A SHORT PATH SYNTHESIS OF α-HYDROXY ESTER FROM ALDEHYDE USING (1-ETHOXYVINYL)LITHIUM AND ITS APPLICATION TO THE SYNTHESES OF THYMINE POLYOXIN C AND URACIL POLYOXIN C

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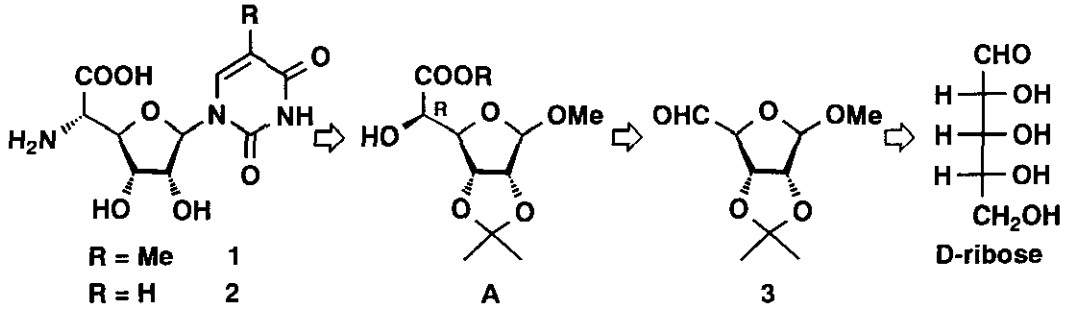
Abstract -A short path synthesis of the α-hydroxy esters (**4** and **5**) from the aldehyde (**3**) using (1-ethoxyvinyl)lithium and its application to the total syntheses of the pyrimidine nucleoside, thymine polyoxin C (**1**) and uracil polyoxin C (**2**), are described.

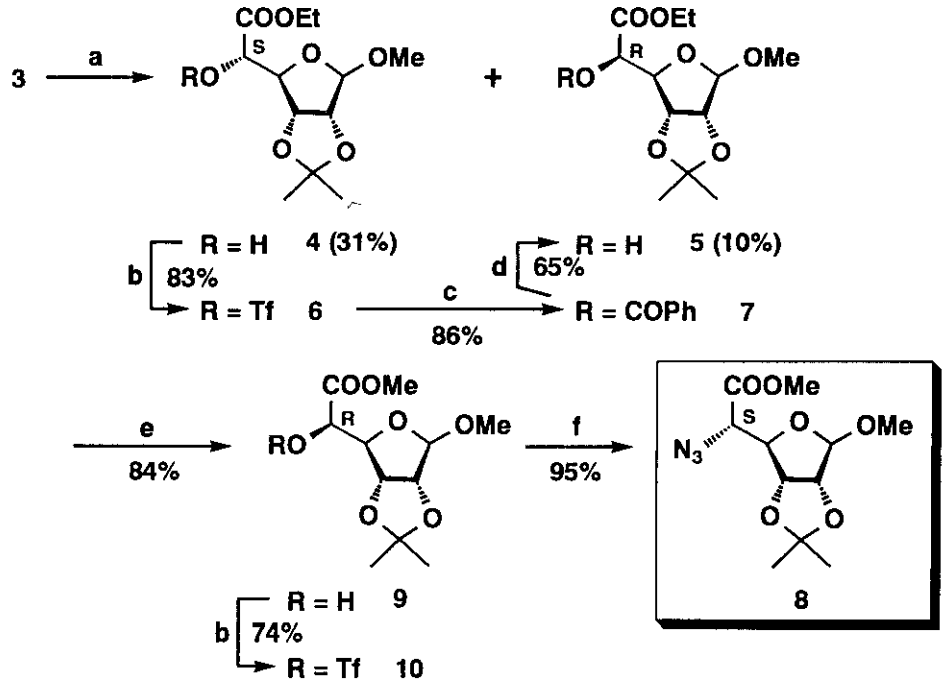
Polyoxins are an important class of peptidyl nucleoside antibiotics isolated from the culture broths of *Streptomyces cacaoi* var. *asoensis*, which are potent competitive inhibitors of chitin synthetase of a variety of phytopathogenic fungi.[1] According to recent studies, polyoxins are also reported to inhibit chitin synthetase of *Candida albicans*, a medically important human fungal pathogen.[2] All members of the polyoxin family bear the 1-(5-amino-5-deoxy-β-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,[3] one of the most important intermediate for the general synthesis of them appeared to be (*R*)-α-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**)[3i] 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[4] followed by ozonolysis and subsequent treatment with Me_2S gave the diastereomeric mixture of α-hydroxy esters which were separated into the major α-hydroxy ester (**4**)[5] {31% from **3**, $[\alpha]_D$ -52.3° (c=1.00, $CHCl_3$)} and the minor one (**5**) {10% from **3**, $[\alpha]_D$ -44.2° (c=1.46, $CHCl_3$)}. The low diastereoselectivity (2:1) against **3** using vinyl magnesium bromide is also reported.[6] 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_2O) afforded the triflate (**6**) (83%) which was treated with PhCOOH in the presence of CsF[7] to provide the α-benzoyloxy ester (**7**) (86%). Alcoholysis of **7** gave the inverted α-hydroxy ester (**5**) (65%) which is consistent with the minor one (**5**). In order to determine the stereochemistry of **5**, the α-hydroxy ethyl ester (**5**) was converted to the reported (5*S*)-azide methyl ester (**8**).[3i] Transesterification of **5** with MeOH into the methyl ester (**9**) in the presence of $Ti(O\text{-}iPr)_4$ was achieved in 84% yield. Triflation of **9** followed by treatment of the triflate (**10**) (74%) with NaN_3 afforded the diastereomerically pure α-azide ester (**8**) {95%, $[\alpha]_D$ -53.3° (c=1.41, $CHCl_3$)} whose spectral data were identical with those {$[\alpha]_D$ -55.3° (c=0.89, $CHCl_3$), ^{1}H-NMR} of the reported (5*S*)-**8**.[3i] Thus, the stereochemistry due to the C-5 position of α-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*)-α-hydroxy ethyl ester (**5**) was converted to the (*S*)-α-azide ethyl ester (**12**) {55% overall yield from **5**, $[\alpha]_D$ -49.1° (c=1.17, $CHCl_3$)} *via* the triflate (**11**) (64%) by the

