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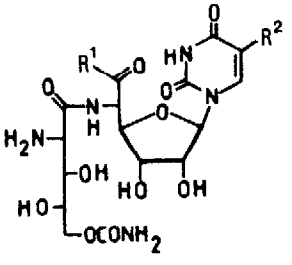
AN ENANTIOSPECIFIC SYNTHESIS OF POLYOXAMIC ACID FROM L-ARABINOSE

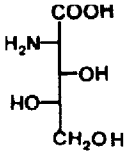
A. Duréault, F. Carreaux, J.C. Depezay
Université René Descartes, UA 400 du CNRS,
Laboratoire de Chimie et Biochimie Pharmacologiques et Toxicologiques,
45 rue des Saints-Pères, 75006 PARIS.

Abstract : Polyoxamic acid , 2-amino-2-deoxy-L-xylonic acid, is synthetized by thiophenoxide opening of a five-carbon chiral hydroxylated aziridine easily derived from L-arabinose. The formation of the carboxy group resulted from a Pummerer reaction.

Polyoxins belong to a group of antifungal antibiotics produced by certain species of Streptomyces, which inhibit the chitin synthetase of a variety of phytopathogenic fungi[1]. Recent studies suggest that these compounds (or their analogues) may also be therapeutically useful against Candida albicans, a fungal pathogen which affects humans[2]. Polyoxins all incorporate a non-proteinic amino acid, polyoxamic acid 1. The unusual polyhydroxy α-amino acid 1 is coupled in polyoxins by a peptide linkage to one of several related nucleoside moieties.



POLYOXINS



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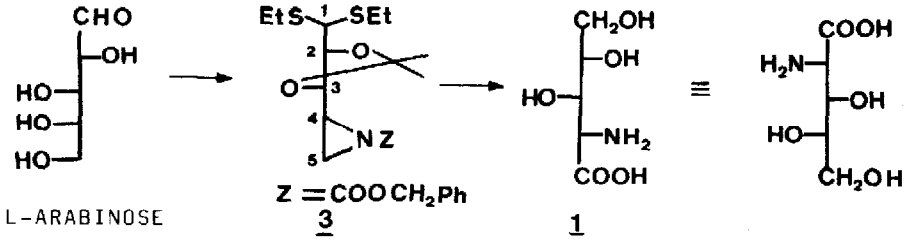
POLYOXAMIC ACID

Different chemical syntheses of polyoxamic acid have been proposed, most of them relying on carbohydrates as chiral building blocks[3] ; recently a stereoselective synthesis starting from D-serine was also reported[4]. We now report a rapid, enantiospecific synthesis of polyoxamic acid 1, and more usefully of the derivative 8 suitably protected for peptide coupling, from the easily available pentose : L-arabinose.

Chiral functionalized aziridines are useful aminoalkylating intermediates for the synthesis of enantiomerically pure amino derivatives. We have recently reported a systematic study of the nucleophilic opening of chiral bis-aziridines synthetized from D-mannitol[5]. This suggested that the conveniently protected aziridine 3 , prepared from L-arabinose, could constitute a good precursor of polyoxamic acid 1.

