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Asymmetric hydrogenation of dehydrodipeptides bearing different protecting groups*

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Summary. *N*-[(*Z*)-*N*-Benzoyl- or *N*-boc-(2-fluorophenyl)dehydroalanyl]-(*R*)- or (*S*)-phenyl-alanines **1**,**2**,**5** and **6** were hydrogenated in the presence of chiral and achiral rhodium complexes. The optical induction is compared to the results obtained using the corresponding esters as substrates.

Keywords: Dehydrodipeptides – Non-proteinogenic dipeptides – Chiral rhodium catalysts – Diastereoselectivity – Asymmetric hydrogenation

Introduction

Dehydropeptides are interesting precursors to modified biologically active peptides since catalytic asymmetric hydrogenation can convert the dehydroamino acid residue into the amino acid component with either a (*R*) or (*S*) configuration.

The hydrogenation of *N*-benzoyl- or *N*-acetyl dehydrodipeptides and their esters derived from alanine or phenylalanine in presence of chiral rhodium complexes has been reported by several authors (Ojima et al., 1980, 1982; Ojima, 1982, 1984; Meyer et al., 1980; Sinou et al., 1981; Yamagishi et al., 1984, 1988; Onuma et al., 1980; Yatagai et al., 1983, 1984a, 1984b).

In the past we reported the Rh-catalyzed asymmetric hydrogenation of dehydrodipeptide esters bearing different substitution patterns as well as different protecting groups in the unsaturated part of the substrate, to give the corresponding phenylalanyl-phenylalanine esters with the same or different configuration at the two chiral centers. With the exception of *N*-Cbz-protected dehydrodipeptide esters, which showed unacceptably slow hydrogenation rates, other protecting groups such as benzoyl and Boc resulted in good to excellent diastereomeric excesses in the asymmetric hydrogenation

* Dedicated to Professor Bernhard Lücke on the occasion of his 65th birthday

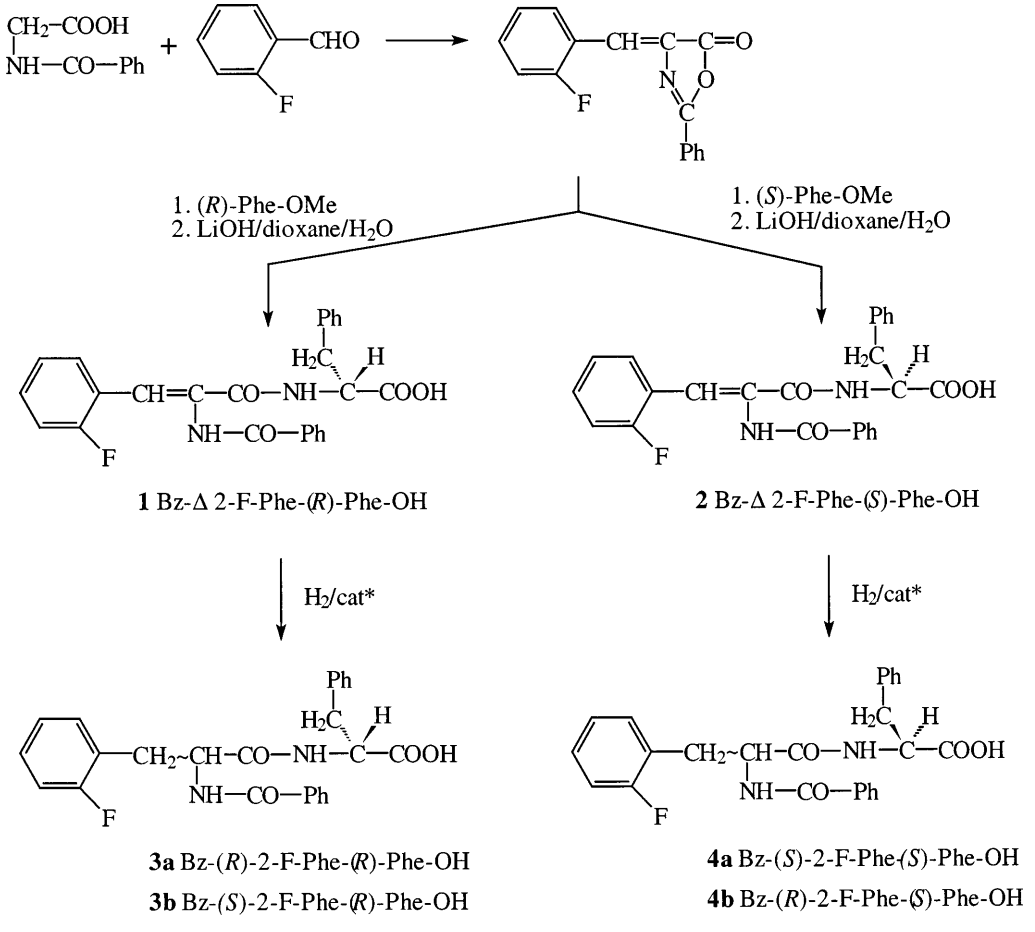
using the "PROPRAPHOS" ligand derived from propranolol (Döbler et al., 1999; Kreuzfeld et al., 1999).

