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STEREOSPECIFIC SYNTHESIS OF (+)-OXYBIOTIN FROM D-XYLOSE[1]. PREPARATION OF THE FINAL CHIRAL (+)-OXYBIOTIN PRECURSOR

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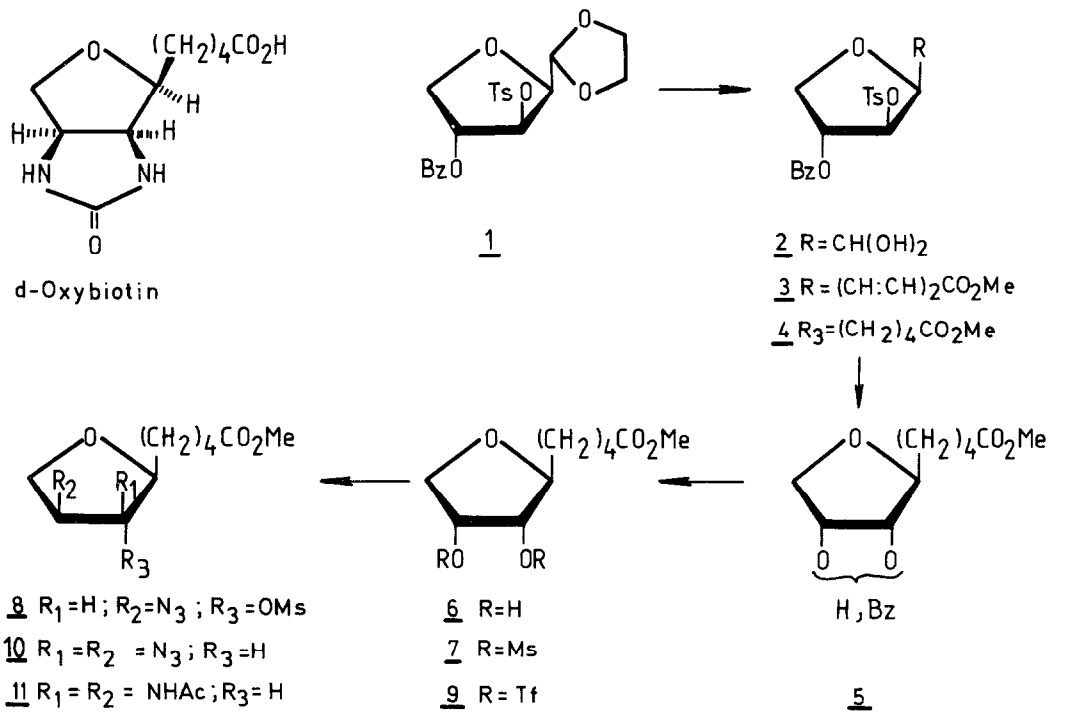
Summary: A stereospecific synthesis of 2(S)-carbomethoxy-butyl-3(R), 4(S)-diacetamido-tetrahydrofurane (11), the final chiral precursor in a new synthesis of (+)-oxybiotin has been achieved from 2,5-anhydro-D-xylose derivative 1.

(+)-Oxybiotin is an oxygen analog of (+)-biotin and shows a high biotin activity towards some microorganisms[2]. Two syntheses of (±)-oxybiotin[3], as well as one stereospecific synthesis of (+)-oxybiotin from D-glucose[4] have been already reported. In this paper, we would like to describe a preparation of the final chiral precursor in a new stereospecific synthesis of (+)-oxybiotin from D-xylose.

Ethylene acetal of 2,5-anhydro-4-O-benzoyl-3-O-p-toluenesulfonyl-D-xylose (1), which is readily available from D-xylose[5], was hydrolysed with a mixture of CF_3COOH-c.HCl (10:1), at room temperature during 18 h, whereupon a hydrated form of the aldehyde 2 was obtained (syrup; 61%, purified by chromatography[6] (C_6H_6-EtOAc 4:1); $|\alpha|_D$ -76.04, c 0.89)[7,8]. Reaction of compound 2

