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Dehydro-β-amino Acid Containing Peptides as Promising Sequences for Drug Development

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In the course of a program devoted to the synthesis of small peptidic molecules mimicking the RGD (Arg-Gly-Asp) motif, the allylic amination of enantiomerically pure carbonates with 4-substituted benzylamines afforded dehydro-β-amino esters through an S_N2' mechanism. The reaction performed with 4-aminobenzylamine occurred with complete chemoselectivity, as the aliphatic amine was much more reactive than the aromatic one. This allowed useful precursors of biologically active compounds to be obtained, avoiding extra protection–deprotection steps. The same reaction performed on glycine-derived amides gave similar results, allowing a novel type of RGD mimetic to be prepared, whose ability to inhibit cell adhesion was found to be very promising.

Introduction

Over the last few years, extensive studies have been undertaken regarding the synthesis of unusual amino acids.[1] Design and synthesis of new enantiopure nonproteinogenic amino acids represent a central issue for chemists working in the wide areas of pharmaceutical and medicinal chemistry.[2] Among them, unsaturated β-amino acids have attracted high interest as valuable intermediates in the synthesis of dehydropeptides, allowing the preparation of conformationally constrained sequences, with improved biological activity and selectivity.[3] The design of receptor-selective peptide and peptidomimetic ligands with highly specific biological properties has become one of the most important areas in bioorganic and medicinal chemistry.[4] In fact, at present there is a rapid growth in the number of biologically active peptides under investigation. In the course of our drug development program, we became interested in the synthesis of small peptidic molecules mimicking the RGD (Arg-Gly-Asp) motif, present in a wide number of extracellular matrix (ECM) proteins.[5] These ligands bind to $\alpha_v\beta_3$ and $\alpha_5\beta_1$ integrins, a large family of heterodimeric transmembrane glycoproteins, involved in the pathogenesis of several diseases, such as atheroschlerosis, osteoporosis, cancer and a variety of inflammatory disorders.[6] The recognition sequence binds to the receptor mainly through electrostatic interactions with regions in the protein having opposite charges: Arg interacts with two Asp situated in the α unit of the protein and Asp with a metal cation.[7]

Several research groups have been recently interested in the development of small constrained nonpeptidic molecules, mimicking the RGD motif, whose enhanced bioavailability could result in more promising drugs. We envisaged the dehydro-β-amino acid as a rigid core that may be easily linked to appendages corresponding to arginine and aspartic acid side chains.

Recently, we reported a practical regio- and stereoselective synthesis of dehydro-β-amino esters through amination of racemic and enantiomerically pure allylic carbonates.[8] The uncatalyzed reaction, carried out with benzylamine as nucleophile, proceeds by an S_N2' mechanism. In contrast, the palladium-catalyzed reaction shows a strong solvent-dependent regiocontrol, affording exclusively one of the two possible regioisomers with complete transfer of chirality from the starting substrate to the product (Figure 1).

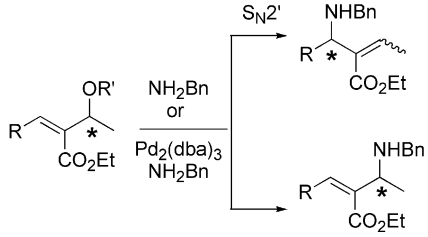

Figure 1. Synthesis of dehydro-β-amino esters through amination of racemic and enantiomerically pure allylic carbonates.

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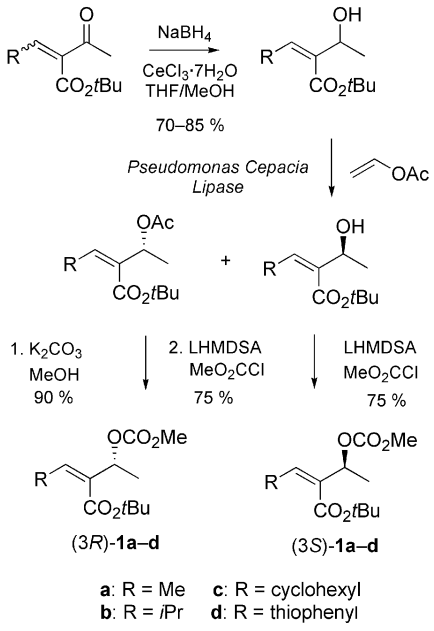
Results and Discussion

We present here the development of the previously reported results obtained by investigating the behaviour of bifunctionalized nucleophiles and appropriate acceptors under S_N2' conditions with the aim to synthesize valuable intermediates for potential RGD mimetic compounds. The starting materials were prepared by treatment of aldehydes with *tert*-butyl acetoacetate (1.5 equiv.) in the presence of proline (0.5 equiv.), as catalyst for the Knoevenagel reaction,[9] in DMSO whilst stirring at room temperature for 16 h. Under these conditions, 80:20 mixtures of *Z*/*E* ketones were obtained in about 80% yield. The two stereoisomers were easily separated by flash chromatography. In an alternative way, the reaction was carried out under microwave-assisted conditions, affording similar results.[10]

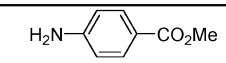
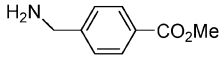
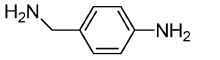
The reduction of ketones to alcohols, their resolution with lipase from *Pseudomonas Cepacia* and their transformation into the corresponding methyl carbonates were carried out following the procedure already reported by us (Scheme 1).[10]



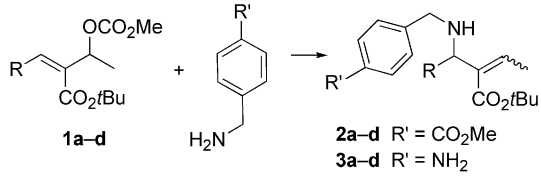
Scheme 1. Synthesis of enantiomerically pure allylic carbonates **1a**–**d**.

In our initial experiments to displace the carbonate from racemic starting material, we used methyl 4-aminobenzoate in CH_3CN at reflux. The substitution reaction did not occur due to the low reactivity of the selected aromatic amine (Table 1, Entry 1). On changing the nucleophile with methyl 4-aminomethyl-benzoate in refluxing CH_3CN (Scheme 2), the corresponding dehydro-β-amino esters **2a**–**d** were obtained in good yield and complete regioselectivity (Table 1, Entries 2–5). The reaction was followed by TLC and stopped with the disappearance of the starting material; the products were isolated and purified by flash chromatography on silica gel.

