Tetrahedron 66 (2010) 8503–8511

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The artificial binaphthyl amino acid 6-amino-6′-carboxyethyl-2-methoxy-2′-hydroxy-1,1′-binaphthyl (Bna): synthesis and assembly of Bna peptides

Melanie Thoß [a], Rüdiger W. Seidel [b], Martin Feigel [a,*]

[a] Organische Chemie, Ruhr-Universität Bochum, Universitätsstr. 150, 44780 Bochum, Germany
[b] Analytische Chemie, Ruhr-Universität Bochum, Universitätsstr. 150, 44780 Bochum, Germany

ARTICLE INFO

Article history:
Received 11 June 2010
Received in revised form 26 August 2010
Accepted 28 August 2010
Available online 23 September 2010

Keywords:
Non-natural amino acids
Chirality
Artificial peptides

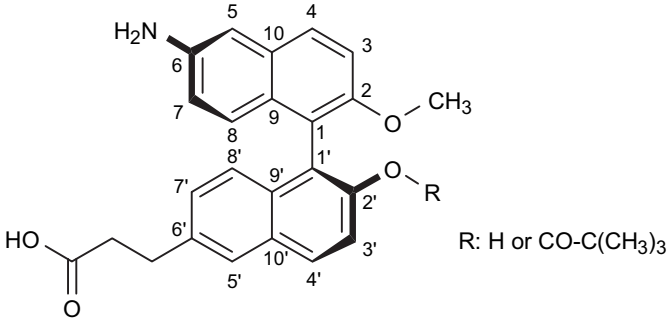
ABSTRACT

The new binaphthyl-based amino acid 6-amino-6′-carboxyethyl-2-methoxy-2′-hydroxy-1,1′-binaphthyl (Bna) is presented, which combines the axially chiral binaphthyl core, a phenolic OH-group as well as terminating amino and carboxyl groups in one structure. The large aromatic rings of the compound provide molecular spacing and π-surface attraction in assembled Bna oligoamides. The synthesis of Bna derivatives is reported, both with the (*R*)- and with the (*S*)-binaphthyl skeleton. Several dipeptides of (*R*)- or (*S*)-Bna units combined with natural amino acids, were prepared as 'building blocks' for the synthesis of extended Bna peptides. The tetrapeptide Boc-(*S*)-Val-(*S*)-Bna(OH)-(*S*)-Val-(*S*)-Bna(OPiv)-*O*-*n*-But (**12**) and the pentapeptide Boc-(*S*)-Val-(*S*)-Bna(OH)-(*S*)-Val-(*S*)-Bna(OH)-Gly-OH (**13**) were prepared via conventional solution phase synthesis and solid phase synthetic techniques, respectively. Compound **12** shows an interesting dynamic ^{1}H NMR spectrum suggesting compact and aggregated forms in dichloromethane. Compound **13** accelerates the enolisation of acetone. The use of more complex Bna peptides as organo catalysts is proposed.

1. Introduction

A variety of molecules have been used for the construction of foldamer backbones.[1] The chemical connections between the building blocks of these oligomers are often amide bonds, which are stable towards hydrolysis, can be formed easily via standard peptide coupling reactions and give a defined trans stereochemistry. The backbone of artificial peptides so formed should be partially rigid and should provide chiral 'space' for the inclusion and transformation of molecular guests in molecular recognition processes or in organo catalysis. Until now, many β- and γ-amino acids have been used as building blocks[2] but few structures exist in which the distances between the amino and the carboxyl group is extended. Known examples are aromatic amino carboxylic acids[3] or the chiral amino cholanic acids.[4] We propose the new chiral binaphthyl amino acid Bna (Scheme 1) as building block which should lead to unusual extended functional oligoamides.

The structure of Bna is based on the 1,1′-binaphthol scaffold providing rigidity, axial chirality and two extended aromatic π-surfaces. The naphthyl rings in the 1,1′-binaphthol unit of Bna are oriented at an angle of nearly 90°; thus, the positions C6 and C6′, where the backbone chain is attached, are well separated and a scissor-like system results. Assembled to a Bna peptide, the structure will presumably provide space for the reception of molecular guests while the phenolic OH/OR-groups are suited for anchoring additional functional groups. The synthesis of Bna derivatives, the combination with natural amino acids building small oligomers and the solid phase synthesis of Bna peptides is described.



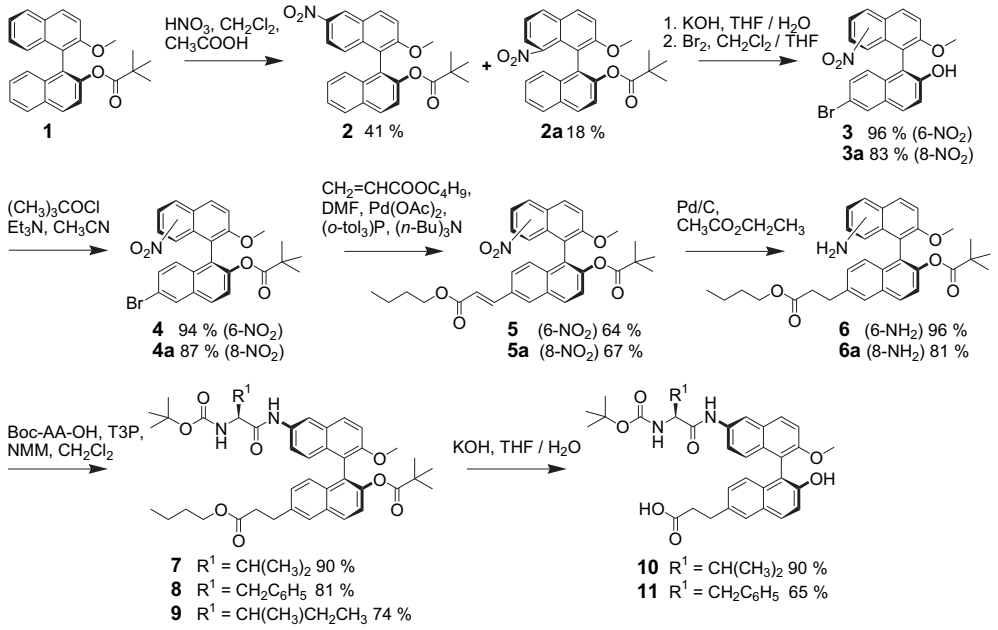
Scheme 1. Structure of the binaphthyl-amino acid (Bna) as (*S*)-Bna(OH) or (*S*)-Bna(OPiv) derivative.

* Corresponding author. Fax: +49 2343214497; e-mail address: feigel@indi-f.nsc.ruhr-uni-bochum.de (M. Feigel).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.08.066

2. Results and discussion

The synthetic route to derivatives of the artificial binaphthylamino acid (Bna) is outlined in Scheme 2. It starts with (*S*)- or (*R*)-2-methoxy-2′-pivaloyloxy-1,1′-binaphthyl (**1**).[5,6] The (*S*)-enantiomer of **1** has been prepared before from (*S*)-2,2′-dihydroxy-1,1′-binaphthyl via the pivaloyl mono ester[6] which has been treated with methyl iodide/potassium carbonate/acetone.[6,7] The (*R*)-enantiomer of **1** was prepared accordingly from (*R*)-2,2′-dihydroxy-1,1′-binaphthyl.



Scheme 2. Synthesis of the amino acid Bna building blocks. The (*S*) form of the binaphthyl skeleton is drawn. The synthesis has been done with racemic material and with (*R*) and (*S*) binaphthyl groups. Some intermediates have been characterized fully only as one enantiomer, see the experimental part and the comment.[8]

Nitration of (*S*)-**1** or (*R*)-**1** by fuming nitric acid in dichloromethane/acetic acid[9] introduces a nitro group at the activated upper ring system giving the (*S*)- and (*R*)-forms of the two regio isomers **2** (NO_2 at C6) and **2a** (NO_2 at C8). The isomers were separated by column chromatography on silica gel with EtOAc/*n*-hexane. Both enantiomeric forms of **2** and **2a** were isolated in yields of 40% and 18% resp. giving the following optical rotations (*c* 0.1, THF): (*S*)-**2** $[\alpha]_D^{20}$ +38.3, (*R*)-**2** $[\alpha]_D^{20}$ −46.7, (*S*)-**2a** $[\alpha]_D^{20}$ −491.6, (*R*)-**2a** $[\alpha]_D^{20}$ +512.6.

Yellow crystals of (*R*)-**2**, suitable for X-ray analysis, were grown from ethyl acetate by slow evaporation of the solvent. Compound (*R*)-**2** crystallizes in the common orthorhombic chiral space group $P2_12_12_1$ with four molecules in the unit cell, Fig. 1 shows a displacement ellipsoid plot. The angle between the least-squares mean planes of the naphthyl ring systems adopts a value of 87.39(7)°. The nitro group is slightly tilted out of the plane of the parent naphthyl ring by 7.1(2)°. The corresponding C–N bond length is 1.465(6) Å.

