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IMPROVED METHODS OF SYNTHESIS OF VALINOMYCINS

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Abstract: Linear depsipeptides have been efficiently cyclised to give cyclodepsipeptide valinomycin analogues via a protocol using activated pentafluorophenyl esters in conjunction with deprotection of a benzylcarbamate by in situ hydrogenolysis. Valinomycins having a 36-membered ring could be obtained in up to 84% yield. Similar cyclisations affording 24- and 48- membered rings also are described.

Valinomycin (**1**) is a 36-membered naturally occurring cyclodepsipeptide, which has been much studied as an ionophore[1], particularly recently in the commercially important area of ion-selective electrodes[2]. Earlier the syntheses of valinomycin[3,4,5] and modified valinomycins[6,7] have been reported by cyclisation of linear depsipeptide precursors. However the methodology then available for such cyclisations could lead only to moderate yields in the cyclisation step. Improved methods of cyclisation are now available[8]. Cyclisations via activated pentafluorophenyl esters have been used in the synthesis of biologically active cyclic peptides[9], and, very recently, in the synthesis of the cyclodepsipeptide didemnins[10]. In this communication we report our use of pentafluorophenyl esters in order to prepare efficiently the cyclodepsipeptide valinomycins. These valinomycins are shown to be highly selective ionophores.

In the synthesis of cyclodepsipeptides the terminal step normally has been the cyclisation by formation of an amide bond rather than an ester bond. Standard methods such as dicyclohexylcarbodiimide (DCC) coupling, coupling using diphenylphosphoryl azide (DPPA) and acid chlorides, and use of activated esters might be used. In the case of valinomycin (**1**), and modified valinomycins the acid chloride route gives moderate yields (formation of the D-Hyiv-D-Val bond in 24% yield[5] and the L-Lac-L-Val bond in 51% yield[4] in valinomycin). The phosphite (mixed anhydride) route gives lower yields[11]. In such cyclisations yields are influenced by certain key features of the structure of the linear depsipeptide precursors. The same configuration at the chiral centres of the precursor[12,13], bulky side-chains[13] and the absence of N-alkyl substitution[12] all diminish cyclisation yields. Therefore in order to establish a general method, which would be applicable to even the more difficult cyclisations we chose to investigate first the cyclisation of the all L-configurated depsipeptide (**2**).

The linear depsipeptide (**2**) and the other peptides shown in the Table were all prepared by standard coupling methods. Ester and amide bonds were formed using DCC coupling. Although cyclisation by the acid chloride method has been applied successfully to the synthesis of valinomycin[3-5], reaction of the linear peptide (**2**) with thionyl chloride followed by exposure to triethylamine in benzene under high dilution conditions failed: only polymeric products were observed. Similarly attempted DCC coupling at high dilution of the peptide (**2**) only gave polymers. Application of the mixed anhydride method using DPPA gave the desired cyclic product (**3**), but only in 3% yield. The consequence of the all L-configuration in the precursor (**2**) is the failure of the previously established methods. This can be attributed to the inability of the chain to adopt conformations in which the two

reacting centres are close together. However by slow injection of the trifluoroacetate salt of the pentafluorophenyl ester (4) into dioxan at 90°C containing dimethylaminopyridine the desired product (3) could be obtained in 14% yield. Again polymerisation was an important side reaction. In order to minimise this polymerisation the cyclisation strategy was modified by an in situ generation of the ester (4) from the benzyloxycarbonyl protected ester (5). The ester (5) was slowly injected into dioxan at 90°C containing dimethylaminopyridine, whilst hydrogen was slowly bubbled into the solution, which contained suspended palladium on charcoal. Under these conditions the benzyloxycarbonyl group was removed, the intermediate aminoester (4) cyclised efficiently, and the 36-membered ring was formed in 70% yield.

Table. Cyclisations to Cyclodepsipeptides.

