

# Synthesis of a new family of 2-ethylidene- $\gamma$ -unsaturated $\delta$ -amino esters via microwave activated Stille coupling

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**Abstract** A simple approach to a new family of enantiomerically enriched polyunsaturated *t*-Boc-protected- $\delta$ -amino esters is described, via microwave promoted Stille coupling of (*Z*)-methyl-2-bromobutenoate with stannylated allylamines. The reaction conditions are mild and selective and disclose a simple way to 1-substituted butenoates of defined geometry.

**Keywords** Amino acids ·  $\delta$ -Amino esters · Stille coupling · Acrylates · Microwave

## Introduction

Peptidomimetics are valuable tools for conformational investigations of bioactive peptides and proteins, and for the development of peptide leads for pharmaceuticals (Olson et al. 1993; Bursavich and Rich 2002; Hanessian et al. 1997). In particular, the replacement of the peptide amidic moiety with a chemically more resistant and in vivo stable functionality is an important research area in medicinal chemistry. In recent years, many non-hydrolysable mimetics have been developed and among the others the relatively rigid tri-substituted (*E*)-alkene  $\Psi$  [(*E*)-C(R) = CH] isosters have been used in a number of

enzyme inhibitors or antibiotics (Wipf et al. 2005; Garbe et al. 2004; Tamamura et al. 2003; Yang et al. 1999).

Basically, in many cases, the isosteric replacement of a dipeptide unit requires the preparation of a  $\delta$ -amino acid. Very recently, this class of compounds has stimulated a great interest since, as in the homologous  $\beta$ - and  $\gamma$ -peptides, conformational analysis of  $\delta$ -peptides revealed a considerable potential of secondary structure formation (Sengupta et al. 2006; Baldauf et al. 2006; Ananda et al. 2005; Baldauf et al. 2004). In particular, it has been shown that the elongation of the backbone of the amino acid constituents might enrich the field of folded structures and for this reason  $\delta$ -peptides and  $\delta$ -amino acids are considered a useful tool also in peptides and foldamers design and in material sciences (Hill et al. 2001; Baldauf et al. 2005). For these reasons, we envisaged unsaturated  $\delta$ -amino acids as those reported in Fig. 1, bearing an ethylidenic conjugated double bond, as an interesting class of new molecules that could be exploited, for instance, as rigid spacers (Chen et al. 1995; Georgsson et al. 2005; Douat-Casassus et al. 2007) and as Michael acceptor-binding sites for the design of new enzyme inhibitors (Johnson et al. 2002; Steindl et al. 2005). To the best of our knowledge, this class of compounds has not been reported so far.

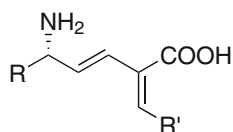
## Results and discussion

Stemming from our interest in the use of naturally occurring amino acids as building blocks for organic synthesis (Reginato et al. 1999; 2005a, b; Ciardi et al. 2007; Reginato et al. 2007) we were particularly attracted by the possibility of designing a new and flexible method to prepare orthogonally protected polyunsaturated- $\delta$ -amino esters such as **3** (Scheme 1). Key intermediates in our

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**Fig. 1** 2-ethylidene-gamma-unsaturated delta-amino esters



approach were chiral *t*-Boc-protected stannylallyl amines **1**, which are easily accessible from amino acids using standard procedures developed in our laboratories (Reginato et al. 1996). These compounds are versatile synthons, and can be coupled with several electrophiles under Pd catalysis (Stille conditions) to afford a wide range of  $\gamma$ -substituted allyl amines **4** (Reginato et al. 1996), or dienyl amines **5** (Reginato et al. 2005a, b) (Scheme 1). This protocol is mild, stereospecific, highly chemoselective and suitable for chiral substrates (Reginato et al. 1997, 1998, 2000).

Accordingly, we envisaged that  $\delta$ -amino esters **3** could be simply obtained using 2-bromo-alkenoates **2** as coupling partners. Although 1-alkenyl halides are probably the most widely used organic electrophiles in Stille coupling (Farina et al. 1998), to our knowledge 2-bromoalkenoates have never been employed before, thus, to select the best experimental conditions, we decided to perform some model reactions. We used stannylallylamine **1a** and the commercially available (*E*)-methyl-2-bromobutenoate **2a** as coupling partners (Scheme 2). The reaction was performed in DMF with the commonly used  $\text{Pd}(\text{PPh}_3)_4$  as catalyst and the anticipated amino ester **3a** was actually recovered in 55% yield after 24 h at 80°C. The use of a different catalyst such as  $\text{Pd}(\text{AsPh}_3)_4$  (Reginato et al. 2005a, b) or a higher reaction temperature did not improve the final yield.

