Tetrahedron Letters No. 42, pp 3657 - 3660, 1975. Pergamon Press. Printed in Great Britain.

STEREOSELECTIVE SYNTHESES OF (+)- AND (-)-AVENACIOLIDE FROM D-GLUCOSE THE CORRECT ABSOLUTE CONFIGURATION OF NATURAL AVENACIOLIDE

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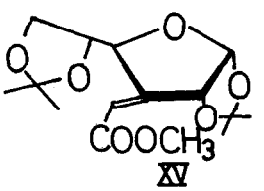
(Received in Japan 11th August 1975; received in UK for publication 8th September 1975)

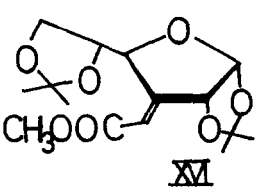
In the course of our studies on the stereoselective syntheses of biologically active compounds in optically active forms by use of the asymmetric carbons of carbohydreates, the syntheses of (+)-Oxybiotin[1], (+)-Dethiobiotin[2], and (+)-Biotin[3] have been already achieved. We would now like to describe the stereoselective syntheses of (+)- and (-)-Avenaciolide from D-glucose and the correct absolute configuration of the natural Avenaciolide.

Avenaciolide is a naturally occurring antifungal compound which was first isolated by Brookes, Tidd, and Turner[4] from Aspergillus avenaceus. The structure XIIa was assigned by Brookes et al.[4,5]. The synthesis of XII in a racemic form was first achieved by Parker and Johnson[6] and then by Herrmann, Berger, and Schlessinger[7]. However, the synthesis of XIIa in an optically active form has not been achieved yet[8], we therefore planned the synthesis of XIIa from D-glucose.

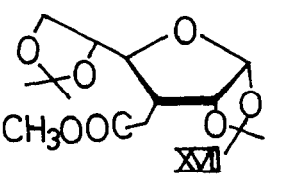
The starting material 1,2:5,6-di-O-isopropylidene-β-D-lyxo-hexofuranos-3-ulose(II) was prepared from D-glucose through D-idose by the method of Paulsen et al.[9] followed by the method of Tracey et al.[10]. Treatment of II with trimethoxy phosphonoacetate in THF in the presence of n-BuLi gave two unsaturated branched chain carbohydrates, III [10%, mp 86-87°, $[\alpha]_D^{25}$ -255.3° (c 0.6, $CHCl_3$), nmr[11] 5.15 (1H, m, H_2, $J_{1,2}$=4Hz, $J_{2,\ vinyl}$=2Hz), 5.58 (1H, m, H_4, $J_{4,vinyl}$=2Hz), 6.18 (1H, t, H_{vinyl}, $J_{2,Vinyl}=J_{vinyl,4}$=2Hz)] and IV [80%, mp 69-70°, $[\alpha]_D^{23}$ -203.6° (c 0.9, $CHCl_3$), nmr 4.89 (1H, q, H_4, $J_{4,5}$=4Hz, $J_{4,vinyl}$=2Hz), 5.70 (1H, m, H_2), 5.96 (1H, d, H_1, $J_{1,2}$=4Hz), 6.0 (1H, t, H_{vinyl}, $J_{2,\ vinyl}=J_{vinyl,4}$=2Hz)]. It was expected that the catalytic reduction of both III and IV would give 3-C-carbomethoxymethyl-3-deoxy-1,2:5,6-di-O-isorpopylidene-β-D-talofuranose (V), since the catalytic reduction of both XV and XVI was known to give 3-C-carbomethoxymethyl-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-allofuranose(XVII)[12]. As expected, the hydrogenation of III over 10% Pd-C gave V as a sole product [V; quantitative, mp 60-61°, $[\alpha]_D^{25}$ -60.1° (c 1.3, $CHCl_3$), nmr 4.82 (1H, t, H_2, $J_{1,2}=J_{2,3}$=4Hz), 5.83 (1H, d, H_1, $J_{1,2}$=4Hz)], however, the hydrogenation of IV under the same conditions gave two products, V and 3-C-carbomethoxymethyl-



