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ASYMMETRIC SYNTHESIS OF AMINO ACIDS VIA THE CATALYTIC REDUCTION OF ACYLAMINOACRYLIC ACID AZLACTONE DERIVATIVES.

24. REDUCTIVE AMINOLYSIS OF 2-METHYL-4-BENZYLIDENE-Δ^2-OXAZOLIN-5-ONE UPON TREATMENT WITH A CATALYTIC SYSTEM BASED ON S-PHENYLALANINE DERIVATIVES

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UDC 541.63:542.941.7+542.958.3:547.787:547.586.2

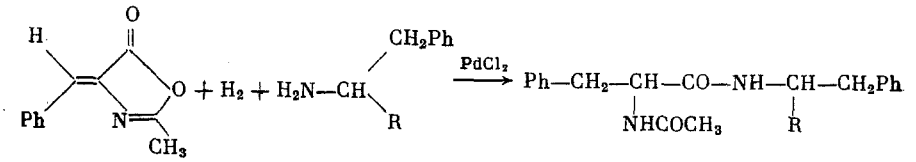
Reductive aminolysis of 2-methyl-4-benzylidene-Δ^2-oxazolin-5-one upon treatment with a $PdCl_2$–S-phenylalanine ester (dimethylamide) catalytic system leads to the formation of the corresponding acylated dipeptide derivatives, with the R,S-configuration (diastereomer) predominating (DE 9-27%). The reaction stereoselectivity in dimethoxyethane increases sharply in the presence of triethylamine additive, and in the case of S-phenylalanine methyl ester reaches 47%. The stepwise mechanism for this process has been studied.

The reductive aminolysis (RA) reaction of Δ^2-oxazolin-5-ones upon treatment with a $PdCl_2$–S-α-phenylethylamine (PEA) catalytic system (CS) leads to the formation of acylamino acid phenylethylamide derivatives, with the SS-configuration predominating; hydrolysis of the latter gives optically active amino acids [1]. Attempts to improve this CS have led us to examine the use of S-phenylalanine dimethylamide and ester derivatives, since the presence of additional functional groups in these ligands should provide new coordination possibilities for the Pd atom in the catalytic complex and in this way affect its reaction stereoselectivity. In addition, the use of S-Phe derivatives as nucleophiles in the RA reaction opens up a pathway for the catalytic synthesis of optically active dipeptides.

DISCUSSION OF RESULTS

The RA of 2-methyl-4-benzylideneoxazolin-5-one (I) was carried out in a variety of solvent media in the presence of $PdCl_2$–chiral nucleophile CS (Scheme 1).

Scheme 1



(I) *S*-(II) (III)

R = COOMe (a), COO*i*-Pr (b), COO*t*-Bu (c), $CON(Me)_2$ (d).

We should point out that regardless of the stereochemical notation "S," all of the nucleophiles used in this reaction had a configuration analogous to that of R-α-PEA (Scheme

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TABLE 1. RA of 2-Methyl-4-benzylideneoxazolin-5-one (I) upon Treatment with S-Phe Dimethylamide (IId) under One- and Two-Step Reaction Conditions [0.3 mmoles (I), 0.45 mmoles (IId), 0.45 mmoles Et_3N, 0.06 mmoles $PdCl_2$, 4.5 ml solvent]

Solvent	Total yield, %	DE RS-(III), %	$k \cdot 10^2$, min^{-1}	Solvent	Total yield, %	DE RS-(III) %	$k \cdot 10^2$, min^{-1}
One-step process				Two-step process			
DME	92	9	1,2	DME	85	26	
DME/Et_3N	86	30	2,5	DME/Et_3N	–	35	
t-BuOH	67	27	1,5	*t*-BuOH	68	18	
t-BuOH/Et_3N	56	16	1,7	*t*-BuOH/Et_3N	–	10	
i-PrOH	–	16	2,7				

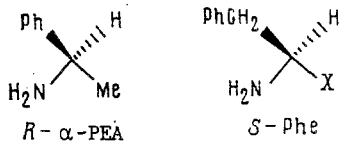
TABLE 2. RA of (I) upon Treatment with Amino Esters [0.4 mmoles (I), 0.6 mmoles (II), 0.6 mmoles Et_3N, 0.08 mmoles $PdCl_2$, 6 ml solvent)