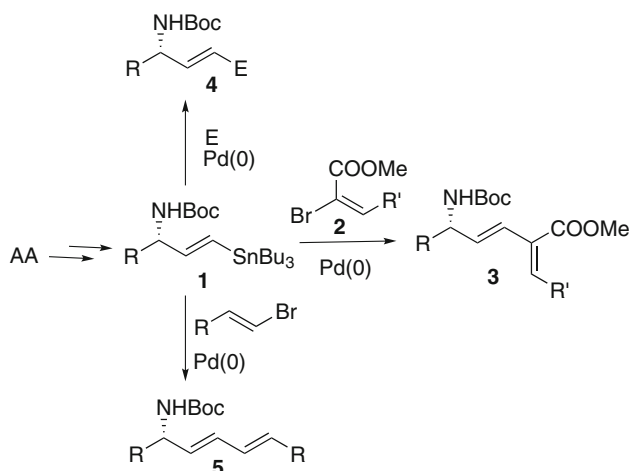
Over the past few years, the efficiency of microwave flash heating in accelerating cross-coupling reactions has been successfully demonstrated and very fast Stille

reactions have been achieved in solution as well as on solid phase (Larhed et al. 2002; Maleczka et al. 2000). Thus, to improve the yields and find milder reaction conditions, we decided to investigate the effect of microwave irradiation on our coupling process, and we were pleased to find that under optimized conditions, namely at 80°C, with a 200 W microwave source for 30 min in toluene, the reaction led to quantitative conversion of stannane **1a**.  $^1\text{H}$  NMR analysis of the crude mixtures showed that no isomerization of the double bonds occurred as exclusively the anticipated isomer **3** having *E*, *Z* geometry was recovered and, after workup and chromatography, isolated in 76% yield.

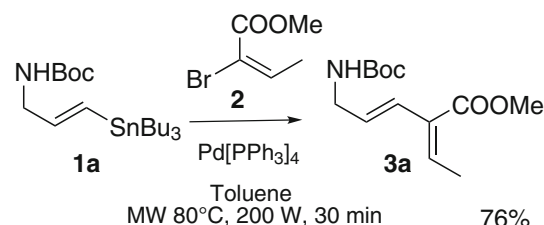
Substituted acrylate fragments are valuable building blocks in organic chemistry participating in many asymmetric transformations; however, few good routes exist to prepare even simple 1-substituted species (Biswas et al. 2005; Mani et al. 2006). To exploit the generality of this reaction, three different stannanes (**6–8**) were used and the results obtained clearly show that the formation of 1-substituted butenoates (**9–11**) always occurs smoothly (Table 1, entries 1–3). Finally, the same reaction conditions were applied to a range of three different chiral non-racemic stannylallyl amines (**1b–d**) derived, respectively, from phenylalanine, valine and leucine and the corresponding  $\delta$ -amino esters (**3a–d**) were recovered in good yields after purification (Table 1, entries 4–6).

It is known that the synthetic elaboration of dipeptides can be challenging because of their sensitivity (Diaz and Ferreira 2001). To verify if our reaction condition were mild enough to be used also with such substrates, we prepared dipeptido stannane **12** according to a reported procedure (Reginato et al. 2005a, b). Once again the expected coupling compound **13** (Scheme 3) was obtained in good yield, after purification.

It is remarkable that compound **13** was obtained as a single diastereoisomer as both  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra showed no peaks due to epimerization at the  $\delta$ -carbon of the amino ester moiety, thus confirming that no racemization of the starting material or isomerization of the double bond occurred. Finally, to demonstrate that  $\delta$ -amino esters **3** are capable of undergoing typical reactions associated with peptide synthesis, *t*-Boc-aminoester **3a** was

