

Asymmetric syntheses of the *N*-terminal α -hydroxy- β -amino acid components of microginins 612, 646 and 680

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Abstract

The asymmetric syntheses of the *N*-terminal α -hydroxy- β -amino acid components of microginins 612, 646 and 680 are reported. Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α -methylbenzyl)amide to the requisite (*E*)- α,β -unsaturated ester followed by *in situ* enolate oxidation with (–)-(camphorsulfonyl)oxaziridine (CSO) gave the corresponding *anti*- α -hydroxy- β -amino esters. Sequential Swern oxidation followed by diastereoselective reduction gave the corresponding *syn*- α -hydroxy- β -amino esters. Subsequent *N*-debenzylation (i.e, hydrogenolysis for microginin 612, and NaBrO₃-mediated oxidative *N*-debenzylation for microginins 646 and 680) followed by acid catalysed ester hydrolysis gave the corresponding *syn*- α -hydroxy- β -amino acids, the *N*-terminal components of microginins 612, 646 and 680, in good yield. An analogous strategy for elaboration of the enantiopure *anti*- α -hydroxy- β -amino esters facilitated the asymmetric synthesis of the corresponding C(2)-epimeric α -hydroxy- β -amino acids.

1. Introduction

The microginins are a sub-class of linear peptides that have been isolated from a genus of cyanobacteria known as *Microcystis*.¹ Microginins typically contain between four to six amino acids (e.g., microginin 478 **1**² and microginin 299-C **2**³) and are characterized by a functionalised β -amino acid at the *N*-terminus as well as the presence of tyrosine residues. Microginin FR1 **3** (often simply called “microginin”) was the first in this class to be isolated from the blue-green alga *Microcystis aeruginosa*.⁴ In 2016, three new microginins, *viz.* microginin 612 **4**, microginin 646 **5** and microginin 680 **6**, were isolated from *Microcystis aeruginosa* UTEX LB2386.⁵ Microginin 612 **4** contains a rare amino acid residue, 3-amino-2-hydroxyoctanoic acid (ahoa)⁶ and microginin 646 **5** and microginin 680 **6** are the first chlorinated examples of the ahoa fragment in a natural product (Figure 1).