Amino ester	Solvent	Yield, %	Product composition, %			DE RS-(III), %	$k \cdot 10^2$, min^{-1}
			dipeptide (III)	AcPhe	unsat. dipeptide		
S-PheOMe (IIa)	DME	93	93	7	–	18	3,8
	DME/Et_3N	71	87	13	–	47	2,6
	t-BuOH	75	85	15	–	15	1,4
	t-BuOH/Et_3N	70	85	15	–	8	1,7
	i-PrOH	77	88	12	–	4	3,2
	Dioxane	65	87	13	–	14	1,7
	DME/H_2O = 15:1	60	85	–	15	4	13,0
S-PheO*i*-Pr (IIb)	DME	65	100	–	–	23	2,7
	DME/Et_3N	60	100	–	–	41	2,7
	t-BuOH	62	88	12	–	11	2,1
	t-BuOH/Et_3N	57	85	15	–	6	1,6
	i-PrOH	64	90	10	–	5	2,0
S-PheO*t*-Bu * (IIc)	DME	69				25	2,3
	DME/Et_3N	67				45	2,0
	t-BuOH	63				13	2,7
	t-BuOH/Et_3N	56				9	2,0

*The main product (IIIc) does not contain many impurities, and it is difficult, therefore, to determine its composition accurately.

2), so that we would expect to observe the formation of the R-configuration at the α-site upon RA; this was in fact realized. In all cases AcPhePhe esters or dimethylamide (III) were formed with an R,S-diastereomer excess (DE).

Scheme 2



R-α-PEA *S*-Phe

X = COOMe, COO*i*-Pr, COO*t*-Bu, $CON(Me)_2$.

The results of our RA experiments are summarized in Tables 1 and 2. Reaction stereoselectivity was determined by PMR and GLC analysis. In the case of S-PheOMe the diastereomer ratio was estimated based on the integrated intensity ratio of the signals corresponding to the OCH_3 protons in their PMR spectra. In all other cases PMR signal resolution for the diastereomers was insufficient for this purpose, and the acidic methanolysis of (III) to AcPheOMe and S-(II)·HCl was used [2]. The ratio of enantiomers was determined by GLC on capillary columns filled with a chiral phase [3]. The results of enantiomeric GLC analysis were then applied to derive the signal assignments in their PMR spectra. The rate of RA, which was measured based on H_2 absorption, can be described in terms of a first-order rate equation with respect to the unsaturated substrate and is only weakly dependent on the nature of the solvent or nucleophile used.

As can be seen from the data in Tables 1 and 2, the reaction stereoselectivity in dimethoxyethane (DME) is relatively low. The Rs-(III) DE is 9% for the dimethylamide and 18-25% for esters, which is significantly lower than that observed upon RA with S-PEA (40%) [1], although the reaction rates for CS based on S-Phe and S-PEA are comparable. It should also be noted that the substituent in the ester group exerts very little effect on the process stereoselectivity; the DE increases from 16 to 25% in the transition from the methyl ester to the tert-butyl ester.

Replacement of aprotic DME by alcohol-type solvents results in variable effects on the stereoselectivity of RA with Phe esters and amide; this suggests there are substantial differences in these CS. In the case of the dimethylamide derivative (IId), a large increase in the DE of RS-(IIId) is observed: from 9% in DME to 16% upon RA in i-PrOH and 27% in t-BuOH. The use of esters (IIa-c) as nucleophiles leads to a small decrease in the stereoselectivity of RA (to 15-11%), although in the case of (IIa) this difference is insignificant; in the transition from (IIb) to (IIc), however, the DE in t-BuOH is reduced twofold. In i-PrOH the reaction stereoselectivity is only 4% RS.