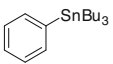
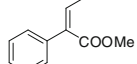
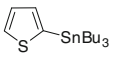
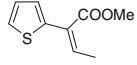
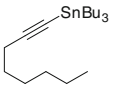
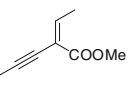
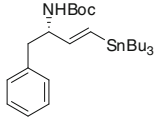
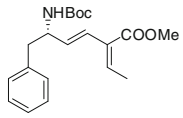
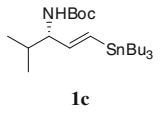
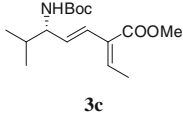
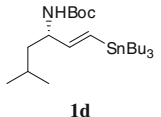
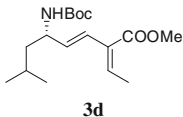


**Scheme 1** Stille coupling of stannylallyl amines with electrophiles



**Scheme 2** Optimized conditions for the coupling of stannylallylamine **1** with methyl-2-bromo-butenoate

**Table 1** MW activated coupling of **2** with stannanes

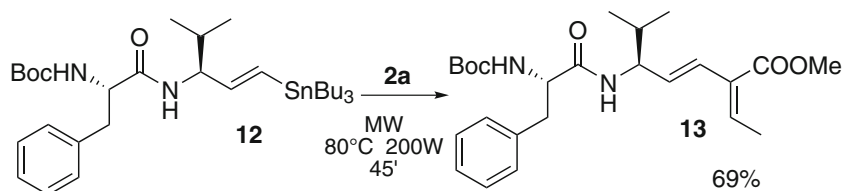
| Entry | Stannane <sup>a)</sup>                                                             | Product                                                                            | Isolated yield |
|-------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|----------------|
| 1     |   |   | 75%            |
|       | <b>6</b>                                                                           | <b>9</b>                                                                           |                |
| 2     |   |   | 68%            |
|       | <b>7</b>                                                                           | <b>10</b> <sup>b)</sup>                                                            |                |
| 3     |   |   | 72%            |
|       | <b>8</b>                                                                           | <b>11</b>                                                                          |                |
| 4     |   |   | 66%            |
|       | <b>1b</b>                                                                          | <b>3b</b>                                                                          |                |
| 5     |   |   | 81%            |
|       | <b>1c</b>                                                                          | <b>3c</b>                                                                          |                |
| 6     |  |  | 70%            |
|       | <b>1d</b>                                                                          | <b>3d</b>                                                                          |                |

<sup>a</sup> Reaction conditions: toluene, [Pd(PPh<sub>3</sub>)<sub>4</sub>] cat; MW, 80°C, 200 W, 30 min

<sup>b</sup> Reaction time: 50 min

deprotected with TFA and the free amine **14** was coupled with *t*-Boc-phenylalanine using DEPC/DIEA (diethylcyano-phosphonate/diisopropylethylamine) procedure. After purification, the expected dipeptide **15** was indeed obtained in 79% yield (Scheme 4).

In summary, we have shown that organostannanes can be coupled with the commercially available (*E*)-methyl-2-bromobutenoate in mild conditions under MW activation. The procedure discloses an easy access to (*Z*)-1-substituted butenoates and has been applied to chiral stannylated allyl amines derived from naturally occurring amino acids

**Scheme 3** Coupling of dipeptido stannane **12** with methyl-2-bromo-butenolate

or dipeptides to obtain a novel family of polyunsaturated  $\delta$ -amino esters which were previously unreported.

## Experimental

### General

Stannanes **1a–d** (Reginato et al. 1996) **8** (Dabdoub et al. 2001) and **12** (Reginato et al. 2005a, b) were synthesized according to the published procedure. [Pd(PPh<sub>3</sub>)<sub>4</sub>] was freshly prepared and stored under nitrogen atmosphere. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without purification. All air-sensitive reactions were performed using Schlenk techniques. Tetrahydrofuran was freshly distilled immediately prior to use from sodium/benzophenone. Toluene and DMSO were dried over sodium and stored under nitrogen over 4-Å molecular sieves. Petroleum ether, unless specified, is 40–60°C boiling fraction. Reactions were monitored by TLC on SiO<sub>2</sub> plates, detection was made using a KMnO<sub>4</sub> basic solution. Flash column chromatography was performed using glass columns (10–50 mm wide) and SiO<sub>2</sub> (230–400 mesh). <sup>1</sup>H-NMR spectra were recorded with 200 or 400 MHz spectrometers. <sup>13</sup>C-NMR spectra were recorded at 50.3 or 100.6 MHz. Chemical shifts were determined relative to the residual solvent peak (CHCl<sub>3</sub>,  $\delta$  7.26 ppm for <sup>1</sup>H-NMR; CHCl<sub>3</sub>,  $\delta$  77.0 ppm for <sup>13</sup>C-NMR). Coupling constants (*J*) were reported in Hertz. Polarimetric measurements were performed in CHCl<sub>3</sub> solution at  $\lambda$  = 589 nm, the temperature was specified case by case.