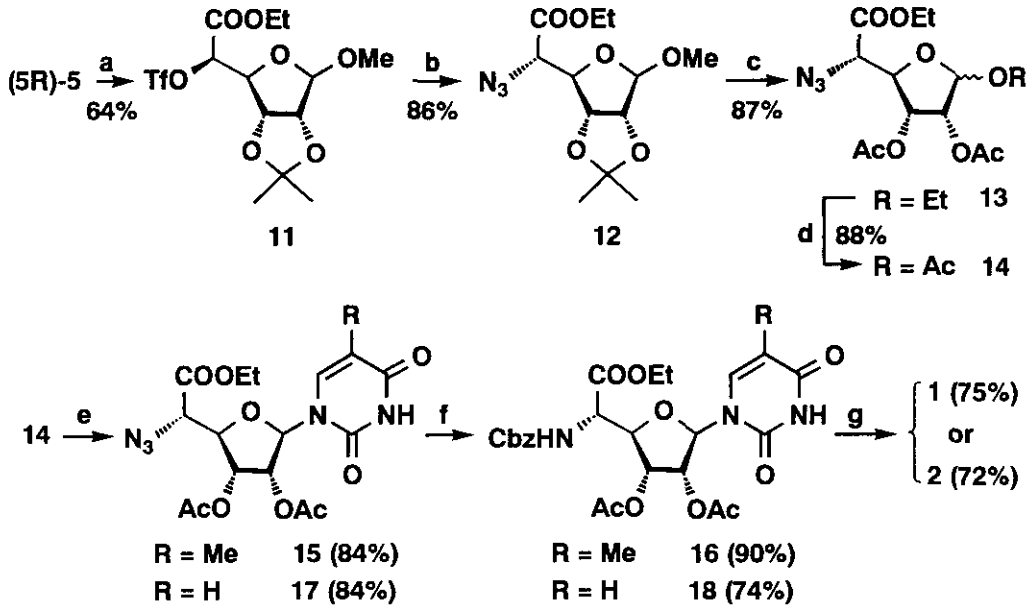


a; 1) Ethyl vinyl ether / *t*-BuLi, THF, -78 °C 2) O_3 / CH_2Cl_2 3) Me_2S / CH_2Cl_2