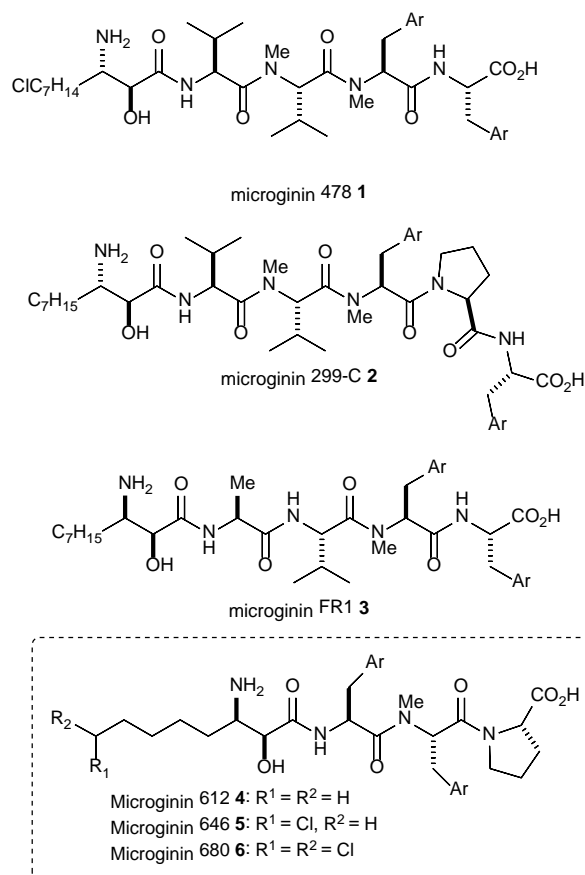
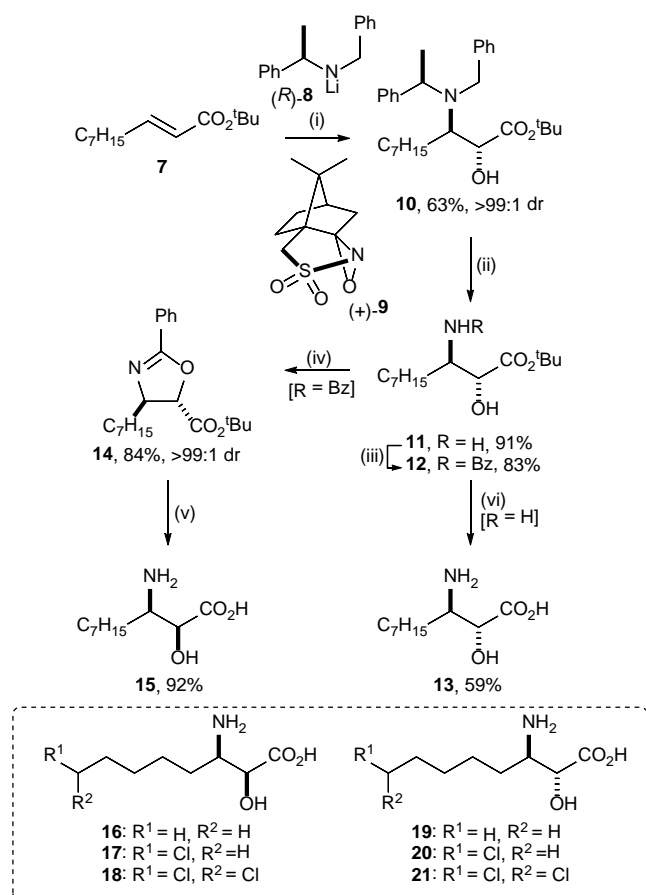


Fig. 1. Examples of microginins **1–3** and the structures of microginin 612 **4**, microginin 646 **5** and microginin 680 **6**. [Ar = *p*-(HO)C₆H₄].

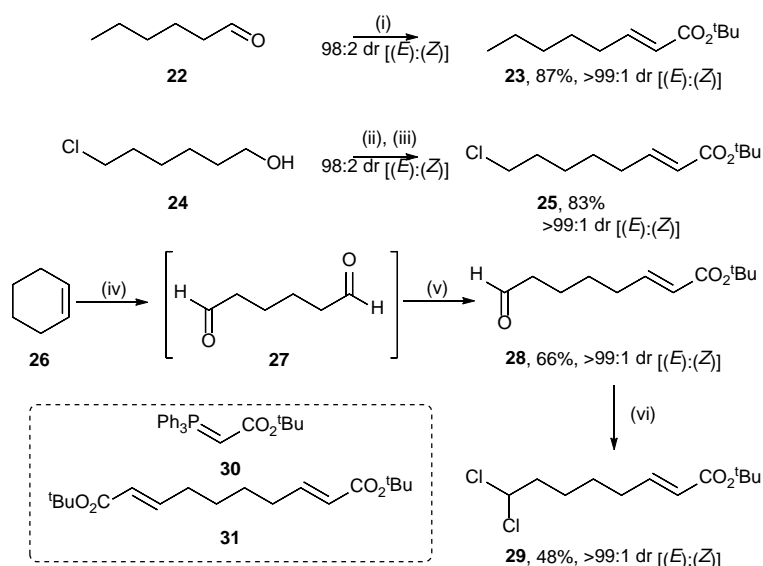
We have previously synthesised both diastereoisomers of 3-amino-2-hydroxydecanoic acid (ahda), **13** and **15** as part of the structural elucidation of microginin FR1 **3**, and concluded the unknown *N*-terminal amino acid component of microginin FR1 **3** was (2*S*,3*R*)-*syn*-ahda **15** by spectroscopic comparison.⁷ Diastereoselective conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α -methylbenzyl)amide (*R*)-**8** to α,β -unsaturated ester **7** followed by *in situ* enolate oxidation with (+)-CSO **9** gave the corresponding *anti*- α -hydroxy- β -amino ester **10** in 63% yield and >99:1 dr. Catalytic hydrogenolysis of **10** gave amine **11**, and subsequent acid-mediated ester hydrolysis gave (2*R*,3*R*)-3-amino-2-hydroxydecanoic acid **13** in 59% yield (from **10**). The corresponding C(2)-epimer **15** was accessed via cyclisation of the corresponding benzamide **12** under Mitsunobu conditions to give oxazoline **14** and global hydrolysis of **14** with 6.0 M HCl furnished (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid **15** in 64% yield (from **12**). Accordingly, it was anticipated that the asymmetric syntheses of *syn*- α -hydroxy- β -amino acids, the *N*-terminal components of microginin 612 **4**, microginin 646 **5** and microginin 680 **6**, and the corresponding C(2)-epimers **19–21** could be achieved via diastereoselective aminohydroxylation of the requisite α,β -unsaturated ester as the key step.