Crystals of a racemic mixture of the isomer **2a** (*rac*-**2a**) were also suitable for X-ray diffraction. Compound *rac*-**2a** crystallizes in the orthorhombic polar space group $Pna2_1$ with eight molecules in the unit cell. The asymmetric unit comprises two molecules of the same chirality; Fig. 2 depicts only one molecule of the (*S*)-enantiomer for clarity. In the crystal structure, the other enantiomer is generated by glide symmetry. The molecular geometry parameters indicate that both crystallographically independent molecules are severely strained as a result of the introduction of the nitro group at C8. The angles between the least-squares mean planes of the naphthyl rings deviate remarkably from the ideal 90° with values of 73.82(6) and 69.84(7)°. The nitro groups are severely tilted out of the planes of the parent naphthyl rings by 59.0(1) and 60.4(1)°. Presumably, face-to-face π···π interactions between the nitro groups and the other naphthyl rings are accountable for the observed tilt. The corresponding C–N bond lengths exhibit values of 1.470(5) and 1.466(5) Å, respectively, and are essentially comparable to that observed for (*R*)-**2**. A search of the Cambridge Structural Database (CSD, Version 5.30 with Sept 2009 Updates[10]) revealed that *rac*-**2a** is the first crystallographically studied example of a binaphthyl scaffold bearing a nitro group at C8.

The next steps in the synthesis towards Bna derivatives are straightforward (Scheme 2): hydrolysis of the ester group in **2** (and **2a**) followed by bromination of C6′ gives **3** (and **3a**). Crystals of *rac*-**3**, obtained in the parallel ongoing racemic synthesis, were

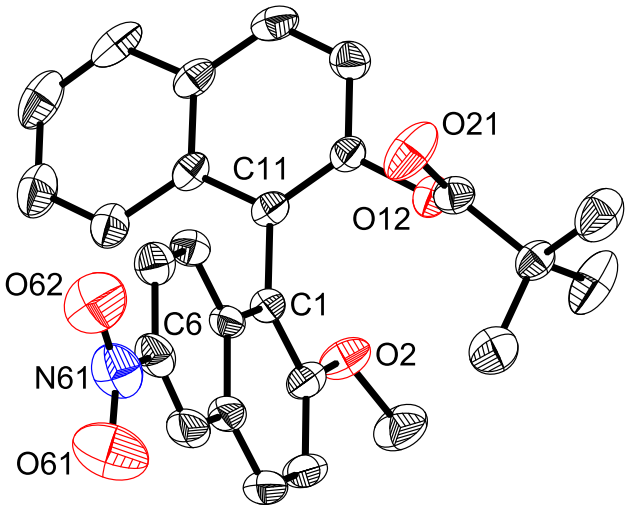


Fig. 1. Molecular structure of (*R*)-**2**. Displacement ellipsoids are drawn at the 30% probability level. Hydrogen atoms are omitted for clarity.

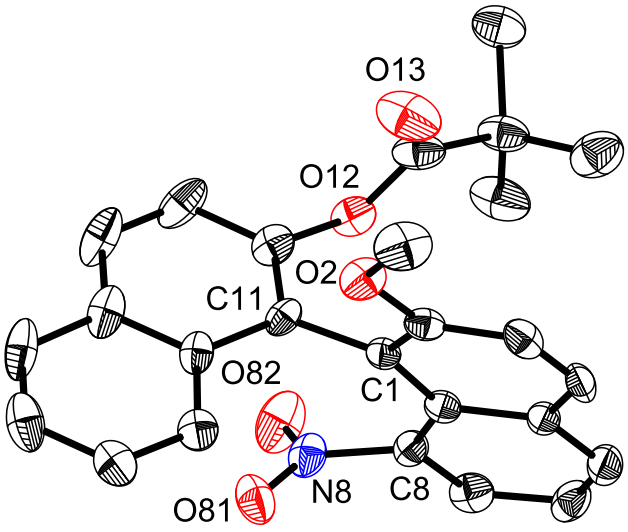


Fig. 2. Molecular structure of the (*S*)-enantiomer of *rac*-**2a**. Displacement ellispsoids are drawn at the 50% probability level. Hydrogen atoms are omitted for clarity.

obtained by slow-diffusion of *n*-hexane into an ethyl acetate solution. Compound *rac*-**3** crystallizes the monoclinic space group $P2_1/c$ with four molecules per unit cell. The crystal structure confirms the position of the bromine substituent at C6′. In the crystal structure, pairs of enantiomers form centrosymmetric dimers via hydrogen bonding interactions between the free hydroxy group and an oxygen atom of the nitro group (Fig. 3). The O–H···O distance is 2.987(2) Å and the graph set description is $R_2^2(22)$.[11] The angle between the mean planes of the naphthyl moieties is 82.21(3)° and the nitro group is tilted out of the mean plane of the parent naphthyl ring by 9.5(1)°. The C6-N6 bond length exhibits a value of 1.473(3) Å.

with propane phosphonic acid anhydride (T3P) and *N*-methyl morpholine (NMM) in dichloromethane.[12] All compounds were purified by column chromatography with EtOAc/*n*-hexane. Attempts to couple the hidden amino group of the isomer **6a** to chiral natural amino acids have been unsuccessful thus far. The use of the amino acid/Bna building blocks **7**, **8** and **9** in an oligoamide synthesis requires the deprotection of the carboxyl ester group. This was achieved with KOH in THF/water giving the Boc-protected acids **10** and **11**. The compounds are ready to be used as amide building blocks either in solution or in solid phase peptide synthesis.

The solution phase Bna foldamer synthesis is exemplified by the combination of **10** and (Boc-deprotected) **7** giving the non-natural tetrapeptide **12** (Scheme 3). Best results were again obtained with T3P as coupling reagent in dichloromethane. The crude reaction product was purified by column chromatography (EtOAc/*n*-hexane) to give **12** in 27% yield. While the ^{1}H NMR spectrum of **12** in DMSO-d_6 at 303 K contains the expected sharp signals, the spectra in chloroform-*d* and dichlorormethane-d_2 are significantly broadened. At lower temperatures, partial splitting of the NMR signals is observed as well as an additional broadening (Fig. 4). At 233 K, at least four different sets of signals of the central valine unit in **12** are observed; several of these signals are located at unusual high field (between 0 and −1 ppm) suggesting an equilibrium between several compact molecular structures where methyl groups are located in the anisotropic environment above aromatic rings. The solvent dependence of the phenomenon suggests that aggregation in the weakly polar solvent dichloromethane is responsible for this observation. All attempts failed so far to attribute the low temperature NMR data in dichloromethane to a single defined conformation. The oligoamide **12**, which contains the relatively short (*S*)-Val-(*S*)-Bna-(*S*)-Val-(*S*)-Bna unit does probably not adopt a kinetically stable (helical) structure. In contrast, a 3^{10}-helix has been found in oligomers of the structurally different but somewhat related (*S*)-Bin

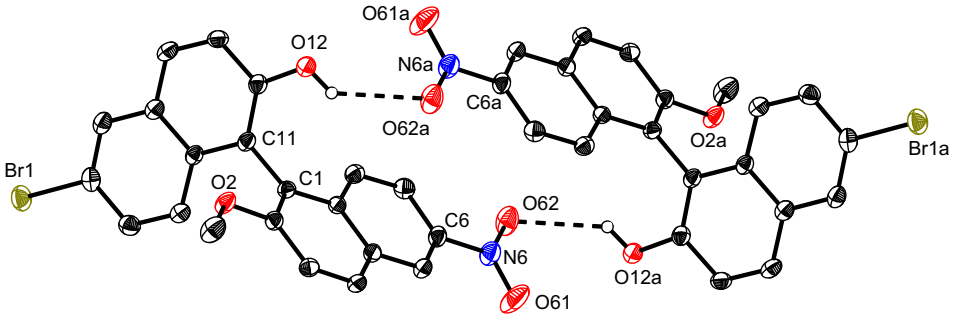


Fig. 3. Hydrogen-bonded dimer of *rac*-**3**. Displacement ellipsoids are drawn at the 50% probability level. Hydrogen atoms attached to carbon are omitted for clarity. Hydrogen bonds are represented by dashed lines. Symmetry code: (a) 1−*x*,−*y*,−*z*.

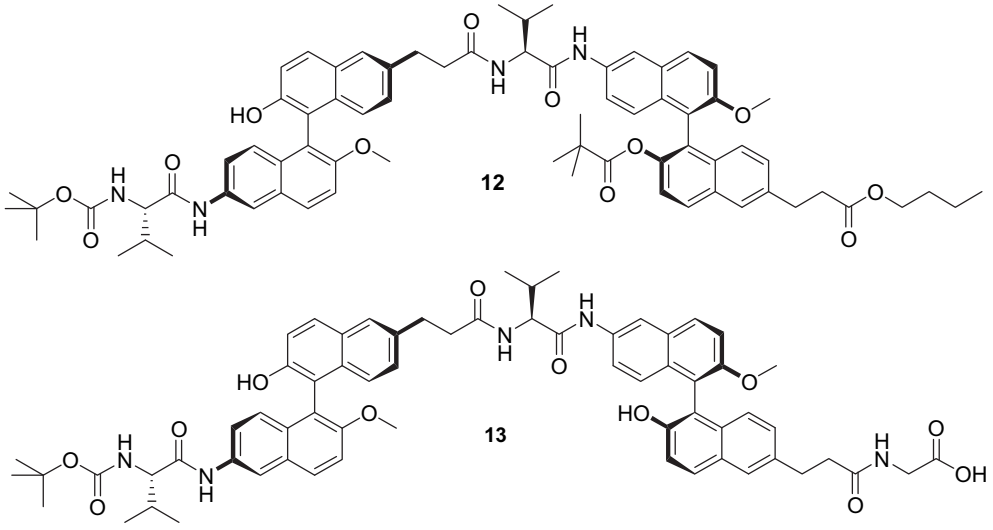
The subsequent acylation of **3** (and **3a**) with pivaloyl chloride yields **4** (and **4a**). The bulky pivaloyl group was again introduced in order to prevent racemisation in the following high temperature Heck-reaction. This reaction was only successful if run under argon, carefully excluding water. Then, *n*-butyl acrylate, tri-*o*-tolylphosphine, Pd(Ac)$_2$ and tri-*n*-butylamine in DMF converted **4** (and **4a**) to **5** (and **5a**) in 57% (46%) yield after chromatography. The reduction of the nitro function at C6 (C8 resp.) and of the double bond at C6′ with 4 bar H_2 over Pd/C in EtOAc gave finally the Bna esters **6** and **6a**.

