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# CONVERSION OF D-GLUCOSE TO (+)-DESTHIOBIOTIN

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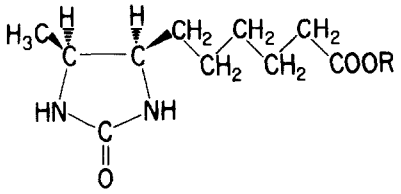
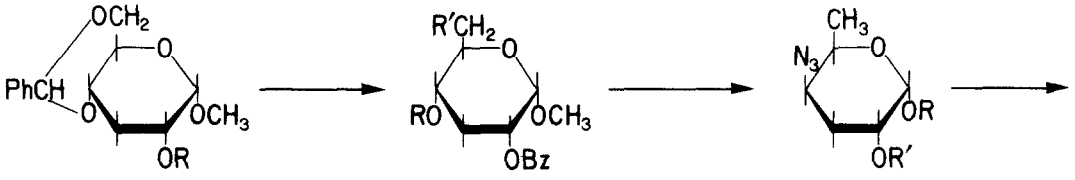
(+)-Desthiobiotin (Ia) was first prepared as the methyl ester (Ib) by desulfurization of (+)-biotin methyl ester with Raney Ni in the course of the work on the structural elucidation of (+)-biotin (1) and found to be biologically as active as (+)-biotin in some microorganisms (2). The preparation of Ia from other source has never been reported although the racemic compound was synthesized by three groups (3). We now describe the preparation of Ia from D-glucose, utilizing the asymmetric carbons of the sugar. This is also a chemical confirmation of the absolute configuration of (+)-biotin, which was recently clarified by the X-ray analysis (4).

The starting material is methyl 4,6-O-benzylidene-3-deoxy-α-D-ribo-hexopyranoside (IIa) which is easily prepared from D-glucose (5). Compound IIa was changed into the 2-benzoate (IIb), m.p. 121-3°; $[\alpha]_D^{22}$ +88° (c 4.61, $CHCl_3$) (6), and then debenzylidenated to IIIa, m.p. 131-3°; $[\alpha]_D^{25}$ +101° (c 3.31, $CHCl_3$), with aqueous $H_2SO_4$ in p-dioxane. Partial tosylation of IIIa afforded the syrupy 6-tosylate (IIIb), $[\alpha]_D^{22}$ +58° (c 2.61, $CHCl_3$), which was subsequently treated with NaI in boiling 2-butanone to give 6-iodide (IV), m.p. 131-2°; $[\alpha]_D^{20}$ +71° (c 2.66, $CHCl_3$). Catalytic reduction of IV was performed with Pd-C (10%) in the presence of $CH_3COONa$, giving syrupy methyl 2-O-benzoyl-3,6-dideoxy-α-D-ribo-hexopyranoside (Va), $[\alpha]_D^{20}$ +96° (c 1.96, $CHCl_3$). After Va had been methylsulfonylated, the resulting 4-mesylate (Vb), m.p. 100-3°; $[\alpha]_D^{21}$ +129° (c 1.64, $CHCl_3$); $\lambda_{max}^{KBr}$ 1180, 1360 ($SO_2$) $cm^{-1}$; δ ($CDCl_3$) 3.82 (H-5, $J_{4,5}$ 10.2 cps) ppm, was heated at 120° in DMF with $NaN_3$ to yield methyl 4-azido-2-O-benzoyl-3,4,6-trideoxy-α-D-xylo-hexopyranoside (VI), m.p. 80-3°; $[\alpha]_D^{21}$ +61° (c 2.27, $CHCl_3$); $\lambda_{max}^{KBr}$ 2100 ($N_3$) $cm^{-1}$;



