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Synthesis of novel functionalized cispentacins through C–C oxidative cleavage of *diendo*-norbornene β-amino acid†

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Difunctionalized cispentacin derivatives with two new stereogenic centres have been synthesized from a *diendo*-norbornene β-amino acid in a stereocontrolled route, involving C–C double bond functionalization by dihydroxylation, followed by oxidative ring cleavage and transformation of the dialdehyde intermediates through a Wittig reaction.

Introduction

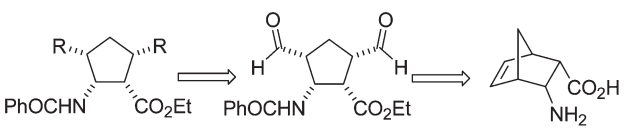
The five-membered carbocyclic natural β-amino acid cispentacin [(1*R*,2*S*)-2-aminocyclopentane-1-carboxylic acid] is known to possess strong antifungal and antibacterial properties. Icofungipen [(1*R*,2*S*)-2-amino-4-methylidenecyclopentane-1-carboxylic acid], another cyclopentane β-amino acid derivative with an extracyclic methylene function, has been described as a strong antifungal agent.[1] The five- or six-membered carbocyclic and heterocyclic β-amino acids are key elements of a series of bioactive products with antitumoural, antibacterial or antiviral activities.[2,3] As conformationally rigid derivatives, alicyclic and *N*-heterocyclic β-amino acids have been used as building elements in the construction of novel bioactive peptides.[4,5] In consequence of the enormous importance of highly functionalized cyclic amino acids, various methodologies have been applied to synthesize a number of multisubstituted carbocyclic β-amino acid derivatives with multiple stereogenic centres.[6,7] However, few routes are available for the preparation of alicyclic β-amino acid regio- and stereoisomers bearing alkyl substituents.[8,9d]

Results and discussion

We recently reported an efficient and convenient procedure for the preparation of *N*-heterocyclic[9a–c] and substituted alicyclic β-amino acid derivatives[9d] from cycloalkene β-amino acids. The syntheses were based on oxidative cleavage of the carbocycle C–C double bond, followed by transformation of the diformyl intermediates. Our present aim was to extend this methodology so as to obtain novel disubstituted cispentacin derivatives. The strategy is outlined in Scheme 1. The target *all-cis*-disubstituted cispentacin derivatives were planned to be prepared by oxidative cleavage of the olefinic bond in *diendo*-norbornene β-amino acid, followed by Wittig transformation of the dialdehyde intermediate (Scheme 1).

Preliminary experiments were carried out on the racemic substances. Racemic *diendo*-norbornene β-amino acid **(±)-1** was readily converted by esterification, *N*-benzoylation and olefinic bond dihydroxylation to amino ester **(±)-4** (see also ref. 9a). Oxidative cleavage of the C–C bond of the vicinal diol **(±)-4** with $NaIO_4$ in THF–H_2O furnished *all-cis* diformyl amino ester **(±)-5** (Scheme 2).

Dialdehyde **(±)-5** was next used to prepare novel disubstituted cyclopentane β-amino esters, *via* the Wittig reaction. The Wittig reagent was generated from benzyltriphenylphosphonium bromide and *t*-BuOK in THF at 0 °C for 15 min. Addition of **(±)-5** to this mixture resulted after 1 h in *all-cis* distyryl cyclopentane amino ester **(±)-6** (37%) (Scheme 3). Surprisingly, the reaction with the Wittig reagent generated from methyltriphenylphosphonium bromide and *t*-BuOK in THF at 0 °C for 15 min yielded not the expected *all-cis* vinyl-substituted β-amino ester after 1 h, but **(±)-7**, which was earlier synthesized from diformyl amino ester **(±)-8**[9d] (Scheme 3). In order to avoid the isomerisation during the reaction of diformyl derivative **(±)-5** with methyltriphenylphosphonium bromide–*t*-BuOK to



Scheme 1 Retrosynthetic route to disubstituted cispentacin derivatives.