Table 1. Amination reaction on compounds **1a**–**d**.

Entry	Substrate	Nucleophile	Product	Time[a] [d]	Yield[b] [%]
1	**1a**		–	4	–
2	**1a**		**2a**	4	45
3	**1b**	"	**2b**	4	70
4	**1c**	"	**2c**	4	65
5	**1d**	"	**2d**	4	35
6	**1a**		**3a**	3	62
7	**1b**	"	**3b**	3	65
8	**1c**	"	**3c**	3	62
9	**1d**	"	**3d**	3	63

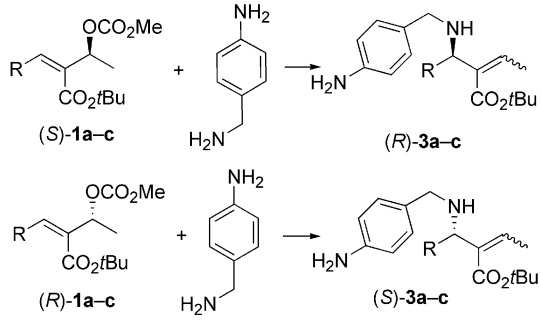
[a] Reaction carried out in refluxing CH_3CN. [b] Configuration *Z*/*E* of the double bond 3:1. Yield of product purified by flash chromatography on silica gel.



Scheme 2. Reaction of carbonates **1a**–**d** with 4-substituted benzylamines.

The regiochemistry of the products was easily assigned on the basis of their ^1H NMR spectra and accounts for nucleophilic displacement occurring by an S_N2' mechanism. The good reactivity of the benzylamine function prompted us to use 4-aminomethylaniline as a nucleophile in refluxing CH_3CN. Under these conditions, compounds **3a**–**d** were isolated in 62–65% yield by flash chromatography on silica gel (Table 1, Entries 6–9).

Although a long reaction time was required to convert the starting material into the products, regioisomers **3a**–**d** were exclusively obtained, confirming the lower reactivity of the aromatic amine relative to that of the aliphatic one. Following the same protocol on chiral nonracemic (*R*)- or (*S*)-**1a**–**c**, compounds (*R*)- or (*S*)-**3a**–**c** were obtained with complete regio- and stereoselectivity (Scheme 3, Table 2).



Scheme 3. Reaction on enantiomerically pure carbonates **1a**–**c**.

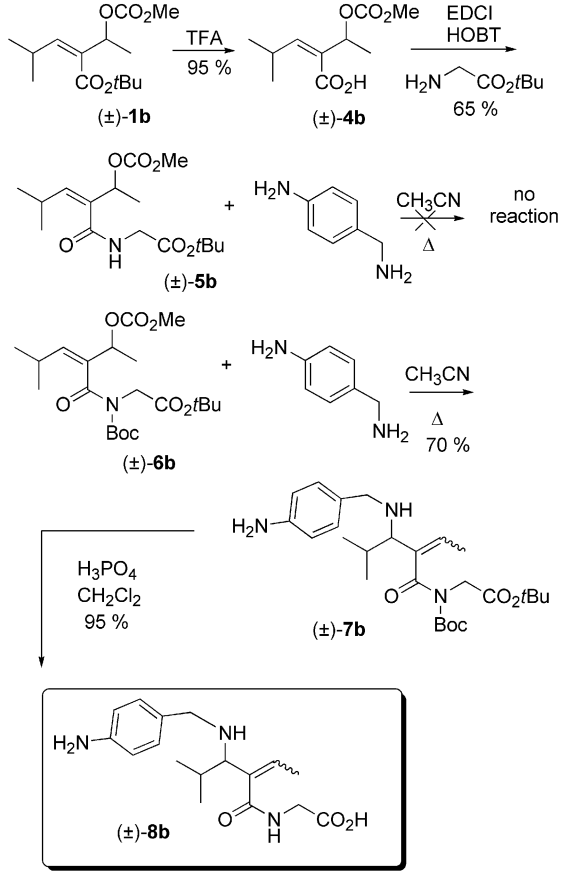
Table 2. Reaction of enantiomerically pure carbonates **1a**–**c** with 4-aminomethylaniline.[a]

Entry	Substrate	Product	Yield[b] [%]	*ee*[c] [%]
1	(*S*)-**1a**	(*R*)-**3a**	65	>99
2	(*R*)-**1a**	(*S*)-**3a**	63	>99
3	(*S*)-**1b**	(*R*)-**3b**	60	>99
4	(*R*)-**1b**	(*S*)-**3b**	65	>99
5	(*S*)-**1c**	(*R*)-**3c**	63	>99
6	(*R*)-**1c**	(*S*)-**3c**	60	>99

[a] Reaction carried out in refluxing CH_3CN. [b] Configuration *Z*/*E* of the double bond 3:1. Yield of product purified by flash chromatography on silica gel. [c] Determined by HPLC analysis on a chiral column.

The enantiomeric excess values of the isolated products (Table 2) were determined by HPLC analysis on a chiral column and confirmed complete transfer of chirality of the starting carbonates to the dehydroamino esters. The stereochemistry of the products was unequivocally attributed on the basis of previously reported research.[8]

Finally, we tried to perform the substitution reaction directly on amide **5b** to obtain a peptidic sequence mimicking the RGD integrin ligand. The amide was prepared in two steps as reported in Scheme 4. By treatment of **1b** with trifluoroacetic acid, the corresponding acid **4b** was obtained in 95% yield. The presence of the methyl carbonate and *tert*-butyl ester allowed the orthogonal deprotection of one of the two moieties by selecting either basic or acidic conditions.



Scheme 4.

