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# REDUCTION OF DEHYDROPEPTIDES CATALYZED BY THE COMPLEX $Rh^I$ · DIOXOP

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## Summary

The reduction of various dehydropeptides with (2*R*, 4*R*)DIOXOP-$Rh^I$ complex gives the corresponding dipeptides, with high stereoselectivity except for those derived from (*R*)phenylalanine. The $^{31}P$ NMR parameters of the intermediate complexes are very similar to those of simple enamide complexes.

Homogeneous asymmetric hydrogenation of olefins and carbonyl functions using chiral rhodium complexes has been much used in recent years [1]. Optical yields higher than 90% have been obtained particularly in the reduction of α-acylaminocinnamic acids [2] and itaconic acid [3]. Hydrogenation of dehydropeptides, previously carried out by heterogeneous catalysis [4], has recently been effected by homogeneous catalysis [5] using rhodium complexes containing *cis*-chelating ligands as DIOP, BPPM and DIPAMP. The chiral centre in the dehydropeptide usually has little influence on the stereoselectivity of the reduction.

DIOXOP, I, behaves quite differently [6]. It is a *trans*-chelating diphosphine, giving a dihydro complex, and reducing the aminoacids precursors with low e.e. (enantiomeric excess). In presence of a base, however, it acts as a *cis*-chelating ligand, giving high e.e. It was thus of interest to know the behaviour of such a ligand in an asymmetric hydrogenation where the reactant carries an optically active centre, as in the reduction of asymmetric dehydropeptides.

## Results and discussion

### *Reduction of dehydropeptides by the complex [Rh(COD)DIOXOP]$^+ClO_4^-$*

The unsaturated peptides, containing a dehydrophenylalanyl residue, were

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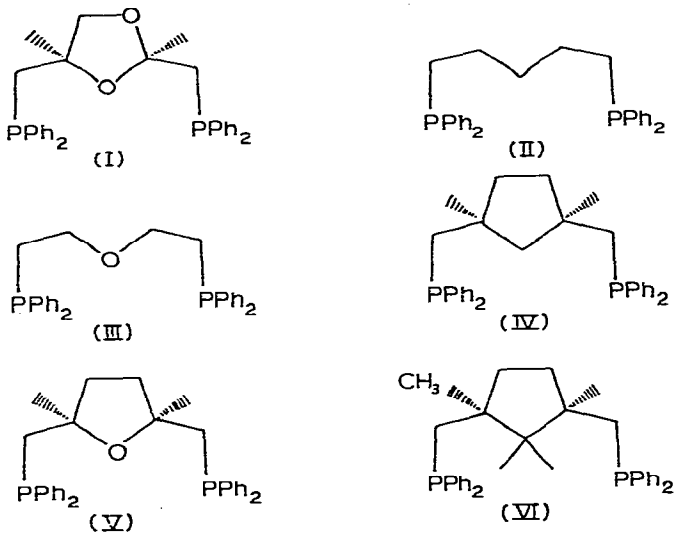
prepared according to Bergmann's procedure [7] by treatment of an azlactone with the sodium salt of the aminoacid. The corresponding methyl esters were obtained by esterification of the acid with diazomethane. All these compounds have the *Z* configuration [8].

The proportion of the two epimers formed on hydrogenation was estimated, after esterification of the crude mixture with diazomethane, either (a) by $^1H$ NMR spectroscopy in the presence of $Eu(fod)_3$ [5] [observation of the ace-




tamido and ester group], and also, for VIIb and VIIc, by observation of the methyl signals [9], or (b) by HPLC (silica, eluent hexane/ethylacetate). As

