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Asymmetric syntheses of enantiopure C(5)-substituted transpentacins *via* diastereoselective Ireland–Claisen rearrangements†

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Asymmetric syntheses of (*S*,*S*,*S*)-2-amino-5-methylcyclopentanecarboxylic acid and (*S*,*S*,*S*)-2-amino-5-phenylcyclopentanecarboxylic acid were achieved in 9 steps from commercially available starting materials *via* the Ireland–Claisen rearrangement of two enantiopure β-amino allyl esters, followed by ring-closing metathesis, reduction and deprotection.

There has been considerable interest in the secondary structural characteristics of oligomers of the cyclic β-amino acids cispentacin and transpentacin (the enantiopure diastereoisomers of 2-amino-cyclopentanecarboxylic acid).[1,2] In order to enhance the structural diversity of enantiopure monomeric cispentacin and transpentacin derivatives available we have developed efficient parallel kinetic resolution (PKR) procedures for the asymmetric syntheses of C(3)- and C(5)-substituted analogues **1**–**3**,[3] and subsequently investigated the secondary structural characteristics of some of their oligomers.[4] Herein we report an alternative procedure for the syntheses of 1,2-*anti*-1,5-*syn*-diastereoisomers **6**, which are not accessible using the PKR protocol. It was predicted that the Ireland–Claisen rearrangement[5] of silyl ketene acetals derived from β-amino allyl esters **4** would proceed *via* a chair-like transition state **7** in which 1,3-allylic strain between the C(3)-substituents and the C(1)–O bond is minimised, and rearrangement occurs on the face opposite the bulky *N*-benzyl-*N*-(α-methylbenzyl) group. The resultant α-substituted β-amino acid products **5** could then be elaborated to the corresponding C(5)-substituted transpentacins **6** *via* ring-closing metathesis and hydrogenolytic reduction/deprotection (Fig. 1).

Rearrangement precursors **11** and **12** were prepared from commercially available sorbic acid **8** in four steps. Esterification of **8** upon treatment with isobutylene/H^+ gave α,β-unsaturated ester **9** in 80% isolated yield. Conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide[6] to **9** produced the known β-amino ester **10**[7,8] as a single diastereoisomer (>99 : 1 dr), which was isolated in 89% yield and >99 : 1 dr after chromatographic purification. Hydrolysis of the *tert*-butyl ester moiety within **10** upon treatment with TFA, conversion of the resultant carboxylic acid to the corresponding acid chloride, and treatment with either alcohol **23** or alcohol **24** (which were both prepared in >99 : 1 dr upon reduction of the corresponding alkynes **21** and **22**) gave β-amino allyl esters **11** and **12** in 57 and 63% yield, respectively, over the two step procedure. Ireland–Claisen rearrangement of **12** was achieved *via* deprotonation with LiHMDS and treatment of the resultant lithium (*E*)-β-amino enolate[9] with TMSCl, followed by heating the corresponding silyl ketene acetal at reflux in PhMe, which gave a 76 : 24 mixture of β-amino acids **15** and **16**, respectively. Conversion of this mixture to the corresponding methyl esters **19** and **20** (for ease of handling and isolation) was then achieved upon treatment with MeI and DBU,[10] and **19** and **20** were then isolated as single diastereoisomers (>99 : 1 dr) in 69 and 16% yield, respectively (Scheme 1). The relative configurations

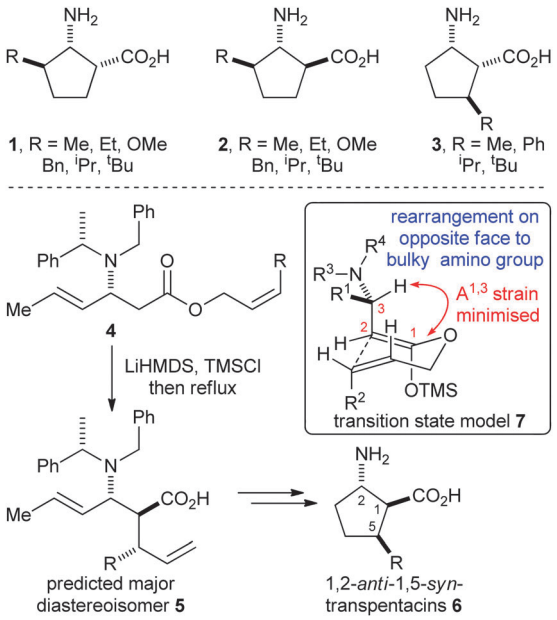

Fig. 1 Substituted cispentacin and transpentacin analogues **1**–**3** and the Ireland–Claisen rearrangement strategy to access transpentacins **6**.

