Tetrahedron Letters No.2, pp. 143-147, 1965. Pergamon Press Ltd.
Printed in Great Britain.

TOTAL SYNTHESIS OF SPORIDESMOLIDE IV

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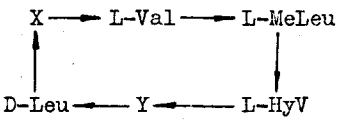
(Received 25 November 1964)

IT has been shown by New Zealand investigators that Pithomyces produce cyclic depsipeptides which in the form of crystalline spicules occur in the surface layer of the spores of these fungi (1). Russell and coworkers isolated from the coating of Pithomyces chartarum spores two cyclohexadepsipeptides, sporidesmolide I and II, whose proposed structure (I) and (II) respectively (2) we were able to confirm synthetically (3,4). Recently it was found that each species of Pithomyces produces a specific depsipeptide so that the depsipeptides may be used for taxonomic purposes (5). In fact, discrimination between P. chartarum and P. maydicus was earlier considered to be questionable (6). However, it was found that whereas P. chartarum produces mainly sporidesmolide I, the metabolic products of P. maydicus contain another depsipeptide, closely related to but not identical with the former (5). This new depsipeptide (m.p. 227-228°, $[\alpha]_D$-195°, c 1 in $CHCl_3$) was called sporidesmolide IV (7).

From a study of the alkaline and acid degradation products of sporidesmolide IV it was ascribed the cyclohexadepsipeptide structure (III), differing from that of sporidesmolide I in having an L-α-hydroxyisocaproic acid residue instead of an L-α-hydroxyisovaleric acid residue (5). It is noteworthy that L-α-hydroxyisocaproic acid had earlier not been revealed among the natural depsipeptides.

