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Asymmetric hydrogenation of dehydrodipeptide esters bearing different protective groups*

Chr. Döbler, H.-J. Kreuzfeld, Chr. Fischer, and **M. Michalik**

Institut für Organische Katalyseforschung an der Universität Rostock e.V., Rostock, Federal Republic of Germany

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Summary. *N*-[(*Z*)-*N*-Benzoyl- or *N*-Boc-(2-fluorophenyl)dehydroalanyl]-(*R*)- or (*S*)-phenylalanine esters were synthesized and hydrogenated to give the corresponding dipeptide derivatives with optical yields in the range of 53–87% *de* using the cationic rhodium complexes of PROPRAPHOS and BPPM. The efficiency of chiral diphosphine ligands as well the effect of the chiral center in the substrate on the catalytic asymmetric induction was studied.

Keywords: Amino acids – Dipeptide derivatives – Non-proteinogenic optically active dipeptide esters – Dehydrodipeptides – Chiral rhodium catalysts – Asymmetric hydrogenation – Diastereoselectivity

Introduction

The asymmetric hydrogenation of dehydroamino acids catalyzed by homogeneous catalysts proved to be an efficient way to achieve amino acids in high optical yields. The method was extended to the asymmetric hydrogenation of dehydrodipeptides giving fragments of various biologically active oligopeptides. One of the most interesting point is whether the chiral center of the dehydrodipeptide exerts a strong influence upon the way of asymmetric induction by chiral catalyst or not. Several authors have investigated this problem. They reported the hydrogenation of dehydropeptide derivatives catalyzed by rhodium complexes of chiral diphosphines (Ojima and Suzuki, 1980; Ojima, 1982, 1984; Ojima et al., 1982; Kagan et al., 1980; Sinou et al., 1981; Yamagishi et al., 1984) or chiral diphosphinites (Onuma et al., 1980; Yatagai et al., 1983, 1984a, 1984b). In all these reactions *N*-benzoyl or *N*-acetyl dehydrodipeptides were hydrogenated, only Yamagishi (Yamagishi et al., 1988) described the hydrogenation of *N*-benzyloxycarbonyl

*Dedicated to Professor Günther Oehme on the occasion of his 60th birthday

dehydrodipeptides besides *N*-acetyl derivatives catalyzed by rhodium complexes of achiral diphosphines and chiral diphosphinites.

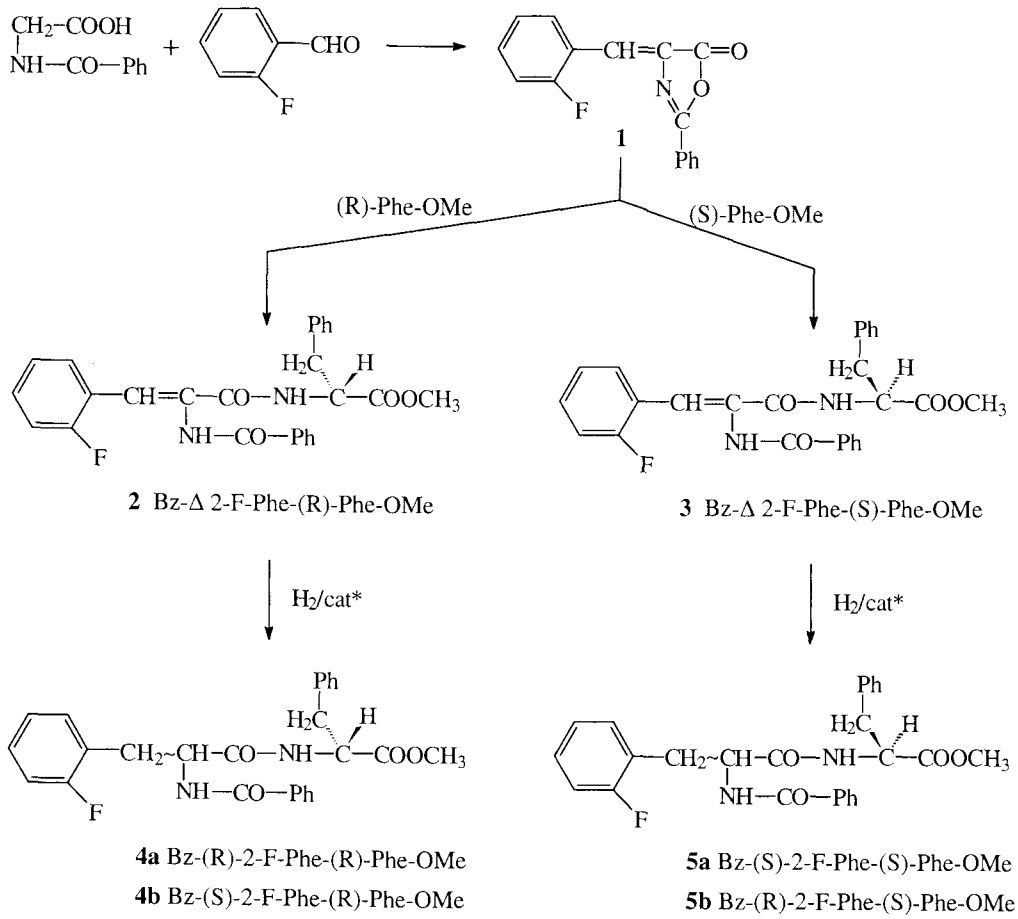
In the last years we investigated the asymmetric synthesis of "unnatural" amino acids by asymmetric hydrogenation using the cationic rhodium complex of "PROPRAPHOS" as catalyst. A summary of the results is given in a review article (Kreuzfeld et al., 1996). It was interesting to investigate the potential of this catalytical system in the preparation of dipeptides by asymmetric hydrogenation of dehydrodipeptides. Now we want to report on some results of the synthesis of "unnatural" dipeptide esters bearing benzoyl or Boc protective groups. To our knowledge, the hydrogenation of *N*-Boc protected dehydrodipeptide derivatives has not been published yet.

