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Stereocontrolled transformation of cyclohexene β-amino esters into *syn*- or *anti*-difunctionalized acyclic $\beta^{2,3}$-amino acid derivatives

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ABSTRACT

A stereocontrolled approach to functionalized acyclic $\beta^{2,3}$-amino acid derivatives was accomplished from *cis*- or *trans*-2-aminocyclohexenecarboxylates derived from bicyclic β-lactam regioisomers. The transformations were based on oxidative ring cleavage through the ring C–C double bond of the cyclohexene β-amino esters, followed by functionalization of the dialdehyde intermediates with different phosphoranes. This stereospecific and stereocontrolled procedure was applied to the synthesis of acylic $\beta^{2,3}$-amino acid derivatives functionalized with ester, nitrile, keto, alkyl or arylalkyl groups.

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1. Introduction

The oxidative ring cleavage of substituted mono- or bicyclic compounds, followed by transformations of the resulting diformyl intermediates, is an efficient and convenient tool for access to functionalized acyclic or monocyclic derivatives.[1] Similar transformations of di- or polysubstituted substances allow the stereocontrolled synthesis of novel functionalized derivatives.[2] Moreover, through reductive ring closure, this oxidative ring-opening synthetic strategy serves for the synthesis of heterocyclic functionalized compounds from carbocyclic precursors.[3]

Due to their valuable biological properties, β-amino acids have been subject to increasing interest in synthetic organic and medicinal chemistry during the last 20 years. These compounds include a number of bioactive natural products, such as the anticancer agent *Taxol* or *Taxotere*, the antitumour agents *Cryptophycin*, *Bestatin*, *Microginin* and *Amastatin*, and the antifungal agent *Jasplakinolide*. β-Amino acids are also building elements for the synthesis of peptides or peptidomimetics.[4] $\beta^{2,3}$-Amino acids constitute a subclass of β-amino acids, and are also found among bioactive natural products. *Dolastatin 11*, *12*, *16* and *D*, *Majusculamide C* and *Onchidin* are natural products with antileukaemia activity, while *Guineamide C* and *D*, *Ulongapeptin* and *Malevamide C* are natural antitumour agents whose structures contain a $\beta^{2,3}$-disubstituted amino acid moiety involving different alkyl groups.[4]

Many synthetic procedures are nowadays available for the preparation of racemic disubstituted $\beta^{2,3}$-amino acids, such as the Curtius rearrangement of 2,3-disubstituted 1,4-dicarboxylic acid derivatives, the ring-opening of disubstituted β-lactams or the oxidation of 2,3-disubstituted 1,3-amino alcohols. Other routes involve the alkylation of β^3-amino acid derivatives in the α position, the rearrangement of imides with hypervalent iodine reagents, the reactions of carboxylic acid esters with imidoyl chlorides, the Ireland-Claisen [3,3] sigmatropic rearrangement of enamino esters, the oxidative ring cleavage of 2,3-dihydropyridones and the opening of 4,5-disubstituted 1,3-oxazinanones. Several methods are available for the synthesis of these compounds in enantiomerically pure form: the Michael conjugate addition of chiral amines to α,β-unsaturated esters, followed by alkylation; the dipolar cycloaddition of nitrones to olefins, followed by isoxazolidine opening and oxidation; the asymmetric hydrogenation of enamino esters; the addition of carboxylic acid derivatives or aldehydes to aldimines under organocatalytic conditions via the Mannich reaction, followed by oxidation; the addition of ester enolates to chiral sulfinylimines and diastereoselective intramolecular radical addition to oxime ethers. These are the main procedures that afford $\beta^{2,3}$-amino acids.[2f]

We recently described an efficient stereocontrolled and stereospecific procedure for the synthesis of acyclic *anti* or *syn* $\beta^{2,3}$-amino acid derivatives, from *cis*- or *trans*-β-aminocyclopent-3-

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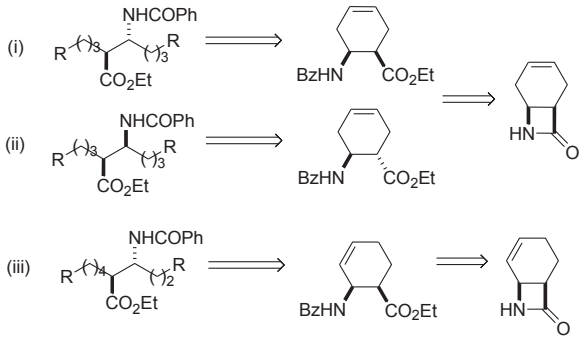
enecarboxylates.[2f] Our aims in the present work were the synthesis of novel β[2,3]-amino acid derivatives through an extension of the above procedure by replacing the five-membered unsaturated β-amino ester starting material containing a cyclopentene 'allylic amine' moiety at a distance of one C atom from the carbamate by the six-membered analogues in which the C–C double bond is at a distance of two C atoms from the carbamate (Scheme 1, (i) and (ii)), and an investigation of the reactivity of the isolated C–C double bond of the β-aminocyclohex-3-enecarboxylates.

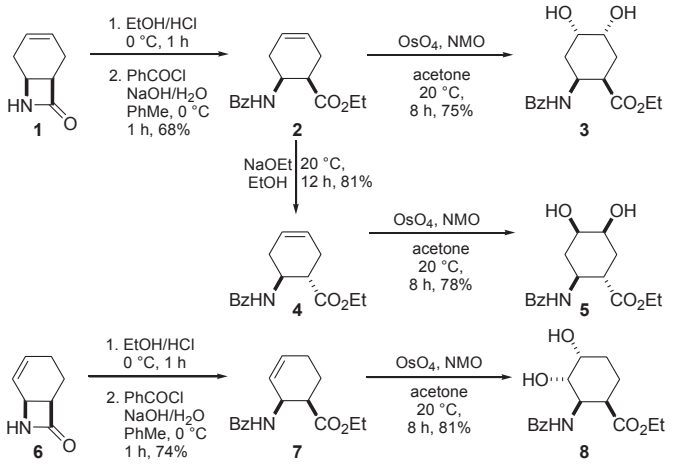


Scheme 1.

2. Results and discussion

During the transformations of the cyclohexene β-amino carboxylates, the stereochemistry of the acyclic target compounds is predetermined by the configuration of the cyclic starting materials. Accordingly, various acyclic *syn*- or *anti*-substituted β-amino acids can be generated from the appropriate unsaturated bicyclic β-lactams, derived in turn from 1,3- or 1,4-cyclohexadienes through the cycloaddition of chlorosulfonyl isocyanate (Scheme 1).

