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TOTAL SYNTHESIS OF THE DIDEMNINS - 2. SYNTHESIS OF DIDEMNIN A, B, C AND PROLYLDIDEMNIN A[1]

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Abstract - Didemnin A, C, prolyldidemnin A and the highly cancerostatic, antiviral and immunosuppressive didemnin B have been prepared by deprotecting the benzyloxycarbonyl compound **5** and constructing the side chain that determines the biological properties.

In the first publication[2] we have described the construction of the linear peptolide **1a** by acylation of the isostatine derivative **3**. This step is critical since the free amine rather quickly forms the γ-lactam **4**. Therefore the liberation of the free amine from its hydrochloride **3** and the acylation with a highly active derivative of **2** have to be performed immediately one after another yielding up to 80 % **1a** using BOP-Cl[3]. Following ring closure of the pentafluorophenyl ester **1b** in a two phase system forms the cyclopeptolide **5** in 70 % yield.
The removal of the benzyloxycarbonyl group by catalytic hydrogenation only proceeds slowly reflecting the shielding of this region of the ring which also makes the subsequent construction of the side chain difficult. - The acylation giving rise to Z-didemnin A could be achieved with the thiol ester of Z-N-methyl-(R)-leucine and 4,6-dimethyl-2-thiopyridone-3-carbonitrile[4] in 68 % yield. The subsequent hydrogenolytic deprotection gave didemnin A (**6**). - Acylations with symmetric anhydrides of O-benzyllactic acid and O-benzyllactylproline respectively were used by Rinehart[5] to synthesize didemnin C (37 % yield) and didemnin B (no yield given). But in our hands O-benzyloxycarbonyllactic acid chloride, O-benzyloxycarbonyllactylproline chloride and N-benzyloxycarbonylproline chloride[6,7] proved to be the reagents of choice and formed Z-didemnin C (80 % yield), Z-didemnin B (85 % yield) and Z-prolyldidemnin A (95 % yield) which were deprotected by catalytic hydrogenation to give didemnin B (**7**), C (**8**) and prolyldidemnin A (**9**) quantitatively.
The synthetic compounds are identical in every respect with the natural compounds.

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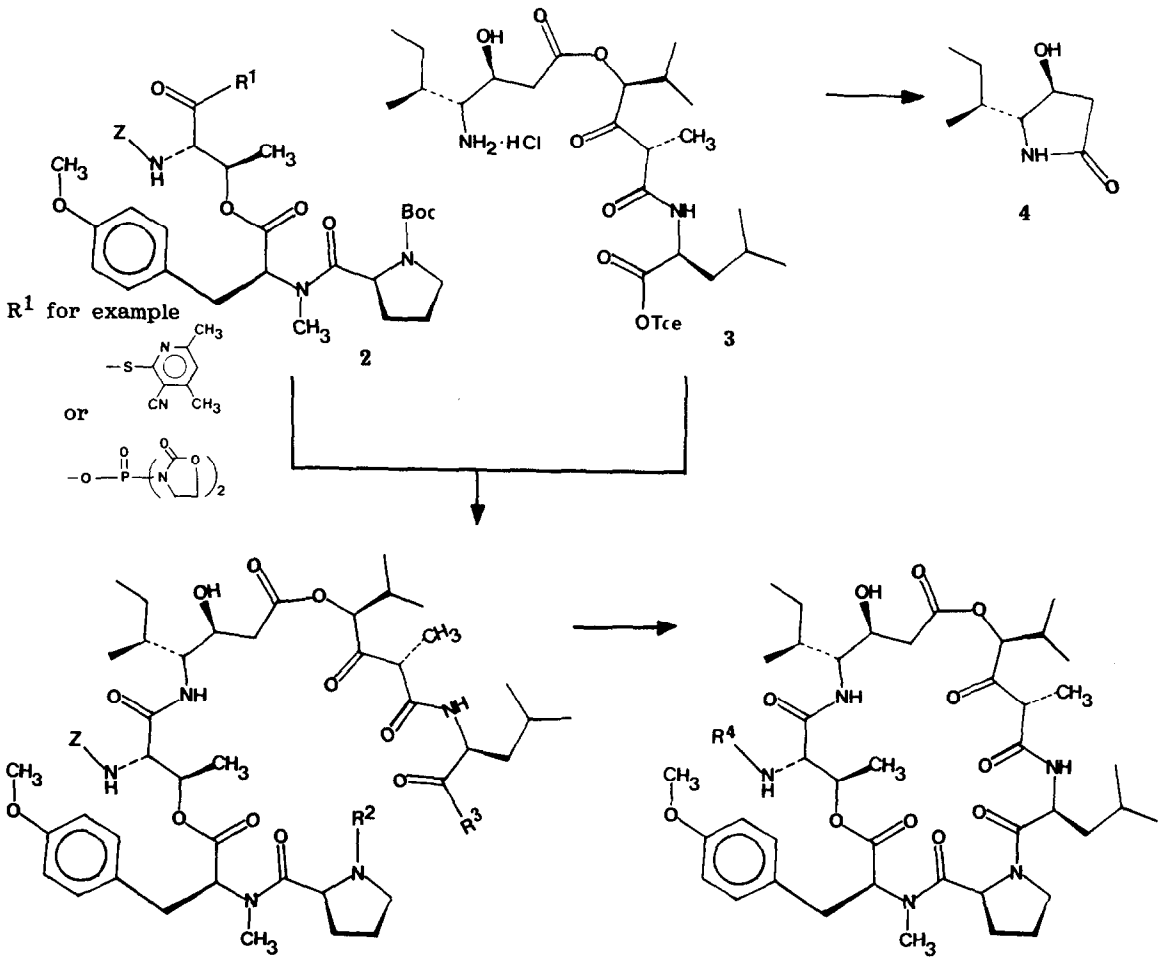

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