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α-Amino acids as acid components in the Passerini reaction: influence of N-protection on the yield and stereoselectivity

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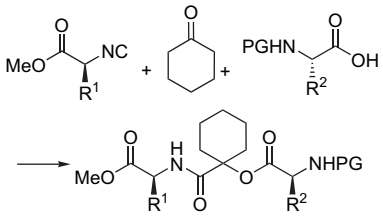
ABSTRACT

The Passerini reaction offers an easy access to depsipeptides, when both acid and isocyanide are derived from α-amino acids. However, racemisation of isocyanides derived from α-amino acid esters severely limits their use in the Passerini reaction. In order to overcome this limitation, a study on the influence of the α-amino acid *N*-protecting group on the yield and diastereoisomeric ratio of the product of the Passerini reaction was performed. Six different protecting groups were tested. Their influence turns out to be crucial and is not constant when the amino acid is changed. After optimisation, the Passerini reaction products with cyclohexanone as the carbonyl component were obtained with 99% yield and >98% de.

1. Introduction

In recent years, the Passerini reaction has became a powerful tool in combinatorial synthesis. Of special interest are cases in which *N*-protected amino acids are used as the acid compounds (Scheme 1). Such reagents allow a convenient synthesis of depsipeptides[1] and β-peptide analogues through a Passerini reaction–deprotection–acyl migration strategy.[2–4] Many such compounds have confirmed the biological activities, such as AM-Toxins,[5] antibiotics (e.g., valinomycines)[6] and protease inhibitors.[7]



Scheme 1. Studied Passerini reaction.

It is noteworthy that in only two cases[3,4] a chiral isocyanide derived from an amino acid other than glycine is used. In both cases, the Boc-protected amino acids are used as the acid components. The authors report no epimerisation on the isocyanide-derived chirality centre in the course of the reaction. We have witnessed, however, that the lability of the proton in the α position of the isocyanide in general results in racemisation. Another drawback of the Passerini reaction is its sensitivity to the steric hindrance of the carbonyl compounds. Therefore, aldehydes perform much better than ketones.

In this paper, we report our studies on the influence of the type of N-protection on the yield and stereoselectivity of the Passerini reaction with ketones. For the model study, we have chosen an isocyanide derived from L-phenylalanine (R^1=Bn), cyclohexanone and two amino acids, L-phenylalanine and D-valine, bearing various protections of the amino group.

2. Results and discussion

The collected results of our study with protected D-valine as the acid component in the Passerini reaction are presented in Table 1.

A great influence of the type of protecting group can be seen, both on the yield and on the diastereoisomeric ratio of the product. In terms of the yield, best results (over 74% in ca. 20 h) were obtained in reactions with Boc and phthaloyl protected amino acids, regardless of the isocyanide's configuration (Table 1, entries 6, 8 and 11, 12). Reaction with CBz-protected substrate proved to be sensitive to the configuration of the isocyanide, as after 25 h of reaction the yield of the diastereoisomer derived from (*R*)-isocyanide (Table 1, entry 5) was higher than the yield of the diastereoisomer derived from (*S*)-isocyanide (Table 1, entry 4) after 27 h. Substrates with benzoyl and acetyl groups (Table 1, entries 1, 2 and 9, 10) reacted much slower, and in the case of the acetylamino acid the influence of isocyanide's configuration is crucial. In the

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Table 1
Results of the study with *N*-protected D-valine (R^4=*i*-Pr)

No.	PG	R–NC config.	*t* [h]	Yield [%]	Comp.	dr[a]
1	Bz	*S*	20	30	**1**	16:84
2		*R*	35	42		81:19
3	Trt	*S*	115	<1	**2**	nd
4	CBz	*S*	27	52	**3**	18:82
5		*R*	25	89		87:13
6	Phth	*S*	17	74	**4**	85:15
7		*RS*	20	84		52:48
8		*R*	20	78		18:82
9	Ac	*S*	21	21	**5**	18:82
10		*R*	60	9		69:31
11	Boc	*S*	20	79	**6**	5:95
12		*R*	23	87		96:4

Reactions in cyclohexanone at 40 °C.
[a] Determined by HPLC analysis.

reaction with the trityl-protected amino acid (Table 1, entry 3), no formation of the product was observed.

The best diastereoisomeric ratio of the product was obtained in the reaction with Boc-protected amino acid (Table 1, entries 11, 12), and Boc protection is clearly the group of choice, as both the yields and the diastereoisomeric ratios are the highest. The acetyl protection is the worst out of those tested, as the yields are low and mixtures of diastereoisomers are formed in the reactions.

To investigate the influence of the type of amino acid, we performed an analogous study using *N*-protected L-phenylalanine. The results are presented in Table 2.

The best yields were obtained in the reactions with Boc and phthaloyl protected amino acids (Table 2, entries 6, 7, and 11, 12), as was the case for the derivatives of D-valine, however, a bigger influence of the isocyanide configuration can be seen. The reaction with CBz-protected phenylalanine yielded no product (Table 2, entry 5). With other protecting groups (Bz, Trt and Ac), the products were obtained in moderate yields, and an influence of the isocyanide configuration on the yield was observed, especially in the case of acetyl-protected phenylalanine (Table 2, entries 8–10).

