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TOTAL SYNTHESIS OF OF4949-III, A NATURAL INHIBITOR OF AMINOPEPTIDASE B FROM EHRLICH ASCITES CARCINOMA CELLS[1]

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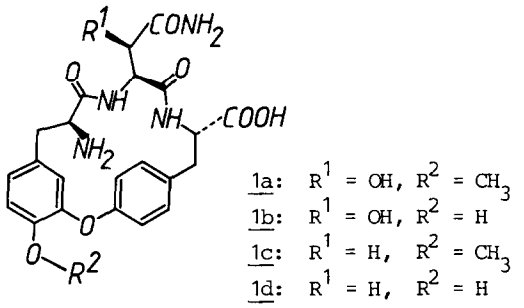
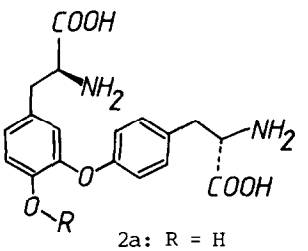
Abstract - The total synthesis of the cyclopeptide OF4949-III 1c is described. Key steps are two preparations of didehydroamino acid moieties by condensations of aldehydes and phosphorylglycine esters and two homogeneous hydrogenations with more than 98% ee and de, respectively, to give derivatives of isodityrosine 8a,b. The peptide ring is constructed by the cyclization of an ω-aminopentafluorophenyl ester in a two phase system in 40% yield.



1a: R^1 = OH, R^2 = CH_3
1b: R^1 = OH, R^2 = H
1c: R^1 = H, R^2 = CH_3
1d: R^1 = H, R^2 = H



2a: R = H
2b: R = CH_3

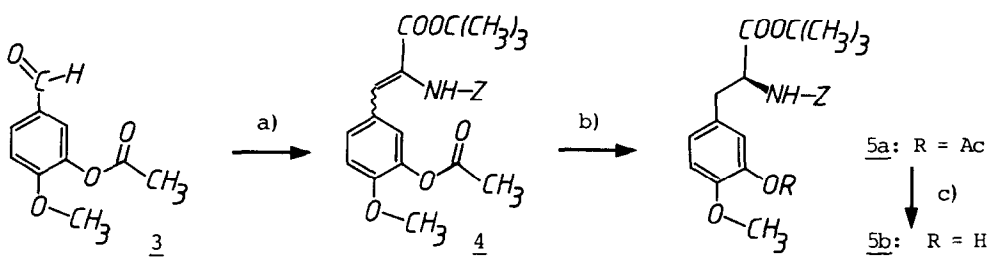
OF4949I-IV 1a-d are inhibitors of aminopeptidase B from Ehrlich ascites carcinoma cells. They have been isolated from the culture filtrate of the fungus Penicillium rugulosum OF4949 by S.Sano and his colleagues, who elucidated the structure and configuration by chemical and spectroscopical methods[2]. The characteristic residue of these cyclopeptides is isodityrosine, a diaminodicarboxylic acid, or its methyl ether 2a,b which was also found in several natural products, e.g. cell wall glycoproteins[3,4], piperacinomycin[5] and the bouvardines, antitumor cyclic hexapeptides[6]. Together with their elucidation study, the Japanese chemists[2] synthesized the methyl ether of isodityrosine by an Ullmann reaction of tyrosine and bromotyrosine derivatives but in very small yield. The lactam of isodityrosine, which represents the characteristic unit of piperacinomycin and deoxybouvardin was constructed in the total syntheses of these natural compounds [7,8] by S.Yamamura's thallium(III)nitrate oxidation of bromotyrosylbromotyrosines using the diphenyl ether formation for the ring closure. Following an analogous route, S.Yamamura[9] recently synthesized OF4949-III by thallium(III)nitrate oxidation of a dibromotyrosylasparaginyldichlorotyrosine derivative and subsequent dehalogenation (ca.10% yield in the ring closure and the following steps).

We now describe the synthesis of isodityrosine via two didehydroamino acid intermediates and their enantioselective or diastereoselective hydrogenations, respectively. In this way, gram amounts of isodityrosine derivatives are accessible without difficulty.