Scheme 1. *Reagents and Conditions:* (i) (*R*)-**8**, THF, -78°C , 2 h, then (+)-CSO **9**, rt, 16 h; (ii) H_2 , Pd/C, AcOH, rt, 16 h; (iii) PhCOCl, Et₃N, CH₂Cl₂, 0°C , 10 min then rt, 6 h; (iv) DEAD, Ph₃P, THF, rt, 26 h; (v) 6.0 M aq HCl, Δ , 7 h then Dowex; (vi) TFA, rt, overnight then 1.0 M aq HCl, Dowex.

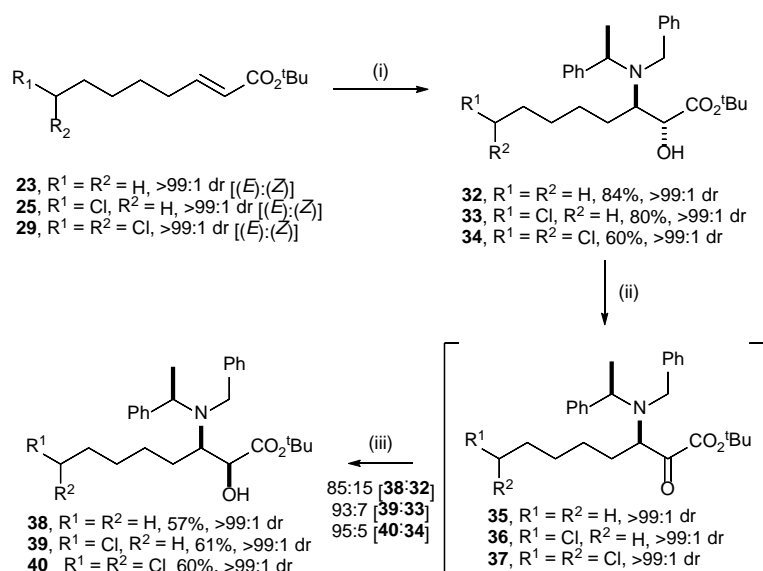
2. Results and Discussion

The requisite α,β -unsaturated esters **23**, **25** and **29** were prepared from the corresponding aldehydes *via* olefination methodology. Hexanal **22** and 6-chlorohexanal (which was prepared from 6-chlorohexan-ol **24** by treatment with IBX) were treated with ylid **30** to give the corresponding α,β -unsaturated esters **23** and **25**, respectively in 98:2 dr [(*E*):(*Z*)] in each case. Purification via flash column chromatography afforded **23** and **25** in 87 and 83% isolated yield, respectively, and >99:1 dr [(*E*):(*Z*)] in each case. Ozonolysis of cyclohexene **26** gave dialdehyde **27**, which was subsequently treated with **30** (1.0 equiv) to give α,β -unsaturated ester **28** in 66% yield and >99:1 dr [(*E*):(*Z*)], in addition to diester **31** (~20%), which could easily be separated via flash column chromatography. Treatment of **28** with ClPPh₂ and NCS⁸ gave dichloroalkyl substituted α,β -unsaturated ester **29** in 48% yield (Scheme 2).



