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Synthesis of Uracil Polyoxin C from Uridine

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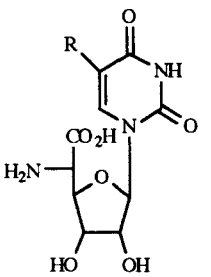
Abstract: An improved procedure is reported for the asymmetric synthesis of uracil polyoxin C (UPOC) from 2',3'-*O*-isopropylideneuridine-5'-aldehyde. The methodology described here is based on the highly diastereocontrolled formation of 1-(β-D-allofuranosyl)uracil and its facile conversion into the corresponding 2,5'-*O*-cyclouridine derivative, a key step for the stereocontrolled formation of the terminal α-amino acid of UPOC.

Polyoxins and nikkomycins form an important class of peptidyl nucleosides which are potent inhibitors of chitin synthetase.[1] 1-(5'-Amino-5'-deoxy-β-D-allofuranuronosyl)pyrimidines **1a-c** constitute the basic terminal amino acid nucleosides common to most members of the polyoxin and nikkomycin dipeptides .



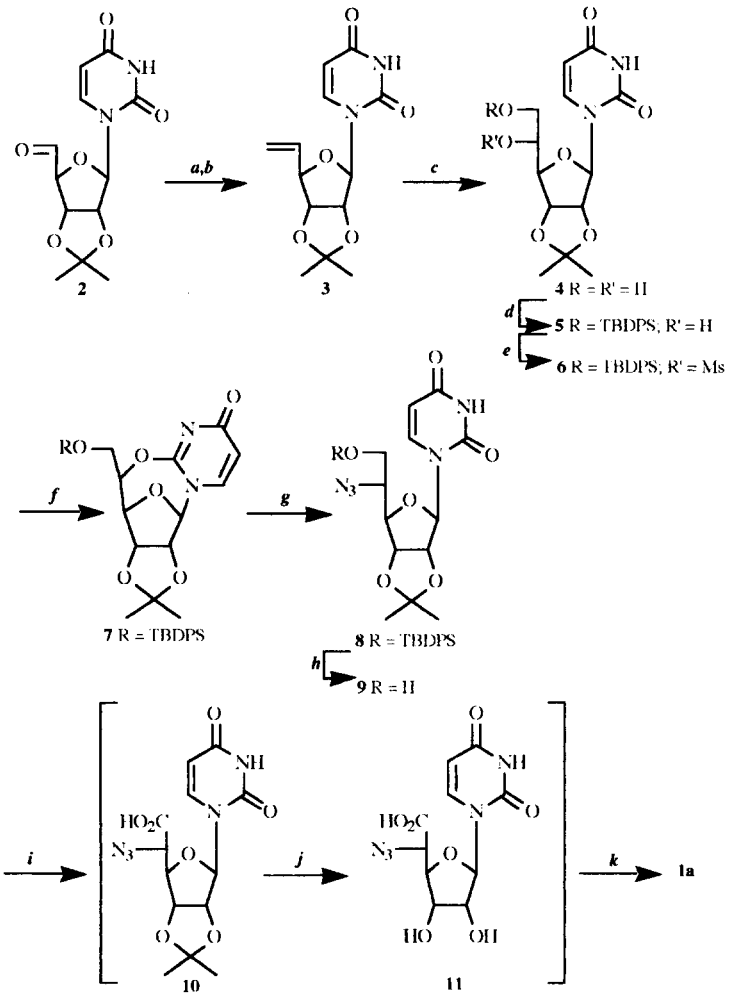
1a R = H: Uracil Polyoxin C
1b R = CH_2OH: Polyoxin C
1c R = CH_3: Thymine Polyoxin C

These important amino acid nucleosides have been obtained by degradation of natural polyoxins[1a,2] and a variety of synthetic approaches have been already reported[3] for their total synthesis. Most of these syntheses are based on the stereocontrolled formation of the sugar component common to amino acids **1a-c**, followed by incorporation of a pyrimidine using Vorbrüggen's glycosylation methodology.[4]

Direct synthesis of uracil polyoxin C from 2',3'-*O*-cyclohexylideneuridine-5'-aldehyde, first described by Moffatt and co-workers *via* cyanohydrin formation at the C-5'-aldehyde, leads to mixtures of β-D-allo and β-L-talofuranuronic acid derivatives which are difficult to separate.[5] Similarly, the synthesis reported by Tsuchida and co-workers using the Ugi reaction suffers also from the lack of diastereomeric control in the formation of the α-amino acid center.[6]

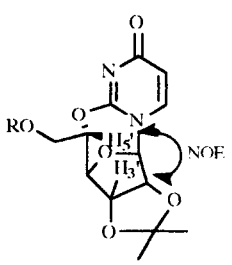
We describe here an asymmetric synthesis of UPOC from uridine. The methodology used is based on the highly diastereocontrolled formation of protected 1-(β-D-allofuranosyl)uracil and its facile conversion into its corresponding 2,5'-*O*-cyclo derivative, a key step in the stereocontrolled formation of the terminal α-amino acid of UPOC. The synthetic sequence to **1a** is shown in Scheme 1.

