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ASYMMETRIC HOMOGENEOUS REDUCTION OF DEHYDROPEPTIDES

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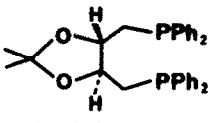
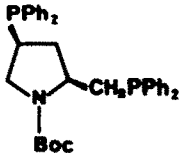
Abstract - Monodehydropeptides with the dehydroaminoacid fragment in C-terminal or N-terminal position were synthetized as well as a family with the general formula Ac-ΔPhe-$(Gly)_n$-Leu-OR (n = 0-2, R = H or Me). Asymmetric reduction of these compounds catalyzed by chiral rhodium complexes was investigated. The results were discussed in terms of double asymmetric induction. A method was developped to avoid the use of both enantiomers of the substrate or of the catalyst, it consists in the total reduction of a racemic dehydropeptide. The products distribution gives access to the two desired facial selectivities.

INTRODUCTION

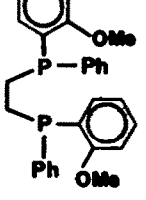
Asymmetric hydrogenation of C=C bonds with chiral rhodium catalysts proceeds in many cases with enantiomeric excesses (ee) higher than 90%. Many reviews are available[1-7]. Most of the catalysts involve chelating chiral phosphorus compounds as ligands, for example (S,S)-diop 1, (S,S)-bppm 2, (R,R)-dipamp 3 or (S,S)-chiraphos 4 (ref.[8-11]).



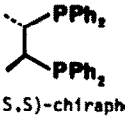
(S,S)-(+)-diop 1



(S,S)-bppm 2

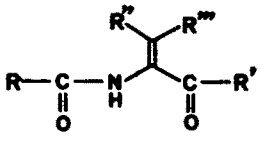


(R,R)-diPAMP 3



(S,S)-chiraphos 4

One fruitful area of investigation was the asymmetric reduction of N-acyl α,β-dehydroaminoacids 5 which culminated with an industrial synthesis of (S)-dopa[5,10].



5

The functional groups connected with the C=C double bond of 5 play an important role in the process of asymmetric reduction, whose mechanism was carefully studied[12,13]. An obvious development in asymmetric synthesis of α-aminoacids is the investigation of the reduction of substrates of general formula 5 in which the double bond is connected to aminoacid moieties (either in R or R' groups). A good stereochemical control of the reduction will give a new tool in peptide chemistry and should allow to introduce deuterium or tritium with defined configuration at the

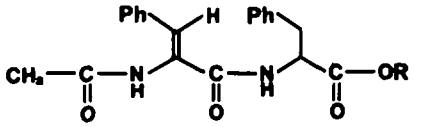
new chiral center*. The main problems are :

i) to find chiral catalysts overthrowing the effect of the chiral centers of the substrate (catalyst strategy control)[14].

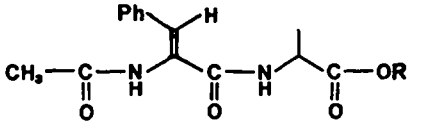
ii) to check the generality of that method, especially on dehydroaminoacids bound to a polypeptide skeleton which could deactivate or modify the catalyst by complexation. We shall describe some of our results on these two points after briefly reviewing what was already published in the reduction of dehydropeptides.

PREVIOUS RESULTS

We initiated our work in this field by a careful investigation of reduction of Ac-ΔPhe-(S)-Phe-OR 6 or Ac-ΔPhe-(S)-Ala-OR 7.



6 a : R = H
b : R = OMe

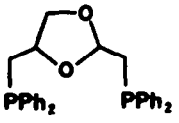


7 a : R = H
b : R = OMe

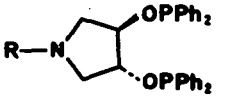
We established that a double asymmetric induction[15] was operating with RhCldiop as catalyst[16]. With (S)-6 an achiral homogeneous catalyst leads to reduction with (S') configuration (20-40% diastereomeric excess (de)).

Ac-ΔPhe-OH when reduced in presence of RhCl(S,S)-diop gives (S') configuration (80% ee) while the combination (S)-6 and RhCl(S,S)-diop gives the (S') configuration and 90% de. The mismatched pair (S)-6 and RhCl(R,R)-diop gave 65% de with newly formed phenylalanine in the opposite configuration. Similar results were obtained by others[17-21], mainly in the Ojima group.

Diastereomeric excesses in the range of 95-98% were easily observed by the use of (R,R)-dipamp 3 or (S,S)-bppm 2. Dioxop 8 and the diphosphinite 9 gave also good results in reduction of 6,7 and analogs[20,21].



dioxop 8



9

The asymmetric tritiation of 6b catalyzed by RhCl(S,S)-diop allowed the preparation of bis-tritiated (S,S)-Ac-Phe-Phe-OMe[22]. A synthesis of a modified enkephalin was based on the controlled reduction of two monodehydropeptides which were subsequently coupled, and on the reduction of Ac-ΔTyr-(R)-Ala-Gly-ΔPhe-(S)-Leu-OMe[23].

