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ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 7647–7653

Studies on the application of the Passerini reaction and enzymatic procedures to the synthesis of tripeptide mimetics

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Received 14 November 2006; revised 24 April 2007; accepted 10 May 2007
Available online 17 May 2007

Abstract—A new, efficient method for the multicomponent synthesis of tripeptide mimetics is presented. Simple, chemoenzymatic transformations of Passerini reaction products enable the introduction of varied amino acid moieties into the tripeptide scaffold, with control of the stereochemistry. Additionally, this method allows the convenient introduction of a methyl group to the amide nitrogen, leading to derivatives of *N*-methylated amino acids—compounds of interest for medicinal chemistry.
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1. Introduction

Small peptides and their simple analogues form a vast group of bioactive compounds. Among them, compounds with various activities can be found, such as anti-parasitic,[1] anti-inflammatory,[2] and anti-tumor[3] agents, HIV-protease inhibitors,[4] calpain,[5] and protesome[6] inhibitors.

The utility of small peptides as potential drugs is severely limited by pharmacokinetic factors, mainly fast metabolic degradation. Synthesis of simple analogues of small peptides, the so-called 'peptidomimetics', aims to solve this problem. Commonly used methods include variations to the structure of the peptide chain,[7] introduction of non-coded amino acids,[8] and N-alkylation of amide groups.[9]

In last few years, combinatorial methods using multicomponent reactions have been closely examined as a fast and convenient solution for the synthesis of diverse classes of compounds.[10] Tripeptide scaffold **6** is readily obtained in the Ugi multicomponent reaction (Scheme 1, 'Ugi pathway'), between isocyanide **1**, aldehyde **2**, amine **3**, and acid component **4**. This approach, despite its simplicity, has several drawbacks, which make it very difficult to use. The main problem is the lack of stereocontrol over the center of asymmetry, which is generated in the Ugi reaction.[10] Moreover, generation of peptide analogues requests the use of chiral isocyanides derived from α-amino acids, which undergo rapid racemization under Ugi reaction conditions.[11]

Generation of a peptide scaffold with no modification of nitrogen in the peptide bond (Scheme 1, R^3=H) requires the use of ammonia as amine component **3**, which is severely limited by the formation of side products.[12]

The aim of our study was to establish a multicomponent procedure that would yield target compounds **6**, with full stereocontrol over the chiral center formed. We were also interested in the possibility of synthesizing both peptides (R^3=H) and their *N*-alkylated analogues (R^3=alkyl). Thus, we decided to employ the Passerini reaction as the multicomponent process, and to use an enzymatic hydrolysis as the key enantiopurity determining step (Scheme 1, 'Passerini pathway'). The synthetic concept is depicted in Scheme 2.

2. Results and discussion

2.1. Synthesis of non-racemic α-hydroxyamides 8

Racemic α-acetoxyamides *rac*-**7** were synthesized by the Passerini reaction (Scheme 2) with good to excellent yields (73–99%). The results are shown in Table 1. Initially, a group of lipases were tested as catalysts for the stereoselective hydrolysis of racemic compounds **7**. The group consisted of: wheat germ lipase, Novozym 435A, porcine pancrease lipase, *Candida rugosa* lipase, Amano AK lipase, *Rhizopus niveus* lipase, *Candida lipolytica* lipase, *Pseudomonas cepacia* lipase, and pig liver esterase. Of the tested enzymes, only wheat germ lipase performed the hydrolysis, and thus it was used on a preparative scale. The results are also shown in Table 1.

Keywords: Tripeptides; Passerini reaction; Enzymatic hydrolysis; Non-coded amino acids; *N*-Methylated peptides.
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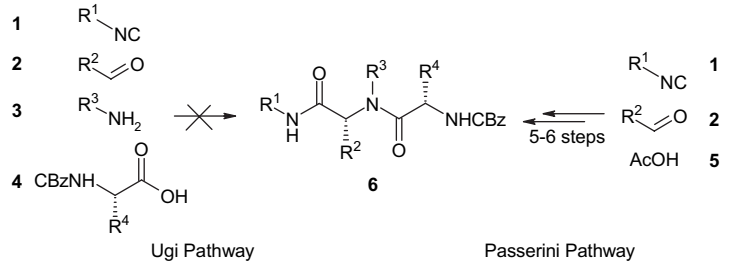
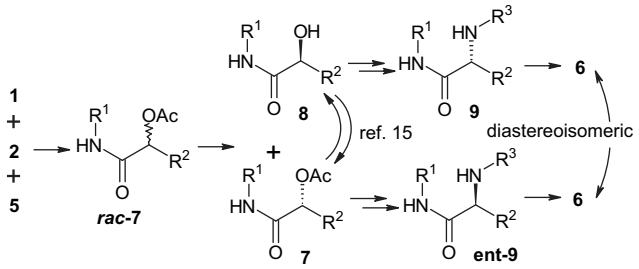
doi:10.1016/j.tet.2007.05.044



Scheme 1. Basic synthetic concepts.



Scheme 2. Synthetic concept.

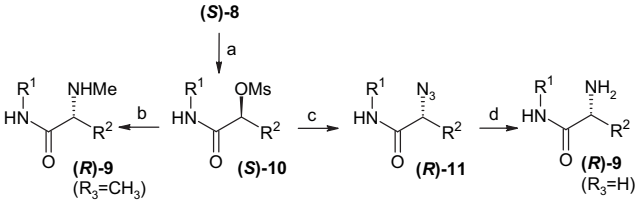
In three out of four cases, it was possible to obtain products with high optical purity (namely (*R*)-**7a**, (*S*)-**8d**, and (*S*)-**8c**), although the reaction time had to be prolonged in the case of product **c**. The enantioselectivity was lowest in the case of leucine analogue **d**, and clearly an additional optimization study is required for improved selectivity. We believe however, that the utility of biocatalysts in enantioselective hydrolysis of racemic α-acetoxyamides is clearly visible.