Boc-protected natural L-amino acids (valine, phenylalanine and isoleucine) were attached to the amino group of **6** obtaining the non-natural dipeptides **7**, **8** and **9**. The coupling was best realised

unit, a C_2-symmetric binaphthyl derived $C^{\alpha,\alpha}$-disubstituted glycine amino acid,[16] whereas oligomers of the corresponding β-amino acid (β^{2,2}-HBin) adopt several different hydrogen bonded forms in dichloromethane and chloroform.[17]

The solid phase synthesis of Bna peptides is exemplified by the preparation of compound **13** (Scheme 3). The sequence was constructed on the tentagel-hydroxy resin. After esterification of the free OH group of the tentagel resin with Boc-Gly-OH and removal of the Boc-group with TFA/dichloromethane, two molecules (*S*)-**11** were attached subsequently using standard coupling (DIC, HOBt, DIPEA) and deprotection techniques (TFA for Boc removal). Remaining free amino groups were capped with acetic anhydride during the synthesis. Finally, the product **13** was released from the

6



Scheme 3. Structures of the Bna peptides **12** (Boc-(*S*)-Val-(*S*)-Bna(OH)-(*S*)-Val-(*S*)-Bna(OPiv)-*O*-*n*-But) and **13** (Boc-(*S*)-Val-(*S*)-Bna(OH)-(*S*)-Val-(*S*)-Bna(OH)-Gly-OH).

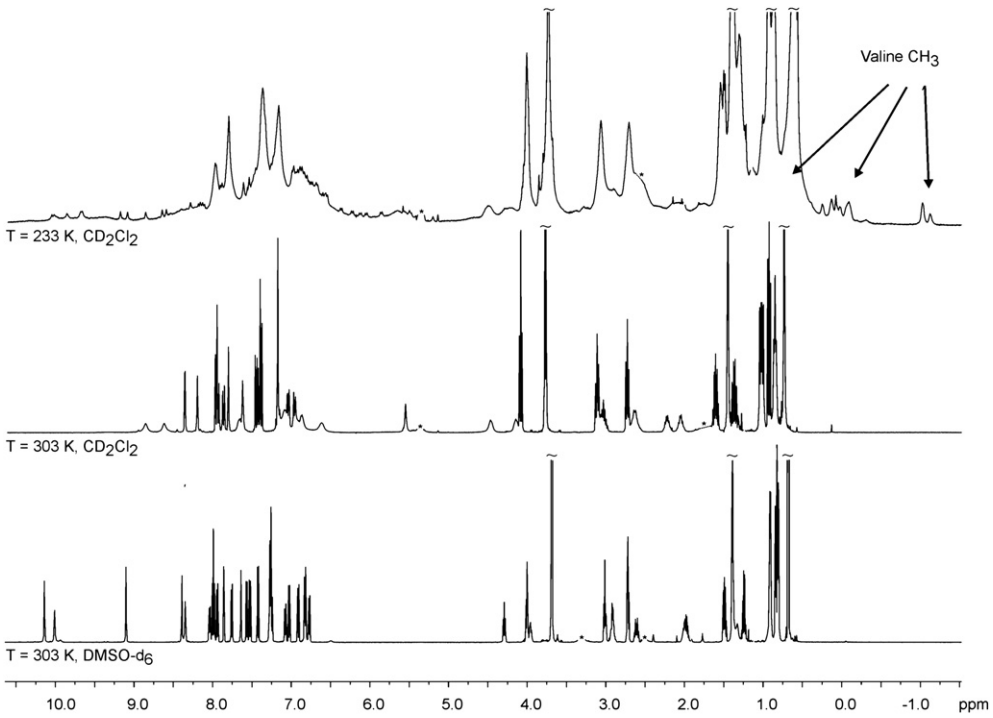


Fig. 4. ^{1}H NMR spectrum (600 MHz) of **12** in dimethylsulfoxide-d_6 at 303 K (lower trace) and temperature dependent spectra of **12** (400 MHz, 233 and 303 K) in dichloromethane-d_2 (upper traces). The positions of the signals of the solvents and of residual water are marked with asterisks. Signals of valine methyl groups appearing in the spectrum in dichloromethane-d_2 at low temperature are marked with arrows.

resin with LiOH in MeOH/water in 42% yield. Interestingly, ^{1}H NMR spectra of the cleaved material contain the signals of an approximately equimolar amount of diisopropyl urea, so the urea produced from the carbodiimide during the amide bond synthesis, probably remains complexed at the peptide resin despite the numerous washing procedures at the workup processes. In addition, the ^{1}H NMR spectra of **13** in acetone-d_6 show that all NH and OH signals had been exchanged by deuterium—a phenomenon normally only observed in NMR spectra measured in D_2O. We also recorded an increase of the aceton-d_5 signal compared to a corresponding peptide free solution, so the compound **13** probably accelerates the keto enol tautomerism of acetone. Further studies towards the catalytic activities of **13** and related (longer) Bna peptides are in progress.

3. Conclusion

This work demonstrates that the artificial amino acid Bna and protected derivatives of Bna are synthetically accessible in both enantiomeric forms. The combination of Bna with natural amino

acids forming binaphthyl peptide hybrids is achieved via solution phase synthesis or on solid support. The 'tetrapeptide' **12** and the 'pentapeptide' **13**, both with two Bna units in the chain, were synthesized. Low temperature NMR spectra of **12** in dichloromethane-d_2 show dynamic line broadening and splitting, which can be interpreted as the result of aggregation of the oligomer in the weakly polar solvent and defined helical conformations could not be derived. The 'pentapeptide' **13** accelerates the enolisation of acetone. The use of more complex Bna peptides as organo catalysts has to be explored.

solved by direct methods with SHELXS-97 and refined by full-matrix least-squares refinement against F^2 using SHELXL-97.[15] In the absence of significant anomalous scattering effects, Friedel pairs have been merged in the case of (*R*)-**2** and *rac*-**2a**. The absolute configuration of (*R*)-**2** was assigned from the known configuration of the starting material, while the absolute structure of the polar crystal structure of *rac*-**2a** was assigned arbitrarily. Anisotropic displacement parameters were introduced for all non-hydrogen atoms.

Crystal data and refinement details are given in Table 1. CCDC 750066, 750067 and 751952 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 1
Crystal data of (*R*)-**2**, *rac*-**2a** and *rac*-**3** and refinement details

	(*R*)-**2**	*rac*-**2a**	*rac*-**3**
Empirical formula	$C_{26}H_{23}NO_5$	$C_{26}H_{23}NO_5$	$C_{21}H_{14}BrNO_4$
M_r	429.45	429.45	424.24
Crystal size	0.59×0.50×0.44	0.26×0.24×0.21	0.34×0.22×0.16
Crystal colour	Yellow	Yellow	Bronze
Crystal system	Orthorhombic	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$	$Pna2_1$	$P2_1/c$
T (K)	294(2)	115(2)	150(2)
λ (Å)	0.71073	0.71073	1.54178
a (Å)	8.5926(11)	15.8256(5)	15.6222(15)
b (Å)	13.399(4)	10.2927(4)	9.0559(9)
c (Å)	19.140(2)	27.1708(9)	13.4357(13)
α (°)	90	90	90
β (°)	90	90	113.674(3)
γ (°)	90	90	90
V (Å^3)	2203.6(8)	4425.8(3)	1740.8(3)
Z	4	8	4
σ (g cm^{-3})	1.294	1.289	1.619
μ (mm^{-1})	0.090	0.090	3.466
$2\theta_{max}$ (°)	52.00	55.00	133.54
Data collected	3171 (R_{int}=0.023)	46,585 (R_{int}=0.086)	38,389 (R_{int}=0.038)
Data unique/observed ($I>2\sigma(I)$)	2446/1742	5163/2808	3061/2942
Refined parameters/restraints	294/0	577/1	246/0
Goodness of Fit on F^2	1.056	0.828	1.120
R_1 ($I>2\sigma(I)$)	0.052	0.032	0.027
wR_2 (all data)	0.145	0.102	0.066
Residuals (eÅ^{-3})	0.13/−0.16	0.26/−0.43	0.42/−0.49

4. Experimental

4.1. General comments

All reactions were carried out under an atmosphere of argon, apart from nitration and reduction. NMR spectra were recorded on Bruker DPX-200 (200.13 MHz), DRX-400 (400.13 MHz) or DRX-600 (600.13 MHz) spectrometers. MALDI spectra were measured with a Bruker Daltonics Autoflex mass spectrometer. EI and FAB mass spectra were recorded on a mass spectrometer of VG Instruments. Optical rotations were determined with an Anton Paar PROPOL instrument.

