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OPTICALLY ACTIVE N-HYDROXYTARTRIMIDES FOR ENANTIOSELECTIVE PEPTIDE SYNTHESIS

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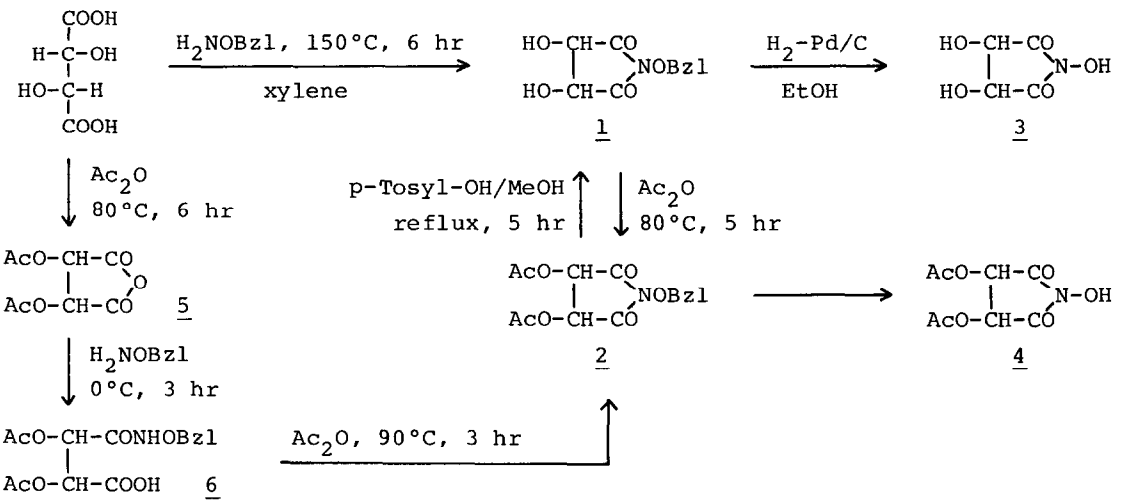
Summary : Preparations of optically active N-hydroxytartrimides were achieved. 1,3,4-Trihydroxysuccinimide ester of Z-L-alanine and 1-hydroxy-3,4-diacetoxysuccinimide ester of Z-D-alanine were allowed to react with D,L-alaninate to produce L-L form and D-D form of Z-Ala-Ala-OEt respectively (optical yield 100%).

There have been reported many studies of hydroxylamine derivatives[1] for peptide synthesis but few studies for selective peptide synthesis[2]. In our previous paper[3], it has been demonstrated that 3-hydroxyhydantoins prepared from L-amino acid have performed excellently enantioselective condensation reaction of D,L-alaninate with N-blocked amino acid. In this study, one of the optically active dicarboxylic acids, d-tartaric acid was employed as a starting material to



gain optically active N-hydroxytartrimides 3 and 4. Here, the expectation refers to effective contribution of two asymmetric centers on the tartrimides to the asymmetric selective reaction.

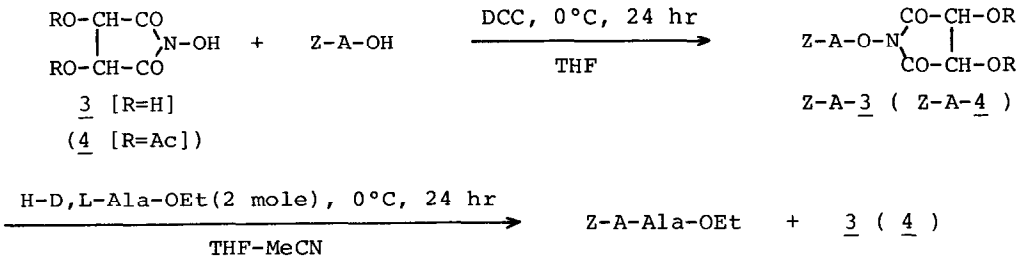
Preparations were carried out as follows. The suspension of d-tartaric acid and benzyloxyamine in xylene was heated at 150°C for 6 hr to give 1-benzyloxy-3,4-dihydroxysuccinimide 1[4]. Acetylation of N-benzyloxytartrimide 1 was carried out at 80°C for 5 hr in acetic anhydride to yield diacetylated tartrimide 2 (1-benzyloxy-3,4-diacetoxysuccinimide) in good yield. Diacetylated derivative 2 was also prepared as follows. O,O'-Diacetylated tartaric anhydride 5 was obtained on treatment of tartaric acid with acetic anhydride at 80°C for 6 hr. The anhydride 5 was allowed to react with benzyloxyamine at 0°C for 3 hr in THF to afford half amide 6 which, on cyclization by heating at 90°C for 3 hr in acetic anhydride, furnished 2. The N-benzyloxytartrimides 1 and 2 were converted to N-hydroxytartrimides 3 and 4 respectively by an usual method.