In order to assign the configuration of the obtained products, compounds (*S*)-**8** and (*S*)-**7** were synthesized from commercially available, optically pure α-amino acids, using procedures described in the literature.[13,14]

It should also be emphasized that during our research on the synthesis of unnatural amino acids,[15] we have established a convenient method for the transformation of compounds (*S*)-**8** and (*R*)-**7** into each other with the inversion of configuration. A method for the basic hydrolysis of compounds (*R*)-**7** to (*S*)-**8** is also described. These transformations allow the synthesis of a chosen enantiomer of compound **8** with high yield, exceeding the theoretical yield of 50% obtained in the kinetic resolution of a racemate.

2.2. Synthesis of primary and secondary amines 9

The next step was to establish an effective procedure for the transformation of alcohols **8** into amine derivatives **9**. This goal was accomplished by S_N2 type substitution of methanesulfonic acid esters derived from alcohols **8** (Scheme 3). Enantiopure compounds obtained from the correlation study were used in these syntheses (Table 2).



Scheme 3. Synthesis of amines **9**. Reagents and conditions: (a) MsCl, Et_3N, DMAP, CH_2Cl_2, 20 °C, 30 min; (b) CH_3NH_2 (40% in water), DMF, 50 °C, 24 h; (c) NaN_3, DABCO, DMAP, benzo-15-crown-5, CH_2Cl_2, 40 °C, 24 h; (d) H_2, Pd/C, methanol, 4 h.

Table 2. Transformation of alcohols **8** into amines **9**

(*S*)-**8**	Yield of (*S*)-**10**/%	Reaction with methylamine		Synthesis of primary amines		
		Product	Yield/%	Yield of (*R*)-**11**/%	Amine	Yield/%
a	99	—	—	63	(*R*)-**9a**	99
b	99	(*R*)-**9c**	77	98	(*R*)-**9b**	99
c	94	—	—	93	(*R*)-**9d**	99
d	97	(*R*)-**9f**	85	91	(*R*)-**9e**	95

Table 1. Chemoenzymatic synthesis of non-racemic compounds **8**

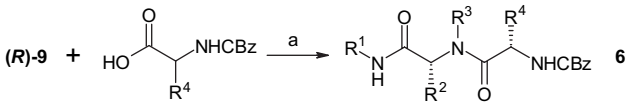
No.	Passerini synthesis of *rac*-**7**		WGL mediated biotransformation of *rac*-**7**				
	Structure	Yield/%	Time	Product	Yield/%	ee/%	E^c
a	R^1=EtOC(O)CH_2	99	24 h	(*S*)-**8**	22	37[a]	7
	R^2=$C_6H_5CH_2$			(*R*)-**7**	43	94[a]	
b	R^1=4-$CH_3OC_6H_4CH_2$	89	48 h	(*S*)-**8**	47	94[b]	59
	R^2=$C_6H_5CH_2$			(*R*)-**7**	52	55[b]	
c	R^1=$C_6H_5CH_2$	79	27 d	(*S*)-**8**	50	94[b]	>150
	R^2=$C_6H_5CH_2$			(*R*)-**7**	29	96[b]	
d	R^1=4-$CH_3OC_6H_4CH_2$	73	22 h	(*S*)-**8**	53	46	3.4
	R^2=$(CH_3)_2CHCH_2$			(*R*)-**7**	43	38	

[a] Optical purity.
[b] Determined by HPLC with Daicel Chiracel OD-H column.
[c] Calculated from the conversion-independent equation.

All the amines **9** were obtained in good overall yields, although the yield in the case of azide (*R*)-**11a** is significantly lower, probably due to the existence of an extra electrophilic center (ester moiety) in the structure of the substrate.

2.3. Synthesis of tripeptide analogues 6

Target tripeptide analogues were prepared by EDC mediated coupling of amines **9** with model amino acids (glycine for **6a**,**d**,**e**,**h**,**i**, (*S*)-alanine for **6j**, and (*S*)-phenylalanine for **6b**,**c**,**f**), bearing a benzyloxycarbonyl (CBz) protecting group on the nitrogen atom (Scheme 4).



Scheme 4. Synthesis of tripeptide analogues **6**. Reagents and conditions: (a) EDC, HOBt, CH_2Cl_2, 20 °C, 20 h.

Yields of compounds **6** are shown in Table 3.

Table 3. Synthesis of compounds **6**

6	R^1	R^2	R^3	R^4	Yield/%
a	$EtOCOCH_2$	$C_6H_5CH_2$	H	H	84
b	$EtOCOCH_2$	$C_6H_5CH_2$	H	$C_6H_5CH_2$	71
c	4-$CH_3OC_6H_4CH_2$	$C_6H_5CH_2$	H	$C_6H_5CH_2$	70
d	4-$CH_3OC_6H_4CH_2$	$C_6H_5CH_2$	H	H	73
e	4-$CH_3OC_6H_4CH_2$	$C_6H_5CH_2$	CH_3	H	70
f	$C_6H_5CH_2$	$C_6H_5CH_2$	H	$C_6H_5CH_2$	97
g	4-$CH_3OC_6H_4CH_2$	$(CH_3)_2CHCH_2$	H	H	80
h	4-$CH_3OC_6H_4CH_2$	$(CH_3)_2CHCH_2$	H	CH_3	87
i	4-$CH_3OC_6H_4CH_2$	$(CH_3)_2CHCH_2$	CH_3	H	42

All of the target compounds were obtained in analytically pure form with moderate yields (42–97%), although the yields of reactions with secondary amines (products **6e** and **6i**) proved to be lower, probably due to steric hindrance.

3. Summary

A method for the multicomponent preparation of tripeptide mimetics is presented. Simple, chemoenzymatic transformations of Passerini reaction product enable the introduction of varied amino acid moieties into the tripeptide scaffold, with control of stereochemistry. Additionally, this method allows the convenient introduction of a methyl moiety to the amide nitrogen, leading to the derivatives of *N*-methylated amino acids, something that is very difficult with conventional procedures.[9]

Considering the enormous number of aldehydes that can be used in the Passerini reaction, the above-described method is capable of yielding enantiomerically enriched tripeptides with non-coded amino acids. Initial experiments were carried out in our laboratory and proved very promising, although a convenient way for the configuration assignment is yet to be established.