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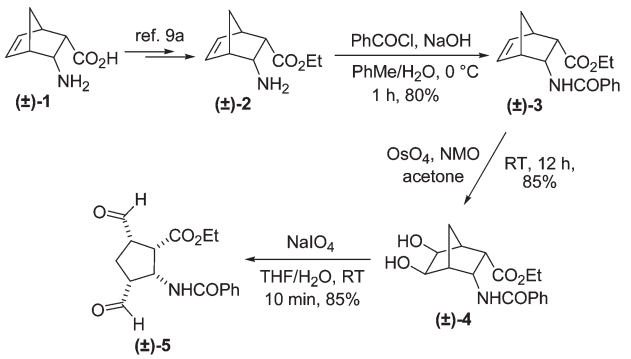


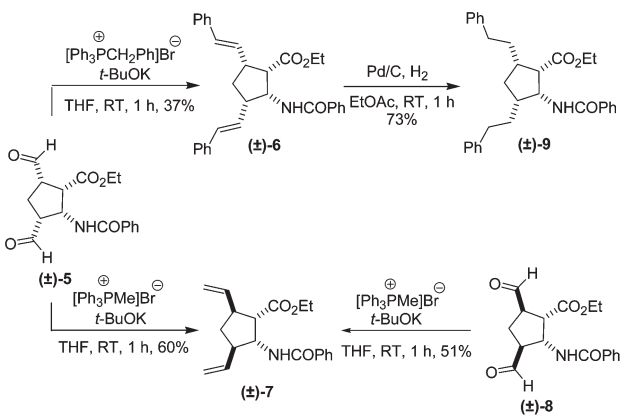
Scheme 2 Synthesis of *all-cis* 3,5-diformyl cispentacin derivative **(±)-5**.

(±)-7 the experimental procedure has been modified by inverse addition: the *in situ* generated phosphorane was added to dialdehyde (±)-**5** to reduce the strongly basic medium. However, carrying out the reaction according to this procedure, after 1 h at room temperature the isomerized product (±)-7 was detected.

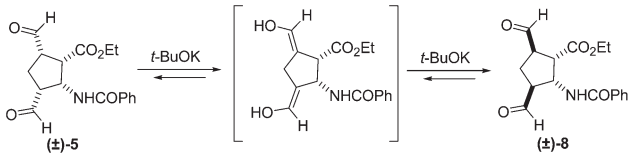
The experimental observation of the formation of (±)-**7** from (±)-**5** may be explained by the isomerization of (±)-**5** in the first step in a keto-enol equilibrium to give the thermodynamically more stable (±)-**8**, catalysed by *t*-BuOK, followed by the Wittig reaction to yield (±)-7 (Scheme 4). This suggested us to suppose that the formation of the phosphorane from methyltriphenylphosphonium bromide with *t*-BuOK required a longer time.

In order to avoid the above isomerisation, the phosphorane was generated by stirring the phosphonium salt with *t*-BuOK not for 15 min, but for 2 h. However, when the resulting phosphorane was reacted with (±)-**5** for either 30 min or 1 h, (±)-7 was again formed.

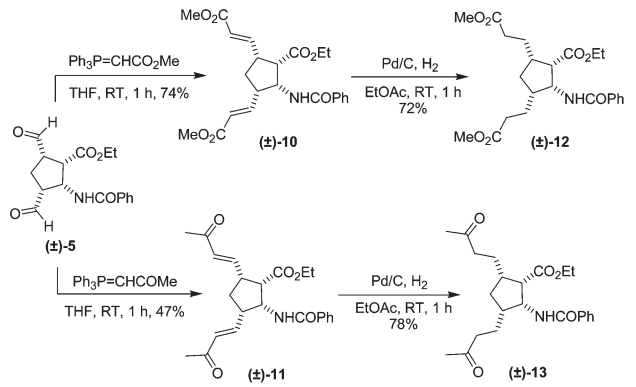
Catalytic hydrogenation of the C–C double bonds in (±)-**6** gave the 3,5-disubstituted cispentacin derivative (±)-**9** (Scheme 3).



Scheme 3 Syntheses of disubstituted cispentacin derivatives **(±)-6**, **(±)-7** and **(±)-9**.



Scheme 4 Interconversion of **(±)-5** and **(±)-8**.



Scheme 5 Syntheses of disubstituted cispentacin derivatives **(±)-10**, **(±)-11**, **(±)-12** and **(±)-13**.

When (±)-**5** was submitted to the Wittig reaction with methyl-(triphenylphosphoranylidene)acetate in THF at room temperature for 1 h, the corresponding *all-cis* 3,5-difunctionalized cispentacin derivative (±)-**10** was formed in good yield (74%) (Scheme 5, Fig. 1).