Compound **4b** was coupled with glycine *tert*-butyl ester to afford amide **5b**. The S_N2' displacement of the carbonate function with 4-aminomethylaniline in refluxing CH_3CN failed and the unreacted starting material was recovered almost quantitatively (Scheme 4). To enhance the reactivity of the amide by reducing the backdonation of nitrogen, an electron-withdrawing *tert*-butyl carbamate group was introduced onto the amide nitrogen, giving **6b** in quantitative yield. This substrate was much more reactive and could be converted into the corresponding amino derivative **7b** by nucleophilic substitution with 4-aminomethylaniline under the above-reported conditions. Finally, simultaneous acidolysis of the *tert*-butyl ester and of the Boc protection with H_3PO_4 in dichloromethane,[11] followed by treatment with Dowex 50WX2–200 ion exchange resin, eluting with NH_4OH 0.5 M, and removal of the aqueous solvent under vacuum, afforded **8b** in almost quantitative yield. The ability of this new ligand to inhibit integrin-mediated cell adhesion gave promising results, having an IC_{50} value in the micromolar range. On this basis, a library of derivatives will be prepared and structure–activity relationship studies will be performed and reported in due course.

Conclusions

In the course of a program devoted to the synthesis of small peptidic molecules mimicking the RGD (Arg-Gly-Asp) motif, the allylic amination of enantiomerically pure carbonates with 4-substituted benzylamines afforded dehydro-β-amino esters by an S_N2' mechanism. The reaction performed with 4-aminobenzylamine occurred with complete chemoselectivity, as the aliphatic amine was much more reactive than the aromatic one. This allowed useful precursors of biologically active compounds to be obtained, avoiding extra protection–deprotection steps. The same reaction performed on glycine-derived amides gave similar results, allowing a novel type of RGD mimetic to be prepare, whose ability to inhibit cell adhesion was very promising.

Experimental Section

General: All chemicals were purchased from commercial suppliers and used without further purification. Anhydrous solvents were purchased in sureseal bottles over molecular sieves and used without further drying. Flash chromatography was performed on silica gel (230–400 mesh). DOWEX® 50WX2–200(H) ion-exchange resin was used for purification of free amino acids or free amines. NMR spectra were recorded with Varian Gemini 200, Mercury Plus 400 or Unity Inova 600 MHz spectrometers. Chemical shifts are reported as δ values (ppm) relative to the solvent peak of $CDCl_3$ set at δ = 7.27 ppm (^{1}H NMR) or at δ = 77.0 ppm (^{13}C NMR) or of CD_3OD set at δ = 3.31 ppm (^{1}H NMR) or at δ = 49.0 ppm (^{13}C NMR). Coupling constant are given in Hz. The enantiomeric excess values of the products were determined by HPLC analyses performed with an HP1100 instrument with a UV/Vis detector and

equipped with a Chiralcel ADcolumn (25 × 0.46 cm), eluted with *n*-hexane/2-propanol. Optical rotations were measured with a Perkin–Elmer 343 polarimeter by using a 1-dm cuvette and are referenced to the Na-D line value. Melting points were determined with a Stuart Scientific SMP3 apparatus and are uncorrected. Compounds **1a**–**d** were prepared following a literature procedure.[8]

1a: Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45 (d, J = 6.6 Hz, 3 H, CH_3CHO), 1.51 [s, 9 H, OC(CH_3)$_3$], 1.99 (d, J = 7.2 Hz, 3 H, CH_3CHC), 3.76 (s, 3 H, CH_3OCO), 5.48 (q, J = 6.6 Hz, 1 H, CH$_3$CHO), 6.23 (q, J = 7.2 Hz, 1 H, CH$_3$CHC) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3 (CH_3), 20.0 (CH_3), 28.3 (3 CH_3), 54.6 (CH_3), 74.1 (CH), 81.3 (C), 134.4 (C), 135.8 (CH), 155.0 (C), 165.5 (C) ppm. (*S*)-**1a** $[\alpha]_D$ = –24.6 (c = 1, $CHCl_3$); (*R*)-**1a** $[\alpha]_D$ = +25.0 (c = 1, $CHCl_3$). LC–ESI-MS (r.t.): t_R = 9.77 min, m/z = 244 [M], 267 [M + Na]. $C_{12}H_{20}O_5$ (244.13): calcd. C 59.00, H 8.25; found C 59.09, H 8.28.

1b: Pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.01 (d, J = 6.6 Hz, 6 H, CH_3CHCH_3), 1.42 (d, J = 6.6 Hz, 3 H, CH_3CHO), 1.50 [s, 9 H, OC(CH_3)$_3$], 3.02–3.17 (m, 1 H, CH$_3$CHCH$_3$), 3.77 (s, 3 H, CH_3OCO), 5.46 (q, J = 6.6 Hz, 1 H, CH$_3$CHO), 5.84 (d, J = 9.6 Hz, 1 H, CHCHC) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.8 (CH_3), 22.5 (2 CH_3), 26.2 (CH), 28.1 (3 CH_3), 54.5 (CH_3), 74.0 (CH), 81.2 (C), 131.3 (C), 146.7 (CH), 155.0 (C), 165.6 (C) ppm. (*S*)-**1b** $[\alpha]_D$ = –30.0 (c = 1, $CHCl_3$); (*R*)-**1b** $[\alpha]_D$ = +28.9 (c = 1, $CHCl_3$). LC–ESI-MS (r.t.): t_R = 11.82 min, m/z = 272 [M], 295 [M + Na]. $C_{14}H_{24}O_5$ (272.16): calcd. C 61.74, H 8.88; found C 61.76, H 8.86.

1c: Pale yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.86–1.30 (m, 6 H, *cyclohexyl*), 1.39 (d, J = 6.2 Hz, 3 H, CH_3CHO), 1.47 [s, 9 H, OC(CH_3)$_3$], 1.66–1.79 (m, 4 H, *cyclohexyl*), 2.78 (m, CH cyclohexyl), 3.74 (s, 3 H, CH_3OCO), 5.43 (q, J = 6.2 Hz, 1 H, CH$_3$CHO), 5.83 (d, J = 9.4 Hz, 1 H, CHCHC) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.9 (CH_3), 25.5 (2 CH_2), 25.8 (CH_2), 28.1 (3 CH_3), 32.4 (2 CH_2), 37.7 (CH), 54.5 (CH_3), 74.0 (CH), 81.0 (C), 131.5 (C), 145.4 (CH), 154.8 (C), 165.5 (C) ppm. (*S*)-**1c** $[\alpha]_D$ = –25.2 (c = 1, $CHCl_3$); (*R*)-**1c** $[\alpha]_D$ = +26.7 (c = 1, $CHCl_3$). LC–ESI-MS (r.t.): t_R = 10.81 min, m/z = 312 [M], 335[M + Na]. $C_{17}H_{28}O_5$ (312.19): calcd. C 65.36, H 9.03; found C 65.51, H 9.05.

