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Preliminary communication

A biomimetic synthesis of (+)-biotin from D-glucose

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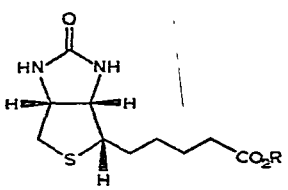
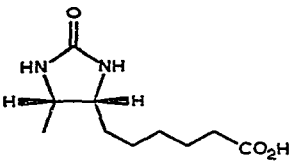
Recent studies[1] on the biosynthesis of (+)-biotin (1) showed that (+)-desthiobiotin (2) is a precursor in the biosynthesis and is transformed by *Aspergillus niger* into



1 R = H
25 R = Me



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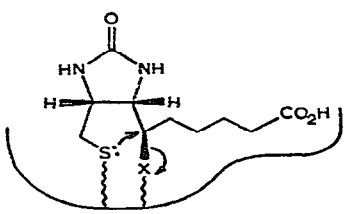
(+)-biotin in a stereospecific manner through an oxidative reaction. A plausible intermediate for this oxidative transformation by enzymes might be visualized as either 3 or 4.

Even though several total syntheses[2] of biotin have been reported, including recent chiral syntheses from D-mannose[3] and from L-cysteine[4], to the best of the authors' knowledge, none of these syntheses employed a biomimetic transformation such as those shown in 3 or 4.



Enzyme

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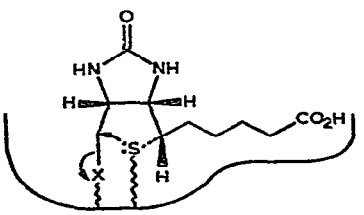

Enzyme

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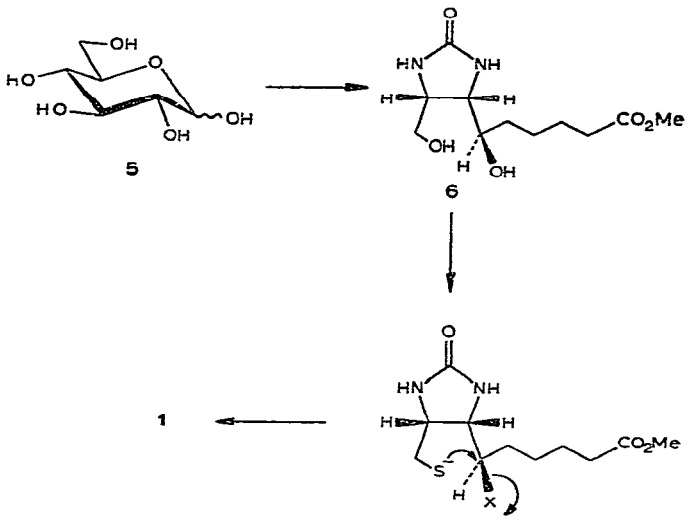
We now report a total synthesis of (+)-biotin from D-glucose (5) which involves in the biomimetic sequence the stereospecific ring-closure to a tetrahydrothiophene at the last stage of the synthesis, as shown in Scheme 1.

For the successful, stereospecific transformation of 5 into the key intermediate 13, use of the conformationally rigid[5] 1,6-anhydro-β-D-glucose (8) as the starting material



SCHEME 1

was essential. Diaxial epoxide opening of 1,6:2,3-dianhydro-4-*O*-benzyl-β-D-mannopyranoside[6] (9), which had already been prepared from 8 in 4 steps, with sodium azide and ammonium chloride in 4:1 2-methoxyethanol–water for 22 h at 120° gave, in 85% yield, 1,6-anhydro-2-azido-4-*O*-benzyl-2-deoxy-β-D-glucopyranoside (10), m. p. 101–103°, $[\alpha]_D^{20}$ −7.2° (ethanol)* .