In this paper we describe the hydrogenation of a variety of dehydrodipeptides, that is as the free acids instead of the corresponding esters.

Results and discussion

N-[(*Z*)-*N*-Benzoyl-dehydro(2-fluorophenyl)alanyl]phenylalanines **1** and **2** and the (*Z*)-dehydrodipeptides **5** and **6** protected with a tert.-butyloxycarbonyl group were synthesized from the corresponding (*R*)- or (*S*)-methyl esters (Döbler et al., 1999). Asymmetric hydrogenation catalyzed by chiral rhodium complexes gave the dipeptides **3a**,**b** and **4a**,**b** (Scheme 1) as well as **7a,b** and **8a,b** (Scheme 2), respectively. The results are shown in Table 1.

In our comparative investigations we found, that in the case of *N*-benzoyl substituted derivatives there were only very small differences in the



1 Bz-Δ 2-F-Phe-(*R*)-Phe-OH

2 Bz-Δ 2-F-Phe-(*S*)-Phe-OH

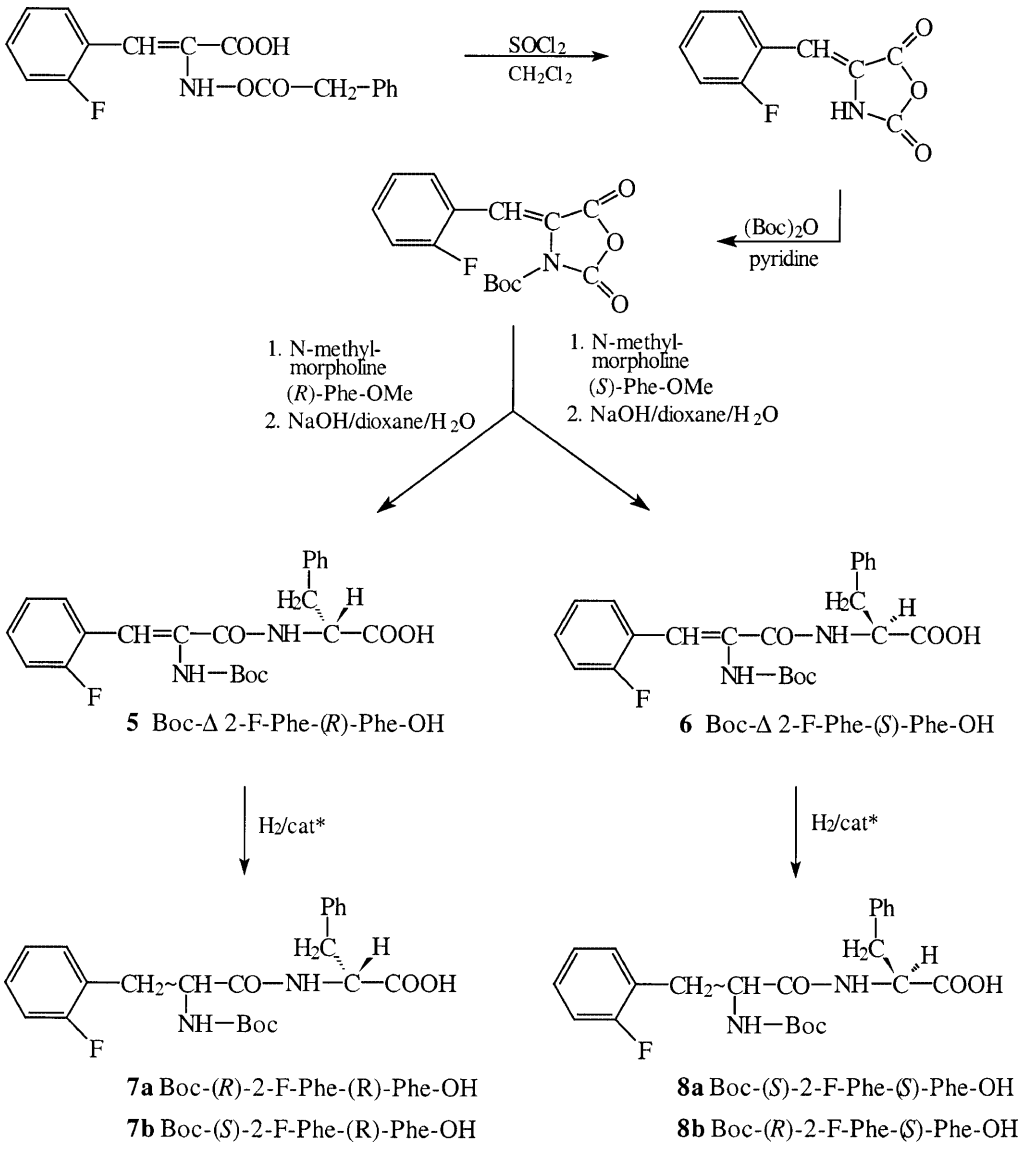
3a Bz-(*R*)-2-F-Phe-(*R*)-Phe-OH

3b Bz-(*S*)-2-F-Phe-(*R*)-Phe-OH

4a Bz-(*S*)-2-F-Phe-(*S*)-Phe-OH

