Tetrahedron 66 (2010) 5030–5035

Contents lists available at ScienceDirect

Tetrahedron

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

Use of the Claisen/metathesis reaction sequence for the synthesis of enantiomerically pure 1-aminocycloalkene-1-carboxylic acids

Karen Plé *, Arnaud Haudrechy, Nicolas P. Probst

Institut de Chimie Moléculaire de Reims, CNRS 6229, UFR Sciences, Bât 18, BP 1039, 51687 Reims Cedex 2, France

ARTICLE INFO

Article history:
Received 5 January 2010
Received in revised form 3 May 2010
Accepted 4 May 2010
Available online 11 May 2010

Keywords:
Rearrangement
Asymmetric Synthesis
Amino acids
Synthetic methods

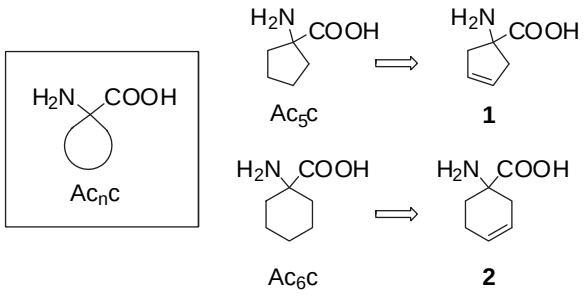
ABSTRACT

An effective method for the preparation of enantiomerically pure 1-aminocycloalkene-1-carboxylic acids is reported using a chelate Claisen rearrangement–metathesis sequence. Enantioselectivity is achieved through substrate control and a highly ordered transition state, without the use of a chiral auxiliary. A synthesis of 1-aminocyclopent-3-ene-1-carboxylic acid **1** in five steps and 47% overall yield is also described.

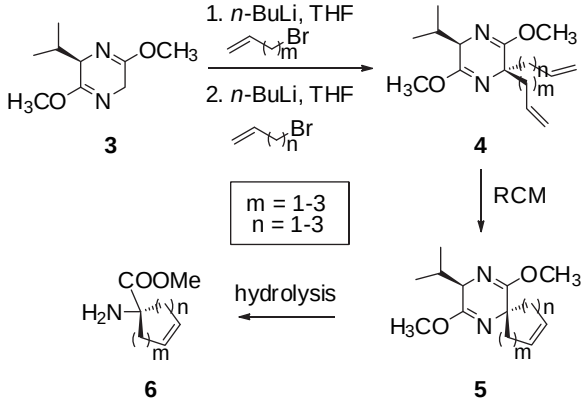
1. Introduction

The incorporation of α-quaternary amino acids into peptides has been extensively used to modify secondary as well as tertiary peptide structures.[1–3] These modified peptides are useful tools that can be used to probe the molecular structure of receptors or even enhance the biological activity of the parent peptide by imposing a pre-determined spatial conformation. The introduction of constrained cyclic α-quaternary amino acids can further rigidify the system and give analogues with well defined backbone conformations. As a result, much effort has been devoted to the synthesis of different cyclic α-quaternary amino acids.[4,5] Among these, the 1-aminocycloalkane-1-carboxylic acids (Ac_nc, *n*=ring size, Scheme 1) are one of the simplest cyclic derivatives which, when introduced in a peptide sequence, significantly modify its secondary structure. 1-Aminocyclo*alkene*-1-carboxylic acids have proven to be synthetically useful intermediates for the preparation of Ac_nc acids and their derivatives. Appropriate functionalization of the double bond could also lead to analogues which, when incorporated into peptides, could further modify their elementary structure or biological activity.

In the case of 1-aminocyclopent-3-ene-1-carboxylic acid **1**, the configuration of the amino acid is irrelevant because of the existing C2 symmetry plane in the molecule. In larger unsymmetrical ring



Scheme 1.



Scheme 2.

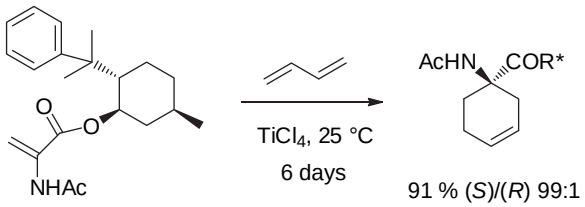
* Corresponding author. Tel.: +33 3 26 91 33 07; fax: +33 3 26 91 31 66; e-mail address: karen.ple@univ-reims.fr (K. Plé).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.05.008

systems however, few methods exist, which give specific control of this chiral center. The enantioselective synthesis of 1-aminocycloalkene-1-carboxylic acids has been reported using the Schöllkopf methodology.[6,7] Stereoselective alkylation of the bislactim **3** followed by RCM and hydrolysis gave the desired 1-aminocycloalkene-1-carboxylic acid methyl esters **6** (Ac_nc, n=5–7) in overall yields ranging from 16 to 42% (Scheme 2).[8,9]

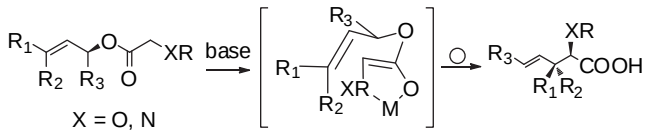
This sequence proved to be highly substrate dependent with difficulties occurring in the RCM step (n=5) and in the sluggish hydrolysis of the chiral auxiliary (3–8 days). More recently, this methodology has been applied to the synthesis of spiro-2,5-diketopiperazines, where improvements were made using microwave irradiation.[10]

In the particular case of the cyclohexene amino acid derivative **2**, an enantioselective Diels–Alder reaction was described with a dehydroalanine derivative and butadiene.[11] Esterification of the starting dehydroalanine with a chiral auxiliary in the presence of trimethyl aluminum followed by Lewis acid catalyzed cycloaddition gave the desired cyclic quaternary amino acid in varying yields and selectivity. The best results were observed with (−)-8-phenylmenthol after 6 days in the presence of $TiCl_4$ (Scheme 3).



Scheme 3.

