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STEREOCONTROLLED SYNTHESIS OF D-α-HYDROXY CARBOXYLIC ACIDS FROM L-AMINO ACIDS

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Summary: Optically active D-α-hydroxy carboxylic acids are obtained from L-amino acids via L-α-halocarboxylic acids and their stereoselective reaction with cesium p-nitrobenzoate.

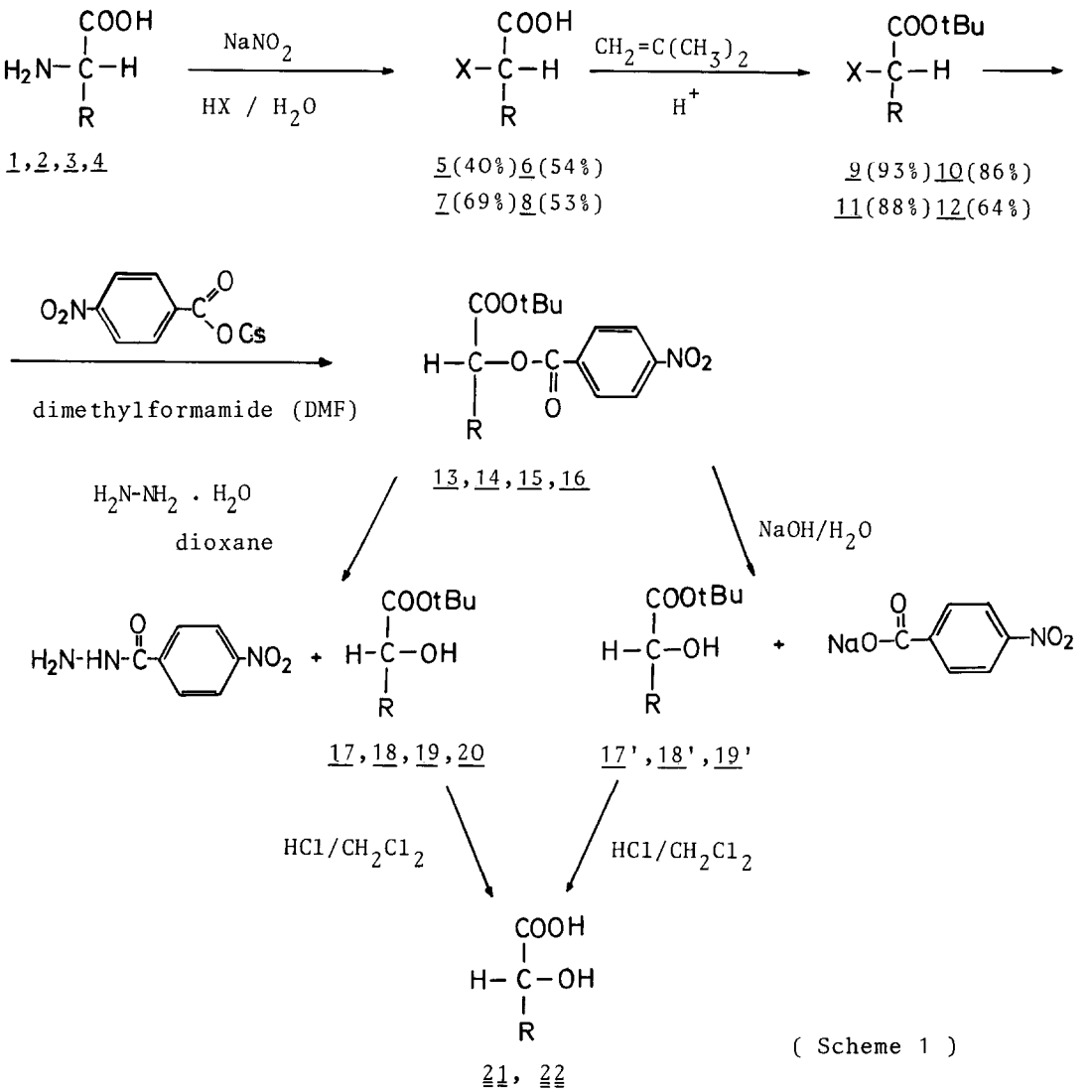
D-α-Hydroxy carboxylic acids are of interest because they represent characteristic partial structures of many natural products, for instance, of peptolides. They are usually obtained from expensive D-amino acids via desamination procedures[1-4].

We recently found an efficient synthesis of depsipeptide derivatives containing D-α-hydroxy carboxylic acids[5]. It consists of the ester formation between N-protected L-amino acids and D-α-hydroxy carboxylic acid esters by means of a S_{N2}-reaction. In this way, L-α-halo carboxylic acid esters (obtained from L-amino acids) were treated with cesium salts of the amino acid derivatives.