5'-Deoxy-5'-methyleneuridine **3** was obtained in 64% overall yield *via* its acetylenic precursor prepared from 2',3'-*O*-isopropylideneuridine-5'-aldehyde **2**[7] by a mild procedure reported by Ohira[8] using the readily available dimethyl-(1-diazo-2-oxopropyl)phosphonate.

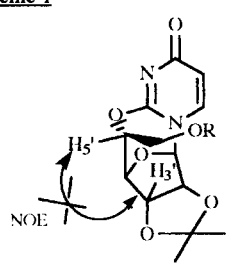


a : $MeC(O)C(N_2)P(O)(OMe)_2$, K_2CO_3, MeOH, 0°C to r.t.; ***b*** : H_2, Pd $CaCO_3$, MeOH ;
c : AD-mix-α, t-BuOH - H_2O (1:1) ; ***d*** : TBDPSCl, imidazole, DMF ; ***e*** : MsCl, pyr. 0°C to r.t. ;
f : DBU, DMF, 70°C ; ***g*** : NaN_3, HMPA, 80°C ; ***h*** : TBAF, THF ; ***i*** : PDC, DMF ;
j : HCO_2H - H_2O (4:1) ; ***k*** : H_2, Pd C, MeOH - H_2O.

Scheme 1



7a (*S*) C-5'
$J_{4'\text{-}5'}$ calculated 0 - 2.9 Hz
$J_{4'\text{-}5'}$ observed 0.8 Hz
NOE between H-5' and H-3'



7b (*R*) C-5'
$J_{4'\text{-}5'}$ calculated 6.1 - 9 Hz
$J_{4'\text{-}5'}$ observed 7.0 Hz
No NOE between H-5' and H-3'

Scheme 2

The synthesis of **3** presented here was found to be particularly valuable since alternative routes to **3**, *via* Wittig chemistry gave moderate yields or complex mixtures.[7,9]

Cis-dihydroxylation of alkene **3** using AD-mix-α under standard conditions[10] proceeded in a highly diastereoselective manner, providing 1-(2',3'-*O*-isopropylidene-β-D allofuranosyl)uracil **4** as an almost unique product (ds ≥ 95%) in 89% yield.[11] The absolute configuration of C-5' was firmly established to be (*R*).[12] The other 5'-epimer was only detected by ^{1}H NMR.[11]

Preparation of UPOC required replacement of the 5'-hydroxyl in **4** by an amino group with retention of configuration. Fortunately, this transformation could be achieved *via* the facile formation of 2,5'-*O*-cyclonucleoside **7**. Thus, **4** was converted into **6** through successive selective silylation of the primary hydroxyl group as its TBDPS ether and mesylation of the 5'-hydroxyl. Heating **6** in DMF with DBU afforded the expected 2,5'-*O*-cyclonucleoside **7**[13] in 61% yield from **4**. Then, **7** treated with sodium azide in HMPA led to the azido derivative **8**. Removal of the TBDPS group gave the 1-(5'-azido-5'-deoxy-2',3'-*O*-isopropylidene-β-D-allofuranosyl)uracil **9**[14] (79% yield from **7**) which was then converted to UPOC.

The final three steps (PDC oxidation, deisopropylidenation and catalytic reduction) were carried out as previously described by H. Ohrui and co-workers on the thymine analogue of **9**[15], without characterization of the intermediates.

UPOC obtained by this route (overall yield 6%) was purified by ion exchange chromatography (DOWEX 50 W H^+- elution with NH_4OH 1N) and crystallized from EtOH/AcOEt, m.p. 238°C (lit.[3b] m.p. 241-245°C), $[\alpha]_D^{20}$ +12.8 (c 0.19 in H_2O) (lit.[3b] $[\alpha]_D^{20}$ +16.5 (c 0.97 in H_2O)), MS (FAB) *m/z* 288 $(MH)^+$. Its ^{1}H NMR spectrum was identical to that reported by Barrett.[3b]

This synthetic route utilizing the enantiomerically pure diol **4** affords a valuable synthesis of uracil polyoxin C starting from uridine and could be applicable to other related molecules of biological interest.