1d: Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.49 [s, 9 H, OC(CH_3)$_3$], 1.53 (d, J = 6.6 Hz, 3 H, CH_3CHO), 3.78 (s, 3 H, CH_3OCO), 5.51 (q, J = 6.6 Hz, 1 H, CH$_3$CHO), 6.72 (s, 1 H, CCHC), 7.14–7.31 (m, 3 H, *thiophenyl*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.1 (CH_3), 28.0 (3CH_3), 54.8 (CH_3), 75.3 (CH), 82.1 (C), 125.3 (CH), 126.5 (CH), 126.7 (CH), 128.2 (C), 133.2 (CH), 136.1 (C), 155.0 (C), 166.6 (C) ppm. LC–ESI-MS (r.t.): t_R = 10.59 min, m/z = 312 [M], 335[M + Na]. $C_{15}H_{20}O_5S$ (312.1): calcd. C 57.67, H 6.45, S 10.26; found C 57.85, H 6.44, S 10.29.

General Procedure for the Preparation of Dehydro-β-amino Esters 2a–d: To a stirred solution of carbonate **1a**–**d** (0.2 mmol) in dry CH_3CN (2 mL), under a nitrogen atmosphere, was added methyl 4-aminomethylbenzoate hydrochloride (1.5 equiv., 0.3 mmol, 61 mg) and triethylamine (1.5 equiv., 0.3 mmol, 42 μL). The solution was stirred at reflux for 4 d and then the solvent was removed under reduced pressure. The residue was diluted with ethyl acetate (10 mL) and washed twice with water (5 mL). The two phases were separated, the organic layer was dried with Na_2SO_4 and solvent was removed under reduced pressure. Compounds **2a**–**d** were isolated by flash chromatography on silica gel (cyclohexane/ethyl acetate, 95:5).

2a: Yield: 45%, 30 mg, isolated as a 3:1 mixture of *Z*/*E* isomers. ^{1}H NMR (200 MHz, $CDCl_3$) major isomer: δ = 1.29 (d, J = 7.0 Hz, 3 H, CH_3CHN), 1.46 [s, 9 H, OC(CH_3)$_3$], 1.64 (d, J = 7.4 Hz, 3 H, CH_3CHC), 2.45 (br. s, 1 H, NH), 3.54–3.79 (m, 3 H, CH_2Ph, NCHCH$_3$), 3.86 (s, 3 H, CH_3OCO), 6.77 (q, J = 7.4 Hz, 1 H, CCHCH$_3$), 7.36 (d, J = 8.4 Hz, 2 H, Ph), 7.94 (d, J = 8.6 Hz, 2 H, Ph) ppm. ^{1}H NMR (200 MHz, $CDCl_3$) minor isomer: δ = 1.23 (d, J = 6.6 Hz, 3 H, CH_3CHN), 1.48 [s, 9 H, OC(CH_3)$_3$], 1.88 (d, J = 7.4 Hz, 3 H, CH_3CHC), 3.31 (q, J = 6.6 Hz, 1 H, NCHCH$_3$), 5.85 (q, J = 7.4 Hz, 1 H, CCHCH$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) major isomer: δ = 13.7 (CH_3), 20.6 (CH_2), 28.3 (3 CH_3), 50.1 (CH_3), 51.1 (CH), 52.0 (CH_3), 80.6 (C), 128.0 (2 CH), 128.7 (C), 129.7 (2 CH), 136.0 (C), 137.7 (CH), 146.2 (C), 166.5 (C), 167.1 (C) ppm. LC–ESI-MS (r.t.): t_R = 11.04 min, m/z = 333 [m], 356 [M + Na]. $C_{19}H_{27}NO_4$ (333.19): calcd. C 68.44, H 8.16, N 4.20; found C 68.33, H 8.17, N 4.20.

2b: Yield: 70%, 51 mg, isolated as a 3:1 mixture of *Z*/*E* isomers. ^{1}H NMR (200 MHz, $CDCl_3$) major isomer: δ = 0.74 (d, J = 6.6 Hz, 3 H, CH_3CHCH$_3$), 1.12 (d, J = 6.6 Hz, 3 H, CH_3CHCH$_3$), 1.50 [s, 9 H, OC(CH_3)$_3$], 1.60 (d, J = 7.0 Hz, 3 H, CH_3CHC), 1.79–2.08 (m, 1 H, CH$_3$CHCH$_3$), 3.02 (d, J = 9.8 Hz, 1 H, CHCHN), 3.56 (d, J = 13.8 Hz, 1 H, NHCH_2Ph), 3.86 (d, J = 13.8 Hz, 1 H, NHCH_2Ph), 3.91 (s, 3 H, CH_3OCO), 6.92 (q, J = 7.0 Hz, 1 H, CCHCH$_3$), 7.43 (d, J = 8.0 Hz, 2 H, Ph), 7.98 (d, J = 8.0 Hz, 2 H, Ph) ppm. ^{1}H NMR (200 MHz, $CDCl_3$) minor isomer: δ = 0.83 (d, J = 6.6 Hz, 3 H, CH_3CHCH$_3$), 1.00 (d, J = 6.6 Hz, 3 H, CH_3CHCH$_3$), 1.93 (d, J = 7.0 Hz, 3 H, CH_3CHC), 2.68 (d, J = 8.4 Hz, 1 H, CHCHN), 5.72 (q, J = 7.0 Hz, 1 H, CCHCH$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) major isomer: δ = 13.7 (CH_3), 20.0 (2 CH_3), 27.9 (3 CH_3), 31.7 (CH), 50.1 (CH_2), 51.6 (CH_3), 61.3 (CH), 80.0 (C), 127.7 (2 CH), 128.3 (C), 129.2 (2 CH), 133.9 (C), 138.5 (CH), 146.5 (C), 166.5 (C), 166.7 (C) ppm. LC–ESI-MS (r.t.): t_R = 13.87 min, m/z = 361 [M], 362 [M + 1]. $C_{21}H_{31}NO_4$ (361.23): calcd. C 69.78, H 8.64, N 3.87; found C 69.75, H 8.62, N 3.88.