The ring-opening of unsaturated β-lactams **1**[5a] and **6**,[5b] followed by N-benzoylation, resulted in the corresponding six-membered β-amino carboxylates **2**[5c] with an isolated C–C bond in the ring and **7** containing an 'allylic amine' olefinic bond system.[5] Compound **2** was then subjected to a base-induced epimerization to afford the *trans*-β-amino acid derivative **4**. Subsequent stereoselective double bond dihydroxylation of **2**, **4** and **7** in the presence of catalytic amounts of OsO_4 and *N*-methylmorpholine-*N*-oxide (NMO) yielded, on the basis of the ^1H NMR spectra of the crude material, the corresponding diols **3**, **5** and **8** as single diastereoisomers (Scheme 2; analogous dihydroxylation transformations and structure identification have been described[2d–f,3a–c]).



Scheme 2.

Oxidative C–C bond cleavage of dihydroxylated derivative **3** with $NaIO_4$ gave the key dialdehyde intermediate **9**. It is noteworthy that intermediate **9** could not be isolated and further experiments were performed with the dialdehyde generated in situ. The Wittig reaction between dialdehyde **9** and ethyl(-triphenylphosphoranylidene) acetate or (triphenylphosphoranylidene)acetonitrile resulted in the *anti* acyclic diolefinic products **10** and **11** in good yields. The catalytic hydrogenation of **10** and **11** afforded the saturated products **12** and **13**. Further *anti* β-amino acid derivatives were synthesized through the in situ Wittig reaction. The ylides prepared in situ from methyltriphenylphosphonium bromide or benzyltriphenylphosphonium bromide were reacted with dialdehyde **9**, to furnish unsaturated compounds **14** and **15** in moderate yields. Saturation of the double bond gave acyclic products **16** and **17** in good yields (Scheme 3).

The above procedure was subsequently extended to the synthesis of acyclic *syn* β-amino acid derivatives. The key dialdehyde intermediate **18**, prepared from diol **5** through $NaIO_4$-mediated oxidative ring cleavage, displayed similar instability as in the case of the previously described analogue **9**. Dialkenylated derivatives **19**, **20** and **21** were successfully obtained from intermediate **18** in moderate yields through the Wittig reaction. Subsequent Pd/C-catalysed hydrogenation led to the *syn*-saturated products **22**, **23** and **24**. Treatment of dialdehyde **18** with the ylide generated from benzyltriphenylphosphonium bromide resulted in the di-substituted Wittig product **25**, which was further reduced to **26** (Scheme 4). For unknown reasons, none of the correct product was observed in the attempted reaction of dialdehyde **18**, with the ylide generated from methyltriphenylphosphonium bromide. However, by monitoring the transformation on TLC, it was found that the unstable dialdehyde decomposed under the reaction condition.

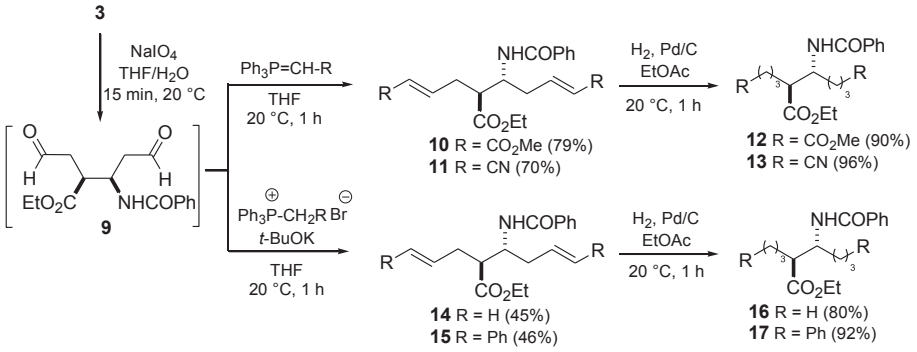
Dialdehyde **27** was synthesized from dihydroxylated derivative **8**, and further dialkenylated species **28**, **29**, **30** and **34**, isomers of the previously synthesized derivatives (Schemes 2 and 3), were prepared via Wittig transformations. Subsequent hydrogenation of these products afforded novel saturated *anti* β-amino acid derivatives **22**, **23**, **24** and **26** in good yields (Scheme 5). As in the previous case, the attempted in situ Wittig reaction between the reactive dialdehyde **27** and the ylide generated from methyltriphenylphosphonium bromide failed, presumably due to decomposition of the starting material.

In conclusion, this efficient stereocontrolled and stereospecific synthetic procedure was extended to the preparation of novel dialkenylated acyclic β-amino acid derivatives from *cis*- or *trans*-cyclohexene β-amino carboxylates derived from unsaturated bicyclic β-lactams. During the synthetic procedure, based on C–C double bond oxidation of six-membered cyclic β-amino esters through dihydroxylation and oxidative ring-opening, Wittig transformation and catalytic reduction, the reactivities of different types of olefinic bond systems were compared. Since the stereochemistry of the stereogenic centres of the starting compounds was not affected during the transformations, the configuration of the chiral centres in the final acylic β-amino acid derivatives was retained.

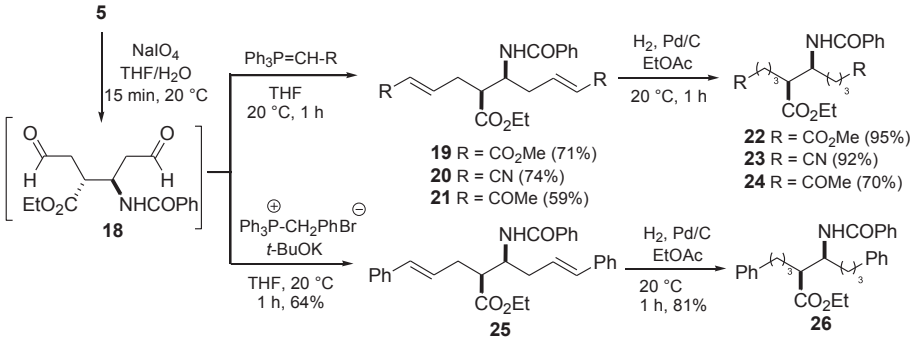
3. Experimental section

3.1. General information

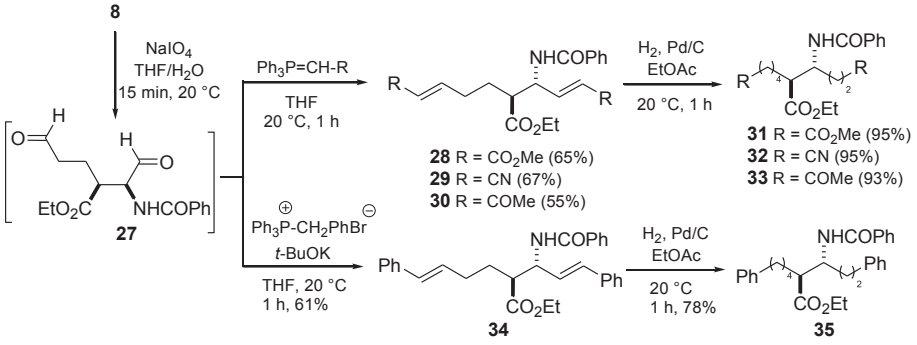
The chemicals were purchased from Sigma–Aldrich. The NMR spectra were recorded at 400 MHz with $CDCl_3$ or [d_6]-dimethylsulfoxide ([d_6]-DMSO) as the solvent and tetramethylsilane as the internal standard. The solvents were used as received from the suppliers. Melting points were determined with a Kofler apparatus. Elemental analyses were recorded on a Perkin–Elmer CHNS-2400 Ser II elemental analyser. Silica gel 60 F254 was purchased from



Scheme 3.