Results and discussion

We want to describe here the synthesis of "unnatural" fluorine containing dipeptide derivatives from the corresponding unsaturated precursors. *N*-[(*Z*)-*N*-Benzoyl-(2-fluorophenyl)dehydroalanyl]phenylalanine esters **2** and **3** were readily synthesized by the reaction of the azlactone **1**, prepared from benzoylglycine and 2-fluorobenzaldehyde, with the (*R*)- or (*S*)-phenylalanine methyl ester (Scheme 1) in a manner similar to Bergmann's method (Doherty et al., 1943; Ojima et al., 1982). Hydrogenation catalyzed by chiral rhodium complexes gives the dipeptides **4a,b** and **5a,b**. The (*Z*)-dehydrodipeptides **9** and **10** with a tert.-butyloxycarbonyl substituent as amino-protecting group were prepared as described in Scheme 2 by the *N*-carboxylic acid method **A** (Shin et al., 1988, 1989) or by reaction of the (*Z*)-2-*N*-Boc-3-(2-fluorophenyl)propenoic acid **8** with the phenylalanine methyl ester (method **B**, Anderson et al., 1967).

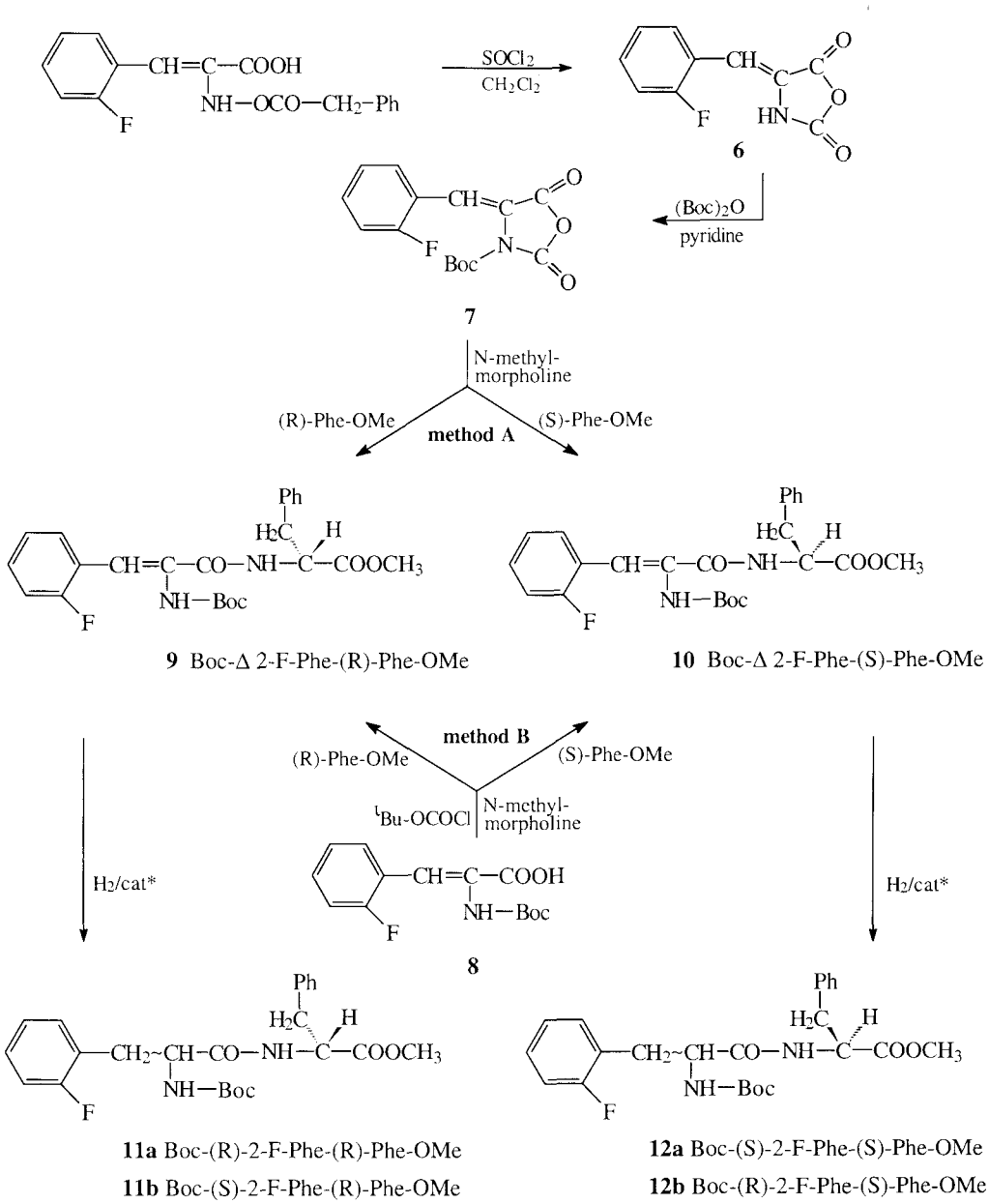
Hydrogenation leads to the dipeptides **11** and **12.** The results obtained in the reduction of the dehydrodipeptides are shown in Table 1.