4.2. X-ray crystallography

The X-ray diffraction intensities for (*R*)-**2** were collected in the ω scan mode on a Siemens P4 four-circle diffractometer. The data collections for *rac*-**2a** were carried out on an Oxford Diffraction Xcalibur™2 diffractometer with a Sapphire2 CCD employing the ω scan mode. The intensity data for *rac*-**3** were measured on a Bruker AXS X8 Proteum diffractometer using ω and φ scans. The data were corrected for Lorentz and polarization effects. Absorption corrections were carried out semi-empirically on the basis of multiple-scanned reflections[13] with the exception of (*R*)-**2**. In the case of (*R*)-**2**, a semi-empirical absorption correction on the basis of ψ scans was applied by using Platon/ABSPsiScan.[14] The crystal structures were

*4.2.1. 6-Nitro-2-methoxy-2′-pivaloyloxy-1,1′-binaphthyl (S)-2, (R)-2 and 8-nitro-2-methoxy-2′-pivaloyloxy-1,1′-binaphthyl (S)-**2a**, (R)-**2a**.* To a solution of 2-methoxy-2′-pivaloyloxy-1,1′-binaphthyl (*S*)-**1** ((*R*)-**1**) (6.07 g, 15.79 mmol) in CH_2Cl_2 (20 ml) and acetic acid (20 ml) was slowly added fuming nitric acid (0.67 ml, 16.3 mmol) at room temperature. After 4 h the reaction mixture was diluted in ether and added to water (30 ml) in a separating funnel. The organic layer was extracted four times with water and dried over anhydrous $MgSO_4$. After evaporation of the solvents the crude product was purified by column chromatography over silica gel with EtOAc/*n*-hexane (1:4). The products were obtained as orange solids. Compound **2**: (2.79 g, 41.2%), R_f=0.37, mp 168−170 °C, (*S*)-**2**: $[\alpha]_D^{20}$ +38.3 (*c* 0.1, THF), (*R*)-**2**: $[\alpha]_D^{20}$ +46.7 (*c* 0.1, THF). ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C) δ=0.75 (s, 9H, R−$(CH_3)_3$), 3.83 (s, 3H, O−CH_3), 7.15−7.20 (m, 1H), 7.22−7.26 (m, 1H), 7.32 (ddd, J_1=8.2 Hz, J_2=6.8 Hz, J_3=1.3 Hz, 1H), 7.40 (d, J=8.9 Hz, 1H), 7.48 (ddd, J_2=8.1 Hz, J_2=6.8 Hz, J_3=1.2 Hz, 1H), 7.56 (d, J=9.1 Hz, 1H), 7.93−8.00 (m, 2H), 8.02 (d, J=8.8 Hz, 1H), 8.17 (d, J=9.0 Hz, 1H), 8.82 (d, J=2.4 Hz, 1H) ppm. HRMS (EI): calcd for $C_{26}H_{23}NO_5$ 429.1576; found 429.1571.

Compound **2a**: (1.19 g, 18%), R_f=0.27, mp 77−82 °C, (*S*)-**2a**: $[\alpha]_D^{20}$ +491.6 (*c* 0.1, THF), (*R*)-**2a**: $[\alpha]_D^{20}$ +512.6 (*c* 0.1, THF). ^{1}H NMR

(400 MHz, $CDCl_3$, 30 °C) δ=0.71 (s, 9H, R–$(CH_3)_3$), 3.72 (s, 3H, O–CH_3), 7.24 (d, J=8.9 Hz, 1H, Ar–H3′), 7.32–7.41 (m, 2H, Ar–H7′, Ar–H6), 7.43–7.54 (m, 3H, Ar–H3, Ar–H8′, Ar–H6′), 7.58 (dd, J_1=7.4 Hz, J_2=1.3 Hz, 1H, Ar–H7), 7.89 (d, J=8.1 Hz, 1H, Ar–H5′), 7.92 (d, J=8.9 Hz, 1H, Ar–H4′), 8.03 (dd, J_1=8.2 Hz, J_2=1.2 Hz, 1H, Ar–H5), 8.07 (d, J=9.1 Hz, 1H, Ar–H4) ppm. HRMS (EI): calcd for $C_{26}H_{23}NO_5$ 429.1561; found 429.1576.

*4.2.2. 6-Nitro-6′-bromo-2-methoxy-2′-hydroxy-1,1′-binaphthyl (S)-3, (R)-**3**.* 6-Nitro-2-methoxy-2′-pivaloyloxy-1,1′-binaphthyl (*S*)-**2** ((*R*)-**2**) (3.25 g, 7.57 mmol) was dissolved in a mixture of KOH (1.50 g, 26.64 mmol), THF (35 ml) and water (35 ml). After stirring over night at reflux the reaction mixture was acidified with 1 M HCl solution. The organic layer was diluted in EtOAc, washed with saturated $NaHCO_3$ and brine and was dried over anhydrous $MgSO_4$. After removal of the solvents the crude product was dissolved in CH_2Cl_2 (45 ml)/THF (23 ml) and cooled to 0 °C. Br_2 (0.9 ml, 17.57 mmol) was slowly added and then stirred for 2 h. Excess of Br_2 was quenched with saturated solution of Na_2SO_3. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated solution of $NaHCO_3$, 1 M HCl solution and brine. The organic layer was dried over anhydrous $MgSO_4$ and the solvents were evaporated. A red-brown foam containing a 1:1 ratio of THF was obtained (3.08 g, 96%). Mp 97–101 °C, (*S*)-**3**: $[\alpha]_D^{20}$ +30.3 (*c* 0.1, THF), (*R*)-**3**: $[\alpha]_D^{20}$ −31.8 (*c* 0.1, THF). ^{1}H NMR (200 MHz, $CDCl_3$, 30 °C) δ=3.88 (s, 3H, O–CH_3), 4.90 (s, 1H, OH), 6.81 (d, J=9.0 Hz, 1H), 7.16–7.43 (m, 3H), 7.63 (d, J=9.2 Hz, 1H), 7.84 (d, J=8.9 Hz, 1H), 7.94–8.10 (m, 2H), 8.27 (d, J=9.2 Hz, 1H), 8.87 (d, J=2.3 Hz, 1H) ppm. HRMS (EI): calcd for $C_{21}H_{14}BrNO_4$ 423.0108; found 423.0106.

*4.2.3. 8-Nitro-6′-bromo-2-methoxy-2′-hydroxy-1,1′-binaphthyl (S)-**3a**.* The preparation was identical to the procedure described for compound **3**. 8-Nitro-2-methoxy-2′-pivaloyloxy-1,1′-binaphthyl (*S*)-**2a** (1.1 g, 2.56 mmol), KOH (0.51 g, 9.06 mmol), THF (12 ml)/water (12 ml); CH_2Cl_2 (13 ml)/THF (7 ml) and Br_2 (0.25 ml, 4.88 mmol) were used. The product was obtained as a yellow foam (0.91 g, 83%). Mp 80–89 °C, (*S*)-**3a**: $[\alpha]_D^{20}$ −248.5 (*c* 0.1, THF). ^{1}H NMR (250 MHz, $CDCl_3$, 30 °C) δ=3.83 (s, 3H, O–CH_3), 5.01 (s, 1H, OH), 6.73 (d, J=9.0 Hz, 1H), 7.23–7.26 (m, 2H), 7.40 (t, J=7.7 Hz, 1H), 7.52 (d, J=7.4 Hz, 1H), 7.60 (d, J=9.4 Hz, 1H), 7.78 (d, J=8.8 Hz, 1H), 7.95 (s, 1H), 8.08 (d, J=7.8 Hz, 1H), 8.18 (d, J=9.2 Hz, 1H) ppm. MS (EI): calcd for $C_{21}H_{14}BrNO_4$ 423.01; found 424.9.

*4.2.4. 6-Nitro-6′-bromo-2-methoxy-2′-pivaloyloxy-1,1′-binaphthyl (S)-4, (R)-**4**.* 6-Nitro-6′-bromo-2-methoxy-2′-hydroxy-1,1′-binaphthyl (*S*)-**3** ((*R*)-**3**) (3.08 g, 7.26 mmol) and triethylamine (3.6 ml, 26 mmol) were diluted in acetonitrile (26 ml). After dropwise addition of pivaloyl chloride (1.04 g, 8.66 mmol) at 0 °C the reaction mixture was allowed to warm up to room temperature and stirred furthermore for 4 h. Subsequent ether was added and the organic layer was washed with saturated solution of $NaHCO_3$, 1 M HCl solution and brine. Drying over anhydrous $MgSO_4$ and evaporation of the solvent gave a brown foam (3.46 g, 94%). Mp 77–81 °C, (*S*)-**4**: $[\alpha]_D^{20}$ +66.2 (*c* 0.1, THF), (*R*)-**4**: $[\alpha]_D^{20}$ −68.2 (*c* 0.1, THF). ^{1}H NMR (200 MHz, $CDCl_3$, 30 °C) δ=0.74 (s, 9H, R–$(CH_3)_3$), 3.83 (s, 3H, O–CH_3), 7.06 (d, J=9.0 Hz, 1H), 7.20 (d, J=9.4 Hz, 1H), 7.35–7.44 (m, 2H), 7.56 (d, J=9.1 Hz, 1H), 7.93 (d, J=8.9 Hz, 1H), 8.00 (dd, J_1=9.4 Hz, J_2=2.3 Hz, 1H), 8.13 (d, J=1.9 Hz, 1H), 8.19 (d, J=9.1 Hz, 1H), 8.83 (d, J=2.3 Hz, 1H) ppm. HRMS (EI): calcd for $C_{26}H_{22}BrNO_5$ 507.0682; found 507.0681.