Scheme 4.



Scheme 5.

Merck. IR spectra were recorded on a Bio-Rad Digilab Division FTS-65A/896 FTIR spectrometer. Wavenumber: 4000–400 cm^{-1}, optical resolution: 4 cm^{-1}, using Harrick's Meridian SplitPea single reflection, diamond, ATR accessory. Scan number: 128. All spectral manipulations were performed by using Thermo Scientific GRAMS/AI Suite software.

3.2. General procedure for preparation of *N*-benzoyl-protected amino esters

Ethyl 2-amino-4-cyclohexenecarboxylate or ethyl 2-amino-3-cyclohexenecarboxylate (5.8 g, 2.8 mmol) was dissolved in 80 mL toluene, then 2.2 g NaOH in 40 mL H_2O was added at 0 °C, followed by the dropwise addition of benzoyl chloride (4 g, 1 equiv). The reaction mixture was stirred for 40 min at 0 °C, then it was diluted with EtOAc (160 mL), washed with H_2O (3×120 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was crystallized from *n*-hexane/Et_2O to give the *N*-benzoyl amino ester.

3.3. General procedure for the dihydroxylation of *N*-benzoyl-protected amino esters

To a solution of *N*-benzoyl-protected β-amino ester **2**, **4** or **7** (2 g, 7.3 mmol) and *N*-methylmorpholine-*N*-oxide (3 mL, 13 mmol) in acetone (40 mL), 0.5 mL OsO_4 (0.73 mmol) in *t*-BuOH (0.06 M) was added and the resulting mixture was stirred at room temperature for 12 h. After completion of the reaction, monitored by TLC, saturated aqueous Na_2SO_3 solution (120 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3×70 mL). The combined organic phases were dried over Na_2SO_4, filtered and evaporated in vacuo.

3.4. General procedure for in situ dialdehyde formation followed by the Wittig reaction

To a solution of **3**, **5** or **8** (200 mg, 0.65 mmol) in THF/H_2O (11 mL, v/v 10:1), $NaIO_4$ (279 mg, 1.3 mmol) was added and the reaction mixture was stirred at room temperature for 1 h under an Ar

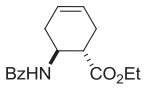
atmosphere, resulting in diformyl derivative **9**, **18** or **27**. Water (20 mL) was then added to the reaction mixture and it was extracted with CH_2Cl_2 (2×15 mL). The combined organic phases were dried over Na_2SO_4, filtered and evaporated in vacuo. The diformyl derivative **9**, **18** or **27** that was formed was dissolved in dry THF (5 mL) and the Wittig reagent (1.3 mmol) was added to the solution. After stirring for 1 h at room temperature, the reaction mixture was concentrated in vacuo and purified by column chromatography on silica gel (*n*-hexane/EtOAc).

3.5. General procedure for in situ dialdehyde formation followed by the in situ Wittig reaction

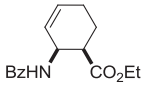
To a solution of **3**, **5** or **8** (200 mg, 0.65 mmol) in THF/H_2O (11 mL, v/v 10:1), $NaIO_4$ (279 mg, 1.3 mmol) was added and the reaction mixture was stirred at room temperature for 1 h under an Ar atmosphere, resulting in diformyl derivative **9**, **18** or **27**. Water (20 mL) was then added to the reaction mixture and it was extracted with CH_2Cl_2 (2×15 mL). The combined organic phases were dried over Na_2SO_4, filtered and evaporated in vacuo. The Wittig reagent was prepared separately by adding *t*-BuOK (1.3 mmol) to a solution of phosphonium salt (1.3 mmol) in dry THF (5 mL) and stirring for 10 min. The diformyl derivative **9**, **18** or **27** (200 mg, 0.65 mmol) was dissolved in dry THF (5 mL) and added dropwise to the solution of the in situ generated Wittig reagent. After stirring at room temperature for 1 h, the reaction mixture was concentrated in vacuo and purified by column chromatography on silica gel (*n*-hexane/EtOAc).

3.6. General procedure for catalytic hydrogenation

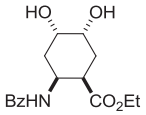
A solution of **10**, **11**, **14**, **15**, **19**, **20**, **21**, **25**, **28**, **29**, **30** or **34** (200 mg) and 10% mol Pd/C (20 mg) in EtOAc (20 mL) was stirred under a H_2 atmosphere for 1 h. The reaction mixture was then filtered through silica gel and Celite. The filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel (*n*-hexane/EtOAc).



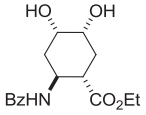
3.6.1. Ethyl (1S,6S*)-6-benzamidocyclohex-3-enecarboxylate (**4**).* Grey solid. Yield: 81% (4.7 g). Mp 85–87 °C; (R_f=0.5, *n*-hexane/EtOAc 1:1). ^{1}H NMR (DMSO, 400 MHz) δ: 1.03 (t, 3H, CH_3, J=7.2 Hz), 2.13–2.36 (m, 3H, H-2, H-5), 2.49–2.52 (m, 1H, H-5), 2.72–2.80 (m, 1H, H-6), 3.93–4.02 (m, 2H, OCH_2), 4.21–4.31 (m, 1H, H-1), 5.63–5.71 (m, 2H, H-3, H-4), 7.43–7.81 (m, 5H, Ar-H), 8.38 (d, 1H, NH, J=8.8 Hz). ^{13}C NMR (DMSO, 400 MHz) δ: 14.8, 28.9, 32.2, 45.4, 47.2, 60.1, 125.6, 125.9, 128.0, 129.1, 131.9, 135.5, 166.3, 174.5.



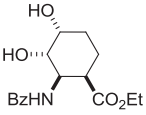
3.6.2. Ethyl (1R,2S*)-2-benzamidocyclohex-3-enecarboxylate (**7**).* Grey solid. Yield: 74% (4.3 g). Mp 90–93 °C; (R_f=0.4, *n*-hexane/EtOAc 1:1). ^{1}H NMR (DMSO, 400 MHz) δ: 1.06 (t, 3H, CH_3, J=7.1 Hz), 1.69–1.77 (m, 1H, H-5), 1.96–2.16 (m, 3H, H-4, H-5), 2.75–2.81 (m, 1H, H-6), 3.90–3.97 (m, 2H, OCH_2), 4.94–5.01 (m, 1H, H-1), 5.62–5.68 (m, 1H, H-3), 5.86–5.91 (m, 1H, H-2), 7.41–7.79 (m, 5H, Ar-H), 8.19 (d, 1H, NH, J=9.3 Hz). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 20.3, 25.0, 44.5, 44.8, 60.6, 126.8, 126.9, 128.4, 130.9, 131.9, 135.6, 167.2, 173.6. IR: ν_{max} 3296, 1725, 1634, 1528, 1177. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 69.98; H, 6.77; N, 4.89.