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. TLCs were performed with silica gel 60 (230–400 mesh, Merck) and silica gel 60 PF254 (Merck). HPLC experiments were carried out on DAICEL CHIRACEL OD-H column with a pre-column, eluent: hexane/isopropanol 9:1 (v/v), flow: 1 mL/min. CHN analysis was performed on Perkin Elmer 240 Elemental Analyzer and CHNS analysis on Heraeus Vario EL III apparatus. MS spectra were recorded on an API-365 (SCIEX) apparatus.

4.1.1. General procedure for the synthesis of Passerini reaction products *rac*-7. To a 1 M solution of acetic acid (1 equiv) in CH_2Cl_2 were added aldehyde (1.1 equiv) and then isocyanide (1.1 equiv) at room temperature. After completion of the reaction, the solvent was evaporated and the product was purified by flash chromatography (silica gel, hexane/ethyl acetate, 4:1, v/v).

4.1.1.1. Ethyl *rac*-(2-acetoxy-3-phenyl-propionylamino)acetate (*rac*-7a). Reaction time: 70 h. Yield: 99%, 318 mg of white crystals. Mp 70–71 °C (ethyl acetate/hexane); R_f=0.07 (ethyl acetate/hexane, 8:2, v/v); Anal. $C_{15}H_{19}NO_5$ requires: C, 61.42%; H, 6.53%; N, 4.78%; found: C, 61.52%; H, 6.62%; N, 4.64%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, 3H, J=7.2 Hz, C**H**$_3$CH$_2$), 2.01 (s, 3H, C**H**$_3$CO), 3.09 (dd, 1H, J=14.4 Hz, J=7.6 Hz, C**H**$_2$CHOAc), 3.23 (dd, 1H, J=14.4 Hz, J=4.8 Hz, C**H**$_2$CHOAc), 3.97 (dd, 2H, J=9.6 Hz, J=5.2 Hz, C**H**$_2$NH$_2$), 4.18 (q, 2H, J=7.2 Hz, CH$_3$C**H**$_2$), 5.40 (dd, 1H, J=7.6 Hz, J=4.8 Hz, C**H**OAc), 6.56 (br s, 1H, N**H**), 7.18–7.27 (m, 5H, Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 20.7, 37.6, 41.0, 61.6, 74.1, 126.9, 128.3, 129.3, 130.3, 135.8, 169.3, 169.4; IR (Nujol): ν 3311, 3261, 1737, 1676, 1658, 1542, 1456, 1375, 1228, 1206, 1056, 1024 cm^{-1}.

4.1.1.2. Acetic acid *rac*-1-(4-methoxy-benzylcarbamoyl)-2-phenylethyl ester (*rac*-7b). Reaction time: 90 h. Yield: 89%, 583 mg of white crystals. Mp 79–81 °C (ethyl acetate/hexane); R_f=0.68 (ethyl acetate/hexane, 4:6, v/v); Anal. $C_{19}H_{21}NO_4$ requires: C, 69.71%; H, 6.47%; N, 4.28%; found: C, 69.75%; H, 6.49%; N, 4.28%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 (s, 3H, C**H**$_3$CO), 3.21 (m, 2H, C**H**$_2$NH), 3.79 (s, 3H, C**H**$_3$O), 4.33 (m, 2H, C**H**$_2$CHO), 5.41 (t, 1H, J=6 Hz, C**H**C(O)), 6.10 (s, 1H, N**H**), 6.80–7.26 (m, 9H, 2Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9, 37.6, 42.6, 55.2, 74.3, 113.9, 126.9, 128.4, 129.0, 129.6, 129.6, 135.7, 159.0, 168.6, 169.4; IR (Nujol): ν 3291, 1749, 1660, 1559, 1514, 1458, 1225, 1247, 1231, 1036 cm^{-1}; retention time of enantiomers: t_R=11.99 min, t_S=13.57 min.

4.1.1.3. Acetic acid *rac*-1-benzylcarbamoyl-2-phenylethyl ester (*rac*-7c). Reaction time: 90 h. Yield: 79%, 942 mg of yellow oil. Mp 83–84 °C (ethyl acetate/hexane); R_f=0.15 (ethyl acetate/hexane, 8:2, v/v); Anal. $C_{18}H_{19}NO_3$ requires: C, 72.71%; H, 6.44%; N, 4.71%; found: 72.48%; H, 6.46%; N, 4.70%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.06

(s, 3H, C**H**$_3$), 3.18–3.23 (m, 2H, C**H**$_2$), 4.35–4.40 (m, 2H, C**H**$_2$), 5.42 (t, 1H, J=5.72 Hz, C(O)C**H**), 6.30 (s, 1H, N**H**), 7.05–7.29 (m, 10H, 2Ar**H**); ^{13}C NMR (50 MHz, $CDCl_3$): δ 21.6, 38.3, 43.8, 75.0, 127.5, 128.1, 128.9, 130.2, 136.3, 138.0, 169.3, 169.9; retention time of enantiomers: t_R=15.61 min, t_S=19.72 min.

4.1.1.4. Acetic acid *rac*-1-{[(4-methoxybenzyl)amine]-carbonyl}-3-methylbutyl ester (*rac*-7d). Reaction time: 96 h. Yield: 73%, 642 mg of yellow oil. R_f=0.12 (ethyl acetate/hexane, 8:2, v/v); Anal. $C_{16}H_{23}NO_4$ requires: C, 65.51%; H, 7.90%; N, 4.77%; found: C, 65.52%; H, 8.00%; N, 4.76%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.86–0.94 (m, 6H, (C**H**$_3$)$_2$CH), 1.66–1.76 (m, 3H, C**H**$_2$C**H**(CH$_3$)$_2$), 2.08 (s, 3H, C**H**$_3$CO), 3.76 (s, 3H, C**H**$_3$O), 4.3–4.4 (m, 2H, ArC**H**$_2$), 5.16–5.24 (m, 1H, COC**H**(O)CH$_2$), 6.32–6.38 (m, 1H, N**H**), 6.82–6.86 (m, 2H, Ar**H**$_2$), 7.12–7.18 (m, 2H, Ar**H**$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 23.0, 24.4, 40.7, 42.5, 55.2, 72.8, 114.0, 128.9, 158.9, 170.1; retention time of enantiomers: t_R=7.26 min, t_S=8.97 min.