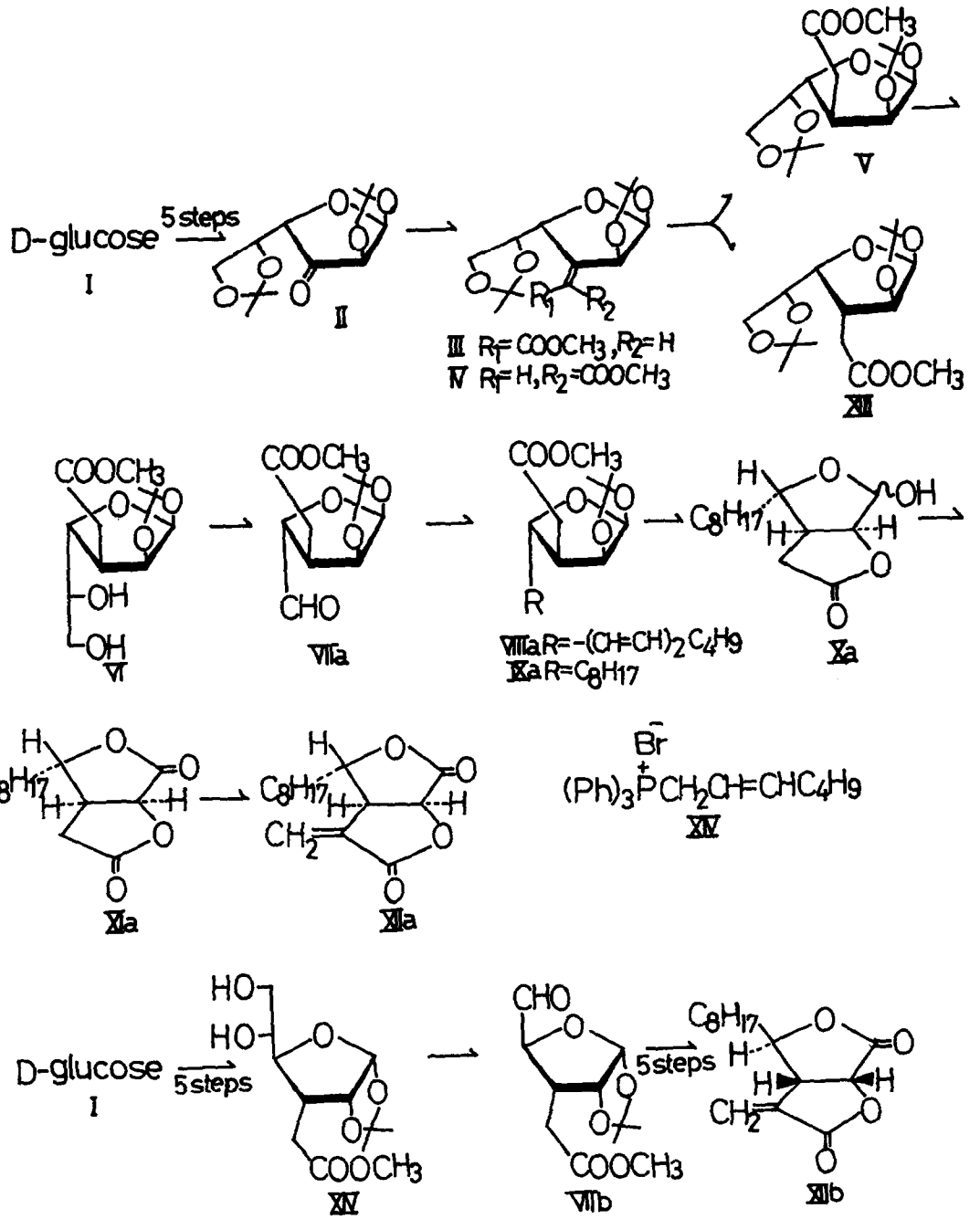
XV



XVI



XVII

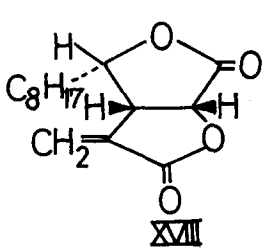

D-glucose
5 steps
I
II
III R1=COOCH3, R2=H
IV R1=H, R2=COOCH3
V
XII
VI
VIIa
VIIIa R=-(CH=CH)2C4H9
Xa R=C8H17
XIa
XIIa
(Ph)3PCH2CH=CHC4H9
XIV
XIII
VIIb
XIIb

3-deoxy-1,2:5,6-di-O-isopropylidene-β-D-idofuranose(XIII) in a ratio of 6 to 4 [XIII; 37%, mp 67-68°, $[\alpha]_D^{29}$ +4.4° (c 1.6, $CHCl_3$), nmr 4.48 (1H, broad d, H_2, $J_{1,2}$=4Hz, $J_{2,3}$≒0Hz), 5.86 (1H, d, H_1, $J_{1,2}$=4Hz). These results indicated that the configuration of the oxygene atom at C-5 was very important for the stereoselectivity in these reductions.