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11. **- 4 - m.p.** 125-130°C. $[\alpha]_D^{20}$ - 9 (c 1 in H_2O). **MS** (DCI) m/z 315 $(MH)^+$. **IR** (KBr): ν 3390, 1690 cm^{-1}. **^{1}H NMR** δ_H ($CDCl_3$, 250 MHz): *major isomer* **4**: 7.32 (1H, d, J 8 Hz, H-6), 5.75 (1H, d, J 8 Hz, H-5), 5.5 (1H, d, J 1.9 Hz, H-1'), 5.08 (2H, m, H-2' and H-3'), 4.15 (1H, t, J 3.4 Hz, H-4'), 4.03 (1H, m, H-5'), 3.78 (1H, dd, J 3.8 and 11 Hz, H-6'a), 3.7 (1H, dd, J 6.1 and 11 Hz, H-6'b), 1.6, 1.45 (6H, s, CH_3) ; *minor isomer* : 7.4 (1H, d, J 8 Hz, H-6), 5.75 (1H, d, J 8 Hz, H-5), 5.6 (1H, d, J 2 Hz, H-1'), 5.02 (2H, m, H-2' and H-3'), 4.23 (1H, m, H-4'), 3.93 (1H, m, H-5'), 3.8-3.7 (2H, m, H-6'a and H-6'b), 1.6, 1.45 (6H, s, CH_3).
    Osmylation of **3** under classical conditions (OsO_4, *N*-methylmorpholine-*N*-oxide) or with AD-mix-β gave diastereomeric mixture of 5',6'-diols, respectively in 2:1 and 1:1 ratios. These mixtures were resolved after protection of the C-5' epimeric diols into their corresponding 5',6'-*O*-isopropylidene derivatives.
12. The absolute (*R*) configuration of diol **4** at the C-5' position was assigned after its conversion to its corresponding 2,5'-*O*-cyclonucleoside derivative **7**. Molecular Mechanics Calculations based on the MM^2 methodology (Allinger, N.L. *J. Am. Chem. Soc.* **1977**, *99*, 8127-8134) allowed the determination of the different constraint energies for the preferred conformers of diastereomeric cyclonucleosides **7a** and **7b** (Scheme 2) and their different 4'-5' dihedral angles and $J_{4',5'}$ coupling constants (**7a** $J_{4',5'}$ 0-2.9 Hz; **7b** $J_{4',5'}$ 6.1-9 Hz). From this method, it was also predicted a close proximity of the 3' and 5' protons (2.82 - 3.05 Å) in **7a**. Results of these calculations agreed well with observed NOE (15%) between H-3' and H-5' and measured $J_{4',5'}$ coupling constant (Scheme 2) for the 2,5'-*O*-cyclonucleoside derivative **7**.
13. **- 7 - m.p.** 108-112°C. $[\alpha]_D^{20}$ +20 (c 1 in $CHCl_3$). **MS** (DCI) m/z 535 $(MH)^+$. **^{1}H NMR** δ_H ($CDCl_3$, 250 MHz) 7.6, 7.4 (10H, m, Ar), 7.18 (1H, d, J 7.6 Hz, H-6), 6.03 (1H, d, J 7.6 Hz, H-5), 5.31 (1H, s, H-1'), 5 (1H, d, J 5.5 Hz, H-3'), 4.9 (1H, s, H-4'), 4.85 (1H, d, J 5.5 Hz, H-2'), 4.45 (1H, ddd, J 0.8, 5.3 and 9.1 Hz, H-5'), 3.95 (1H, dd, J 5.3 and 9.9 Hz, H-6'a), 3.65 (1H, dd, J 9.1 and 9.9 Hz, H-6'b), 1.55, 1.38 (6H, s, CH_3), 1.05 (9H, s, *t*-Bu).
14. **- 9 - m.p.** 73-78°C. $[\alpha]_D^{20}$ - 3 (c 1 in $CHCl_3$). **MS** (DCI) m/z 340 $(MH)^+$. **IR** (KBr) : ν 3230, 3120, 2120, 1705 cm^{-1}. **^{1}H NMR** δ_H ($CDCl_3$, 250 MHz) 7.08 (1H, d, J 8 Hz, H-6), 5.78 (1H, d, J 8 Hz, H-5), 5.6 (1H, d, J 1.9 Hz, H-1'), 5 (2H, m, H-2' and H-3'), 4.07 (1H, dd, J 3.4 and 6.5 Hz, H-4'), 3.95-3.7 (3H, m, H-5', H-6'a and H-6'b), 2.6 (1H, br s, OH), 1.55, 1.35 (6H, s, CH_3).
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