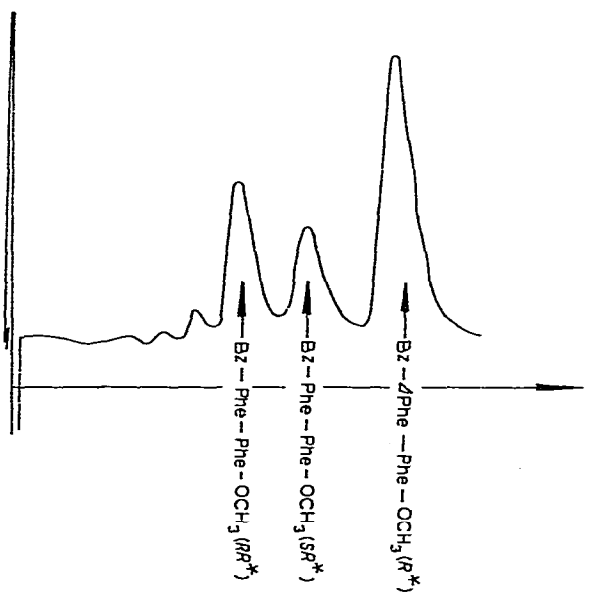



**Fig. 1. HPLC chromatogram of the product of reduction of Bz-Δ-Phe-Phe-OH after methylation.**

TABLE 1

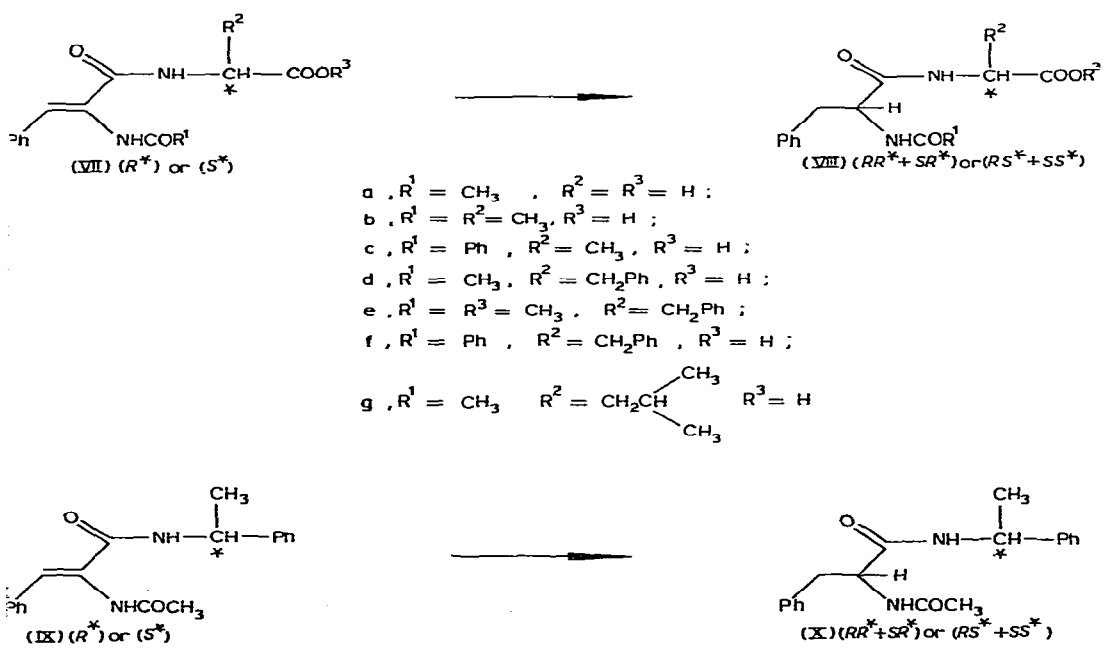
HYDROGENATION WITH [Rh(COD)DIOXOP]$^+ClO_4^-$ [a]

| Run | Substrate | $Et_3N$ [b] | Diastereomeric ratio (%) | | e.e. (%) (config.) [c] |
|---|---|---|---|---|---|
| 1 | VIIa | — | | — | 8 (*S*) [e] |
| 1a | VIIa | yes | | — | 3 (*R*) [e] |
| 2 | VIIb (*S*) | — | *SS**/*RS** | 86/14 | 72 (*S*) |
| 2a | VIIb (*S*) | yes | *SS**/*RS** | 76/24 | 52 (*S*) |
| 3 | VIIb (*R*) | — | *RR**/*SR** | 20/80 | 60 (*S*) |
| 3a | VIIb (*R*) | yes | *RR**/*SR** | 21/79 | 58 (*S*) |
| 4 | VIIc (*S*) | — | *SS**/*RS** | 72/28 | 44 (*S*) |
| 5 | VIIc (*R*) | — | *RR**/*SR** | 20/80 | 60 (*S*) |
| 6 | VIId (*S*) | — | *SS**/*RS** | 93/7 | 86 (*S*) |
| 6a | VIId (*S*) | yes | *SS**/*RS** | 93/7 | 86 (*S*) |
| 7 | VIIe (*S*) | — | *SS**/*RS** | 89/11 | 78 (*S*) |
| 8 | VIId (*R*) | — | *RR**/*SR** | 40/60 | 20 (*S*) |
| 8a | VIId (*R*) | yes | *RR**/*SR** | 27/73 [d] | 46 (*S*) |
| 9 | VIIe (*R*) | — | *RR**/*SR** | 34/66 | 32 (*S*) |
| 10 | VIIf (*S*) | — | *SS**/*RS** | 81/19 | 62 (*S*) |
| 11 | VIIf (*R*) | — | *RR**/*SR** | 48/52 | 4 (*S*) |
| 12 | VIIg (*S*) | — | *SS**/*RS** | 90/10 | 80 (*S*) |
| 13 | IX (*S*) | — | *SS**/*RS** | 95/5 | 90 (*S*) |
| 14 | IX (*R*) | — | *RR**/*SR** | 32/68 | 36 (*S*) |

