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Stereocontrolled One-Step Synthesis of Difunctionalised Cispentacin Derivatives through Ring-Opening Metathesis of Norbornene β-Amino Acids

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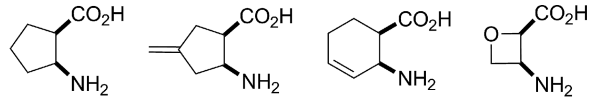
Through the ring-opening metathesis of norbornene or oxanorbornene β-amino acids with ethylene in the presence of certain Ru catalysts, a facile and convenient stereocontrolled one-step method was devised for the preparation of divinylated cispentacins and oxacyclic cispentacin stereoisomers with four chiral centres. The products are interesting scaffolds for peptide chemistry and for the synthesis of novel functionalised materials through olefinic bond transformations. The ring-opening metathesis proceeds without affecting the chiral centres of the starting molecules, so that their stereochemistry was conserved and determines the configuration of the chiral centres in the products.

Introduction

Metathesis is one of the most useful transition-metal-catalysed reactions for the creation of one or more C–C double bonds in a molecule. Its variations have been utilised efficiently for the synthesis of various classes of compounds, natural products, polymers and small biomolecules.[1] A number of amino acids and peptides have been synthesised or modified and a series of other structural manipulations have been achieved by applying cross-metathesis (CM) reactions.[2] Conformationally restricted unusual, nonproteinogenic amino acids or oligopeptides containing an alkene moieties play a crucial role in the construction of novel "new-generation" peptides that exhibit improved stabilities against enzymes or metabolic degradation. The carbon–carbon double-bond-linked cyclic oligopeptides may have significant effects on helical structures, and may therefore play an important role in influencing biological properties, and consequently may have a considerable impact in drug research.[2]

Cyclic β-amino acids have been a focus of interest of synthetic and medicinal chemists over the past two decades due to the increasing importance of such small molecules, for example, (1*R*,2*S*)-2-aminocyclopentanecarboxylic acid (cispentacin; **1**), (1*R*,2*S*)-2-amino-4-methylenecyclopentanecarboxylic acid (icofungipen; **2**), BAY Y9379 (**3**), (2*R*,3*S*)-3-aminooxetane-2-carboxylic acid (oxetin; **4**) and some highly functionalised derivatives, in pharmaceutical research (Figure 1). These compounds are of great significance as precursors of β-lactams, as key elements of various bioactive products, and as antitumoral, antibacterial, antiviral and cardioprotective agents.[3a,3b] As conformationally rigid building blocks, these small molecules are of appreciable interest for the synthesis of peptides, and they therefore have a considerable impact in the fields of biomolecules and drug discovery.[3c–3f] Starting from acyclic alkenylated β-amino acid stereoisomers, ring-closing metathesis (RCM) has been used efficiently for the synthesis of cyclic β-amino acids with a ring C–C double bond in their structure that are otherwise difficult to access.[4] Moreover, π-π or CH-π interactions play significant roles in the structural stabilisation of peptides, influencing their secondary structures, strands and helices, and they have therefore found applications in medicinal chemistry.[5]



1 (cispentacin) **2** (icofungipen) **3** (BAY Y9379) **4** (oxetin)

Figure 1. Several bioactive β-amino acids.

The goal of the present work was to develop a stereocontrolled route to novel divinylated cispentacin stereoisomers, which, because of the newly created olefinic bonds, are useful precursors for further functionalisation. The Ru-catalysed ring-opening metathesis (ROM) of di-*exo*- or di-*endo*-norbornene β-amino acids allowed the stereocontrolled preparation of a series of divinyl-substituted cispentacins, which, with the exception of one isomer, were not accessible by previously described methods (Schemes 1 and 2).[6]

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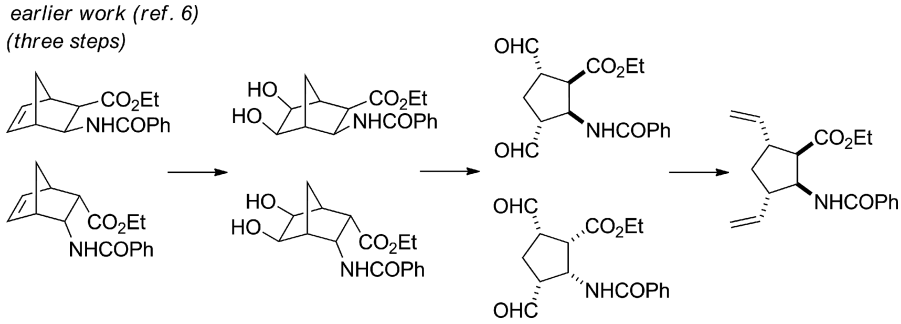
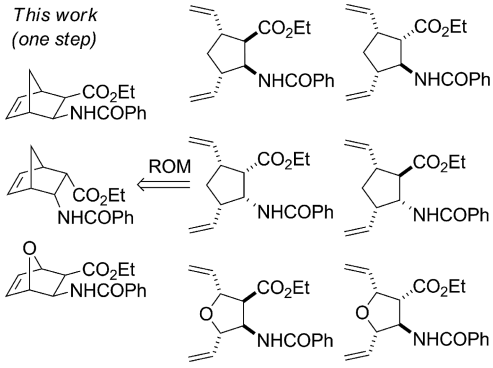