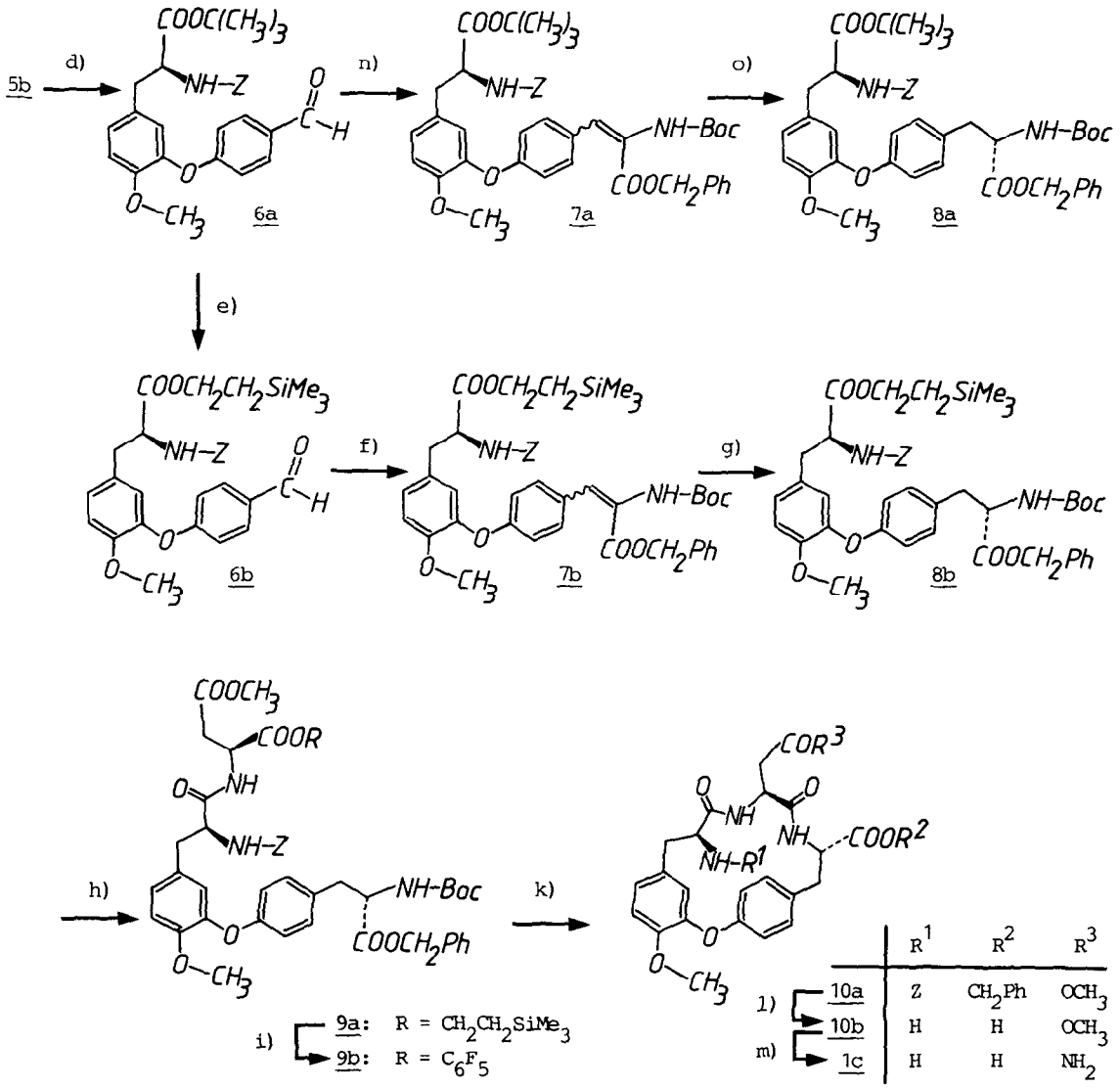
The synthesis of OF4949-III is described in scheme I. The cyclopeptide contains three very polar groups (COOH, NH_2, $CONH_2$), which were protected as benzyl ester, benzyloxycarbonyl amide and methyl ester to facilitate the isolation and purification of the synthetic intermediates and the product of the ring closure reaction.

The didehydroamino acids 4,7a and 7b with predominant Z-configuration were synthesized by condensation of the aldehydes 3, 6a and 6b with phosphorylglycine derivatives following our method[10]. Their homogeneous hydrogenations to give the S-amino acid derivatives 5a,8a and 8b with ee or de >98% were catalyzed by $[Rh(DIPAMP)]^+$ [11]. In the Ullmann reaction of 5b and p-bromobenzaldehyde the diphenyl ether 6a was formed in very good yield. As all attempts to split the t-butyl ester in 8a failed, we transformed 6a into the trimethylsilylethyl ester 6b. Using this protecting group[12] the construction of the diaminodicarboxylic acid derivative 8b as well as the subsequent synthesis of the dipeptide 9a were achieved by conventional methods.

