Novel Stereospecific Synthesis of (±)-Dethiobiotin

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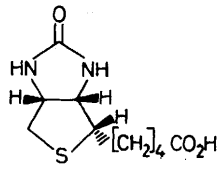
Summary A new stereospecific synthesis of dethiobiotin (**2**), the biological precursor of the vitamin biotin (**1**), is described.

THE immediate precursor of the vitamin (+)-biotin (**1**) in a number of microbial systems has been found[1] to be (+)-dethiobiotin (**2**). As part of an investigation of biotin formation and metabolism, we attempted to prepare several specifically tritiated forms of dethiobiotin by using published syntheses[2] of this compound. However, these attempts led to scrambling of the tritium labels. We have therefore developed a new synthesis of (±)-dethiobiotin which will be useful for labelling purposes. This approach differs from prior syntheses of (**2**) in that the *cis* relationship between the substituents on the imidazolone ring is achieved by means other than the catalytic reduction of an unsaturated imidazolone.

Rosemund reduction of 5-ethoxycarbonyl-n-pentanoyl chloride[3] followed by immediate acetalization of the ester aldehyde yielded the acetal ester (**3**) (62%), ν_{max} 1740 cm^{-1}, δ 1·22 (3H, t, J 7 Hz, OCH_2Me), 4·12 (2H, q, J 7 Hz,



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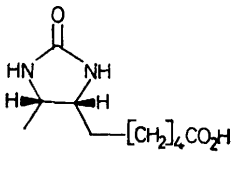
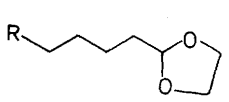
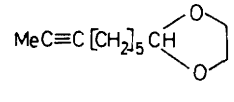


(2)

OCH_2Me), and 4·85 (1H, t, J 4·3 Hz, acetal-H). Treatment of (**3**) with $LiAlH_4$ afforded the acetal alcohol (**4**) (90%) which was converted by PPh_3 and CBr_4 into the bromoacetal (**5**) (75%), δ 3·41 (2H, t, J 6·5 Hz, CH_2Br) and 4·82 (1H, t, acetal-H). Alkylation of propyne with (**5**) produced the acetylenic acetal (**6**) (60%), δ 1·73 (3H, t, J 2·5 Hz, $MeC\equiv CCH_2$) and 4·80 (1H, t, acetal H). Na–NH_3 reduction of (**6**) led to the *trans*-acetal olefin (**7**) (93%) with an i.r. absorption (965 cm^{-1}) characteristic of a *trans*-substituted double-bond.[4] In order to provide additional evidence for the *trans* geometry of (**7**), the *cis*-acetal olefin (**8**) was synthesized by reduction (Lindlar) of the acetylene (**6**). The *cis*-olefin (**8**) exhibited i.r. absorption of 700 cm^{-1} as expected for a *cis*-substituted double-bond,[4] and g.l.c. analysis of the *trans*-olefin (**7**) shows that none of the *cis*-olefin (**8**) was present. The *trans*-acetal olefin was subsequently used as the olefinic component of a stereospecific aziridine synthesis devised by Hassner.[5] Sequential treatment of (**7**) with IN_3, $P(OEt)_3$, and $LiAlH_4$ afforded the *trans*-substituted aziridine (**9**) (70% from **7**), δ 1·17 (3H, d, J 5 Hz, aziridinyl-Me) and 4·80 (1H, t, acetal-H). Ring-opening of the aziridine with NaN_3 in acidic, aqueous alcohol[6] followed by acylation with $ClCO_2Et$ yielded a mixture of two isomeric azido-urethanes (**10**) (85%), ν_{max} 2110 and 1725 cm^{-1}, δ 1·25 (3H, t, J 7 Hz, OCH_2Me) and 4·12 (2H, q, J 7 Hz, OCH_2Me). Ozonolysis[7] of the mixture (**10**) at −78 °C in MeOH cleanly produced a mixture of two isomeric ethylene glycol esters (**11**), ν_{max} 2110, 1725, and 1715 cm^{-1}, δ 2·31 (2H, t, J 7 Hz, CH_2CO_2), and 3·80 (2H, t, OCH_2CH_2OH). Catalytic reduction of the ester mixture (**11**) gave a mixture of two isomeric amino esters (**12**) which was treated with NaOEt in EtOH to afford



(3) R = CO_2Et
(4) R = CH_2OH
(5) R = CH_2Br



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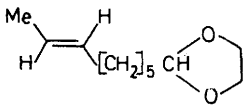

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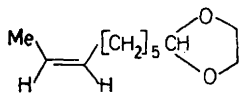

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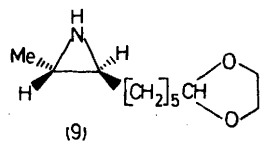

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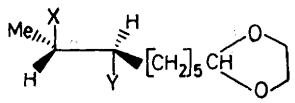
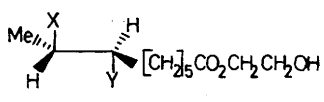


(10) X = N_3, Y = $NHCO_2Et$ and X = $NHCO_2Et$, Y = N_3



(11) X = N_3, Y = $NHCO_2Et$ and X = $NHCO_2Et$, Y = N_3

(12) X = NH_2, Y = $NHCO_2Et$ and X = $NHCO_2Et$, Y = NH_2

the ethyl ester of (±)-dethiobiotin (60% from **10**). Alkaline hydrolysis of this ester yielded crystalline (±)-dethiobiotin whose identity was established by comparison with a sample of (±)-dethiobiotin synthesized *via* previously published methods. The two samples of (±)-(**2**) were identical in all respects, including mixed m.p.

We thank the National Science Foundation for financial support.

(*Received*, 13*th February* 1975; *Com.* 180.)

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