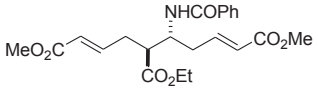
3.6.3. Ethyl (1R,2S*,4S*,5R*)-2-benzamido-4,5-dihydroxycyclohexanecarboxylate (**3**).* Grey solid. Yield: 75% (1.5 g). Mp 121–123 °C; (R_f=0.3, *n*-hexane/EtOAc 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.28–1.33 (m, 3H, CH_3), 2.09–2.27 (m, 4H, H-2, H-5), 3.06–3.11 (m, 1H, H-6), 3.78–3.87 (m, 1H, H-3), 4.05–4.10 (m, 1H, H-4), 4.20–4.27 (m, 2H, OCH_2), 4.68–4.78 (m, 1H, H-1), 7.41–7.80 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 29.6, 34.2, 46.2, 60.8, 67.5, 68.1, 69.9, 128.3, 128.9, 131.8, 135.8, 167.5, 174.1. IR: ν_{max} 3469, 3320, 1718, 1634, 1527, 1181, 1021. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.19; H, 7.10; N, 4.20.



3.6.4. Ethyl (1S,2S*,4S*,5R*)-2-benzamido-4,5-dihydroxycyclohexanecarboxylate (**5**).* Grey solid. Yield: 78% (1.6 g). Mp 113–117 °C; (R_f=0.3, *n*-hexane/EtOAc 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.00–1.04 (m, 3H, CH_3), 1.55–1.98 (m, 4H, H-2, H-5), 2.79–2.91 (m, 1H, H-6), 3.52–3.60 (m, 1H, H-3), 3.77–3.83 (m, 1H, H-4), 3.90–4.00 (m, 2H, OCH_2), 4.07–4.15 (m, 1H, H-1), 7.41–7.81 (m, 5H, Ar-H), 8.39 (d, 1H, NH, J=8.6 Hz). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 33.5, 35.2, 42.8, 49.0, 60.6, 67.7, 70.3, 128.1, 129.1, 131.9, 135.6, 166.2, 174.8. IR: ν_{max} 3420, 3336, 1711, 1635, 1535, 1185, 1023. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.21; H, 6.56; N, 4.19.

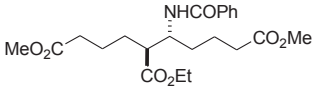


3.6.5. Ethyl (1R,2R*,3S*,4R*)-2-benzamido-3,4-dihydroxycyclohexanecarboxylate (**8**).* Grey solid. Yield: 81% (1.62 g). Mp 102–105 °C; (R_f=0.3, *n*-hexane/EtOAc 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.32 (t, 3H, CH_3, J=7.1 Hz), 1.51–1.61 (m, 1H, H-4), 1.89–2.22 (m, 3H, H-4, H-5), 3.03–3.09 (m, 1H, H-6), 3.94–4.00 (m, 1H, H-2), 4.10–4.15 (m, 1H, H-3), 4.18–4.30 (m, 2H, OCH_2), 4.62–4.69 (m, 1H, H-1), 7.41–7.85 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 21.7, 27.9, 52.5, 60.6, 67.8, 71.4, 128.4, 128.9, 131.9, 135.8, 168.0, 174.2. IR: ν_{max} 3488, 3339, 1719, 1625, 1531, 1183, 1065. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.78; H, 6.59; N, 4.82.

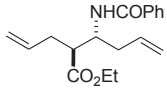


3.6.6. (1E,4S,5R*,7E)-4-Ethyl 1,8-dimethyl 5-benzamidoocta-1,7-diene-1,4,8-tricarboxylate (**10**).* White solid. Yield: 79% (158 mg). Mp 40–43 °C; (R_f=0.4, *n*-hexane/EtOAc 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.32 (t, 3H, CH_3, J=7.1 Hz), 2.46–2.64 (m, 3H, H-3, H-6), 2.69–2.80 (m, 1H, H-6), 2.88–2.97 (m, 1H, H-4), 3.72–3.75 (m, 6H, OCH_3), 4.23 (q, 2H, OCH_2, J=7.2 Hz), 4.52–4.63 (m, 1H, H-5), 5.90–5.96 (m, 2H, H-1, H-8), 6.55 (d, 1H, NH, J=9.1 Hz), 6.88–6.99

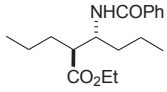
(m, 2H, H-2, H-7), 7.41–7.85 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.8, 31.9, 35.6, 49.3, 50.1, 52.1, 61.3, 123.1, 123.6, 128.2, 129.2, 132.2, 135.2, 146.3, 146.8, 166.6, 167.3, 173.1, 173.2. IR: ν_{max} 3355, 1719, 1640, 1173. Anal. Calcd for $C_{22}H_{27}NO_7$: C, 63.30; H, 6.52; N, 3.36. Found: C, 63.67; H, 6.13; N, 3.01.



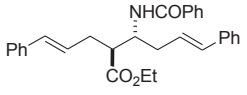
3.6.7. (4S,5R*)-4-Ethyl 1,8-dimethyl 5-benzamidooctane-1,4,8-tricarboxylate (**12**).* White solid. Yield: 90% (180 mg). Mp 37–38 °C; (R_f=0.3, *n*-hexane/EtOAc 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.32 (t, 3H, CH_3, J=7.1 Hz), 1.46–1.91 (m, 9H, H-1, H-2, H-3, H-6), 2.32–2.47 (m, 3H, H-6, H-7), 2.65–2.72 (m, 1H, H-4), 3.68 (s, 6H, OCH_3), 4.18–4.26 (q, 2H, OCH_2), 4.36–4.44 (m, 1H, H-5), 6.52 (d, 1H, NH, J=9.0 Hz), 7.44–7.84 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 28.5, 29.2, 29.5, 32.8, 35.6, 51.0, 60.8, 126.5, 128.1, 129.1, 132.0, 135.5, 142.6, 142.9, 147.2, 167.2, 174.7. IR: ν_{max} 3265, 1724, 1170, 1156. Anal. Calcd for $C_{22}H_{31}NO_7$: C, 62.69; H, 7.41; N, 3.32. Found: C, 62.39; H, 7.08; N, 2.99.