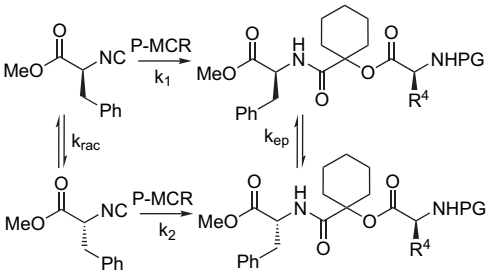
Virtually only one diastereoisomer was obtained in the reactions with amino acids bearing the trityl, phthaloyl and Boc protections (Table 2, entries 3, 4, 6, 7 and 11, 12). These results, combined with the yields, again point to the Boc protection as the best choice.

We also carried out a study on the possible cause of the different distributions of the product diastereoisomers (Scheme 2). Two basic assumptions were taken. First, the Passerini reaction is irreversible.[8] Second, the epimerisation of the depsipeptide product under the reaction conditions is negligible (Scheme 2, $k_{ep} \cong 0$). An experiment was performed to support this thesis—diastereoisomerically enriched depsipeptide was stirred in the Passerini reaction conditions for 40 h and no change in diastereoisomeric excess was observed. Based on these assumptions, we propose two distinct kinetic relationships, which would lead to differences in the influence of amino acid protecting group on the diastereoisomeric ratio.

Table 2
Results of the study with *N*-protected L-phenylalanine (R^4=Bn)

No.	PG	R–NC config.	*t* [h]	Yield [%]	Comp.	dr[a]
1	Bz	*S*	20	39	**7**	94:6
2		*R*	20	48		7:93
3	Trt	*S*	24	66	**8**	<1:99
4		*R*	20	49		>99:1
5	CBz	*S*	60	<1	**9**	—
6	Phth	*S*	14	84	**10**	<1:99
7		*R*	40	82		>99:1
8	Ac	*S*	20	67	**11**	16:84
9		*RS*	20	51		54:46
10		*R*	23	36		75:25
11	Boc	*S*	20	86	**12**	99:1
12		*R*	16	>99		1:99

Reactions in cyclohexanone at 40 °C.
[a] Determined by HPLC analysis.



Scheme 2. System kinetics.

According to the first hypothesis, the reactions with some of the protected amino acids proceed faster, and the racemisation rate of the isocyanide is relatively lower ($k_1 > k_{rac}$), which leads to conversion of the substrate before it racemises. According to the second hypothesis, the racemisation of isocyanide is fast ($k_{rac} > k_1$, k_2), but with some of the protected amino acids one of the diastereoisomeric products is formed faster ($k_1 > k_2$), which leads to the dynamic kinetic resolution (DKR) of the isocyanide.

It is possible to suggest a correlation of the yield and diastereoselectivity of the reactions. The fastest reactions (giving products in highest yields after comparable time) also give products with high diastereoisomeric ratios (e.g., Table 1, entries 11, 12, and Table 2 entries 6, 7, and 11, 12). This is also valid when two enantiomers of isocyanide are compared in the reaction with one amino acid (e.g., Table 2, entries 1, 2 and 8, 10). This observation strongly supports the first hypothesis.

In order to obtain further information on the nature of the phenomenon, we studied the reactions with racemic isocyanides (Table 1, entry 8 and Table 2, entry 9). In these reactions, roughly equimolar mixtures of diastereoisomeric products were obtained, which suggests that the second hypothesis is not occurring.

3. Summary

A study on the influence of the protecting group in the amino acid as the acid component of the Passerini reaction on the yield and diastereoselectivity of this reaction was performed. Six different protecting groups were tested and the influence of the protecting group proved to be crucial. *tert*-Butoxycarbonyl (Boc) group was chosen as the best N-protecting group in the studied system. An initial study on the nature of this phenomenon was also conducted. It leads to a suggestion that with some N-protections used for amino acids, the reaction proceeds faster and the racemisation of the isocyanide is slower. This results in fast formation of one diastereoisomer of the product.

The use of Boc-protected amino acids in the Passerini reaction with cyclic ketone leads to the product in very high yields and high diastereoisomeric ratios, for both of the studied model amino acids.

4. Experimental

4.1. General

Optical rotations were measured with a JASCO DIP-360 polarimeter. NMR spectra were measured with a Varian 200 GEMINI and

Varian 400 GEMINI spectrometers, with TMS used as an internal standard. CHN analyses were performed on Perkin Elmer 240 Elemental Analyzer. MS spectra were recorded on an API-365 (SCIEX) apparatus.