*4.2.5. 8-Nitro-6′-bromo-2-methoxy-2′-pivaloyloxy-1,1′-binaphthyl (S)-**4a**.* The preparation was identical to the procedure described for compound **4**. 8-Nitro-6′-bromo-2-methoxy-2′-hydroxy-1,1′-binaphthyl (*S*)-**3a** (0.91 g, 2.15 mmol), triethylamine (0.9 ml, 6.5 mmol), pivaloyl chloride (0.27 g, 2.25 mmol) and acetonitrile (7 ml) were used. The product was obtained as a yellow foam (0.95 g, 87%). Mp 73–80 °C, $[\alpha]_D^{20}$ +439.0 (*c* 0.1, THF). ^{1}H NMR (200 MHz, $CDCl_3$, 30 °C) δ=0.68 (s, 9H, R–$(CH_3)_3$), 3.72 (s, 3H, O–CH_3), 7.23–7.27 (m, 1H), 7.31–7.45 (m, 3H), 7.51 (d, J=9.1 Hz, 1H), 7.61 (dd, J_1=7.5 Hz, J_2=1.2 Hz, 1H), 7.82 (d, J=8.9 Hz, 1H), 7.99–8.13 (m, 3H) ppm. HRMS (EI): calcd for $C_{26}H_{22}BrNO_5$ 507.0677; found 507.0681.

*4.2.6. 6-Nitro-6′-((E)-1-(n-butyloxycarbonyl)ethen-2-yl)-2-methoxy-2′-pivaloyloxy-1,1′-binaphthyl (S)-**5**.* 6-Nitro-6′-bromo-2-methoxy-2′-pivaloyloxy-1,1′-binaphthyl (*S*)-**4** (3.46 g, 6.8 mmol) was dissolved in DMF (20 ml) under argon. Tri-*o*-tolylphosphine (117 mg, 0.38 mmol), *n*-butyl acrylate (1.08 g, 8.42 mmol), tri-*n*-butylamine (7.12 g, 38.42 mmol) and $Pd(OAc)_2$ (42.3 mg, 0.188 mmol) were added. The reaction mixture was stirred for 2 days at 130 °C. After cooling down to room temperature, ether was added. The organic phase was washed with solutions of 1 M HCl, saturated $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography over silica gel with EtOAc/*n*-hexane (1:3) gave a yellow foam (2.31 g, 64%). R_f=0.32, mp 87–94 °C, (*S*)-**5**: $[\alpha]_D^{20}$ +157.3 (*c* 0.1, THF). ^{1}H NMR (200 MHz, $CDCl_3$, 30 °C) δ=0.74 (s, 9H, R–$(CH_3)_3$), 0.97 (t, J=7.2 Hz, 3H, R–CH_2–CH_2–CH_2–CH_3), 1.34–1.52 (m, 2H, R–CH_2–CH_2–CH_2–CH_3), 1.60–1.80 (m, 2H, R–CH_2–CH_2–CH_2–CH_3), 3.84 (s, 3H, O–CH_3), 4.22 (t, J=6.6 Hz, 2H, R–CH_2–CH_2–CH_2–CH_3), 6.49 (d, J=16.0 Hz, 1H, Ar–CH=CH–R), 7.13–7.25 (m, 2H), 7.43 (d, J=8.9 Hz, 1H), 7.50 (dd, J_1=8.9 Hz, J_2=1.6 Hz, 1H), 7.57 (d, J=9.1 Hz, 1H), 7.83 (d, J=16.0 Hz, 1H, Ar–CH=CH–R), 7.94–8.08 (m, 3H), 8.19 (d, J=9.1 Hz, 1H), 8.83 (d, J=2.3 Hz, 1H) ppm. HRMS (EI): calcd for $C_{33}H_{33}NO_7$ 555.2257; found 555.2247.

*4.2.7. 8-Nitro-6′-((E)-1-(n-butyloxycarbonyl)ethen-2-yl)-2-methoxy-2′-pivaloyloxy-1,1′-binaphthyl (S)-**5a**, (R)-**5a**.* The preparation was identical to the procedure described for compound **5**. 8-Nitro-6′-bromo-2-methoxy-2′-pivaloyloxy-1,1′-binaphthyl (*S*)-**4a** ((*R*)-**4a**) (1.03 g, 2.03 mmol), DMF (5 ml), tri-*o*-tolylphosphine (31 mg, 0.1 mmol), *n*-butyl acrylate (0.29 g, 2.26 mmol), tri-*n*-butylamine (1.87 g, 10.1 mmol) and $Pd(OAc)_2$ (12 mg, 0.05 mmol) were used. The product was purified by column chromatography over silica gel with EtOAc/*n*-hexane (1:3) giving 67% (0.70 g) yield of a yellow oil. R_f=0.27, mp 70–77 °C, (*S*)-**5a**: $[\alpha]_D^{20}$ −420.5 (*c* 0.1, THF), (*R*)-**5a**: $[\alpha]_D^{20}$ +407.2 (*c* 0.1, THF). ^{1}H NMR (200 MHz, $CDCl_3$, 30 °C) δ=0.69 (s, 9H, R–$(CH_3)_3$), 0.97 (t, J=7.3 Hz, 3H, R–CH_2–CH_2–CH_2–CH_3), 1.37–1.54 (m, 2H, R–CH_2–CH_2–CH_2–CH_3), 1.61–1.84 (m, 2H, R–CH_2–CH_2–CH_2–CH_3), 3.72 (s, 3H, O–CH_3), 4.23 (t, J=6.6 Hz, 2H, R–CH_2–CH_2–CH_2–CH_3), 6.51 (d, J=16.0 Hz, 1H, Ar–CH=CH–R), 7.27 (d, J=8.9 Hz, 1H), 7.31–7.43 (m, 1H), 7.46–7.66 (m, 4H), 7.85 (d, J=16.0 Hz, 1H, Ar–CH=CH–R), 7.93 (d, J=8.9 Hz, 1H), 8.97–8.12 (m, 3H) ppm. MS (FAB): calcd for $C_{33}H_{33}NO_7$ 555.23; found 555.4.

*4.2.8. 6-Amino-6′-(n-butyloxycarbonyl)ethyl-2-methoxy-2′-pivaloyloxy-1,1′-binaphthyl (R)-**6**.* 6-Nitro-6′-((*E*)-1-(*n*-butyloxycarbonyl)ethen-2-yl)-2-methoxy-2′-pivaloyloxy-1,1′-binaphthyl (*R*)-**5** (2.31 g, 4.16 mmol) was dissolved in EtOAc (31 ml) and Pd/C (50 mg, 0.47 mmol) was added. The reaction mixture was slowly shaken under hydrogen atmosphere at 4 bar and room temperature for 23 h. Subsequent Pd/C was filtered by using alkaline Celite. Removal of the solvent gave a yellow oil (2.11 g, 96%). Compound (*R*)-**6**: $[\alpha]_D^{20}$ −101.9 (*c* 0.1, THF). ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C) δ=0.76 (s, 9H, R–$(CH_3)_3$), 0.89 (t, J=7.4 Hz, 3H, R–CH_2–CH_2–CH_2–CH_3), 1.30–1.43 (m, 2H, R–CH_2–CH_2–CH_2–CH_3), 1.50–1.62 (m, 2H, R–CH_2–CH_2–CH_2–CH_3), 2.69 (t, 2H, Ar–CH_2–CH_2–R), 3.08 (t, J=7.8 Hz, 2H, Ar–CH_2–CH_2–R), 3.69 (s, 3H, O–CH_3), 4.07 (t, J=6.7 Hz, 2H, R–CH_2–CH_2–CH_2–CH_3), 6.71 (dd, J_1=9.0 Hz, J_2=2.4 Hz, 1H), 6.94 (d, J=9.0 Hz, 1H), 7.00 (d,

J=2.3 Hz, 1H), 7.14 (dd, J_1=8.6 Hz, J_2=1.7 Hz, 1H), 7.24 (d, J=8.7 Hz, 1H), 7.30 (d, J=9.0 Hz, 1H), 7.35 (d, J=8.8 Hz, 1H), 7.69 (d, J=9.0 Hz, 1H), 7.72 (s, 1H), 7.88 (d, J=8.9 Hz, 1H) ppm. HRMS (EI): calcd for $C_{33}H_{37}NO_5$ 527.2671; found 527.2670.

