Chiral Environments for Asymmetric Hydrogenation of Model Didehydro-Amino Acid Residues

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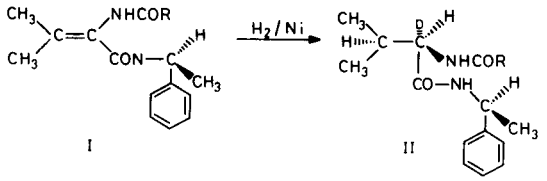
Dedicated to Professor John C. Sheehan on the occasion of his sixty-fifth birthday

Nmr and glc analysis of diastereoisomeric mixtures of dipeptides has been used to study the asymmetric hydrogenation of model benzoyldidehydro- and trifluoroacetyldidehydro-dipeptide methyl esters. Chiral enhancement of one isomeric form appears to be independent of the *N*-terminal acyl group, but is significantly influenced by the choice of amino-acid in the *C*-terminal position. *C*-Terminal aromatic amino-acids and their derivatives give the best chiral enhancement during hydrogenation of a neighbouring dehydroamino-acid residue.

J. Heterocyclic Chem., **17**, 1813 (1980).

Sir:

In 1961, Sheehan and Chandler (1) predicted and observed that the D-isomer (II) should predominate in the reduction of *N*-benzoyl-Δ-Val-L-α-methylbenzamide (I). With Raney Nickel as a catalyst, 18% excess of D-Val was

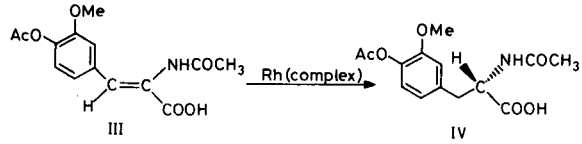


I II

formed. In an analogous study (2) reduction of *N*-acetyl-Δ-Phe-D-ValOR gave 18-45% excess of the peptide containing D-phenylalanine, depending on the nature of the R group.

However, recent interest in didehydroaminoacid residues (3) and the commercial impetus of synthesising optically pure amino acids from dehydroaminoacid precursors have resulted in detailed studies on asymmetric hydrogenation of these systems (4). Significant chiral enhancements have been achieved (5) in Ac-Δ-Phe-X when X is L-Val or L-Leu, implying that the bulkiness of the side chain of X favours asymmetric hydrogenation. Stereoselective hydrogenation has also been achieved (6) in the asymmetric synthesis of cyclic peptides from didehydro cyclic precursors, with one optical form being obtained in > 90% yield.

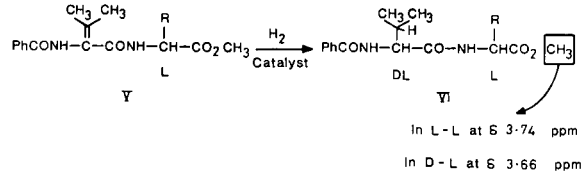
The alternative approach to asymmetric induction using chiral centres already contained in the molecule, is to use 'external' chiral reagents, such as the Wilkinson's complex catalysts carrying optically active phosphine ligands on rhodium. In fact *S*-DOPA can be synthesised on an industrial scale (7) using the rhodium complex of 1,2 bis[2-methoxyphenyl-phenylphosphino]ethane, the key step being the conversion of III to IV. Subsequently,



III IV

many impressive results using homogeneous hydrogenation catalysed by rhodium complexes of chiral phosphines have been reported (4).

Our own interest in this field was initiated by the development of a convenient nmr method for estimating the composition of diastereoisomeric mixtures (8). The method makes use of the fact that diastereoisomers such as VI give different proton chemical shifts for the methyl



V VI

In L-L at δ 3·74 ppm

In D-L at δ 3·66 ppm

ester protons, so that integration of these ester signals is an assessment of the amount of each diastereoisomer present. With this facility we have initiated a detailed investigation of the parameters required in the environment of the didehydro amino-acid residue to achieve maximum chiral induction during hydrogenation. However, our initial studies showed that the tetrasubstituted alkene was too highly hindered for hydrogenation by palladium on charcoal catalysts and that the planar π-system (PhCO-NH-C=C(CH$_3$)$_3$) was completely reduced to cyclohexyl-CO-NH-CH-CH(CH$_3$)$_2$ using Adams catalyst. Reverting to Sheehan and Chandler's (1) technique of using Raney Nickel, we have recorded the results summarised in the Table (9).

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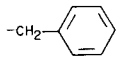
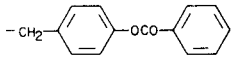
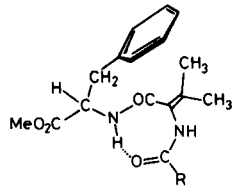
Table

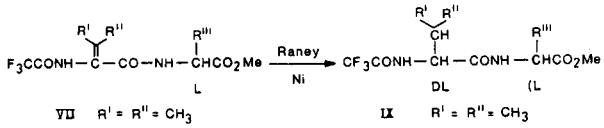
Compound V R =	Ratio of Diastereoisomers (D-L:L-L) in VI
$-CH(CH_3)_2$	52:48
$-CH_3$	47:43
	72:28
	77:23

These obviously imply that increasing the "aromatic character" of the chiral residue neighbouring on to the alkene, increases the degree of asymmetric induction, and that this is more significant than the bulkiness of the side chain. It is attractive to speculate that a conformation such as the one illustrated in the Figure exists in solution where the aromatic side-chain bends over the didehydro-amino-acid residue, thus reducing access to one side of the



double bond. Indeed, nmr evidence indicates that the isopropylidene methyl protons in V when R = $PhCH_2$ appear 0.1 ppm upfield of their non-aromatic counterparts.

It is also possible that the benzoyl group might exert some influence on the pathway of the reaction, so trifluoracetyl dehydropeptides VII and VIII were investigated (samples kindly given by Prof. Charles Stammer, University of Georgia at Athens). Although compounds IX and X show distinguishable ester methyl signals for each of their diastereoisomers, the much smaller separation (0.02 ppm) made accurate integration impossible. Thus the diastereoisomeric ratios in IX and X formed *via*



VII $R^I = R^{II} = CH_3$, $R^{III} = PhCH_2$-

VIII $R^I = CH_3$, $R^{II} = C_2H_5$, $R^{III} = CH_2CH(CH_3)_2$

IX $R^I = R^{II} = CH_3$, $R^{III} = PhCH_2$-

X $R^I = CH_3$, $R^{II} = C_2H_5$, $R^{III} = CH_2CH(CH_3)_2$

Raney Nickel hydrogenation of VII and VIII, respectively were monitored using glc based on the method of Weygand, *et al.* (10). Using a 4 foot glass column packed with silicon gum rubber E301 (SE-30), successful diastereomeric analyses were achieved. Product IX showed an isomeric ratio, DL:LL 75:25 and product (X), 52:48. Although VII and VIII are not exactly the same series of analogues, we feel that the *N*-acyl group makes no significant contribution to the isomeric ratios.

Very recently the project has concentrated on the hydrogenation of less hindered dehydroamino-acid residues, so that palladium catalysts can be used. Thus, in the hydrogenation of PhCONHC(=CHMe)CONHCH(CH_2Ph)OMe using $Pd(OAc)_2$ in methanol the diastereoisomeric ratio again favoured the D-L form (D-L:L-L 66:34). Based on our survey of criteria necessary for chiral induction, the project is currently being extended to the investigation of chiral polymeric resins.

Acknowledgment.

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