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STEREOSPECIFIC SYNTHESIS OF (+)-BIOTIN

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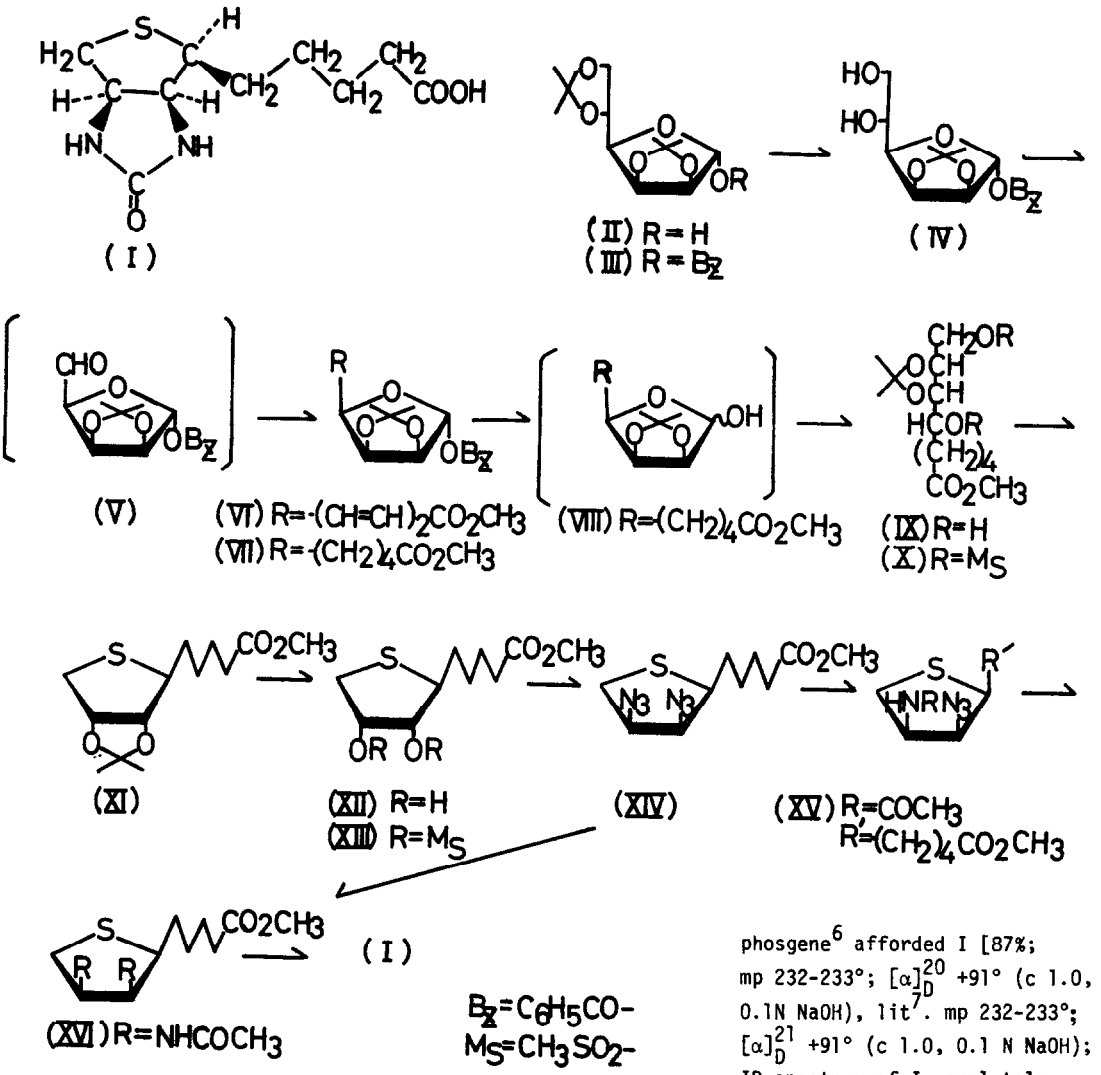
In the course of our studies on the stereospecific syntheses of optically active Biotin Vitamers by use of the asymmetric carbons of carbohydrates, the syntheses of (+)-Oxybiotin[1] and (+)-Dethiobiotin[2] have been already achieved. We would now like to describe the stereospecific total synthesis of (+)-Biotin from D-mannose.