4.1.2. General procedure for the enzymatic hydrolysis of Passerini reaction products. Ester *rac*-**7** (50 mg) was dissolved in 10 mL of solvent (water/Et_2O, 8:2, v/v). Lipase from wheat germ (E.C. 3.1.1.3, 3 mg) was added in one portion to the suspension and stirred on a shaker at 300 rpm at room temperature for the amount of time given in Table 1. Extraction with ethyl acetate, concentration in vacuo, and purification of the resulting residue by flash chromatography (silica gel, hexane/ethyl acetate) afforded ester (*R*)-**7** and alcohol (*S*)-**8**.

4.1.2.1. Ethyl (*R*)-(2-acetoxy-3-phenyl-propionyl-amino)acetate ((*R*)-7a). Yield: 43%. $[\alpha]_D^{20}$=+13.3 (*c* 0.5, $CHCl_3$). Optical purity: 94%. Other analyses are consistent with *rac*-**7a**.

4.1.2.2. Ethyl (*S*)-(2-hydroxy-3-phenyl-propionylamine)acetate ((*S*)-8a). Yield: 22%, 15.5 mg of yellow oil. $[\alpha]_D^{20}$=−25.1 (*c* 0.5, $CHCl_3$). Optical purity: 37%; R_f=0.55 (ethyl acetate/hexane, 4:6, v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, 3H, J=7.2 Hz, C**H**$_3$CH$_2$), 2.85 (dd, 1H, J=14.0 Hz, J=8.8 Hz, C**H**$_2$CHOH), 3.23 (dd, 1H, J=14.0 Hz, J=4.0 Hz, C**H**$_2$CHOH), 3.92–4.08 (m, 2H, C**H**$_2$NH$_2$), 4.18 (q, 2H, J=7.2 Hz, CH$_3$C**H**$_2$), 4.34 (dd, 1H, J=8.8 Hz, J=3.6 Hz, C**H**OH), 7.15 (br s, 1H, N**H**), 7.21–7.32 (m, 5H, Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 40.62, 40.79, 61.49, 72.83, 126.8, 128.5, 129.4, 137.0, 169.7, 173.4. HRMS (ESI, [M+Na]$^+$) 274.1054 ($C_{13}H_{17}NO_4Na$: 274.1050).

4.1.2.3. Acetic acid (*R*)-1-(4-methoxy-benzylcarbamoyl)-2-phenylethyl ester ((*R*)-7b). Yield: 52%. ee$_R$ (HPLC): 55%. Other analyses are consistent with *rac*-**7b**.

4.1.2.4. (*S*)-2-(4-Methoxybenzyl)carbamoyl-1-phenylethanol ((*S*)-8b). Yield: 47%, 20.7 mg of white crystals. ee$_S$ (HPLC): 94%; $[\alpha]_D^{20}$=−49.7 (*c* 1.0, $CHCl_3$); R_f=0.43 (ethyl acetate/hexane, 4:6, v/v); mp 78–80 °C (ethyl acetate/hexane); Anal. $C_{17}H_{19}NO_3$ requires: C, 71.56%; H, 6.71%; N, 4.91%; found: C, 71.62%; H, 6.76%; N, 4.87%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.60 (br s, 1H, O**H**), 2.90 (dd, 1H, J=13.9 Hz, J=8.2 Hz, C**H**$_2$CHO), 3.23 (dd, 1H, J=13.9 Hz, J=4.1 Hz, C**H**$_2$CHO), 3.72 (s, 2H, C**H**$_2$), 4.28–4.34 (m, 3H, ArC**H**$_2$N, C**H**OH), 6.77 (s, 1H, N**H**), 6.80–7.31 (m, 9H, 2Ar**H**); ^{13}C NMR (50 MHz, $CDCl_3$): δ 41.0, 42.7, 55.4, 73.0, 114.1, 127.1, 128.8, 129.2, 129.7, 130.0, 136.9, 159.1, 172.5; IR (Nujol): ν 3363, 1633, 1537, 1513, 1456, 1255, 1086, 1027, 698 cm^{-1}; retention time of enantiomers: t_R=9.74 min, t_S=10.62 min.

4.1.2.5. Acetic acid (*R*)-1-benzylcarbamoyl-2-phenylethyl ester ((*R*)-7c). Yield: 29%. ee$_R$ (HPLC): 94%. Other analyses are consistent with *rac*-**7c**.

4.1.2.6. (*S*)-1-Benzylcarbamoyl-2-phenylethanol ((*S*)-8c). Yield: 50%, 21.5 mg of white crystals. ee$_S$ (HPLC): 96%; $[\alpha]_D^{20}$=−44.4 (*c* 3.4, ethyl acetate); mp 87–89 °C (ethyl acetate/hexane); R_f=0.52 (ethyl acetate/hexane, 4:6, v/v); Anal. $C_{16}H_{17}NO_2$ requires: C, 75.27%; H, 6.71%; N, 5.49%; found: C, 75.43%; H, 6.85%; N, 5.47%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.90 (m, 2H, PhC**H**$_2$NH), 3.22 (m, 1H, C(O)C**H**), 4.38 (m, 2H, C**H**$_2$CHOH), 6.82 (s, 1H, N**H**), 7.14–7.30 (m, 10H, 2Ar**H**); ^{13}C NMR (50 MHz, $CDCl_3$): δ 41.4, 43.6, 73.4, 127.5, 128.0, 128.3, 129.2, 129.2, 129.2, 130.1, 137.3, 138.3, 173.1; IR (Nujol): ν 3395, 3368, 1629, 1533, 1455, 1089, 700; retention time of enantiomers: t_R=15.23 min, t_S=21.00 min.

