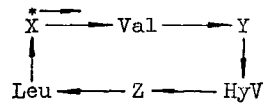
Tetrahedron Letters No.16, pp. 1111-1115, 1965. Pergamon Press Ltd.
Printed in Great Britain.

TOTAL SYNTHESIS OF SPORIDESMOLIDE III

Yu.A.Ovchinnikov, A.A.Kiryushkin and M.M.Shemyakin
Institute for Chemistry of Natural Products,
USSR Academy of Sciences, Moscow, USSR

(Received 4 March 1965)

The depsipeptide fraction of Pithomyces chartarum metabolites contains besides the major components, sporidesmolides I and II (Formulas I and II) very small amounts of still another cyclodepsipeptide, sporidesmolide III (m.p. 277-278°; $[\alpha]_D$ -80.0±1.2°, c 1.6 in acetic acid)(1). Because of the insignificant amounts available the structure of this substance remained unresolved for some time and only after establishment of the basic routes for the mass-spectrometric fragmentation of cyclodepsipeptides (2,3) could this structure be elucidated with the minimal amounts of substance at hand. It was found that sporidesmolide III differs from sporidesmolide I only by the absence of an N-methyl group in the L-leucine residue (Formula III)(4).



(I) LLLLDD; X=HyV; Y=MeLeu; Z=Val
(II) LLLLDD; X=HyV; Y=MeLeu; Z=aIle
(III) LLLLDD; X=HyV; Y=Leu; Z=Val
(IV) LLLLDD; X=HyC; Y=MeLeu; Z=Val
(V) LDDLDD; X=HyV; Y=Leu; Z=Val

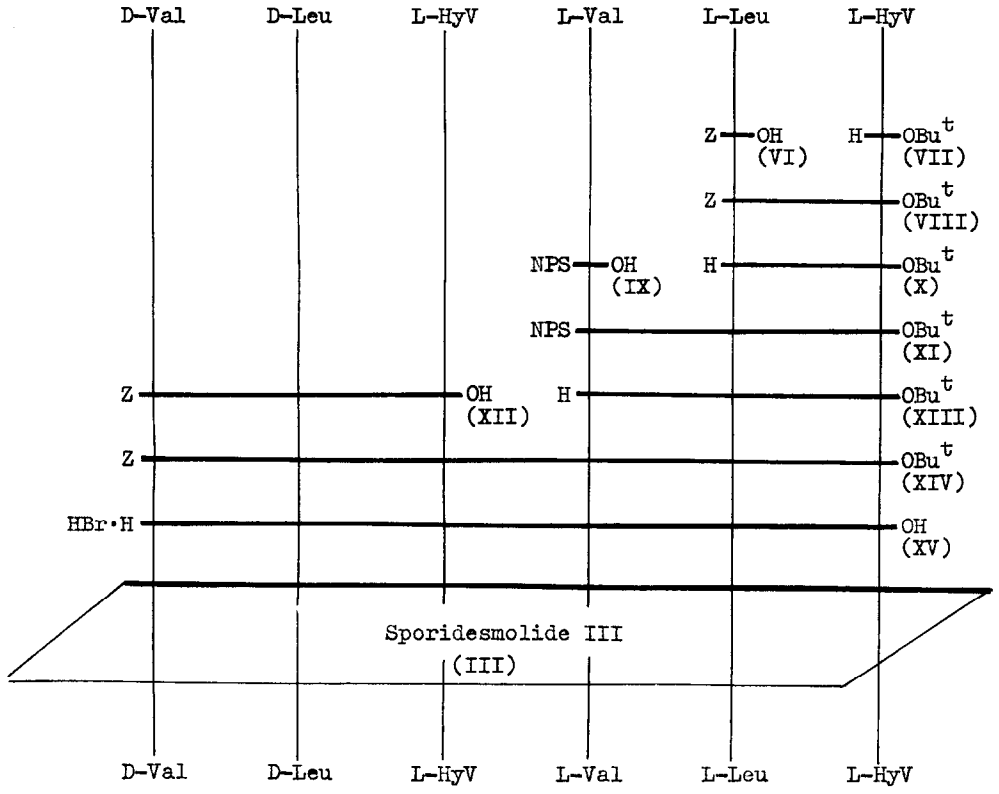
HyV = -OCHCO- (CH(CH$_3$)$_2$) HyC = -OCHCO- (CH$_2$CH(CH$_3$)$_2$)

In order to confirm the structure of sporidesmolide III, we undertook its synthesis according to the scheme we had used priorly for the synthesis of sporidesmolides I, II and IV (5-7)* (see Scheme 1). The only difference in the synthesis of sporidesmolide III from that of the other sporidesmolides was the use of the o-nitrophenylsulfenyl group (NPS) (9) for protection of the N-terminal amino acid. It turned out that this protective group can be selectively removed in the presence of tert.-butyl ester; this shows its use to be quite promising in the synthesis of peptides and depsipeptides of complex nature.