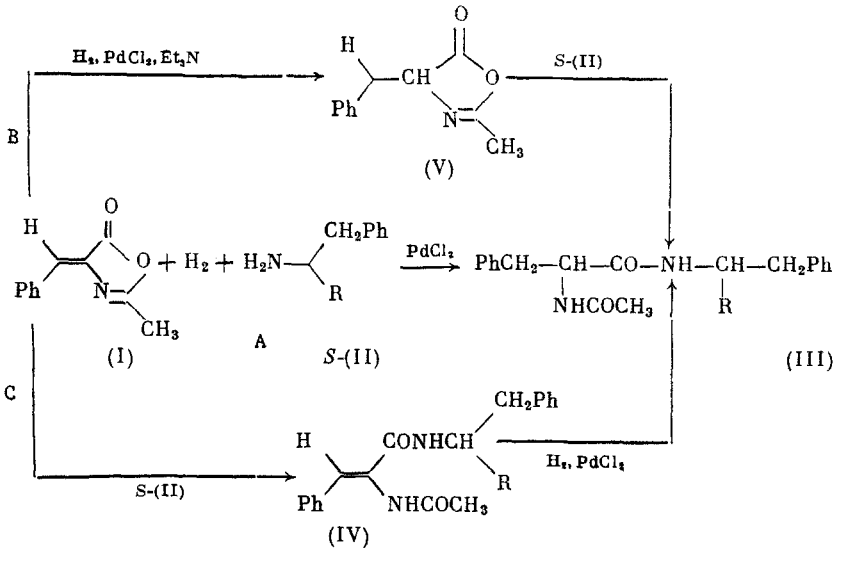
A distinguishing feature of CS based on S-Phe derivatives compared to S-PEA is the strong effect of the addition of an achiral component Et_3N on the process stereoselectivity. Upon RA in DME addition of Et_3N in an equimolar ratio based on the amount of nucleophile leads to a sharp increase in the DE magnitude: to 30% RS for the dimethylamide (Table 1) and to 41-47% for esters (Table 2). The stereoselectivity remains practically unchanged upon further increases in the Et_3N:nucleophile ratio, while the amount of side products increases. An inverse effect of Et_3N addition is observed when the solvent is changed from DME to t-BuOH; addition of Et_3N reduced the DE to 16% RS-(IIId) and to 6-9% for esters.

The factors responsible for the effects of Et_3N on the stereoselectivity of RA are not clear, but they are probably different for different catalytic systems.

Another interesting observation is the catalytic activity of H_2O upon RA involving S-PheOMe. The reaction rate increases by an order of magnitude upon addition of small amounts of water (Table 2), although the stereoselectivity falls correspondingly and the reaction products contain up to 15% unsaturated dipeptide (IV). In addition to increasing the rate of hydrogenation H_2O also apparently catalyzes the aminolysis of (I).

In studying the stepwise mechanism for the RA of azlactones we should consider the following possible pathways for the process to occur (Scheme 3).

Scheme 3



It has previously been shown [1] that the RA of (I) upon treatment with S-α-PEA in DME represents a combination of hydrogenation and aminolysis processes within the inner sphere of the catalytic complex (path A). In t-BuOH the reaction mechanism changes and the process occurs via the intermediate formation of a saturated azlactone (V) (path B).

TABLE 3. Aminolysis of 2-Methyl-4-benzyloxyoxazolin-5-one (V) by Amino Esters [0.4 mmoles (V), 0.6 mmoles (II), 0.6 mmoles Et_3N, 6 ml solvent]

Amino ester	Solvent	Yield, %	Product comp., %		DE RS-(III), %
			dipeptide	AcPhe	
S-PheOMe (IIa)	DME	90	100	–	11
	DME/Et_3N	85	94	6	46
	t-BuOH	71	91	9	14
	t-BuOH/Et_3N	78			7
	DME/H_2O = 15:1	92	100	–	3
S-PheO*i*-Pr (IIb)	DME	75	95	5	36
	DME/Et_3N	80	100	–	40
	t-BuOH	70	95	5	14
	t-BuOH/Et_3N	70	85	15	7
S-PheO*t*-Bu * (IIc)	DME	70			24
	DME/Et_3N	75			42
	t-BuOH	70			13
	t-BuOH/Et_3N	80			8

*The main product (IIId) does not contain much impurity and an accurate composition was therefore difficult to determine.