4.1.2.7. Acetic acid (*R*)-1-{[(4-methoxybenzyl)amine]-carbonyl}-3-methylbutyl ester ((*R*)-7d). Yield: 43%. ee$_R$ (HPLC): 46%. Other analyses are consistent with *rac*-**7d**.

4.1.2.8. (*S*)-2-Hydroxy-*N*-(4-methoxybenzyl)-4-methylpentanamide ((*S*)-8d). Yield: 53%, 25 mg of white crystals. ee$_S$ (HPLC): 38%; $[\alpha]_D^{20}$=−11.5 (*c* 1.0, $CHCl_3$); mp 106–107 °C (methylene chloride/hexane); R_f=0.62 (ethyl acetate/hexane, 4:6, v/v); Anal. $C_{14}H_{21}NO_3$ requires: C, 66.85%; H, 8.35%; N, 5.57%; found: C, 67.07%; H, 8.53%; N, 5.57%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82–1.2 (m, 6H, (C**H**$_3$)$_2$CH), 1.46–1.73 (m, 2H, C**H**$_2$), 1.73–1.96 (m, 1H, C**H**(CH$_3$)$_2$), 3.768 (s, 3H, C**H**$_3$O), 4.06–4.18 (m, 1H, COC**H**(OH)CH$_2$), 4.22–4.46 (m, 2H, ArC**H**$_2$), 6.819–6.840 (d, 2H, J=8.4 Hz, Ar**H**$_2$), 6.88–7.03 (m, 1H, N**H**), 7.10–7.20 (m, 2H, Ar**H**$_2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 23.4, 24.4, 42.5, 43.7, 55.2, 70.6, 114.0, 129.0, 158.9, 174.6.

4.1.3. Synthesis of compounds 6e and 6i. The transformation of alcohols (*S*)-**8b** and (*S*)-**8d** into *N*-methylated amides **6e** and **6i**, respectively, is further exemplified by the synthesis of **6e**.

4.1.3.1. Methanesulfonic acid (*S*)-1-(4-methoxybenzylcarbamoyl)-2-phenylethyl ester ((*S*)-10b). Solution of alcohol (*S*)-**8** (571 mg, 2.0 mmol, from correlation study[15]) in CH_2Cl_2 (6 mL) was cooled to −50 °C. Triethylamine (1.12 mL, 8.0 mmol) and methanesulfonyl chloride (232 μL, 3.0 mmol) were added in one portion. The mixture was stirred for 30 min at room temperature, the solvent was evaporated and the product was purified by flash chromatography (silica gel, hexane/ethyl acetate, 4:6, v/v). Yield: 99%, 716 mg of white crystals. $[\alpha]_D^{20}$=−66.1 (*c* 1.0, $CHCl_3$); R_f=0.60 (hexane/ethyl acetate, 4:6, v/v); mp 119–120 °C (ethyl acetate/hexane); Anal. $C_{18}H_{21}NO_5S$ requires: C, 59.49%; H, 5.82%; N, 3.58%; found: 59.48%; H, 5.86%; N, 3.88%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.53 (s, 3H,

CH_3SO_2), 3.12 (dd, 1H, J=14.4 Hz, J=9.1 Hz, CH_2CHO), 3.53 (dd, 1H, J=14.4 Hz, J=3.6 Hz, CH_2CHO), 3.86 (s, 3H, CH_3O), 4.42–4.50 (m, 2H, $ArCH_2N$), 5.22 (dd, 1H, J=9.1 Hz, J=3.6 Hz, CHC(O)), 6.67 (s, 1H, NH), 6.89–7.43 (m, 9H, 2ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 37.89, 38.71, 43.07, 55.42, 81.66, 114.21, 127.60, 128.89, 129.08, 129.87, 135.64, 167.56.

4.1.3.2. (*R*)-*N*-(4-Methoxybenzyl)-2-methylamine-3-phenyl-propionamide ((*R*)-9c). To a solution of methanesulfonic acid ester (*S*)-**10b** (182 mg, 0.50 mmol) in DMF was added methylamine (40% solution in water, 2.5 mL) and the mixture was stirred at 50 °C for 22 h. Then the reaction mixture was dissolved in ethyl ether (10 mL) and water (3 mL). The phases were separated and the aqueous phase was extracted with ether (3×7 mL). Collected organic phases were dried ($MgSO_4$) and the product was purified by flash chromatography (silica gel, ethyl acetate/methanol, 9:1, v/v). Yield: 77%, 128 mg of colorless oil; R_f=0.40 (ethyl acetate/methanol, 9:1, v/v); ^1H NMR (200 MHz, $CDCl_3$): δ 2.30 (s, 3H, CH_3NH), 2.83 (dd, 1H, J=13.6 Hz, J=8.4 Hz, $PhCH_2$), 3.16 (dd, 1H, J=13.6 Hz, J=5.6 Hz, $PhCH_2$), 3.43 (dd, 1H, J=8.4 Hz, J=5.6 Hz, $CHNHCH_3$), 3.77 (s, 3H, CH_3O), 4.31–4.34 (m, 2H, $ArCH_2N$), 6.07 (s, 1H, CH_3NH), 6.80–7.29 (m, 9H, 2ArH), 7.48 (s, 1H, NHCO). This compound was used in further synthesis without purification.