[a] [substrate] = 5 × $10^{-2}$ *M*; [substrate]/[Rh] = 25; solvent = ethanol; *T* = 25°C $p(H_2)$ = 1.1 atm. Yield quantitative except run 8a. [b] [$Et_3N$]/[Rh] = 3. [c] e.e. obtained after removal of the chiral inductor. [d] 60% hydrogenation. [e] Based on $[\alpha]_D^{22}$ = −14.5 (*c* 10, DMF) for (*S*)-Ac-Phe-Gly-$OCH_3$ [16].

previously noted [5,10], the *RR** and *SS** isomers are eluted more rapidly (Fig. 1).

The stereochemistries of the products were established by comparison of their $^1H$ NMR spectra (compounds VIIIb and VIIIc) [9,11] and their optical



rotations (compounds VIIId, VIIIe and VIIIf) [12] with those given in the literature. The results obtained in the reduction of some dehydropeptides are shown in Table 1.

Without a chiral centre in the substrate (run 1), the stereoselectivity is very low, the value of the asymmetric induction [8(*S*)] being the same as in the reduction of α-acetamidocinnamic acid [13(*S*)] with the same ligand. Addition of triethylamine (run 1a) has little influence. With an (*S*)aminoacid (runs 2, 4, 6, 7, 10 and 12) or a (*S*)amine (run 13) the stereoselectivity is generally high, and the configuration of the newly created asymmetric center is (*S*). The lowering of selectivity observed from $R^1 = CH_3$ to $R^1 = Ph$ can be compared to that found in the reduction of α-acetamido and α-benzamidocinnamic acid [13% (*S*) and 0% (*S*), respectively] with the $Rh^{(I)}$-DIOXOP complex [14]. With an (*R*)aminoacid or an (*R*)amine, the stereoselectivity is high for the alanine derivative (runs 3, 3a and 5), but low for the phenylalanine derivative and the α-phenylethylamide (runs 8, 9a, 11 and 14). The configuration of the newly created asymmetric center is (*S*) however.

Thus, whatever the configuration of the existing chiral centre, the newly created asymmetric center is always (*S*). The reduction of some esters of Z-N-acetyl-Δ-phenylalanine XI, with DIOXOP, I, gives the (*S*)amino acids with very low enantioselectivity (<18%) [14]. By contrast, (*S*) dehydropeptides are reduced with good stereoselectivity. This is an example of a double asymmetric induction [15], where the induction due to the chiral inducer is important. In view of the results obtained previously in the reduction of dehydroaminoacids, this high stereoselectivity is unexpected.

When the chiral aminoacid is (*R*), alanine and phenylalanine behave different. With an (*R*)alanyl side chain, the stereoselectivity is the same as with (*S*)alanine but with (*R*)phenylalanine, the stereoselectivity is very low. In this latter case, the asymmetric induction due to the calatyst and the existing chiral centre are opposite.

Addition of triethylamine has little influence on these stereoselectivities. Only for (*R*) VIId (run 8a) is a smaller reactivity and a greater stereoselectivity observed. It has been shown previously that the role of the amine is to promote the formation of a complex in which the DIOXOP I is a *cis*-chelating ligand [6].