We have recently shown that the chelate Claisen/metathesis reaction sequence can be applied to the diastereoselective synthesis of quaternary hydroxy and amino acid carbocycles.[12] The excellent diastereoselectivity observed is a result of the highly ordered six-member chairlike transition state and the use of a chiral allylic alcohol in the starting ester. The α-heteroatom stabilizes the enolate through a five-member chelate ring, resulting in almost exclusive formation of a (*Z*)-enolate (Scheme 4).[13] An extremely efficient chirality transfer occurs from the carbinol center to the newly formed stereocenters at C2 and C3 of the acid product.



Scheme 4.

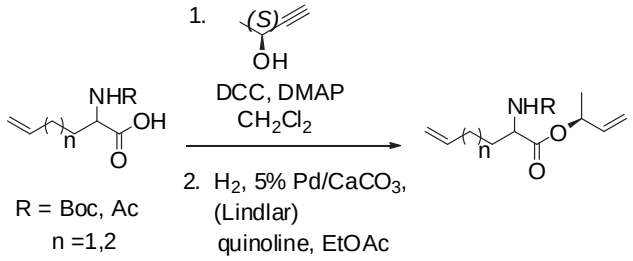
This methodology has been described for the enantioselective synthesis of tertiary amino acids as part of the synthesis of Chlamydocin[14] or cylindrospermopsin alkaloids,[15] as well as simple tertiary and quaternary amino acids.[16]

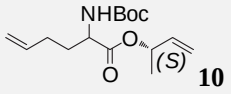
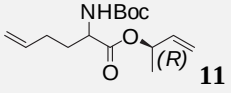
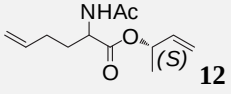
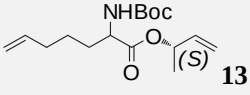
In order to further demonstrate the efficiency of the chelate Claisen/metathesis reaction sequence, the enantioselective synthesis of several 1-aminocycloalkene-1-carboxylic esters based on a highly effective 1,4-chirality transfer is presented. The enantioselectivity of the reaction is controlled by the stereogenic center of the simple chiral allylic alcohol precursor, and either enantiomer can be obtained based on the configuration of the starting alcohol. An alternative route for the preparation of 1-aminocyclopent-3-ene-1-carboxylic acid (**1**)[17–28] is also described.

2. Results and discussion

The commercially available (*R*) or (*S*)-but-3-yn-2-ol (98% ee) served as the starting point for the synthesis of the desired esters. Esterification was performed using standard DCC coupling techniques, and Lindlar reduction of the triple bond led to the protected amino esters in good to excellent yields (Table 1).

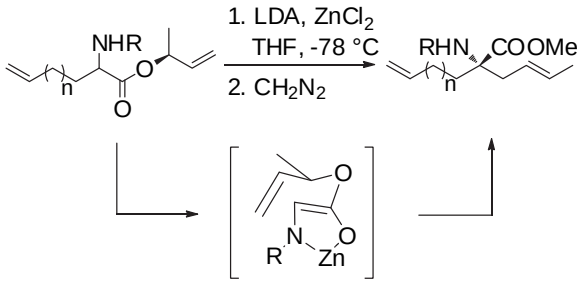
Table 1
Ester synthesis

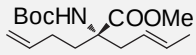
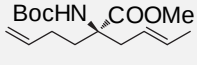
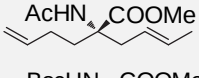
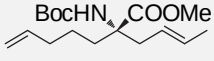


Alcohol	Acid	Ester	Yield (%)
	n=1, R=Boc (**7**)	 **10**	63
	n=1, R=Boc (**7**)	 **11**	69
	n=1, R=Ac (**8**)	 **12**	57
	n=2, R=Boc (**9**)	 **13**	59

The resulting products (**10**–**13**) were then treated with LDA in the presence of zinc(II) chloride to give, after esterification with diazomethane, the rearranged esters (Table 2).

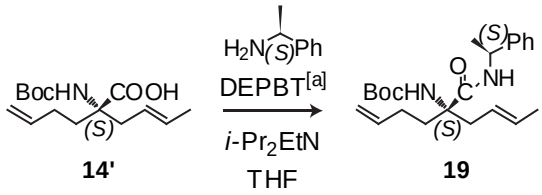
Table 2
Chelate Claisen rearrangement



Ester	Quaternary amido ester	Yield (%)
10, n=1, R=Boc	 **14**	63
11, n=1, R=Boc	 **15**	68
12, n=1, R=Ac	 **16**	84
13, n=2, R=Boc	 **17**	71

In order to evaluate the enantioselectivity of the reaction, the crude chiral acids **14′** and **15′** were coupled to both (*R*) and (*S*)-methylbenzyl amine (≥99% ee) (Table 3). These amides were then compared with those formed using the racemic acid **18**.

Table 3
Chiral amide formation



Acid	Amine	Amide
BocHN COOH (S) **14'**	H_2N(R)Ph	(R)Ph, O, NH, BocHN, (S) **20**
	H_2N(S)Ph	(S)Ph, O, NH, BocHN, (R) **21**
BocHN COOH (R) **15'**		
	H_2N(R)Ph	(R)Ph, O, NH, BocHN, (R) **22**
	H_2N(S)Ph	(S)Ph, O, NH, BocHN **19/21**
BocHN COOH **18**		
	H_2N(R)Ph	(R)Ph, O, NH, BocHN **20/22**

[a] DEPBT=3-(diethoxyphosphoryloxy)-1,2,3-benzo-triazin-4(3*H*)-one.

NMR spectral analysis (500 MHz) of the chiral amides (**19**–**22**) showed the presence of one major diastereoisomer with only minor amounts of the other in each case. Comparison of compounds **19** and **21** with amide **19**/**21** (prepared from the racemic acid **18**) clearly reflected the excellent enantioselectivity of the chelate Claisen rearrangement (Fig. 1). The exact ratio of the two compounds was difficult to determine by NMR as peak overlaps made integration unreliable. Chemical shift differences were seen in two areas: the vinyl alkene hydrogens (5.5 ppm) and the terminal methyl group of the trans double bond (1.62 ppm).