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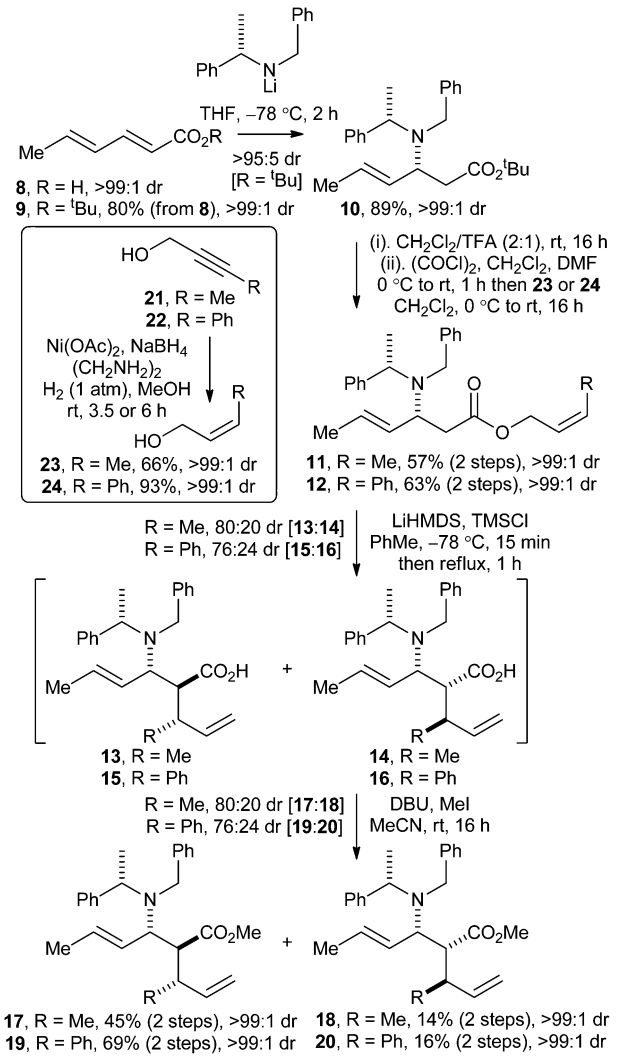
† Electronic supplementary information (ESI) available: Experimental procedures, characterisation data, copies of ^{1}H and ^{13}C NMR spectra, and crystallographic data. CCDC 936128–936131. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc43250e



Scheme 1

within both **19**·HBF_4 and **20** were unambiguously assigned by single crystal X-ray diffraction analyses (Fig. 2),[11] with the absolute configurations within (*S*,*S*,*S*,*S*,*E*)-**19** and (2*R*,3*S*,1′*R*,α*S*,*E*)-**20** being assigned from the known configuration of the (*S*)-α-methylbenzyl fragment. Analogous Ireland–Claisen rearrangement of **11** produced a (separable) 80 : 20 mixture of β-amino acids **13** and **14**, which after esterification gave **17** and **18** in >99 : 1 dr and 45 and 14% isolated yield, respectively (Scheme 1). The configurations within both **17** and **18** were initially assigned by analogy to those within **19** and **20**, and these assignments were subsequently confirmed by chemical correlation and single crystal X-ray diffraction analysis of a derivative (*vide infra*). In both cases, the configurations within the major diastereoisomers **17** and **19** were consistent with the predicted stereochemical outcome of transition state model **7** (Fig. 1).

The configuration within **18** (the minor diastereoisomer derived from rearrangement of **11**) was unambiguously established by chemical correlation: ring-closing metathesis of **18** (>99 : 1 dr) upon treatment with Grubbs I catalyst gave **25** in 77% yield and >99 : 1 dr. Subsequent hydrogenolytic reduction of **25** in the presence of Pd/C gave a complex mixture of products including the known β-amino ester **26**, which was isolated in 9% yield after exhaustive purification