*4.2.9. 8-Amino-6′-(n-butyloxycarbonyl)ethyl-2-methoxy-2′-pivaloyloxy-1,1′-binaphthyl (S)-**6a**.* 8-Nitro-6′-((*E*)-1-(*n*-butyloxycarbonyl)ethen-2-yl)-2-methoxy-2′-pivaloyloxy-1,1′-binaphthyl (*S*)-**5a** (0.39 g, 0.70 mmol) was dissolved in EtOAc (5 ml) and Pd/C (50 mg, 0.47 mmol) was added. The reaction mixture was slowly shaken at 30 °C under hydrogen atmosphere (4 bar) for 22 h. Subsequent Pd/C was filtered by using alkaline Celite. Removal of the solvent gave a yellow oil (0.54 g, 81%). Compound (*S*)-**6a**: $[\alpha]_D^{20}$ +125.0 (*c* 0.1, THF). ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C) δ=0.81 (s, 9H, R–$(CH_3)_3$), 0.90 (t, J=7.4 Hz, 3H, R–CH_2–CH_2–CH_2–CH_3), 1.29–1.39 (m, 2H, R–CH_2–CH_2–CH_2–CH_3), 1.54–1.62 (m, 2H, R–CH_2–CH_2–CH_2–CH_3), 2.70 (t, J=7.84 Hz, 2H, Ar–CH_2–CH_2–R), 3.09 (t, J=7.8 Hz, 2H, Ar–CH_2–CH_2–R), 3.66 (s, 3H, O–CH_3), 4.08 (t, J=6.6 Hz, 2H, R–CH_2–CH_2–CH_2–CH_3), 6.50 (dd, J_1=7.4 Hz, J_2=1.1 Hz, 1H), 7.08–7.15 (m, 1H), 7.19 (dd, J_1=8.7 Hz, J_2=1.8 Hz, 1H), 7.26–7.38 (m, 4H), 7.70 (s, 1H), 7.88 (dd, J_1=8.9 Hz, J_2=3.0 Hz, 2H) ppm. HRMS (EI): calcd for $C_{33}H_{37}NO_5$ 527.2671; found 527.2651.

4.3. General procedure (A) for synthesis of the compounds 7, 8 and 9

6-Amino-6′-(*n*-butyloxycarbonyl)ethyl-2-methoxy-2′-pivaloyloxy-1,1′-binaphthyl **6** (1 equiv), Boc-amino acid-OH (3 equiv), NMM (4.8 equiv), PPA (7.5 equiv) and CH_2Cl_2 (30 ml) were added into a flask. After stirring for 2 days at room temperature the solvent was evaporated under reduced pressure. Subsequent EtOAc was added and the mixture was washed with solutions of saturated $NaHCO_3$, brine, 5% $NaHSO_4$ and brine again. Then the organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo.

*4.3.1. 6-(tert-Butyloxycarbonyl)-(S)-valinyl-6′-(n-butyloxycarbonyl) ethyl-2-methoxy-2′-pivaloyloxy-(R)-1,1′-binaphthyl **7**.* The procedure is listed for the *R*-binaphthyl isomer, NMR data of the corresponding isomer with (*S*)-binaphthyl chirality are almost identical. Compound (*R*)-**6** (0.63 g, 1.19 mmol), (*S*)-Boc-Val-OH (0.78 g, 3.58 mmol), NMM (0.58 g, 5.71 mmol), PPA (2.85 g, 8.95 mmol) and CH_2Cl_2 (30 ml) were used. The crude product was purified by column chromatography over silica gel with EtOAc/*n*-hexane (2:1). A beige foam (0.77 g, 90%) was obtained. R_f=0.81, mp 87–91 °C, $[\alpha]_D^{20}$ −72.6 (*c* 0.1, THF). ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C) δ=0.75 (s, 9H, R–$(CH_3)_3$), 0.89 (t, J=7.4 Hz, 3H, R–CH_2–CH_2–CH_2–CH_3), 1.02 (dd, J_1=17.5 Hz, J_2=6.8 Hz, 6H, Val-CH_3), 1.29–1.39 (m, 2H, R–CH_2–CH_2–CH_2–CH_3), 1.45 (s, 9H, Boc), 1.53–1.64 (m, 2H, R–CH_2–CH_2–CH_2–CH_3), 2.23–2.35 (m, 1H, Val-βH), 2.69 (t, J=7.8 Hz, 2H, Ar–CH_2–CH_2–R), 3.08 (t, J=7.7 Hz, 2H, Ar–CH_2–CH_2–R), 3.73 (s, 3H, O–CH_3), 3.97–4.04 (m, 1H, Val-αH), 4.07 (t, J=6.7 Hz, 2H, R–CH_2–CH_2–CH_2–CH_3), 5.06 (s, 1H, Val-NH), 6.99–7.08 (m, 2H), 7.11–7.20 (m, 2H), 7.36 (d, J=11.8 Hz, 1H), 7.39 (d, J=12.1 Hz, 1H), 7.73 (s, 1H), 7.85–7.94 (m, 3H, Ar–NH, Ar–H), 8.39 (s, 1H) ppm. MS (EI): calcd for $C_{43}H_{54}N_2O_8$ 726.39; found 726.4.

*4.3.2. 6-(tert-Butyloxycarbonyl)-(S)-phenylalanyl-6′-(n-butyloxycarbonyl)ethyl-2-methoxy-2′-pivaloyloxy-(S)-1,1′-binaphthyl **8**.* Prepared by using general method **A**: (*S*)-**6** (0.5 g, 0.9 mmol), (*S*)-Boc-Phe-OH (0.72 g, 2.7 mmol), NMM (0.44 g, 4.32 mmol), PPA (2.1 g, 6.75 mmol) and CH_2Cl_2 (22.5 ml) were used. The crude product was purified by column chromatography over silica gel with EtOAc/*n*-hexane (1:1) and yielded in a foam (0.56 g, 81%). R_f=0.74, mp 88–95 °C, $[\alpha]_D^{20}$ +33 (*c* 0.1, THF). ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C) δ=0.73 (s, 9H, R–$(CH_3)_3$), 0.89 (t, J=7.4 Hz, 3H, R–CH_2–CH_2–CH_2–CH_3), 1.29–1.38 (m, 2H, R–CH_2–CH_2–CH_2–CH_3), 1.42 (s, 9H, Boc), 1.52–1.56 (m, 2H, R–CH_2–CH_2–CH_2–CH_3), 2.69 (t, J=7.8 Hz, 2H, Ar–CH_2–CH_2–R), 3.09 (t, J=7.8 Hz, 2H, Ar–CH_2–CH_2–R), 3.16 (d, J=7.0 Hz, 2H, Phe-βH), 3.73 (s, 3H, O–CH_3), 4.08 (t, J=6.7 Hz, 2H, R–CH_2–CH_2–CH_2–CH_3), 4.43–4.50 (m, 1H, Phe-αH), 5.12 (br s, 1H, Phe-NH), 6.82 (dd, J_1=9.1 Hz, J_2=2.1 Hz, 1H), 7.01 (d, J=9.0 Hz, 1H), 7.17 (dd, J_1=11.5 Hz, J_2=5.1 Hz, 2H), 7.20–7.31 (m, 5H, Phe-ArH), 7.35 (d, J=8.8 Hz, 1H), 7.38 (d, J=9.1 Hz, 1H), 7.68 (s, 1H, Ar–NH), 7.73 (s, 1H), 7.89 (dd, J_1=8.9 Hz, J_2=4.0 Hz, 2H), 8.28 (d, J=1.8 Hz, 1H) ppm. MS (EI): calcd for $C_{47}H_{54}N_2O_8$ 674.3 $(M-Boc+2H)^+$; found 674.3.

*4.3.3. 6-(tert-Butyloxycarbonyl)-(S)-isoleucinyl-6′-(n-butyloxycarbonyl)ethyl-2-methoxy-2′-pivaloyloxy-(R)-1,1′-binaphthyl **9**.* Prepared by using general method **A**: (*R*)-**6** (0.2 g, 0.38 mmol), (*S*)-Boc-Ile-OH (0.27 g, 1.14 mmol), NMM (0.18 g, 1.82 mmol), PPA (0.90 g, 2.85 mmol) and CH_2Cl_2 (10 ml) were used. Purifying of the crude product by column chromatography over silica gel with EtOAc/*n*-hexane (1:4) yielded in a beige foam (0.2 g, 74%). R_f=0.33, mp 89–93 °C, $[\alpha]_D^{20}$ +78.4 (*c* 0.1, THF). ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C) δ=0.75 (s, 9H, R–$(CH_3)_3$), 0.89 (t, J=7.4 Hz, 3H, R–CH_2–CH_2–CH_2–CH_3), 0.94 (t, J=7.4 Hz, 3H, Ile-CH_3), 1.01 (d, J=6.8 Hz, 3H, Ile-CH_3), 1.12–1.23 (m, 1H, Ile-CH_2), 1.29–1.38 (m, 2H, R–CH_2–CH_2–CH_2–CH_3), 1.44 (s, 9H, Boc), 1.52–1.66 (m, 3H, Ile-CH_2, R–CH_2–CH_2–CH_2–CH_3), 1.93–2.1 (m, 1H, Ile-βH), 2.69 (t, J=7.8 Hz, 2H, Ar–CH_2–CH_2–R), 3.08 (t, J=7.8 Hz, 2H, Ar–CH_2–CH_2–R), 3.73 (s, 3H, O–CH_3), 4.08 (t, J=6.7 Hz, 3H, R–CH_2–CH_2–CH_2–CH_3, Ile-αH), 5.07 (d, J=7.3 Hz, 1H, Ile-NH), 6.99–7.01 (m, 2H), 7.10–7.20 (m, 2H), 7.36 (d, J=8.87 Hz, 1H), 7.38 (d, J=9.2 Hz, 1H), 7.73 (s, 1H), 7.90 (dd, J_1=9.0 Hz, J_2=2.9 Hz, 2H), 7.99 (s, 1H, Ar–NH), 8.39 (s, 1H) ppm. MS (EI): calcd for $C_{44}H_{56}N_2O_8$ 639.3 $(M-Boc+H)^+$; found 639.9.