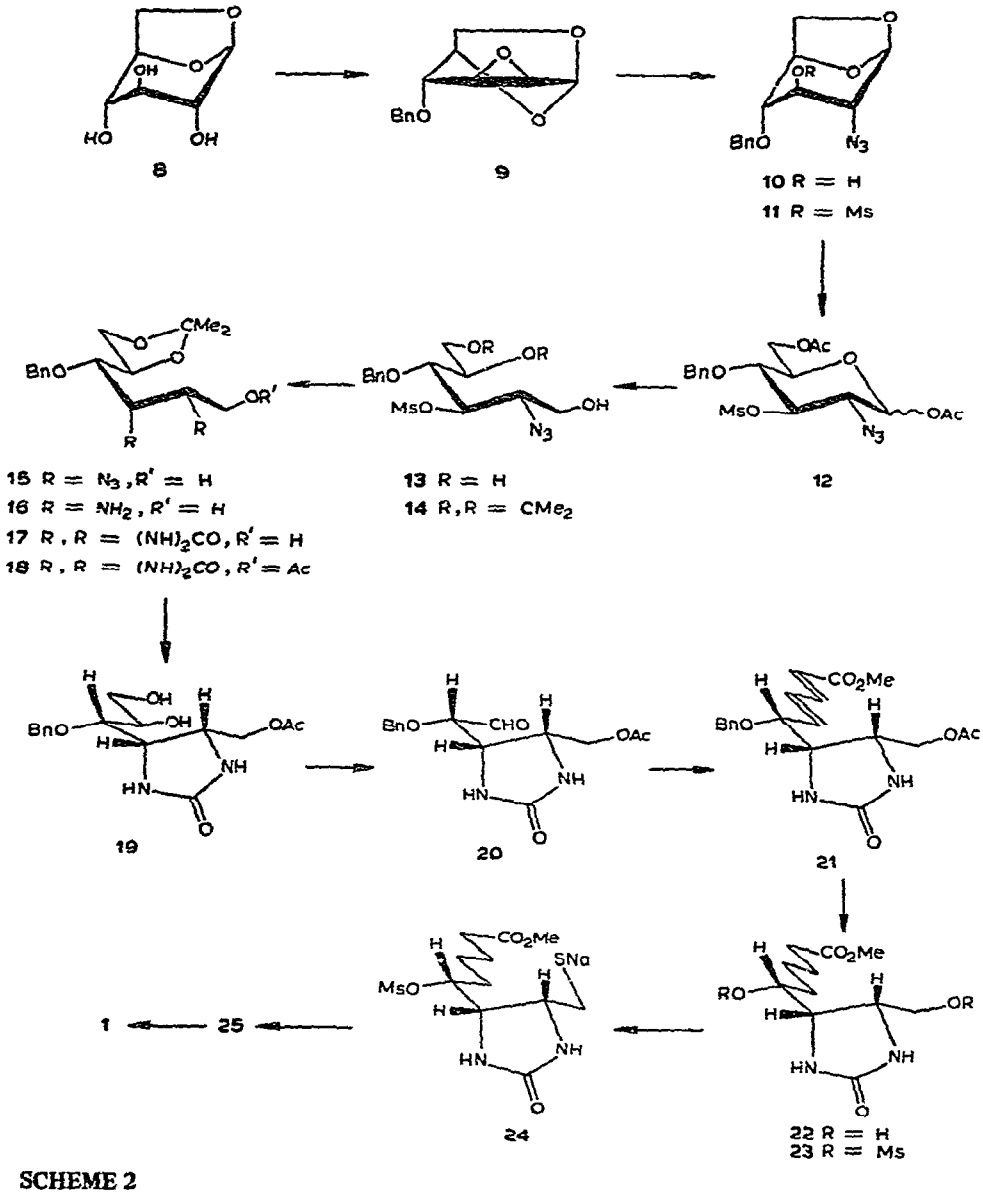
The alteration of the steric environment at C-3 of methanesulfonate 11, m.p. 58–59°, $[\alpha]_D^{20}$ +66.2° (chloroform), which was obtained from 10 by the conventional method, is necessary in order to achieve smooth SN2 displacement[7] of the sulfonate group by azide anion, as the attacking azide ion has two 1,2-interactions with axial substituents at C-2 and C-4 in 11. For this purpose, a flexible, acyclic structure, such as 14, seemed to be more promising than the conformationally rigid, 1,6-anhydro structure.