PREPARATION OF THE DEHYDROPEPTIDES

The chemistry of dehydroaminoacids is an important topic which was recently reviewed[24-26]. Introduction of the α,β-unsaturated dehydroaminoacid fragment into a peptide system is usually performed by the azlactone route, by β-elimination in a serine or phenylserine unit or by a peptide coupling on a N-protected α,β-dehydroaminoacid. Synthesis of small dehydropeptides is frequently not easy and we had to select suitable methods, according to the structure of the target. ΔPhe, ΔTyr and ΔVal groups were introduced at various places in dipeptide or higher peptides (till heptapeptides) containing aminoacids such as phenylalanine, tyrosine, leucine, valine and glycine.

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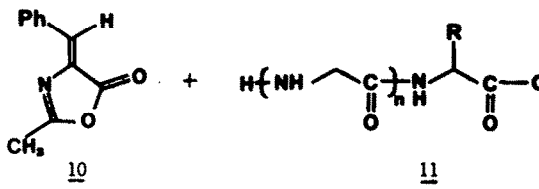
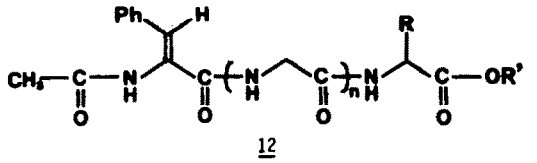
* These new chiral centers are labelled : R' or S', in order to show the difference with the already present chiral centers.

The azlactone approach is illustrated by the transformations 10⟶12, 13⟶14 and 16⟶17 which allow to connect Ac-ΔPhe, Ac-ΔTyr or Ac-ΔVal to a polypeptide chain. New dehydropeptides were prepared by this way and are described in the experimental section. The azlactone route allows also to introduce a dehydroaminoacid unit at the C-terminal position as in the conversion 19⟶20.

The coupling between fragments such as Ac-ΔPhe-$(Gly)_n$-OH 12a and 12b (R= R'= H) with Leu-OMe in presence of DCCI was used to obtain some N-acetyl dehydropeptides, here Ac-ΔPhe-$(Gly)_n$-Leu-OMe (n= 0 to 2) 12d, 12b and 12g.

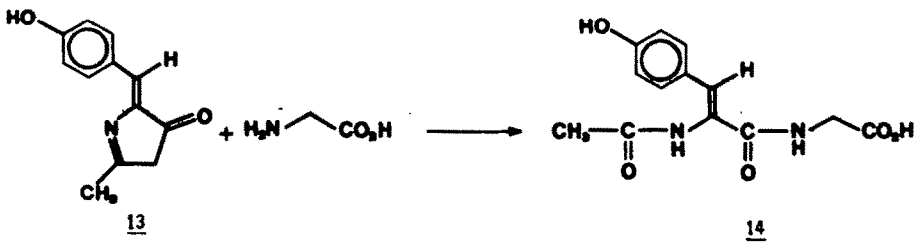


10 + 11 ⟶



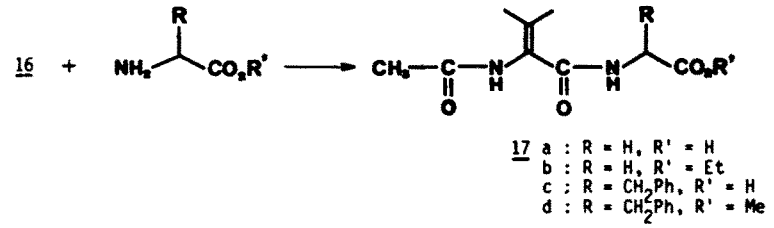
12

a : n = 0, R = R' = H
b : n = 0, R = R' = H
c : n = 0, R = CH_2iPr, R' = H
d : n = 0, R = CH_2iPr, R' = Me
e : n = 1, R = CH_2iPr, R' = H
f : n = 1, R = CH_2iPr, R' = Me
g : n = 2, R = CH_2iPr, R' = Me
h : n = 1, R = H, R' = Et
i : n = 2, R = H, R' = Et



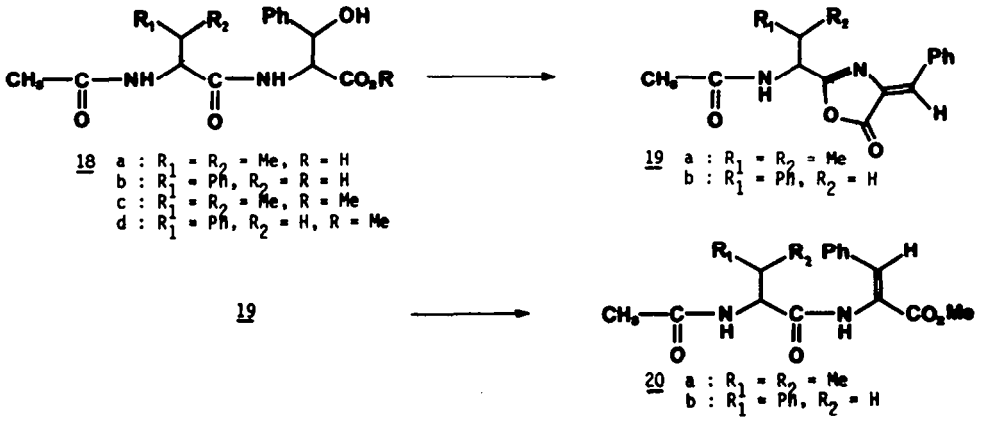
13 + $H_2N-CH_2-CO_2H$ ⟶ 14

15 ⟶ 16



16 + $NH_2-CH(R)-CO_2R'$ ⟶ 17

17 a : R = H, R' = H
b : R = H, R' = Et
c : R = CH_2Ph, R' = H
d : R = CH_2Ph, R' = Me