4.1.3.3. ({[(*R*)-1-(4-Methoxy-benzylcarbamoyl)-2-phenylethyl]-methyl-carbamoyl}-methyl)-carbamic acid benzyl ester (6e). To a solution of amine (*R*)-**9c** (24 mg, 0.07 mmol) in CH_2Cl_2 (2.0 mL) were added Cbz-protected glycine (15 mg, 0.07 mmol) and 1-hydroxybenzotriazole (15 mg, 0.11 mmol). The solution was cooled to 0 °C and EDC (16 mg, 0.08 mmol) was added in one portion. After 20 h the solvent was evaporated and the residue was taken up in ethyl acetate (15 mL). This solution was washed with 5% aqueous citric acid solution (2×5 mL), saturated $NaHCO_3$ solution (2×5 mL), and brine (5 mL). The organic phase was dried ($MgSO_4$) and evaporated to yield the analytically pure compound. Yield: 70%, 24 mg of yellow oil. R_f=0.66 (hexane/ethyl acetate, 4:6, v/v); $[\alpha]_{20}^{D}$=37.6 (*c* 1.0, chloroform); ^1H NMR (400 MHz, $CDCl_3$): δ 2.91 (s, 3H, CH_3N), 2.97 (dd, 1H, J=8 Hz, J=14.4 Hz, phe CH_2), 3.34 (dd, 1H, J=7.2 Hz, J=14.4 Hz, phe CH_2), 3.77 (s, 3H, CH_3O), 3.74–4.38 (m, 5H, $PhCH_2NH$, gly CH_2, phe CH), 5.09 (s, 2H, $PhCH_2O$), 5.24–5.29 (m, 1H, NH), 5.60 (s, 1H, NH), 6.28 (s, 1H, NH), 6.78–7.35 (m, 14H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.7, 30.2, 34.1, 42.9, 55.2, 58.1, 66.9, 114.0, 126.8, 128.0, 128.5, 128.6, 128.9, 129.9, 136.3, 136.6, 156.1, 158.9, 169.0, 169.3; HRMS (ESI, $[M+Na]^+$) 512.2163 ($C_{28}H_{31}N_3O_5Na$: 554.2156).

In an analogous manner, compound **6i** was synthesized using (*S*)-**8d** as a substrate.

4.1.3.4. ({[(*R*)-1-(4-Methoxy-benzylcarbamoyl)-3-methyl-butyl]-methyl-carbamoyl}-methyl)-carbamic acid benzyl ester (6i). Yield: 42%, 49 mg of yellow oil. R_f=0.53 (hexane/ethyl acetate, 4:6, v/v); $[\alpha]_{20}^{D}$=84.8 (*c* 1.0, chloroform); ^1H NMR (400 MHz, $CDCl_3$): δ 0.84–0.98 (m, 6H, $(CH_3)_2CH$), 1.41–1.74 (m, 3H, $CH_2CH(CH_3)_2$), 2.88 (s, 3H, $CH_3N(CH)CO$), 3.78 (s, 3H, CH_3O), 3.94–4.04 (m, 2H, $COCH_2NH$), 4.22–4.38 (m, 2H, $ArCH_2NH$), 5.0–5.1 (m, 1H, $COCHCH_2$), 5.1–5.14 (m, 2H, $ArCH_2$), 5.68–5.74 (m, 1H, NH), 6.28–6.34 (m, 1H, NH), 6.8–7.4 (m, 9H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 23.0, 24.8, 29.6, 36.3, 42.9, 54.9, 55.2, 66.9, 76.6 114.0, 114.1, 120.2, 128.0, 128.2, 128.5, 128.9, 129.0, 130.1, 136.3, 156.2, 158.9, 169.4, 169.9; HRMS (ESI, $[M+Na]^+$) 478.2336 ($C_{25}H_{33}N_3O_5Na$: 478.2312).

4.1.4. Synthesis of compounds 6a–6d and 6f–6h. The transformation of alcohols (*S*)-**8a–d** into amides **6a–6d** and **6f–6h** is further exemplified by the synthesis of **6c**.

4.1.4.1. (*R*)-2-Azido-*N*-(4-methoxy-benzyl)-3-phenyl-propionamide ((*R*)-11b). To a solution of methanesulfonic acid ester (*S*)-**10b** (200 mg, 0.55 mmol) in CH_2Cl_2 (3.0 mL) were added 1,4-diaza-bicyclo[2.2.2]octane (102 mg, 0.90 mmol), 4-dimethylaminopyridine (10 mg), sodium azide (72 mg, 1.1 mmol), and benzo-15-crown-5 (10 mg). After 20 h the product was purified by flash chromatography (silica gel, hexane/ethyl acetate, 4:1, v/v). Yield: 98%, 169 mg of colorless oil. R_f=0.83 (hexane/ethyl acetate, 4:6, v/v); $[\alpha]_{20}^{D}$=−29.8 (*c* 1.0, chloroform); Anal. $C_{17}H_{18}N_4O_2$ requires: C, 65.79%; H, 5.85%; N, 18.05%; found: C, 65.60%; H, 6.08%; N, 17.95%; ^1H NMR (400 MHz, $CDCl_3$): δ 3.06 (dd, 1H, J=8.0 Hz, J=14.4 Hz, $PhCH_2$), 3.35 (dd, 1H, J=4.4 Hz, J=14.4 Hz, $PhCH_2$), 3.86 (s, 3H, CH_3O), 4.22 (dd, 1H, J=4.4 Hz, J=8.0 Hz, CHN_3), 4.30–4.37 (m, 2H, $PhCH_2NH$), 6.48 (br s, 1H, NH), 6.82–7.29 (m, 9H, 2ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.4, 42.9, 55.2, 65.4, 114.0, 127.1, 128.6, 129.9, 129.4, 129.5, 136.0, 159.0, 168.2; IR (Nujol): ν 3322, 2097, 2061, 1640, 1535, 1453, 1245 cm^{-1}.

4.1.4.2. (*R*)-2-Amino-*N*-(4-methoxy-benzyl)-3-phenyl-propionamide ((*R*)-9b). Azide (*R*)-**11b** (115 mg, 0.37 mmol) was dissolved in methanol (8 mL). To this mixture, 10% Pd/C (10 mg) was added and hydrogen was fluxed through the solution (from a rubber balloon through a needle) for a period of 2 h. Then the reaction mixture was filtered through a bed of Celite and the solvent was evaporated. Yield: 99%, 104 mg of yellow greasy solid. Recrystallization from ethyl acetate/hexane afforded analytical sample. $[\alpha]_{20}^{D}$=−58.0 (*c* 1.0, chloroform); mp 84–85 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 1.54 (s, 2H, NH_2), 2.73 (dd, 1H, J=9.2 Hz, J=13.6 Hz, $PhCH_2CH$), 3.25 (dd, 1H, J=4.0 Hz, J=13.6 Hz, $PhCH_2CH$), 3.63 (dd, 1H, J=4.0 Hz, J=8.8 Hz, $CHNH_2$), 3.77 (s, 3H, CH_3O), 4.30–4.40 (m, 2H, $PhCH_2NH$), 6.82–7.31 (m, 9H, 2ArH), 7.56 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.8, 42.4, 55.1, 56.3, 113.8, 126.6, 128.5, 128.8, 128.9, 129.2, 130.3, 137.7, 158.7, 173.8; IR (Nujol): ν 3236, 1626, 1510, 1450, 1244, 1021 cm^{-1}.