Scheme 1. Stereocontrolled synthesis of divinylated cispentacin derivative from norbornene β-amino esters through oxidative ring opening and Wittig reaction.[6]



Scheme 2. Stereocontrolled synthesis of divinylated cispentacin derivatives from norbornene β-amino esters through ROM.

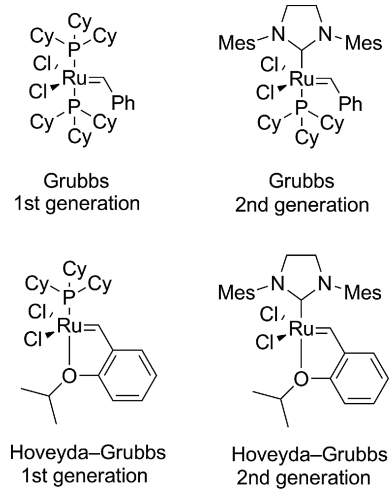


Figure 2. Commercially available catalysts used in this work.

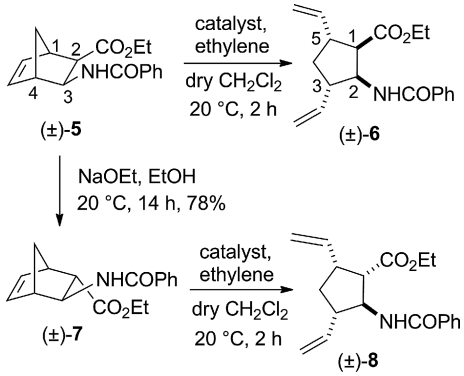
Results and Discussion

ROM is a convenient method for the synthesis of functionalised olefins from cyclic or bicyclic unsaturated precursors.[1] The ROM of unsaturated bicyclic systems such as norbornene[7] or oxanorbornene derivatives[8] is a widely and efficiently used method for the synthesis of novel fused, spiro or bridged systems or polycyclic (carbocyclic or heterocyclic) derivatives.

We started our investigations into the synthesis of 3,5-difunctionalised cispentacins by reacting racemic di-*exo*-norbornene *N*-benzoylated ethyl ester (±)-**5**[6a] with ethylene in the presence of a number of commercially available common catalysts (Figure 2). The reactions were performed systematically in anhydrous CH_2Cl_2 under an Ar and ethylene atmosphere in the presence of Grubbs 1st generation (G1), Grubbs 2nd generation (G2), Hoveyda–Grubbs 1st generation (HG1), and Hoveyda–Grubbs 2nd generation (HG2) catalysts.

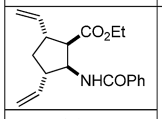
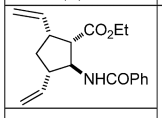
During stirring of the mixture of (±)-**5** and catalyst in anhydrous CH_2Cl_2 at 20 °C for 2 h (reaction monitored by TLC), the desired divinylated product (±)-**6**, in which the two novel vinyl groups are *trans* with respect to the ester and amide moieties, was isolated in moderate yields (33–41%) after separation from the accompanying polymeric materials by column chromatography, with the best yield being attained with HG2 catalyst (Scheme 3 and Table 1). Notably, with G1 and HG1 catalyst, an amount of starting material was also recovered. The configuration of the stereogenic centres in the product (±)-**6** was predetermined by the structure of the starting norbornene β-amino ester (±)-**5**. Compound (±)-**6** was synthesised earlier in 30% overall yield from (±)-**5** by OsO_4-catalysed C–C double bond dihydroxylation, followed by $NaIO_4$ oxidation by ring cleavage and a Wittig reaction with triphenylmethylphosphonium bromide/*t*BuOK.[6a] Not only was the yield of the ROM of (±)-**5** to (±)-**6** significantly higher in comparison with the oxidative ring-opening method,[6a] but the transformation could also be accomplished in one step instead of three steps, without the use of large amounts of solvents, silica gel, or toxic OsO_4 and phosphorane.