On treatment with triphenylphosphoranylidene-2-propanone, (±)-**5** gave in moderate yield the *all-cis* disubstituted cyclopentane β-amino acid derivative (±)-**11** (Scheme 5). When subjected to olefinic bond saturation under catalytic hydrogenation, (±)-**10** and (±)-**11** yielded the corresponding functionalized cispentacin derivatives (±)-**12** and (±)-**13** (Scheme 5).

The synthetic method described above was extended to the preparation of the enantiomerically pure substances, *via* the protocol described for the racemic substances. Treatment of the racemic *diendo*-norbornene β-amino ester (±)-**2**[9a] with 1 equivalent of D-(−)-mandelic acid in EtOAc for 10 min gave the corresponding diastereomeric salt mixture. After repeated

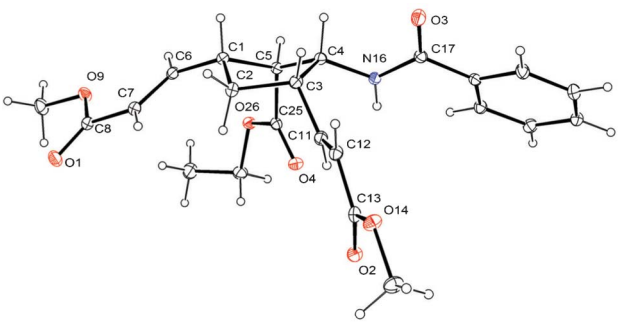
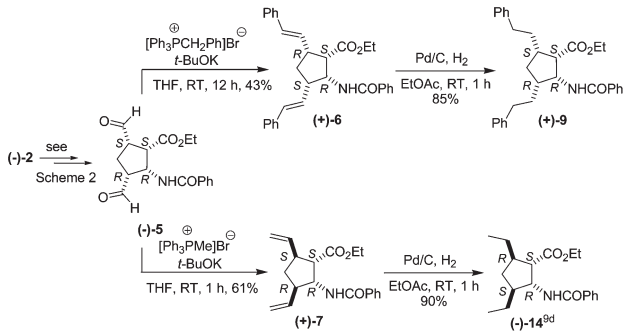
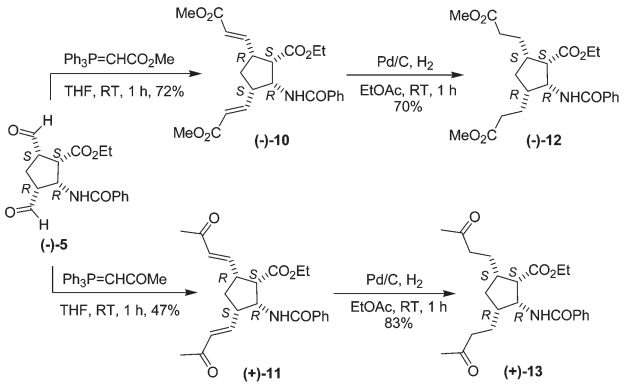


Fig. 1 Ortep diagram of compound **10**.



Scheme 6 Syntheses of optically pure disubstituted cispentacin derivatives **(+)-6**, **(+)-7**, **(+)-9** and **(−)-14**.



Scheme 7 Syntheses of enantiomerically pure disubstituted cispentacin derivatives **(−)-10**, **(+)-11**, **(−)-12** and **(+)-13**.

crystallization (twice) from EtOAc–EtOH 10 : 1, the pure diastereomer (monitored by ^{1}H NMR) was filtered off and treated with a solution of $NaHCO_3$, which resulted in the enantiomerically pure **(−)-2** (25%, *ee* = 99.9%).

Analogously to the racemic counterpart, **(−)-2** was converted by *N*-benzoylation, dihydroxylation and oxidative ring opening to the *all-cis* 3,5-diformyl enantiomer **(−)-5** (Scheme 6).