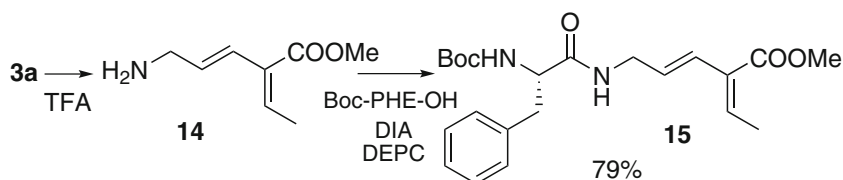
The mass spectra were recorded under electronic impact conditions (EIMS) at 70 eV ionizing potential.

All microwave irradiation experiments were carried out using a CEM Focused Microwave<sup>TM</sup> Synthesis System, Model Discover microwave oven equipped with an infrared temperature control system. All microwave reactions were performed in sealed 10 mL microwave vials.

General procedure for cross-coupling reaction with methyl 2-bromo-but-2-enoic carboxylate

Methyl-2-bromo-but-2-enoic carboxylate **2** (2 eq) was dissolved in toluene together with a catalytic amount of Pd(PPh<sub>3</sub>)<sub>4</sub> (0.05 eq). Stannane **1a–d** (1 eq) was then added and the mixture heated to 80°C by microwave irradiation at

**Scheme 4** Deprotection and coupling with Boc-PHE-OH of delta-amino ester



200 W (value previously settled on the Microwave oven) for 30 min or 1 h depending on the substrate. The solution was diluted with ether and treated with a NaOH (1 M) solution. The mixture was filtered, extracted with ether and the organic phase washed with brine and dried. The crude product obtained after evaporation was purified by flash chromatography.

*(E)-5-tert-Butoxycarbonylamino-2-eth-(Z)-ylidene-pent-3-enoic acid methyl ester 3a*

Methyl-2-bromo-but-2-enoic carboxylate **2** (70 mg, 0.4 mmol) was dissolved into toluene (1 mL) together with Pd(PPh<sub>3</sub>)<sub>4</sub> (23 mg, 0.02 mmol) and stannane **1a** (115 mg, 0.3 mmol). The mixture was heated to 80°C by microwave irradiation for 30 min. After work-up and purification (petroleum ether–AcOEt = 4:1), 58 mg of pure **3a** were obtained as a colorless oil (yield 76%). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 6.82 (q, 1H, *J* = 7.3 Hz); 6.30–6.22 (d<sub>app</sub>, 1H, *J*<sub>AB</sub> = 16.4 Hz); 6.09–5.98 (dt<sub>app</sub>, 1H, *J*<sub>AB</sub> = 16.4 Hz, *J* = 5.9 Hz); 4.63 (bs, 1H); 3.88–3.80 (m, 2H); 3.74 (s, 3H); 1.85 (d, 3H, *J* = 7.3 Hz); 1.42 (s, 9H). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>): δ: 166.7; 155.7; 148.1; 132.2; 128.9; 122.5; 79.9; 51.9; 42.5; 28.2; 14.6. MS *m/z* 199 (29); 57(100). Elemental analysis: found: C, 61.22; H, 8.26; N, 5.51. Calc. for C<sub>13</sub>H<sub>21</sub>NO<sub>4</sub>: C, 61.16; H, 8.29; N 5.49.

*(5S)-(E)-5-tert-butoxycarbonylamino-2-eth-(Z)-ylidene-6-phenyl-hex-3-enoic acid methyl ester 3b*