A novel divinylated cispentacin derivative (±)-**8** (which could not be prepared by a previously published method),[6] a stereoisomer of (±)-**6**, was accessed from norbornene amino ester (±)-**7**, which was obtained by epimerisation at C-2 of di-*exo*-derivative (±)-**5** in the presence of NaOEt in EtOH. The ROM was performed at room temperature with each catalyst, and afforded the corresponding disubstituted cyclopentane β-amino ester (±)-**8**, with the ester and amide groups in a *trans* relationship, in 20–80% isolated yields, the highest yield being achieved with the HG1 catalyst (Table 1).

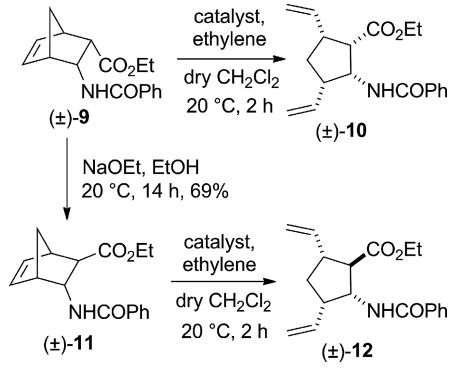


Scheme 3. Stereocontrolled synthesis of divinylated cispentacin stereoisomers (±)-**6** and (±)-**8**.

Table 1. Isolated yields for compounds (±)-**6** and (±)-**8** in ROM reactions with various catalysts.

Catalyst / Product	G1 catalyst	G2 catalyst	HG1 catalyst	HG2 catalyst
 (±)-**6**	37%	33%	38%	41%
 (±)-**8**	46%	20%	80%	28%

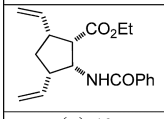
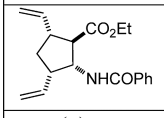
Racemic di-*endo*-norbornene β-amino ester (±)-**9** was then subjected to ROM with ethylene, with all four catalysts, and gave the novel *all-cis* 3,5-divinyl-substituted cispentacin derivative (±)-**10**, albeit in rather modest yields (6–31%); the highest yield was obtained with the HG2 catalyst (Scheme 4, Table 2).



Scheme 4. Stereocontrolled synthesis of divinylated cispentacin stereoisomers (±)-**10** and (±)-**12**.

The *all-cis* divinylated amino ester (±)-**10** could not be synthesised by oxidative ring opening and Wittig reaction methodology.[6b] Epimerisation of di-*endo*-amino ester (±)-**9** led, through a change in the configuration, to amino ester (±)-**11**, ring opening of which resulted in the new divinylated cispentacin stereoisomer (±)-**12** in 68% yield after purification from the polymeric materials formed; interestingly, the best yield in this case was achieved with the G1 catalyst, however a quantity of starting material was also recovered (Scheme 4, Table 2).

Table 2. Isolated yields for compounds (±)-**10** and (±)-**12** in ROM reactions with various catalysts.

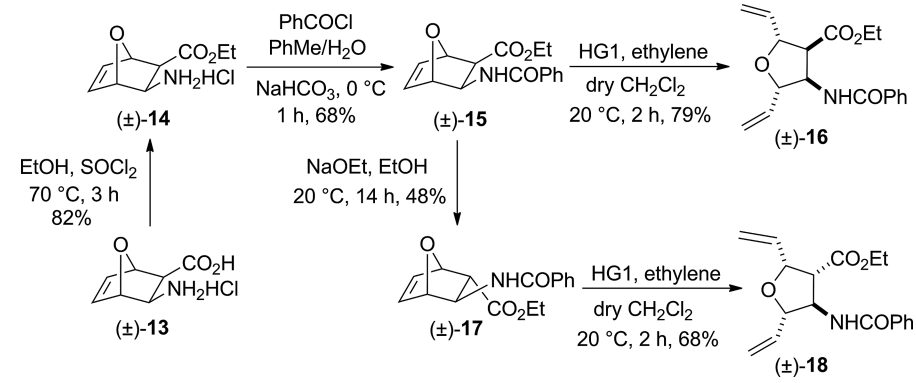
Catalyst / Product	G1 catalyst	G2 catalyst	HG1 catalyst	HG2 catalyst
 (±)-**10**	6%	26%	29%	31%
 (±)-**12**	68%	29%	45%	16%

In view of the relevance of heteroatom-containing cyclic β-amino acids and, in particular, O-containing derivatives such as oxetin (**4**), we extended the synthesis to the preparation of *O*-heterocyclic counterparts. Thus, oxanorbornene amino ester (±)-**14**[7e,9] derived from amino acid (±)-**13** was transformed under standard conditions into the *N*-benzoylated derivative (±)-**15**. *O*-Heterocyclic amino ester (±)-**15** and its stereoisomer (±)-**17** [prepared from (±)-**15** by epimerisation with NaOEt] were then submitted to ROM reactions in the presence of ethylene with different catalysts (Figure 2). However, in contrast to their carbocyclic analogues (Schemes 3 and 4), only the HG1 catalyst proved suitable in these transformations, giving the corresponding tetrahydrofuran β-amino ester stereoisomers (±)-**16** and (±)-**18** in good yields after purification by column chromatography (Scheme 5).