TABLE 4. Hydrogenation of Unsaturated Dipeptides (IVa) and (IVd) [0.4 mmole (IV), 0.08 mmole $PdCl_2$, 6 ml DME, 0.6 mmole (II)]

Substrate	Nucleophile	Yield, %	DE(III), %	Configuration	$k \cdot 10^2$, min^{-1}
(IVa)	–	100	11	*RS*	2,4
(IVa)	*S*-PheOMe	100	12	*SS*	1,5
(IVd)	–	75	21,5	*RS*	1,4
(IVd)	*S*-PheN(Me)$_2$	75	21	*SS*	1,3

In the present paper, using CS derived from S-Phe derivatives we have also examined the possibility of the intermediate formation of both a saturated azlactone (V) and dipeptide (IV) (path C) during the course of RA.

It should be noted that in the case of CS derived from S-Phe esters in practically all of the experiments carried out on the RA of (I) the reaction products contained up to 15% AcPhe, which is the hydrolysis product of (V) upon workup of the catalyzate mixture. This suggests, probably, that the hydrogenation and aminolysis steps in this case are nonsynchronous, and RA occurs according to path B via a saturated azlactone intermediate. Infrared spectroscopic analysis of the reaction mixture during the course of RA in DME in the presence of S-PheOMe revealed the presence of a CO band at 1820 cm^{-1}, corresponding to (V). This band was also observed upon RA with Et_3N additive. The IR spectroscopic data thus confirm our hypothesis that there is a change in the stepwise mechanism for RA in DME upon using CS derived from amino esters.

In order to verify this assumption, we have also examined the aminolysis of the saturated azlactone (V) upon treatment with S-Phe esters. Compound (V) was prepared by hydrogenation of (I) in DME on $PdCl_2$ in the presence of Et_3N as base, which facilitates hydrogenation, but does not promote oxazolone ring opening. The results of this two-step process are shown in Table 3. In all cases dipeptide esters (III) were obtained with the RS-diastereomer predominating, just as in RA. In fact, the stereoselectivity of the RA and two-step processes are practically identical. A small discrepancy is noted only in the case of the aminolysis of (V) upon treatment with (IIb) in DME, where the DE (IIIb) is 36% RS. We note also that addition of Et_3N has the same effect on stereoselectivity that was observed upon RA.

All of these effects taken together, namely the identical stereodirectedness of the reaction, the similar DE RS-(III) values, the singular effect of Et_3N on the reaction stereoselectivity, and the presence of (V) in the reaction mixture, lead us to conclude unequivocally that the RA of (I) upon treatment with $PdCl_2$–S-Phe esters Cs in either DME or t-BuOH solution occurs in two steps via the intermediate formation of a saturated azlactone. In the case of S-PheO(i-Pr) this pathway is not exclusive, but probably predominates here aswell.

AcPhe is not detected among the reaction products upon RA of (I) via reaction with S-Phe dimethylamide (IId). Investigation of the aminolysis of (V) in the presence of (IId) revealed significant differences in the stereoselectivity of RA and of the two-step process (Table 1) both in DME and in t-BuOH. Addition of Et_3N had the same influence, however, as in all the other experiments: upon aminolysis of (V) in DME the DE increases from 26 to 35%, while in t-BuOH it decreases from 18 to 10% RS-(IIId).

It would seem, therefore, that RA of (I) upon treatment with the $PdCl_2$–S-Phe dimethylamide CS proceeds by bypassing the saturated azlactone formation stage, although addition of Et_3N may direct the process via path B, since the stereoselectivity of the one- and two-step processes narrows at this point: in DME the DE is 30 and 35% RS-(IIId), respectively, while in t-BuOH the DE is 16 and 10%, respectively.