(Ia) R=H (Ib) R=$CH_3$

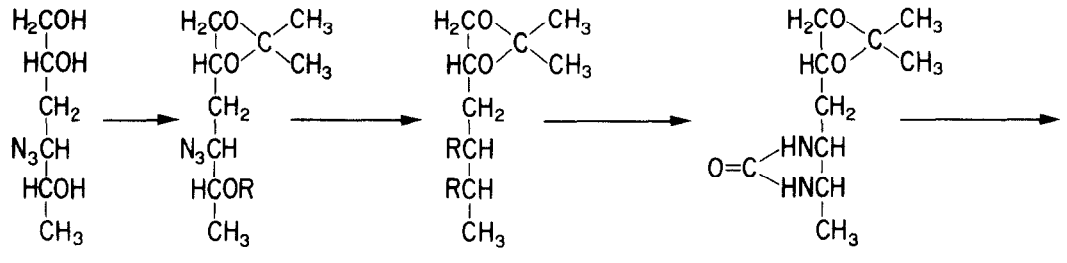
Bz = Benzoyl
Ph = Phenyl
Ts = p-Tolylsulfonyl
Ms = Methylsulfonyl



(IIa) R=H
(IIb) R=Bz

(IIIa) R=H, R′=OH
(IIIb) R=H, R′=OTs
(IV) R=H, R′=I
(Va) R=H, R′=H
(Vb) R=Ms, R′=H

(VI) $R=CH_3$, R′=Bz
(VII) R=H, R′=H

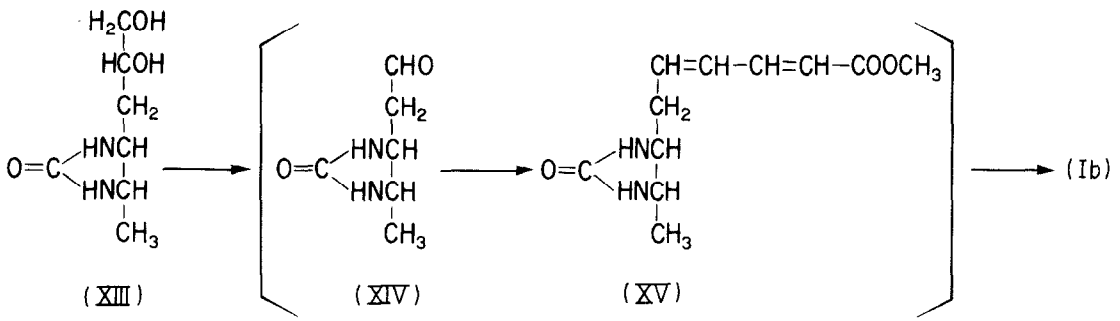


(VIII)

(IXa) R=H
(IXb) R=Ms

(X) $R=N_3$
(XI) $R=NH_2$

(XII)



(XIII) (XIV) (XV)

(Ib)

$(Ph)_3-P=CH_2-CH=CH-COOCH_3$

(XVI)