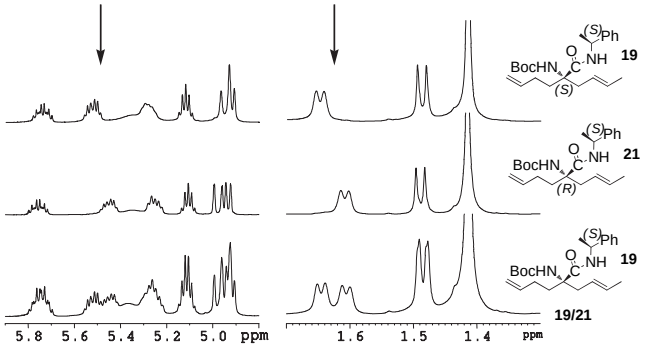
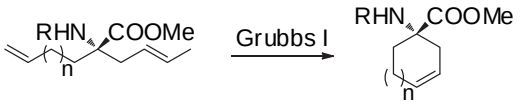


Figure 1. Comparative NMR spectra.

The rearranged derivatives then underwent a ring closing metathesis reaction in the presence of Grubbs first generation catalyst to give the desired carbocycles in good yield (Table 4).

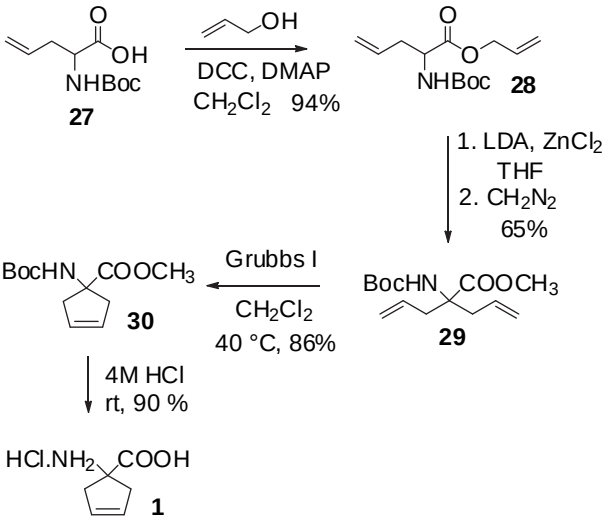
In order to better quantify reaction enantioselectivity, the cyclic derivatives **23**–**26** were subjected to chiral column analysis using a Chiralcel IC or OD-H column. An excellent enantioselectivity was observed (ee≥96%) for all substrates. The absolute configuration of the obtained products was assigned based on the use of chiral auxiliaries and ^{1}H NMR published in our previous paper.[12]

Table 4
Ring closing metathesis



Amido-ester	Carbocycle	Yield (%)	ee (%)
14	BocHN COOMe **23**	95	≥97
15	BocHN COOMe **24**	90	≥97
16	AcHN COOMe **25**	83	≥98
17	BocHN COOMe **26**	72	≥96

In order to prepare 1-aminocyclopent-3-ene-1-carboxylic acid **1**, coupling of the Boc protected allyl glycine derivative **27** with allyl alcohol gave ester **28** (Scheme 5). Claisen rearrangement in the presence of zinc(II) chloride, treatment with diazomethane and



Scheme 5.

RCM gave the desired cyclopentene derivative **30** in good yield. Final deprotection with aqueous HCl then gave the desired compound **1** as a hydrochloride salt.

3. Conclusions and summary

We have described the enantioselective preparation of several 1-aminocycloalkene-1-carboxylic acids. The obtained selectivity was based on the configuration of the starting allylic alcohol and is an example of a highly stereoselective 1,4-chirality transfer from a simple chiral alcohol precursor. One of the advantages of this method is the preparation of unsymmetrical unsaturated carbocycles, which are not easily available by controlled alkylation of a glycine equivalent. A straightforward synthesis of 1-aminocyclopent-3-ene-1-carboxylic acid **1** was also described.

4. Experimental section

4.1. General

All reactions were performed under argon with magnetic stirring unless otherwise specified. Moisture or air-sensitive reactions were conducted under an argon atmosphere in oven-dried glassware. Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone under argon prior to use. Dichloromethane was distilled from calcium hydride under argon. Diisopropylamine, triethylamine, and diisopropylethylamine were dried with potassium hydroxide and freshly distilled before use. Commercial anhydrous zinc(II) chloride was used without further purification. All other reagents were used as supplied. Flash chromatography was performed on an Armen SpotFlash with silica gel 60 (particle size 15–40 μm). Optical rotations were recorded at 20 °C. Mass spectra (MS and HRMS) were acquired using ESI techniques. NMR spectra were obtained using a 500 or a 250 MHz spectrometer. Chemical shifts were measured in δ (ppm) and coupling constants J in hertz (solvent peak reference: δ=7.27 for ^{1}H, 77.0 for ^{13}C). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), qui (quintuplet), m (multiplet) or br (broad). Elemental analyses were performed on a Flash EA 1112 apparatus. Enantiomeric excess was determined by chiral HPLC analysis using a Chiralcel IC column (*n*-hexane/isopropanol 92:8 with a flow rate of 0.7 mL/min for compounds **23** and **24**; *n*-hexane/isopropanol 80:20 with a flow rate of 0.8 mL/min for compound **25**) or a Chiralcel OD-H column (*n*-hexane/isopropanol 99:1 with a flow rate of 1.0 mL/min for compound **26**). Peak detection was done at 220 nm.

^{1}H and ^{13}C spectra are described only once for each pair of enantiomers.

4.2. 2-*tert*-Butoxycarbonylamino-hex-5-enoic acid (7)

This acid was prepared from diethylacetamidomalonate and 4-bromo-1-pentene using a slightly modified procedure to obtain compound **7** in the last step.[29] 2-Acetylamino-hex-5-enoic acid (**8**) was an intermediate in this reaction sequence.