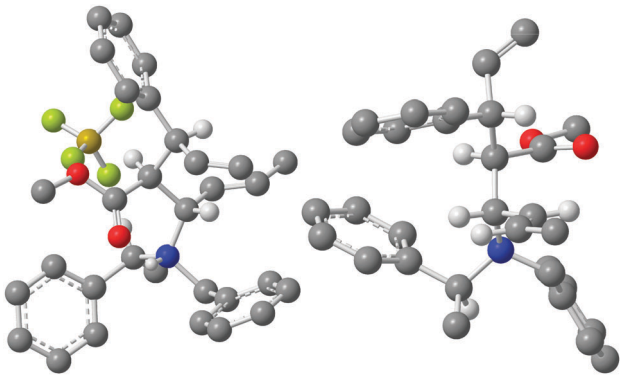
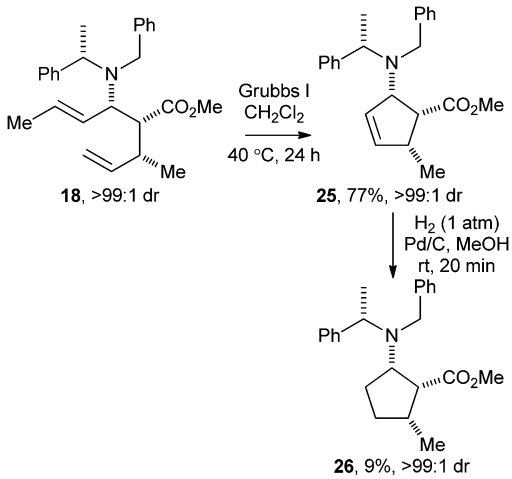


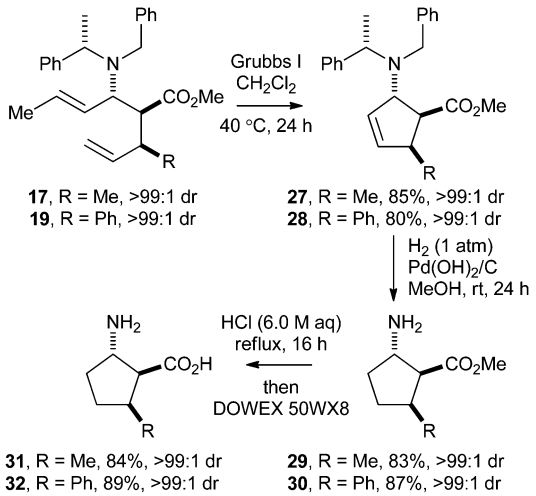
Fig. 2 X-ray crystal structures of (*S*,*S*,*S*,*S*,*E*)-**19**·HBF_4 [left] and (2*R*,3*S*,1′*R*,α*S*,*E*)-**20** [right] (selected H atoms are omitted for clarity).

of the crude reaction mixture by flash column chromatography (Scheme 2). The ^1H and ^{13}C NMR data for this sample of **26** were in excellent agreement with those reported previously;[3d] this analysis therefore enabled the configurations within **18**, **25** and **26** to be assigned.

For both **17** and **19** (the major diastereoisomers arising from Ireland–Claisen rearrangement of **11** and **12**, respectively), ring-closing metathesis in the presence of Grubbs I catalyst gave **27** and **28** as single diastereoisomers (>99 : 1 dr) in 85 and 80% yield,[12] respectively, and subsequent tandem hydrogenation/hydrogenolysis gave primary amines **29** and **30** as single diastereoisomers (>99 : 1 dr) in 83 and 87% yield (Scheme 3). The relative configurations within **27**–**30** were initially assigned by ^1H NMR nOe analyses and these assignments were subsequently confirmed unambiguously by single crystal X-ray diffraction analyses (Fig. 3):[11] in the case of **29**, single crystal X-ray diffraction analysis of the corresponding 2,6-difluorobenzoic acid salt and the determination of a Flack *x* parameter[13] of 0.005(11) for this crystal structure allowed the assigned absolute (*S*,*S*,*S*)-configuration within **29** to be confirmed, whilst for **30**, single crystal X-ray diffraction analysis of the corresponding HBF_4 salt and the determination of a Flack *x* parameter[13] of −0.03(16) for the crystal structure of **30**·HBF_4 allowed the assigned absolute (*S*,*S*,*S*)-configuration within **30** to also be confirmed.



Scheme 2



Scheme 3

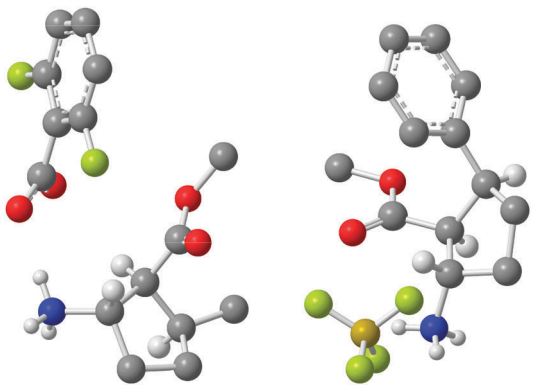


Fig. 3 X-ray crystal structures of (*S*,*S*,*S*)-**29**·2,6-difluorobenzoic acid·$CHCl_3$ [left] and (*S*,*S*,*S*)-**30**·HBF_4 [right] (selected H atoms and $CHCl_3$ are omitted for clarity).