4.1.4.3. {(*S*)-1-[(*R*)-1-(4-Methoxy-benzylcarbamoyl)-2-phenyl-ethylcarbamoyl]-2-phenylethyl}-carbamic acid benzyl ester (6c). To a solution of amine (*R*)-**11b** (47 mg, 0.16 mmol) in CH_2Cl_2 (1.5 mL) were added Cbz-protected phenylalanine (50 mg, 0.16 mmol) and 1-hydroxybenzotriazole (33 mg, 0.25 mmol). The solution was cooled to 0 °C and EDC (35 mg, 0.18 mmol) was added in one portion. After 20 h the solvent was evaporated and the residue was taken up in ethyl acetate (15 mL). This solution was washed with 5% aqueous citric acid solution (2×5 mL), saturated

$NaHCO_3$ solution (2×5 mL), and brine (5 mL). The organic phase was dried ($MgSO_4$) and evaporated to yield the analytically pure compound. Yield: 70%, 65 mg of white crystals. R_f=0.55 (hexane/ethyl acetate, 4:6, v/v); mp 198–199 °C (ethyl acetate/hexane); $[\alpha]_{20}^{D}$=5.4 (*c* 1.0, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.48–2.50 (m, 2H), 2.60–2.61 (m, 2H), 2.78–2.79 (m, 2H), 3.00–3.01 (m, 2H), 3.34–3.35 (m, 2H), 3.70 (s, 3H), 4.22–4.23 (m, 3H), 4.56 (m, 1H), 4.86–4.88 (m, 2H), 6.85–8.48 (m, 19H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 37.4, 37.9, 40.4, 41.5, 54.0, 55.0, 65.2, 113.7, 126.2, 126.3, 127.5, 127.7, 127.9, 128.0, 128.2, 128.5, 129.2, 129.3, 130.9, 136.9, 137.8, 138.0, 155.9, 158.2, 170.8, 171.3; HRMS (ESI, [M+Na]$^+$) 588.2494 ($C_{34}H_{35}N_3O_5Na$: 588.2469); IR (Nujol): ν 3288, 1692, 1643, 1541, 1513, 1263, 748, 699.

In an analogous manner, compounds **6a**, **6b**, **6d**, and **6f–6h** were synthesized.

4.1.4.4. [(*R*)-2-(2-Benzyloxycarbonylamino-acetyl-amino)-3-phenyl-propionylamino]-acetic acid ethyl ester (6a). Yield: 84%, 46 mg of transparent oil. R_f=0.31 (hexane/ethyl acetate, 4:6, v/v); $[\alpha]_{20}^{D}$=13.8 (*c* 1.0, ethanol); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.54 (t, 3H, *J*=7.2 Hz, C**H**$_3$CH$_2$), 2.94–3.01 (m, 2H, C**H**$_2$ phe), 3.62–3.89 (m, 4H, 2×gly), 4.07 (q, 2H, *J*=7.2 Hz, CH$_3$C**H**$_2$), 4.72–4.76 (m, 1H, C**H** phe), 5.69 (s, 1H, N**H**), 6.93 (s, 1H, N**H**), 7.05–7.24 (m, 10H, 2Ar**H**); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4, 38.5, 41.6, 44.7, 54.6, 61.8, 67.5, 127.3, 128.3, 128.5, 128.8, 128.8, 129.6, 136.5, 136.6, 157.0, 169.7, 169.8, 171.5. HRMS (ESI, [M+Na]$^+$) 464.1776 ($C_{23}H_{27}N_3O_6Na$: 446.1792).

4.1.4.5. [(*R*)-2-((*S*)-2-Benzyloxycarbonylamino-3-phenyl-propionylamino)-3-phenyl-propionylamino]-acetic acid ethyl ester (6b). Yield: 71%, 31 mg of white crystals. R_f=0.60 (hexane/ethyl acetate, 4:6, v/v); mp 155–157 °C (ethyl acetate/hexane); $[\alpha]_{20}^{D}$=18.4 (*c* 1.0, dioxane); Anal. $C_{30}H_{33}N_3O_6$ requires: C, 67.78%; H, 6.26%; N, 7.90%; found: C, 67.90%; H, 6.45%; N, 8.06%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, 3H, *J*=7.2 Hz, C**H**$_3$CH$_2$), 2.84–2.94 (m, 2H, C**H**$_2$ phe), 2.97–3.02 (m, 2H, C**H**$_2$ phe), 3.78 (s, 2H, CBz), 4.14 (q, 2H, *J*=7.2 Hz, CH$_3$C**H**$_2$), 4.28–4.32 (m, 1H, C**H** phe), 4.72–4.74 (m, 1H, C**H** phe), 4.97–5.03 (m, 2H, gly), 5.40 (s, 1H, N**H**), 6.62 (s, 1H, N**H**), 7.09 (s, 1H, N**H**), 7.17–7.34 (m, 15H, 3Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 36.3, 38.1, 41.3, 53.9, 56.7, 61.4, 67.1, 127.0, 127.1, 127.9, 128.2, 128.5, 128.6, 128.7, 129.2, 129.3, 136.0, 136.1, 136.1, 156.1, 169.4, 170.8, 171.2; HRMS (ESI, [M+Na]$^+$) 554.2284 ($C_{30}H_{33}N_3O_6Na$: 554.2261).