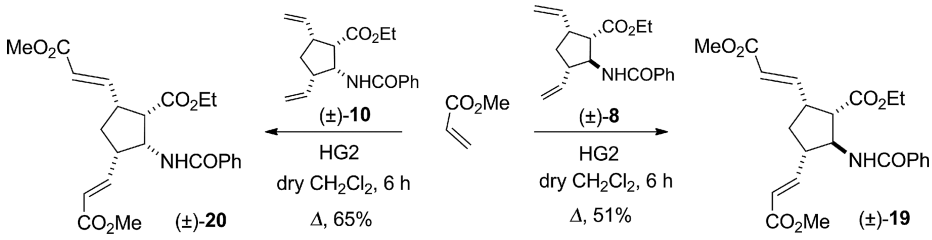
We then set out to develop a functionalisation procedure for the divinylated cispentacin derivative through a cross metathesis (CM) reaction. Accordingly, we selected an α,β-unsaturated ester, methyl acrylate, which was used as a CM reaction partner in transformations with two stereoisomers of divinylated cispentacin derivatives, (±)-**8** and (±)-**10**.

The reactions were carried out with all four catalysts in anhydrous CH_2Cl_2 heated to reflux under an Ar atmosphere for 6 h; the best yields of the corresponding CM adducts (±)-**19** and (±)-**20** were attained in both cases with the HG2 catalyst; only trace amounts of the target substances were formed with the other three catalysts (Figure 2). Given that (±)-**20** was identical to the material prepared earlier by an alternative route,[6b] it may be concluded that the CM reaction proceeded with *E* selectivity; the configuration of the newly created C–C double bonds in (±)-**19** and (±)-**20** involves *E* geometry (Scheme 6).

The above synthetic approach was adapted for access to enantiomerically pure target substances. We present here a synthetic route for the preparation of two optically pure products. Enantiomerically enriched forms of **6** and **8**, for example, were synthesised from β-lactam enantiomer (+)-

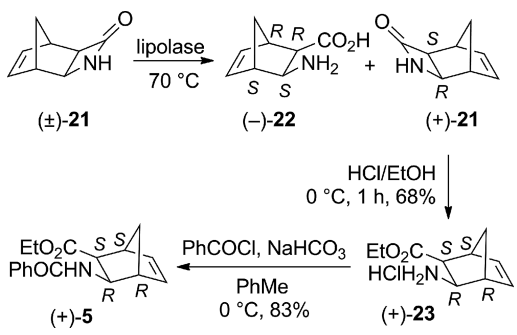


Scheme 5. Stereocontrolled synthesis of divinylated oxacispentacin stereoisomers (±)-**16** and (±)-**18**.



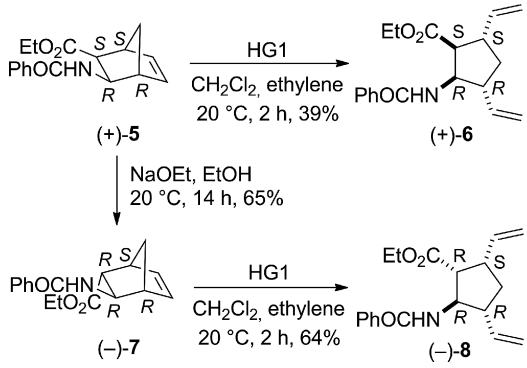
Scheme 6. Synthesis of functionalised cispentacin derivatives (±)-**19** and (±)-**20** by CM.

21 with an enantiomeric excess (*ee*) value of >98% (enantiomeric ratio, *er* 99:1), by enantioselective enzymatic ring opening of racemic azetidinone (±)-**21**.[10] Lactam (+)-**21** was converted by ethanolysis through (+)-**23**, followed by benzoylation into optically active ester (+)-**5** (Scheme 7). The *er* of this compound, determined by chiral HPLC analysis (see the Experimental Section) was found to be 95:5.



Scheme 7. Synthesis of optically pure amino ester (+)-**5**.