with [3-carbomethoxy-propen-(2)-yl-(1)]-triphenylphosphoniumbromide[9] (CH_2Cl_2; H_2O; NaOH; vigorously stirring for 0.5 hours at RT), gave unsaturated ester 3 (syrup; 59%, purified by chromatography(C_6H_6); $[\alpha]_D$ -9.78, c 0.87). By catalytic hydrogenation of compound 3 (PtO_2; AcOH; RT; 20 h), saturated ester 4 was obtained as the only reaction product (75%; mp 101-3°, crystallized from EtOH; $[\alpha]_D$ -65.76, c 1.04). Solvolysis of compound 4 in 95% DMF (5% H_2O; $CaCO_3$; bath temp. 160°; 4.5 h), gave a mixture of isomeric benzoyl derivatives 5 (syrup; 65%, isolated by chromatography C_6H_6-EtOAc 9:1); $[\alpha]_D$ -47.79, c 1.17). Debenzoylation of 5 with methanolic NaOMe (0.1 M; RT; 15 min.), afforded diol 6 (syrup; 81%, obtained by chromatography (Bz-Me_2CO 4:1); $[\alpha]_D$ -37.6, c 0.95). Compound 6 with methanesulfonyl chloride in pyridine afforded the corresponding dimesylate 7 (76%; mp 70-1°, upon crystallization from EtOH; $[\alpha]_D$ -62.6, c 1.06).



At first,we assumed that compound 7 can be suitably use for subsequent introduction of the C-3 and C-4 azido functions needed for final (+)-oxybiotin

ureido system building. This idea was based on a work of Ohrui and Emoto[10] wno described a solvolytic reaction of a tetrahydrothiophene analog of dimesylate 7, whereupon the corresponding diazide was obtained (NaN_3; HMPT; 80°)[10]. However, when we applied similar reaction conditions to dimesylate 7, the corresponding monoazide 8 was obtained as the only reaction product (syrup; 70%, purified by chromatography (C_6H_6-EtOAc 9:1); $[\alpha]_D$ +18.73, c 1.73). In order to obtain needed diazide 10, we had to use more reactive leaving groups at the positions C-3 and C-4. Therefore, we prepared the corresponding ditriflate 9, by an action of $(CF_3SO_2)_2O$ on diol 6 (CH_2Cl_2-Py; 0°C; 0.5 h), whereupon syrupy 9 was obtained ($[\alpha]_D$ -40.43, c 1.82). Compound 9 with NaN_3 in HMPT (100°C; 1 h) gave diazide 10 as the only reaction product (syrup; $[\alpha]_D$ +35.5, c 1.79). By catalytic hydrogenation of crude compound 10 (PtO_2; AcOH-Ac_2O 1:1; RT; 20 h), the corresponding diacetamido derivative 11 was obtained (43% from 4; mp 151-2°, upon crystallization from CH_2Cl_2-hexane; $[\alpha]_D$ +8.75, c 1.17)[11]. (+)-Oxybiotin can be obtained from compound 11 according to relevant literature[4,10].

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1. Part IV of the series: "Studies Directed Towards Stereospecific Syntheses of Oxybiotin, Biotin and Their Analogs". (For parts I, II and III se references 5a, 5b and 7). This work was performed within the framework of Yugoslav-EEC common project.

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8. The $[\alpha]_D$ values were determined in chloroform solutions. Compounds: 2 (unstable), 3 (a mixture of cis-trans isomers) and 5 (a mixture of positional isomers), were characterized only by IR data. The structures of all other compounds were confirmed by IR-, ^{1}H NMR-, ^{13}C NMR- and mass spectra. For all crystalline compounds satisfactory microanalyses were obtained.

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11. Spectral data for compound 11: IR (KBr): 3290, 3080, 1730, 1650, 1550. ^{1}H-NMR ($CDCl_3$+DMSO-d_6): 1.57 (Broad signal, 6H, 3CH_2-groups from the side chain), 1.94 (s, 3H, CH_3CONH from C-4), 2.03 (s, 3H, CH_3CONH from C-3), 2.28 (t, 2H, CH_2COOMe), 3.58 (m, 1H, H-5), 3.65 (s, 3H, COOCH_3), 3.78 (m, 1H, H-2), 3.96 (t, 1H, H-5´, $J_{5,5'}$=$J_{4,5'}$=9.0 Hz), 4.56 (m, 1H, H-4), 4.70 (m, 1H, H-3), 7.22 and 7.26 (broad signals dissapeared upon deuteration, 2H, MeCONH). ^{13}C-NMR spectrum: 22.27 (CH_3CONH), 24.29 (C-1´), 24.99 C-2´), 28.76 (C-3´), 33.23 (C-4´), 50.69 (COOCH_3), 51.09 and 52.11 (C-3 and C-4), 69.00 (C-5), 80.36 (C-2), 169.85 and 170.27 (CONH), 173.19 (COOMe). FAB-Mass spectrum (m/e): 323 (MNa^+), 301 (MH^+).

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