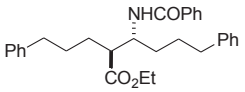
3.6.8. Ethyl (2S,3R*)-2-allyl-3-benzamidohex-5-enoate (**14**).* Yellow solid. Yield: 45% (90 mg). Mp 45–46 °C; (R_f=0.3, *n*-hexane/EtOAc 3:1). ^{1}H NMR (DMSO, 400 MHz) δ: 1.31 (t, 3H, CH_3, J=7.1 Hz), 2.28–2.65 (m, 4H, H-3, H-6), 2.78–2.85 (m, 1H, H-4), 4.21 (q, 2H, OCH_2, J=7.2 Hz), 4.50–4.58 (m, 1H, H-5), 5.07–5.18 (m, 4H, H-1, H-8), 5.78–5.91 (m, 2H, H-2, H-7), 6.46 (d, 1H, NH, J=9.5 Hz), 7.41–7.81 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 15.1, 33.9, 37.6, 50.2, 50.8, 60.9, 117.6, 118.0, 128.1, 129.1, 132.0, 135.4, 135.8, 136.2, 167.2, 173.8. IR: ν_{max} 3245, 1724, 1633, 1333, 1178. Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.50; H, 7.99; N, 4.31.



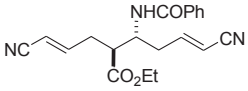
3.6.9. Ethyl (2S,3R*)-3-benzamido-2-propylhexanoate (**16**).* White solid. Yield: 80% (160 mg). Mp 63–65 °C; (R_f=0.4, *n*-hexane/EtOAc 5:1). ^{1}H NMR (DMSO, 400 MHz) δ: 1.27–1.33 (m, 3H, CH_3), 1.34–1.89 (m, 14H, H-1, H-2, H-3, H-6, H-7, H-8), 2.36–2.69 (m, 1H, H-4), 4.17–4.25 (m, 2H, OCH_2), 4.36–4.45 (m, 1H, H-5), 6.42 (d, 1H, NH, J=8.6 Hz), 7.42–7.85 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.5, 14.7, 15.0, 19.7, 20.9, 31.9, 35.4, 51.0, 60.8, 128.1, 129.2, 132.0, 135.5, 167.4, 174.8. IR: ν_{max} 3332, 1721, 1635, 1532, 1177. Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.46; H, 9.28; N, 4.27.



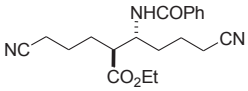
3.6.10. Ethyl (2S,3R*,E)-3-benzamido-2-cinnamyl-6-phenylhex-5-enoate (**15**).* White solid. Yield: 46% (92 mg). Mp 129–131 °C; (R_f=0.4, *n*-hexane/EtOAc 3:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25–1.31 (m, 3H, CH_3), 2.42–2.99 (m, 5H, H-3, H-4, H-6), 4.14–4.25 (m, 2H, OCH_2), 4.58–4.73 (m, 1H, H-5), 6.18–6.30 (m, 2H, H-1, H-8), 6.47–6.63 (m, 2H, H-2, H-7), 7.17–7.80 (m, 15H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 15.0, 33.5, 37.2, 50.6, 51.3, 60.9, 126.7, 128.1, 129.1, 129.4, 132.0, 132.3, 132.7, 135.6, 137.8, 138.0, 167.3, 173.8. IR: ν_{max} 3338, 1723, 1635, 1526, 1147. Anal. Calcd for $C_{30}H_{31}NO_3$: C, 79.44; H, 6.89; N, 3.09. Found: C, 79.07; H, 6.51; N, 2.77.



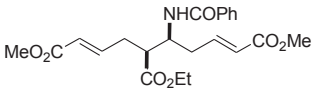
3.6.11. Ethyl (2S,3R*)-3-benzamido-6-phenyl-2-(3-phenylpropyl) hexanoate (**17**).* White solid. Yield: 92% (185 mg). Mp 54–55 °C; (R_f=0.3, *n*-hexane/EtOAc 3:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.26 (t, 3H, CH_3, J=6.9 Hz), 1.40–1.91 (m, 10H, H-1, H-2, H-3, H-6, H-7), 2.56–2.82 (m, 3H, H-4, H-8), 4.13–4.21 (m, 2H, OCH_2), 4.39–4.48 (m, 1H, H-5), 6.32 (d, 1H, NH, J=9.0 Hz), 7.13–7.77 (m, 15H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 22.0, 23.1, 29.0, 32.5, 33.6, 33.9, 50.8, 52.1, 60.9, 128.1, 129.1, 132.0, 135.5, 167.4, 174.5. IR: ν_{max} 3301, 1720, 1628, 1547, 1141. Anal. Calcd for $C_{30}H_{35}NO_3$: C, 78.74; H, 7.71; N, 3.06. Found: C, 78.49; H, 8.07; N, 3.40.



3.6.12. Ethyl (2S,3R*,E)-ethyl 3-benzamido-6-cyano-2-((E)-3-cyanoallyl)hex-5-enoate (**11**).* Yellow oil. Yield: 70% (140 mg). (R_f=0.4, *n*-hexane/EtOAc 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.32–1.36 (m, 3H, CH_3), 2.11–3.34 (m, 5H, H-3, H-4, H-6), 4.20–4.31 (m, 2H, OCH_2), 4.54–4.72 (m, 1H, H-5), 5.52–5.60 (m, 2H, H-2, H-7), 6.49–6.84 (m, 2H, H-1, H-8), 7.43–7.83 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.8, 36.8, 38.3, 45.7, 58.8, 61.6, 102.4, 102.7, 118.7, 128.2, 128.7, 129.1, 131.4, 132.3, 136.8, 169.9, 173.6. IR: ν_{max} 3341, 2222, 1728, 1613, 1392, 1179, 1028. Anal. Calcd for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.68; H, 5.76; N, 12.29.

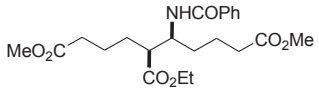


3.6.13. Ethyl (2S,3R*)-3-benzamido-6-cyano-2-(3-cyanopropyl)hexanoate (**13**).* Colourless oil. Yield: 96% (192 mg). (R_f=0.3, *n*-hexane/EtOAc 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.31–1.37 (m, 3H, CH_3), 1.49–2.55 (m, 12H, H-1, H-2, H-3, H-4, H-6, H-7, H-8), 4.20–4.31 (m, 2H, OCH_2), 4.54–4.72 (m, 1H, H-5), 7.41–7.77 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 17.0, 22.1, 34.4, 46.5, 59.4, 61.5, 121.2, 121.4, 128.1, 128.6, 129.0, 137.0, 169.8, 174.3. IR: ν_{max} 3340, 2246, 1727, 1613, 1393, 1179, 1027. Anal. Calcd for $C_{20}H_{25}N_3O_3$: C, 67.58; H, 7.09; N, 11.82. Found: C, 67.22; H, 6.78; N, 11.51.