Table 1. Preparations and Properties of Tartaric Acid Derivatives

			IR Spectra (cm^{-1})			
	Yield(%)	mp (°C)	C=O	NH(OH)	CH_{Ph}	$[\alpha]_D$ a)
1	80.0	173-5	1805, 1705	3240	750	+154.0
1 (from 2)	85.5					
2	88.0	62-3	1810, 1735, 1710		755	
2 (from 6)	94.0					
3	79.5	86-9	1800, 1720	3140		+175.3
4	85.5	142-3	1805, 1730, 1710	3240		+115.6
5	76.5	128-9	1900, 1820, 1745			
6	69.0	190.5-191.5	1750, 1660	3260	750	

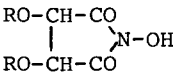
a) c=1, at 25°C in EtOH

The optically active N-hydroxytartrimides 3 and 4 were used for enantioselective peptide synthesis. One is the active ester method in which N-hydroxy derivatives were treated with N-carbobenzoxyamino acids at 0°C for 24 hr in the presence of dicyclohexylcarbodiimide (DCC) followed by stirring with racemic ethyl alaninate (2 mole) at 0°C for 24 hr. The results are summarized in Table 2. Some negative optical yields show excess of D, L-D and D-D isomers in Table 2.



Z ; $C_6H_5CH_2OCO$- , -A- ; -Gly-, -L-Ala-, -D-Ala-

Table 2. Enantioselective Peptide Synthesis by Using N-Hydroxytartrimides



Dipeptide obtained[a]	Compound	(R)	Yield[b] (%)	$[\alpha]_D$[c]	L-Content (%)	Optical Yield[d] (%)
Z-Gly-Ala-OEt	3	(H)	84.0	+ 1.0	48.2	- 3.6
	4	(Ac)	91.5	+ 7.5	36.1	-27.7
Z-L-Ala-Ala-OEt	3	(H)	93.0	-42.9	100	100
	4	(Ac)	96.5	-29.8	73.3	46.6
Z-D-Ala-Ala-OEt	3	(H)	92.0	+20.9	39.7	-20.6
	4	(Ac)	92.5	+44.0	0	-100

a) Their purities were checked by thin-layer chromatography, IR spectroscopy and NMR spectroscopy.

b) based on Z-A-OH

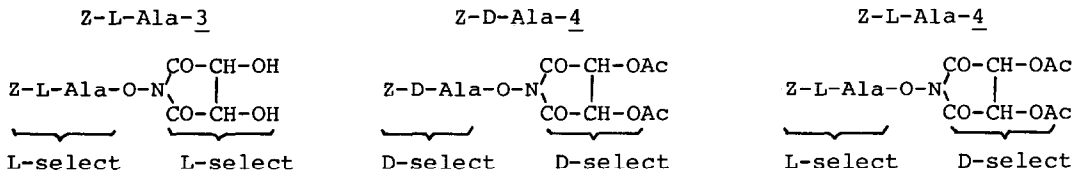
c) c=1, at 25°C in EtOH

d) Optical yield (enantiomeric excess of Z-Gly-Ala-OEt and diastereomeric excess of Z-Ala-Ala-OEt) was calculated by using $[\alpha]_D$ of Z-Gly-Ala-OEt (L; -27.0, D; +27.0) and Z-Ala-Ala-OEt (L-L; -42.4, L-D; + 4.8, D-L; -11.8, D-D; +42.4). Optical Yield (%) = 100(L -D)/(L + D)

The reaction of 1-hydroxy-3,4-diacetoxysuccinimide ester of Z-glycine (Z-Gly-4) with D,L-ethyl alaninate afforded 27% excess of Z-Gly-D-Ala-OEt. That is to say, asymmetric centers in the tartrimide ring facilitate to some extent the selective reaction of Z-A-4 with D-isomer in racemic alaninate. The 100% diastereomeric excess of Z-Ala-Ala-OEt (D-D) evidences the contribution of the two kinds of asymmetric centers on the imide ring and N-blocked alanine. So, it is reasonable that the reaction of Z-L-alanine with D,L-alaninate via Z-A-4 gives only 47% diastereomeric excess of Z-Ala-Ala-OEt (L-L) because configuration of

the imide 4 might increase the reactivity with D-alaninate while configuration of Z-L-alanine might decrease the reactivity with D-isomer. As for the tartrimide 3 which induced the 100% excess of Z-L-Ala-L-Ala-OEt, explanation could not be developed clearly. However, one of important factors for the selectivity appears to be function of hydrogen bond by hydroxyl group.

The enantioselectivity was dramatically governed by structure of N-hydroxytartrimide esters as depicted below. The imide 3 yields entirely optically pure L-L diastereomer of Z-Ala-Ala-OEt whereas the other imide 4 yields D-D diastereomer.



References and Notes

1. N-hydroxyphthalimide ; G.H.L.Nefkens and G.I.Tesser, J. Am. Chem. Soc., 83, 1263 (1961), N-hydroxysuccinimide ; G.W.Anderson, J.E.Zimmerman and F.Callahan, J. Am. Chem. Soc., 85, 3039 (1963), 86, 1839 (1964), N-hydroxyglutarimide ; H.Jaschkeit, Z. Chem., 8, 20 (1968).
2. Recently, enantioselective acylation of racemic 1-phenylethylamine was reported with rather poor optical purity (6-13%) by use of trifluoroacetylated chiral polyamide ; E.J.Gunster and R.C.Schulz, Makromol. Chem., 181, 643 (1980).
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4. If the suspension was heated at 120°C, the main product was neither tartaric monoamide nor N-benzyloxytartrimide 1 but N,N'-dibenzyloxytartramide (Yield 44%; mp 183-5°C; IR 1640, 3240 cm^{-1}). The diamide was easily converted to imide 1 by heating at 80°C for 4 hr in acetic anhydride (Yield 75.5%).

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