Amino ester (+)-**5**, in the presence of ethylene and the HG1 catalyst, underwent ring opening to furnish divinylated cispentacin derivative (+)-**6** (*er* = 95:5). Similar to the racemates, epimerisation of (+)-**5** provided (–)-**7**, ROM transformation of which led to divinylated transpentacin derivative (–)-**8** (*er* = 95:5; Scheme 8).



Scheme 8. Synthesis of optically pure divinylated amino esters (+)-**6** and (–)-**8**.

Conclusions

A stereocontrolled, one-step method for the preparation of stereoisomers of novel divinylated cispentacin derivatives and oxacyclic cispentacins with multiple chiral centres from di-*exo*- and di-*endo*-norbornene or oxanorbornene β-amino acids has been developed by ROM. Since the stereocentres are unaffected during the transformation, the configuration of the stereogenic centres of the target molecules is predetermined by the configuration of the chiral centres of the starting materials. Functionalisation of divinylated cispentacin derivatives with an unsaturated ester has been performed by CM, giving highly functionalised derivatives with multiple stereocentres. Due to the olefinic bond in

their structure, the divinylated cispentacin stereoisomers may be regarded as valuable small molecule precursors for further functionalisations, as demonstrated by a CM example and for the construction of novel peptides containing π-bond systems.

Experimental Section

General Procedure for the Ring-opening Metathesis Reaction: To a solution of norbornene amino ester **5**, **7**, **9**, **11**, **15** or **17** (142 mg) in anhydrous CH_2Cl_2 (15 mL), catalyst (5 mol-%) was added and the mixture was stirred at 20 °C under an ethylene atmosphere for 2 h (reaction monitored by TLC). H_2O (2 drops) was then added and the mixture was concentrated under reduced pressure and purified by column chromatography on silica gel.

Ethyl (1*R,2*S**,3*S**,5*R**)-2-Benzamido-3,5-divinylcyclopentanecarboxylate (6):** Yield 33–41% (52–65 mg);[6a] white solid; m.p. 99–101 °C; R_f = 0.52 (*n*-hexane/EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (t, J = 7.10 Hz, 3 H, CH_3), 1.52–1.58 (m, 1 H, CH_2), 2.04–2.12 (m, 1 H, CH_2), 2.77–2.82 (m, 1 H, 1-H), 2.96–3.11 (m, 2 H, 3-H and 5-H), 4.08–4.17 (m, 2 H, OCH_2), 4.60–4.66 (m, 1 H, 2-H), 5.03–5.12 (m, 4 H, =CH), 5.80–5.89 (m, 2 H, =CH), 6.80 (br. s, 1 H, NH), 7.42–7.58 (m, 3 H, Ar-H), 7.78–7.83 (m, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 14.8, 40.0, 45.7, 48.6, 53.8, 56.8, 60.7, 115.5, 116.0, 128.2, 129.0, 131.9, 135.3, 140.5, 141.2, 167.0, 172.7 ppm. MS (ESI, pos): m/z = 314 [M + 1]. $C_{19}H_{23}NO_3$ (313.40): calcd. C 72.82, H 7.40, N 4.47; found C 72.58, H 7.20, N 4.10.

Ethyl (1*R,2*S**,3*S**,4*S**)-3-Benzamidobicyclo[2.2.1]hept-5-ene-2-carboxylate (7):** Yield 78% (620 mg); white solid; m.p. 129–131 °C; R_f = 0.25 (*n*-hexane/EtOAc, 3:1). ^{1}H NMR (400 MHz, DMSO): δ = 1.19 (t, J = 7.10 Hz, 3 H, CH_3), 1.48–1.52 (m, 1 H, CH_2), 1.77–1.81 (m, 1 H, CH_2), 2.74–2.77 (m, 1 H, 1-H), 3.07–3.11 (m, 2 H, 2-H and 4-H), 3.95–4.08 (m, 3 H, OCH_2, 3-H), 6.04–6.10 (m, 1 H, 6-H), 6.27–6.31 (m, 1 H, 5-H), 7.46–7.54 (m, 3 H, Ar-H), 7.82–7.86 (m, 2 H, Ar-H), 8.46 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 15.0, 45.3, 47.4, 49.5, 50.4, 54.7, 60.8, 128.2, 129.0, 132.0, 135.4, 136.3, 137.2, 137.2, 173.4 ppm. MS (ESI, pos): m/z = 286 [M + 1]. $C_{17}H_{19}NO_3$ (285.34): calcd. C 71.56, H 6.71, N 4.91; found C 71.20, H 6.99, N 4.56.