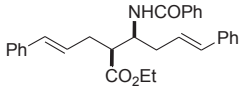


3.6.14. (1E,4S*,5S*,7E*)-4-Ethyl 1,8-dimethyl 5-benzamidoocta-1,7-diene-1,4,8-tricarboxylate (**19**).* White solid. Yield: 71% (142 mg). Mp 121–123 °C; (R_f=0.4, *n*-hexane/EtOAc 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.33 (t, 3H, CH_3, J=7.2 Hz), 2.42–2.68 (m, 4H, H-3, H-6), 2.82–2.88 (m, 1H, H-4), 3.73 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.20–4.30 (m, 2H, OCH_2), 4.51–4.60 (m, 1H, H-5), 5.85–5.97 (m, 2H, H-1, H-8), 6.84–6.99 (m, 2H, H-2, H-7), 7.38–7.87 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 31.6, 34.8, 49.2, 50.1, 52.1, 61.2, 123.3, 123.5, 128.2, 129.2, 132.2, 135.3, 146.7, 147.1, 166.8, 167.2, 172.9. IR: ν_{max} 3261, 1715, 1637, 1024, 1151, 1028. Anal. Calcd for

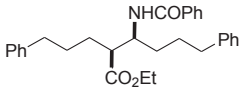
$C_{22}H_{27}NO_7$: C, 63.30; H, 6.52; N, 3.36. Found: C, 63.68; H, 6.19; N, 3.02.



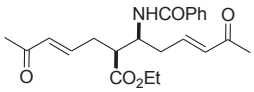
3.6.15. (4S,5S*)-4-Ethyl 1,8-dimethyl 5-benzamidooctane-1,4,8-tricarboxylate (**22**).* Colourless oil. Yield: 95% (190 mg). (R_f=0.3, *n*-hexane/EtOAc 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.34 (t, 3H, CH_3, J=7.0 Hz), 1.55–1.80 (m, 9H, H-1, H-2, H-3, H-6), 2.29–2.41 (m, 3H, H-6, H-7), 2.66–2.72 (m, 1H, H-4), 3.65 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 4.24 (q, 2H, OCH_2, J=7.2 Hz), 4.36–4.44 (m, 1H, H-5), 7.44–7.88 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 31.7, 34.8, 49.3, 50.3, 52.2, 61.2, 123.3, 123.6, 128.1, 129.2, 132.2, 135.3, 146.7, 147.1, 166.7, 167.1, 172.9. IR: ν_{max} 2951, 1730, 1642, 1524, 1167. Anal. Calcd for $C_{22}H_{31}NO_7$: C, 62.69; H, 7.41; N, 3.32. Found: C, 62.33; H, 7.10; N, 3.01.



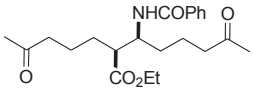
3.6.16. Ethyl (2S,3S*,E*)-3-benzamido-2-cinnamyl-6-phenylhex-5-enoate (**25**).* White solid. Yield: 64% (128 mg). Mp 129–131 °C; (R_f=0.4, *n*-hexane/EtOAc 3:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.28–1.36 (m, 3H, CH_3), 1.57–1.62 (m, 1H, H-3), 2.74–3.02 (m, 3H, H-3, H-6), 3.12–3.20 (m, 1H, H-4), 4.17–4.31 (m, 2H, OCH_2), 5.76–5.85 (m, 1H, H-5), 6.02–6.08 (m, 1H, H-1), 6.22–6.29 (m, 1H, H-8), 6.79 (dd, 2H, H-2, H-7, J_1=6.9 Hz, J_2=6.9 Hz), 7.19–7.82 (m, 15H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 35.4, 50.7, 58.3, 61.2, 124.2, 127.0, 128.2, 129.2, 129.7, 132.1, 132.8, 135.4, 137.9, 142.0, 166.9, 175.1. IR: ν_{max} 3294, 1733, 1631, 1529, 1179. Anal. Calcd for $C_{30}H_{31}NO_3$: C, 79.44; H, 6.89; N, 3.09. Found: C, 79.11; H, 7.12; N, 2.78.



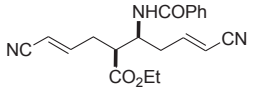
3.6.17. Ethyl (2S,3S*)-3-benzamido-6-phenyl-2-(3-phenylpropyl) hexanoate (**26**).* White solid. Yield: 81% (162 mg). Mp 121–123 °C; (R_f=0.3, *n*-hexane/EtOAc 3:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.19–1.36 (m, 3H, CH_3), 1.65–2.14 (m, 9H, H-1, H-2, H-3, H-6, H-7), 2.58–2.84 (m, 4H, H-4, H-7, H-8), 4.13–4.22 (m, 2H, OCH_2), 4.35 (q, 1H, H-5, J=8.8 Hz), 6.01 (d, 1H, NH, J=7.7 Hz), 7.15–7.80 (m, 15H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 28.5, 29.2, 29.5, 32.8, 35.5, 35.6, 51.0, 60.8, 126.5, 128.1, 129.2, 131.9, 135.6, 167.2, 174.7. IR: ν_{max} 3293, 1725, 1634, 1532, 1173. Anal. Calcd for $C_{30}H_{35}NO_3$: C, 78.74; H, 7.71; N, 3.06. Found: C, 78.41; H, 7.40; N, 2.79.



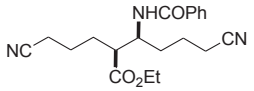
3.6.18. Ethyl (2S,3S*,E)-3-benzamido-7-oxo-2-((E)-4-oxopent-2-enyl)oct-5-enoate (**21**).* Yellow oil. Yield: 59% (118 mg). (R_f=0.4, *n*-hexane/EtOAc 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.31–1.36 (m, 3H, CH_3), 2.23 (s, 3H, $COCH_3$), 2.26 (s, 3H, $COCH_3$), 2.50–2.70 (m, 4H, H-3, H-6), 2.83–2.89 (m, 1H, H-4), 4.21–4.31 (m, 2H, OCH_2), 4.56–4.64 (m, 1H, H-5), 6.11 (s, 1H, H-1), 6.15 (s, 1H, H-8), 6.70–6.84 (m, 2H, H-2, H-7), 7.43–7.87 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 27.5, 27.6, 31.9, 35.2, 49.2, 50.4, 61.1, 128.1, 129.2, 129.6, 132.8, 133.8, 135.4, 145.5, 145.7, 167.2, 173.0, 198.7. IR: ν_{max} 3191, 1727, 1634, 1534, 1253, 1177. Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.19; H, 6.72; N, 3.30.