The absolute configurations of the stereocentres in **(−)-5** were determined by chemical correlation. When **(−)-5** was reacted with the Wittig reagent generated from methyltriphenylphosphonium bromide and *t*-BuOK, it furnished divinyl-substituted **(+)-7** (Scheme 6). Hydrogenolysis of **(+)-7** led to **(−)-14**; the NMR spectra, HPLC analysis (HPLC ChiralPak IA, *n*-hexane–IPA, 0.5 ml min^{-1}, 210 nm, the same retention time: 10.05 min, opposite enantiomer 9.09) and comparison of optical rotations revealed that this compound was identical to earlier prepared[9d] by our group from optically pure **(+)-8**: ethyl (1*S*,2*R*,3*S*,4*R*)-2-benzoylamino-3,5-diformylcyclopentanecarboxylate, with known absolute configurations (see also Scheme 3). Since the stereocentres were not affected in the C–C double bond hydrogenolysis step, it can be assumed from these results that **(−)-5** is ethyl (1*S*,2*R*,3*R*,4*S*)-2-benzoylamino-3,5-diformylcyclopentanecarboxylate, and hence **(−)-2** has the 1*R*,2*S*,3*R*,4*S* absolute configuration.

Enantiomer **(−)-5** readily reacted with the Wittig reagent generated from benzyltriphenylphosphonium bromide and *t*-BuOK to afford **(+)-6**, C–C bond saturation of which provided **(+)-9** (Scheme 6).

When reacted with the commercially available phosphoranes methyl-(triphenylphosphoranylidene)acetate and triphenylphosphoranylidene-2-propanone, **(−)-5** resulted in optically pure **(−)-10** and **(+)-11**, and saturation of the olefinic bonds yielded **(−)-12** and **(+)-13** (Scheme 7).

In conclusion, we have described a convenient way to access difunctionalized cispentacin derivatives from *diendo*-norbornene β-amino acid, involving C–C double bond dihydroxylation, vicinal diol oxidation through ring cleavage and conversion of the dialdehyde derivative formed to functionalized cispentacins through a Wittig reaction. The structure of the starting compound determines the configurations of the newly formed stereogenic centres on the cyclopentane skeleton. The synthetic procedure was extended to the preparation of enantiomerically pure products.

Experimental

The chemicals were purchased from Sigma-Aldrich. The NMR spectra were recorded at 400 MHz with $CDCl_3$ or DMSO as solvent and tetramethylsilane as 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 Analyzer. Silica gel 60 F254 was purchased from Merck. Mass spectra were recorded on a Finnigan MAT 95S spectrometer. X-ray crystallography: an Agilent Supernova diffractometer equipped with an Atlas area-detector, using Cu-Kα radiation (λ = 1.54184 Å).

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

To a solution of *N*-benzoyl-protected β-amino ester **3** (2 g, 7.7 mmol) and NMO (3 ml, 29 mmol) in acetone (40 ml), a solution of OsO_4 (0.5 ml, 0.03 mmol) in t-BuOH (0.06 M) was added. The resulting mixture was stirred for 12 h at room temperature. 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 × 100 ml). The combined organic phases were dried over Na_2SO_4, filtered and evaporated *in vacuo* yielding compound **4**.

General procedure for the oxidative cleavage of 4

To a solution of **4** (200 mg, 0.63 mmol) in THF–H_2O (11 ml, v/v 10 : 1), $NaIO_4$ (269 mg, 1.26 mmol) was added and the reaction mixture was stirred for 15 min at room temperature under an Ar atmosphere, which resulted in diformyl derivative **5**. The mixture was then quenched by the addition of water (20 ml) and extracted with CH_2Cl_2 (2 × 15 ml). The combined organic

phases were dried over Na_2SO_4, filtered and evaporated *in vacuo*.

General procedure for the Wittig reaction

Diformyl derivative **5** (200 mg, 0.63 mmol) was dissolved in dry THF (5 ml) and the appropriate phosphorane (Wittig reagent) (1.26 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).

General procedure for the *in situ* Wittig reaction

The Wittig reagent was prepared by adding *t*-BuOK (1.26 mmol) to a solution of the phosphonium salt (1.26 mmol) in dry THF (5 ml), with stirring for 10 min. Diformyl derivative **5** (200 mg, 0.63 mmol) was dissolved in dry THF (5 ml) and added dropwise to the solution of the *in situ* generated Wittig reagent. 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).

General procedure for C–C double bond saturation

A solution of **7**, **10** or **11** (100 mg, 0.32 mmol), containing in EtOAc (20 mL) 10% mol Pd/C (20 mg) 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).