2c: Yield: 65%, 52 mg, isolated as a 3:1 mixture of *Z*/*E* isomers. ^{1}H NMR (200 MHz, $CDCl_3$) major isomer: δ = 1.13–1.36 (m, 4 H, *cyclohexyl*), 1.50 [s, 9 H, OC(CH_3)$_3$], 1.47–1.81 (m, 6 H, *cyclohexyl*), 1.59 (d, J = 7.2 Hz, 3 H, CH_3CHC), 2.40 (m, 1 H, CH cyclohexyl), 3.13 (d, J = 9.4 Hz, 1 H, CHCHN), 3.57 (d, J = 13.8 Hz, 1 H, NHCH_2Ph), 3.81 (d, J = 13.8 Hz, 1 H, NHCH_2Ph), 3.91 (s, 3 H, CH_3OCO), 6.92 (m, J = 7.2 Hz, 1 H, CCHCH$_3$), 7.43 (d, J = 8.2 Hz, 2 H, *Ph*), 7.98 (d, J = 8.2 Hz, 2 H, *Ph*) ppm. ^{1}H NMR (200 MHz, $CDCl_3$) minor isomer: δ = 1.92 (d, J = 7.0 Hz, 3 H, CH_3CHC), 2.72 (d, J = 8.8 Hz, 1 H, CHCHN), 5.68 (q, J = 7.0 Hz, 1 H, CCHCH$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) major isomer: δ = 13.9 (CH_3), 26.2 (CH_2), 26.3 (CH_2), 26.6 (CH_2), 28.2 (3 CH_3), 30.6 (CH_2), 31.6 (CH_2), 41.4 (CH), 50.6 (CH_2), 51.8 (CH_3), 60.0 (CH), 80.3 (C), 127.9 (2 CH), 128.4 (2 CH), 129.4 (CH), 133.6 (C), 138.8 (C), 146.7 (C), 166.8 (C), 167.1 (C) ppm. LC–ESI-MS (r.t.): t_R = 5.31 min, m/z = 401 [M], 424 [M + Na]. $C_{24}H_{35}NO_4$ (401.26): calcd. C 71.79, H 8.79, N 3.49; found C 71.83, H 8.78, N 3.48.

2d: Yield: 35%, 28 mg, isolated as a 3:1 mixture of *Z*/*E* isomers. ^{1}H NMR (200 MHz, $CDCl_3$) major isomer: δ = 1.34 [s, 9 H, OC(CH_3)$_3$], 1.75 (d, J = 7.2 Hz, 3 H, CH_3CHC), 2.56 (br. s, 1 H, NH), 3.77 (d, J = 13.8 Hz, 1 H, NHCH_2Ph), 3.90 (s, 3 H, CH_3OCO), 3.94 (d, J = 13.8 Hz, 1 H, NHCH_2Ph), 4.75 (s, 1 H, CHNH), 6.95–7.05 (m, 2 H, CCHCH$_3$, CH *thiophenyl*), 7.19–7.27 (m, 2 H, *thiophenyl*), 7.48 (d, J = 8.4 Hz, 2 H, *Ph*), 8.00 (d, J = 8.4 Hz, 2 H, *Ph*) ppm. ^{1}H NMR (200 MHz, $CDCl_3$) minor isomer: δ = 1.99 (d, J = 7.0 Hz, 3 H, CH_3CHC), 6.04 (q, J = 7.0 Hz, 1 H, CCHCH$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) major isomer: δ = 13.9 (CH_3), 28.1 (3 CH_3), 50.6 (CH_3), 52.1 (CH_2), 54.4 (CH), 80.8 (C), 120.3 (CH), 125.2 (CH), 126.8 (CH), 128.0 (2 CH), 128.9 (C), 129.7 (2 CH), 134.4 (C), 139.0 (CH), 144.2 (C), 146.1 (C), 166.4

(C), 167.1 (C) ppm. LC–ESI-MS (r.t.): t_R = 12.67 min, *m*/*z* = 401 [M], 424 [M + Na]. $C_{22}H_{27}NO_4S$ (401.17): calcd. C 65.81, H 6.78, N 3.49, S 7.99; found C 65.77, H 6.80, N 3.50, S 7.98.

General Procedure for the Preparation of Dehydro-β-amino Esters 3a–d: To a stirred solution of carbonate **1a–d** (0.2 mmol) in dry CH_3CN (2 mL), under a nitrogen atmosphere, was added 4-aminomethylaniline (1.5 equiv., 0.3 mmol, 34 μL). The solution was heated at reflux for 3 d and then the solvent was removed under reduced pressure. Compounds **3a–d** were isolated by flash chromatography on silica gel (cyclohexane/ethyl acetate, 85:15).

3a: Yield: 62–65%, 35–37 mg, isolated as a 3:1 mixture of *Z*/*E* isomers. ^{1}H NMR (200 MHz, $CDCl_3$) major isomer: δ = 1.47 (d, *J* = 6.8 Hz, 3 H, C*H*$_3$CHN), 1.49 [s, 9 H, OC(C*H*$_3$)$_3$], 1.73 (d, *J* = 7.4 Hz, 3 H, C*H*$_3$CHC), 3.52 (d, *J* = 12.6 Hz, 1 H, NHC*H*$_2$Ph), 3.68 (d, *J* = 12.6 Hz, 1 H, NHC*H*$_2$Ph), 3.81 (q, *J* = 6.8 Hz, 1 H, CH$_3$C*H*N), 6.59 (d, *J* = 8.4 Hz, 2 H, Ph), 6.93 (q, *J* = 7.4 Hz, 1 H, CC*H*CH$_3$), 7.16 (d, *J* = 8.4 Hz, 2 H, Ph) ppm. ^{1}H NMR (200 MHz, $CDCl_3$) minor isomer: δ = 1.37 (d, *J* = 6.8 Hz, 3 H, C*H*$_3$CHN), 1.95 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$CHC), 4.02 (q, *J* = 6.8 Hz, 1 H, CH$_3$C*H*N), 6.23 (q, *J* = 7.0 Hz, 1 H, CC*H*CH$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) major isomer: δ = 13.7 (CH_3), 20.6 (CH_3), 28.3 (3 CH_3), 49.9 (CH), 50.9 (CH_2), 80.5 (C), 115.2 (2 CH), 129.4 (2 CH), 130.5 (C), 136.3 (C), 137.7 (CH), 145.3 (C), 166.7 (C) ppm. (*S*)-**3a** $[\alpha]_D$ = –14.0 (*c* = 1, $CHCl_3$); (*R*)-**3a** $[\alpha]_D$ = +14.0 (*c* = 1, $CHCl_3$). HPLC (*n*-hexane/2-propanol, 99:1 to 96:4 over 30 min; 1.0 mL min^{-1}; AD column; r.t): t_R = 23.52 [(*R*)-**3a**], 26.12 min [(*S*)-**3a**]. LC–ESI-MS (r.t.): t_R = 8.39 min, *m*/*z* = 290 [M], 313 [M + Na]. $C_{17}H_{26}N_2O_2$ (290.2): calcd. C 70.31, H 9.02, N 9.65; found C 70.08, H 9.00, N 9.65.