Linear Depsipeptide Precursor	Cyclisation Conditions (Time, hours)	Cyclodepsipeptide	Yield
(2)	via acid chloride or DCC coupling	(3)	0
(2)	DPPA	(3)	3%
(4)	Dioxan (36)	(3)	14%
(5)	Dioxan (6)	(3)	70%
(6)	Dioxan (6)	(7)	48%
(6)	Dioxan (24)	(7)	84%
(8)	Dioxan (48)	(9)	24%
(10)	Dioxan (24)	(12)	26%[a]
(13)	Dioxan (24)	(14)	0

[a] The octacyclodepsipeptide (11) was also obtained in 5% yield.

Having established a methodology applicable to more difficult cyclisations we investigated the synthesis of analogues of valinomycin (1). Using the procedure described above the linear dodecapeptide (6) in an injection period of 6 hours gave the modified valinomycin (7) in 48% yield. Injection over 24 hours gave in 84% yield the product (7) in which the phenyl substituents are placed close to the entrances of a valinomycin held in a bracelet conformation. Similarly the linear peptide (8) gave in 24% yield the product (9) in which the phenyl substituents are placed around the outside surface of a bracelet conformation. The lower yield in the latter cyclisation can be attributed to the adverse siting of the phenyl groups.

The improved cyclisation permits an efficient access to potentially interesting valinomycin analogues. Both the products (7) and (9) can adopt the bracelet conformation of a valinomycin, and bind metal ions efficiently. The ionophores (7) and (9) have the same high affinity for potassium ion as valinomycin (1), and show similar high ion selectivity (uptake of potassium ion favoured over sodium ion by $>10^4$)

The application of this improved cyclisation procedure avoids polymer formation. Although a palladium surface effect[14] may assist cyclisation the formation of the 36-membered rings of valinomycins is particularly favoured. Thus the all L-configurated octadepsipeptide (10) gives both the cyclodepsipeptides (11) and (12) having 24- and 48-membered rings respectively. The tetradepsipeptide (13) fails to afford the cyclodepsipeptide (14). The unprecedented high efficiency of cyclisation of the pentafluorophenyl esters in the valinomycin series may not have a wide range of application in formation of cyclodepsipeptides, but it provides a satisfactory route to a wide range of aryl substituted valinomycins.

Cyclo-(D-Val-L-Lac-L-Val-D-Hyiv)$_3$
(1)

H-(L-Val-L-Hyiv-L-Val-L-Hyiv)$_3$-OH
(2)

Cyclo-(L-Val-L-Hyiv-L-Val-L-Hyiv)$_3$
(3)

H-(L-Val-L-Hyiv-L-Val-L-Hyiv)$_3$-OPfp
(4)

Z-(L-Val-L-Hyiv-L-Val-L-Hyiv)$_3$-OPfp
(5)

Z-(D-Phe-L-Hyiv-L-Phe-D-Lac)$_3$-OPfp
(6)

Cyclo-(D-Phe-L-Hyiv-L-Phe-D-Lac)$_3$
(7)

Z-(D-Ala-L-Hyhc-L-Val-D-Hyhc)$_3$-OPfp
(8)

Cyclo-(D-Ala-L-Hyhc-L-Val-D-Hyhc)$_3$
(9)

Z-(L-Val-L-Hyiv-L-Val-D-Hyiv)$_2$-OPfp
(10)

Cyclo-(L-Val-L-Hyiv-L-Val-L-Hyiv)$_2$
(11)

Cyclo-(L-Val-L-Hyiv-L-Val-L-Hyiv)$_4$
(12)

Z-L-Val-L-Hyiv-L-Val-L-Hyiv-OPfp
(13)

Cyclo-(L-Val-L-Hyiv-L-Val-L-Hyiv)
(14)

Val = valyl; Lac = lactyl; Hyiv = -hydroxyisovaleryl;

Phe = phenylalanyl; Ala = alanyl; Hyhc = -hydroxyhydrocinnamyl;

Z = benzyloxycarbonyl; Pfp = pentafluorophenyl.

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