Ethyl (1*S**,2*R**,3*R**,5*S**)-2-benzamido-3,5-diformylcyclopentanecarboxylate [(±)-5)]

Yellow oil. Yield: 85%. (R_f 0.2, *n*-hexane–EtOAc 1 : 4). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.11 (t, 3H, CH_3, J = 7.07 Hz), 2.14–2.34 (m, 1H, H-4), 2.57–2.66 (m, 1H, H-4), 3.16–3.24 (m, 1H, H-5), 3.38–3.46 (m, 1H, H-3), 3.56–3.61 (m, 1H, H-1), 4.00–4.18 (m, 2H, OCH_2), 5.21-5.24 (m, 1H, H-2), 7.38–7.91 (m, 5H, Ar-H), 9.74 (s, 1H, COH), 9.95 (s, 1H, COH). ^{13}C NMR (DMSO, 400 MHz) δ: 14.7, 24.8, 49.8, 50.8, 53.5, 54.0, 61.4, 127.8, 129.3, 132.4, 134.8, 167.6, 171.9, 203.1, 205.1. Anal. Calcd. for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.02; H, 5.70; N, 4.07.

Ethyl (1*S**,2*R**,3*S**,5*R**)-2-benzamido-3,5-(*E*,*E*)-distyrylcyclopentanecarboxylate [(±)-6]

White solid. Yield: 37%. M.p. 162–165 °C; (R_f 0.3, *n*-hexane–EtOAc 3 : 1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.18 (t, 3H, CH_3, J = 6.80 Hz), 2.03–2.16 (m, 2H, CH_2), 2.85–2.92 (m, 1H, H-3), 2.96–3.03 (m, 1H, H-5), 3.22–3.33 (m, 1H, H-1), 4.14–4.18 (m, 2H, OCH_2), 4.47–4.50 (m, 1H, H-2), 6.12–6.28 (m, 2H, =C–H), 6.41–6.49 (m, 2H, =C–H), 7.15–7.80 (m, 15H, Ar–H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 36.3, 43.9, 47.9, 56.5, 60.2, 60.8, 126.8, 126.9, 128.0, 128.1, 129.1, 129.4, 129.5, 130.0, 130.5, 132.0, 132.7, 133.4, 135.3, 137.6, 137.8, 167.0, 173.7. Anal. Calcd. for $C_{31}H_{31}NO_3$: C, 79.97; H, 6.71; N, 3.01. Found: C, 79.64; H, 6.40; N, 2.68.

Ethyl (1*S**,2*R**,3*R**,5*S**)-2-benzamido-3,5-diphenethylcyclopentanecarboxylate [(±)-9]

White solid. Yield: 73%. M.p. 89–92 °C, (R_f 0.2, *n*-hexane–EtOAc 3 : 1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.18 (t, 3H, CH_3, J = 6.80 Hz), 2.03–2.36 (m, 6H, CH_2), 2.85–2.92 (m, 1H, H-1), 2.96–3.03 (m, 1H, H-3), 3.22–3.33 (m, 1H, H-5), 3.44–3.65 (m, 4H, $ArCH_2$), 4.14–4.18 (m, 2H, OCH_2), 4.46–4.50 (m, 1H, H-2), 7.15–7.80 (m, 15H, Ar–H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 36.3, 43.9, 47.9, 56.5, 60.2, 60.8, 126.8, 126.9, 128.0, 128.1, 129.1, 129.4, 129.5, 130.0, 130.5, 132.0, 132.7, 133.4, 135.3, 137.6, 137.8, 167.0, 173.7. MS: (ESI) m/z = 470.51 (M + 1). Anal. Calcd. for $C_{31}H_{35}NO_3$: C, 79.28; H, 7.51; N, 2.98. Found: C, 78.97; H, 7.20; N, 2.66.