Benzyloxycarbonyl-L-leucine (VI) was condensed with tert.-butyl L-α-hydroxyisovalerate (VII) by the mixed anhydride method ($PhSO_2Cl$ in pyridine) to give the diester (VIII)(oil, $[\alpha]_D^{18}$ -27°, c 2 in benzene). The product was subjected to catalytic hydrogenation over Pd-black to give the aminodiester (X)(b.p. 102-104°/0.5 mm; $[\alpha]_D^{18}$ -2°, c 2.5 in benzene) which, when treated with o-nitrophenylsulfenyl-L-valine (IX)(9) in the presence of dicyclohexylcarbodiimide gave rise to the depsipeptide (XI)(oil, $[\alpha]_D^{18}$ -74.5°, c 1.8 in benzene). The NPS grouping of the tridepsipeptide (XI) was removed with the calculated amount of HCl in ether to give the hydrochloride of the ester (XIII)(yield 70%; $[\alpha]_D^{18}$ -28°,

*After sending our paper on the synthesis of sporidesmolide IV (Formula IV) for publication, we were able to make direct comparision of our preparation, further purified by crystallization from alcohol and sublimation, with a natural specimen kindly sent to us by D.W.Russell. The comparision confirmed the identity of the synthetic specimen (m.p. 230-231°(corr.); $[\alpha]_D^{18}$ -215°, c 0.5 in $CHCl_3$) and the naturally occurring substance (m.p. 233° (corr.); $[\alpha]_D$ -211°, c 2 in $CHCl_3$)(8).

Scheme 1



c 1.2 in alcohol). Condensation of the latter with N-benzyloxycarbonyltridepsipeptide (XII)(5) by the acid chloride method (1. PCl_5 in ether; 2. Et_3N in tetrahydrofuran) led to the protected hexadepsipeptide (XIV)(yield 75%; m.p. 203-204°; $[\alpha]_D^{18}$ -20.4°, c 0.9 in dimethylformamide). Simultaneous removal of the protecting groups and cyclization of the resultant hexadepsipeptide hydrobromide (XV) by the acid chloride method (1. $SOCl_2$;

2. Et_3N in a mixture of benzene with methylene chloride) afforded the cyclohexadepsipeptide (III) in 70% yield (after chromatography on alumina and recrystallization from $CHCl_3$); m.p. 294-295°(corr.); $[\alpha]_D^{18}$-79.2°(c 0.7 in acetic acid). The sample of the naturally occurring sporidesmolide III, which we received from D.W.Russell, had m.p. 287-288°(corr.) and displayed no drop in melting point when mixed with the synthetic specimen. Comparision of the chromatographic behaviour of the synthetic and naturally occurring specimens as well as their IR spectra gave final proof of their complete identity.

It should be pointed out that earlier in a study of the doubling reaction observed in the cyclization of depsipeptides we had synthesized the cyclohexadepsipeptide (V) a very close analog of sporidesmolide III, differing from the latter only by the configuration of one leucine and one valine residues (10).

Acknowledgement. We are greatly indebted to Dr. D.W.Russell for the specimens of the naturally occurring depsipeptides and for valuable information about the results of his investigations into the structures of these compounds.

REFERENCES

1. D.W.Russell, J. Chem. Soc. 1962, 753.

2. N.S.Wulfson, V.A.Puchkov, V.N.Bochkarev, B.V.Rosinov, A.M.Zyakoon, M.M.Shemyakin, Yu.A.Ovchinnikov, V.T.Ivanov, A.A. Kiryushkin, E.I.Vinogradova, M.Yu.Feigina and N.A.Aldanova, Tetrahedron Letters 1964, 951.

3. C.G.Macdonald, J.C.Shannon and A.Taylor, Tetrahedron Letters 1964, 2087.

4. D.W.Russell, C.G.Macdonald and J.C.Shannon, Tetrahedron Letters 1964, 2759.

5. M.M.Shemyakin, Yu.A.Ovchinnikov, V.T.Ivanov and A.A. Kiryushkin, Tetrahedron 19, 995 (1963).

6. M.M.Shemyakin, Yu.A.Ovchinnikov, V.T.Ivanov and A.A. Kiryushkin, Tetrahedron Letters 1963, 1927.

7. A.A.Kiryushkin, Yu.A.Ovchinnikov and M.M.Shemyakin, Tetrahedron Letters 1965, 143.

8. D.W.Russell, private communication.

9. L.Zervas, D.Borovas and E.Gazis, J. Am. Chem. Soc. 85, 3660 (1963).

10. Yu.A.Ovchinnikov, V.T.Ivanov, A.A.Kiryushkin and M.M. Shemyakin, Dokl. Akad. Nauk SSSR 153, 122 (1963).