In the past we have demonstrated that PROPRAPHOS (PPP) gives a rhodium catalyst which is able to induce asymmetric reduction of (*Z*)-*N*-acyldehydrophenylalanine derivatives resulting in a strong (*S*)-stereoselectivity using (*R*)-PPP (Kreuzfeld et al., 1996). In the hydrogenation of methyl (Z)-α-*N*-benzoylamino-β-(2-fluorophenyl)acrylate (*R*)-PPP yielded 90% ee (*S*), (Krause et al., 1992). The same trend could be expected for the double bond of **2** and **3**. Indeed, the (*S*)-PPP induces an excess of (*R*)-configured product at the new asymmetric center and vice versa (see Table 1). The *N*-benzoyl substituted derivatives exhibit high double induction. The substrates give more than 90% of the (*R,R*)- or (*S,S*)-diastereomer when the intrinsic asymmetric induction of the substrate and the catalyst are in the same direction (entries 1 and 2). However, the stereoselectivity was less pronounced in the combination of (*R*)-PPP/(*R*)-**2** and (*S*)-PPP/(*S*)-**3** (entries 3 and 4). In our comparative investigation using the ligand BPPM (entries 5 and 6) we found high enantioselectivity for (−)-BPPM not only for the (*R*)-dehydrodipeptide but also for the substrate with the opposite induction. The achiral ligand DPPB gives 30% *de*, where the induction due to the chiral inducer is (*R*) or (*S*) (entries 7 and 8). Quite similar results were found in the hydrogenation of



Scheme 1

Bz-ΔPhe-(S)-Phe-OMe (Ojima et al., 1982). They achieved 98.2% and 97.4% *de*, respectively, by BPPM/Rh$^+$ and 24.4% *de* by DPPB/Rh$^+$. Our results established the usefulness of the investigated catalytic system for the hydrogenation of Boc-Δ2F-Phe-Phe-OMe, but the activity decreases markedly by introduction of the *N*-Boc instead of the *N*-benzoyl group (entries 9–16). Now, in contrast to the corresponding dehydroamino acid derivatives (Kreuzfeld et al., 1996) the *N*-Boc compounds **9** and **10** show a lower *de* (entries 9 and 10) compared with **2** and **3** (entries 1 and 2). Entries 9, 10 and 11, 12 reveal the greater influence of the chiral center in the *N*-Boc enamide series (80% *de* against 52% *de*, Δ*de* 30%) compared with that in the *N*-benzoyl derivatives (entries 1,2 and 3,4, Δ*de* 17%). This fact is even more expressed looking at the *N*-Boc enamides in the reaction with BPPM/Rh$^+$ (entries 13 and 14, Δ*de* 45%). The absolute configuration of the chiral catalyst controls also here, to a great extent, the steric course of the reduction, but, of course, influenced by the chiral center in the substrate. The simple asymmetric induction using DPPB as achiral ligand disclosed 25% *de* (entries 15 and 16),



9 Boc-Δ 2-F-Phe-(R)-Phe-OMe

10 Boc-Δ 2-F-Phe-(S)-Phe-OMe

8

11a Boc-(R)-2-F-Phe-(R)-Phe-OMe

11b Boc-(S)-2-F-Phe-(R)-Phe-OMe

12a Boc-(S)-2-F-Phe-(S)-Phe-OMe

12b Boc-(R)-2-F-Phe-(S)-Phe-OMe

Scheme 2

which is comparable with the results given with Bz-Δ2F-Phe-Phe-OMe as the substrate.

Material and methods

General

All reactions with air or moisture sensitive reactants and solvents were carried out in oven dried glassware under dry argon. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker

Table 1. Asymmetric hydrogenation of dehydrodipeptide esters

Entry	Substrate	Cat.*[a]	$t/_2$[b] (min)	Dipeptide ester	Diastereomeric ratio		de (%)
1	**2** *(R)*	*(S)*-PPP-Rh$^+$	3.0	**4a/4b**	*R,R/S,R*	93.5/6.5	87
2	**3** *(S)*	*(R)*-PPP-Rh$^+$	3.0	**5a/5b**	*S,S/R,S*	93.0/7.0	87
3	**2** *(R)*	*(R)*-PPP-Rh$^+$	4.0	**4a/4b**	*R,R/S,R*	15.5/84.5	69
4	**3** *(S)*	*(S)*-PPP-Rh$^+$	4.0	**5a/5b**	*S,S/R,S*	15.0/85.0	70
5	**2** *(R)*	(−)-BPPM-Rh$^+$	4.0	**4a/4b**	*R,R/S,R*	99.0/1.0	98
6	**3** *(S)*	(−)-BPPM-Rh$^+$	4.5	**5a/5b**	*S,S/R,S*	2.0/98.0	96
7	**2** *(R)*	DPPB-Rh$^+$	4.5	**4a/4b**	*R,R/S,R*	65.0/35.0	30
8	**3** *(S)*	DPPB-Rh$^+$	4.5	**5a/5b**	*S,S/R,S*	65.0/35.0	30
9	**9** *(R)*	*(S)*-PPP-Rh$^+$	52	**11a/11b**	*R,R/S,R*	84.5/15.5	79
10	**10** *(S)*	*(R)*-PPP-Rh$^+$	50	**12a/12b**	*S,S/R,S*	85.0/15.0	80
11	**9** *(R)*	*(R)*-PPP-Rh$^+$	63	**11a/11b**	*R,R/S,R*	24.0/76.0	52
12	**10** *(S)*	*(S)*-PPP-Rh$^+$	65	**12a/12b**	*S,S/R,S*	23.5/76.5	53
13	**9** *(R)*	(−)-BPPM-Rh$^+$	30	**11a/11b**	*R,R/S,R*	88.0/12.0	76
14	**10** *(S)*	(−)-BPPM-Rh$^+$	28	**12a/12b**	*S,S/R,S*	34.5/65.5	31
15	**9** *(R)*	DPPB-Rh$^+$	25	**11a/11b**	*R,R/S,R*	62.5/37.5	25
16	**10** *(S)*	DPPB-Rh$^+$	27	**12a/12b**	*S,S/R,S*	62.5/37.5	25

[a] *PPP-Rh*$^+$ [Rh(PPP)COD]$^+BF_4^-$, crystallized complex. *PPP* 2,3-O,N-bis(diphenylphosphino)-1-naphthoxy-2-hydroxy-3-isopropylaminopropane (PROPRAPHOS). *BPPM-Rh*$^+$ and *DPPB-Rh*$^+$ L+[Rh(COD)$_2$]$^+BF_4$ in situ. *(−)BPPM* (2S,4S)-N-tert-butyloxycarbonyl-4-diphenylphosphino-2-diphenylphosphinometylpyrrolidine. *DPPB* 1,4-bis-(diphenylphosphino)butane. [b] $t/_2$ time for uptake of 50% of theoretical hydrogen volume.