18 a : $R_1 = R_2 = Me$, $R = H$
b : $R_1 = Ph$, $R_2 = R = H$
c : $R_1 = R_2 = Me$, $R = Me$
d : $R_1 = Ph$, $R_2 = H$, $R = Me$

19 a : $R_1 = R_2 = Me$
b : $R_1 = Ph$, $R_2 = H$

20 a : $R_1 = R_2 = Me$
b : $R_1 = Ph$, $R_2 = H$

ASYMMETRIC HYDROGENATION

The use of an achiral rhodium catalyst such as $[Rh(Ph_2P(CH_2)_4PPh_2)COD]^+$ enables to estimate the stereochemical effect of the asymmetric center of the already present aminoacid. Every time a dehydroaminoacid moiety is placed in a N-terminal position the substrate control appears to be small, giving less than 50% de. This was previously observed with Ac-ΔPhe-Phe-OR or Ac-ΔPhe-Ala-OR.

We had similar trends in the reduction of Ac-ΔPhe-$(Gly)_{1-2}$-Leu-OMe (13% - 2.4% de). It was interesting to see what happens with the unsaturation located at a C-terminal position. Till now there were few reports of such reactions. We found that the stereoselectivity is much higher (42% de (R'), R'/S' = 71/29) with Ac-(S)-Phe-ΔPhe-OMe. In the most favorable cases the asymmetric induction given by one aminoacid residue, whatever is its location, remains low. The diastereofacial selectivity is at best 3:1. This gives good hope to control the stereochemistry of reduction by the chirality of the catalyst if its enantiofacial selectivity on the achiral models is high. The double asymmetric induction[15] in the matched pair should lead to high de while in the mismatched pair the reverse stereochemistry and a lower de is generally observed : Masamune gave a detailed discussion on these concepts in the context of new strategies for total synthesis using for example asymmetric aldolisation or asymmetric epoxidation[14].

All the published work on hydrogenation of dehydropeptides in presence of chiral rhodium catalysts is in agreement with the possibility to have the "catalyst control" in the mismatched situation, even with ligands such as diop which give enantiofacial ratio of 4/1 to 10/1 according to the structure of the achiral unsaturated substrate.

Before discussing the new results obtained here we shall describe the procedures for the stereochemical analyses. The ratio of the two diastereomeric peptides obtained in each hydrogenation was measured by nmr or hplc. A more accurate value is also obtained by an acidic cleavage of the crude products and derivatization into a mixture of N-trifluoroacetyl isopropyl aminoesters. This procedure performed on a microscale allows the measure of ee of the aminoacids by glc on a chiral stationary phase[27].

In order to do a full discussion on the double asymmetric induction it is necessary to know the results of hydrogenation in a pair of diastereomeric experiments : (R)-substrate/(R)catalyst and (R)-substrate/(S)-catalyst or (R)-substrate /(R)-catalyst and (S)-substrate/(R)-catalyst.

It is often difficult to get both enantiomers of a chiral ligand or of a chiral substate. In these cases we suggest to use the available enantiomer of the catalyst and the racemic substrate. The total conversion of the latter is equivalent of performing together the pair of the desired diastereomeric experiments. As explained in the Appendix it is easy, by suitable analytical methods, to know the asymmetric inductions obtained in the two cases. The results obtained by the various methods are listed in Tables 1 and 2.

We investigated the asymmetric reduction of Ac-Phe-ΔPhe-OMe as the first model of a chiral

C-terminal dehydropeptide. The results are indicated in Table 1, they are obtained by hydrogenation of the racemic dehydrodipeptide using diop, bppm or dipamp as the ligand in the catalyst. It is clear that the steric course of the reduction is under substrate control when RhCldiop is the catalyst.

TABLE 1

Hydrogenation of racemic dehydropeptides with homogeneous chiral catalysts[a]