4.2. General procedure for the synthesis of Passerini reaction products

Protected amino acid (0.50 mmol) was placed in a 10 mL round bottom flask followed by methyl (*S*)-(−)- or (*R*)-(+)-2-isocyano-3-phenylpropionate (0.50 mmol) and 1 mL of cyclohexanone. The mixture was stirred at 40 °C for the time given in Tables 1 and 2. The dr was determined by analytical HPLC (250×4,6) filled with Kromasil C-18 5μm, eluting with isocratic mixture of methanol/water (7:3 v/v) (1 mL/min), with Merck Hitashi UV detector L-7400, h=228 nm and Merck Hitashi L-6000A pump. The volatiles were evaporated under reduced pressure, and the residue was separated via semi-preparative HPLC (250×20) filled with Poligroprep RP-18 12u, eluting with isocratic mixture of methanol/water (7:3 v/v) (20 mL/min), with Shimadzu RID-6A RI detector and Shimadzu LC-8A preparative liquid chromatography. Both diastereoisomers were received in the form of a white foam.

*Compound (R,R)-**1***: $[\alpha]_D^{20}$ −34.8 (*c* 1.5, benzene). Anal. $C_{29}H_{36}N_2O_6$ requires: C, 68.48%; H, 7.13%; N, 5.51%. Found: C, 68.13%; H, 7.24%; N, 5.35%. ^{1}H NMR (200 MHz, C_6D_6): δ 0.95 (d, *J*=7.0 Hz, 3H, C*H*$_3$CH), 1.01 (d, *J*=6.8 Hz, 3H, C*H*$_3$CH), 1.20–2.40 (m, 11H, (CH$_3$)$_2$C*H*, (C*H*$_2$)$_5$), 3.10–3.25 (m, 1H, PhC*H*$_2$), 3.24 (s, 3H, C*H*$_3$O), 4.88 (dd, *J*=7.8, 5.2 Hz, 1H, BnC*H*), 5.04–5.20 (m, 1H, *i*-PrC*H*), 6.69 (d, *J*=7.8 Hz, 1H, NH), 6.94 (d, *J*=7.8 Hz, 1H, NH), 7.00–7.82 (m, 10H, 2×Ar*H*); ^{13}C NMR (50 MHz, C_6D_6): δ 18.8, 20.3, 22.4, 25.9, 31.7, 33.1, 33.8, 52.3, 54.5, 59.5, 84.3, 127.7, 129.2, 129.4, 129.4, 130.4, 132.2, 135.2, 137.7, 168.4, 171.7, 172.6, 172.8; IR (CH_2Cl_2) ν: 3439, 2942, 2864, 1741, 1671, 1513, 1485, 1451, 1205, 1140 cm^{-1}; retention time: t_R=8.0 min.

*Compound (R,S)-**1***: $[\alpha]_D^{20}$ 58.2 (*c* 1.5, benzene); HRMS (ESI) 521.2478 ($C_{29}H_{36}N_2O_6Na$: 521.2466); ^{1}H NMR (200 MHz, C_6D_6): δ 0.96 (d, *J*=7.2 Hz, 3H, C*H*$_3$CH), 1.01 (d, *J*=6.8 Hz, 3H, C*H*$_3$CH), 1.20–2.40 (m, 11H, (CH$_3$)$_2$C*H*, (C*H*$_2$)$_5$), 3.18 (s, 3H, C*H*$_3$O), 3.20–3.40 (m, 1H, PhC*H*$_2$), 4.60–4.80 (m, 1H, BnC*H*), 5.04–5.20 (m, 1H, *i*-PrC*H*), 6.80–8.00 (m, 12H, 2×Ar*H*, 2×N*H*); ^{13}C NMR (50 MHz, C_6D_6): δ 19.3, 20.3, 22.4, 25.9, 31.4, 32.3, 34.4, 38.6, 52.3, 54.6, 60.1, 84.4, 127.6, 128.2, 129.2, 129.3, 130.4, 132.4, 135.2, 138.0, 168.8, 171.6, 172.8; IR (CH_2Cl_2) ν: 3436, 2967, 2942, 2865, 1742, 1670, 1514, 1485, 1451, 1205, 1216, 1158, 1140 cm^{-1}; retention time: t_R=12.0 min.

*Compound (R,R)-**3***: $[\alpha]_D^{20}$ −29.8 (*c* 1.6, benzene). Anal. $C_{30}H_{38}N_2O_7$ requires: C, 66.90%; H, 7.11%; N, 5.20%. Found: C, 66.85%; H, 7.11%; N, 5.18%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.93 (d, *J*=6.8 Hz, 3H, C*H*$_3$CH), 1.03 (d, *J*=6.8 Hz, 3H, C*H*$_3$CH), 1.10–2.40 (m, 10H, (C*H*$_2$)$_5$, (CH$_3$)$_2$C*H*), 3.05–3.18 (m, 2H, PhC*H*$_2$), 3.68 (s, 3H, C*H*$_3$O), 4.21–4.37 (m, 2H, BnC*H*), 4.78–4.92 (m, 1H, *i*-PrC*H*), 5.10 (s, 2H, PhC*H*$_2$O), 5.21 (d, *J*=8.4 Hz, 1H, CBzN*H*), 6.50 (d, *J*=8.0 Hz, 1H, N*H*), 7.03–7.50 (m, 10H, 2×Ar*H*, N*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.6, 19.7, 21.6, 25.2, 31.0, 32.1, 32.9, 38.0, 52.5, 53.4, 59.7, 67.4, 83.2, 127.2, 128.4, 128.5, 128.8, 128.8, 129.6, 136.4, 156.9, 170.7, 172.1; IR (CH_2Cl_2) ν: 3435, 3334, 3055, 3034, 2942, 2865, 1741, 1724, 1681, 1510, 1453, 1362, 1349, 1312, 1215, 1140 cm^{-1}; retention time: t_R=17.0 min.