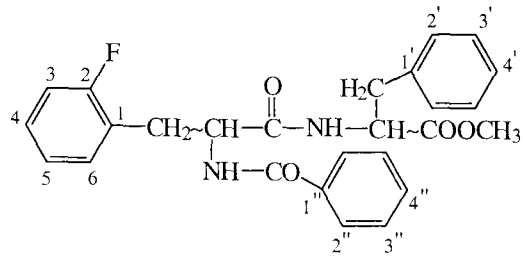


Fig. 1. Denotation for NMR

ARX-300 spectrometer (^{1}H: 300.13 MHz, ^{13}C: 75.47 MHz). The calibration of spectra was carried out by means of solvent peaks ($CDCl_3$: δ ^{1}H = 7.25; δ ^{13}C = 77.0). The assignment of ^{1}H and ^{13}C signals were performed by recording of two-dimensional ^{1}H/^{1}H cosy and ^{13}C/^{1}H correlation spectra. The coupling constants were determined using Gaussian multiplication and a first order analysis.

Optical rotation was measured on a GYROMAT-HP polarimeter (Fa. Dr. Kernchen, Seelze). The diastereomeric excesses (% *de*) were determined by HPLC on a Hewlett-Packard 1090 chromatograph series II, fitted with a 250 × 4.6 mm CHIRACEL OD-H column (eluent: n-hexane/isopropanol). Appropriate dipeptide derivatives for comparison were prepared. Melting points are uncorrected and were determined on a Boëtius microscope.

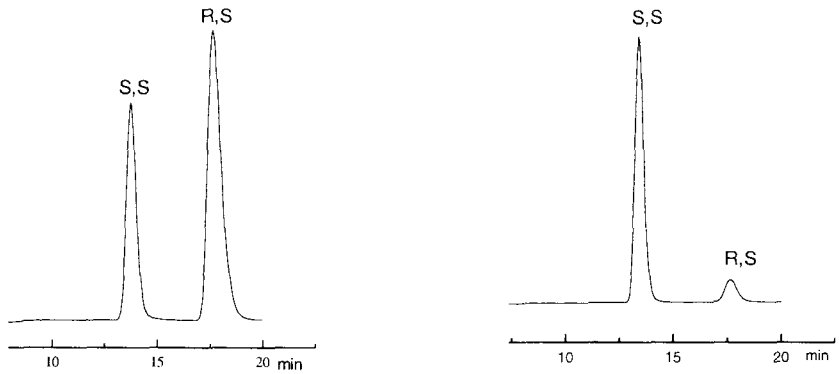


Fig. 2. HPLC resolution of **5a** and **5b**. Stationary phase: Chiralcel OD-H, eluent: n-Hexane/isopropanol (90:10), flow: 1 ml/min

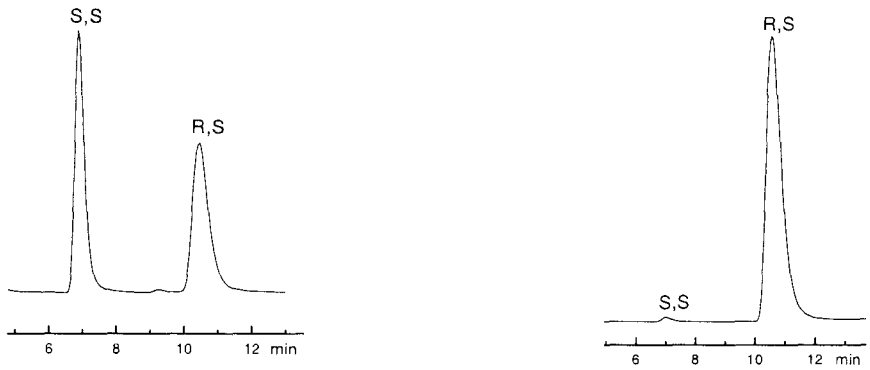


Fig. 3. HPLC resolution of **12a** and **12b**. Stationary phase: Chiralcel OD-H, eluent: n-Hexane/isopropanol (97:3), flow: 1 ml/min

Hydrogenation

The hydrogenation experiments were performed in a standard apparatus. Conditions: 1 mmol of substrate, 15 ml methanol, 25°C and 0.1 MPa H_2, 0.01 mmol catalyst, substrate:catalyst = 100:1. A small amount of the methanol solution from the hydrogenation was taken for HPLC measurements. The residue was freed from solvent under reduced pressure and the product recrystallized. Nearly optically pure compounds could be isolated by recrystallization from ethanol or ethylacetate/hexane.

(Z)-2-Phenyl-4-(2-fluorobenzylidene)-2-oxazolin-5-one ***1***

Hippuric acid (21.3 g, 0.12 mol) and sodium acetate (9.8 g, 0.12 mol) were dissolved in acetic acid (33 ml) with stirring. After addition of 2-fluorobenzaldehyde (12.5 ml, 0.12 mol) the mixture was heated to 90°C for 60 min. After cooling for 24 h in the refrigerator 40% aqueous ethanol was added. The precipitate was filtered off, washed with water and dried. Recrystallization from toluene gave 22.7 g (71%) pure (*Z*)-**1**. Mp 166–167°C [lit. 167–169°C (Bennett and Niemann, 1950)].

N-[(Z)-N-Benzoyl-(2-fluorophenyl)dehydroalanyl]phenylalanine esters ***2*** *and* ***3***

Triethylamine (2.03 g, 20 mmol) was added to (*R*)- or (*S*)-phenylalanine methylester hydrochloride (2.79 g, 20 mmol) in 150 ml chloroform with stirring at ambient temperature.