Substrate	Catalyst	Products[b] l:u	ee_l	ee_u	$\frac{R'-S'}{R'+S'}$ (%)	R'/S'
Ac-(R)-Phe-ΔPhe-OMe	Rh(S,S)-diopCl	25.5:74.5	21.3	7.2	-38.2	1:2.2
Ac-(S)-Phe-ΔPhe-OMe					59.8	4.0:1
Ac-(R)-Phe-ΔPhe-OMe	Rh(S,S)-bppmCl	48.9:51.1	48.9	46.8	45.6	2.7:1
Ac-(S)-Phe-ΔPhe-OMe					50.0	3.0:1
Ac-(R)-Phe-ΔPhe-OMe	Rh(R,R)-dipamp+	51.8:48.2	-91.9	-98.8	-91.6	1:22.8
Ac-(S)-Phe-ΔPhe-OMe					-98.8	1:166
Ac-(R)-Phe-ΔPhe-OMe	$RhPh_2P(CH_2)_4PPh_2Cl$[e]	29.0:71.0	0	0	-42.0	1:2.4
Ac-(S)-Phe-ΔPhe-OMe					42.0	2.4:1
Ac-(R)-Val-ΔPhe-OMe	Rh(S,S)-diopCl	24.9:75.1	31.7	10.5	-34.4	1:2.0
Ac-(S)-Val-ΔPhe-OMe					66.0	4.9:1
Ac-(R)-Val-ΔPhe-OMe	Rh(R,R)-dipamp+ [d]	47.2:52.8	-70.1	-62.7	-71.8	1:6.1
Ac-(S)-Val-ΔPhe-OMe					-60.6	1:4.1
Ac-(R)-Val-ΔPhe-OMe	Rh(S,S)-bppmCl	46.7:53.3	29.4	25.8	20.9	1.5:1
Ac-(S)-Val-ΔPhe-OMe					34.1	2.1:1
Ac-ΔVal-(R)-Phe-OMe	Rh(R,R)-dipamp+ [c]	51.1:48.9	-47.3	-49.4	-46.2	1:2.7
Ac-ΔVal-(S)-Phe-OMe					-50.6	1:3.0

[a] [substrate]/[catalyst] = 15-20, [substrate] = 0.1 M in MeOH, pH_2 = 1 bar, 20°C. Hydrogenations are quantitative (hplc and nmr analysis).
[b] l (like) = RR,SS diastereomer ; u (unlike) = RS,SR diastereomer. ee is positive if R' > S', and negative if S' > R'.
[c] [substrate]/[catalyst] = 3.5, pH_2 = 80 bar.
[d] pH_2 = 80 bar.
[e] Benzene-methanol (1:2) is used as solvent.

With (S,S)-diop and (S)-dehydropeptide the new asymmetric center was created with a R'/S' stereoselectivity = 4:1, while the combination (R,R)-diop/(S)-dehydropeptide gives a ratio of 2:1. With the achiral rhodium catalyst $Rh(Ph_2P(CH_2)_4PPh_2)Cl$ on the (S)-dehydropeptide excess of (R') configuration (R'/S' = 2.4:1) was observed. RhCl(R,R)diop catalyses the hydrogenation of various types of dehydrophenylalanine derivatives[16-18] with a (R')-stereoselectivity in the range R'/S' = 3:1 to 10:1.

It is obvious from the above data set that there is a "substrate control", the catalyst with (R,R)-diop is not stereoselective enough to overcome the inherent (R)-stereoselectivity of the (S)-substrate. Surprisingly the highest diastereofacial selectivity (4:1) is obtained in the pair ((S,S)-diop/(S)-substrate) which should expected to be the "a priori" mismatched pair, where the asymmetric inductions are predicted to be opposite. It is an additional case where even semiquantitative calculations cannot lead to the production of the double asymmetric induction, as pointed out by Masamune[14].

This is very different from reduction of Ac-ΔPhe-(S)-Phe-OMe where a "catalyst control" was obtained with RhdiopCl[16,17]. It is known that bppm and dipamp give rhodium catalysts more stereoselective than diop in reduction of various dehydroaminoacids (R and S stereoselectivity). The same trend was observed for the reduction of Ac-Phe-ΔPhe-OMe as indicated by results in Table 1. Both catalysts are now able to direct the steric course of the reduction, whatever is the absolute configuration of the substrate. In the "predicted mismatched pair" (S,S)-bppm/(R)-sub-

strate on excess of (R)-configuration was created (2.7:1) as well as in the matched pair (S,S)-bppm/(S)-substrate (3.00:1). As always found with dehydropeptides[16,18,21] dipamp gives the best stereoselective rhodium catalyst. In the "predicted matched pair" (R,R)-dipamp/(R)-substrate led to a high ratio (22.8:1) in (S) configuration, in the "predicted mismatched pair" (R,R)-dipamp (S)-substrate this ratio amounted up to 166:1.

It is interesting to see in this case of "catalyst control" that the multiplicative model of facial stereoselectivities[19] fail to predict which of the two pairs will lead to the highest stereoselectivity since it is the "predicted mismatched pair" which indeed gives the highest de. Ac-Val-ΔPhe-OMe behaves similarly to Ac-Phe-ΔPhe-OMe. (R,R)-diop does not control the stereochemistry in the reduction of the (R)-substrate (mismatched pair) which leads to a (R,S')-dipeptide (S'/R' = 4.9:1). (R,R)-dipamp and (S,S)-bppm impose their usual stereochemistry (S' and R' respectively) in the reduction of Ac-(S)-Val-ΔPhe-OMe although the stereoselectivities are less impressive than in the reduction of Ac-(S)-Phe-ΔPhe-OMe.

Hydrogenation of a set of homologous dehydropeptides of general formula Ac-ΔPhe-$(Gly)_n$-Leu-OR (R = H or Me) leads to interesting experiments. In order to identify a possible effect of the chain length (between leucine residue and the prochiral double bond) on the steric course of the reaction some hydrogenations were performed with an achiral catalyst or with the rhodium-diop catalyst (Table 2).