*Compound (R,S)-**3***: $[\alpha]_D^{20}$ 51.5 (*c* 1.2, benzene). Anal. $C_{30}H_{38}N_2O_7$ requires: C, 66.90%; H, 7.11%; N, 5.20%. Found: C, 66.84%; H, 6.92%; N, 5.06%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.93 (d, *J*=6.8 Hz, 3H, C*H*$_3$CH), 1.02 (d, *J*=6.6 Hz, 3H, C*H*$_3$CH), 1.10–2.35 (m, 10H, (C*H*$_2$)$_5$, (CH$_3$)$_2$C*H*), 3.00–3.20 (m, 2H, PhC*H*$_2$), 3.65 (s, 3H, C*H*$_3$O), 4.05–4.22 (m, 2H, BnC*H*), 4.75–4.95 (m, 1H, *i*-PrC*H*), 5.11 (s, 2H, PhC*H*$_2$O), 5.21 (d, *J*=8.2 Hz, 1H, CBzN*H*), 6.58 (d, *J*=7.2 Hz, 1H, N*H*), 7.03–7.42 (m, 10H, 2×Ar*H*, N*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.0, 19.7, 21.6, 25.3, 30.9, 32.0, 33.0, 38.0, 52.5, 53.5, 60.1, 67.5, 83.4, 127.2, 128.6, 128.7, 128.9, 129.6, 136.6, 170.8, 172.2; IR (CH_2Cl_2) ν: 3436, 3347, 3055, 3034, 2942, 2865, 1741, 1680, 1510, 1453, 1349, 1311, 1217, 1140 cm^{-1}; retention time: t_R=12.7 min.

*Compound (R,R)-**4***: $[\alpha]_D^{20}$ −7.7 (*c* 1.7, benzene). Anal. $C_{30}H_{34}N_2O_7$ requires: C, 67.40%; H, 6.41%; N, 5.24%. Found: C, 67.55%; H, 6.37%; N, 5.09%. ^{1}H NMR (200 MHz, C_6D_6): δ 0.89 (d, *J*=6.6 Hz, 3H, C*H*$_3$CH), 1.09 (d, *J*=6.8 Hz, 3H, C*H*$_3$CH), 1.18–1.50 (m, 6H, (C*H*$_2$)$_3$), 1.60–2.40 (m, 4H, C*H*$_2$CC*H*$_2$), 2.70–2.95 (m, 1H, PhC*H*$_2$), 3.20 (s, 3H, C*H*$_3$O), 3.21–3.40 (m, 2H, PhC*H*$_2$, (CH$_3$)$_2$C*H*), 4.90 (d, *J*=7.6 Hz, 1H, *i*-PrC*H*), 5.17 (dd, *J*=14.4, 6.8 Hz, 1H, BnC*H*), 6.82–7.60 (m, 10H, 2×Ar*H*, N*H*); ^{13}C NMR (50 MHz, C_6D_6): δ 19.5, 21.2, 21.6, 25.2, 29.2, 31.5, 33.7, 38.4, 51.5, 54.0, 58.4, 84.2, 123.6, 127.0, 128.7, 129.6, 132.0, 134.2, 137.2, 167.0, 168.4, 171.8, 172.4; IR (CH_2Cl_2) ν: 3380, 3057, 2942, 2863, 1774, 1746, 1716, 1680, 1514, 1451, 1389, 1364, 1208, 1140 cm^{-1}; retention time: t_R=14.9 min.

*Compound (R,S)-**4***: $[\alpha]_D^{20}$ 3.0 (*c* 1.8, benzene). Anal. $C_{30}H_{34}N_2O_7$ requires: C, 67.40%; H, 6.41%; N, 5.24%. Found: C, 67.08%; H, 6.69%; N, 5.13%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.02 (d, *J*=6.8 Hz, 3H, C*H*$_3$CH), 1.21 (d, *J*=6.8 Hz, 3H, C*H*$_3$CH), 1.10–2.40 (m, 6H, (C*H*$_2$)$_3$), 2.65–3.65 (m, 7H, C*H*$_2$CC*H*$_2$, PhC*H*$_2$, (CH$_3$)$_2$C*H*), 3.76 (s, 3H, C*H*$_3$O), 4.72 (d, *J*=7.0 Hz, 1H, *i*-PrC*H*), 4.90 (dd, *J*=12.2, *J*=8.4 Hz, 1H, BnC*H*), 6.86 (d, *J*=7.6 Hz, 1H, NH), 7.25–7.95 (m, 9H, 2×Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.5, 21.3, 21.4, 25.0, 29.5, 30.2, 34.2, 38.0, 52.5, 53.5, 58.0, 83.9, 123.9, 127.0, 128.6, 129.5, 131.8, 134.8, 136.9, 166.7, 168.5, 172.1, 172.3; IR (CH_2Cl_2) ν: 3373, 3056, 2942, 2863, 1774, 1747, 1715, 1679, 1521, 1451, 1388, 1364, 1210, 1141 cm^{-1}; retention time: t_R= 13.2 min.