δ ($CDCl_3$) 4.10 (H-5, $J_{4,5}$ 1.8 cps) ppm, with an inversion at C-4. In acetolysis follwed by alkaline hydrolysis (7), VI gave 4-azido-3,4,6-trideoxy-α-D-xylo-hexose (VII), m.p. 87-90°; $[\alpha]_D^{20}$ -15° (6 min)⟶ -43° (66 min) (c 1.43, $H_2O$); $\lambda_{max}^{KBr}$ 2100 ($N_3$), 3300-3500 (OH) $cm^{-1}$; δ (DMSO-$d_6$) 4.88 (H-1, $J_{1,2}$ 3.6 cps), 4.10 (H-5, $J_{4,5}$ 1.8 cps) ppm. Reduction of VII in methanol for 40 min at 0° with $NaBH_4$ afforded syrupy 4-azido-3,4,6-trideoxy-D-xylo-hexitol (VIII), $[\alpha]_D^{22}$ +49° (c 2.57, p-dioxane); $\lambda_{max}^{film}$ 2150 ($N_3$) $cm^{-1}$. Compound VIII was treated for 3.5 hr at a room temperature with aceton in the presence of Dowex 50W ($H^+$) to give syrupy IXa, $[\alpha]_D^{22}$ +28° (c 1.52, $CHCl_3$) and subsequently methylsulfonylated to the syrupy 5-mesylate (IXb), $[\alpha]_D^{26}$ +73° (c 1.72, $CHCl_3$); $\lambda_{max}^{film}$ 1175, 1360 ($SO_2$), 2100 ($N_3$) $cm^{-1}$. The second azide group was introduced by the treatment of IXb in DMF at 120° with $NaN_3$ and syrupy 4,5-diazido-1,2-O-isopropylidene-3,4,5,6-tetradeoxy-L-arabino-hexitol (X), $[\alpha]_D^{23}$ +127° (c 1.16, $CHCl_3$); $\lambda_{max}^{film}$ 2100 ($N_3$) $cm^{-1}$, was obtained with an inversion at C-5 (8). Catalytic reduction of X with Raney Ni at a room temperature under pressure (ca. 4kg/$cm^2$) gave a syrupy diamine (XI), $\lambda_{max}^{film}$ no absorption for $N_3$, 3300, 3400 ($NH_2$) $cm^{-1}$, which, without purification, was treated in water with $COCl_2$ in the presence of $Na_2CO_3$ to give 4,5-N-carbonyl-4,5-diamino-1,2-O-isopropylidene-3,4,5,6-tetradeoxy-L-arabino-hexitol (XII), m.p. 128-9°; $[\alpha]_D^{24}$ +33° (c 1.04, $CHCl_3$); $\lambda_{max}^{KBr}$ 1710 (C=O), 3250 (NH) $cm^{-1}$. Isopropylidene group of XII was removed in water with Dowex 50W ($H^+$) at a room temperature, giving XIII, m.p. 125-30°; $[\alpha]_D^{20}$ +44° (c 2.55, $C_2H_5OH$). The overall yield of XIII was 4% from the starting material (IIa).

The next three steps of reactions ($NaIO_4$ oxidation, Wittig reaction, and catalytic reduction) were carried out continuously without characterization of the products. Compound XIII was cleaved in water at 0° with $NaIO_4$ between C-1 and C-2 and the resulting aldehyde (XIV) was extracted with absolute ethanol after concentration by freeze drying. Although the aldehyde group of XIV might be masked (9), XIV was put into the next reaction because Wittig reaction had been found successful with the masked aldehyde such as hemiacetal (10). Thus, two equivalents of Wittig reagent (XVI) (11) was added to the alcoholic extract of XIV and the mixture was kept at a room temperature for two days to afford two products derived from XIV in the ratio of ca. 3:1 with a trace of unchanged XIV. After the major

product (XV) had been isolated by the combination of column chromatography [silica gel G, $CHCl_3$-$CH_3OH$ (94:6)] (12) and preparative t.l.c. [2 mm thick, silica gel $GF_{254}$, $CHCl_3$-$CH_3OH$ (94:6), detection by UV absorption] (13), it was hydrogenated with Adams Pt, giving crude Ib which was purified by high vacuum distillation ($10^{-5}$ mmHg, 110°) and subsequent column chromatography [silica gel G, $CHCl_3$-$CH_3OH$ (96:4)]. The resulting pure Ib was identical with the authentic one prepared from (+)-biotin methyl ester (1) on t.l.c. and hydrolyzed with aqueous NaOH (1 N) to afford Ia (yield, 6% from XIII), m.p. 160-2° (no depression when mixed with the authentic Ia); $[\alpha]_D^{19}$ +7.0° (c 0.91, $C_2H_5OH$); IR spectrum completely agreed with that of the authentic Ia, $\lambda_{max}^{KBr}$ 1660 (C=O of 2-imidazolidone ring), 1710 (C=O of acid) $cm^{-1}$.

Judging from the agreement of the sign of $[\alpha]_D$ values between Ia derived from the sugar and the authentic one, $[\alpha]_D^{17}$ +10.4° (c 0.57, $C_2H_5OH$), the absolute configuration of (+)-desthiobiotin is established as shown in the figure. This also means the determination of the absolute configuration of (+)-biotin, which is well consistent with the result obtained by the physical method (4).

## REFERENCES AND FOOTNOTES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9. Compound XIV may exist in the form of a dimer or a complex with formaldehyde.
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13. The isolated minor product was not pure enough for further study.