Thus, acetolysis of 11 in 4% BF_3 etherate–acetic anhydride for 3 h at 20° gave, in 95% yield, an anomeric mixture of diacetates 12 in the ratio of $\alpha:\beta = 8:3$; ^{1}H-n.m.r. ($CDCl_3$): δ 6.35 (d, *J* 4 Hz, H-1 of α anomer) and 5.57 (d, *J* 9 Hz, H-1 of β anomer). On solvolysis with 1% HCl in methanol for 16 h at 20° and subsequent reduction with $NaBH_4$

*All compounds for which $[\alpha]_D$ is recorded gave satisfactory elemental analyses, and i.r. and ^{1}H-n.m.r. data.

in the presence of boric acid in ethanol at 0–5°, **12** gave the oily triol **13**, $[\alpha]_D^{20}$ +37.3° (chloroform), in 45% yield from **11**.

Introduction of the azide group could be achieved by initial treatment of the triol **13** with 2,2-dimethoxypropane in $HCONMe_2$ in the presence of a catalytic amount of $TsOH \cdot H_2O$ for 15 h at 20°, to give the oily monoisopropylidene derivative **14**, $[\alpha]_D^{20}$ +31.1° (chloroform); ^{1}H-n.m.r. ($CDCl_3$): δ 1.35 and 1.44 (two 3-proton s, C-Me_2) and



SCHEME 2

2.98 (s, 3 H, SO_2Me). Reaction of **14** with LiN_3 in $HCONMe_2$ for 40 h at 80° gave oily diazide **15**, $[\alpha]_D^{20}$ +11.2°, in 52% yield from **13**.

Selective hydrogenation[8] of the azide groups of **15** in the presence of the benzyl ether group could be effected by Lindler catalyst in ethanol, to give, in quantitative yield, diamine **16**, m.p. 116–117°, $[\alpha]_D^{20}$ +45.7° (chloroform), which, by reaction with $COCl_2$–CCl_4 in aq. Na_2CO_3 at 0–5°, gave ureide **17**, m.p. 116–116.5°, $[\alpha]_D^{20}$ −66.2° (chloroform), in 87% yield from **15** (see Scheme 2).

Selective transformation of the dioxolane moiety of **17** into the C_5 side-chain moiety of the key intermediate **21** could be achieved in 6 steps (in 40% yield): (*1*) acetylation (Ac_2O–py) of **17** to monoacetate **18**, m.p. 74–76°, $[\alpha]_D^{20}$ −87.1° (chloroform); (*2*) deisopropylidenation of **18** in 80% aq. AcOH for 3.5 h at 70° to diol **19**, $[\alpha]_D^{20}$ −66.1°; (*3*) $NaIO_4$ oxidation of **19** in 50% aq. EtOH for 1 h at 20° to aldehyde **20**, which was (*4*) immediately submitted to the Wittig reaction with [3-(carbomethoxy)-2-propen-1-ylidene]triphenylphosphorane[3,9] in CH_2Cl_2 at 20° to give ester **21**, $[\alpha]_D^{20}$ + 4.0° (chloroform); (*5*) hydrogenation of **21** over 10% Pd–C in MeOH; and (*6*) subsequent deacetylation by MeONa in MeOH, to give diol ester **22**, m.p. 194–195°, $[\alpha]_D^{20}$ −20.3° (MeOH).

Final transformation, which involves formation of the tetrahydrothiophene ring by inversion of the stereochemistry at C-4, could be achieved in 30% yield by two successive reactions: (*1*) methanesulfonylation of **22** with 15 equivalents of MsCl in pyridine–dichloroethane for 15 h at −10°, and (*2*), without isolation* of **23**, treatment with a large excess of Na_2S in $HCONMe_2$ for 3 h at 100°, to afford **24** and thence (+)-biotin methyl ester (**25**), m.p. 165–166°, $[\alpha]_D^{20}$ +82.0° (methanol), which was identical in all respects with an authentic sample of **25**, and was further converted into (+)-biotin (**1**), m.p. 232–233°, $[\alpha]_D^{20}$ +91.0° (0.1M NaOH).

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*Even though the reaction product could be seen as a single spot in t.l.c. (silica gel), attempted isolation of **23** was not successful, most probably due to its instability during processing.

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