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ENZYME CATALYSED HYDROLYSIS OF DIALKYLATED PROPANEDIOIC ACID DIESTERS, SYNTHESIS OF OPTICALLY PURE (S)-α-METHYLPHENYLALANINE, (S)-α-METHYL-TYROSINE AND (S)-α-METHYL-3,4-DIHYDROXYPHENYLALANINE

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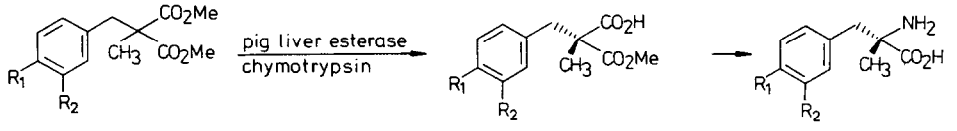
ABSTRACT: Pig liver esterase and α-chymotrypsin catalysed hydrolysis of the meso-diesters 1, 2 and 3 gave the corresponding monoesters which then could be transformed into enantiomerically pure (S)-α-methylphenylalanine, (S)-α-methyltyrosine and (S)-α-methyl-3,4-dihydroxyphenylalanine.

Enzyme catalysed hydrolysis of prochiral diesters is an attractive method for the preparation of chiral synthons for the synthesis of more complex compounds of biological or pharmacological interest.[1,2,3] In this paper we report enzyme catalysed enantioselective syntheses of the biologically and pharmacologically important (S)-α-methylphenylalanine, (S)-α-methyltyrosine and (S)-α-methyl-3,4-dihydroxyphenylalanine ((L)-α-methyl DOPA) (Scheme).



	R_1	R_2
1	H	H
2	OMe	H
3	OMe	OMe

	R_1	R_2
(R)-4	H	H
(R)-5	OMe	H
(R)-6	OMe	OMe

	R_1	R_2
(S)-7	H	H
(S)-8	OMe	H
(S)-9	OMe	OMe
(S)-10	OH	H
(S)-11	OH	OH

Scheme

The substrates 1,[1] 2[4] and 3[5] were prepared by alkylation of methylpropanedioic acid dimethyl ester with benzylbromide, 4-methoxybenzylbromide and 3,4-dimethoxybenzylbromide respectively, in good yields (80-90 %).[6] Pig liver esterase catalysed hydrolyses of 1, 2, and 3 gave the products (R)-4 (45 % e.e.),[1] (R)-5(82 % e.e.),[7] and (R)-6, (93 % e.e.)[8] respectively. This increase of the enantioselectivity depending on the size of

the alkyl groups as well as the absolute configurations of the products were in accordance with our previous findings.[1] The enantiomeric excess in the pig liver esterase hydrolysis was influenced very much by the concentration of DMSO used in the incubation mixture. The highest enantiomeric excess was obtained with 50 % DMSO. All hydrolyses were performed with good yields (85-100%) and the rates of the reactions were sufficient for gram scale experiments.[9] Crystallisation of the monoester (R)-6 of 93 % e.e. gave material with no detectable (S)-isomer according to NMR-analysis.[10]

The use of α-chymotrypsin as catalyst gave enantiomerically pure monoesters (R)-4, (R)-5 and (R)-6. However, the reaction rates with the substrates 2 and 3 were very low and incubation times of several weeks were needed.

The enantiomerically pure monoesters (R)-4, (R)-5 and (R)-6 were transformed to the desired aminoacids (S)-7,[1] (S)-8,[11,12] and (S)-9[11,13] via acyl azide formations followed by Curtius rearrangements[14] in yields of 86 %, 63 %, and 74 % respectively. Treatment of (S)-8 and (S)-9 with aqueous HBr (48 %-aq) is known to give (S)-10 and (S)-11 in good yields.[15]

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4. Compound 2 : ^{1}H NMR δ: 7.02 (d,2H), 6.79 (d,2H), 3.77 (s,3H), 3.72 (s,6H), 3.17 (s,2H), 1.34 (s,3H). ^{13}C NMR δ: 172.1, 158.4, 130.9, 127.7, 113.4, 54.9, 54.8, 52.2, 40.2, 19.5.
5. Compound 3 : ^{1}H NMR δ: 6.8-6.65 (m,3H), 3.85 (s,3H), 3.84 (s,3H), 3.73 (s,6H), 3.17 (s,2H), 1.35 (s,3H). ^{13}C NMR δ: 172.3, 148.5, 148.0, 128.4, 122.3, 113.3, 110.9, 55.7, 52.4, 40.9, 19.8.
6. NaH, THF, 0-25°C.
7. Compound (R)-5 : $[\alpha]_D$=4.2°(c=2.6, $CHCl_3$) ^{1}H NMR δ: 7.03 (d,2H), 6.78 (d,2H), 3.76 (s,3H), 3.74 (s,3H), 3.29 (d,J=13.9 Hz,1H), 3.10 (d,J=13.9 Hz,1H), 1.38 (s,3H). ^{13}C NMR δ: 177.3, 172.3, 158.7, 131.1, 127.6, 113.7, 55.1, 55.0, 52.6, 40.6, 19.8.
8. Compound (R)-6 : $[\alpha]_D$=5.8°(c=0.85, $CHCl_3$) ^{1}H NMR δ:6.8-6.6 (m,3H), 3.82 (s,3H), 3.79 (s,3H), 3.73 (s,3H), 3.23 (d,J=13.9 Hz,1H), 3.10 (d,J=13.9 Hz,1H), 1.38 (s,3H). ^{13}C NMR δ : 177.5, 172.3, 148.6, 148.1, 128.0, 122.4, 113.3, 111.0, 55.7, 55.0, 52.6, 41.0, 19.9.
9. Incubations were carried out in buffered batches at 22-25°C containing DMSO (50 %), potassium phosphate (0.095 M, pH 7.0), substrate and pig liver esterase (8-14 g/mol substrate) or α-chymotrypsin (300-2500 g/mol substrate).
10. Enantiomeric excess was detemined by NMR of the monoesters 4, 5 and 6 in presence of optically pure 1-phenylethylamine.
11. Isolated as its hydrochloride salt.
12. Compound (S)-8, hydrochloride : cryst. from butanol-ether, mp 218-219°C,$[\alpha]_D$=-7° (c=1,H_2O), (Litt.[15] mp 218°C, $[\alpha]_D$=-1.8°(c=1,H_2O)). ^{1}H NMR (D_2O) δ: 7.2 (d,2H), 6.98 (d,2H), 3.81 (s,3H), 3.30 (d,J=14.4 Hz,1H), 3.0 (d,J=14.4 Hz,1H), 1.59 (s,3H). ^{13}C NMR δ: 176.8, 161.1, 133.8, 128.5, 117.0, 63.7, 57.9, 44.0, 24.1.
13. Compound (S)-9, hydrochloride : cryst. from aqueous aceton, mp 150-151°C, $[\alpha]_D$=-4.2° (c=1,H_2O), (Litt.[15] mp 174°C, $[\alpha]_D$=-4.3°(c=1,H_2O)) ^{1}H NMR (D_2O) δ: 7.1-6.8 (m,3H), 3.83 (bs,6H), 3.31 (d,J=14.1 Hz,1H), 3.0 (d,J=14.1 Hz,1H), 1.67 (s,3H). ^{13}C NMR (D_2O) δ: 176.2, 150.8, 150.5, 128.5, 125.4, 116.0, 114.7, 63.4, 58.3, 44.4, 24.0.
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