3b: Yield: 60–65%, 38–41 mg, isolated as a 3:1 mixture of *Z*/*E* isomers. ^{1}H NMR (200 MHz, $CDCl_3$) major isomer: δ = 0.74 (d, *J* = 6.8 Hz, 3 H, C*H*$_3$CHCH$_3$), 1.10 (d, *J* = 6.8 Hz, 3 H, C*H*$_3$CHCH$_3$), 1.49 [s, 9 H, OC(C*H*$_3$)$_3$], 1.67 (d, *J* = 7.2 Hz, 3 H, C*H*$_3$CHC), 1.80–2.05 (m, 1 H, CH$_3$C*H*CH$_3$), 3.06 (d, *J* = 9.6 Hz, 1 H, CHC*H*N), 3.38 (d, *J* = 12.8 Hz, 1 H, NHC*H*$_2$Ph), 3.70 (d, *J* = 12.8 Hz, 1 H, NHC*H*$_2$Ph), 6.63 (d, *J* = 8.2 Hz, 2 H, *Ph*), 6.92 (q, *J* = 7.2 Hz, 1 H, CC*H*CH$_3$), 8.20 (d, *J* = 8.2 Hz, 2 H, *Ph*) ppm. ^{1}H NMR (200 MHz, $CDCl_3$) minor isomer: δ = 0.83 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$CHCH$_3$), 0.97 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$CHCH$_3$), 1.93 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$CHC), 2.77 (d, *J* = 8.6 Hz, 1 H, CHC*H*N), 5.77 (q, *J* = 7.0 Hz, 1 H, CC*H*CH$_3$) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) major isomer: δ = 14.0 (CH_3), 20.1 (2 CH_3), 28.3 (3 CH_3), 32.1 (CH), 50.7 (CH_2), 61.3 (CH), 80.2 (C), 114.9 (2 CH), 129.1 (2 CH), 131.1 (C), 134.4 (C), 138.7 (CH), 144.9 (C), 167.0 (C) ppm. (*S*)-**3b** $[\alpha]_D$ = –11.7 (*c* = 1, $CHCl_3$); (*R*)-**3b** $[\alpha]_D$ = +12.0 (*c* = 1, $CHCl_3$). HPLC (*n*-hexane/2-propanol, 99:1 to 90:10 over 30 min; 1.0 mL min^{-1}; AD column; r.t.): t_R = 10.39 [(*R*)-**3b**], 10.95 min [(*S*)-**3b**]. LC–ESI-MS (r.t.): t_R = 5.87 min, *m*/*z* = 318 [M], 341 [M + Na]. $C_{19}H_{30}N_2O_2$ (318.23): calcd. C 71.66, H 9.50, N 8.80; found C 71.52, H 9.51, N 8.83.

3c: Yield: 60–63%, 43–46 mg, isolated as a 3:1 mixture of *Z*/*E* isomers. ^{1}H NMR (200 MHz, $CDCl_3$) major isomer: δ = 1.07–1.27 (m, 4 H, *cyclohexyl*), 1.41–1.81 (m, 6 H, *cyclohexyl*), 1.50 [s, 9 H, OC(C*H*$_3$)$_3$], 1.65 (d, *J* = 7.2 Hz, 3 H, C*H*$_3$CHC), 2.36 (m, 1 H, C*H* cyclohexyl), 3.17 (d, *J* = 9.6 Hz, 1 H, CHC*H*N), 3.39 (d, *J* = 13.2 Hz, 1 H, NHC*H*$_2$Ph), 3.70 (d, *J* = 13.2 Hz, 1 H, NHC*H*$_2$Ph), 6.64 (d, *J* = 8.4 Hz, 2 H, *Ph*), 6.92 (q, *J* = 7.2 Hz, 1 H, CC*H*CH$_3$), 7.12 (d, *J* = 8.4 Hz, 2 H, *Ph*) ppm. ^{1}H NMR (200 MHz, $CDCl_3$) minor isomer: δ = 1.93 (d, *J* = 7.4 Hz, 3 H, C*H*$_3$CHC), 2.10 (m, 1 H, C*H* cyclohexyl), 2.80 (d, *J* = 8.8 Hz, 1 H, CHC*H*N), 3.41 (d, *J* = 12.8 Hz, 1 H, NHC*H*$_2$Ph), 3.72 (d, *J* = 12.8 Hz, 1 H, NHC*H*$_2$Ph), 5.73 (q, *J* = 7.4 Hz, 1 H, CC*H*CH$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) major isomer: δ = 13.9 (CH_3), 26.0 (CH_2), 26.2 (CH_2), 26.5 (CH_2), 28.0 (3 CH_3), 30.3 (CH_2), 31.4 (CH_2), 41.3 (CH), 50.2 (CH_2), 59.6 (CH), 80.2 (C), 114.8 (2 CH), 129.0 (2 CH), 130.3 (C), 133.5 (C), 138.9 (CH), 144.9 (C), 166.9 (C) ppm. (*S*)-**3c** $[\alpha]_D$ = –9.0 (*c* = 1, $CHCl_3$); (*R*)-**3c** $[\alpha]_D$ = +13.4 (*c* = 1, $CHCl_3$). HPLC (*n*-hexane/2-propanol, 99:1 to 90:10 over 30 min; 1.0 mL min^{-1}; AD column; r.t.): t_R = 12.44 [(*S*)-**3c**], 15.14 min [(*R*)-**3c**]. LC–ESI-MS (r.t.): t_R = 5.28 min, *m*/*z* = 358 [m], 381 [M + Na]. $C_{22}H_{34}N_2O_2$ (358.26): calcd. C 73.70, H 9.56, N 7.81; found C 73.83, H 9.54, N 7.83.