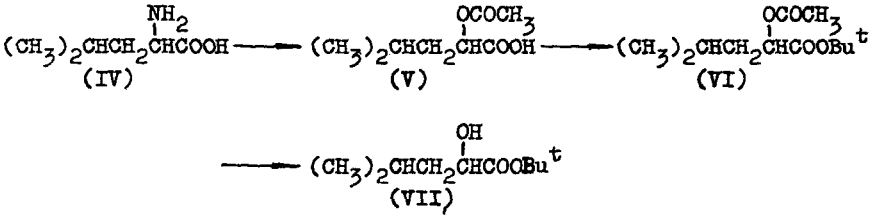


(I) X=L-HyV; Y=D-Val
(II) X=L-HyV; Y=D-aIle
(III) X=L-HyC; Y=D-Val

HyV = -O-CH(CH(CH$_3$)$_2$)-CO- HyC = -O-CH(CH$_2$CH(CH$_3$)$_2$)-CO-

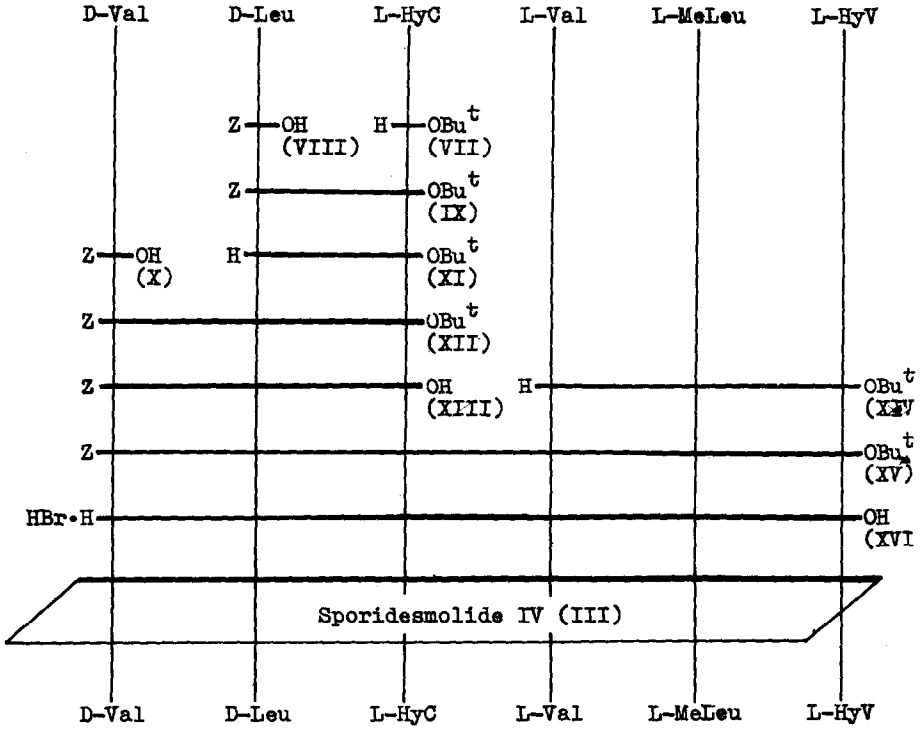
In order to verify the structure proposed for sporidesmolide IV we undertook its synthesis, according to the scheme we had earlier employed for the synthesis of sporidesmolides I and II (3,4) (Scheme 1). The tert.-butyl L-α-hydroxyisocaproate (VII) we require for the synthesis was prepared from L-leucine (IV) by a procedure similar to that described earlier by Plattner et al. (8) for the synthesis of tert.-butyl L-α-hydroxyisovalerate from L-valine. Treatment of L-leucine (IV) with isoamyl nitrite in glacial acetic acid in the presence of sodium acetate yielded L-α-acetoxyisocaproic acid (V) (b.p. 150-152°/0.5 mm Hg, $[\alpha]_D^{18}$ -40.5°, c 3.6 in benzene), which was transformed in the usual

vay (isobutylene, H_2SO_4) into the corresponding tert.-butyl ester (VI) (b.p. 105-107°/15 mm Hg, $[\alpha]_D^{18}$-39.5°, c 6.6 in benzene). Removal of the acetyl group from the acetoxy-tert.-butyl



ester (VI) by alkaline hydrolysis afforded tert.-butyl L-α-hydroxyisocaproate (VII) (b.p. 92-93°/12 mm Hg, $[\alpha]_D^{18}$-7°, c 4 in benzene). Condensation of the latter with benzyloxycarbonyl-D-leucine (VIII) by the mixed anhydride method ($PhSO_2Cl$ in pyridine) yielded the crystalline diester (IX) (m.p. 68-69°, $[\alpha]_D^{18}$ -5°, c 1.4 in benzene) which by hydrogenolysis over Pd-black was converted into the amino ester (XI) (b.p. 110-113°/0.5 mm Hg, $[\alpha]_D^{18}$-32°, c 2.7 in benzene). The amino ester (XI) was further condensed with benzyloxycarbonyl-D-valine (X) by the mixed anhydride method (ClCOOEt, Et_3N in tetrahydrofuran) and the resultant tridepsipeptide (XII) (oil, $[\alpha]_D^{18}$+15°, c 4 in benzene) was converted into the corresponding acid (XIII) (oil, $[\alpha]_D^{18}$ +34°, c 5 in benzene) by trifluoroacetic acid. The acid (XIII) was reacted with PCl_5 in ether to give the chloride which on condensation with the amino ester (XIV) (3) formed the protected hexadepsipeptide (XV) (m.p. 112-113°, $[\alpha]_D^{18}$-22°, c 0.7 in benzene). Simultaneous removal of the blocking groups from (XV)

Scheme 1



and cyclization of the resultant linear hexadepsipeptide hydrobromide (XVI) (m.p. 213°, $[\alpha]_D^{18}$ -47.5°, c 0.8 in alcohol) by the acid chloride method (1. $SOCl_2$; 2. Et_3N in benzene) then led to the cyclic hexadepsipeptide (III) in 55% yield (after chro-

*Compounds (XII) and (XIII) were purified by chromatography on neutral alumina in benzene - ethyl acetate solvent system (gradient elution). Analyses of all the intermediate compounds are in accord with the calculated values.

matography on alumina and recrystallization from alcohol).

The compound was found to have the same properties (m.p. 227-228°, $[\alpha]_D^{18}$-199°, c 0.8 in chloroform) as the natural sporidesmolide IV, the validity of whose structure has thus received final confirmation.

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