Treatment of 2,3:5,6-di-O-isopropylidene-α-D-mannofuranose(II)[3] with benzoyl chloride in pyridine gave 1-O-benzoate(III)[4][97%; mp 127-128°; $[\alpha]_D^{20}$ +33.4° (c 2.3, $CHCl_3$)]. Selective hydrolysis of the 5,6-O-isopropylidene group of III with 70% acetic acid at 20° for 48 hr gave 1-O-benzoyl-2,3-O-isopropylidene-α-D-mannofuranose(IV)[93%; glass; $[\alpha]_D^{20}$ +52.5° (c 1.7, C_2H_5OH)]. Periodate oxidation of IV in a mixture of acetone and water afforded the aldehyde V, which was treated with excess [3-carbomethoxy-propen-(2)-ylidene-(1)]-triphenylphosphorane[5] in CH_2Cl_2 to give methyl 1-O-benzoyl-2,3-O-isopropylidene-5,6,7,8-tetradeoxy-α-D-lyxo-non-5,7-dieno-1,4-furanuronate(VI)[5:6 trans 6:7 trans isomer; 85% from IV; mp 91-92°; $[\alpha]_D^{20}$ -33.6° (c 0.3, $CHCl_3$), 5:6 cis 6:7 trans isomer; 5%; mp 141-142°; $[\alpha]_D^{20}$ -120.5° (c 1.1, $CHCl_3$)]. Hydrogenation of IV with 10% Pd-C in methanol gave 1-O-benzoyl-2,3-O-isopropylidene-5,6,7,8-tetradeoxy-α-D-lyxo-1,4-furanuronate(VII)[97%; mp 68-69°; $[\alpha]_D^{20}$ +30.0° (c 2.0, $CHCl_3$)]. Treatment of VII with $NaOCH_3$ in methanol, followed by the reduction of the resulting aldehyde VIII with $NaBH_4$ afforded methyl 2,3,4,5-tetradeoxy-7,8-O-isopropylidene-L-lyxo-nononate(IX)[85% from VII; syrup; $[\alpha]_D^{20}$ +12.3° (c 2.0, $CHCl_3$)]. Methanesulfonylation of IX gave a syrupy dimesylate X [96%; $[\alpha]_D^{20}$ +19.6° (c 3.0, $CHCl_3$)]. Treatment of X with sodium sulfide in hexamethylphosphoramide (HMPA) at 100° for 2 hr afforded a syrupy tetrahydrothiophene derivative XI [75%; $[\alpha]_D^{20}$ -91.2° (c 1.8, $CHCl_3$)]. Treatment of XI with 90% formic acid at 20° for 15 min gave a diol XII [92%; mp 55-56°; $[\alpha]_D^{20}$ -108.6° (c 1.4, $CHCl_3$)]. Methanesulfonylation of XII gave a syrupy dimesylate XIII [95%; $[\alpha]_D^{20}$ -86.5° (c 2.1, $CHCl_3$)]. Treatment of XIII with sodium azide in HMPA at 80° for 7 hr afforded a syrupy diazido compound XIV [78%; $[\alpha]_D^{20}$ +42.1° (c 2.3, $CHCl_3$)]. Catalytic reduction of the azido groups of XIV with PtO_2 in a mixture of methanol and acetic anhydride at 20° for 1 hr gave 2(S)-4'-carbomethoxy-butyl-1'-3(S)-azido-4(R)-acetamido-tetrahydrothiophene(XV)[73%; mp 115-116°; $[\alpha]_D^{20}$ -181.0° (c 1.0, $CHCl_3$); nmr ($CDCl_3$) δ 1.8 (6H, m, mehtylenes), 2.40 (3H, s, $NCOCH_3$), 2.34 (2H, t, J=6.5Hz, $CH_2CO_2CH_3$), 2.85 (2H, m, H_5), 3.61 (1H, m, H_2), 3.58 (3H, s, CO_2CH_3), 4.20 (1H, t, $J_{2,3}=J_{3,4}=4Hz$, H_3) 4.60 (1H, m, H_4) 6.75 (1H, d, J=8.0Hz, NH)]. Further reduction of XV under similar conditions for 3 hr afforded a diacetamido derivative XVI [80%; syrup; $[\alpha]_D^{20}$-123.9° (c 1.7, C_2H_5OH)]. Compound XVI was obtained(60%) directly from XIV without the isolation of XV. Treatment of XVI with $Ba(OH)_2$ in water at 140° for 14 hr, followed by the treatment with



phosgene[6] afforded I [87%; mp 232-233°; $[\alpha]_D^{20}$ +91° (c 1.0, 0.1N NaOH), lit[7]. mp 232-233°; $[\alpha]_D^{21}$ +91° (c 1.0, 0.1 N NaOH); IR spectrum of I completely agreed with that of authentic I.

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