Ethyl (1*S,2*S**,3*S**,5*R**)-2-Benzamido-3,5-divinylcyclopentanecarboxylate (8):** Yield 20–80% (32–127 mg); white solid; m.p. 114–116 °C R_f = 0.36 (*n*-hexane/EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.15 Hz, 3 H, CH_3), 1.69–1.77 (m, 1 H, CH_2), 2.03–2.08 (m, 1 H, CH_2), 2.74–2.79 (m, 1 H, 5-H), 3.04–3.09 (m, 1 H, 3-H), 3.10–3.15 (m, 1 H, 1-H), 4.06–4.13 (m, 2 H, OCH_2), 4.42–4.49 (m, 1 H, 2-H), 4.98–5.20 (m, 4 H, =CH), 5.67–5.76 (m, 2 H, =CH), 6.18 (br. s, 1 H, NH), 7.47–7.55 (m, 3 H, Ar-H), 7.74–7.77 (m, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 15.1, 37.0, 44.4, 49.4, 54.4, 58.5, 60.6, 116.0, 116.7, 128.1, 129.1, 132.0, 135.3, 139.0, 140.4, 166.7, 173.5 ppm. MS (ESI, pos): m/z = 314 [M + 1]. $C_{19}H_{23}NO_3$ (313.40): calcd. C 72.82, H 7.40, N 4.47; found C 72.50, H 7.11, N 4.11.

Ethyl (1*S,2*R**,3*S**,5*R**)-2-Benzamido-3,5-divinylcyclopentanecarboxylate (10):** Yield 6–31% (10–50 mg); colourless oil; R_f = 0.53 (*n*-hexane/EtOAc, 3:1). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.17 (t, J = 7.10 Hz, 3 H, CH_3), 1.82–1.97 (m, 2 H, CH_2), 2.91–3.00 (2 H, 3-H and 5-H), 3.27–3.32 (m, 1 H, 1-H), 3.97–4.08 (m, 2 H, OCH_2), 4.81–4.88 (m, 1 H, 2-H), 5.01–5.19 (m, 4 H, =CH), 5.79–6.02 (m, 2 H, =CH), 7.29 (br. s, 1 H, NH), 7.48–7.59 (m, 3 H, Ar-H), 7.68–7.74 (m, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO): δ = 15.0, 36.4, 45.1, 46.2, 52.8, 54.1, 60.6, 116.3, 117.5, 127.9, 129.2, 132.1, 125.5, 139.2, 139.3, 166.9, 172.1 ppm. MS (ESI, pos): m/z = 314 [M + 1]. $C_{19}H_{23}NO_3$ (313.40): calcd. C 72.82, H 7.40, N 4.47; found C 72.51, H 7.72, N 4.12.

Ethyl (1*R,2*R**,3*R**,4*S**)-3-Benzamidobicyclo[2.2.1]hept-5-ene-2-carboxylate (11):** Yield 69% (560 mg); white solid; m.p. 107–109 °C; R_f = 0.28 (*n*-hexane/EtOAc, 3:1). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.16 (t, J = 7.10 Hz, 3 H, CH_3), 1.38–1.43 (m, 1 H, CH_2), 1.67–1.72 (m, 1 H, CH_2), 2.31–2.34 (m, 1 H, 1-H), 2.96–2.99 (m, 1 H, 4-H), 3.17–3.20 (m, 1 H, 2-H), 4.06–4.14 (m, 2 H, OCH_2), 4.50–4.54 (m, 1 H, 3-H), 6.17–6.21 (dd, J_1 = 2.5, J_2 = 6.12 Hz, 1 H, 6-H), 5.42–5.47 (m, 1 H, 5-H), 7.40–7.52 (m, 3 H, Ar-H), 7.73–7.77 (m, 2 H, Ar-H), 7.99 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 15.0, 46.2, 46.3, 47.9, 50.7, 55.6, 61.0, 128.2, 129.0, 132.0, 135.1, 135.4, 138.9, 167.5, 174.8 ppm. MS (ESI, pos): m/z = 286 [M + 1]. $C_{17}H_{19}NO_3$ (285.34): calcd. C 71.56, H 6.71, N 4.91; found C 71.90, H 6.40, N 4.58.

Ethyl (1*R,2*R**,3*S**,5*R**)-2-Benzamido-3,5-divinylcyclopentanecarboxylate (12):** Yield 16–68% (25–107 mg); white solid; m.p. 69–71 °C; R_f = 0.4 (*n*-hexane/EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, J = 7.15 Hz, 3 H, CH_3), 1.62–1.67 (m, 1 H, CH_2), 2.31–2.36 (m, 1 H, CH_2), 2.58–2.63 (m, 1 H, 1-H), 2.97–3.03 (m, 1 H, 3-H), 3.11–3.15 (m, 1 H, 5-H), 4.16–4.22 (m, 2 H, OCH_2), 4.74–4.78 (m, 1 H, 2-H), 5.06–5.25 (m, 4 H, =CH), 5.82–5.87 (m, 2 H, =CH), 6.19 (br. s, 1 H, NH), 7.42–7.55 (m, 3 H, Ar-H), 7.72–7.77 (m, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 15.0, 37.7, 46.4, 46.9, 55.6, 56.3, 60.9, 115.9, 116.5, 128.1, 129.1, 131.9, 135.5, 138.9, 140.7, 166.7, 174.2 ppm. MS (ESI, pos): m/z = 314 [M + 1]. $C_{19}H_{23}NO_3$ (313.40): calcd. C 72.82, H 7.40, N 4.47; found C 73.12, H 7.09, N 4.73.