b; Tf_2O, pyridine / CH_2Cl_2 c; PhCOOH, CsF / DMF d; EtONa / EtOH

e; MeOH, $Ti(O\text{-}i\,Pr)_4$ / PhH, reflux f; NaN_3 / DMF

Scheme 2



a; Tf_2O, pyridine / CH_2Cl_2 b; NaN_3 /DMF c; 1) Dowex 50 WH^+ / EtOH, reflux
2) Ac_2O / pyridine d; Ac_2O, AcOH, *conc.* H_2SO_4 / CH_2Cl_2
e; for 15: 5-methyl-2,4-bis(trimethylsilyloxy)pyrimidine, TMSOTf / CH_2Cl_2, reflux
e; for 17: 2,4-bis(trimethylsilyloxy)pyrimidine, TMSOTf / CH_2Cl_2, reflux
f; for 16: 1) H_2, 20% $Pd(OH)_2$-C / MeOH 2) CbzCl, 7% $NaHCO_3$ aq. / dioxane
f; for 18: 1) H_2, 5% Pd-$BaSO_4$ / MeOH 2) CbzCl, 7% $NaHCO_3$ aq. / dioxane
g; 1) $LiOH \cdot H_2O$ / THF 2) 0.1 N HCl 3) H_2, 10% Pd-C / MeOH

Scheme 3

same way as in the case of conversion of **9** to **8**. Deisopropylidenation (Dowex 50W H^+, EtOH, reflux) afforded the diol, which was acetylated directly (Ac_2O, 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[8] under the conditions reported by Vorbruggen[9] {trimethylsilyl trifluoromethanesulfonate (TMSOTf), $ClCH_2CH_2Cl$, reflux} gave exclusively the β-nucleoside (**15**)[10] (84%). Hydrogenation of the azide (**15**) in the presence of 20% $Pd(OH)_2$-C afforded the α-amino acid ester which was treated with carbobenzyloxy chloride (CbzCl) in the presence of 7% aqueous $NaHCO_3$ to provide the (5*S*)-**16** (90%). Alkaline hydrolysis of **16** followed by hydrogenation gave thymine polyoxin C (**1**)(75%). The synthetic material (**1**){$[\alpha]_D$ +8.5° (c=0.53, H_2O), mp 190-192 °C, ^{1}H-NMR} was identical with authentic material {$[\alpha]_D$ +8.2° (c=0.7, H_2O),[3a] $[\alpha]_D$ +8.0° (c=0.37, H_2O),[3c] mp 190-194 °C,[3c] mp 180-190 °C,[3f] ^{1}H-NMR[3c,d]}. Likewise, reaction of the key triacetate (**14**) with 2,4-bis(trimethylsilyloxy)pyrimidine[8] under similar conditions afforded exclusively the β-nucleoside (**17**)[10] (84%). Hydrogenation of the azide (**17**) in the presence of 5% Pd-$BaSO_4$ and followed by protection of amino group with Cbz group, alkaline hydrolysis and deprotection of Cbz group afforded uracil polyoxin C (**2**) {$[\alpha]_D$ +15.9° (c=0.58, H_2O), mp 247-250 °C, ^{1}H-NMR)} which was identical with authentic material (**2**) {$[\alpha]_D$ +15.8° (c=0.205, H_2O),[1a] mp 240-247

°C,[1a] ^{1}H-NMR[3i]}. The syntheses described herein demonstrate the utility of (1-ethoxyvinyl)lithium for the short path synthesis of the α-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**).

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10. **15**; colorless oil, $[\alpha]_D$ -66.9° (c=1.12, $CHCl_3$), IR(neat) 2116, 1749, 1693 cm^{-1}, HRMS (FAB-MS) Calcd for $C_{17}H_{22}N_5O_9$ (M+H); 440.1418. Found; 440.1422. NMR($CDCl_3$) δ 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, CH_2), 2.12 (s, 3H, $OCOCH_3$), 2.08 (s, 3H, $OCOCH_3$), 1.96 (d, *J*=1 Hz, 3H, CH_3), 1.35 (t, *J*=7 Hz, 3H, CH_3). **17**; colorless oil, $[\alpha]_D$ -63.4° (c=1.57, $CHCl_3$), IR(neat) 2117, 1729 cm^{-1}, HRMS (FAB-MS) Calcd for $C_{16}H_{20}N_5O_9$ (M+H); 426.1261. Found; 426.1263. NMR($CDCl_3$) δ 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, CH_2), 2.13 (s, 3H,$OCOCH_3$), 2.08 (s, 3H, $OCOCH_3$), 1.34 (t, *J*=7 Hz, 3H, CH_3).

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