Oxazolone **1** (5.34 g, 20 mmol) was added and the mixture stirred 24 h at ambient temperature. The reaction mixture was washed with saturated aqueous sodium chloride, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residual solid was recrystallized from ethyl acetate/hexane to give colorless crystalline esters.

(*R*)-**2.** 7.5 g (84% yield); mp 151–152°C; $[\alpha]_D^{25}$ −63.4 (c 1, $CHCl_3$). Anal. calcd. for $C_{26}H_{23}FN_2O_4$ (446.5): C 69.94 H 5.19 N 6.28; found: C 69.84 H 5.14 N 6.34 (*S*)-**3**. 7.8 g (87% yield); mp 151–152°C; $[\alpha]_D^{25}$ 63.7 (c 1, $CHCl_3$). Anal. calcd. for $C_{26}H_{23}FN_2O_4$ (446.5): C 69.94 H 5.19 N 6.28; found: C 69.79 H 5.08 N 6.14 ^{1}H NMR ($CDCl_3$): δ 8.10 (br, 1H, =CNH); 7.83–7.76 (m, 2H, H—2″); 7.55–7.48 (m, 1H, H—4″); 7.47–7.37 (m, 3H, H—6, H—3″); 7.30–7.22 (m, 1H, H—4); 7.22–7.00 (m, 7H, H—3, H—5, H—2′, H—3′, H—4′); 7.05 (s, 1H, CH=); 6.79 (d, 1H, $^3J_{NH,CH} \approx 7.6$ Hz, CHN<u>H</u>); 4.95 (dt, 1H, $^3J_{NH,CH} \approx 7.6$ Hz, $^3J_{CH,CH2} \approx 5.7$ Hz, CH); 3.70 (s, 3H, OCH_3); 3.18 (dd, 1H, $^2J_{A,B} \approx 13.8$ Hz, $^3J_{CH,CH2} \approx 5.7$ Hz, $CH_{2(A)}$); 3.14 (dd, 1H, $^2J_{A,B} \approx 13.8$ Hz, $^3J_{CH,CH2} \approx 5.7$ Hz, $CH_{2(B)}$).

^{13}C NMR ($CDCl_3$): δ 171.7 (<u>C</u>OO); 165.9 (phCO); 164.8 (=C<u>C</u>O); 160,1 (d, $^1J_{F,C} \approx 249.9$ Hz, C—2); 135.7 (C—1′); 132.9 (C—1″); 132.2 (C—4″); 131.0 (d, $^4J_{F,C} \approx 1.0$ Hz, =C<); 130.6 (d, $^3J_{F,C} \approx 8.6$ Hz, C—4); 129.9 (d, $^3J_{F,C} \approx 2.8$ Hz, C—6); 129.4 (C—3′); 128.6 (C—2′); 128.6 (C—3″); 127.5 (C—2″); 127.1 (C—4′); 124.3 (d, $^4J_{F,C} \approx 3.3$ Hz, C—5); 121.7 (d, $^2J_{F,C} \approx 13.3$ Hz, C—1); 119.7 (d, $^3J_{F,C} \approx 3.0$ Hz, CH=); 115.9 (d, $^2J_{F,C} \approx 22.4$ Hz, C—3); 53.6 (CH); 52.3 (OCH_3); 37.8 (CH_2).

*N-[(Z)-N-Boc-(2-fluorophenyl)dehydroalanyl]phenylalanine methyl esters **9** and **10***

Method **A**

*1. (Z)-N-Carboxy-(2-fluorophenyl)dehydroalanine anhydride **6***: Into a suspension of (*Z*)-2-benzyloxycarbonylamino-3-(2-fluorophenyl)propenoic acid (Krause et al., 1996) (6.3 g, 0.02 mol) in dry CH_2Cl_2 (40 ml), $SOCl_2$ (30 ml) was added below 0°C with stirring. The resulting solution was stirred continuously at room temperature for 2 h. After removing the solvent and excess $SOCl_2$ under reduced pressure, CCl_4 was added and then the mixture concentrated under reduced pressure. This procedure was repeated. The residual crystals were recrystallized from ethyl acetate/hexane to yield pure **6**. 3.6 g (87% yield); mp 233–234°C. Anal. calcd. for $C_{10}H_6FNO_3$ (207.2): C 57.98 H 2.92 N 6.76; found: C 57.81 H 2.74 N 6.59

2. N-[(Z)-N-Boc-(2-fluorophenyl)dehydroalanyl]-(R)-phenylalanine methyl ester **9**: A solution of **6** (3.11 g, 15 mmol) and $(Boc)_2O$ (3.93 g, 18 mmol) in dry THF (50 ml) was stirred in the presence of pyridine (150 μl) at room temperature for 10 h. With stirring, to the solution a suspension of (*R*)-phenylalanine methyl ester hydrochloride (4.3 g, 20 mmol) and triethylamine (2 ml, 20 mmol) in dry THF (30 ml) was added. To the resulting solution *N*-methylmorpholine (2.2 ml, 20 mmol) was given and then it was stirred continuously at room temperature for 4 h. After removing the solvent under reduced pressure, the residue was dissolved in ethyl acetate, the resultant solution washed with cold 10% citric acid, a saturated aqueous solution of $NaHCO_3$, water and then dried over anhydrous Na_2SO_4. The concentration of the solution under reduced pressure gave a crude syrup, which was purified on a silica-gel column using benzene/acetone as an eluent (15 : 1 v/v). Recrystallization from ethyl acetate/hexane gave **9** as colorless crystals. 5.4 g (82% yield); mp 125–126°C; $[\alpha]_D^{25}$-64.5 (c 1, $CHCl_3$). Anal. calcd. for $C_{24}H_{27}FN_2O_5$ (442.5): C 65.14 H 6.15 N 6.33; found: C 64.94 H 6.24 N 6.54

Method **B**

1. (Z)-2-tert-Butyloxycarbonylamino-3-(2-fluorophenyl)propenoic acid **8**: Prepared from the methyl ester (Krause et al., 1996) by hydrolysis with LiOH in dioxane/water. Yield 88%; mp 161–162°C. Anal. calcd. for $C_{14}H_{16}FNO_4$ (281.3): C 59.78 H 5.73 N 4.98; found: C 59.83 H 5.54 N 4.88.