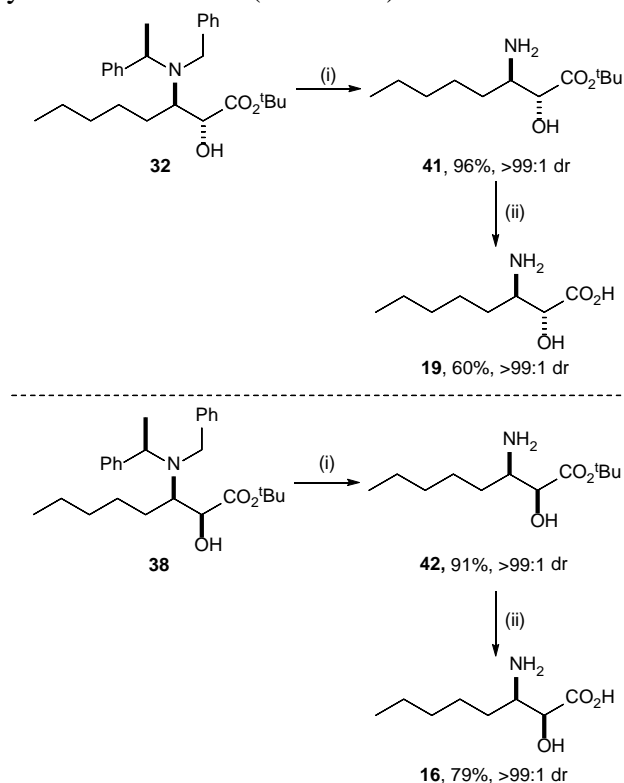
Scheme 2. *Reagents and Conditions:* (i) **30**, CH₂Cl₂, rt, 48 h; (ii) IBX, EtOAc, 70 °C, 24 h; (iii) **30**, EtOAc, rt, 18 h; (iv) O₃, CH₂Cl₂, –78 °C, 50 min then PPh₃, –78 °C to 0 °C, 4 h; (v) **30**, CH₂Cl₂, rt, 18 h; (vi) NCS, ClPPh₂, CH₂Cl₂, rt, 4 h.

Conjugate addition of lithium amide (*R*)-**8** to α,β -unsaturated ester **23** ($R^1 = R^2 = H$) followed by *in situ* enolate oxidation with (–)-CSO **9** gave *anti*- α -hydroxy- β -amino ester **32** as a single diastereoisomer (>99:1 dr) in 84% isolated yield. Similarly, treatment of **25** ($R^1 = Cl$, $R^2 = H$) and **29** ($R^1 = R^2 = Cl$)⁹ with (*R*)-**8** followed by (–)-CSO **9** afforded *anti*- α -hydroxy- β -amino esters **33** and **34** in 80 and 60% yield, respectively, and >99:1 dr in each case. The relative configurations within **32–34** were assigned based on the well-established stereochemical outcome of this *anti*-aminohydroxylation process.^{10,11} The corresponding *syn*- α -hydroxy- β -amino esters **38–40** were then prepared from *anti*- α -hydroxy- β -amino esters **32–34**.¹² Swern oxidation of **32** resulted in 100% conversion to the corresponding ketone **35**, and treatment of **35** with NaBH₄ at –20 °C gave an 85:15 mixture of *syn*-**38** and *anti*-**32**, respectively. Purification via flash column chromatography gave *syn*-**38** as a single diastereoisomer (>99:1 dr) in 57% yield. The same protocol was applied for the preparation of *syn*-**39** and *syn*-**40**. Swern oxidation of **33** and **34** promoted 100% conversion to the corresponding ketones **36** and **37**, and subsequent reduction with NaBH₄ gave a 93:7 mixture of *syn*-**39** and *anti*-**33**, and a 95:5 mixture of *syn*-**40** and *anti*-**34**, respectively. Purification via column chromatography gave *syn*-**39** and *syn*-**40** in 61 and 60% yield, respectively, and >99:1 dr in each case (Scheme 3).