Dimethyl (2*E*,2'*E*)-3,3'-((1*R**,3*S**,4*R**,5*S**)-4-benzamido-5-(ethoxycarbonyl) cyclopentane-1,3-diyl)diacrylate [(±)-10]

White solid. 74% yield. M.p. 70–74 °C. (R_f 0.3, *n*-hexane–EtOAc 1 : 1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.16 (t, 3H, CH_3, J = 7.16 Hz), 1.53–1.63 (m, 2H, H-1), 2.89–3.00 (m, 1H, H-3), 3.10–3.25 (m, 2H, H-3, H-5), 3.70 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.02–4.18 (m, 2H, OCH_2), 4.70–4.74 (m, 1H, H-4), 5.90 (t, 2H, =C–H), 6,75 (d, 1H, NH, J = 8.77 Hz), 6.87–6.97 (m, 2H, =C–H), 7.37–7.79 (m, 5H, Ar–H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.8, 36.1, 44.2, 47.2, 52.2, 53.1, 56.2, 60.9, 121.6, 121.9, 128.1, 129.0, 132.1, 135.0, 150.1, 150.8, 166.8, 167.0, 172.2. Anal. Calcd. for $C_{23}H_{27}NO_7$: C, 64.32; H, 6.34; N, 3.26. Found: C, 64.01; H, 6.02; N, 2.92.

Dimethyl 3,3'-((1*S**,3*R**,4*R**,5*S**)-4-benzamido-5-(ethoxycarbonyl)cyclopentane-1,3-diyl)dipropanoate [(±)-12]

Yellow oil, Yield: 72%. (R_f 0.2, *n*-hexane–EtOAc 1 : 1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.24–1.29 (m, 3H, CH_3), 1.64–2.53 (m, 12H, H-1, H-3, 2 x H-4, 4 x CH_2), 3.27–3.34 (m, 1H, H-5), 3.65 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 4.08–4.31 (m, 2H, OCH_2), 4.93–5.10 (m, 1H, H-4), 6,98 (br s, 1H, NH), 7.42–7.84 (m, 5H, Ar–H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.9, 25.7, 27.5, 29.5, 32.9, 33.2, 36.9, 41.4, 51.2, 52.1, 53.1, 53.7, 60.6, 128.1, 129.1, 132.0, 135.6, 167.3, 172.6, 174.1. MS: (ESI) m/z = 434.43 (M + 1). Anal. Calcd. for $C_{23}H_{31}NO_7$: C, 64.73; H, 7.21; N, 3.23. Found: C, 64.43; H, 6.90; N, 2.91.

Ethyl (1*S**,2*R**,3*S**,5*R**)-2-benzamido-3,5-bis((*E*)-3-oxobut-1-enyl)cyclopentanecarboxylate [(±)-11]

Yellow oil, Yield: 47%. (R_f 0.4, *n*-hexane–EtOAc 1 : 4). ^{1}H NMR (DMSO, 400 MHz) δ: 0.97–1.10 (m, 3H, CH_3), 2.08–2.16 (m, 2H, CH_2), 2.19–2.22 (m, 6H, $2CH_3$), 2.98–3.20 (m, 1H, H-3), 3.31–3.45 (m, 1H, H-5), 3.73–3.78 (m, 1H, H-1), 3.93–4.05 (m, 2H, OCH_2), 5.03–5.23 (m, 1H, H-2), 5.81–5.88 (m, 2H, =C–H), 6.69–6.80 (m, 2H, =C–H), 7.40–7.90 (m, 5H, Ar–H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.7, 35.6, 43.2, 45.3, 52.1, 52.5, 55.2, 60.9, 121.2, 122.9, 128.2, 129.0, 132.0, 135.7, 149.1, 150.7, 166.7, 167.8, 171.2. Anal. Calcd. for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.18; H, 6.52; N, 3.20.

Ethyl (1*S**,2*R**,3*R**,5*S**)-2-benzamido-3,5-bis(3-oxobutyl)cyclopentanecarboxylate [(±)-13]

Yellow oil. Yield: 78%. (R_f 0.4, *n*-hexane–EtOAc 1 : 4). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.20 (t, 3H, CH_3, J = 7.16 Hz), 2.48–2.70

(m, 12H, 5 x CH_2, H-3 and H-5) 2.66 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 3.00–3.08 (m, 1H, H-1), 4.05–4.09 (m, 2H, OCH_2), 4.62–4.70 (m, 1H, H-2), 7.44–7.82 (m, 5H, Ar–H), 8.16 (br s, 1H, N–H). MS: (ESI) m/z = 400.78 (M + 1). Anal. Calcd. for $C_{23}H_{31}NO_5$: C, 68.80; H, 7.78; N, 3.49. Found: C, 68.45; H, 7.46; N, 3.18.