*2. N-[(Z)-N-Boc-(2-fluorophenyl)dehydroalanyl]-(S)-phenylalanine methyl ester **10***: With stirring, a solution of **8** (2.81 g, 10 mmol) and *N*-methylmorpholine (1.12 ml,

10 mmol) in THF (50 ml) was chilled to −15°C and isobutyl chloroformate (1.34 ml, 10 mmol) was added. After about 1 min, a solution of (*S*)-PheOMe·HCl (2.16 g, 10 mmol) and *N*-methylmorpholine(1.12 ml, 10 mmol) in DMF (20 ml) was added. Then the bath was removed and after warming to room temperature the hydrochloride was filtered off. The solvent was removed in vacuo and ethyl acetate (150 ml) and then water (50 ml) were added. After shaking and separation of the ethyl acetate solution the latter was washed with 5% sodium bicarbonate solution (50 ml), 0.5 N hydrochloric acid (50 ml) and water (50 ml). The solution was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate/hexane to give 3.5 g (79% yield) ester **10**. Mp 125–126°C; $[\alpha]_D^{25}$ 64.2 (c 1, $CHCl_3$). Anal. calcd. for $C_{24}H_{27}FN_2O_5$ (442.5): C 65.14 H 6.15 N 6.33; found: C 65.27 H 6.07 N 6.21. ^{1}H NMR ($CDCl_3$): δ 7.48–7.40 (m, 1H, H—6); 7.33–7.02 (m, 8H, H—3, H—4, H—5, H—2′, H—3′, H—4′); 7.00 (s, 1H, CH=); 6.71 (d, 1H, $^3J_{NH,CH} \approx 7.6$ Hz, CHN<u>H</u>); 6.04 (br, 1H, =CNH); 4.97 (dt, 1H, $^3J_{NH,CH} \approx 7.6$ Hz, $^3J_{CH,CH2} \approx 5.8$ Hz, CH); 3.71 (s, 3H, OCH_3); 3.20 (d, 2H, $^3J_{CH,CH2} \approx 5.8$ Hz, CH_2); 1.38 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$): δ 171.7 (CH<u>C</u>OO); 164.6 (=C<u>C</u>O); 160.2 (d, $^1J_{F,C} \approx 250.5$ Hz, C—2); 153.0 (NHCOO); 135.8 (C—1′); 130.6 (d, $^4J_{F,C} \approx 1.0$ Hz, =C<); 130.4 (d, $^3J_{F,C} \approx 8.6$ Hz, C—4); 129.8 (d, $^3J_{F,C} \approx 3.0$ Hz, C—6); 129.3 (C—3′); 128.6 (C—2′); 127.1 (C—4′); 124.2 (d, $^4J_{F,C} \approx 3.8$ Hz, C—5); 121.9 (d, $^2J_{F,C} \approx 13.4$ Hz, C—1); 118.9 (br, CH=); 115.9 (d, $^2J_{F,C} \approx 22.0$ Hz, C—3); 81.4 (<u>C</u>$(CH_3)_3$); 53.7 (CH); 52.3 (OCH_3); 38.0 (CH_2); 28.0 ($C(CH_3)_3$).

N-[N-Benzoyl-(2-fluorophenyl)-(R)-alanyl]-(R)-phenylalanine methyl ester ***4a***

Mp 193–194°C (ethanol), $[\alpha]_D^{25}$ 16.9 (c 1, $CHCl_3$), *de* > 99% (HPLC). Anal. calcd. for $C_{26}H_{23}FN_2O_4F$ (448.5): C 69.63 H 5.62 N 6.25; found: C 69.80 H 5.44 N 6.38.

N-[N-Benzoyl-(2-fluorophenyl)-(S)-alanyl]-(S)-phenylalanine methyl ester ***5a***

Mp 194–195°C (ethanol), $[\alpha]_D^{25}$ −17.2 (c 1, $CHCl_3$), *de* > 99% (HPLC). Anal. calcd. for $C_{26}H_{23}FN_2O_4F$ (448.5): C 69.63 H 5.62 N 6.25; found: C 69.70 H 5.56 N 6.22. ^{1}H NMR ($CDCl_3$): δ 7.71–7.65 (m, 2H, H—2″); 7.54–7.47 (m, 1H, H—4″); 7.44–7.38 (m, 2H, H—3″); 7.23 (m, 1H, H—6); 7.18 (m, 1H, H—4); 7.14–7.09 (m, 3H, H—2′, H—4′); 7.07–6.96 (m, 4H, H—3, H—5, H—3′); 6.72 (d, 1, H, $^3J_{CH,NH} \approx 7.8$ Hz, NH); 6.69 (d, 1H, $^3J_{CH,NH} \approx 7.8$ Hz, NH); 4.86 (dt,1H, $^3J_{CH,CH2} \approx 7.2$ Hz, $^3J_{CH,NH} \approx 7.8$ Hz, C<u>H</u>CONH); 4.82 (ddd, 1H, $^3J_{CH,CH2(A)} \approx 6.5$ Hz, $^3J_{CH,CH2(B)} \approx 5.8$ Hz, $^3J_{CH,NH} \approx 7.8$ Hz, C<u>H</u>COO) ; 3.69 (s, 3H, OCH_3), 3.20 (dd, 2H, $^3J_{CH,CH2} \approx 7.2$ Hz, $^4J_{F,H} \approx 1.0$ Hz, FphCH_2); 3.11 (dd, 1H, $^2J_{A,B} \approx 13.7$ Hz, $^3J_{CH,CH2(B)} \approx 5.8$ Hz, ph$CH_{2(B)}$); 3.00 (dd, 1H, $^2J_{A,B} \approx 13.7$ Hz, $^3J_{CH,CH2(A)} \approx 6.5$ Hz, ph$CH_{2(A)}$). ^{13}C NMR ($CDCl_3$): δ 171.4 (COO); 170.3 (CH<u>C</u>ONH); 167.3 (<u>C</u>OC_6H_5); 161.4 (d, $^1J_{F,C} \approx 244.5$ Hz, C—2); 135.6 (C—1′); 133.5 (C—1″); 131.8 (C—4″); 131.7 (d, $^3J_{F,C} \approx 4.8$ Hz, C—6); 129.2 (C—3′); 128.9 (d, $^3J_{F,C} \approx 8.5$ Hz, C—4); 128.5 (C—2′); 128.5 (C—3″); 127.1 (C—2″); 127.0 (C—4′); 124.4 (d, $^4J_{F,C} \approx 3.8$ Hz, C—5); 123.6 (d, $^2J_{F,C} \approx 16.2$ Hz, C—1); 115.3 (d, $^2J_{F,C} \approx 22.6$ Hz, C—3); 53.9 (<u>C</u>HCONH); 53.5 (<u>C</u>HCOO); 52.3 (OCH_3); 38.0 (phCH_2); 31.1 (FphCH_2).