TABLE 2

Hydrogenation of some dehydropeptides with Rh(R,R)-diopCl as catalyst[a]

Substrate	ee = $\frac{R'-S'}{R'+S'}$ (%)	R'/S'
Ac-ΔPhe-Gly-OH	64.0	4.6:1
Ac-ΔPhe-Gly_2-OH	53.3	3.3:1
Ac-ΔPhe-(S)-Leu-OH	57.7	3.7:1
Ac-ΔPhe-Gly-(S)-Leu-OH	61.6	4.2:1
Ac-ΔPhe-$(Gly)_2$-OEt	51.7	3.1:1
Ac-ΔPhe-$(Gly)_3$-OEt	51.2	3.1:1
Ac-ΔPhe-(R)-Leu-OMe	63.9	4.5:1
Ac-ΔPhe-(S)-Leu-OMe	13.7	1.3:1
Ac-ΔPhe-Gly-(R)-Leu-OMe	37.7	2.2:1
Ac-ΔPhe-Gly-(S)-Leu-OMe	60.5	4.1:1
Ac-ΔPhe-$(Gly)_2$-(R)-Leu-OMe	65.7	4.8:1
Ac-ΔPhe-$(Gly)_2$-(S)-Leu-OMe	40.9	2.4:1
Ac-ΔPhe-$(Gly)_2$-(S)-Leu-OMe	39.4	2.3:1

[a] [substrate]/[catalyst] = 85, [substrate] = 0.25 M in MeOH, pH_2 = 1 bar, 20°C
Hydrogenations are quantitative (hplc and nmr analysis).

The asymmetric induction given by Rh(R,R)-diopCl is moderate (ee = 51 to 61%, R' configuration) and fairly constant whatever is the structure of the dehydropeptides (Table 2). When a (S)-leucine residue is introduced at various distances of the ΔPhe moiety, a very small asymmetric induction was found with $Rh(Ph_2P(CH_2)_4PPh_2)COD^+$ as the achiral catalyst : Ac-ΔPhe-Gly-(S)-Leu-OMe (de = 13%, (R') configuration), Ac-ΔPhe-$(Gly)_2$-(S)-Leu-OMe (de = 2.4%, (R') configuration).

These results led to the expectation that Rh(R,R)-diopCl will behave with a "reagent control"[14], imposing the (R')-configuration at the newly created asymmetric center. This was indeed observed when n = 1 or 2 (Table 2), the (S)-substrate (n = 1) or the (R)-substrate (n = 2) giving the highest stereoselectivity and beeing likely involved in the matched pair. For n = 0 the (R)-substrate leads to the highest diastereofacial selectivity. It cannot be decided here if the reaction is under "susbtrate control" since we do not yet know the sign of the asymmetric induction with an achiral catalyst.

The first picture which emerges from these preliminary experiments is consistent with a moderate but definite contribution of the (S)-leucine residue, whatever is its location, on the steric course of the reduction in presence of Rh(R,R)-diopCl. We are currently preparing higher homologues (n>2) in order to see if for n large enough a conformational transmission could amplify the influence of the (S)-leucine moiety thanks to a tertiary structure.

EXPERIMENTAL SECTION

General procedures

All melting points were obtained on a Riechert apparatus. Mass spectra were recorded on a Ribermag R-10 10 spectrometer. HPLC analyses were accomplished using columns (4.6 x 250 mm) packed with Zorbax ODS C_{18} (Du Pont, particules 5-6 µm diameter) on an apparatus equiped with a Du Pont 8800 pump and a UV ISCO 1850 detector at 230 nm. For preparative HPLC the internal diameter of columns was 9.4 mm. Speed was 1 mL/min (analysis) or 4-5 mL/min (chromatographic isolations). Hydrogenations catalyzed by rhodium complexes were performed in methanol according to the general procedure of ref 28. Reactions under pressure were runned in a glass coated stainless steel autoclave, fitted with an inlet septum for introduction of the solvent. Cleavage and derivatization for the glc enantiomers analysis of the products were performed as described in ref 28.

NMR Spectra

All 90 MHz ^1H NMR spectra were recorded on a Perkin-Elmer R32 spectrometer. Samples were prepared in $CDCl_3$, d^6-DMSO mixtures, with TMS as internal standard. Chemical shifts are reported in δ values. The spectra of compounds 12a-12i are in agreement with the proposed structures and present the following characteristic signals : Acetyl : 2.0-2.1 (s) ; NH (ΔPhe) : 9-10 (s) ; NH (Gly) : 7.5-8 (t) ; NH (Leu) : 7.5-8 (d) ; Ar (ΔPhe) and CH (ΔPhe) : 7.2-7.6 (m) ; CH_2 (Gly) : 3.9-4 (t) ; CH (Leu) : 4.4-4.5 (m) ; CH_2 (Leu) : 1.6-1.7 (m) ; CH_3 (Leu) : 0.9-1 (dd) ; OCH_3 (ester) : 3.6-3.7 (s) ; CH_2 (ethyl ester) : 4.15 (q) ; CH_3 (ethyl ester) : 1.2-1.3 (t).