*Compound (R,S)-**5***: $[\alpha]_D^{20}$ 75.2 (*c* 1.7, benzene); HRMS (ESI) 469.2330 ($C_{24}H_{34}N_2O_6Na$: 469.2309); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.03 (d, *J*=7.2 Hz, 3H, C*H*$_3$CH), 1.07 (d, *J*=6.8 Hz, 3H, C*H*$_3$CH), 1.10–2.40 (m, 11H, (C*H*$_2$)$_5$, (CH$_3$)$_2$C*H*), 2.08 (s, 3H, C*H*$_3$CO), 3.05–3.30 (m, 2H, PhC*H*$_2$), 3.76 (s, 3H, C*H*$_3$O), 4.45 (dd, *J*=7.4, 6.0 Hz, 1H, *i*-PrC*H*), 4.80–4.93 (m, 1H, BnC*H*), 6.07 (d, *J*=7.8 Hz, 1H, NH), 6.65 (d, *J*=7.8 Hz, 1H, NH), 7.16–7.45 (m, 5H, Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.4, 19.7, 21.6, 21.7, 23.4, 25.3, 30.8, 31.3, 33.7, 37.9, 52.5, 53.4, 58.4, 83.4, 127.2, 128.7, 129.6, 136.6, 164.1, 171.0, 171.2, 172.4; IR (CH_2Cl_2) ν: 3436, 3330, 3055, 3034, 2941, 2862, 1742, 1679, 1509, 1451, 1371, 1208, 1139 cm^{-1}; retention time: t_R=5.2 min.

*Compound (R,R)-**5***: $[\alpha]_D^{20}$ −19.5 (*c* 1.3, benzene). Anal. $C_{24}H_{34}N_2O_6$ requires: C, 64.55%; H, 7.67%; N, 6.27%. Found: C, 64.73%; H, 7.91%; N, 6.05%. NMR (200 MHz, $CDCl_3$): δ 0.96 (d, *J*=7.0 Hz, 3H, C*H*$_3$CH), 1.02 (d, *J*=6.8 Hz, 3H, C*H*$_3$CH), 1.18–2.33 (m, 11H, (C*H*$_2$)$_5$, (CH$_3$)$_2$C*H*), 2.01 (s, 3H, C*H*$_3$CO), 3.08–3.18 (m, 2H, PhC*H*$_2$), 3.69 (s, 3H, C*H*$_3$O), 4.49 (dd, *J*=9.0, 4.6 Hz, 1H, *i*-PrC*H*), 4.76–4.80 (m, 1H, BnC*H*), 5.88 (d, *J*=8.2 Hz, 1H, NH), 6.48 (d, *J*=7.8 Hz, 1H, NH), 7.08–7.38 (m, 5H, Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.0, 19.7, 21.7, 23.5, 25.3, 31.0, 32.5, 32.6, 39.0, 52.5, 53.5, 58.1, 83.3, 127.3, 128.8, 129.6, 136.5, 170.7, 171.0, 172.2; IR (CH_2Cl_2) ν: 3435, 3333, 3055, 3033, 2942, 2864, 1742, 1678, 1511, 1451, 1371, 1210, 1189, 1138 cm^{-1}; retention time: t_R=4.0 min.

*Compound (R,R)-**6***: $[\alpha]_D^{20}$ −32.4 (*c* 1.5, benzene). Anal. $C_{27}H_{40}N_2O_7$ requires: C, 64.30%; H, 7.94%; N, 5.56%. Found: C, 64.36%; H, 8.19%; N, 5.52%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.99 (d, *J*=6.8 Hz, 3H, C*H*$_3$CH), 1.08 (d, *J*=6.8 Hz, 3H, C*H*$_3$CH), 1.50 (s, 9H, (C*H*$_3$)$_3$), 1.20–2.40 (m, 11H, (CH$_3$)$_2$C*H*, (C*H*$_2$)$_5$), 3.10–3.25 (m, 1H, PhC*H*$_2$), 3.75 (s, 3H, C*H*$_3$O), 4.20–4.30 (m, 1H, BnC*H*), 4.80–5.10 (m, 2H, *i*-PrC*H*, BocN*H*), 6.60–70 (m, 1H, NH), 7.00–7.40 (m, 5H, Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.6, 19.8, 21.6, 25.3, 28.6, 30.9, 32.0, 33.1, 38.0, 52.5, 53.3, 59.3, 80.2, 83.0, 127.2, 128.8, 129.5, 136.4, 156.3, 170.9, 172.1, 172.2; IR (CH_2Cl_2) ν: 3440, 3318, 3056, 3033, 2971, 2941, 2866, 1742, 1712, 1682, 1502, 1452, 1367, 1211, 1174, 1160, 1140 cm^{-1}; retention time: t_R=11.6 min.