Separation of racemic amino ester 2

A solution of D-(−)-mandelic acid (1 equiv., 1.9 g) in EtOAc (15 mL) was slowly added to a solution of racemic bicyclic *diendo*-aminoester **2** (2.3 g) in EtOAc (20 mL). The resulting mixture was stirred at RT for 10 min. The salt formed was filtered off and recrystallized twice from EtOAc–EtOH 10 : 1. The ratio of the diastereomeric salts was monitored by ^{1}H NMR. The pure diastereomeric salt was then treated with a saturated solution of $NaHCO_3$, resulting in enantiomerically pure bicyclic *diendo*-aminoester **(−)-2** (25%, *ee* = 99.9%; HPLC, Chiralpack IA column, eluent: *n*-hexane–IPA (80 : 20), flow rate: 0.5 mL min^{-1}, detection at 210 nm).

Ethyl (1*R*,2*S*,3*R*,4*S*)-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylate[(−)-2]

Colourless oil. $[\alpha]_D^{25}$ −5 (*c* 0.45, EtOH).

Characterization of the enantiomers

All the ^{1}H NMR spectra recorded on the enantiomeric substances were the same as those of the corresponding racemic counterparts.

The *ee* values were determined by HPLC [Chiralpack IA column, eluent: *n*-hexane–IPA 80 : 20, flow rate: 0.5 mL min^{-1}, detection at 260 nm].

Ethyl (1*R*,2*S*,3*R*,4*S*)-3-benzoylaminobicyclo[2.2.1]hept-5-ene-2-carboxylate [(−)-3]

White solid, yield: 80%. M.p. 88–90 °C. $[\alpha]_D^{25}$ −62 (*c* 0.32, EtOH). ^{1}H NMR (DMSO, 400 MHz) δ: 1.04 (t, 3H, CH_3, J = 7.20 Hz), 1.39–1.42 (m, 1H, CH_2), 1.47–1.52 (m, 1H, CH_2), 3.02–3.08 (m, 1H, H-2), 3.26–3.38 (m, 2H, H-1 and H-4), 3.82–4.03 (m, 2H, OCH_2), 4.79–4.86 (m, 1H, H-2), 6.33–6.42 (m, 2H, H-5 and H-6), 7.38–7.51 (m, 3H, Ar–H), 7.53 (br s, 1H, N–H), 7.60–7.64 (m, 2H, Ar–H). ^{13}C NMR (DMSO, 400 MHz) δ: 17.8, 46.8, 47.3, 47.6, 47.9, 53.3, 60.8, 127.5, 129.3, 132.1, 134.9, 135.3, 138.2. 166.8, 173.5. Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.19; H, 6.99; N, 4.67.

Ethyl (1*S*,2*S*,3*R*,4*R*,5*R*,6*S*)-3-benzoylamino-5,6-dihydroxybicyclo[2.2.1]heptane-2-carboxylate [(−)-4]

White solid, yield: 85%. M.p. 170–172 °C. $[\alpha]_D^{25}$ −14 (*c* 0.26, EtOH). ^{1}H NMR (DMSO, 400 MHz) δ: 1.14 (t, 3H, CH_3, J = 7.20 Hz), 1.28–1.32 (m, 1H, CH_2), 1.76–1.80 (m, 1H, CH_2), 2.33–2.40 (m, 2H, H-1 and H-4), 3.05–3.11 (m, 1H, H-2), 3.78–3.84 (m, 1H, H-3), 4.01–4.12 (m, 3H, OCH_2 and H-6), 4.40–4.44 (m, 1H, H-5), 4.55 (br s, 1H, O–H), 4.72 (br s, 1H, O–H), 7.46–7.52 (m, 3H, Ar–H), 7.76–7.82 (m, 2H, Ar–H), 8.47 (br s, 1H, N–H). ^{13}C NMR (DMSO, 400 MHz) δ: 14.8, 31.1, 41.1, 48.2, 48.9, 49.7, 61.1, 67.4, 69.9, 127.8, 129.3, 132.1, 135.3, 167.0, 173.5. Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.72; H, 6.32; N, 4.63.

Ethyl (1*S*,2*R*,3*R*,4*S*)-2-benzoylamino-3,5-diformylcyclopentanecarboxylate [(−)-5]

Yellow oil, yield: 78%. $[\alpha]_D^{25}$ −20 (*c* 0.24, EtOH).