TABLE 2

HYDROGENATION WITH [Rh(COD)DIOXOP]$^+ClO_4^-$. INFLUENCE OF THE AMINE [a]

| Run | Substrate | $[C_6H_5-\overset{*}{C}H(CH_3)-NH_2]$/[substrate] | e.e. (%) (config) [b] |
|---|---|---|---|
| 15 | XI | 0 | 13 (*S*) [6] |
| 15a | XI | 0.13 (*R*) | 84 (*S*) |
| 15b | XI | 0.13 (*S*) | 84 (*S*) |
| 1 | VIIa | 0 | 8 (*S*) |
| 1b | VIIa | 0.13 (*R*) | 3 (*R*) |
| 1c | VIIa | 0.13 (*S*) | 2 (*S*) |
| 1d | VIIa | 1 (*R*) | 10 (*R*) |

[a] [substrate] = $5 \times 10^{-2}$ *M*; [substrate]/[Rh] = 25; solvent = ethanol; T = 25°C; $p(H)_2$ = 1.1 atm.; yield quantitative. [b] e.e. based on the values: (*R*)-*N*-acetylphenylalanine, $[\alpha]_D^{25} = -46.0$ (*c* 1, $C_2H_5OH$) [18]; (*S*)-Ac-Ph-Gly-$OCH_3$, $[\alpha]_D^{22} = -14.5$ (*c* 10, DMF) [16].

TABLE 3

HYDROGENATION OF VIIb AND VIId WITH VARIOUS CATALYSTS $[Rh(COD)L_2]^+ClO_4^-$ [a]

| Run | Substrate | $L_2$ | Diastereomeric ratio (%) | | e.e. (%) (config.) [b] |
|---|---|---|---|---|---|
| 6 | VIId (*S*) | 1 | *SS**/*RS** | 93/7 | 86 (*S*) |
| 16 | VIId (*S*) | 2 | *SS**/*RS** | 67/33 | 34 (*S*) |
| 17 | VIId (*S*) | 3 | *SS**/*RS** | 40/60 | 20 (*R*) |
| 18 | VIId (*S*) | 4 | *SS**/*RS** | 64/36 | 28 (*S*) |
| 19 | VIId (*S*) | 5 | *SS**/*RS** | 60/40 [c] | 20 (*S*) |
| 20a | VIId (*S*) | 6 | *SS**/*RS** | 38/62 [d] | 24 (*R*) |
| 20b | VIId (*R*) | 6 | *RR**/*SR** | — [e] | — |
| 2 | VIIb (*S*) | 1 | *SS**/*RS** | 86/14 | 72 (*S*) |
| 21 | VIIb (*S*) | 2 | *SS**/*RS** | 60/40 | 20 (*S*) |
| 22 | VIIb (*S*) | 3 | *SS**/*RS** | 48/52 | 4 (*R*) |
| 23a | VIIb (*S*) | 6 | *SS**/*RS** | — [f] | — |
| 23b | VIIb (*R*) | 6 | *RR**/*SR** | 58/42 [g] | 4 (*R*) |

[a] [substrate] = $5 \times 10^{-2}$ *M*; [substrate]/[Rh] = 25; solvent = ethanol; $T = 25°C$; $p(H_2) = 1.1$ atm; time = 24 h. [b] e.e. obtained after removal of the chiral inductor. [c] 70% hydrogenation. [d] 50% hydrogenation; [e] 10% hydrogenation. [f] 10% hydrogenation. [g] 50% hydrogenation.

the reduction taking place by the "unsaturate" route and so giving high e.e. In order to define precisely the role of the amine in the reduction of dehydropeptides, we used (*R*)- and (*S*)-α-phenylethylamine in the reduction of Ac-Δ-Phe-Gly-OH, VIIa. In presence of (*R*)- or (*S*)-α-phenylethylamine, the *N*-acetylcinnamic acid XI gives (*R*)-*N*-acetylphenylalanine with 84% e.e. These results confirm the mechanism previously obtained by NMR spectroscopy [6], where the amine promoted only the formation of the enamido complex.

The presence of amine in the reduction of VIIa (Table 2) does not enhance the stereoselectivity. However, the different values obtained with (*R*)- and (*S*)-α-phenylethylamine, although low, show that the reduction probably takes place via the "dihydro" route, the dehydropeptide acting as a monodentate ligand and being reduced as the ammonium salt.

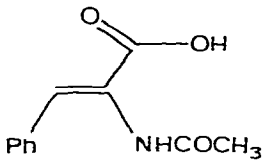
*Reduction by various oxadiphosphines*

In order to provide more information on the mechanism of the reduction with DIOXOP I, we reduced dehydropeptides VIIb and VIId with $H_2$ in the presence of rhodium catalysts containing oxadiphosphines III and V, their carbon analogs II and IV, and camphos VI. The results obtained, summarized in Table 3, clearly show that:

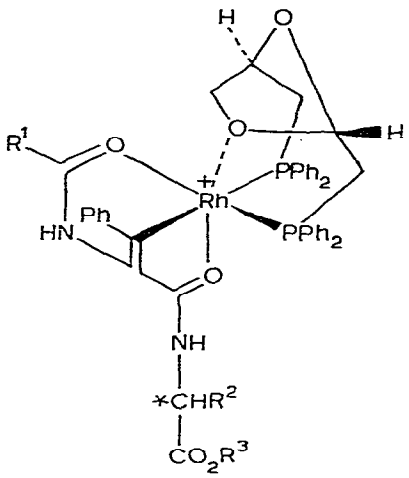
a) Use of the achiral ligands II and IV leads to an excess of the *SS** diastereoisomer in the reduction of the (*S*)-dehydropeptide [5]

b) The achiral oxadiphosphines III and V behave differently, III , giving an excess of the *RS** diastereoisomer and V an excess of the *SS** diastereoisomer. Since the last ligand has the structure most closely resembling DIOXOP I, it seems that the dioxolan ring induces the formation of the *SS** isomer from the (*S*)-dehydropeptide. This same trend is found in the reduction of XI by DIOXOP I.

c) Camphos, VI, shows a very low reacticity and stereoselectivity, analogous to that found in the reduction of XI [17]. So camphos VI and DIOXOP I, without amine, seem to behave differently in hydrogenation.



(XI)



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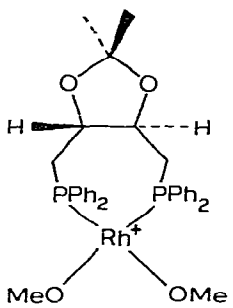

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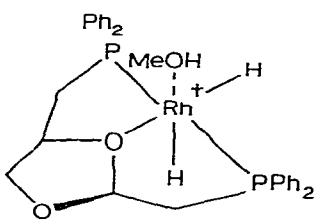

(XII)

*$^{31}P$ NMR studies*

Under the conditions described previously [6,20], dehydrodipeptides VII react with the DIOXOP-rhodium complex XII formed by hydrogenation of the corresponding cyclooctadiene complex in methanol solution. The species observed by $^{31}P$ NMR spectroscopy are very similar to those described for simple DIOXOP enamide complexes. At room temperature a sharp 8-line multiplet is seen, and the chemical shifts and coupling constants are listed in Table 4. Triethylamine has little effect, although traces of a second species were observed in one experiment with VIIf in the absence of $NEt_3$, but not in its presence. Structure XIII, which is based on previous observations, is suggested. Since the same type of complex is observed for a wide range of stereoselectivities, its structure cannot be critical in determining the optical course of reaction.

TABLE 4

$^{31}$P NMR PARAMETERS FOR THE ENAMIDO COMPLEXES [a, b]

| Substrate | Ligand | δ (ppm) | | J(Rh—P(1)) | J(Rh—P(2)) | J(P(1)—P(2)) |
|---|---|---|---|---|---|---|
| | | P(1) | P(2) | | | |
| VIIa | DIOXOP | 50.2 | 10.9 | 158 | 114 | 28 |
| VIIc (*R*) | DIOXOP | 49.4 | 11.4 | 157 | 115 | 27 |
| VIIc (*S*) | DIOXOP | 49.4 | 11.4 | 159 | 115 | 26 |
| VIIf (*R*) | DIOXOP | 47.9 | 11.6 | 160 | 116 | 25 |
| VIIf (*S*) | DIOXOP | 49.1 | 10.1 | 159 | 117 | 26 |
| VIIf (*R*) | DIOP [c] | 38.8 | 14.4 | 150 | 145 | 51 |
| VIIf (*S*) | DIOP [c] | 38.2 | 14.9 | 153 | 155 | 53 |

[a] External reference $H_3PO_4$ (85%) at 300 K. [b] Coupling constants in Hz. [c] DIOP = *trans*-4,5-bisdiphenylphosphinomethyl-2,2-dimethyldioxolan; Spectrum at 225 K.

Parallel experiments were carried out with (*R*)- or (*S*)-VIIb and the related DIOP solvate XIV. Again, one diastereoisomeric complex was formed, but it was necessary to record spectra at —50°C in order to obtain sharp lines. Thus the rate of dissociation is in this case much greater than with simple dehydroamino acids, which give sharp spectra at —15°C. Amides are much more basic than esters, and olefin dissociation may be assisted by prior coordination of the second amide group of VIIf. In contrast, both carbonyl groups are thought to be coordinated in DIOXOP complexes [6].