Scheme 3. Reagents and Conditions: (i) (*R*)-**8**, THF, -78°C , 2 h then (–)-CSO **9**, -78°C to rt, 18 h; (ii) (COCl)₂, DMSO, CH₂Cl₂, -78°C , 30 min then Et₃N, -78°C , 30 min; (iii) NaBH₄, MeOH, -20°C , 2 h.

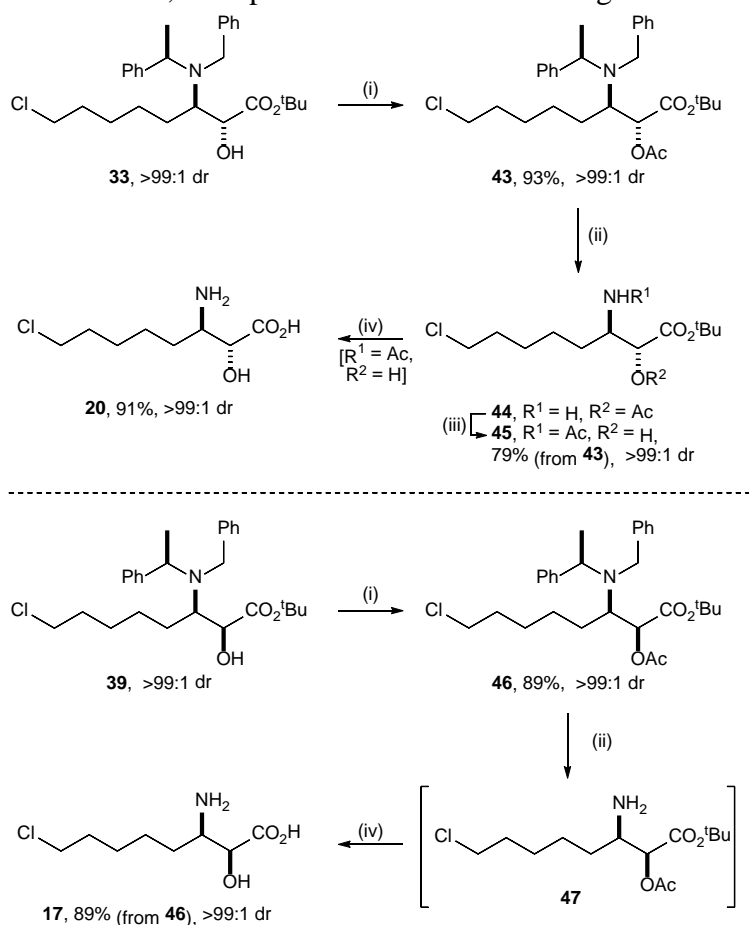
Hydrogenolysis of **32** in the presence of Pd(OH)₂/C (25% w/w) under H₂ (1 atm) afforded *anti*-α-hydroxy-β-amino ester **41** in 96% yield. Subsequent ester hydrolysis using 6.0 M aq HCl followed by purification on Dowex 50WX8-200 ion exchange resin gave (*R,R*)-2-hydroxy-3-aminooctanoic acid [(*R,R*)-ahoa] **19** in 60% yield and >99:1 dr. Similarly, hydrogenolytic *N*-debenzylation of **38** using Pd(OH)₂/C (25% w/w) under H₂ (1 atm) gave *syn*-α-hydroxy-β-amino ester **42** in 91% yield. Acid-mediated ester hydrolysis and purification via ion exchange chromatography gave (2*S*,3*R*)-2-hydroxy-3-aminooctanoic acid [(2*S*,3*R*)-ahoa] **16** in 79% yield and >99:1 dr (Scheme 4).