4b Bz-(*R*)-2-F-Phe-(*S*)-Phe-OH

Scheme 1



5 Boc-Δ 2-F-Phe-(*R*)-Phe-OH

6 Boc-Δ 2-F-Phe-(*S*)-Phe-OH

7a Boc-(*R*)-2-F-Phe-(R)-Phe-OH

7b Boc-(*S*)-2-F-Phe-(R)-Phe-OH

8a Boc-(*S*)-2-F-Phe-(*S*)-Phe-OH

8b Boc-(*R*)-2-F-Phe-(*S*)-Phe-OH

Scheme 2

hydrogenation of the (2-flurophenyl-dehydroalanyl)phenylalanines or the esters with respect to the *de* values and hydrogenation rate (see Table 1, entries 1–9, column 8 and 9). The halflife-time of 3–4 min, which we found was comparable for both the dipeptides (Table 1, column 4) and the dipeptide esters (Döbler et al., 1999). The (*S*)-PPP induced an excess of (*R*)-configurated product at the new asymmetric center and *vice versa*. The *N*-benzoyl substituted derivatives exhibited high double induction, resulting in more than 90% of the (*R*,*R*)- or (*S*,*S*)-diastereomer when the intrinsic asymmetric induction in the substrate and the catalyst were in the same direction (entries 1 and 2). The stereoselectivity was less pronounced for the