*Compound (R,S)-**6***: $[\alpha]_D^{20}$ 52.3 (*c* 1.8, benzene). Anal. $C_{27}H_{40}N_2O_7$ requires: C, 64.30%; H, 7.94%; N, 5.56%. Found: C, 64.46%; H, 8.16%; N, 5.45%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.00 (d, *J*=6.6 Hz, 3H, C*H*$_3$CH), 1.08 (d, *J*=6.8 Hz, 3H, C*H*$_3$CH), 1.52 (s, 9H, (CH$_3$)$_3$), 1.20–2.40 (m, 11H,

(CH_3)$_2$C*H*, (CH_2)$_5$), 3.10–3.25 (m, 1H, PhCH_2), 3.73 (s, 3H, CH_3O), 4.10–4.20 (m, 1H, BnC*H*), 4.80–5.10 (m, 2H, *i*-PrC*H*, BocN*H*), 6.78–6.90 (m, 1H, NH), 7.20–7.50 (m, 5H, Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.9, 19.8, 21.6, 25.3, 28.7, 30.7, 32.0, 33.1, 37.9, 52.5, 53.8, 59.6, 80.2, 83.2, 127.2, 128.7, 129.6, 136.7, 156.5, 170.8, 172.3, 172.5; IR (CH_2Cl_2) ν: 3443, 3326, 3056, 3033, 2970, 2941, 2866, 1742, 1700, 1681, 1501, 1453, 1368, 1209, 1175, 1161, 1140 cm^{-1}; retention time: t_R=14.6 min.

*Compound (S,S)-***7**: $[\alpha]_D^{20}$ 3.0 (*c* 1.1, benzene). Anal. $C_{33}H_{36}N_2O_6$ requires: C, 71.20%; H, 6.52%; N, 5.03%. Found: C, 70.86%; H, 6.75%; N, 4.81%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.05–2.30 (m, 10H, *c-Hex*), 3.05–3.60 (m, 4H, 2×PhCH_2), 3.69 (s, 3H, CH_3O), 4.78–4.90 (m, 2H, 2×BnC*H*), 6.58 (d, *J*=6.6 Hz, 1H, N*H*), 6.80 (d, *J*=7.8 Hz, 1H, N*H*), 7.03–7.72 (m, 14H, 3×Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.5, 25.2, 32.2, 32.8, 37.6, 38.0, 52.5, 53.6, 54.7, 83.9, 97.3, 127.1, 127.3, 127.6, 128.7, 129.0, 129.1, 129.5, 129.6, 168.0, 170.4, 172.4; IR (CH_2Cl_2) ν: 3436, 3329, 3055, 3033, 2986, 2942, 2861, 1744, 1660, 1603, 1581, 1515, 1485, 1452, 1364, 1350, 1212, 1180, 1140 cm^{-1}; retention time: t_R=11.8 min.

*Compound (S,R)-***7**: $[\alpha]_D^{20}$ −34.9 (*c* 1.2, benzene). Anal. $C_{33}H_{36}N_2O_6$ requires: C, 71.20%; H, 6.52%; N, 5.03%. Found: C, 70.97%; H, 6.55%; N, 5.12%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95–2.22 (m, 10H, *c-Hex*), 3.02–3.36 (m, 4H, 2×PhCH_2), 3.56 (s, 3H, CH_3O), 4.75–4.92 (m, 2H, 2×BnC*H*), 6.60 (d, *J*=6.6 Hz, 1H, N*H*), 6.88 (d, *J*=7.8 Hz, 1H, N*H*), 7.13–7.80 (m, 14H, 3×Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.3, 21.5, 25.2, 31.6, 33.3, 37.6, 37.8, 52.5, 53.5, 56.0, 83.9, 127.2, 127.3, 127.6, 128.7, 129.0, 129.2, 129.5, 129.6, 132.3, 133.8, 136.2, 136.9, 168.1, 170.4, 172.3, 172.4; IR (CH_2Cl_2) ν: 3436, 3335, 2985, 2942, 2861, 1744, 1660, 1603, 1580, 1515, 1485, 1453, 1364, 1212, 1180, 1140 cm^{-1}; retention time: t_R=14.5 min.