Scheme 4. Reagents and Conditions: (i) Pd(OH)₂/C (25% w/w), H₂ (1 atm), MeOH, rt, 18 h; (ii) 6.0 M aq HCl, rt, 3 h then Dowex.

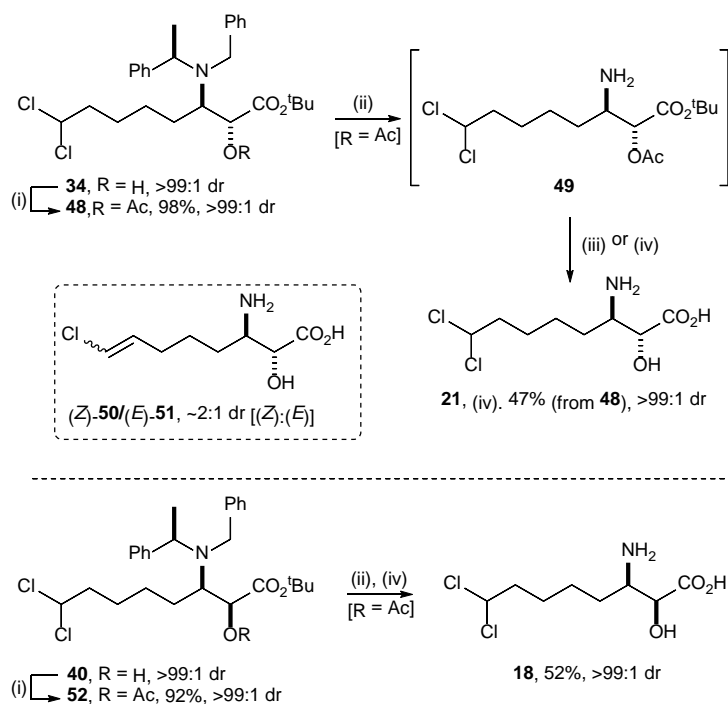
Hydrogenolytic *N*-debenzylation was attempted for chlorinated β-amino esters **33**, **34**, **39** and **40**. However, a significant amount of competitive de-chlorination was observed under various hydrogenolysis conditions.¹³

We have recently employed the NaBrO₃ and Na₂S₂O₄ under biphasic conditions (EtOAc and H₂O)¹⁴ as an alternative, oxidative method for the *N*-debenzylation of tertiary α -amino esters in the synthesis of *anti*- β -fluorophenylalanines, where standard hydrogenolytic *N*-debenzylation conditions also resulted in dehalogenation of the benzylic fluoride substrates.¹⁵ Treatment of **33** under these conditions resulted in the formation of a complex mixture. The free hydroxyl group within **33** was therefore protected by derivatisation to the corresponding *O*-acetate upon treatment with Ac₂O, which gave **43** in 93% yield. Treatment of **43** with NaBrO₃/Na₂S₂O₄ promoted complete *N*-debenzylation to give initially **44**. Upon purification of the crude sample of **44** by flash column chromatography on silica gel, migration of the *O*-acetyl group to the amino moiety was observed, giving **45** in 79% yield (from **43**) and >99:1 dr. Global hydrolysis of the amide and *tert*-butyl ester groups within **45** using 6.0 M aq HCl at 100 °C for 3 h followed by purification via ion-exchange chromatography gave (*R,R*)-2-hydroxy-3-amino-8-chlorooctanoic acid [(*R,R*)-chloro-ahoa] **20** in 91% yield and >99:1 dr. Treatment of the *syn*-analogue **39** with Ac₂O in pyridine gave **46** in 89% yield, and NaBrO₃ mediated oxidative *N*-debenzylation of **46** followed by ester hydrolysis gave (2*S*,3*R*)-2-hydroxy-3-amino-8-chlorooctanoic acid [(2*S*,3*R*)-chloro-ahoa] **17** in 89% yield (from **46**) and >99:1 dr, after purification *via* ion-exchange chromatography (Scheme 5).