Materials

(Z)-Ac-ΔPhe-OH was purchased from Fluka or obtained by hydrolysis of the azlactone 10 prepared according to Erlenmeyer[28] from acetylglycine and benzaldehyde.
Ac-ΔPhe-Gly-OH[31] 12a and Ac-ΔPhe-Gly-Gly-OH[32] 12b were prepared by aminolysis of azlactone 10 using the suitable aminoacid or dipeptide sodium salt.

Ac-ΔPhe-(S)-Leu-OH 12c

Prepared by reaction of sodium salt of (S)-leucine on oxazolone 10, as for the synthesis of 12a. The product is crystallized from methanol (94% yield).
mp = 220-222°C.

$$[\alpha]_D^{20} = +5.4^\circ \ (c = 2, \ Py)$$

Analysis $C_{17}H_{23}O_4N_2$ Calc : C = 64.13 H = 6.97 N = 8.80
Found : C = 63.40 H = 6.98 N = 8.81

Racemic Ac-ΔPhe-Leu-OH 12c

Similar preparation starting from racemic leucine. 63% yield, mp=225-228°C

Analysis $C_{17}H_{22}O_4N_2$ Calc : C = 64.13 H = 6.97 N = 8.80
Found : C = 63.47 H = 6.97 N = 8.93

Ac-ΔPhe-(S)-Leu-OMe 12d

(S)-12c dissolved in methanol was quantitatively esterified at 0°C by diazomethane dissolved in ether. mp = 189°C

$$[\alpha]_D^{20} = -0.2^\circ \ (c = 2, \ MeOH) \ ; \quad [\alpha]_{436}^{20} = +5.5^\circ \ (c = 2, \ MeOH)$$

Analysis $C_{18}H_{24}O_4N_2$ Calc : C = 65.04 H = 7.28 N = 8.43
Found : C = 64.81 H = 7.30 N = 8.60

Racemic Ac-ΔPhe-Leu-OMe 12d

Prepared as above, from racemic 12c. Quantitative yield, mp = 170°C.

Analysis $C_{18}H_{24}O_4N_2$ Calc : C = 65.04 H = 7.28 N = 8.43
Found : C = 63.79 H = 7.13 N = 8.48

Ac-ΔPhe-Gly-(S)-Leu-OH 12e

Prepared by reaction of Gly-(S)-Leu-ONa on 10. Yield 63% mp = 200-202°C,

$[\alpha]_D^{20}$ = - 107.2° (c = 2, Py)

Analysis $C_{19}H_{25}O_5N_3$ Calc : C = 60.73 H = 6.66 N = 11.19
Found : C = 60.52 H = 6.68 N = 11.10

Ac-ΔPhe-Gly-(S)-LeuOMe 12f

In 40 ml CH_2Cl_2 cooled at 0°C are successively added (S)-LeuOMe,HCl (0.9 g, 5 mmol), NEt_3 (0.7 ml, 5 mmol), Ac-ΔPhe-Gly-OH (1.31 g, 5 mmol), DCCI (1.03 g, 5 mmol). After 18 h at room temperature dicyclohexylurea was removed by filtration. The solution was washed by N HCl, water, $NaHCO_3$, water. After evaporation of solvent and column chromatography on silicagel (eluent : ethyl acetate) the product was isolated in 68% yield. mp = 133-137°C.

$[\alpha]_D^{20}$ = 64.3° (c = 2, MeOH)

Analysis $C_{20}H_{27}O_5N_3$ Calc : C = 61.68 H = 6.99 N = 10.79
Found : C = 61.34 H = 6.91 N = 10.52

Racemic Ac-ΔPhe-Gly-Leu-OMe 12f

Same preparation as above, from racemic Leu-OMe,HCl. The product was crystallized in ether. 79% yield. mp = 136-137°C.

Analysis $C_{20}H_{27}O_5N_3$ Calc : C = 61.68 H = 6.99 N = 10.79
Found : C = 61.64 H = 6.95 N = 10.69

Ac-ΔPhe-Gly-Gly-(S)-Leu-OMe 12g

Prepared by coupling of 12b with (S)-Leu-OMe,HCl in presence of DCCI (same procedure as in the synthesis of (S)-12f). 75% yield. mp = 136-140°C,

$[\alpha]_D^{20}$ = 7.5° (c = 2, MeOH)

Analysis $C_{22}H_{30}O_6N_4$ Calc : C = 59.18 H = 6.77 N = 12.55
Found : C = 59.02 H = 6.83 N = 12.75

Racemic Ac-ΔPhe-Gly-Gly-Leu-OMe 12g

Prepared similarly to above. 45% yield. mp = 166-170°C

Analysis $C_{22}H_{30}O_6N_4$ Calc : C = 59.18 H = 6.77 N = 12.55
Found : C = 59.85 H = 7.16 N = 12.20

Ac-ΔPhe-Gly-Gly-OEt 12h

Obtained by coupling between 12a and Gly-OEt,HCl in presence of DCCI.45% yield after crystallization in ethyl acetate. mp = 133-134°C.