In order to check the feasibility of the intermediate formation of an unsaturated dipeptide (IV) upon RA using CS based on S-Phe derivatives, we have also examined the diastereoselective hydrogenation of (IVa) and (IVd) (Table 4). Upon hydrogenation of (IV) in DME on $PdCl_2$ in the absence of nucleophiles compounds (IIIa) and (IIId) are formed, respectively, with the RS-diastereomer in excess, just as is observed upon RA. The stereoselectivity is not high, however, corresponding to 11% RS-(IIIa) and 21.5% (IIId); in the case of the dimethylamide derivative the DE exceeds by a factor of two the result obtained for RA. Hydrogenation in the presence of $PdCl_2$–S-(IIa, d) CS leads to products with the opposite configuration, the stereoselectivity being 12% SS-(IIIa) and 21% SS-(IIId). In these two CS, therefore, we can infer double asymmetric induction, acting in opposite directions, since the presence of a chiral nucleophile in the reaction medium leads to inversion of configuration in the product. Comparison of the results of diastereoselective hydrogenation and RA reactions using CS based on S-Phe derivatives leads us to predict that intermediate formation of unsaturated (IV) probably does not take place upon RA.

Based on these results we also conclude that RA of (I) upon treatment with the $PdCl_2$–S-Phe dimethylamide CS occurs within the inner sphere of the catalytic complex without diffusion of the intermediate products to the bulk solution. Using $PdCl_2$–S-Phe ester CS produces a change in the stepwise mechanism, where RA proceeds via intermediate formation of a saturated azlactone, at least to a significant extent.

The best results were obtained for the one- and two-step process in DME upon treatment with a $PdCl_2$–S-PheOMe CS in the presence of Et_3N, where the DE for RS-(IIIa) was 47%. RS-AcPhePheOMe was isolated with a diastereomeric purity of 91% after two recrystallizations.

EXPERIMENTAL

PMR spectra were recorded on a Bruker WP-250 spectrometer (δ, ppm), IR spectra on a UR-20 spectrophotometer, GLC analysis was carried out on a BioKhrom-1 chromatograph equipped with a flame ionization detector using a glass capillary column (15 m × 0.25 mm) filled with tert-butylamide N-docosanoyl-L-valine chiral phase [3]. Enantiomer ratios were determined in the form of AcPheOMe at 165°C and a (nitrogen) carrier gas flow rate of 1 ml/min. Specific rotations were measured using an AI-EPO photoelectronic polarimeter, while optical rotatory dispersion (curves) were measured on a Spectropol-1 spectropolarimeter. $PdCl_2$ was pure grade, 2-methyl-4-benzylidene-Δ^2-oxazolin-5-one (I) had mp 150°C, S-phenylalanine tert-butyl ester (IIc) $[\alpha]_D$ 41.6° (C 2, ethanol), optical purity 94% [4].

S-Phenylalanine Methyl Ester Hydrochloride (IIa). Prepared according to [4] in 72% yield, mp 159-160°C (absolute MeOH:absolute ether = 1:2), $[\alpha]_D$ −4.6° (C 5, H_2O).

S-Phenylalanine Isopropyl Ester Hydrochloride (IIb). To 3 g S-Phe was added 60 ml absolute i-PrOH, and the suspension was refluxed for 7 h with a condenser while passing a slow stream of dry HCl through the mixture. The mixture was allowed to stand overnight fitted with a calcium chloride drying tube. The solvent was evaporated and the product crystallized from i-PrOH. Yield 3.12 g (IIb), 71%. $[\alpha]_D$ −3.7° (C 5, H_2O). Enantiomeric GLC analysis revealed pure S-isomer. Found, %: C 59.44, H 7.94, N 5.80, Cl 14.52%. Calculated, %: C 59.14, H 7.39, N 5.75, Cl 14.58.

S-PHENYLALANINE DIMETHYLAMIDE (IId)

N-tert-Butyloxycarbonyl-S-phenylalanine N-Hydroxysuccinimide Ester (VI). At −5°C to a solution of 3.97 g BOC-S-Phe (0.015 moles) and 2.29 g N-hydroxysuccinimide (0.02 moles) in 90 ml CH_2Cl_2 was added with stirring a cooled solution of 3.13 g (0.015 moles) dicyclo-

hexylcarbodiimide in 12 ml CH_2Cl_2. The mixture was maintained for 2 h at −5°C and 40 h at 4°C. The dicyclohexylurea precipitated product was removed by filtration and the filtrate was washed with water, dried over $MgSO_4$, and the solvent evaporated. Yield 5.21 g (96%) (VI). IR spectrum ($CHCl_3$, ν, cm^{-1}): 3450, 3100-2900, 1820, 1790, 1745, 1715, 1500. PMR spectrum ($CDCl_3$): 1.40 s (CH_3, 2.82 s (CH_2CO), 3.24 m ($C\underline{H}_2CH$), 4.98 m (CH), 7.2-7.4 m (C_6H_5).