2-Amino-hex-5-enoic acid hydrochloride (2.48 g, 15 mmol) was suspended in a 1:1 1,4-dioxane/water mixture (50 mL) at rt. To this mixture was added di-*tert*-butyldicarbonate (3.92 g, 17.9 mmol 1.2 equiv) followed by diisopropylethylamine (5.8 g, 45 mmol, 7.8 mL, 3 equiv). The reaction mixture was allowed to stir overnight before removing the dioxane under reduced pressure. The aqueous layer was then extracted with diethyl ether (2×30 mL) and acidified with aqueous 4 N HCl. The acidified aqueous layer was then extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered, and evaporated under reduced pressure to give a colorless oil (3.2 g, 94%). The acid was used without further purification in the coupling steps. ^{1}H NMR (mixture of rotamers) (250 MHz, $CDCl_3$): δ=1.45 (s, 9H), 1.78 (m, 1H), 1.96 (m, 1H), 2.17 (m, 2H), 4.14 (m, 0.35H, C*H*NHBoc), 4.36 (m, 0.65H, C*H*NHBoc), 5.07 (m, 2H), 5.14 (br s, 0.65H, N*H*Boc), 5.80 (m, 1H), 6.49 (s, 0.35H, N*H*Boc), 10.78 (br s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=28.2, 29.4, 31.6, 52.9, 80.15, 115.8, 136.8, 155.5, 177.3.

4.3. 2-*tert*-Butoxycarbonylamino-hept-6-enoic acid (9)

This acid was prepared using the same procedure as for compound **7**[29] using diethylacetamidomalonate and 5-bromo-1-pentene. ^{1}H NMR (mixture of rotamers) (250 MHz, $CDCl_3$): δ=1.45 (s, 11H), 1.70 (m, 1H), 1.85 (m, 1H), 2.09 (m, 2H), 4.11 (m, 0.35H, C*H*NHBoc), 4.33 (m, 0.65H, C*H*NHBoc), 5.00 (m, 2H), 5.22 (d, J=8.1 Hz, 0.65H, N*H*Boc), 5.78 (m, 1H), 6.60 (d, J=6.4 Hz, 0.35H, N*H*Boc), 10.89 (br s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=24.4, 28.2, 31.4, 31.8, 33.0, 53.1, 54.4, 80.0, 81.6, 115.0, 137.8, 155.5, 156.9, 177.1. ESI-MS: m/z=266 $[M+Na]^+$, 509 $[2M+Na]^+$.

4.4. Two-step general procedure for esterification and alkyne reduction

(a) Esterification

The carboxylic acid (1.1 equiv) was dissolved in dry methylene chloride (10 mL) and cooled to 0 °C. The chiral alcohol [(*R*) or (*S*)-but-3-yn-2-ol (both 98% ee)] (1 equiv) was then added followed by a catalytic amount of DMAP (0.1 equiv). A solution of DCC (1.2 equiv) in CH_2Cl_2 was slowly added dropwise. The mixture was allowed to warm to rt and was stirred overnight. The solvent was evaporated, a minimal amount of EtOAc was added, and the reaction mixture was filtered on Celite to remove most of the precipitated urea. The crude product was used without further purification in the next step.

(b) Alkyne reduction

Lindlar's catalyst (palladium (5%) on calcium carbonate, poisoned with lead, 10 wt %) was added to a solution of freshly distilled quinoline (0.25 equiv) and the chiral ester in EtOAc at rt. The reaction flask was then evacuated and flushed with hydrogen gas three times, and the reaction mixture was left to stir under a balloon of hydrogen gas. After 15–30 min, the mixture was filtered through a pad of Celite and evaporated under reduced pressure. After ^{1}H and ^{13}C NMR analysis of the crude reaction mixture to verify the absence of the starting alkyne as well as the fully saturated alkane, it was purified by column chromatography to give the desired ester.

*4.4.1. 2-tert-Butoxycarbonylamino-hex-5-enoic acid (S)-1-methyl-allyl ester (**10**).* Yield 63% (two steps, colorless oil, mixture of diastereoisomers). R_f=0.38 (petroleum ether/EtOAc 95:5). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.34/1.35 (2×d, J=2.7 Hz, 3H), 1.45 (s, 9H), 1.73 (m, 1H), 1.90 (m, 1H), 2.11 (m, 2H), 4.30 (m, 1H), 5.04 (m, 2H), 5.16 (dd, J=10.5, 1.1 Hz, 1H), 5.26 (dd, J=17.3, 1.2 Hz, 1H), 5.39 (m, 1H), 5.82 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=19.8, 19.9, 28.3, 29.4, 32.0, 53.1, 72.0, 72.1, 79.7, 115.6, 116.2, 116.3, 137.0, 155.3, 171.9. ESI-MS: m/z=329.3 $[M+2Na]^+$. $C_{15}H_{25}NO_4$ (283.36): calcd C 63.58, H 8.89, N 4.94; found C 63.26, H 8.91, N 4.84.

*4.4.2. 2-tert-Butoxycarbonylamino-hex-5-enoic acid (R)-1-methyl-allyl ester (**11**).* Yield 69% (two steps, colorless oil, mixture of diastereoisomers). ESI-MS: m/z=329.3 $[M+2Na]^+$. $C_{15}H_{25}NO_4$ (283.36): calcd C 63.58, H 8.89, N 4.94; found C 63.24, H 8.93, N 4.86.