N-[N-Benzoyl-(2-fluorophenyl)-(R)-alanyl]-(S)-phenylalanine methyl ester ***5b***

Mp 168–169°C (ethanol), $[\alpha]^{25}{}_D$ 65.2 (c 1, $CHCl_3$), *de* > 99% (HPLC). Anal. calcd. for $C_{26}H_{23}FN_2O_4F$ (448.5): C 69.63 H 5.62 N 6.25; found: C 69.74 H 5.74 N 6.19. ^{1}H NMR ($CDCl_3$): δ 7.70–7.65 (m, 2H, H—2″); 7.52–7.45 (m, 1H, H—4″); 7.42–7.35 (m, 2H, H—3″); 7.24–7.14 (m, 5H, H—4, H—6, H—2′, H—4′); 7.07–6.98 (m, 4H, H—3, H—5, H—3′); 6.80 (d, 1H, $^3J_{CH,NH} \approx 7.7$ Hz, phCON<u>H</u>); 6.74 (d, 1H, $^3J_{CH,NH} \approx 8.2$ Hz, CHCON<u>H</u>); 4.89 (dt, 1H, $^3J_{CH,NH} \approx {}^3J_{CH,CH2(B)} \approx 7.8$ Hz, $^3J_{CH,CH2(A)} \approx 6.2$ Hz, C<u>H</u>CONH); 4.83 (dt,1H, $^3J_{CH,NH} \approx 8.2$ Hz, $^3J_{CH,CH2} \approx 6.2$ Hz, CHCOO); 3.62 (s, 3H, OCH_3); 3.21 (ddd, 1H, $^2J_{A,B} \approx 13.9$ Hz, $^3J_{CH,CH2(A)} \approx 6.2$ Hz, $^4J_{F,H} \approx 1.0$ Hz, Fph$CH_{2(A)}$); 3.14 (ddd, 1H, $^2J_{A,B} \approx 13.9$ Hz; $^3J_{CH,CH2(B)} \approx 7.8$ Hz, $^4J_{F,H} \approx 1.0$ Hz, Fph$CH_{2(B)}$); 3.06 (dd, 1H, $^2J_{A,B} \approx 13.8$ Hz, $^3J_{CH,CH2} \approx 6.2$ Hz, ph$CH_{2(A)}$); 3.01 (dd, 1H, $^2J_{A,B} \approx 13.8$ Hz, $^3J_{CH,CH2} \approx 6.2$ Hz, ph$CH_{2(B)}$). ^{13}C NMR ($CDCl_3$): δ 171.5 (COO); 170.4

(CHCONH); 167.4 (phCO); 161.4 (d, $^1J_{F,C} \approx 244.7$ Hz, C—2); 135.7 (C—1′) ; 133.1 (C—1″); 131.8 (C—4″); 131.7 (d, $^3J_{F,C} \approx 4.6$ Hz, C—6); 129.2 (C—3′); 128.9 (d, $^3J_{F,C} \approx 8.2$ Hz, C—4); 128.6 (C—2′); 128.5 (C—3″); 127.1 (C—4′); 127.0 (C—2″); 124.4 (d, $^4J_{F,C} \approx 3.5$ Hz, C—5); 123.6 (d, $^2J_{F,C} \approx 15.6$ Hz, C—1); 115.3 (d, $^2J_{F,C} \approx 22.3$ Hz, C—3); 54.0 (CHCONH); 53.3 (CHCOO); 52.2 (OCH_3); 37.9 ($phCH_2$); 31.4 ($FphCH_2$).

N-[N-Boc-(2-fluorophenyl)-(R)-alanyl]-(R)-phenylalanine methyl ester ***11a***

Mp 135–136°C (ethyl acetate/hexane), $[\alpha]_D^{25}$ −30.4 (c 1, $CHCl_3$), *de* > 99% (HPLC). Anal. calcd. for $C_{24}H_{29}FN_2O_5$ (444.5): C 64.85 H 6.58 N 6.30; found: C 64.74 H 6.34 N 6.39.