Methyl-2-bromo-but-2-enoic carboxylate **2** (270 mg, 1.5 mmol) was dissolved into toluene (3 mL) together with Pd(PPh<sub>3</sub>)<sub>4</sub> (60 mg, 0.05 mmol) and stannane **1b** (527 mg, 1.0 mmol). The mixture was heated to 80°C by microwave irradiation for 45 min. After work-up and purification (petroleum ether–AcOEt = 5:1), 228 mg of pure **3b** were obtained as a pale yellow oil (yield 66%). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 7.41–7.10 (m, 5H); 6.78 (q, 1H, *J* = 7.4 Hz); 6.21–6.13 (d<sub>app</sub>, 1H, *J*<sub>AB</sub> = 16.0 Hz); 6.07–5.96 (dd<sub>app</sub>, 1H, *J*<sub>AB</sub> = 16.0 Hz, *J* = 5.4 Hz); 4.61–4.38 (m, 2H); 3.72 (s, 3H); 2.88–2.84 (m, 2H); 1.81 (d, 3H, *J* = 7.4 Hz); 1.40 (s, 9H). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>): δ: 166.4; 155.1; 138.5; 137.3; 134.8; 130.1; 129.6; 128.2; 126.4; 122.0; 79.4; 53.9; 51.6; 41.7; 28.3; 14.6. MS *m/z* 289 (3); 57(100). Elemental analysis: found: C, 69.57; H,

7.90; N, 4.01. Calc. for C<sub>20</sub>H<sub>27</sub>NO<sub>4</sub>: C, 69.54; H, 7.88; N, 4.05 [ $\alpha$ ]<sub>D</sub><sup>23</sup> = −5.1 (*c* = 0.84, CHCl<sub>3</sub>).

*(5S)-(E)-5-tert-butoxycarbonylamino-2-eth-(Z)-ylidene-7-methyl-oct-3-enoic acid methyl ester 3c*

Methyl-2-bromo-but-2-enoic carboxylate **2** (133 mg, 0.7 mmol) was dissolved into toluene (2 mL) together with Pd(PPh<sub>3</sub>)<sub>4</sub> (30 mg, 0.025 mmol) and stannane **1c** (250 mg, 0.5 mmol). The mixture was heated to 80°C by microwave irradiation for 45 min. After work-up and purification (petroleum ether–AcOEt = 5:1), 126 mg of pure **3c** were obtained as a pale yellow oil (yield 81%). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 6.81 (q, 1H, *J* = 7.4 Hz); 6.29–6.22 (d<sub>app</sub>, 1H, *J*<sub>AB</sub> = 15.9 Hz); 6.01–5.90 (dd<sub>app</sub>, 1H, *J*<sub>AB</sub> = 15.9 Hz, *J* = 6.2 Hz); 4.42 (bs, 1H); 4.26–4.07 (m, 1H); 3.74 (s, 3H); 1.89 (d, 3H, *J* = 7.4 Hz); 1.79–1.52 (m, 2H); 1.44–1.33 (m, 1H); 1.43 (s, 9H); 0.92 (d, 3H, *J* = 6.6 Hz); 0.91 (d, 3H, *J* = 6.6 Hz). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>): δ: 167.5; 155.3; 138.2; 136.2; 130.3; 121.1; 79.3; 51.6; 51.4; 44.8; 28.4; 24.8; 22.6; 22.5; 14.7. MS *m/z* 198 (6); 57(100). Elemental analysis: found: C, 65.60; H, 9.41; N, 4.37. Calc. for C<sub>17</sub>H<sub>29</sub>NO<sub>4</sub>: C, 65.57; H, 9.39; N, 4.50. [ $\alpha$ ]<sub>D</sub><sup>23</sup> = −20.8 (*c* = 0.77, CHCl<sub>3</sub>).

*(5S)-(E)-tert-butoxycarbonylamino-2-eth-(Z)-ylidene-6-methyl-hept-3-enoic acid methyl ester 3d*

Methyl-2-bromo-but-2-enoic carboxylate **2** (186 mg, 1.0 mmol) was dissolved into toluene (2 mL) together with Pd(PPh<sub>3</sub>)<sub>4</sub> (35 mg, 0.03 mmol) and stannane **1d** (352 mg, 0.7 mmol). The mixture was heated to 80°C by microwave irradiation for 45 min. After work-up and purification (petroleum ether–AcOEt = 6:1), 144 mg of pure **3d** were obtained as a pale yellow oil (yield 70%). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 6.80 (q, 1H, *J* = 7.4 Hz); 6.27–6.19 (d<sub>app</sub>, 1H, *J*<sub>AB</sub> = 16.0 Hz); 6.01–5.90 (dd<sub>app</sub>, 1H, *J*<sub>AB</sub> = 16.0 Hz, *J* = 6.4 Hz); 4.53 (bs, 1H); 4.11–3.94 (m, 1H); 3.73 (s, 3H); 1.88 (d, 3H, *J* = 7.4 Hz); 1.87–1.70 (m, 1H); 1.44 (s, 9H); 0.93 (d, 3H, *J* = 2.19 Hz); 0.89 (d, 3H, *J* = 2.19 Hz). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>): δ: 167.5; 155.5; 138.1; 134.3; 130.4; 122.4; 79.3; 58.3; 51.6; 32.7; 28.4; 18.7; 18.3; 14.6. MS *m/z* 198 (38); 57(100). Elemental analysis: found: C, 64.57; H, 9.11; N, 4.69. Calc. for C<sub>16</sub>H<sub>27</sub>NO<sub>4</sub>: C, 64.62; H, 9.15; N, 4.71. [ $\alpha$ ]<sub>D</sub><sup>23</sup> = −9.0 (*c* = 1.25, CHCl<sub>3</sub>).