*4.4.3. 2-Acetylamino-hex-5-enoic acid (S)-1-methyl-allyl ester (**12**).* Yield 57% (two steps, colorless oil, mixture of diastereoisomers). R_f=0.23 (petroleum ether/EtOAc 70:30). ^{1}H NMR (500 MHz, $CDCl_3$):

δ=1.34/1.35 (2×d, J=2.7 Hz, 3H), 1.77 (m, 1H), 1.96 (m, 1H), 2.03 (s, 3H), 2.09 (m, 2H), 4.63 (dt, J=7.7, 5.4 Hz, 1H), 5.02 (m, 2H), 5.17 (d, J=10.5 Hz, 1H), 5.27 (dd, J=17.3, 1.2 Hz, 1H), 5.39 (m, 1H), 5.81 (m, 2H), 6.21 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=19.8, 19.9, 23.1, 29.3, 29.4, 31.7, 31.7, 51.9, 72.3, 72.4, 115.6, 116.4, 116.6, 136.9, 137.0, 169.8, 171.8. ESI-MS: m/z=226.2 $[M+H]^+$. $C_{12}H_{19}NO_3$ (225.28): calcd C 63.98, H 8.50, N 6.22; found C 63.93, H 8.62, N 6.19.

*4.4.4. 2-tert-Butoxycarbonylamino-hept-6-enoic acid (S)-1-methyl-allyl ester (**13**).* Yield 59% (two steps, colorless oil, mixture of diastereoisomers). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.33/1.35 (2×d, J=3.9 Hz, 3H), 1.44 (br s, 11H), 1.65 (m, 1H), 1.80 (m, 1H), 2.07 (m, 2H), 4.29 (m, 1H), 4.91–5.32 (m, 4H), 5.39 (m, 1H), 5.80 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=19.7, 19.8, 24.3, 28.2, 32.0, 33.0, 53.3, 71.8, 79.5, 114.9, 116.1, 116.2, 137.0, 137.1, 137.8, 155.2, 171.9. ESI-MS: m/z=320.3 $[M+Na]^+$. $C_{16}H_{27}NO_4$ (297.39): calcd C 64.62, H 9.15, N 4.71; found C 64.47, H 9.20, N 4.58.

4.5. General procedure for the Claisen rearrangement

Zinc(II) chloride (1.5 equiv) was melted under vacuum with a heat gun and then cooled. In a separate flask, *n*-BuLi (2.7 equiv, 2.3 M solution in hexanes) was added to diisopropylamine (3.4 equiv) in anhydrous THF at 0 °C. After 15 min, the solution was cooled to −78 °C. THF (1 mL) was then added to the melted $ZnCl_2$, and the solution was stirred at rt to dissolve all of the white solid. The starting ester (1 equiv) suspended in a minimum amount of THF was added to the $ZnCl_2$ solution and this mixture was cooled to 0 °C. This solution was then slowly added by cannula to the LDA flask at −78 °C. The mixture was allowed to stir for a further 5 min before being placed at −5 °C for 4–6 h. After addition of an aqueous 1 M $KHSO_4$ solution, the phases were separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried with $MgSO_4$, filtered, and the solvent evaporated in vacuo. The crude reaction mixture was treated with diazomethane to generate the corresponding methyl ester and purified by flash chromatography (petroleum ether/EtOAc, 95:5 (Boc derivative) or 70:30 (Ac derivative)). Alternatively, in the presence of unreacted starting material, the acid was purified by flash chromatography (petroleum ether/EtOAc, 90:10 to 50:50). The clean acid was then treated with a solution of diazomethane in ether to give the corresponding methyl ester.

*4.5.1. (E)-(S)-2-But-3-enyl-2-tert-butoxycarbonylamino-hex-4-enoic acid methyl ester (**14**).* Yield 63% (colorless oil). R_f=0.60 (petroleum ether/EtOAc 95:5). $[\alpha]_D^{20}$ +19.8 (*c* 0.55, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.44 (s, 9H), 1.63 (d, J=5.8 Hz, 3H), 1.84 (m, 2H), 2.06 (m, 1H), 2.35 (m, 1H), 2.40 (dd, J=13.8, 7.1 Hz, 1H), 2.96 (br s, 1H), 3.74 (s, 3H), 4.93 (d, J=10.1 Hz, 1H), 4.99 (dd, J=17.1, 1.2 Hz, 1H), 5.22 (m, 1H), 5.48 (m, 2H), 5.75 (ddt, J=16.6, 10.2, 6.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=18.1, 28.3, 28.5, 34.3, 38.7, 52.5, 63.5, 79.1, 114.9, 124.6, 129.6, 137.6, 153.8, 174.0. ESI-MS: m/z=298.2 $[M+Na]^+$. $C_{16}H_{27}NO_4$ (297.39): calcd C 64.62, H 9.15, N 4.71; found C 64.49, H 9.11, N 4.86.

*4.5.2. (E)-(R)-2-But-3-enyl-2-tert-butoxycarbonylamino-hex-4-enoic acid methyl ester (**15**).* Yield 68% (colorless oil). $[\alpha]_D^{20}$ −18.2 (*c* 0.53, $CHCl_3$). ESI-MS: m/z=343.3 $[M+2Na]^+$. $C_{16}H_{27}NO_4$ (297.39): calcd C 64.62, H 9.15, N 4.71; found C 64.27, H 9.12, N 4.68.

*4.5.3. (E)-(S)-2-Acetylamino-2-but-3-enyl-hex-4-enoic acid methyl ester (**16**).* Yield 84% (colorless oil). R_f=0.32 (petroleum ether/EtOAc 70:30). $[\alpha]_D^{20}$ +34.9 (*c* 0.97, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.64 (d, J=5.8 Hz, 3H), 1.80 (m, 1H), 1.86 (m, 1H), 2.02 (s, 3H), 2.05 (br s, 1H), 2.42 (dd, J=13.8, 7.3 Hz, 1H), 2.57 (m, 1H), 3.14 (dd, J=13.8, 7.4 Hz, 1H), 3.77 (s, 3H), 4.95 (d, J=9.6 Hz, 1H), 5.00 (dd, J=17.1, 1.3 Hz, 1H), 5.21 (m, 1H), 5.51 (m, 1H), 5.75 (m, 1H), 6.39 (br s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=18.0, 24.0, 28.6, 33.7, 38.2, 52.6, 64.7, 115.0, 124.5, 129.5, 137.4, 169.0, 174.2. ESI-MS: m/z=240.2 $[M+H]^+$. $C_{13}H_{21}NO_3$ (239.31): calcd C 65.25, H 8.84, N 5.85; found C 64.91, H 8.84, N 5.88.