4.1.4.6. {[(*R*)-1-(4-Methoxy-benzylcarbamoyl)-2-phenyl-ethylcarbamoyl]-methyl}-carbamic acid benzyl ester (6d). Yield: 73%, 57 mg of white crystals. R_f=0.22 (hexane/ethyl acetate, 4:6, v/v); mp 186–188 °C (ethyl acetate/hexane); $[\alpha]_{20}^{D}$=−5.1 (*c* 1.0, dioxane); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.48–2.50 (m, 2H), 2.85–2.90 (m, 2H), 2.96–2.97 (m, 2H), 3.34–3.35 (m, 2H), 3.55–3.63 (m, 2H), 3.70 (s, 3H), 4.17–4.18 (m, 2H), 4.52–4.53 (m, 2H), 4.99 (s, 2H), 6.83–8.43 (m, 14H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 37.9, 41.5, 43.4, 54.1, 55.0, 65.4, 113.6, 119.8, 127.7, 127.8, 128.1, 128.3, 128.5, 129.2, 131.0, 137.0, 137.7, 156.5, 158.2, 168.8, 170.6; HRMS (ESI, [M+Na]$^+$) 498.2010 ($C_{27}H_{29}N_3O_5Na$: 498.1999).

4.1.4.7. [(*S*)-1-((*R*)-1-Benzylcarbamoyl-2-phenyl-ethylcarbamoyl)-2-phenylethyl]-carbamic acid benzyl ester (6f). Yield: 97%, 35 mg of yellow oil. R_f=0.50 (hexane/ethyl acetate, 4:6, v/v); $[\alpha]_{20}^{D}$=12.8 (*c* 1.0, chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.67–3.54 (m, 4H), 4.20–4.30 (m, 2H), 4.80–4.92 (m, 2H), 5.01–5.11 (m, 1H), 5.49–5.51 (m, 1H), 6.89–7.42 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 40.7, 41.5, 51.0, 55.0, 65.2, 65.4, 113.6, 126.2, 126.3, 127.1, 127.4, 127.7, 128.3, 128.4, 129.2, 129.3, 131.2, 136.9, 137.8, 138.0, 139.0, 155.8, 158.1, 178.8, 171.6, 172.6; HRMS (ESI, [M+Na]$^+$) 588.2385 ($C_{33}H_{33}N_3O_4Na$: 588.2363).

4.1.4.8. {[(*R*)-1-(4-Methoxy-benzylcarbamoyl)-3-methyl-butylcarbamoyl]-methyl}-carbamic acid benzyl ester (6g). Yield: 80%, 94 mg of white crystals. R_f=0.39 (hexane/ethyl acetate, 4:6, v/v); mp 137–139 °C (ethyl acetate/hexane); $[\alpha]_{20}^{D}$=21.3 (*c* 1.0, chloroform); Anal. $C_{24}H_{31}N_3O_5$ requires: C, 65.29%; H, 7.08%; N, 9.25%; found: C, 65.08%; H, 6.97%; N, 9.51%; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.8–1.0 (m, 6H, (C**H**$_3$)$_2$CH), 1.5–1.7 (m, 3H, C**H**$_2$C**H**(CH$_3$)$_2$), 3.74 (s, 3H, C**H**$_3$O), 3.78–3.85 (d, 2H, J_{HH}=4.4 Hz, COC**H**$_2$NH), 4.18–4.4 (m, 2H, ArC**H**$_2$(NH)), 4.4–4.6 (m, 1H, COC**H**(NH)(CH$_2$)), 5.0–5.1 (m, 2H, ArC**H**$_2$), 5.7–5.8 (m, 1H, N**H**), 6.88–7.0 (m, 1H, N**H**), 6.8–7.4 (m, 9H, Ar**H**); ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.4, 23.2, 25.1, 41.6, 43.4, 44.9, 52.2, 55.6, 67.5, 114.4, 128.4, 128.5, 128.9, 129.3, 165.2, 169.5, 172.0; IR (Nujol): ν 3315, 3276, 1728, 1656, 1629, 1548, 1516, 1255, 1222, 1034, 696 cm^{-1}.

4.1.4.9. {(*S*)-1-[(*R*)-1-(4-Methoxy-benzylcarbamoyl)-3-methyl-butylcarbamoyl]-ethyl}-carbamic acid benzyl ester (6h). Yield: 87%, 64 mg of white crystals. R_f=0.41 (hexane/ethyl acetate, 4:6, v/v); mp 146–148 °C (ethyl acetate/hexane); $[\alpha]_{20}^{D}$=15.5 (*c* 1.0, chloroform); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.8–1.0 (m, 6H, (C**H**$_3$)$_2$CH), 1.2–1.38 (m, 3H, C**H**$_3$CH), 1.46–1.8 (m, 3H, (CH$_3$)$_2$C**H**C**H**$_2$), 3.72 (s, 3H, C**H**$_3$O), 4.16–4.42 (m, 3H, C**H**CH$_3$, ArC**H**$_2$NH), 4.42–4.56 (m, 1H, COC**H**(NH)CH$_2$), 4.8–5.2 (dd, 2H, J_{HH}=12 Hz, ArC**H**$_2$), 5.56–5.64 (m, 1H, N**H**), 6.85–6.9 (m, 1H, N**H**), 6.95–7.01 (m, 1H, N**H**), 6.75–7.35 (m, 9H, Ar**H**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.9, 22.9, 24.8, 29.7, 40.8, 42.9, 43.4, 54.1, 55.2, 67.0, 113.9, 126.9, 127.5, 127.9, 128.0, 128.2, 128.4, 128.5, 128.6, 128.7, 128.7, 128.9, 136.0, 158.8, 171.2, 171.8; HRMS (ESI, [M+Na]$^+$) 478.2320 ($C_{25}H_{33}N_3O_5Na$: 478.2312).

Acknowledgements

This work was financially supported by Warsaw University of Technology and by Polish State Committee for Scientific Research, Grant PBZ–KBN 126/T09/07.

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