*Compound (S,S)-***8**: $[\alpha]_D^{20}$ 33.5 (*c* 1.3, benzene). Anal. $C_{45}H_{46}N_2O_5$ requires: C, 77.78%; H, 6.69%; N, 4.03%. Found: C, 77.73%; H, 6.73%; N, 3.84%. HRMS (ESI) 717.3278 ($C_{45}H_{46}N_2O_5$Na: 717.3299); ^{1}H NMR (200 MHz, C_6D_6): δ 0.90–2.04 (m, 10H, *c-Hex*), 2.65–3.30 (m, 4H, 2×PhCH_2), 3.20 (s, 3H, CH_3O), 3.82–3.97 (m, 1H, BnC*H*), 5.10–5.20 (m, 1H, BnC*H*), 6.31 (d, *J*=8.0 Hz, 1H, N*H*), 6.95–7.70 (m, 26H, 5×Ar*H*, N*H*); ^{13}C NMR (50 MHz, C_6D_6): δ 21.8, 22.5, 25.4, 31.2, 38.5, 41.6, 51.8, 53.7, 58.6, 72.3, 82.3, 126.8, 126.9, 127.4, 128.2, 128.4, 128.8, 129.4, 129.5, 130.2, 130.3, 130.5, 137.0, 139.1, 146.9, 171.7, 172.3, 172.9; IR (CH_2Cl_2) ν: 3417, 2942, 2862, 1740, 1680, 1602, 1509, 1495, 1495, 1449, 1419, 1361, 1211, 1181, 1156, 1138 cm^{-1}; retention time: t_R=25.5 min.

*Compound (S,R)-***8**: $[\alpha]_D^{20}$ −42.5 (*c* 1.2, benzene); HRMS (ESI) 717.3304 ($C_{45}H_{46}N_2O_5$Na: 717.3299); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.97–2.00 (m, 10H, *c-Hex*), 2.40–3.20 (m, 4H, 2×PhCH_2), 3.60–3.75 (m, 1H, BnC*H*), 3.78 (s, 3H, CH_3O), 4.82–4.96 (m, 1H, BnC*H*), 6.12 (d, *J*=7.6 Hz, 1H, N*H*), 7.05–7.65 (m, 26H, 5×Ar*H*, N*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.5, 22.1, 25.1, 31.5, 33.2, 38.0, 41.0, 52.6, 53.4, 58.3, 71.9, 82.4, 126.8, 127.3, 128.2, 128.6, 128.8, 129.2, 129.7, 129.9, 136.3, 138.3, 146.4, 172.1, 172.2, 172.6; IR (CH_2Cl_2) ν: 3430, 3336, 2942, 2862, 2151, 1741, 1680, 1741, 1680, 1602, 1496, 1449, 1361,1209, 1181, 1155, 1138 cm^{-1}; retention time: t_R=25.9 min.

*Compound (S,R)-***10**: $[\alpha]_D^{20}$ −103.6 (*c* 1.4, benzene); HRMS (ESI) 582.2349 ($C_{34}H_{34}N_2O_7$: 582.2366); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.00–2.40 (m, 10H, *c-Hex*), 3.00–3.60 (m, 4H, 2×PhCH_2), 3.75 (s, 3H, CH_3O), 4.80–5.00 (m, 1H, NHC*H*), 5.18 (dd, *J*=11.0, 5.6 Hz, 1H, NC*H*), 6.69 (d, *J*=8.0 Hz, 1H, NH), 7.05–7.92 (m, 14H, 3×Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.2, 21.3, 24.9, 30.3, 33.9, 35.0, 38.0, 52.4, 53.2, 53.6, 84.1, 123.6, 126.9, 127.0, 128.5, 128.7, 128.9, 129.4, 131.5, 134.4, 136.6, 166.8, 167.8, 171.9, 171.9; IR (CH_2Cl_2) ν: 3376, 2943, 2862, 1775, 1746, 1715, 1681, 1605, 1511, 1489, 1469, 1453, 1390, 1363, 1234, 1211, 1240 cm^{-1}; retention time: t_R=15.0 min.

*Compound (S,S)-***10**: $[\alpha]_D^{20}$ −87.5 (*c* 1.8, benzene). Anal. $C_{34}H_{34}N_2O_7$ requires: C, 70.10%; H, 5.88%; N, 4.80%. Found: C, 69.90%; H, 5.76%; N, 4.71%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.05–2.35 (m, 10H, *c-Hex*), 3.08–3.65 (m, 4H, 2×PhCH_2), 3.69 (s, 3H, CH_3O), 4.80–4.95 (m, 1H, NHC*H*), 5.17 (dd, *J*=11.6, 5.0 Hz, 1H, NC*H*), 6.62 (d, *J*=6.6 Hz, 1H, N*H*), 7.05–7.82 (m, 14H, 3×Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.4, 21.5, 25.2, 30.6, 34.1, 35.1, 38.0, 52.5, 53.6, 53.9, 84.3, 123.9, 127.2, 128.8, 128.9, 129.1, 129.5, 131.7, 134.6, 136.6, 136.8, 167.2, 168.0, 172.3, 172.5; IR (CH_2Cl_2) ν: 3384, 2944, 2863, 1775, 1747, 1716, 1682, 1605, 1513, 1469, 1453, 1390, 1364, 1211, 1140 cm^{-1}; retention time: t_R=14.1 min.