*4.5.4. (E)-(S)-2-But-2-enyl-2-tert-butoxycarbonylamino-hept-6-enoic acid methyl ester (**17**).* Yield 71% (colorless oil). R_f=0.58 (petroleum ether/EtOAc 95:5). $[\alpha]_D^{20}$ +15.9 (*c* 0.48, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.13 (m, 1H), 1.44 (br s, 10H), 1.63 (d, J=6.1 Hz, 3H), 1.75 (m, 1H), 2.02 (q, J=7.1 Hz, 2H), 2.23 (m, 1H), 2.40 (dd, J=13.9, 7.0 Hz, 1H), 2.93 (m, 1H), 3.74 (s, 3H), 4.97 (m, 2H), 5.22 (m, 1H), 5.47 (m, 2H), 5.75 (tdd, J=16.8, 10.1, 6.6 Hz, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=18.0, 23.2, 28.3, 33.3, 34.6, 38.5, 52.4, 63.7, 78.9, 114.7, 124.7, 129.4, 138.2, 153.8, 174.1. ESI-MS: m/z=312.4 $[M+H]^+$. $C_{17}H_{29}NO_4$ (311.41): calcd C 65.57, H 9.39, N 4.50; found C 65.90, H 9.49, N 4.48.

*4.5.5. [(E)-(S)-1-But-3-enyl-1-((S)-1-phenyl-ethylcarbamoyl)-pent-3-enyl]-carbamic acid tert-butyl ester (**19**).* To a solution of the crude acid **14**′ (0.073 g, 0.26 mmol) in dry THF (2 mL) was added (*S*)-methylbenzylamine (0.94 g, 0.77 mmol, 0.100 mL, 3 equiv), diisopropylethylamine (0.067 g, 0.51 mmol, 0.90 mL, 2 equiv), and 3-(diethoxyphosphoryloxy)-1,2,3-benzo-triazin-4(3*H*)-one (DEPBT)[30] (0.154 g, 0.51 mmol, 2 equiv) at rt. After stirring overnight, a saturated aqueous NaCl solution was added (2 mL), and the amide extracted with EtOAc (3×2 mL). The combined organic layers were washed with aqueous 1 N HCl, water, aqueous 5% Na_2CO_3, brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude reaction purified by flash column chromatography to give 0.059 g of the amide **19** as a white amorphous powder. Yield 59%. $[\alpha]_D^{20}$ −36.7 (*c* 0.22, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.42 (s, 9H, C(CH_3)$_3$), 1.49 (d, J=6.9 Hz, 3H, CH_3CHPh), 1.61 (d, J=6.1 Hz, 3H, CH_3CH=CH−), 1.79 (m, 1H, CH_2), 1.91 (m, 1H, CH_2), 2.01 (m, 1H, CH_2), 2.19 (br s, 1H, CH_2), 2.50 (dd, J=14.2, 6.7 Hz, 1H, CH_2), 2.67 (br s, 1H, CH_2), 4.93 (d, J=10.1 Hz, 1H, CH_2=CH−), 4.98 (dd, J=17.1, 1.4 Hz, 1H, CH_2=CH−), 5.11 (qui, J=7.0 Hz, 1H, CH_3C*H*Ph), 5.25 (m, 1H, −CH=C*H*CH_3), 5.45 (td, J=13.0, 6.1 Hz, 1H, −C*H*=CHCH_3), 5.76 (tdd, J=16.8, 10.1, 6.5 Hz, 1H, CH_2=C*H*−), 6.49 (br s, 1H, NH), 7.26 (m, 1H, Ph), 7.32 (m, 4H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$): δ=18.1, 21.5, 28.1, 28.3, 34.9, 38.7, 48.9, 62.2, 114.9, 124.7, 126.2, 127.3, 128.6, 130.2, 137.7, 143.0, 154.5, 171.9. ESI HRMS: m/z calcd for $C_{23}H_{34}N_2O_3$ $(M+Na)^+$ 409.2467, found 409.2459. $C_{23}H_{34}N_2O_3$ (386.50): calcd C 71.47, H 8.87, N 7.25; found C 71.39, H 8.88, N 7.09.

*4.5.6. [(E)-(S)-1-But-3-enyl-1-((R)-1-phenyl-ethylcarbamoyl)-pent-3-enyl]-carbamic acid tert-butyl ester (**20**).* This compound was prepared using the same procedure as for **19**.

Yield 55%. $[\alpha]_D^{20}$ +3.2 (*c* 0.29, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.41 (s, 9H, C(CH_3)$_3$), 1.49 (d, J=6.9 Hz, 3H, CH_3CHPh), 1.65 (d, J=6.0 Hz, 3H, CH_3CH=CH−), 1.81 (m, 2H, CH_2), 2.02 (m, 1H, CH_2), 2.21 (br s, 1H, CH_2), 2.53 (m, 1H CH_2), 2.71 (br s, 1H, CH_2), 4.95 (m, 2H, CH_2=CH), 5.12 (m, 1H, CH_3C*H*Ph), 5.30 (m, 1H, −CH=C*H*CH_3), 5.52 (dt, J=12.6, 6.0 Hz, 1H, −C*H*=CHCH_3), 5.74 (tdd, J=12.8, 9.9, 6.4 Hz, 1H, CH_2=C*H*−), 6.49 (br s, 1H, NH), 7.27 (m, 1H, Ph), 7.32 (m, 4H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$): δ=18.1, 21.6, 28.1, 28.2, 35.0, 38.8, 48.8, 62.2, 114.9, 124.8, 126.1, 127.3, 128.6, 130.1, 137.6, 143.0, 154.4, 171.9. ESI HRMS: m/z calcd for $C_{23}H_{34}N_2O_3$ $(M+Na)^+$ 409.2467, found 409.2465. $C_{23}H_{34}N_2O_3$ (386.50): calcd C 71.47, H 8.87, N 7.25; found C 71.73, H 8.93, N 7.17.