N-BOC-S-Phenylalanine Dimethylamide (VII). To 2.0 g (0.0057 moles) VI in 60 ml dry dioxane (DO) was added 5.1 g (0.012 moles) dimethylamine in 20 ml DO and the reaction mixture stirred for 4 days. The reaction mixture was then diluted with water and extracted with $CHCl_3$ (3 × 30 ml). The organic layer was washed with water, 2% HCl, and again with water to pH 7, then dried over $MgSO_4$ and the solvent evaporated. Yield 1.51 g (91%) (VII). IR spectrum ($CHCl_3$, ν, cm^{-1}): 3440, 3100-2900, 1700, 1640, 1495. PMR spectrum ($CDCl_3$): 1.40 s (CH_3), 2.60 s and 2.85 s (CH_3N), 2.95 m ($C\underline{H}_2CH$), 4.91 m (CH), 5.49 d (NH), 7.14-7.32 m (C_6H_5).

S-Phenylalanine Dimethylamide Hydrochloride (IId)·HCl. The BOC protecting group was removed according to [5], mp 202-203°C (ethyl acetate:ethanol = 2:1). Yield 80%. PMR spectrum ($CDCl_3$): 2.41 and 2.80 s (CH_3N), 3.1-3.6 m (CH_2), 4.84 m (CH), 7.20-7.35 m (C_6H_5), 8.63 br.s and (NH_3^+).

S-Phenylalanine Dimethylamide (IId). The hydrochloride (VIII) was dissolved in water and 0.5 N NaOH was added to give a basic reaction, and the solution was extracted with $CHCl_3$. The organic layer was washed with water and evaporated. The product was obtained in the form of a light yellow oil, in quantitative yield. PMR spectrum (CD_3OD): 2.5-2.85 (CH_3N, $C\underline{H}_2CH$), 4.0 t (CH), 7.13 m (C_6H_5). $[\alpha]_D$ +104° (C 0.5, ethanol). According to [6], $[\alpha]_D$ = +103.9° (C 0.5, ethanol).

Reduction Aminolysis of (I). The procedure was carried out in a thermostated, stirred reactor at 20°C and 1.2 atm H_2. A mixture of 0.08 mmoles $PdCl_2$, 0.6 mmoles S-(II) hydrochloride, and 0.6 mmoles Et_3N [or 0.6 mmoles S-(II) in its free base form] in 3 ml solvent was purged with H_2 for 5 min, then the catalyst was reduced with stirring an additional 10 min. The reactor was then charged with 0.4 mmoles (I) in 3 ml solvent and the rate of H_2 absorption was measured. After the reaction was complete, the catalyst was removed by centrifugation and the solution worked up according to [7]. A mixture of diastereomers (III) was obtained, which was analyzed by PMR and GLC.

Two-Step Process. A solution of 0.4 mmoles (I) in 6 ml absolute DME was hydrogenated in the presence of 0.08 mmoles $PdCl_2$ and 0.6 mmoles Et_3N for 5 h. The catalyst was removed by centrifugation and the solvent was evaporated at 20°C. The residue was dissolved in 6 ml of the corresponding solvent and 0.6 mmoles S-(II) hydrochloride and 0.6 mmoles Et_3N were added [or 0.6 mmoles of S-(II) in the form of the free base]. The reaction mixture was allowed to stand for 24 h. The mixture was then passed through a Dowex column (50 × 4, H^+ form), the solvent was evaporated and the resulting mixture of diastereomers (III) analyzed.

Preparation of N-Acetyldehydrophenylalanylphenylalanine Dimethylamide or Methyl Ester (IV). To a solution of 1 mmole (I) in 15 ml DME was added 1.5 mmoles S-(IIa, d) hydrochloride and 1.5 mmoles Et_3N. The reaction mixture was allowed to stand for 3 days. It was then passed through a Dowex column (50 × 4) and evaporated. Yield 60-70% after recrystallization from an appropriate solvent.