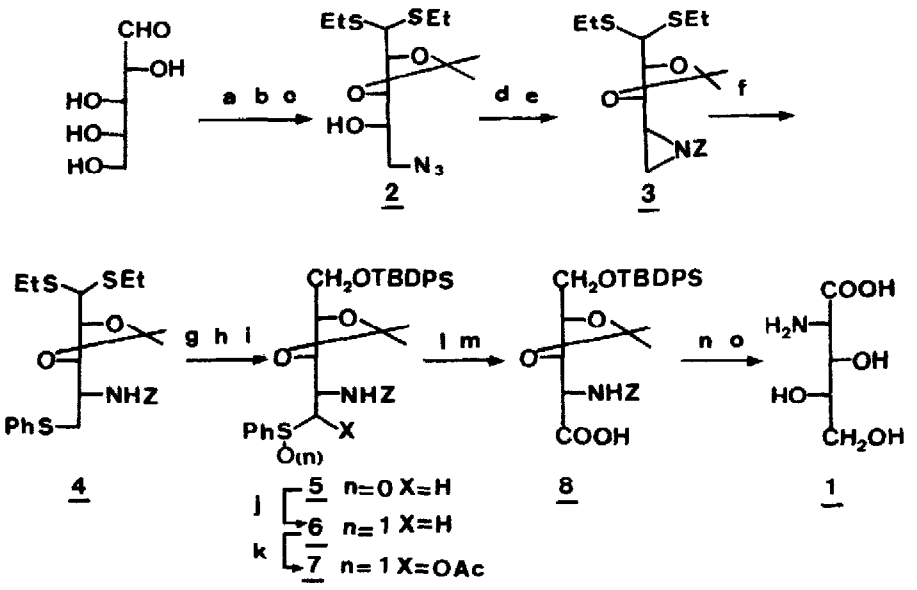


The three chiral centers of polyoxamic acid 1 are already in place in the aziridine 3 (C-4, C-3, C-2) with the right configuration. The key step of the synthesis in our strategy is the nucleophilic thiophenoxide opening of the aziridine ring followed by a Pummerer reaction, allowing the formation of a carboxy group at C-5 of 3.

Aziridine 3 was obtained with 18% overall yield starting from L-arabinose by nitrogen introduction with configuration inversion at C-4 of the starting pentose.

L-arabinose was converted in five steps into the azido alcohol 2[6] , $[\alpha]_D$ - 88° (C 3, CH_3OH)[7] by standard methods[8] in 28% overall yield. Reductive ring closure of 2 by triphenylphosphine led to the N-H aziridine which was protected as its N-benzyloxycarbonyl derivative 3 , $[\alpha]_D$ + 6° (C 1, CH_2Cl_2); such a protective group activates the aziridine ring toward nucleophilic opening and is convenient for peptide synthesis.

Nucleophilic opening of 3 was performed by sodium thiophenoxide in 75% yield ; thioacetal hydrolysis of the resulting sulfide 4 , $[\alpha]_D$ - 19° (C 1.7, CH_2Cl_2) effected by I_2 , followed by reduction at C-1 with Na BH_4 and silylation of the resulting alcohol, led to the completely and selectively protected sulfide 5 in 54% overall yield from 3. Compound 5 was oxidized with MCPBA in 85% yield in sulfoxide 6 , which was in turn converted into a diastereomeric mixture of acetoxy sulfides 7 by a Pummerer rearrangement performed in Ac_2O / $(CF_3CO)_2O$ / NaOAc at 20°C[9]. We could convert the acetoxy sulfides 7 into the protected polyoxamic acid 8 without any epimerization at C-4 by complete reduction of 7 (using Na BH_4) followed by Ru Cl_3 oxidation of the resulting alcohol in acid 8 [10] , $[\alpha]_D$ - 21°(C 1.3, CH_2Cl_2). Hydrogenolytic removal of the Z protecting group of 8 followed by aqueous trifluoracetic acid hydrolysis gave, after purification by ion exchange chromatography, polyoxamic acid 1 , $[\alpha]_D$ + 3° (C 1., H_2O) ; $[\alpha]_{365}$ + 22° (C 1 , H_2O) [lit + 2.8° and + 23°, respectively[11]] . Enantiomerically pure polyoxamic acid 1 was thus obtained in 26% overall yield starting from aziridine 3.



(a) ref 8 ; (b) TsCl, Py, -5°C, 4h, 75% ; (c) NaN_3, DMF, 65°C, 4h (80%) ; (d) PPh_3, toluene, 100°C, 45 min. ; (e) $PhCH_2OCOCl$, N Et_3, CH_2Cl_2, r.t., 2h, (65% from 2) ; (f)PhSH, NaH, THF, r.t., 4h (75%) ; (g) I_2, $NaHCO_3$, acetone-H_2O, r.t., 48h ; (h) $NaBH_4$, MeOH, 0°C, 3h ; (i) t-$BuPh_2SiCl$, Imidazole, DMF, r.t. (72% from 4) ; (j) MCPBA, CH_2Cl_2, 0°C, 1h30 (87%) ; (k) Ac_2O, $(CF_3CO)_2O$, NaOAc, 2,6-lutidine, r.t., 4h ; (l) $NaBH_4$, EtOH, 0°C, 2h ; (m) $RuCl_3.3H_2O$, $NaIO_4$, CCl_4-CH_3CN-H_2O, r.t., 2h (59% from 6) ; (n) H_2,10%Pd/C, MeOH ; (o) CF_3COOH-H_2O (9 : 1), r.t., 10h, then Dowex 50W-X8 (94% from 8)

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