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ASYMMETRIC HYDROGENATION OF MODEL DEHYDROVALYL PEPTIDES

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Recent interest[1,2] in naturally occurring 2,3-dehydro-amino acid residues, and their possible role as intermediates in the biosynthesis of D-amino acids[3] has prompted us to investigate the criteria necessary for stereoselective hydrogenation of such residues in the vicinity of chiral centres. It is already known that catalytic hydrogenation of a N-methyldehydrophenylalanine residue in tentoxin, yields N-methyl-D-phenylalanine[2], and there have been reports[4] of up to 40% increase in one enantiomer when a dehydro-amino acid residue near a chiral centre is hydrogenated. Stereoselective hydrogenation has also been achieved[5] in the asymmetric synthesis of amino acids. An alternative approach, recently highlighted, involves the use of 'external' chiral reagents[6] for stereoselective hydrogenation of acyldehydrophenylalanine derivatives. Optical purities of >95% have been reported in this technique.

Our own studies are based on a n.m.r. method[7] for estimating the composition of a mixture of diastereoisomers. The method makes use of the observation that diastereoisomers of N-benzoyl dipeptide methyl esters give different proton chemical shifts for the methyl ester protons, so that integration of these ester peaks is an assessment of the amount of each diastereoisomer present. Thus in the scheme outlined hydrogenation of the dehydropeptides II - IV gives rise to diastereoisomeric mixtures of V, VI and VII. Authentic samples of V, VI and VII show methyl ester signals given in the table. Integration of these signals gave an assessment of the stereoselectivity of the hydrogenation step.

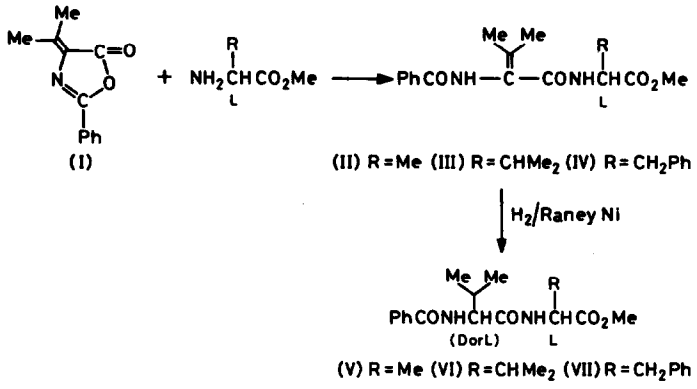
Compounds II - IV were synthesised† by coupling the oxazolone I[8] with the appropriate amino acid ester hydrochlorides in chloroform/triethylamine. The dehydropeptides could not be hydrogenated over palladium, and platinum (Adams catalyst) saturated both the double bond and the benzoyl group. However, hydrogenation at atmospheric pressure over freshly prepared Raney nickel[9] gave quantitative yields of the peptides V - VII. Integration of the diastereoisomeric ester peaks gave the ratios recorded in the table, which represent average figures of three experiments in each case. It can be seen that significant asymmetric induction only occurs when the dehydro-amino acid is linked to phenylalanine. In fact in one experiment using compound IV with freshly-prepared catalyst, a ratio of L-L:D-L of 10:90 was achieved.

From the results available a possible deduction is that the phenylalanyl side-chain overlaps the π-system of the dehydro-amino acid residue, thus reducing access to one side of

† All new compounds synthesised gave satisfactory analysis

the double bond. Some support for this explanation comes from a comparison of the n.m.r. spectra of the dehydropeptides II - IV. The isopropylidene methyl protons in IV appear 0.1 ppm upfield of their counterparts in II and III, and is in line with the tendency for side chain aromatic residues to magnetically shield other side chain protons[10]. Further development of asymmetric control by side chain aromatic groups is currently being investigated.

Scheme



Table

Compound (in $CDCl_3$)	^1H n.m.r. Me ester signals (δ in ppm) L-L	D-L	Ratio of diastereoisomers from hydrogenation (D-L:L-L)
V	3.74	3.67	47:53
VI	3.74	3.66	52:48
VII	3.71	3.65	72:28

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