Table 1. Asymmetric hydrogenation of dehydrodipeptides

Entry	Substr.	Cat*[a]	t/2[b] (min)	Dipeptide	Diastereomeric ratio		de (%)	Ester[c] (% de)
1	**1** (*R*)	S-PPP-Rh$^+$	3.0	**3a/3b**	*R,R/S,R*	95.0/5.0	90	87
2	**2** (*S*)	R-PPP-Rh$^+$	3.5	**4a/4b**	*S,S/R,S*	94.0/6.0	88	87
3	**1** (*R*)	R-PPP-Rh$^+$	4.0	**3a/3b**	*R,R/S,R*	17.0/83.0	66	69
4	**2** (*S*)	S-PPP-Rh$^+$	4.0	**4a/4b**	*R,R/S,R*	17.5/82.5	65	70
5	**1** (*R*)	(−)-BPPM-Rh$^+$	3.5	**3a/3b**	*R,R/S,R*	98.5/1.5	97	98
6	**2** (*S*)	(−)-BPPM-Rh$^+$	3.0	**4a/4b**	*S,S/R,S*	2.5/97.5	95	96
7	**1** (*R*)	DPPB-Rh$^+$	3.0	**3a/3b**	*R,R/S,R*	69.5/30.5	39	30
8	**2** (*S*)	DPPB-Rh$^+$	3.0	**4a/4b**	*S,S/R,S*	69.0/31.0	38	30
9	**5** (*R*)	S-PPP-Rh$^+$	–[d]	**7a/7b**	*R,R/S,R*	83.0/17.0	66	79
10	**6** (*S*)	R-PPP-Rh$^+$	–	**8a/8b**	*S,S/R,S*	82.0/18.0	64	80
11	**5** (*R*)	R-PPP-Rh$^+$	–	**7a/7b**	*R,R/S,R*	41.0/59.0	18	52
12	**6** (*S*)	S-PPP-Rh$^+$	–	**8a/8b**	*S,S/R,S*	40.0/60.0	20	53
13	**5** (*R*)	(−)-BPPM-Rh$^+$	–	**7a/7b**	*R,R/S,R*	90.0/10.0	80	76
14	**6** (*S*)	(−)-BPPM-Rh$^+$	–	**8a/8b**	*S,S/R,S*	41.0/59.0	18	31
15	**5** (*R*)	DPPB-Rh$^+$	–	**7a/7b**	*R,R/S,R*	70.0/30.0	40	25
16	**6** (*S*)	DPPB-Rh$^+$	–	**8a/8b**	*S,S/R,S*	69.0/31.0	38	25

[a] *PPP-Rh*$^+$: [Rh(PPP)COD]$^+$BF$_4^-$, crystallized complex. *PPP*: 2,3-*O*,*N*-bis(diphenyl-phosphino)-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.-butyloxy-carbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine. *DPPB*: 1,4-bis-(diphenylphosphino)butane. [b] t/2 time for uptake of 50% of theoretical hydrogen volume.
[c] hydrogenation of the corresponding methyl esters. [d] total hydrogenation after 24 h.

combination of (*R*)-PPP/(*R*)-**1** and (*S*)-PPP/(*S*)-**2** (entries 3 and 4). The BPPM ligand exhibited high enantioselectivity for (*R*)- and (*S*)-dehydrodipeptide (entries 5 and 6). The achiral DPPB ligand gave lower *de* values for the ester substrates. In this case the optical induction only depended on the chirality of the substrates (entries 7 and 8).

The results of the hydrogenation of Boc-Δ2-F-Phe-Phe-OH indicate, that the activity decreases markedly with the introduction of *N*-Boc instead of the *N*-benzoyl group (entries 9–16, 24 h for total hydrogenation compared to t/2 = 3–4 min) or in comparison to Boc-Δ2-F-Phe-Phe-OMe (t/2 between 27 and 65 min). The *N*-Boc compounds **7** and **8** show a lower *de* (entries 9 and 10) compared with the esters and with the benzoyl derivatives **3** and **4** (entries 1 and 2).

