hz, 1H, 5'-H), 4.46 (t,  $J=3$  Hz, 1H, 4'-H), 4.33 (q,  $J=7$  Hz, 2H,  $\text{CH}_2$ ), 2.12 (s, 3H,  $\text{OCOCH}_3$ ), 2.08 (s, 3H,  $\text{OCOCH}_3$ ), 1.96 (d,  $J=1$  Hz, 3H,  $\text{CH}_3$ ), 1.35 (t,  $J=7$  Hz, 3H,  $\text{CH}_3$ ). **17**; colorless oil,  $[\alpha]_{\text{D}}^{-63.4^{\circ}}$  ( $c=1.57$ ,  $\text{CHCl}_3$ ), IR(neat) 2117, 1729  $\text{cm}^{-1}$ , HRMS (FAB-MS) Calcd for  $\text{C}_{16}\text{H}_{20}\text{N}_5\text{O}_9$  (M+H); 426.1261. Found; 426.1263. NMR( $\text{CDCl}_3$ )  $\delta$  9.44 (br, 1H, NH), 7.53 (d,  $J=8$  Hz, 1H, 6-H), 6.20 (d,  $J=7$  Hz, 1H, 1'-H), 5.86 (d,  $J=8$  Hz, 1H, 5-H), 5.40 (dd,  $J=6.3$ , 3 Hz, 1H, 3'-H), 5.32 (dd,  $J=7$ , 6.3 Hz, 1H, 2'-H), 4.50 (d,  $J=3$  Hz, 1H, 5'-H), 4.47 (t,  $J=3$  Hz, 1H, 4'-H), 4.33 (q,  $J=7$  Hz, 2H,  $\text{CH}_2$ ), 2.13 (s, 3H,  $\text{OCOCH}_3$ ), 2.08 (s, 3H,  $\text{OCOCH}_3$ ), 1.34 (t,  $J=7$  Hz, 3H,  $\text{CH}_3$ ).

Received, 27th February, 1997