Analysis $C_{17}H_{21}N_3O_5$ Calc : C = 58.78 H = 6.09 N = 12.10
Found : C = 58.79 H = 6.12 N = 11.9

Ac-ΔPhe-Gly-Gly-Gly-OEt 12i

Prepared by reaction of Ac-ΔPhe-$(Gly)_2$-OH 12b on Gly-OEt,HCl in presence of DCCI in DMF (4 mL for each mmol of DCCI). After filtration of dicyclohexylurea, DMF was distilled at 30°C under 1 mmHg. The product crystallizes after addition of ethyl acetate. Crystals are washed with N HCl , water, N $NaHCO_3$, water, and recrystallized in methanol,ethyl acetate (1:10).
67% yield, mp = 171°C.

Analysis $C_{19}H_{24}O_6N_4$ Calc : C = 56.43 H = 5.98 N = 13.85
Found : C = 56.25 H = 5.82 N = 13.73

Ac-ΔVal azlactone 16

5g (25.76 mmol) of racemic N-chloroacetylvaline 15 and 33 mL Ac_2O are stirred at 60°C for 3h. After one night at 25°C, distillation of Ac_2O and AcOH, the azlactone 16 was distilled at 55°C,0.1 mmHg. 2.75g (77% yield) of crystals, mp = 35-36°C. This azlactone is very sensitive to moisture.

NMR ($CDCl_3$) : 2.22 (d) : isopropylidene ; 2.32 (s) : Me.

Racemic Ac-ΔVal-Phe-OMe 17d

2.3g (16.5 mmol) of azlactone 16 freshly distilled was added at 0°C to freshly prepared racemic H-Phe-OMe dissolved in ether. After two days at 25°C some ether was evaporated. A white product was obtained and crystallized in water, to give 500 mg of pure compound, mp = 165-167°C.

NMR ($CDCl_3$) : 7.25 (m) : Ar and NH ; 6.95 (m) : NH (Phe) ; 4.85 (m) : CH (Phe) ; 3.7 (s) : CH_3 (OMe) ; 3.12 (m) : CH_2 (Phe) ; 2.0 (s) : Ac ; 1.85 (s) : CH_3 (Val) ; 1.65 (s) : CH_3 (Val).

Analysis $C_{17}H_{22}O_4N_2$ Calc C = 64.13 H = 6.97 O = 20.10
Found C = 63.84 H = 9.06 O = 20.08

Ac-(R,S)-Val-(R,S)-PhSer-OMe 18c

Prepared according to the method described in ref 33. To 6.1 g (38.3 mmol) of racemic N-acetyl valine, 7.36 g (31.8 mmol) of racemic PhSer-OMe,HCl and 16.9 g (38.3 mmol) of BOP[33] in 103 mL CH_2Cl_2, are added 12.4 g (95.8 mmol) of iPr_2EtN. After one night at room temperature water was added. 5.11 g of a white powder were recovered after standing at 0°C. The nmr spectra (in $CDCl_3$, DMSO) is in agreement with structure 18c.

Ac-(R,S)-Phe-(R,S)-PhSer-OMe 18d

Prepared as for 18c using racemic N-acetyl phenylalanine.

NMR ($CDCl_3$,DMSO) : 6.9-8.1 (m) : 2 Ar and 2 NH ; 5.6 (s) : OH ; 5.2 (m) : CHOH ; 4.5-4.8 (m) : CH (Phe and PhSer) ; 3.65 (s) and 3.7 (s) : CH_3 (OMe, diastereomers) ; 2.5-3.0 (m) : CH_2 (Phe) ; 1.8 (s) : CH_3 (Ac).

Ac-(R,S)-Val-(R,S)-PhSer-OH 18a

To a suspension of 4.2 g (12.5 mmol) 18c in water was added 15 mL (30 mmol) of 2N NaOH. After one night at room temperature, the solution was neutralized by 2N HCl. The product precipitates as a white powder, 3.8 g (95% yield).

Ac-(R,S)-Phe-(R,S)-PhSer-OH 18b

Prepared as 18a by saponification of 18d.

NMR ($CDCl_3$,DMSO) : 6.9-8.0 (m) : 2 Ar and 2 NH ; 5.8 (s) : OH ; 5.3 (dd) : CHOH ; 4.5-4.8 (m) : CH (Phe and PhSer) ; 2.5-3.1 (m) : CH_2 (Phe) ; 1.83 (s) : CH_3 (Ac).

Racemic Ac-Val-ΔPhe azlactone 19a

3.7 g (11.6 mmol) of 18a and 490 mg (5.7 mmol) of NaOAc were added to 24 mL Ac_2O. After 24 h at room temperature iced water was added. 2.73 g of azlactone 19a precipitate (83% yield).

NMR ($CDCl_3$,DMSO) : 7-8.5 (m) : Ar, NH and HC=C ; 4.7 (m) : 2 Me ; 1.98 (s) : Ac and (m) CH ; 1.05 (m) : 2 Me.

Racemic Ac-Phe-ΔPhe azlactone 19b

Prepared from 18b as described for 19a.

Racemic Ac-Val-ΔPhe-OMe 20a

To a suspension of 2.73 g of 19a in methanol was added a catalytic amount of NaOMe. After a few hours at room temperature a clear solution was obtained. The product was precipitated by addition of water and was recrystallized from water. 1.6 g (52% yield) , mp = 205°C.