The chiral center in the *N*-Boc dehydropeptides (entries 9,10 and 11,12) shows a greater influence in determining the *de* (66% *de* compared to 18% *de*, Δ*de* 48%) compared with that in the *N*-benzoyl derivatives (entries 1,2 and 3,4 Δ*de* 34%). This is similar to the dipeptide ester series (Δ*de* 27% compared to Δ*de* 17%). This becomes even more clear looking at the *N*-Boc substrates in the reaction with BPPM/Rh$^+$ (entries 13 and 14, Δ*de* 62% and 45% compared to Δ*de* 2%). The absolute configuration of the chiral catalyst also controls the steric course of the reduction to a great extent, but is influenced by the chiral centre of the substrate. The simple asymmetric induction using DPPB as

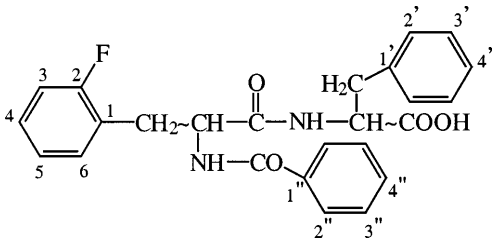


Fig. 1. Denotation for NMR

achiral ligand (entries 15 and 16) resulted in a higher *de* value for the dipeptides (40% *de* against 25% *de*), which is comparable with the results found for Bz-Δ2-F-Phe-Phe-OH. In general we found a lower stereoselectivity of the PPP/Rh catalyst for the dipeptides compared with the esters.

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 ARX-300 spectrometer (^{1}H: 300.13 MHz, ^{13}C: 75.47 MHz) at ambient temparature. Under this conditions several signal appeared broadened due to the hindered rotation about the amide bonds. Calibration of spectra was carried out be means of solvent peaks (DMSO-d_6: $\delta^{1}H = 2.50$; $\delta^{13}C = 39.7$). 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. 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) after esterification. Melting points are uncorrected and were determined on a Boetius microscope.

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 removed for HPLC measurements.

The substrates **1**,**2** and **5**,**6** were prepared by alkaline hydrolysis of the corresponding ester derivatives (Döbler et al., 1999):

N-[(Z)-N-Benzoyl-(2-fluorophenyl)dehydroalanyl])phenylalanines ***1*** *and* ***2***

To a solution of (*R*)- or (*S*)- *N*-[(*Z*)-*N*-benzoyl(2-fluorophenyl)dehydroalanyl]) phenylalanine methyl ester (3.0 g, 6.7 mmol) in dioxane (70 mL) was added a solution of $LiOH \times H_2O$ (420 mg, 10 mmol) in 60 mL of water. The reaction mixture was stirred at r.t. for 4 h and then the solvent was removed under reduced pressure. The residue was dissolved in water, the solution was acidified with HCl and kept at 0°C overnight. The resultant crystals were recrystallized from $EtOH/H_2O$ and dried over KOH *in vacuo*.

(*R*)-**1.** 2.5 g (86% yield); mp 146–148°C; $[\alpha]^{25}_{D}$-43.9 (c1, $CHCl_3$). Anal.calcd. for $C_{25}H_{21}FN_2O_4$ (432.5): C69.43 H4.89 N6.48; found: C69.38 H4.98 N6.57

^{1}H NMR (DMSO-d_6): δ 12.50 (br, 1H, COOH); 9.87 (s, 1H, NH); 8.24 (d, 1H, $^3J_{NH,CH}$~8.0 Hz, NH); 7.93 (m, 2H, H-2″); 7.60 (m, 2H, H-4″, H-6); 7.50 (m, 2H, H-3″): 7.35 (m, 1H, H-4); 7.28-7.16 (m, 7H, H-3, H-2′, H-3′, H-4′, CH olef); 7.13 (m, 1H, H-5); 4.56 (dt, 1H, CH); 3.11, 3.06 (AB part of ABX, 2H, ^2J~13.6 Hz, $^3J_{CH,CH2a}$~8.5 Hz, $^3J_{CH,CH2b}$~5.3 Hz, CH_2).