*Conclusion*

Although reduction of aminoacids precursors with $Rh^I$-(2*R*,4*R*)DIOXOP in the absence of amine gives low e.e., dehydropeptides are generally reduced, under the same conditions, with high stereoselectivity, especially when derived from an (*S*)aminoacid. With phenylalanine derivatives, the existing chiral center has the greatest influence in the reduction of the dehydropeptide, and this contrasts markedly with the results for DIOP and Dipamp [5].

## Experimental

$^1$H NMR spectra were recorded on a Brucker WP 80 CW (90 MHz) spectrometer and $^{31}$P NMR spectra on a Brucker WH 90 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The optically pure amino acids [(*R*)- and (*S*)-alanine, (*R*)- and (*S*)-phenylalanine, (*S*)-leucine] and (*R*)- and (*S*)-α-phenylethylamine were commercial samples. The preparation of the complexes was previously described [6,19].

*Dehydropeptides synthesis*

The dehydropeptides were prepared according to Bergmann [7] by reaction of the sodium salt of the (*S*)- or (*R*)aminoacid with the unsaturated azlactone of *N*-acetyl- or *N*-benzoylphenylalanine.

*Ac-Δ-Phe-(S)-Phe-OCH$_3$, VIIe.* Obtained by diazotation of (*S*)-VIId. yield: 90%; $[\alpha]_D^{20}$ = —9.5 (*c*1, pyridine); m.p. 188°C [litt. [5] $[\alpha]_D^{20}$ = —9.6 (*c*2, pyridine); m.p. 188—189°C].

*Ac-Δ-Phe-(R)-Phe-OCH$_3$, VIIe.* Obtained by diazotation of (*R*) VIId yield = 92%; $[\alpha]_D^{20}$ = +9.5 (*c*1, pyridine); m.p. 188°C.

*Bz-Δ-Phe-(S)-Ala-OH, VIIc.* $[\alpha]_D^{20}$ = +62.0 (*c*1, pyridine); m.p. 173°C.

*Bz-Δ-Phe-(R)-Ala-OH, VIIc.* $[\alpha]_D^{20}$ = —62.5 (*c*1, pyridine); m.p. 172—173°C.

*Bz-Δ-Phe-(S)-Phe-OH, VIIb.* $[\alpha]_D^{20}$ = +47.5 (*c*1, pyridine), m.p. 183°C.

*Bz-Δ-Phe-(R)-Phe-OH, VIIb.* $[\alpha]_D^{20}$ = —48.0 (*c*1, pyridine); m.p. 183°C.

*Ac-Δ-Phe-(R)- or (S)-α-phenylethylamide, IX*

The azlactone of *N*-acetylphenylalanine (3.93 g, 21 mmol) is refluxed for 2 hours in dry benzene (50 ml) containing (*R*)- or (*S*)-α-phenylethylamine (2.55 g, 21 mmol). The solution is added to HCl (0.5 *N*, excess) and the solid is filtered off and recrystallized from water/methanol. Yield 85%.

(*R*) isomer: $[\alpha]_D^{20}$ = —45.5 (*c*1, pyridine), m.p. = 192°C.

(*S*) isomer; $[\alpha]_D^{20}$ = +46.5 (*c*1, pyridine), m.p. = 192°C.

*Hydrogenation*

Hydrogenations are performed at room temperature following the usual procedure. After 24 h, the solution is treated with an acidic resin and directly esterified with $CH_2N_2$. The proportions of the isomers are measured by $^1$H NMR spectroscopy in $CDCl_3$ in the presence of small amounts of Eu(fod)$_3$ or by HPLC (support: Lichroprep Si 60; eluent: hexane/ethylacetate 70/30).

*$^{31}$P NMR studies*

$^{31}$P NMR experiments are carried out, as previously described, in 8 mm tubes sealed under argon, and run with an external concentric lock ($D_2O$ or $CD_3OD$) [20].

*Determination of the configuration of X*

Reduction of (*S*)-IX in ethanol with Pd/C gives a mixture of two epimers

$$CH_3(d)\ 1.4\text{ and }1.2;\ CH_3\overset{O}{\overset{\|}{C}}\text{-}(s)\ 1.9\text{ and }1.8$$

in the proportions 46/54 corresponding to 8% e.e. (*R*) given by Sheehan [4].

Hydrolysis of X obtained from (*S*)-IX according to Sheehan [4] gives (*S*)-phenylalanine, $[\alpha]_D^{20}$ = —35.0 (*c*2, water) corresponding to ~90% e.e.

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