A New Method for the Stepwise Synthesis of Depsipeptides

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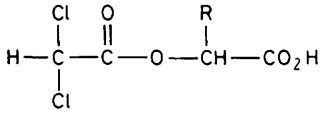
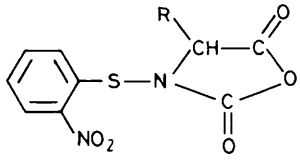
Depsipeptides have been prepared in a stepwise fashion by a method using the dichloroacetyl (Dca) group as a suitable protecting group for the hydroxy group of hydroxy acids and 2-nitrophenylsulphenyl (Nps) *N*-carboxy α-amino acid anhydrides (NCAs) as a highly reactive amino acid derivative to acylate the hydroxy compounds.

Depsipeptides have previously been prepared only by condensation of fragments having a *C*-terminal hydroxy acid moiety which could be synthesized without protection of the hydroxy group of the hydroxy acid. To date no hydroxy-protecting groups suitable for the synthesis of depsipeptides have been found.[1–3] This restricts the strategy for depsipeptide synthesis, so that a stepwise method which freely introduces a hydroxy acid at any position of the depsipeptide is desirable. We report here a new stepwise method for the synthesis of depsipeptides involving the use of hydroxy acids protected by the dichloroacetyl group[4] (**1**) together with Nps–NCAs (Nps = 2-nitrophenylsulphenyl, NCAs = N-carboxy α-amino acid anhydride) (**2**) being highly reactive towards the hydroxy group.[5,6]

The successful stepwise synthesis of depsipeptides was demonstrated by the preparation of a hexadepsipeptide consisting of alternate L-lactic acid (Lac) and L-alanine (Ala) units Dca-(Lac-Ala)$_3$-OBzl. L-Alanine benzyl ester was allowed to react, in the presence of dicyclohexylcarbodiimide (DCC), with Dca-Lac-OH which had been prepared without racemization by the reaction of lactic acid with dichloroacetyl chloride.† The didepsipeptide Dca-Lac-Ala-OBzl was obtained as pure crystals and showed three C=O stretching i.r. bands at 1766 (Dca), 1728 (the ester), and 1655 cm^{-1} (the amide). The Dca group of the didepsipeptide was almost instantly removed with an equimolar amount of sodium hydroxide[4] to give H-Lac-Ala-OBzl, which was treated with Nps-Ala NCA[7] in the presence of pyridine to yield an oily tridepsipeptide Nps-Ala-Lac-Ala-OBzl, showing i.r. bands at 1740 (the ester C=O) and 1678 cm^{-1} (the amide C=O). The Nps group of the tridepsipeptide was removed on treatment with hydrochloric acid to give the *N*-unprotected tridepsipeptide, which was allowed to react again with Dca-Lac-OH to give a crystalline tetradepsipeptide Dca-(Lac-Ala)$_2$-OBzl. The tetradepsipeptide was sequentially treated by the same procedure as above with Nps-Ala NCA and Dca-Lac-OH to give the hexadepsipeptide Dca-(Lac-Ala)$_3$-OBzl. Results of the synthesis and analytical data of the products are summarised in Table 1.



(**1**)



(**2**)

† Dca-L-Lac-OH (0.02 mol) was dissolved in methanol (5 ml), an aqueous solution of sodium hydroxide (4 M, 10 ml) added, and the solution diluted with water to 20 ml. An authentic solution was prepared as follows: L-lactic acid (0.02 mol), dichloroacetic acid (0.02 mol), methanol (5 ml) and NaOH (4 M 10 ml) were mixed in a flask and the solution was diluted with water to 20 ml. The optical rotation of these samples was measured at 20 °C with a Jasco DIP-SL automatic polarimeter. The hydrolysed sample of Dca-L-Lac-OH and the authentic sample showed optical rotations −1.12° and −1.11°, respectively. This shows that Dca-L-Lac-OH is of chiral integrity.

Table 1. Analytical data for oligodepsipeptides.[a]

Depsipeptide	% Yield	M.p. (°C)	$[\alpha]_D$[b]	R_F
Dca-Lac-Ala-OBzl	85	50—51	−32.1	0.64[c]
Nps-Ala-Lac-Ala-OBzl	74	oil	−79.0	0.44[c]
Dca-(Lac-Ala)$_2$-OBzl	92	119—120	−46.0	0.45[d]
Nps-Ala-(Lac-Ala)$_2$-OBzl	78	oil	−74.8	0.33[d]
Dca-(Lac-Ala)$_3$-OBzl	95	171—172	−52.7	0.19[d]
Nps-D-Val-Lac-OBzl	93	49—50	+41.7	0.82[c]
Dca-D-Hiv-D-Val-Lac-OBzl	96	oil	+13.5	0.76[c]
Nps-Val-D-Hiv-D-Val-Lac-OBzl	85	88—89	−54.5	0.74[c]

[a] Satisfactory elemental analyses for C, H, and N were obtained for all compounds in tetrahydrofuran. [b] (THF) (*c* 0.5). [c] Eluant: EtOAc–benzene–hexane (2:2:1). [d] Eluant EtOAc–benzene (1:1).

Another example, of interest from a biological aspect, is shown by the stepwise synthesis of a tetradepsipeptide Dca-valyl-D-hydroxyisovaleryl-D-valyl-lactic acid benzyl ester (Dca-Val-D-Hiv-D-Val-Lac-OBzl) which is the repeating unit in valinomycin.[1] Lactic acid benzyl ester was treated with Nps-D-Val NCA in the presence of pyridine to give a didepsipeptide Nps-D-Val-Lac-OBzl. The Nps group of the didepsipeptide was removed with hydrochloric acid and the resulting HCl·H-D-Val-Lac-OBzl was treated with Dca-D-Hiv-OH and DCC to give a tridepsipeptide Dca-D-Hiv-D-Val-Lac-OBzl. After removal of the Dca group of the tridepsipeptide, the resulting OH-unprotected tridepsipeptide was allowed to react with Nps-Val NCA to give a tetradepsipeptide Nps-Val-D-Hiv-D-Val-Lac-OBzl. Results of the synthesis are summarised in Table 1.

This study demonstrates that depsipeptides can be successfully synthesised in a stepwise fashion using Dca-hydroxy acids and Nps–NCAs. The protecting groups used: Dca for OH group and the Nps for NH_2 group, can be removed almost instantly so that deprotection of these groups does not affect the ester or amide linkages in the depsipeptides.

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