Here we describe the extension of this reaction to a general synthesis of D-α-hydroxy carboxylic acids. L-α-Halo carboxylic acid t-butylesters, obtained from L-amino acids[5], can be converted to O-acyl-D-α-hydroxy carboxylic acid t-butylesters by the reaction with cesium carboxylates. These salts are very nucleophilic and the cesium effect[6] accounts for the complete inversion of configuration[7]. We found cesium p-nitrobenzoate to be an effective nucleophile. It has the additional advantage that the p-nitro benzoates formed can be cleaved under very mild conditions (vide infra).

To obtain the hydroxy acid derivatives 13-16 in acceptable yields at room temperature, reaction times of 4-6 weeks are required. Working at higher temperatures results in side reactions:Under these conditions the products 13-16 are subject to a thermal cis elimination of p-nitrobenzoic acid. Furthermore, since the solubility of cesium halides is increased at elevated temperatures, Finkelstein exchange of the halide in the haloesters 9-12 occurs.

However, by careful elaboration of the reaction conditions (concentrations of the reactands, reaction time and temperature) the p-nitro-benzoates 13-16 can be synthesized efficiently in enantiomerically pure form. (Table 1)



(Scheme 1)

1, 5, 9, 13, 17, 17':	R=-CH_3, X=Cl
2, 6, 10, 14, 18, 18', 21:	R= -CH_2-Ph, X=Cl
3, 7, 11, 15, 19, 19':	R= -$CH(CH_3)_2$, X=Br
4, 8, 12, 16, 20, 22 :	R= -CH_2-$CH(CH_3)_2$, X=Cl

Table 1: Optimal conditions for the synthesis of O-p-nitrobenzoyl-α-hydroxy carboxylic acid t-butylesters with 5 mmol starting materials

product [a]	T (°C)	t (h)	V (ml)	yield (%)	$[\alpha]_D^{22}$ (c in C_6H_6)
13	80	2	7	70	- 38.5 (o.9)
14	70	18	10	65	- 14.2 (0.6)
15	80	1.5	8	46	- 32.3 (0.8)
16	80	4	10	45	- 9.8 (0.4)

a) All compounds gave correct elemental analysis.

The p-nitrobenzoyl group can be removed by hydrazinolysis or with sodium hydroxide at pH 10. The configuration of the asymmetric center remains unchanged and the yields are excellent.

Table 2: α-D-Hydroxy carboxylic acid t-butylesters and α-D-hydroxy carboxylic acids according to Scheme 1

	product	yield (%)	mp (°C)	$[\alpha]_D^{22}$	$[\alpha]_D$ - Lit)
17	D-Lac-tBu	70	41	+ 8.7 (0.26, C_6H_6)	L-Lac-tBu
17'	D-Lac-OtBu	30	41	+ 7.8 (0.9, C_6H_6)	- 10.5 (C_6H_6) [9]
18	D-3Ph-Lac-OtBu	82	39-40	+ 9.3 (0.6, $CHCl_3$)	-
18'	D-3Ph-Lac-OtBu	93	39-40	+ 9.5 (0.6, $CHCl_3$)	-
19'	D-Hyiv-OtBu	80	31	+ 2.6 (0.7, C_6H_6)	+2.9 (0.8, C_6H_6) [10]
19	D-Hyiv-OtBu	92	31	+ 2.9 (0.9, C_6H_6)	
20	D-Hyicap-OtBu	93	oil	+ 4.5 (0.89, C_6H_6)	-
21	D-3Ph-Lac-OH	91	121-123	+ 33.2 (0.3, acetone)	+ 32.8 (acetone) [3]
22	D-Hyicap-OH	86	79-80	+ 12.7 (0.4, water)	+ 13.3 (water) [4]

The specific rotations of 17, 17', 19, 19' are in good agreement with those as reported. In addition, the α-hydroxy acids 3-phenyl-lactic acid 21 and leucinic acid 22, obtained after removal of the t-butylester group from 18, 18' and 20, show specific rotations, wich are identical with those described in the literature. Thus, D-α-hydroxy carboxylic acids can effectively and selectively be synthesized from inexpensive L-α-amino acids.

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8) Procedure: 0.84 g (5 mmol) of p-nitrobenzoic acid is suspended in 200 ml methanol/water (10:1 V/V). The pH is adjusted to 7 with a 20% aqueous solution of cesium carbonate and the solvents are removed in vacuo. The remaining residue is taken up in 120 ml dimethylformamide and evaported. After repeated evaporation yellow crystals of cesium-p-nitrobenzoate are obtained in quantitative yield. These crystals are suspended in DMF at the optimal temperature (see Table 1) and the α-halo carboxylic acid t-butylester is added. After the reaction is complete the solvent is evaporated in vacuo and the remaining residue is taken up in CH_2Cl_2/water. The organic layer is separated, dried over Na_2SO_4 and the solvent is removed in vacuo. The pure products can be obtained by flash chromatographie (petroleum ether/ethyl acetate 25:1) or by distillation.

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