4.6. General procedure for ring closing metathesis

The methyl ester (1 equiv) was dissolved in CH_2Cl_2 (0.2 M solution). First generation Grubbs catalyst (0.1 equiv) was added and the reaction mixture heated to 40 °C until disappearance of the

starting material as indicated by TLC (1–3 h). At the end of the reaction, the catalyst was effectively removed by filtering the crude mixture through a pad of silica gel. The filtered solution was then treated with activated charcoal overnight,[31] filtered, and purified by flash chromatography.

*4.6.1. (S)-1-tert-Butoxycarbonylamino-cyclohex-3-enecarboxylic acid methyl ester (**23**).* Yield 95% (white amorphous powder). R_f=0.28 (petroleum ether/EtOAc 90:10). $[\alpha]_D^{20}$ +53.0 (*c* 0.91, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ=1.43 (s, 9H), 1.92 (m, 1H), 2.11 (m, 2H), 2.24 (m, 2H), 2.57 (br d, *J*=17.7 Hz, 1H), 3.74 (s, 3H), 4.83 (br s, 1H), 5.59 (m, 1H), 5.74 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=21.7, 27.5, 28.3, 34.1, 52.3, 56.9, 79.8, 122.4, 127.1, 154.9, 174.7. ESI HRMS *m*/*z* calcd for $C_{13}H_{21}NO_4$ $(M+Na)^+$ 278.1368, found 278.1361. $C_{13}H_{21}NO_4$ (255.31): calcd C 61.16, H 8.29, N 5.49; found C 61.29, H 8.31, N 5.40.

*4.6.2. (R)-1-tert-Butoxycarbonylamino-cyclohex-3-enecarboxylic acid methyl ester (**24**).* Yield 90% (amorphous white powder). $[\alpha]_D^{20}$ −51.5 (*c* 0.84, $CHCl_3$). ESI HRMS: *m*/*z* calcd for $C_{13}H_{21}NO_4$ $(M+Na)^+$ 278.1368, found 278.1360. $C_{13}H_{21}NO_4$ (255.31): calcd C 61.16, H 8.29, N 5.49; found C 61.10, H 8.25, N 5.43.

*4.6.3. (S)-1-Acetylamino-cyclohex-3-enecarboxylic acid methyl ester (**25**).* Yield 83% (white amorphous powder). R_f=0.13 (petroleum ether/EtOAc 50:50). $[\alpha]_D^{20}$ +85.8 (*c* 0.51, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ=1.92 (m, 1H), 1.99 (s, 3H), 2.04 (br m, 1H), 2.14 (m, 1H), 2.24 (br d, 2.25, *J*=17.3 Hz, 1H), 2.36 (m, 1H), 2.57 (d, *J*=17.9 Hz, 1H), 3.73 (s, 3H), 5.60 (m, 1H), 5.77 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=21.7, 23.1, 26.8, 33.9, 52.4, 56.8, 122.3, 127.3, 169.8, 174.1. ESI HRMS: *m*/*z* calcd for $C_{10}H_{15}NO_3$ $(M+H)^+$ 198.1130, found 198.1140. $C_{10}H_{15}NO_3$ (197.23): calcd C 60.90, H 7.67, N 7.10; found C 60.98, H 7.70, N 7.10.

*4.6.4. (S)-1-tert-Butoxycarbonylamino-cyclohept-3-enecarboxylic acid methyl ester (**26**).* Yield 72% (white amorphous powder). R_f=0.35 (petroleum ether/EtOAc 90:10). $[\alpha]_D^{20}$ −57.4 (*c* 0.73, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ=1.43 (s, 10H), 1.67 (m, 1H), 2.05 (m, 1H), 2.13 (m, 1H), 2.24 (m, 1H), 2.39 (br d, *J*=10.7 Hz, 1H), 2.62 (m, 2H), 3.73 (s, 3H), 4.80 (br s, 1H), 5.58 (m, 1H), 6.02 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=20.9, 28.3, 28.6, 35.1, 37.7, 52.3, 59.0, 124.7, 136.0, 154.5, 175.1. ESI-MS: *m*/*z*=292.3 $[M+Na]^+$. $C_{14}H_{23}NO_4$ (269.34): calcd C 62.43, H 8.61, N 5.20; found C 62.11, H 8.60, N 5.13.

*4.6.5. 2-tert-Butoxycarbonylamino-pent-4-enoic acid allyl ester (**28**).* This compound was prepared as described in the general esterification protocol with 2-*tert*-butoxycarbonylamino-pent-4-enoic acid[3] and an excess (3 equiv) of allyl alcohol. Yield 94% (colorless oil). R_f=0.24 (petroleum ether/EtOAc 95:5). ^1H NMR (500 MHz, $CDCl_3$): δ=1.44 (s, 9H), 2.53 (m, 2H), 4.40 (m, 1H), 4.63 (m, 1H), 5.05 (d, *J*=7.3 Hz, 1H), 5.13 (m, 2H), 5.25 (d, *J*=10.4 Hz, 1H), 5.34 (dd, *J*=17.2, 1.1 Hz, 1H), 5.69 (m, 1H), 5.90 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ=28.3, 36.7, 52.9, 65.9, 79.9, 118.8, 119.2, 131.6, 132.2, 155.2, 171.8. ESI-MS: *m*/*z*=278.2 $[M+Na]^+$. $C_{13}H_{21}NO_4$ (255.31): calcd C 61.16, H 8.29, N 5.49; found C 61.11, H 8.18, N 5.57.

*4.6.6. 2-Allyl-2-tert-butoxycarbonylamino-pent-4-enoic acid methyl ester (**29**).* This compound was prepared using the general procedure for the Claisen rearrangement. Yield 63% (colorless oil). R_f=0.39 (petroleum ether/EtOAc 95:5). ^1H NMR (250 MHz, $CDCl_3$): δ=1.43 (s, 9H), 2.53 (dd, *J*=13.8, 7.3 Hz, 2H), 3.0 (m, 2H), 3.75 (s, 3H), 5.09 (m, 4H), 5.40 (br s, 1H), 5.64 (m, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=28.4, 39.6, 52.6, 63.4, 79.4, 119.1, 132.4, 154.0, 173.5. ESI HRMS: *m*/*z* calcd for $C_{14}H_{23}NO_4$ $(M+H)^+$ 270.1705, found 270.1699.