*(Z)*-2-phenyl-but-2-enoic acid methyl ester **9**

Methyl-2-bromo-but-2-enoic carboxylate **2** (85 mg, 0.5 mmol) was dissolved into toluene (1 mL) together with Pd(PPh<sub>3</sub>)<sub>4</sub> (21 mg, 0.02 mmol) and stannane **6** (110 mg, 0.3 mmol). The mixture was heated to 80°C by microwave irradiation for 30 min. After work-up and purification (petroleum ether–AcOEt = 5:1) 41 mg of pure **9** were obtained as a colorless oil (yield 75%). Spectroscopic data were in agreement with those reported in the literature (Mani et al. 2006).

*(E)*-2-thiophen-2-yl-but-2-enoic acid methyl ester **10**

Methyl-2-bromo-but-2-enoic carboxylate **2** (70 mg, 0.4 mmol) was dissolved into toluene (1 mL) together with Pd(PPh<sub>3</sub>)<sub>4</sub> (25 mg, 0.02 mmol) and stannane **7** (150 mg, 0.4 mmol). The mixture was heated to 80°C by microwave irradiation for 50 min. After work-up and purification (petroleum ether–AcOEt = 5:1) 51 mg of pure **10** was obtained as a pale yellow oil (yield 68%). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$  7.37 (d, 1H,  $J$  = 5.1 Hz); 7.23 (q, 1H,  $J$  = 7.3 Hz); 7.07–7.03 (m, 1H); 6.97 (d, 1H,  $J$  = 3.7 Hz); 3.77 (s, 3H); 1.91 (d, 3H,  $J$  = 7.3 Hz). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>):  $\delta$  167.1; 142.0; 135.2; 128.3; 127.8; 126.1; 126.3; 52.2; 15.9. MS  $m/z$  182 (90); 123 (100). Elemental analysis: found: C, 59.37; H, 5.57. Calc. for C<sub>9</sub>H<sub>10</sub>O<sub>2</sub>S, C, 59.32; H, 5.53.

*(E)*-2-ethylidene-dec-3-ynoic acid methyl ester **11**

Methyl-2-bromo-but-2-enoic carboxylate **2** (70 mg, 0.4 mmol) was dissolved into toluene (1 mL) together with Pd(PPh<sub>3</sub>)<sub>4</sub> (25 mg, 0.02 mmol) and stannane **8** (80 mg, 0.2 mmol). The mixture was heated to 80°C by microwave irradiation for 30 min. After work-up and purification (petroleum ether–AcOEt = 30:1) 31 mg of pure **11** were obtained as a pale yellow oil (yield 72%). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$  7.22 (q, 1H,  $J$  = 7.1 Hz); 3.77 (s, 3H); 2.42 (t, 2H,  $J$  = 6.7 Hz); 2.00 (d, 3H,  $J$  = 7.1 Hz); 1.34–1.17 (m, 8H); 0.92 (t, 5H,  $J$  = 6.2 Hz). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>):  $\delta$  166.1; 147.3; 130.9; 118.2; 98.0; 51.2; 31.3; 29.4; 28.7; 22.7; 19.7; 16.6; 14.1. Elemental analysis: found: C, 75.02; H, 9.91. Calc. for C<sub>13</sub>H<sub>20</sub>O<sub>2</sub>, C, 74.96; H, 9.68.