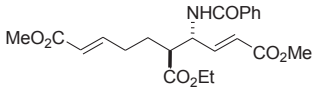
3.6.19. Ethyl (2S,3S*)-3-benzamido-7-oxo-2-(4-oxopentyl)octanoate (**24**).* Colourless oil. Yield: 70% (140 mg). (R_f=0.3, *n*-hexane/EtOAc 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.34 (t, 3H, CH_3, J=7.2 Hz), 1.51–1.76 (m, 9H, H-1, H-2, H-3, H-6, H-7), 2.13 (s, 3H, $COCH_3$), 2.15 (s, 3H, $COCH_3$), 2.41–2.56 (m, 3H, H-7, H-8), 2.65–2.71 (m, 1H, H-4), 4.24 (q, 2H, OCH_2, J=7.1 Hz), 4.34–4.42 (m, 1H, H-5), 7.44–7.87 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 20.8, 22.3, 28.6, 30.5, 31.6, 43.2, 43.3, 50.6, 51.0, 60.7, 128.0, 129.1, 132.0, 135.6, 166.9, 174.4, 208.9, 209.2. IR: ν_{max} 3340, 1710, 1643, 1527, 1180. Anal. Calcd for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02; N, 3.60. Found: C, 67.50; H, 7.73; N, 3.28.



3.6.20. Ethyl (2S,3S*,E)-3-benzamido-6-cyano-2-((E)-3-cyanoallyl) hex-5-enoate (**20**).* Yellow oil. Yield: 74% (148 mg). (R_f=0.4, *n*-hexane/EtOAc 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.34–1.40 (m, 3H, CH_3), 2.48–2.70 (m, 4H, H-3, H-6), 2.74–2.82 (m, 1H, H-4), 4.25–4.33 (m, 2H, OCH_2), 4.54–4.61 (m, 1H, H-5), 5.42–5.50 (m, 2H, H-2, H-7), 6.62–6.75 (m, 2H, H-1, H-8), 7.47–7.87 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.8, 32.8, 35.9, 48.9, 49.9, 61.4, 102.3, 102.7, 118.6, 128.1, 129.2, 132.3, 135.2, 153.8, 154.2, 167.2, 172.6. IR: ν_{max} 3312, 2223, 1725, 1635, 1534, 1177. Anal. Calcd for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.02; H, 5.73; N, 11.60.

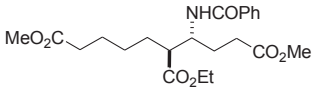


3.6.21. Ethyl (2S,3S*)-3-benzamido-6-cyano-2-(3-cyanopropyl)hexanoate (**23**).* Colourless oil. Yield: 92% (184 mg). (R_f=0.2, *n*-hexane/EtOAc 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.36 (t, 3H, CH_3, J=7.1 Hz), 1.66–1.95 (m, 8H, H-1, H-2, H-3, H-6), 2.30–2.57 (m, 4H, H-7, H-8), 2.67–2.72 (m, 1H, H-4), 4.27 (q, 2H, OCH_2, J=7.2 Hz), 4.41–4.49 (m, 1H, H-5), 7.46–7.91 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 16.8, 17.0, 22.7, 23.9, 28.2, 31.1, 50.0, 50.5, 61.0, 121.2, 121.3, 128.1, 129.2, 132.1, 135.4, 167.2, 173.9. IR: ν_{max} 3296, 2244, 1722, 1635, 1535, 1241. Anal. Calcd for $C_{20}H_{25}N_3O_3$: C, 67.58; H, 7.09; N, 11.82. Found: C, 67.21; H, 6.76; N, 11.50.

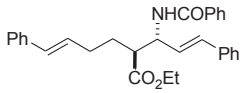


3.6.22. (1E,3R,4S*,7E)-4-Ethyl 1,8-dimethyl-3-benzamidoocta-1,7-diene-1,4,8-tricarboxylate (**28**).* Colourless oil. Yield: 65% (130 mg). (R_f=0.4, *n*-hexane/EtOAc 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.28–1.35 (m, 3H, CH_3), 1.68–1.77 (m, 1H, H-3), 2.01–2.08 (m, 1H, H-3), 2.31–2.42 (m, 2H, H-4), 2.79–2.85 (m, 1H, H-5), 3.75–3.77 (m, 6H, OCH_3), 4.24 (q, 2H, OCH_2, J=7.0 Hz), 4.08–4.19 (m, 1H, H-6), 5.90 (d, 1H, H-1, J=15.6 Hz), 6.07 (d, 1H, H-8, J=15.6 Hz), 6.90–7.00 (m, 2H, H-2, H-7), 7.43–7.86 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.8, 27.7, 30.0, 49.3, 52.1, 52.4, 52.6, 61.3, 122.2, 122.7, 128.2, 132.4, 134.9, 146.3, 149.1, 166.6, 166.9, 167.1, 173.2. IR: ν_{max}

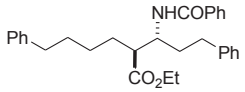
3366, 1715, 1640, 1522, 1211, 1151. Anal. Calcd for $C_{22}H_{27}NO_7$: C, 63.30; H, 6.52; N, 3.36. Found: C, 63.66; H, 6.18; N, 3.01.



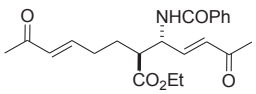
3.6.23. (3R,4S*)-4-Ethyl 1,8-dimethyl-3-benzamidooctane-1,4,8-tricarboxylate (**31**).* Colourless oil. Yield: 95% (190 mg). (R_f=0.3, *n*-hexane/EtOAc 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.32 (t, 3H, CH_3, J=7.2 Hz), 1.38–2.04 (m, 9H, H-1, H-2, H-3, H-4, H-7), 2.31–2.54 (m1, 3H, H-7, H-8), 2.65–2.72 (m, 1H, H-5), 3.61 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 4.18–4.27 (m, 2H, OCH_2), 4.36–4.45 (m, 1H, H-6), 6.68 (d, 1H, NH, J=9.4 Hz), 7.43–7.84 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 25.1, 27.0, 28.3, 29.3, 31.2, 33.9, 50.7, 50.9, 52.0, 52.1, 60.9, 128.1, 129.1, 132.1, 135.3, 167.4, 173.8, 174.0, 174.4. IR: ν_{max} 3314, 1728, 1638, 1532, 1171. Anal. Calcd for $C_{22}H_{31}NO_7$: C, 62.69; H, 7.41; N, 3.32. Found: C, 62.36; H, 7.08; N, 3.00.



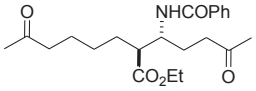
3.6.24. (S,E)-Ethyl 2-((R*,E)-1-benzamido-3-phenylallyl)-6-phenylhex-5-enoate (**34**).* White solid. Yield: 61% (122 mg). Mp 124–126 °C; (R_f=0.4, *n*-hexane/EtOAc 3:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.29 (t, 3H, CH_3, J=7.2 Hz), 1.71–1.84 (m, 1H, H-3), 2.00–2.15 (m, 1H, H-3), 2.33–2.52 (m, 2H, H-4), 2.87–2.96 (m, 1H, H-5), 4.18–4.27 (m, 2H, OCH_2), 5.10–5.18 (m, 1H, H-6), 6.18–6.32 (m, 2H, H-2, H-9), 6.43–6.51 (m, 1H, H-1), 6.66–6.74 (m, 1H, H-10), 6.93 (d, 1H, NH, J=8.8 Hz), 7.19–7.87 (m, 15H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 29.3, 31.3, 50.6, 54.2, 60.9, 126.7, 127.1, 127.6, 128.6, 128.7, 129.1, 129.4, 130.1, 130.5, 131.1, 131.9, 132.2, 132.4, 135.3, 137.2, 137.9, 166.8, 173.8. IR: ν_{max} 3317, 1725, 1634, 1520, 1170. Anal. Calcd for $C_{30}H_{31}NO_3$: C, 79.44; H, 6.89; N, 3.09. Found: C, 79.09; H, 6.59; N, 2.75.