We achieved the ring closure by our well proved pentafluorophenyl ester method[13] in a two phase reaction. Deprotection of the trimethylsilylethyl ester group of 9a without saponification of the benzyl and methyl esters using tetrabutylammonium fluoride and subsequent esterification gave the pentafluorophenyl ester 9b. After deprotection of the Boc group, the ring closure was performed by a slow addition (3h) of the ω-amino pentafluorophenyl ester to a rapidly stirred mixture of chloroform and saturated sodium hydrogencarbonate solution at room temperature. Separation and evaporation of the chloroform solution gave nearly pure cyclopeptide 10a in 40% yield. Catalytic hydrogenation deprotected the benzyl groups and reaction of the methyl ester 10b with methanolic ammonia formed the cyclopeptide OF4949-III, which was identical in every respect with the natural compound. All intermediates gave satisfactory ^{1}H-NMR[14] and MS data.



a) N-Benzyloxycarbonyl-2-dimethoxyphosphoryl-glycine tert.-butyl ester/KOtBu/CH_2Cl_2/ -60°C→ 20°C/12h/78%; b) $[Rh(DIPAMP)]^+/H_2/CH_3OH$/20°C/75h/quant.; c) NaOH/CH_3OH/20°C/ 15h/86%;



Scheme 1

d) p-bromobenzaldehyde/CuO/K_2CO_3/pyridine/130°C/12h/93%; e) 1. CF_3COOH/20°C/5h; 2. DCC/2-trimethylsilylethanol/DMAP/ethyl acetate/-10°C → 20°C/12h/75%; f) N-tert.-butyloxycarbonyl-2-dimethoxyphosphoryl-glycine benzyl ester/KOtBu/CH_2Cl_2/-60°C → 20°C/12h/73%; g) $[Rh(DIPAMP)]^+/H_2/C_2H_5OH$/30°C/75h/quant.; h) 1. $(Bu)_4N^+F^-$/DMF/0.5h/quant.; 2. H-S-Asp(OCH_3)-$OCH_2CH_2SiMe_3$/N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride/dioxane/0°C → 20°C/15h/82%; i) 1. $(Bu)_4N^+F^-$/DMF/0.5h/20°C/quant.; 2. C_6F_5OH/DCC/ethyl acetate/-10°C → 20°C/12h/quant.; k) 1. $Me_3SiOSO_2CF_3/CH_2Cl_2$/-40°C → 20°C/2h; 2. 150 ml $CHCl_3$/150 ml saturated $NaHCO_3$/20°C/3h/40%; l) Pd/C (5%)/isopropanol/20°C/20h/91%; m) 50 ml CH_3OH/NH_3 (saturated)/ 20°C/120h/93%; n) N-tert.-butyloxycarbonyl-2-dimethoxyphosphoryl-glycine benzyl ester/KOtBu/CH_2Cl_2/-60°C → 20°C/12h/67%; o) $[Rh(DIPAMP)]^+/H_2/CH_3OH$/20°C/75h/quant.

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We wish to thank Dr.Susumu Sano (Central Research Laboratories, Takara Shuzo Co. Ltd.) and Professor Shosuke Yamamura (Keio University, Yokohama) for providing us ^{1}H-NMR spectra and samples of natural and synthetic OF4949-III.

Notes and references.

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14 10a: ^{1}H-NMR (300MHz, $CDCl_3$) 7.40-7.10 (m,12H), 6.98 (m,2H), 6.81 (m,2H), 6.65 (d, J=8.2Hz,1H), 6.45 (d,d,J=1.9Hz,J'=8.2Hz,1H). 5.78 (d,J=2.0Hz,1H), 5.53 (d,J=7.8Hz, 1H), 5.20-5.0 (m,4H), 4.86 (m,1H), 4.47 (m,2H), 3.81 (s,3H), 3.59 (s,3H), 3.30 (d,d, J=4.1Hz,J'=13.1Hz,1H), 3.02 (d,d,J=5.5Hz,J'=14.2Hz,1H), 2.70-2.45 (m,4H).

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