Ethyl (1*R,2*S**,3*R**,4*S**)-3-Benzamido-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate (15):** Yield 68% (330 mg); white solid; m.p. 117–119 °C; R_f = 0.42 (*n*-hexane/EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, J = 7.10 Hz, 3 H, CH_3), 2.86–2.90 (m, 1 H, 2-H), 4.12–4.24 (m, 2 H, OCH_2), 4.73–4.78 (m, 1 H, 3-H), 4.88–4.91 (dd, J_1 = 8.15, J_2 = 3.08 Hz, 1 H, 1-H), 5.19–5.22 (m, 1 H, 4-H), 6.57–6.61 (m, 2 H, 5-H and 6-H), 7.39 (br. s, 1 H, NH), 7.42–7.57 (m, 3 H, Ar-H), 7.77–7.82 (m, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 14.7, 48.1, 52.4, 60.9, 80.4, 82.8, 128.1, 129.0, 132.1, 135.1, 136.4, 139.0, 167.2, 172.1 ppm. MS (ESI, pos): m/z = 286 [M + 1]. $C_{16}H_{17}NO_4$ (287.31): calcd. C 66.89, H 5.96, N 4.88; found C 66.50, H 5.61, N 5.14.

Ethyl (2*R,3*S**,4*R**,5*S**)-4-Benzamido-2,5-divinyltetrahydrofuran-3-carboxylate (16):** Yield 79% (123 mg); white solid; m.p. 98–100 °C; R_f = 0.5 (*n*-hexane/EtOAc, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.15 Hz, 3 H, CH_3), 3.14–3.18 (m, 1 H, 3-H), 4.16–4.23 (m, 2 H, OCH_2), 4.44–4.48 (m, 1 H, 2-H), 4.72–4.77 (m, 2 H, 5-H, 4-H), 5.27–5.32 (m, 2 H, =CH), 5.41–5.49 (m, 2 H, =CH), 5.96–6.04 (m, 2 H, =CH), 7.12 (br. s, 1 H), 7.45–7.56 (m, 3 H, Ar-H), 7.79–7.83 (m, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 14.7, 53.7, 57.2, 61.1, 81.3, 83.1, 117.8, 117.9, 128.2, 129.0, 132.2, 135.0, 137.6, 138.0, 168.0, 172.2 ppm. MS (ESI, pos): m/z = 314 [M + 1]. $C_{18}H_{21}NO_4$ (315.37): calcd. C 68.55, H 6.71, N 4.44; found C 68.20, H 6.39, N 4.10.

Ethyl (1*R,2*R**,3*R**,4*S**)-3-Benzamido-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate (17):** Yield 48% (310 mg); white solid;; m.p. 118–120 °C R_f = 0.44 (*n*-hexane/EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.15 Hz, 3 H, CH_3), 2.89–2.93 (m, 1 H, 2-H), 4.14–4.20 (m, 2 H, OCH_2), 4.58–4.63 (m, 1 H, 3-H), 4.93–4.96 (dd, J_1 = 8.15, J_2 = 3.18 Hz, 1 H, 1-H), 5.22–5.25 (m, 1 H, 4-H), 6.39 (br. s, 1 H, NH), 6.47–6.50 (m, 1 H, 5-H), 5.56–5.59 (m, 1 H, 6-H), 7.49–7.56 (m, 3 H, Ar-H), 7.80–7.84 (m, 2 H, Ar-H) ppm.

^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 14.9, 49.9, 64.8, 61.2, 78.8, 85.1, 128.5, 128.8, 132.2, 134.8, 136.3, 136.7, 167.5, 171.2 ppm. MS (ESI, pos): *m*/*z* = 288 [M + 1]. $C_{16}H_{17}NO_4$ (287.31): calcd. C 66.89, H 5.96, N 4.88; found C 66.51, H 6.30, N 4.53.