These crystallographic studies therefore also secured the assigned configurations within **17**, **27** and **28**. Finally hydrolysis of the methyl ester functionalities within both **29** and **30**, upon treatment with 6.0 M aq HCl at reflux for 16 h, gave β-amino acids **31** and **32** which were isolated as single diastereoisomers (>99 : 1 dr) in 84 and 89% yield, respectively, after purification on Dowex 50WX8 ion exchange resin (Scheme 3).

In conclusion, the Ireland–Claisen rearrangement of two enantiopure β-amino allyl esters, followed by ring-closing metathesis, reduction and deprotection, enabled the asymmetric syntheses of (*S*,*S*,*S*)-2-amino-5-methylcyclopentanecarboxylic acid and (*S*,*S*,*S*)-2-amino-5-phenylcyclopentanecarboxylic acid in 9 steps and >99 : 1 dr in both cases, and 18 and 19% overall yield, respectively, from commercially available starting materials.

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11 X-ray crystal structure data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation, using standard procedures at 150 K. The structures were solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. X-ray crystal structure data for **19**·HBF_4 [$C_{31}H_{36}BF_4NO_2$]: M = 541.43, orthorhombic, $P2_12_12_1$, a = 9.3325(1) Å, b = 15.3112(2) Å, c = 20.0967(2) Å, V = 2871.65(5) Å^3, Z = 4, μ = 0.784 mm^{-1}, colourless block, crystal dimensions = 0.23 × 0.26 × 0.30 mm^3. A total of 6010 unique reflections were measured for 4 < θ < 77 and 5068 reflections were used in the refinement. The final parameters were wR_2 = 0.102 and R_1 = 0.038 [$I > -3.0\sigma(I)$]. CCDC 936128.† X-ray crystal structure data for **20** [$C_{31}H_{35}NO_2$]: M = 453.62, monoclinic, $P2_1$, a = 7.9925(2) Å, b = 16.7779(4) Å, c = 10.6442(3) Å, β = 111.582(3)°, V = 1327.29(7) Å^3, Z = 2, μ = 0.541 mm^{-1}, colourless plate, crystal dimensions = 0.05 × 0.20 × 0.24 mm^3. A total of 4653 unique reflections were measured for 4 < θ < 77 and 4635 reflections were used in the refinement. The final parameters were wR_2 = 0.083 and R_1 = 0.034 [$I > -3.0\sigma(I)$]. CCDC 936129.† X-ray crystal structure data for **29**·$C_7H_4F_2O_2$·$CHCl_3$ [$C_{16}H_{20}Cl_3F_2NO_4$]: M = 434.69, monoclinic, $C2$, a = 25.0016(5) Å, b = 6.6915(1) Å, c = 12.9605(2) Å, β = 110.830(2)°, V = 2026.55(7) Å^3, Z = 4, μ = 4.452 mm^{-1}, colourless prism, crystal dimensions = 0.11 × 0.12 × 0.29 mm^3. A total of 4226 unique reflections were measured for 4 < θ < 76 and 4207 reflections were used in the refinement. The final parameters were wR_2 = 0.082 and R_1 = 0.033 [$I > -3.0\sigma(I)$]. CCDC 936130.† X-ray crystal structure data for **30**·HBF_4 [$C_{13}H_{18}BF_4NO_2$]: M = 307.09, monoclinic, $P2_1$, a = 5.5150(2) Å, b = 7.6423(3) Å, c = 17.2563(6) Å, β = 90.531(3)°, V = 727.27(5) Å^3, Z = 2, μ = 1.099 mm^{-1}, colourless block, crystal dimensions = 0.22 × 0.23 × 0.27 mm^3. A total of 2045 unique reflections were measured for 5 < θ < 76 and 2038 reflections were used in the refinement. The final parameters were wR_2 = 0.092 and R_1 = 0.036 [$I > -3.0\sigma(I)$]. CCDC 936131†.

12 Compounds **27** and **28** were also isolated in 63 and 51% overall yield from **11** and **12**, respectively, for the 3 step procedure, without purification of any intermediates.

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