4.4. General procedure (B) for synthesis of the compounds 10 and 11

To a solution of 6-(*tert*-butyloxycarbonyl)-(*S*)-amino acid-6′-(*n*-butyloxycarbonyl)ethyl-2-methoxy-2′-pivaloyloxy-1,1′-binaphthyl (1 equiv) in THF (4 ml)/water (4 ml) was added KOH (6 equiv). The mixture was stirred at reflux for 2 days and was then acidified with 1 M HCl solution. After addition of EtOAc and extraction with saturated solutions of $NaHCO_3$ (three times) and brine the mixture was dried over anhydrous $MgSO_4$. Finally, the solvent was removed in vacuo.

*4.4.1. 6-(tert-Butyloxycarbonyl)-(S)-valinyl-6′-carboxyethyl-2-methoxy-2′-hydroxy-(R)-1,1′-binaphthyl **10**.* Prepared by using general method **B**. The procedure is listed for the (*R*)-binaphthyl isomer, NMR data of the corresponding isomer with (*S*)-binaphthyl chirality are almost identical. 6-(*tert*-Butyloxycarbonyl)-(*S*)-valinyl-6′-(*n*-butyloxycarbonyl)ethyl-2-methoxy-2′-pivaloyloxy-(*R*)-1,1′-binaphthyl **7** (0.34 g, 0.45 mmol), KOH (0.16 g, 2.8 mmol) and THF (4 ml)/water (4 ml) were used. A yellow foam (253 mg, 90%) was obtained. Mp 144–146 °C, $[\alpha]_D^{20}$ −85.1 (*c* 0.1, THF). ^{1}H NMR (400 MHz, DMSO, 30 °C) δ 0.91 (d, J=6.6 Hz, 6H, Val-CH_3), 1.39 (s, 9H, Boc), 1.95–2.06 (m, 1H, Val-βH), 2.58 (t, J=7.6 Hz, 2H, Ar–CH_2–CH_2), 2.90 (t, J=7.5 Hz, 2H, Ar–CH_2–CH_2–R), 3.69 (s, 3H, O–CH_3), 3.96 (t, J=7.8 Hz, 1H, Val-αH), 6.71–6.87 (m, 2H, Ar–H8′, Val-NH), 6.93 (d, J=9.1 Hz, 1H, Ar–H8), 7.07 (dd, J_1=8.7 Hz, J_2=1.6 Hz, 1H, Ar–H7′), 7.28 (d, J=8.8 Hz, 2H, Ar–H3′, Ar–H7), 7.54 (d, J=9.2 Hz, 1H, Ar–H3), 7.65 (s, 1H, Ar–H5), 7.78 (d, J=8.8 Hz, 1H, Ar–H4′), 7.95 (d, J=9.1 Hz, 1H, Ar–H4), 8.35 (s, 1H, Ar–H5), 9.13 (s, 1H, OH), 10.01 (s, 1H, Ar–NH), 12.09 (br s, 1H, COOH) ppm. MS (EI): calcd for $C_{34}H_{38}N_2O_7$ 486.2 $(M-Boc+2\ H)^+$; found 486.1.

*4.4.2. 6-(tert-Butyloxycarbonyl)-(S)-phenylalanyl-6′-carboxyethyl-2-methoxy-2′-hydroxy-(S)-1,1′-binaphthyl **11**.* Prepared by using

general method **B**. 6-(*tert*-Butyloxycarbonyl)-(*S*)-phenylalanyl-6′-(*n*-butyloxycarbonyl)ethyl-2-methoxy-2′-pivaloyloxy-(*S*)-1,1′-binaphthyl **8** (0.85 g, 1.1 mmol), KOH (0.37 g, 6.58 mmol) and THF (10 ml)/water (10 ml) were used. A beige foam (0.45 g, 65%) was obtained. Mp 131–134 °C, $[\alpha]_D^{20}$ +32.1 (*c* 0.1, THF). ^{1}H NMR (200 MHz, DMSO, 30 °C) δ=1.31 (s, 9H, Boc), 2.57 (t, 2H, Ar–CH_2–CH_2–R), 2.76–3.0 (m, 4H, Ar–CH_2–CH_2–R, Phe-βH), 3.69 (s, 3H, O–CH_3), 4.27–4.43 (m, 1H, Phe-αH), 6.76 (d, *J*=8.7 Hz, 1H), 6.92 (d, *J*=9.1 Hz, 1H), 7.0–7.38 (m, 9H), 7.54 (d, *J*=9.1 Hz, 1H), 7.65 (s, 1H), 7.78 (d, *J*=8.9 Hz, 1H), 7.96 (d, *J*=9.1 Hz, 1H), 8.32 (s, 1H), 9.19 (s, 1H), 10.10 (s, 1H), 12.16 (br s, 1H, COOH) ppm. MS (FAB): calcd for $C_{38}H_{38}N_2O_7$ 634.3; found 634.4.

4.4.3. Boc-(S)-Val-(S)-Bna(OH)-(S)-Val-(S)-Bna(OPiv)-O-n-But ***12***. In a first step 6-(*tert*-butyloxycarbonyl)-(*S*)-valinyl-6′-(*n*-butyloxycarbonyl)ethyl-2-methoxy-2′-pivaloyloxy-(*S*)-1,1′-binaphthyl **7** (0.11 g, 0.15 mmol) was added to a solution of CH_2Cl_2 (8 ml) and TFA (4 ml). After stirring for 2 h at 0 °C the mixture was coevaporated with CH_2Cl_2 for five times.

In a second step the crude product (used without further purification) (0.075 g, 0.12 mmol) and 6-(*tert*-butyloxycarbonyl)-(*S*)-valinyl-6′-carboxyethyl-2-methoxy-2′-hydroxy-(*S*)-1,1′-binaphthyl **11** (0.071 g, 0.12 mmol) were dissolved in a solution of CH_2Cl_2 (3 ml), NMM (0.06 g, 0.55 mmol) and PPA (0.32 g, 1.02 mmol). The mixture was stirred for 2 d at room temperature. Subsequently, the solvent was evaporated under reduced pressure. EtOAc was added and the mixture was washed with solutions of saturated $NaHCO_3$, brine, 5% $NaHSO_4$ and brine again. The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed. Finally the crude product was purified over silica gel by column chromatography with EtOAc/*n*-hexane (2:1) and gave a clear foam (60.7 mg, 27%). R_f=0.59. ^{1}H NMR (600 MHz, DMSO, 30 °C) δ=0.67 (s, 9H, R–$(CH_3)_3$), 0.76–0.85 (m, 9H, R–CH_2–CH_2–CH_2–CH_3, Val-CH_3), 0.90 (d, *J*=6.4 Hz, 6H, Val-CH_3), 1.19–1.27 (m, 2H, R–CH_2–CH_2–CH_2–CH_3), 1.38 (s, 9H, Boc), 1.45–1.51 (m, 2H, R–CH_2–CH_2–CH_2–CH_3), 1.92–2.03 (m, 2H, Val-βH), 2.45–2.54 (m, 1H, Ar–CH_2–CH_2–R), 2.56–2.63 (m, 1H, Ar–CH_2–CH_2–R), 2.71 (t, *J*=7.5 Hz, 2H, Ar–CH_2–CH_2–R), 2.87–2.94 (m, 2H, Ar–CH_2–CH_2–R), 3.00 (t, *J*=7.4 Hz, 2H, Ar–CH_2–CH_2–R), 3.67 (s, 3H, O–CH_3), 3.68 (s, 3H, O–CH_3), 3.95 (t, *J*=8.2 Hz, 1H, Val-αH), 3.99 (tt, J_1=6.2 Hz, J_2=3.2 Hz, 2H, R–CH_2–CH_2–CH_2–CH_3), 4.28 (t, *J*=8.0 Hz, 1H, Val-αH), 6.76 (d, *J*=8.7 Hz, 1H), 6.81 (d, *J*=9.1 Hz, 2H, Ar–H, Val-NH), 6.90 (d, *J*=9.1 Hz, 1H), 7.01 (d, *J*=8.7 Hz, 1H), 7.06 (dd, J_1=8.8 Hz, J_2=1.3 Hz, 1H), 7.21–7.28 (m, 4H), 7.41 (d, *J*=8.9 Hz, 1H), 7.51 (d, *J*=9.2 Hz, 1H), 7.55 (d, *J*=9.2 Hz, 1H), 7.63 (s, 1H), 7.74 (d, *J*=8.9 Hz, 1H), 7.85 (s, 1H), 7.93 (d, *J*=9.1 Hz, 1H), 7.98 (t, *J*=9.0 Hz, 2H), 8.02 (d, *J*=8.5 Hz, 1H, Val-NH), 8.34 (s, 1H), 8.38 (d, *J*=1.7 Hz, 1H), 9.09 (s, 1H, OH), 10.00 (s, 1H, Ar–NH), 10.13 (s, 1H, Ar–NH) ppm. MS (MALDI): calcd for $C_{72}H_{82}N_4O_{12}$ 1218.58 $(M+Na)^+$; found 1218.724.