3d: Yield: 63%, 45 mg, isolated as a 3:1 mixture of *Z*/*E* isomers. ^{1}H NMR (200 MHz, $CDCl_3$) major isomer: δ = 1.35 [s, 9 H, OC(C*H*$_3$)$_3$], 1.82 (d, *J* = 7.4 Hz, 3 H, C*H*$_3$CHC), 3.61 (d, *J* = 13.0 Hz, 1 H, NHC*H*$_2$Ph), 3.78 (d, *J* = 13.0 Hz, 1 H, NHC*H*$_2$Ph), 4.81 (s, 1 H, C*H*NH), 6.66 (d, *J* = 8.4 Hz, 2 H, *Ph*), 6.96–7.06 (m, 2 H, CC*H*CH$_3$, C*H* *thiophenyl*), 7.13–7.26 (m, 4 H, 2 CH *thiophenyl* and 2 CH, *Ph*) ppm. ^{1}H NMR (200 MHz, $CDCl_3$) minor isomer: δ = 2.00 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$CHC), 4.51 (s, 1 H, C*H*NH), 6.09 (q, *J* = 7.0 Hz, 1 H, CC*H*CH$_3$) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) major isomer: δ = 14.1 (CH_3), 28.1 (3 CH_3), 50.6 (CH_2), 54.3 (CH), 80.7 (C), 115.2 (2 CH), 120.3 (CH), 125.0 (CH), 127.0 (CH), 129.4 (2 CH), 130.4 (C), 134.8 (C), 138.9 (CH), 144.6 (C), 145.4 (C), 166.6 (C) ppm. LC–ESI-MS (r.t.): t_R = 10.22 min, *m*/*z* = 358 [M], 381 [M + Na]. $C_{20}H_{26}N_2O_2S$ (358.17): calcd. C 67.01, H 7.31, N 7.81, S 8.94; found C 67.19, H 7.32, N 7.84, S 8.96.

Procedure for the Preparation of Acid 4b: To a stirred solution of carbonate **1b** (0.2 mmol) in CH_2Cl_2 (2 mL) at 0 °C, was added trifluoroacetic acid (15 equiv., 3 mmol, 223 μL). After 2 h, the mixture was washed twice with acidic water (5 mL), the organic layer was dried with Na_2SO_4, and the solvent was removed under reduced pressure. Compound **4b** was isolated in 95% yield (41 mg). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 5.4 Hz, 6 H, C*H*$_3$CHC*H*$_3$), 1.40 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$CHO), 3.25–3.42 (m, 1 H, CH$_3$C*H*CH$_3$), 3.70 (s, 3 H, C*H*$_3$OCO), 5.46 (q, *J* = 6.6 Hz, 1 H, CH$_3$C*H*O), 6.11 (d, *J* = 10.0 Hz, 1 H, CHC*H*C), 10.41 (br. s, 1 H, OCO*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.1 (CH_3), 21.9 (2 CH_3), 31.8 (CH), 54.4 (CH_3), 73.3 (CH), 128.9 (C), 142.5 (CH), 154.7 (C), 171.4 (C) ppm. LC–ESI-MS (r.t.): t_R = 6.65 min, *m*/*z* = 216 [M], 239 [M + Na]. $C_{10}H_{16}O_5$ (216.1): calcd. C 55.55, H 7.46; found C 55.59, H 7.49.

Procedure for the Preparation of Amide 5b: To a stirred solution of acid **4b** (0.2 mmol) in dry CH_2Cl_2 (2 mL), under a nitrogen atmosphere, was added EDCI (1.2 equiv., 0.24 mmol, 46 mg) and triethylamine (2.4 equiv., 0.48 mmol, 67 μL). After 30 min, HOBT (1.2 equiv., 0.24 mmol, 33 mg) and glycine *tert*-butyl ester hydrochloride (1.2 equiv., 0.24 mmol, 41 mg) were added. The solution was stirred overnight, and then the mixture was diluted with CH_2Cl_2 and washed twice with acidic water (5 mL) and twice with basic water (5 mL). The two phases were separated, the organic layer was dried with Na_2SO_4 and the solvent was removed under reduced pressure. Compound **5b** was isolated in 65% yield (43 mg) after flash chromatography on silica gel (cyclohexane/ethyl acetate, 80:20). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 6.6 Hz, 6 H, C*H*$_3$CHC*H*$_3$), 1.45 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$CHO), 1.49 [s, 9 H, OC(C*H*$_3$)$_3$], 2.70–2.88 (m, 1 H, CH$_3$C*H*CH$_3$), 3.79 (s, 3 H, C*H*$_3$OCO), 4.00 (d, *J* = 4.8 Hz, 2 H, NHC*H*$_2$), 5.27 (q, *J* = 6.6 Hz, 1 H, CH$_3$C*H*O), 5.67 (d, *J* = 10.2 Hz, 1 H, CHC*H*C), 6.57 (br. t, 1 H, N*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.9 (CH_3), 22.7 (2 CH_3), 26.8 (CH), 28.0 (3 CH_3), 41.9 (CH_2), 54.8 (CH_3), 76.0 (CH), 82.2 (C), 131.8 (C), 137.3 (CH), 155.1 (C), 167.3 (C), 168.8 (C) ppm. LC–ESI-MS (r.t.): t_R = 10.82 min, *m*/*z* = 329 [M], 352 [M + Na]. $C_{16}H_{27}NO_6$ (329.18): calcd. C 58.34, H 8.26, N 4.25; found C 58.31, H 8.24, N 4.25.