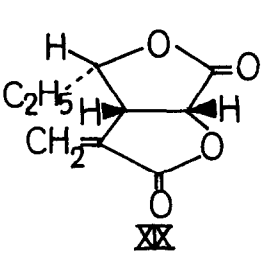
Selective hydrolysis of 5,6-O-isopropylidene group of V with 70% acetic acid gave a syrupy diol VI [92%, $[\alpha]_D^{29}$ -64.6° (c 3.0, $CHCl_3$)]. Periodate oxidation of VI gave the aldehyde VIIa, which was treated with phosphonium salt XIV[13] in DMSO in the presence of sodium methylsulfinyl-methide[14] to give a syrupy VIIIa [70%, $[\alpha]_D^{25}$ -9.0° (c 1.0, $CHCl_3$)]. Hydrogenation of VIIIa over 10% Pd-C gave a syrapy IXa [95%, $[\alpha]_D^{25}$ -69.9° (c 1.5, $CHCl_3$), nmr 0.88 (3H, t, terminal CH_3) 1.27 (14H,-C_7H_{14}-), 1.30 and 1.48 (two 3H, isopropylidene group), 2.0 (1H, m, H_3), 2.48 (2H, m, $\underline{CH_2}COOCH_3$), 3.70 (3H, s, $COOCH_3$), 3.76 (1H, m, H_4), 4.76 (1H, t, H_2, $J_{1,2}$=$J_{2,3}$=4Hz), 5.82 (1H, d, H_1, $J_{1,2}$=4Hz). Treatment of IXa with MeOH-KOH followed by the treatment with a mixture of 1% sulfuric acid and formic acid at room temperature overnight gave a lactone hemiacetal Xa [92%, mp 70-72, $[\alpha]_D^{29}$+45.6° (c 1.0, $CHCl_3$)]. Nmr showed that Xa was a mixture of OH-<u>exo</u> and OH-<u>endo</u> isomers in a ratio of 2 to 1. Oxidation of Xa with DMSO-Ac_2O gave a bislactone XIa [95%, mp 39-40°, $[\alpha]_D^{27}$ +6.17 (c 1.5, $CHCl_3$), which had been prepared in a racemic form by Johnson et al.[6] in their synthesis of (±)-Avenaciolide. Compound XIa was transformed to XIIa in 48% yield by the method reported by these people[6]. The resulting XIIa, mp 54-56°, had a nmr completely identical with that of the natural Avenaciolide reported by Brookes et al.[4,5]. However, XIIa had a rotation of $[\alpha]_D^{25}$ +41.3° (c 1.0, EtOH) that was the same magnitude but in opposite sign as was reported for the natural Avenaciolide[4]. These results indicate that the natural Avenaciolide would have the absolute configuration shown as XIIb.

In order to confirm the absolute configuration of Avenaciolide, the stereoselective synthesis of XIIb was carried out. D-Glucose was converted to 3-C-carbomethoxymethyl-3-deoxy-1,2-O-isopropylidene-α-D-allofuranose(XIV)[mp 90-91°, $[\alpha]_D^{29}$ =68.2° (c 1.0, $CHCl_3$), lit.[15] mp 89-90°, $[\alpha]_D^{22}$ +63° (c 1.0, $CHCl_3$)] by a slightly modified method described by Rosenthal et al.[12,15]. Periodate oxidation of XIV gave the aldehyde VIIb, which was transformed to XIIb by the same synthetic pathway described for XIIa. The resulting XIIb had mp 54-56°, nmr spectrum identical with that of XIIa, and a rotation of $[\alpha]_D^{25}$ -41.6° (c 1.0, EtOH) that was the same magnitude and the same sign as that reported for the natural Avenaciolide.

The results described above indicated that the absolute configurarion of Avenaciolide was XIIb and not XIIa. In addition the reported absolute configurations of Isoavenaciolide and Ethiolide may be incorrect and will be revised as XVIII and XIX respectively, since these have been related to Avenaciolide[16].



XVIII



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