N-Acetyldehydrophenylalanylphenylalanine Methyl Ester (IVa). Mp 185-186°C (ethanol: water = 1:1). PMR spectrum (CD_3OD): 1.93 s ($COCH_3$), 3.04 d ($C\underline{H}_2CH$), 3.60 s (OCH_3), 4.65 t ($C\underline{H}CH_2$), 6.78 s (CH=C), 7.0-7.4 (C_6H_5).

N-Acetylphenylalanylphenylalanine Dimethylamide (IVd). PMR spectrum (CD_3OD): 2.0 s ($COCH_3$), 2.69 s and 2.74 s (CH_3N), 2.97 d ($C\underline{H}_2CH$), 6.05 t ($C\underline{H}CH_2$), 6.98 s (CH=C), 7.1-7.5 m (C_6H_5).

Hydrogenation of (IV). A mixture of 0.08 mmole $PdCl_2$ in 3 ml DME was reduced with hydrogen and then 0.4 mmole (IV) in 3 ml DME was added. Catalyst reduction was also carried out in the presence of S-(IIa, d). The rate of hydrogen consumption was measured. After hydrogenation was complete, the catalyst was removed by centrifugation and the reaction mixture passed through Dowex (50 × 4); the solvent was evaporated and the product analyzed.

N-Acetylphenylalanylphenylalanine Methyl Ester (IIIa). PMR spectrum (CD_3OD): 1.79 s [$COCH_3$ in SS-(IIIa)], 1.81 s [$COCH_3$ in RS-(IIIa)], 2.6-3.1 m ($C\underline{H}_2CH$), 3.59 s [OCH_3 in

SS-(IIIa)], 3.63 s [OCH_3 in RS-(IIIa)], 4.58 m ($C\underline{H}CH_2$), 7.0-7.25 m (C_6H_5). After two recrystallizations from 2:1 ethyl acetate–hexane mixture the pure RS-diastereomer was isolated, mp 149-151°C, $[\alpha]_\lambda$ (λ, nm) (C 0.707, ethanol): −25.4 (589), −26.9 (500), −31.2 (450), −33.9 (400), −24.0 (350), −7.1 (320), +4.2 (310), +21.2 (300), +82.0° (280). The diastereomeric purity was 91% according to GLC analysis.

N-Acetylphenylalanylphenylalanine Isopropyl Ester (IIIb). PMR spectrum (CD_3OD): 1.02-1.29 m ($C\underline{H}_3CH$), 1.79 s [$COCH_3$ in SS-(IIIb)], 1.81 s [$COCH_3$ in RS-(IIIb)], 2.6-3.1 m ($C\underline{H}_2CH$), 4.55 m ($C\underline{H}CH_2$), 7.02-7.25 m (C_6H_5).

N-Acetylphenylalanylphenylalanine tert-Butyl Ester (IIIc). PMR spectrum (CD_3OD): 1.32 s [CH_3C in SS-(IIIc)], 1.34 s [CH_3C in RS-(IIIc)], 1.82 br s ($COCH_3$, 2.6-3.1 m ($C\underline{H}_2CH$), 4.52 m ($C\underline{H}CH_2$), 7.0-7.25 m (C_6H_5).

N-Acetylphenylalanylphenylalanine Dimethylamide (IIId). PMR spectrum ($CDCl_3$): 1.94 s [$COCH_3$ in RS-(IIId)], 1.96 s [$COCH_3$ in SS-(IIId)], 2.6-3.07 m (CH_3N and $C\underline{H}_2CH$), 4.78 m ($C\underline{H}CH_2$), 5.05 m ($C\underline{H}CH_2$), 7.05-7.35 m (C_6H_5).

Methanolysis of (III). The procedure in [2] was used. Compound (III) (0.4 mmole) was dissolved in 5 ml absolute MeOH, and a vigorous stream of dry HCl was passed through the solution for 7 min (the mixture became hot and boiled). The reaction mixture was transferred to a Teflon ampul and heated at 90°C for 90 min. The solvent was evaporated and the residue dissolved in water and extracted with ether. After solvent evaporation the yield of AcPheOMe was 70%.

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