*Compound (S,R)-***11**: $[\alpha]_D^{20}$ −21.8 (*c* 1.2, benzene); HRMS (ESI) 517.2316 ($C_{28}H_{34}N_2O_6$: 517.2309); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90–2.20 (m, 10H, *c-Hex*), 1.97 (s, 3H, CH_3CO), 2.95–3.23 (m, 4H, 2×PhCH_2), 3.69 (s, 3H, CH_3O), 4.60–4.90 (m, 2H, 2×BnC*H*), 6.04 (d, *J*=7.0 Hz, 1H, N*H*), 6.70 (d, *J*=7.8 Hz, 1H, N*H*), 7.11–7.42 (m, 10H, 2×Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.2, 21.5, 23.3, 25.2, 31.2, 33.6, 37.5, 37.8, 52.5, 53.4, 54.5, 83.8, 127.2, 127.5, 128.7, 129.1, 129.5, 129.6, 136.2, 136.8, 170.6, 171.1, 172.5; IR (CH_2Cl_2) ν: 3376, 2943, 2862, 1775, 1746, 1715, 1681, 1605, 1511, 1489, 1469, 1453, 1390, 1363, 1234, 1211, 1240 cm^{-1}; retention time: t_R=8.8 min.

*Compound (S,S)-***11**: $[\alpha]_D^{20}$ 24.0 (*c* 0.9, benzene). Anal. $C_{28}H_{34}N_2O_6$ requires: C, 67.98%; H, 6.96%; N, 5.66%. Found: C, 67.76%; H, 7.19%; N, 5.58%. NMR (200 MHz, $CDCl_3$): δ 1.10–2.22 (m, 10H, *c-Hex*), 1.88 (s, 3H, CH_3CO), 2.95–3.23 (m, 4H, 2×PhCH_2), 3.66 (s, 3H, CH_3O), 4.60–4.83 (m, 2H, 2×BnC*H*), 5.87 (d, *J*=6.8 Hz, 1H, N*H*), 6.60 (d, *J*=7.8 Hz, 1H, N*H*), 7.07–7.32 (m, 10H, 2×Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.4, 23.2, 25.2, 32.3, 32.6, 37.6, 37.9, 52.5, 53.5, 54.2, 83.7, 127.2, 127.4, 128.7, 129.0, 129.4, 129.6, 136.4, 136.7, 170.7, 172.2; IR (CH_2Cl_2) ν: 3434, 3332, 3056, 3032, 2942, 2862, 1744, 1676, 1604, 1510, 1451, 1370, 1211, 1180, 1140 cm^{-1}; retention time: t_R=6.6 min.

*Compound (S,R)-***12**: $[\alpha]_D^{20}$ −36.2 (*c* 1.6, benzene). Anal. $C_{31}H_{39}N_2O_7$ requires: C, 67.48%; H, 7.14%; N, 5.08%. Found: C, 67.32%; H, 7.34%; N, 4.92%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.90–2.20 (m, 10H, *c-Hex*), 1.49 (s, 9H, (CH_3)$_3$), 2.60–3.35 (m, 4H, 2×PhCH_2), 3.74 (s, 3H, CH_3O), 4.35–5.05 (m, 3H, 2×BnC*H*, BocN*H*), 6.90–7.00 (m, 1H, N*H*), 7.00–7.60 (m, 10H, 2×Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.4, 25.2, 28.6, 31.8, 33.1, 37.8, 52.4, 53.7, 55.6, 80.6, 83.6, 127.1, 127.4, 128.7, 129.1, 129.5, 136.4, 156.1, 170.4, 172.3; IR (CH_2Cl_2) ν: 3437, 3331, 2983, 2941, 2863, 1744, 1699, 1680, 1604, 1498, 1453, 1393, 1368, 1207, 1168, 1140 cm^{-1}; retention time: t_R=18.7 min.

*Compound (S,S)-***12**: $[\alpha]_D^{20}$ 8.0 (*c* 1.3, benzene). Anal. $C_{31}H_{39}N_2O_7$ requires: C, 67.48%; H, 7.14%; N, 5.08%. Found: C, 67.29%; H, 7.35%; N, 4.92%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.10–2.40 (m, 10H, *c-Hex*), 1.47 (s, 9H, (CH_3)$_3$), 3.00–3.60 (m, 4H, 2×PhCH_2), 3.77 (s, 3H, CH_3O), 4.45–5.05 (m, 3H, 2×BnC*H*, BocN*H*), 6.75–6.90 (m, 1H, N*H*), 7.18–7.42 (m, 10H, 2×Ar*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.4, 25.2, 28.6, 31.9, 33.1, 38.1, 52.5, 53.4, 55.3, 80.6, 83.5, 127.3, 128.7, 129.0, 129.5, 136.7, 156.1, 170.5, 172.2; IR (CH_2Cl_2) ν: 3436, 3326, 2983, 2941, 2863, 1743, 1709, 1604, 1499, 1499,1453, 1392, 1367, 1211, 1169, 1140 cm^{-1}; retention time: t_R=18.7 min.

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