4.4.4. Boc-(S)-Val-(S)-Bna(OH)-(S)-Val-(S)-Bna(OH)-Gly-OH ***13***. Attachment of Boc-protected amino acids to NovaSyn® TG hydroxy resin (50 mg, 0.014 mmol) followed the standard coupling methods with HOBt, DIC and DIPEA (10 equiv).[18] The amino acid Boc-Gly-OH was applied in 10-fold excess (reaction time: 3.5 h), (*S*)-Boc-Val-(*S*)-Bna-OH **11** was only applied in 3.5-fold excess (reaction time: over night). Capping occurred with acetic anhydride (10 equiv) and DIPEA (10 equiv) for 45 min. The Boc-protecting group was removed by using 25% TFA (in CH_2Cl_2). The product was released from the resin by using LiOH (5 equiv) in MeOH/water (1:1) for 3 h. The resin was filtered off and washed with ethyl acetate and 5% $NaHSO_4$. The combined solutions were concentrated in vacuo and extracted with ethyl acetate. The organic phase was washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo giving a beige solid (7 mg, 42%). ^{1}H NMR (600 MHz, DMSO, 30 °C) δ=0.80 (d, *J*=6.7 Hz, 3H, Val-CH_3), 0.83 (d, *J*=6.7 Hz, 3H, Val-CH_3), 0.90 (d, *J*=6.4 Hz, 6H, Val-CH_3), 1.38 (s, 9H, Boc), 1.93–1.97 (m, 2H, Val-βH), 2.45–2.53 (m, 3H, Ar–CH_2–CH_2–R), 2.56–2.63 (m, 1H, Ar–CH_2–CH_2–R), 2.58–2.95 (m, 4H, Ar–CH_2–CH_2–R), 3.66 (s, 3H, O–CH_3), 3.69 (s, 3H, O–CH_3), 3.74 (d, *J*=5.8 Hz, 2H, Gly-αH), 3.94 (t, *J*=7.7 Hz, 1H, Val-αH), 4.30 (t, *J*=8.1 Hz, 1H, Val-αH), 6.73–6.78 (m, 2H), 6.82 (d, *J*=8.8 Hz, 1H, Val-NH), 6.90 (dd, J_1=8.9 Hz, J_2=6.6 Hz, 2H), 7.06 (t, *J*=8.0 Hz, 2H), 7.27 (dd, J_1=11.7 Hz, J_2=9.0 Hz, 4H), 7.50 (d, *J*=9.1 Hz, 1H), 7.54 (d, *J*=9.2 Hz, 1H), 7.63 (s, 1H), 7.65 (s, 1H), 7.75 (d, *J*=9.0 Hz, 1H), 7.78 (d, *J*=8.9 Hz, 1H), 7.92 (d, *J*=9.1 Hz, 2H), 8.02 (d, *J*=8.5 Hz, 1H), 8.19 (t, *J*=6.1 Hz, 1H, Gly-NH), 8.33 (s, 2H), 9.10 (d, *J*=14.6 Hz, 2H, OH), 10.00 (s, 1H, Ar–NH), 10.12 (s, 1H, Ar–NH), 11.67 (br s, 1H, COOH) ppm. MS (MALDI): calcd for $C_{65}H_{69}N_5O_{12}$ 1036.442 $(M-Boc+Na+4\ H)^+$; found 1036.055.

Acknowledgements

Thanks are due to Dr. Richard Goddard (Max-Planck-Institut für Kohlenforschung, Mülheim/Ruhr, Germany) for the X-ray intensity data collection of *rac*-**3**. MT thanks the Evonik Foundation for a Ph.D. scholarship, RWS would like to thank Professor William S. Sheldrick for generous support.

Supplementary data

^{13}C NMR spectra of compounds **2**, **2a**, **3**, **3a**, **4**, **4a**, **5**, **5a**, **6**, **6a**, **7**, **8**, **9**, **10** and **11**; TOCSY, HMQC and HMBC spectra of compounds **12** and **13**; tables of ^{13}C chemical shifts of **12** and **13**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.08.066.

References and notes

1. (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173–180; (b) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893–4012; (c) Goodman, C. M.; Choi, S.; Shandler, S.; DeGrado, W. F. *Nat. Chem. Biol.* **2007**, *3*, 252–262.
2. (a) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodiv.* **2004**, *1*, 1111–1239; (b) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232.
3. (a) Huc, I. *Eur. J. Org. Chem.* **2004**, 17–29; (b) Delsuc, N.; Godde, F.; Kauffmann, B.; Léger, J.-M.; Huc, I. *J. Am. Chem. Soc.* **2007**, *129*, 11348–11349; (c) Gallmeier, C.; König, B. *Eur. J. Org. Chem.* **2003**, 3473–3483; (d) Cernovska, K.; Kemter, M.; Gallmeier, H.-C.; Rzepecki, P.; Schrader, T.; König, B. *Org. Biomol. Chem.* **2004**, *2*, 1603–1611; (e) Gothard, C. M.; Rao, N. A.; Nowick, J. S. *J. Am. Chem. Soc.* **2007**, *129*, 7272–7273; (f) Khasanova, T. V.; Khakshoor, O.; Nowick, J. S. *Org. Lett.* **2008**, *10*, 5293–5296; (g) Plante, J.; Campbell, F.; Malkova, B.; Kilner, C.; Warriner, S. L.; Wilson, A. J. *Org. Biomol. Chem.* **2008**, *1*, 138–146; (h) Gothard, C. M.; Nowick, J. S. *J. Org. Chem.* **2010**, *75*, 1822–1830.
4. Feigel, M.; Ladberg, R.; Engels, S.; Herbst-Irmer, R.; Fröhlich, R. *Angew. Chem.* **2006**, *118*, 5827–5831; *Angew. Chem., Int. Ed.* **2006**, *45*, 5698–5702.
5. Tamai, Y.; Qian, P.; Matsunaga, K.; Miyano, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 817–823.
6. Hocke, H.; Uozumi, Y. *Tetrahedron* **2003**, *59*, 619–630.
7. Even though it has been observed in Ref. 6 that the double esterification is suppressed using the sterically demanding pivaloyl chloride; the 2,2′-dipivalate was occasionally obtained during our preparations. The structure of the dipivalate has been analysed by X-ray crystallography: Thoss, M.; Seidel, R. W.; Feigel, M. *Acta Crystallogr.* **2009**, *E65*, o243.
8. The compounds **1**, **2**, **2a**, **3**, **4** and **5a** have been isolated and characterized in both enantiomeric forms, compounds **3a**, **4a**, **5** and **6a** are described as the (*S*) enantiomer in the experimental part and compound **6** as the (*R*) enantiomer. The L-amino acid/Bna hybrides **7**, **9** and **10** have been characterized with (*R*)-chiral binaphthyl groups, the compounds **8** and **11** with (*S*) binaphthyl groups.
9. Hu, H.-Y.; Xiang, J.-F.; Yang, Y.; Chen, C.-F. *Org. Lett.* **2008**, *10*, 69–72.
10. Allen, F. H. *Acta Crystallogr.* **2002**, *B58*, 380–388.
11. Bernstein, J.; Davis, R. E.; Shimoni, L.; Chang, N.-L. *Angew. Chem.* **1995**, *107*, 1689–1708; *Angew. Chem., Int. Ed.* **1995**, *34*, 1555–1573.
12. (a) Wissmann, H.; Kleiner, H. J. *Angew. Chem.* **1980**, *92*, 129–130; *Angew. Chem., Int. Ed.* **1980**, *19*, 133–134; (b) Escher, R.; Bünning, P. *Angew. Chem.* **1986**, *98*, 264–265; *Angew. Chem., Int. Ed.* **1986**, *108*, 277–278.
13. Blessing, R. H. *Acta Crystallogr.* **1995**, *A51*, 33–38.
14. Spek, A. L. *Acta Crystallogr.* **2009**, *D65*, 148–155.
15. Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.

16. (a) Mazaleyrat, J.-P.; Gaucher, A.; Wakselman, M.; Tchertanov, L.; Guilhem, J. *Tetrahedron Lett.* **1996**, *37*, 2971–2974; (b) Mazaleyrat, J.-P.; Wright, K.; Gaucher, A.; Wakselman, M.; Oancea, S.; Formaggio, F.; Toniolo, T.; Setnička, V.; Kapitán, J.; Keiderling, T. A. *Tetrahedron: Asymmetry* **2003**, *14*, 1879–1893.
17. (a) Gaucher, A.; Bintein, F.; Wakselman, M.; Mazaleyrat, J.-P. *Tetrahedron Lett.* **1998**, *39*, 575–578; (b) Gaucher, A.; Dutot, L.; Barbeau, O.; Wakselman, M.; Mazaleyrat, J.-P.; Peggion, C.; Oancea, S.; Formaggio, F.; Crisma, M.; Toniolo, C. *Tetrahedron: Asymmetry* **2006**, *17*, 30–39.
18. HOBt: (a) Miyazawa, T.; Otomatsu, T.; Fukui, Y.; Yamada, T.; Kuwata, S. *J. Chem. Soc., Chem. Commun.* **1988**, 419–420; (b) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397–4398; DMAP: Takeda, K.; Ayabe, A.; Suzuki, M.; Konda, Y.; Harigaya, Y. *Synthesis* **1991**, 689–691; DIC: Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*, 2nd ed.; Springer: Berlin, 1994.