Ethyl (2*R,3*R**,4*R**,5*S**)-4-Benzamido-2,5-divinyltetrahydrofuran-3-carboxylate (18):** Yield 68% (106 mg); white solid; m.p. 128–130 °C; R_f = 0.3 (*n*-hexane/EtOAc, 2:1). ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 1.18 (t, *J* = 7.15 Hz, 3 H, CH_3), 3.42–3.46 (m, 1 H, 3-H), 3.99–4.11 (m, 2 H, OCH_2), 4.21–4.28 (m, 1 H, 4-H), 4.52–4.57 (m, 1 H, 2-H), 4.63–4.67 (m, 1 H, 5-H), 5.14–5.19 (m, 2 H, =CH), 5.30–5.36 (m, 2 H, =CH), 5.74–5.79 (m, 1 H, =CH), 5.91–5.98 (m, 1 H, =CH), 7.44–7.53 (m, 3 H, Ar-H), 7.84–7.91 (m, 2 H, Ar-H), 8.62 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO): δ = 15.0, 54.9, 58.1, 61.1, 80.1, 83.6, 118.2, 118.6, 128.1, 129.1, 129.3, 132.3, 135.6, 137.2, 169.5, 171.4 ppm. MS (ESI, pos): *m*/*z* = 314 [M + 1]. $C_{18}H_{21}NO_4$ (315.37): calcd. C 68.55, H 6.71, N 4.44; found C 68.19, H 6.37, N 4.79.

(2*E*,2′*E*)-Dimethyl 3,3′-[(1*R,3*S**,4*S**,5*S**)-4-Benzamido-5-(ethoxycarbonyl)cyclopentane-1,3-diyl]diacrylate (19):** Yield 51% (42 mg); white solid; m.p. 78–80 °C; R_f = 0.47 (*n*-hexane/EtOAc, 1:1). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.16 (t, *J* = 7.15 Hz, 3 H, CH_3), 1.58–1.64 (m, 1 H, CH_2), 2.03–2.10 (m, 1 H, CH_2), 2.97–3.03 (m, 1 H, 5-H), 3.21–3.35 (m, 1 H, 1-H), 3.38–3.44 (m, 1 H, 3-H), 3.61 (s, 3 H, OCH_3), 3.63 (s, 3 H, OCH_3), 3.93–4.09 (m, 2 H, OCH_2), 4.50–4.57 (m, 1 H, 4-H), 5.86–5.94 (m, 2 H, =CH), 6.85–6.90 (m, 1 H, =CH), 6.94–7.00 (m, 1 H, =CH), 7.45–7.58 (m, 3 H, Ar-H), 7.80–7.86 (m, 2 H, Ar-H), 8.61 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 14.9, 35.8, 42.5, 47.8, 52.1, 52.2, 54.1, 58.1, 61.0, 121.8, 122.3, 128.1, 129.1, 132.2, 134.9, 148.7, 150.1, 166.6, 166.7, 166.9, 172.9 ppm. MS (ESI, pos): *m*/*z* = 430 [M + 1]. $C_{23}H_{27}NO_7$ (429.47): calcd. C 64.32, H 6.34, N 3.26; found C 64.01, H 6.02, N 2.88.

Characterisation of the Enantiomers: All the NMR spectra recorded for the enantiomeric substances were the same as for the corresponding racemic materials.

The *er* values were determined by HPLC [Chiralpack IA column; *n*-hexane/IPA (90:10); flow rate: 0.5 mL/min; detection at 260 nm].

Ethyl (1*S*,2*S*,3*R*,4*R*)-3-Benzamidobicyclo[2.2.1]hept-5-ene-2-carboxylate [(+)-5]:[6a] Yield 83%; white solid; $[\alpha]_D^{25}$ = +50.4 (*c* = 0.5, EtOH); R_t = 18.30 min (antipode: 19.64).

Ethyl (1*S*,2*R*,3*R*,5*S*)-2-Benzamido-3,5-divinylcyclopentanecarboxylate [(+)-6]:[6a] Yield 39%; white solid; $[\alpha]_D^{25}$ = +48.5 (*c* = 0.5, EtOH); R_t = 12.24 min (antipode: 10.57).

Ethyl (1*S*,2*R*,3*R*,4*R*)-3-Benzamidobicyclo[2.2.1]hept-5-ene-2-carboxylate [(–)-7]: Yield 65%;white solid; $[\alpha]_D^{25}$ = –102.7 (*c* = 0.5, EtOH); R_t = 12.37 min (antipode: 17.98).

Ethyl (1*R*,2*R*,3*R*,5*S*)-2-Benzamido-3,5-divinylcyclopentanecarboxylate [(–)-8]: Yield 64%; white solid; $[\alpha]_D^{25}$ = –22.5 (*c* = 0.5, EtOH); R_t = 25.17 min (antipode: 22.69).

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