^{13}C NMR (DMSO-d_6): δ173.0 (COOH); 166.2 (PhCO); 165.1 (=C<u>C</u>O); 160.2 (d, $^1J_{F,C}$~248.5 Hz, C-2); 137.9 C-1′); 133.8 (C-1″); 132.2 (C-4″); 132.0 (d, $^4J_{F,C}$~1.5 Hz, C olef.); 131.0 (d, $^3J_{F,C}$~8.8 Hz, C-4); 129.7 (d, $^3J_{F,C}$~2.5 Hz, C-6); 129.5 (C-3′); 128.7 (C-3″); 128.5 (C-2′); 128.1 (C-2″); 126.8 (C-4′); 124.7 (d, $^4J_{F,C}$~3.3 Hz, C-5); 122.4 (d, $^2J_{F,C}$~12.5 Hz, C-1); 121.3 (d, $^3J_{F,C}$~4.3 Hz, CH olef.); 115.9 (d, $^2J_{F,C}$~21.8 Hz, C-3); 54.4 (CH); 36.8 (CH_2).

(*S*)-**2.** 2.6 g (88% yield); mp 148–149°C; $[\alpha]^{25}_{D}$ 43.7 (c1, $CHCl_3$). Anal.calc. for $C_{25}H_{21}FN_2O_4$ (432.5): C69.43 H4.89 N6.48; found: C69.22 H4.94 N6.38

^{1}H NMR (DMSO-d_6): δ 12.50 (br, 1H, COOH); 9.90 (s, 1H, NH); 8.32 (d, 1H, $^3J_{NH,CH}$~8.0 Hz, NH); 7.95 (m, 2H, H-2″); 7.60 (m, 2H, H-4″, H-6); 7.51 (m, 2H, H-3″): 7.36 (m, 1H, H-4); 7.30-7.17 (m, 7H, H-3, H-2′, H-3′, H-4′, CH olef); 7.14 (m, 1H, H-5); 4.54 (dt, 1H, CH); 3.12, 3.06 (AB part of ABX, 2H, ^2J~13.9 Hz, $^3J_{CH,CH2a}$~8.5 Hz, $^3J_{CH,CH2b}$~5.3 Hz, CH_2).

^{13}C NMR (DMSO-d_6): δ173.0 (COOH); 166.2 (PhCO); 165.1 (=C<u>C</u>O); 160.2 (d, $^1J_{F,C}$~248.5 Hz, C-2); 137.9 (C-1′); 133.8 (C-1″); 132.2 (C-4″); 132.0 (d, $^4J_{F,C}$~1.5 Hz, C olef.); 131.0 (d, $^3J_{F,C}$~8.8 Hz, C-4); 129.7 (d, $^3J_{F,C}$~2.5 Hz, C-6); 129.5 (C-3′); 128.7 (C-3″); 128.5 (C-2′); 128.1 (C-2″); 126.8 (C-4′); 124.7 (d, $^4J_{F,C}$~3.3 Hz, C-5); 122.4 (d, $^2J_{F,C}$~12.5 Hz, C-1); 121.3 (d, $^3J_{F,C}$~4.3 Hz, CH olef.); 115.9 (d, $^2J_{F,C}$~21.8 Hz, C-3); 54.4 (CH); 36.8 (CH_2).

*N-[(Z)-N-Boc-(2-fluorophenyl)dehydroalanyl]phenylalanines **5** and **6***

(*R*)- or (*S*)-*N*-[(*Z*)-*N*-Boc-(2-fluorophenyl)dehydroalanyl]phenylalanine methyl ester (4.8 g, 10.8 mmol) was dissolved in dioxane (35 mL) and 1N NaOH (18 mL) was added in portions.

The mixture was stirred for 4 h at r.t. The reaction solution was similar worked up as described for the benzoyl derivatives. The resultant crystals were recrystallized from ethyl acetate/n-hexane and dried over KOH *in vacuo*.