Procedure for the Preparation of the *N*-Boc-protected Amide 6b: To a stirred solution of amide **5b** (0.2 mmol) in dry THF (1 mL) was added DMAP (0.2 equiv., 0.04 mmol, 5 mg), triethylamine (1.2 equiv., 0.24 mmol, 34 μL) and $(Boc)_2O$ (1.3 equiv., 0.26 mmol, 60 μL). The solution was stirred overnight, and then the solvent was removed under reduced pressure. The residue was diluted with ethyl acetate (10 mL) and washed twice with water (5 mL). The two phases were separated, the organic layer was dried with Na_2SO_4 and the solvent was removed under reduced pressure. Compound **6b** was isolated in 90% yield (77 mg) by flash chromatography on silica gel (cyclohexane/ethyl acetate, 95:5). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.99 (d, J = 6.6 Hz, 6 H, CH_3CHCH_3), 1.42 (d, J = 6.6 Hz, 3 H, CH_3CHO), 1.48 [s, 18 H, OC(CH_3)$_3$], 2.41–2.49 (m, 1 H, CH_3CHCH_3), 3.75 (s, 3 H, CH_3OCO), 4.28 (d, J = 16.8 Hz, 1 H, NCH_2), 4.45 (d, J = 16.8 Hz, 1 H, NCH_2), 5.42–5.53 (m, 2 H, CH_3CHO, CHC*H*C) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.2 (CH_3), 22.6 (2 CH_3), 27.2 (CH), 27.8 (3 CH_3), 28.0 (3 CH_3), 45.9 (CH_2), 54.5 (CH_3), 74.7 (CH), 81.8 (C), 83.8 (C), 126.7 (C), 137.6 (CH), 151.4 (C), 155.1 (C), 167.6 (C), 169.8 (C) ppm. LC–ESI-MS (r.t.): t_R = 12.26 min, m/z = 429 [M], 452 [M + Na]. $C_{21}H_{35}NO_8$ (429.24): calcd. C 58.72, H 8.21, N 3.26; found C 58.61, H 8.19, N 3.27.

Procedure for the Preparation of Amino Derivative 7b: To a stirred solution of amide **6b** (0.2 mmol) in dry CH_3CN (2 mL), under a nitrogen atmosphere, was added 4-aminomethylaniline (1.5 equiv., 0.3 mmol, 34 μL). The solution was heated at reflux for 16 h, and then the solvent was removed under reduced pressure. Compound **7b** was isolated in 70% yield (66 mg) by flash chromatography on silica gel (cyclohexane/ethyl acetate, 95:5). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.83 (d, J = 6.6 Hz, 6 H, CH_3CHCH_3), 1.42 (d, J = 7.4 Hz, 3 H, CH_3CHC), 1.47 [s, 18 H, OC(CH_3)$_3$], 2.60–2.81 (m, 1 H, CH_3CHCH_3), 3.59 (br. s, 2 H, NH_2), 3.83–3.98 (m, 3 H, NCH_2, C*H*NH), 4.34–4.61 (m, 2 H, CH_2Ph), 6.61 (d, J = 8.0 Hz, 2 H, *Ph*), 6.83 (q, J = 7.4 Hz, 1 H, CC*H*CH$_3$), 7.01 (d, J = 8.0 Hz, 2 H, *Ph*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.5 (CH_3), 20.2 (2 CH_3), 28.1 (3 CH_3), 28.5 (3 CH_3), 31.8 (CH), 42.2 (CH_2), 47.3 (CH), 50.1 (CH_2), 79.8 (C), 82.1 (C), 115.0 (2 CH), 127.9 (2 CH), 130.7 (C), 131.3 (C), 139.6 (CH), 144.9 (C), 156.0 (C), 169.1 (C), 169.9 (C) ppm. LC–ESI-MS (r.t.): t_R = 9.15 min, m/z = 475 [M], 498 [M + Na]. $C_{26}H_{41}N_3O_5$ (475.3): calcd. C 65.66, H 8.69, N 8.83; found C 65.55, H 8.71, N 8.80.

Procedure for the Preparation of Amino Acid 8b: To a stirred solution of compound **7b** (0.2 mmol) in CH_2Cl_2 (0.5 mL) was added H_3PO_4 85% (5 equiv., 1 mmol, 69 μL). After 3 h the solvent was removed under reduced pressure, and the crude compound was treated with Dowex 50WX2–200 ion-exchange resin, eluting with 0.5M NH_4OH. Compound **8b** was isolated after removal of the aqueous solvent in 95% yield (61 mg). ^{1}H NMR (200 MHz, CD_3OD) major isomer: δ = 0.93 (d, J = 6.6 Hz, 6 H, CH_3CHCH_3), 1.82 (d, J = 7.2 Hz, 3 H, CH_3CHC), 2.18–2.28 (m, 1 H, CH_3CHCH_3), 3.83–4.38 (m, 5 H, C*H*NH, NHCH_2, CH_2Ph), 6.74 (d, J = 8.4 Hz, 2 H, *Ph*), 6.90 (q, J = 7.2 Hz, 1 H, CC*H*CH$_3$), 7.21 (d, J = 8.4 Hz, 2 H, *Ph*) ppm. ^{1}H NMR (200 MHz, CD_3OD) minor isomer: δ = 2.06 (d, J = 7.2 Hz, 3 H, CH_3CHC), 6.06 (q, J = 7.2 Hz, 1 H, CC*H*CH$_3$) ppm. ^{13}C NMR (50 MHz, CD_3OD) major isomer: δ = 14.3 (CH_3), 19.9 (2 CH_3), 31.9 (CH), 46.9 (CH_2), 50.9 (CH_2), 62.4 (CH), 116.3 (2 CH), 121.1 (C), 128.8 (CH), 132.0 (2 CH), 140.7 (C), 148.5 (C), 161.6 (C), 178.2 (C) ppm. LC–ESI-MS (r.t.): t_R = 1.06 min, m/z = 319 [M], 342 [M + Na]. $C_{17}H_{25}N_3O_3$ (319.19): calcd. C 63.93, H 7.89, N 13.16; found C 63.99, H 7.90, N 13.11.

Supporting Information (see footnote on the first page of this article): ^{1}H NMR spectra of compounds **1a**–**d**, **2a**–**d** and **3a**–**d**.

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