*(5S)*-(*E*)-[*(2S)*-2-tert-butoxycarbonylamino-3-phenylpropionylamino]-2-eth-(*Z*)-ylidene-6-methyl-hept-3-enoic acid methyl ester **13**

Methyl-2-bromo-but-2-enoic carboxylate **2** (74 mg, 0.4 mmol) was dissolved into toluene (1 mL) together with Pd(PPh<sub>3</sub>)<sub>4</sub> (35 mg, 0.03 mmol) and stannane **12** (100 mg,

0.2 mmol). The mixture was heated to 80°C by microwave irradiation for 45 min. After work-up and purification (petroleum ether–AcOEt = 6:1) 63 mg of pure **13** were obtained as a pale yellow oil (69%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.22–7.12 (m, 5H); 6.73 (q, 1H,  $J$  = 7.3 Hz); 6.42 (bs, 1H); 6.12 (d, 1H,  $J_{AB}$  = 16.0 Hz); 6.14–6.10 (dd<sub>app</sub>, 1H,  $J_{AB}$  = 16.0 Hz,  $J$  = 6.8 Hz); 5.03–4.90 (m, 1H); 4.20–3.90 (m, 1H); 4.32–4.15 (m, 1H); 3.66 (s, 3H); 3.01–2.96 (m, 2H); 1.78 (d, 3H,  $J$  = 7.2 Hz); 1.71–1.63 (m, 1H); 1.33 (s, 9H); 0.82 (d, 3H,  $J$  = 6.5 Hz); 0.91 (d, 3H,  $J$  = 6.5 Hz). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>):  $\delta$  170.3; 166.3; 155.4; 138.5; 136.7; 134.8; 132.9; 129.3; 128.6; 123.4; 80.2; 56.9; 56.3; 51.7; 38.2; 32.4; 28.3; 18.7; 18.2; 14.7. MS  $m/z$  388 (2); 91 (76), 57(100). Elemental analysis: found: C, 67.58; H, 8.21; N, 6.27. Calc. for C<sub>25</sub>H<sub>36</sub>N<sub>2</sub>O<sub>5</sub>: C, 67.54; H, 8.16; N, 6.30.  $[\alpha]_D^{23}$  = –13.0 ( $c$  = 1.25, CHCl<sub>3</sub>).

*(E)*-5-[*(2S)*-2-tert-butoxycarbonylamino-3-phenylpropionylamino]-2-eth-(*Z*)-ylidene-pent-3-enoic acid methyl ester **15**

Amino ester **3a** (50 mg, 0.22 mmol) was dissolved into CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and, after cooling at –10°C, reacted with TFA (0.5 mL). After 15 min, the solvent was evaporated to give the deprotected amino acid **14** which was immediately reacted with Boc-Phe-OH (58 mg, 0.22 mmol) and diisopropylamine (67 mg, 0.7 mmol) and diethylcyanophosphonate (54 mg, 0.33 mmol). The reaction mixture was stirred overnight, then diluted with ethyl acetate (5 mL) and an NH<sub>4</sub>Cl saturated solution (5 mL). After extraction, evaporation and purification (petroleum ether–AcOEt = 5:1) 76 mg of **15** were obtained (yield 79%). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$  7.30–7.26 (m, 2H); 7.23–7.19 (m, 3H); 6.82 (q, 1H,  $J$  = 7.4 Hz); 6.21–6.17 (d<sub>app</sub>, 1H,  $J_{AB}$  = 16.0 Hz); 5.98–5.89 (m, 1H + 1H); 5.04 (bs, 1H); 4.35–4.27 (m, 1H); 3.92–3.88 (m, 2H); 3.74 (s, 3H); 3.10–3.01 (m, 2H); 1.86 (d, 3H,  $J$  = 7.0 Hz); 1.39 (m, 9H). <sup>13</sup>C NMR (50.3 MHz, CDCl<sub>3</sub>):  $\delta$  170.8; 167.2; 155.3; 138.9; 136.6; 130.2; 129.8; 129.2; 128.6; 126.9; 123.9; 80.2; 56.1; 51.8; 41.8; 38.7; 28.3; 14.8. MS  $m/z$  402 (1); 346 (3); 57(100). Elemental analysis: found: C, 65.70; H, 7.49; N, 6.98. Calc. for C<sub>22</sub>H<sub>30</sub>N<sub>2</sub>O<sub>5</sub>: C, 65.65; H, 7.51; N, 6.96.  $[\alpha]_D^{23}$  = –0.32 ( $c$  = 1.05, CHCl<sub>3</sub>).

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