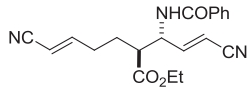
3.6.25. (S)-Ethyl 2-((R*)-1-benzamido-3-phenylpropyl)-6-phenylhexanoate (**35**).* Colourless oil. Yield: 78% (156 mg). (R_f=0.3, *n*-hexane/EtOAc 3:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25–1.30 (m, 3H, CH_3), 1.48–2.02 (m, 9H, H-1, H-2, H-3, H-4, H-7), 2.56–2.80 (m, 4H, H-5, H-7, H-8), 4.15–4.23 (m, 2H, OCH_2), 4.43–4.52 (m, 1H, H-6), 6.48 (d, 1H, NH, J=9.5 Hz), 7.15–7.80 (m, 15H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 27.2, 29.3, 31.5, 32.8, 35.1, 35.7, 51.0, 51.2, 60.8, 126.5, 126.6, 128.2, 129.2, 132.0, 135.6, 142.5, 142.9, 167.5, 174.6. IR: ν_{max} 3316, 1720, 1631, 1547, 1148. Anal. Calcd for $C_{30}H_{35}NO_3$: C, 78.74; H, 7.71; N, 3.06. Found: C, 78.45; H, 8.02; N, 2.77.



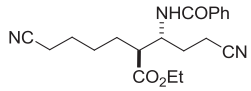
3.6.26. (S,E)-Ethyl 2-((R*,E)-1-benzamido-4-oxopent-2-enyl)-7-oxooct-5-enoate (**30**).* Yellow oil. Yield: 55% (110 mg). (R_f=0.4, *n*-hexane/EtOAc 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.28–1.35 (m, 3H, CH_3), 1.76–1.86 (m, 1H, H-3), 1.97–2.22 (m, 2H, H-3, H-4), 2.62–2.96 (m, 2H, H-4, H-5), 2.27–2.30 (m, 6H, $COCH_3$), 5.10–5.17 (m, 2H, OCH_2), 6.15 (d, 1H, H-1, J=16.1 Hz), 6.30 (d, 1H, H-8, J=9.5 Hz), 5.90 (d, 1H, H-1, J=15.6 Hz), 6.07 (d, 1H, H-8, J=16.1 Hz), 6.73–6.84 (m, 2H, H-2, H-7), 6.94 (d, 1H, NH, J=8.7 Hz), 7.43–7.86 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.8, 27.6, 28.1, 30.3, 43.1, 43.5, 49.4, 52.6, 62.2, 128.2, 128.4, 129.2, 129.5, 131.8, 134.9, 144.8, 148.1, 167.3, 173.3, 199.2, 207.4. IR: ν_{max} 2979, 1725, 1638, 1527, 1361, 1253, 1162. Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.17; H, 6.70; N, 3.99.



3.6.27. (S)-Ethyl 2-((R*)-1-benzamido-4-oxopentyl)-7-oxooctanoate (**33**).* Colourless oil. Yield: 93% (186 mg). (R_f=0.3, *n*-hexane/EtOAc 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.28–1.35 (m, 3H, CH_3), 1.47–1.71 (m, 3H, H-2, H-3), 1.73–1.96 (m, 4H, H-3, H-4, H-8), 2.12–2.16 (m, 6H, $COCH_3$), 2.42–2.85 (m, 7H, H-1, H-4, H-5, H-6, H-7). 4.19–4.26 (m, 2H, OCH_2), 7.40–7.83 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 19.1, 23.9, 27.2, 29.5, 30.5, 30.7, 31.2, 43.2, 43.5, 50.9, 60.9, 128.1, 129.2, 132.1, 135.4, 167.5, 174.7. IR: ν_{max} 3358, 1713, 1642, 1375, 1160, 1131. Anal. Calcd for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02; N, 3.60. Found: C, 67.52; H, 8.36; N, 3.28.



3.6.28. (S,E)-Ethyl 2-((R*,E)-1-benzamido-3-cyanoallyl)-6-cyanohex-5-enoate (**29**).* Colourless oil. Yield: 67% (134 mg). (R_f=0.4, *n*-hexane/EtOAc 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.31–1.39 (m, 3H, CH_3), 1.65–1.77 (m, 1H, H-4), 1.98–2.07 (m, 1H, H-4), 2.33–2.46 (m, 2H, H-3), 2.77–2.83 (m, 1H, H-5), 4.24–4.32 (m, 2H, OCH_2), 5.03–5.10 (m, 1H, H-6), 5.54 (dd, 2H, H-2, H-7, J_1=16.2 Hz, J_2=8.5 Hz), 6.65–6.78 (m, 2H, H-1, H-8), 6.94 (d, 1H, NH, J=8.5 Hz), 7.44–7.82 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 27.1, 31.1, 48.9, 53.2, 61.6, 101.2, 102.5, 118.3, 118.8, 128.3, 129.3, 132.5, 134.8, 153.1, 156.3, 167.3, 172.9. IR: ν_{max} 3322, 2224, 1725, 1634, 1525, 1183. Anal. Calcd for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.00; H, 5.73; N, 12.30.



3.6.29. (S)-Ethyl 2-((R*)-1-benzamido-3-cyanopropyl)-6-cyanohexanoate (**32**).* Colourless oil. Yield: 95% (190 mg). (R_f=0.2, *n*-hexane/EtOAc 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.35 (t, 3H, CH_3, J=7.2 Hz), 1.56–2.82 (m, 13H, H-1, H-2, H-3, H-4, H-5, H-7, H-8), 4.22–4.31 (m, 2H, OCH_2), 4.42–4.51 (m, 1H, H-6), 7.44–7.84 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.7, 14.9, 16.8, 25.4, 26.8, 28.5, 28.7, 50.2, 50.7, 61.1, 121.2, 121.3, 128.3, 129.2, 132.2, 135.3, 167.4, 174.3. IR: ν_{max} 3320, 2246, 1725, 1638, 1532, 1178, 1026. Anal. Calcd for $C_{20}H_{25}N_3O_3$: C, 67.58; H, 7.09; N, 11.82. Found: C, 67.22; H, 7.41; N, 11.55.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.02.063.

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