N-[N-Boc-(2-fluorophenyl)-(S)-alanyl]-(S)-phenylalanine methyl ester ***12a***

Mp 134–135°C (ethyl acetate/hexane), $[\alpha]_D^{25}$ 30.6 (c 1, $CHCl_3$), *de* > 99% (HPLC). Anal. calcd. for $C_{24}H_{29}FN_2O_5$ (444.5): C 64.85 H 6.58 N 6.30; found: C 64.63 H 6.40 N 6.50. ^{1}H NMR ($CDCl_3$): δ 7.29–7.15 (m, 5H, H—4, H—6, H—2′, H—4′); 7.07–6.70 (m, 4H, H—3, H—5, H—3′); 6.43 (d, 1H, $^3J_{CH,NH} \approx 7.8$ Hz, CHCONH); 4.95 (br, 1H, NHCOO); 4.80 (dt, 1H, $^3J_{CH,CH2} \approx 6.0$ Hz, $^3J_{CH,NH} \approx 7.8$ Hz, CHCOO); 4.34 (br, 1H, CHCONH); 3.66 (s, 3H, OCH_3); 3.13 (ddd, 1H, $^2J_{A,B} \approx 14.0$ Hz, $^3J_{CH,CH2(A)} \approx 5.8$ Hz, $^4J_{F,H} \approx 1.0$ Hz, $FphCH_{2(A)}$); 3.10 (dd, 1H, $^2J_{A,B} \approx 13.8$ Hz, $^3J_{CH,CH2(A)}) \approx 6.0$ Hz, $phCH_{2(A)}$); 3.04 (dd, 1H, $^2J_{A,B} \approx 13.8$ Hz, $^3J_{CH,CH2(B)} \approx 6.0$ Hz, $phCH_{2(B)}$); 2.95 (br, 1H, $FphCH_{2(B)}$); 1.36 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$): δ 171.4 (CHCOO); 170.6 (CHCONH); 161.4 (d, $^1J_{F,C} \approx 244.5$ Hz, C—2); 155.3 (NHCOO); 135.7 (C—1′); 131.7 (d, $^3J_{F,C} \approx 4.2$ Hz, C—6); 129.2 (C—3′); 128.7 (d, $^3J_{F,C} \approx 8.2$ Hz, C—4); 128.5 (C—2′); 127.1 (C—4′); 124.2 (d, $^4J_{F,C} \approx 3.5$ Hz, C—5); 123.7 (d, $^2J_{F,C} \approx 15.8$ Hz, C—1); 115.3 (d, $^2J_{F,C} \approx 22.5$ Hz, C—3); 80.2 ($C(CH_3)_3$); 55.0 (CHCONH); 53.3 (CHCOO); 52.2 (OCH_3); 38.0 ($phCH_2$); 31.6 ($FphCH_2$); 28.1 ($C(CH_3)_3$).

N-[N-Boc-(2-fluorophenyl)-(S)-alanyl]-(R)-phenylalanine methyl ester ***11b***

Mp 136–137°C (ethyl acetate/hexane), $[\alpha]_D^{25}$ −49.5 (c 1, $CHCl_3$), *de* > 99% (HPLC). Anal. calcd. for $C_{24}H_{29}FN_2O_5$ (444.5): C 64.85 H 6.58 N 6.30; found: C 64.67 H 6.47 N 6.49.

N-[N-Boc-(2-fluorophenyl)-(R)-alanyl]-(S)-phenylalanine methyl ester ***12b***

Mp 135–137°C (ethyl acetate/hexane), $[\alpha]_D^{25}$ 49.2 (c 1, $CHCl_3$) *de* > 99% (HPLC). Anal. calcd. for $C_{24}H_{29}FN_2O_5$ (444.5): C 64.85 H 6.58 N 6.30; found: C 64.75 H 6.63 N 6.44. ^{1}H NMR ($CDCl_3$): δ 7.27–7.13 (m, 5H, H—4, H—6, H—2′, H—4′); 7.08–6.97 (m, 4H, H—3, H—5, H—3′); 6.50 (br, 1H, CHCONH); 4.96 (br, 1H, NHCOO); 4.83 (dt, 1H, $^3J_{CH,NH} \approx 8.0$ Hz, $^3J_{CH,CH2} \approx 6.0$ Hz, CHCOO); 4.37 (br, 1H, CHCONH); 3.67 (s, 3H, OCH_3); 3.99 (dd, 1H, $^2J_{A,B} \approx 13.8$ Hz, $^3J_{CH,CH2} \approx 6.0$ Hz, $phCH_{2(A)}$); 3.14 (ddd, 1H, $^2J_{A,B} \approx 13.9$ Hz, $^3J_{CH,CH2(A)} \approx 6.0$ Hz, $^4J_{F,H} \approx 1.0$ Hz, $FphCH_{2(A)}$; 3.05 (dd, 1H, $^2J_{A,B} \approx 13.8$ Hz, $^3J_{CH,CH2} \approx 6.0$ Hz, $phCH_{2(B)}$); 2.92 (br, 1H, $FphCH_{2(B)}$); 1.34 ($C(CH_3)_3$). ^{13}C NMR ($CDCl_3$): δ 171.5 (CHCOO); 170.7 (CHCONH); 161.4 (d, $^1J_{F,C} \approx 245.0$ Hz, C—2); 155.3 (NHCOO); 135.6 (C—1′); 131.7 (d, $^3J_{F,C} \approx 4.8$ Hz, C—6); 129.2 (C—3′); 128.7 (d, $^3J_{F,C} \approx 8.5$ Hz, C—4); 128.6 (C—2′); 127.1 (C—4′); 124.2 (d, $^4J_{F,C} \approx 3.9$ Hz, C—5); 123.8 (d, $^2J_{F,C} \approx 15.8$ Hz, C—1); 115.3 (d, $^2J_{F,C} \approx 22.0$ Hz, C—3); 80.2 ($C(CH_3)_3$); 54.9 (CHCONH); 53.1 (CHCOO); 52.2 (OCH_3); 38.0 ($phCH_2$); 31.6 ($FphCH_2$); 28.1 ($C(CH_3)_3$).

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Authors' address: Dr. Christian Döbler, Institut für Organische Katalyseforschung an der Universität Rostock e.V., Buchbinderstraße 5–6, D-18055 Rostock, Federal Republic of Germany, E-mail: cdoebl@chemie1.uni-rostock.de

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