NMR ($CDCl_3$,DMSO) : 9.5 (s) : NH (Ac) ; 7.1-8.1 (m) : Ar, NH (ΔPhe) and HC=C ; 4.35 (m) : CH ; 3.73 (s) : CO_2Me ; 2.05 (m) : CH ; 1.95 (s) : Ac ; 0.98 (m) : 2 Me.

Analysis $C_{17}H_{22}O_4N_2$ Calc : C = 64.13 H = 6.97 N = 8.80 O = 20.10
Found : C = 63.75 H = 6.79 N = 8.67 O = 20.68

Racemic Ac-Phe-ΔPhe-OMe 20b

Prepared as for 20a, recrystallized from ethanol-water. mp = 181-183°C.

NMR ($CDCl_3$,DMSO) : 9.05 (s) : NH (ΔPhe) ; 7.2-7.6 (m) : Ar, NH (Ac) and HC=C ; 4.87 (m) : CH (Phe) ; 3.75 (s) : OCH_3 ; 2.9 (dd, J = 14 Hz, J = 8 Hz) and 3.25 (dd, J = 14 Hz, J = 6 Hz) : CH_2 (Phe) ; 1.9 (s) : CH_3 (Ac).

Analysis $C_{21}H_{22}O_4N_2$ Calc : C = 68.83 H = 6.05
Found : C = 68.33 H = 5.98

APPENDIX

Determination of the various stereoselectivities involved in asymmetric hydrogenation of racemic dehydropeptides in presence of a chiral catalyst

Let assume that (R)-catalyst was used and that conversion of a racemic dehydrodipeptide was complete.

$$\text{(R)-substrate} \xrightarrow{H_2} \text{(RR')} + \text{(RS')}$$

$$\text{(S)-substrate} \xrightarrow{H_2} \text{(SR')} + \text{(SS')}$$

The stereoselectivity in the individual reduction of the (R)-substrate can be expressed by the diastereomeric ratio (RR'/RS') or by the diastereomeric excess :

$$de_R = (RR'-RS')/(RR'+RS')$$

Similarly the stereoselectivity of the reduction of the (S)-substrate is given by the diastereofacial selectivity (SR'/SS') or by the diastereomeric excess :

$$de_S = (SR'-SS')/(SR'+SS')$$

The values of de_R and de_S can be obtained by several methods.

1) The four stereoisomeric products are resolved by a chiral shift reagent (NMR) or by a chromatographic method (with chiral stationary phase). Let also assume that peak assignments are possible thanks to reference samples or literature data. In these conditions de_R and de_S (or the diastereofacial selectivities) are directly calculated using the observed relative amounts of stereoisomers.

2) A chromatographic method on an achiral stationary phase (HPLC in the present case) allows to measure the relative amounts of the diastereomeric products (RR'+SS') and (SR'+RS'). The result will be expressed as the molar fraction D of the (RR'+SS') diastereomer :

$$D = (RR'+SS')/(RR'+SS'+SR'+SS').$$

The mixture of dipeptides is then cleaved into individual aminoacids which are derivatized (see experimental section) for enantiomer analysis by capillary glc (on chiral stationary phase). The aminoacid initially present in the racemic substrate will appear in glc as a racemic mixture. The aminoacid created by the asymmetric reduction of the (R) and the (S)-substrate will have an enantiomeric excess :

$$ee_{RS} = \frac{(RR'+SR')-(RS'+SS')}{(RR'+SR'+RS'+SS')}$$

A simple calculation shows that de_R and de_S can be obtained from the values of D and ee_{RS} by the following relations :

$$de_S = ee_{RS} - 2D + 1$$

$$de_R = ee_{RS} + 2D - 1$$

3) The situation is the same as in 2) but the u and l diastereomers (see note b, table 1) are separated by preparative chromatography before hydrolytic cleavage and derivatization. The glc analysis (on chiral stationary phase) is there performed to measure the ee of the aminoacid coming from each diastereomer.

One obtains from l-diastereomer :

$$ee_l = (RR'-SS')/(RR'+SS').$$

The other diastereomer gives :

$$ee_u = (SR'-RS')/(SR'+RS').$$

It is not necessary to have reference samples to identify each diastereomer since the l diastereomer will lead to two aminoacids with the same absolute configuration (easy to see by glc on a chiral stationary phase).
The stereoselectivities de_R and de_S can be calculated by the relations given in 2) since ee_{RS} is related to ee_l or ee_u :

$$ee_{RS} = 2D\ ee_l = 2(1-D)ee_u$$

4) If the HPLC separation of the diastereomers is not possible then the hydrolytic cleavage and derivatization is performed on the crude reaction mixture.The value ee_{RS} is obtained as in 2). Let us assume that D can be measured by nmr. Then de_R and de_S are calculated by the previous relations. If D cannot be measured it is necessary to make an additional reaction on (R) or (S) substrate in order to get de_R or de_S, de_S or de_R beeing obtained by calculation. The validity of this method was checked in the hydrogenation of several dehydrodipeptides and of Ac-ΔPhe-$(Gly)_2$-Leu-OMe in presence of Rh(R,R)-diopCl using either the racemic or the (S)-dehydropeptide.

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