*4.6.7. 1-tert-Butoxycarbonylamino-cyclopent-3-enecarboxylic acid methyl ester (**30**).* This compound was prepared using the general procedure for ring closing metathesis. Yield 86% (white amorphous solid). R_f=0.28 (petroleum ether/EtOAc 90:10). ^1H NMR (250 MHz, $CDCl_3$): δ=1.43 (s, 9H), 2.62 (br d, *J*=16.5 Hz, 2H), 3.06 (br d, *J*=15.9 Hz, 2H), 3.75 (s, 3H), 5.15 (br s, 1H), 5.66 (s, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=28.2, 44.9, 52.5, 64.2, 79.9, 127.6, 154.9, 174.7. ESI HRMS: *m*/*z* calcd for $C_{12}H_{19}NO_4$ $(M+Na)^+$ 264.1212, found 264.1212. $C_{12}H_{19}NO_4$ (241.28): calcd C 59.73, H 7.94, N 5.81; found C 59.77, H 7.99, N 5.79.

*4.6.8. 1-Aminocyclopent-3-ene-1-carboxylic acid hydrochloride (**1**).* Compound **30** (0.21 g, 0.87 mmol) was stirred with HCl (4 M, 20 mL) at rt for 14 h. The reaction mixture was filtered and concentrated under vacuum to give 0.128 g (90%) of the hydrochloride salt of carboxylic acid **1**. ^1H and ^{13}C NMR were performed in D_2O and were in agreement with published data.[28]

Acknowledgements

We would like to thank the University of Champagne Ardennes and the Centre National de Recherche Scientifique (CNRS) for their financial support, as well as AstraZeneca for the PhD scholarship awarded to N.P. Special thanks are due to Mme Sylvie Lanthony for performing the chiral HPLC analyses.

Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.05.008.

References and notes

1. Toniolo, C.; Formaggio, F.; Kaptein, B.; Broxterman, Q. B. *Synlett* **2006**, 1295–1310.
2. Venkatraman, J.; Shankaramma, S. C.; Balaram, P. *Chem. Rev.* **2001**, *101*, 3131–3152.
3. Kaptein, B.; Broxterman, Q. B.; Schoemaker, H. E.; Rutjes, F. P. J. T.; Veerman, J. J. N.; Kamphuis, J.; Peggion, C.; Formaggio, F.; Toniolo, C. *Tetrahedron* **2001**, *57*, 6567–6577.
4. Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732.
5. Cativiela, C.; Ordóñez, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1–63.
6. Schöllkopf, U.; Groth, U.; Deng, C. *Angew. Chem.* **1981**, *93*, 793–795.
7. Schöllkopf, U.; Hinrichs, R.; Lonsky, R. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 143–145.
8. Hammer, K.; Undheim, K. *Tetrahedron* **1997**, *53*, 2309–2322.
9. Undheim, K. *Amino Acids* **2008**, *34*, 357–402.
10. Jam, F.; Tullberg, M.; Luthman, K.; Grøtli, M. *Tetrahedron* **2007**, *63*, 9881–9889.
11. Avenoza, A.; Cativiela, C.; Fernández-Recio, M. A.; Peregrina, J. M. *Tetrahedron: Asymmetry* **1996**, *7*, 721–728.
12. Probst, N. P.; Haudrechy, A.; Plé, K. *J. Org. Chem.* **2008**, *73*, 4338–4341.
13. Kazmaier, U. In *The Claisen Rearrangement*; Hiersemann, M., Nubbemeyer, U., Eds.; Wiley-VCH GmbH KgaA: Weinheim, 2007; pp 233–299.
14. Quirin, C.; Kazmaier, U. *Eur. J. Org. Chem.* **2009**, *2009*, 371–377.
15. Looper, R. E.; Runnegar, M. T. C.; Williams, R. M. *Tetrahedron* **2006**, *62*, 4549–4562.
16. Kazmaier, U.; Schneider, C. *Synthesis* **1998**, 1321–1326.
17. Deprés, J. P.; Greene, A. E. *J. Org. Chem.* **1984**, *49*, 928–931.
18. Doller, D.; Chackalamannil, S.; Stamford, A.; McKittrick, B.; Czarniecki, M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1381–1386.
19. Hodgson, D. M.; Thompson, A. J.; Wadman, S. *Tetrahedron Lett.* **1998**, *39*, 3357–3358.
20. Hodgson, D. M.; Thompson, A. J.; Wadman, S.; Keats, C. J. *Tetrahedron* **1999**, *55*, 10815–10834.
21. Park, K.-H.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 6579–6585.
22. Park, K.-H.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 113–117.
23. Park, K.-H.; Kurth, T. M.; Olmstead, M. M.; Kurth, M. J. *Tetrahedron Lett.* **2001**, *42*, 991–992.
24. Amori, L.; Costantino, G.; Marinozzi, M.; Pellicciari, R.; Gasparini, F.; Flor, P. J.; Kuhn, R.; Vranesic, I. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1447–1450.
25. Larionov, O. V.; Kozhushkov, S. I.; de Meijere, A. *Synthesis* **2005**, 158–160.
26. Kotha, S.; Sreenivasachary, N. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 257–260.
27. Kotha, S.; Sreenivasachary, N.; Mohanraja, K.; Durani, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1421–1423.
28. Casabona, D.; Cativiela, C. *Synthesis* **2006**, 2440–2443.
29. Biagini, S. C. G.; Gibson, S. E.; Keen, S. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2485–2500.
30. Ye, Y.-h.; Li, H.; Jiang, X. *Pept. Sci.* **2005**, *80*, 172–178.
31. Cho, J. H.; Kim, B. M. *Org. Lett.* **2003**, *5*, 531–533.