(*R*)-**5.** 3.9 g (84% yield); mp 77–79°C; $[\alpha]^{25}_{D}$-58.6 (c1, $CHCl_3$). Anal.calcd. for $C_{23}H_{25}FN_2O_4$ (428.5): C64.47 H5.88 N6.54; found: C64.22 H5.82 N6.41

^{1}H NMR (DMSO-d_6): δ8.42 (br, 1H, COOH); 8.08 (d, 1H, $^3J_{NH,CH}$~8.0 Hz, NH); 7.63 (m, 1H, H-6); 7.35 (m, 1H, H-4); 7.30-7.13 (m, 8H, H-3, H-5, H-2′, H-3′, H-4′, CH olef); 6.99 (br, 1H, NH); 4.54 (dt, 1H, CH); 3.13, 3.06 (AB part of ABX, 2H, ^2J~13.6 Hz, $^3J_{CH,CH2a}$~8.5 Hz, $^3J_{CH,CH2b}$~5.3 Hz, CH_2); 1.29 (s, 9H, CMe_3).

^{13}C NMR (DMSO-d_6): δ172.9 (COOH); 165.0 (=C<u>C</u>O); 160.0 (d, $^1J_{F,C}$~248.5 Hz, C-2); 153.3 (NHCOO); 137.8 (C-1′); 131.6 (br, C olef.); 130.4 (d, $^3J_{F,C}$~8.7 Hz, C-4); 129.6 (d, $^3J_{F,C}$~1.5 Hz, C-6); 129.4 (C-3′); 128.3 (C-2′); 126.5 (C-4′); 124.4 (d, $^4J_{F,C}$~3.2 Hz, C-5); 122.5 (d, $^2J_{F,C}$~12.5 Hz, C-1); 118.6 (br, CH olef.); 115.6 (d, $^2J_{F,C}$~21.8 Hz, C-3); 79.2 (<u>C</u>Me$_3$); 54.3 (CH); 36.8 (CH_2); 28.0 (C<u>Me</u>$_3$).

(*S*)-**6.** 4.0 g (86% yield); mp 78–80°C; $[\alpha]^{25}_{D}$ 58.3 (c1, $CHCl_3$). Anal.calcd. for $C_{23}H_{25}FN_2O_4$ (428.5): C64.47 H5.88 N6.54; found; C64.28 H5.98 N6.63

^{1}H NMR (DMSO-d_6): δ8.50 (br, 1H, COOH); 8.17 (d, 1H, $^3J_{NH,CH}$~8.0 Hz, NH); 7.63 (m, 1H, H-6); 7.35 (m, 1H, H-4); 7.30-7.13 (m, 8H, H-3, H-5, H-2′, H-3′, H-4′, CH olef); 6.97 (br, 1H, NH); 4.54 (dt, 1H, CH); 3.13, 3.06 (AB part of ABX, 2H, ^2J~13.8 Hz, $^3J_{CH,CH2a}$~8.5 Hz, $^3J_{CH,CH2b}$~5.3 Hz, CH_2); 1.30 (s, 9H, CMe_3).

^{13}C NMR (DMSO-d_6): δ173.0 (COOH); 165.1 (=C<u>C</u>O); 160.1 (d, $^1J_{F,C}$~248.5 Hz, C-2); 153.3 (NHCOO); 137.9 (C-1′); 131.6 (br, C olef.); 130.5 (d, $^3J_{F,C}$~8.7 Hz, C-4); 129.7 (br, C-6); 129.4 (C-3′); 128.4 (C-2′); 126.6 (C-4′); 124.5 (d, $^4J_{F,C}$~3.3 Hz, C-5); 122.6 (d, $^2J_{F,C}$~12.5 Hz, C-1); 118.7 (br, CH olef.); 115.7 (d, $^2J_{F,C}$~21.7 Hz, C-3); 79.3 (<u>C</u>Me$_3$); 54.3 (CH); 36.8 (CH_2); 28.1 (C<u>Me</u>$_3$).

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