Ethyl (1*S*,2*R*,3*R*,4*S*)-2-benzoylamino-3,5-divinylcyclopentanecarboxylate [(+)-7]

White solid, yield: 61%. M.p. 93–95 °C. $[\alpha]_D^{25}$ = +27.3 (*c* 0.35, EtOH).[9d]

Ethyl (1*S*,2*R*,3*S*,4*R*)-2-benzoylamino-3,5-diethylcyclopentanecarboxylate [(−)-14]

White solid, yield: 90%. M.p. 76–78 °C. $[\alpha]_D^{25}$ −30 (*c* 0.26, EtOH). *ee* = 81%.[9d]

Ethyl (1*S*,2*R*,3*S*,4*R*)-2-benzoylamino-3,5-(*E*,*E*)-distyrylcyclopentanecarboxylate [(+)-6]

White solid, yield: 43%. M.p. 160–162 °C. $[\alpha]_D^{25}$ = +68 (*c* 0.31, EtOH).

Ethyl (1*S*,2*R*,3*R*,4*S*)-2-benzoylamino-3,5-diphenethylcyclopentanecarboxylate [(+)-9]

White solid, yield: 85%. M.p. 87–89 °C. $[\alpha]_D^{25}$ = +38 (*c* 0.27, EtOH). *ee* = 99%.

Ethyl (1*S*,2*R*,3*S*,4*R*)-2-benzoylamino-3,5-(*E*,*E*)-*bis*-(2-methoxycarbonylvinyl)-cyclopentanecarboxylate [(−)-10]

White solid, yield: 72%. M.p. 68–71 °C. $[\alpha]_D^{25}$ −6.5 (*c* 0.33, EtOH).

Ethyl (1*S*,2*R*,3*R*,4*S*)-2-benzoylamino-3,5-*bis*-(2-methoxycarbonylethyl)cyclopentanecarboxylate [(−)-12]

Yellow oil, yield: 70%. $[\alpha]_D^{25}$ −7.8 (*c* 0.36, EtOH); ee = 98%.

Ethyl (1*S*,2*R*,3*S*,4*R*)-2-benzoylamino-3,5-(*E*,*E*)-*bis*-(3-oxobut-1-enyl)cyclopentanecarboxylate [(+)-11]

Yellow oil, yield: 47%. $[\alpha]_D^{25}$ = +43 (*c* 0.175, EtOH).

Ethyl (1*S*,2*R*,3*R*,4*S*)-2-benzoylamino-3,5-*bis*-(3-oxobutyl)cyclopentanecarboxylate [(+)-13]

Yellow oil, yield: 83%. $[\alpha]_D^{25}$ = +28 (*c* 0.27, EtOH); ee = 96%.

Crystal data for **10**:

$C_{23}H_{27}NO_7$, M_r = 552.64, triclinic, space group $P\bar{1}$; a = 10.5092(14) Å, b = 11.2202(16) Å, c = 11.4916(16) Å, α = 115.706(14), β = 94.335(11), γ = 113.346(13)°, V = 1069.6(3) Å^3, Z = 2, D_c = 1.333 g cm^{-3}, λ = 1.54184 Å, μ(Cu-Kα) = 0.080 mm^{-1}, F(000) = 456, and T = 123(2)K. A crystal with the dimensions 0.20 × 0.20 × 0.25 mm was selected for X-ray analysis. An empirical absorption correction using spherical harmonics implemented in the SCALE3 ABSPACK scaling algorithm, was applied with the CrysAlisPro program package.[10] A total of 18 491 reflections yielded 4065 unique reflections in the range 4.48° ⩽ θ ⩽ 69.96° (R_{int} = 0.0217). The structure was solved by using direct methods with SHELXS[11] and was refined by full-matrix least-squares on F^2 with SHELXL.[11] Non-hydrogen atoms were refined anisotropically. CH hydrogen atoms were fixed at calculated positions and refined by using a riding model, and NH hydrogen was refined isotropically. The final indices were R_1 = 0.0348 ($F^2 > 2\sigma(F^2)$), R_1 = 0.384 (all data), with a goodness-of-fit = 1.045. Crystallographic data for the

structure of **10** have been deposited in the Cambridge Crystallographic Data Centre (deposition number: CCDC 919638).

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