Scheme 5. Reagents and Conditions: (i) Ac₂O, DMAP, pyridine, rt, 18 h; (ii) NaBrO₃, Na₂S₂O₄, EtOAc/H₂O (1:2), rt, 4 h; (iii) purification via column chromatography; (iv) 6.0 M aq HCl, 100 °C, 3 h, then Dowex.

The same deprotection protocol was applied to dichloro-analogues **34** and **40**. Treatment of **34** with Ac₂O in pyridine gave **48** in 98% yield. *N*-Debenzylation of **48** using NaBrO₃/Na₂S₂O₄ promoted 100% conversion to **49**, and subsequent acid mediated hydrolysis at 100 °C gave a mixture of products including **21**. The by-products in this sample were tentatively assigned as a ~2:1 mixture of (*Z*)-**50** (³*J*_{7,8} = 7.0 Hz) and (*E*)-**51** (³*J*_{7,8} = 13.2 Hz) based upon ¹H NMR spectroscopic and mass spectrometric analyses. However, hydrolysis of the crude sample of **49** with 6.0 M HCl at rt for 16 h followed by purification via ion-exchange chromatography afforded (*R,R*)-2-hydroxy-3-amino-8,8-dichlorooctanoic acid [(*R,R*)-dichloro-ahoa] **21** as a single diastereoisomer in 47% yield. Treatment of *syn*-dichloro compound **40** with Ac₂O gave **52** in 92% yield. *N*-Debenzylation of **52** with NaBrO₃/Na₂S₂O₄ followed by hydrolysis of the crude reaction mixture with 6.0 M aq HCl at rt for 80 h¹⁶ gave (2*S*,3*R*)-2-hydroxy-3-amino-8,8-dichlorooctanoic acid [(2*S*,3*R*)-dichloro-ahoa] **18** in 52% yield as a single diastereoisomer (Scheme 6).



Scheme 6. Reagents and Conditions: (i) Ac₂O, DMAP, pyridine, rt, 18 h; (ii) NaBrO₃, Na₂S₂O₄, EtOAc/H₂O (1:2), rt, 4 h; (iii) 6.0 M aq HCl, 100 °C, 3 h; (iv) 6.0 M aq HCl, rt, 18 h then Dowex.

3. Conclusion

In conclusion, the asymmetric syntheses of the *N*-terminal α -hydroxy- β -amino acid components of microginins 612, 646 and 680 were achieved via diastereoselective aminohydroxylation of the requisite (*E*)- β -alkyl- α,β -unsaturated ester followed by epimerisation of the resultant *anti*- α -hydroxy- β -amino esters at the C(2)-position via sequential Swern oxidation/diastereoselective reduction to give the corresponding *syn*- α -hydroxy- β -amino esters as the key steps. Suitable *N*-debenzylation (either catalytic hydrogenolysis or NaBrO₃-mediated oxidative *N*-debenzylation) of those *syn*- and *anti*- α -hydroxy- β -amino esters followed by

acid mediated hydrolysis gave the *N*-terminal *syn*- α -hydroxy- β -amino acid components of microginins 612, 646 and 680, and the corresponding C(2)-epimeric *anti*- α -hydroxy- β -amino acids.

4. Experimental

4.1. General Experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.¹⁷ BuLi was purchased as a solution in hexanes and titrated against diphenylacetic acid before use. All other reagents were used as supplied without prior purification. Organic layers were dried over MgSO₄. Thin layer chromatography was performed on aluminium plates coated with 60 F₂₅₄ silica. Plates were visualised using UV light (254 nm), 1% aq KMnO₄ or Dragendorff's reagent. Flash column chromatography was performed on Kieselgel 60 silica. Melting points are uncorrected. Specific rotations are reported in 10⁻¹ deg cm² g⁻¹ and concentrations in g/100 mL. IR spectra were recorded using an ATR module. Selected characteristic peaks are reported in cm⁻¹. NMR spectra were recorded in the deuterated solvent stated. Spectra were recorded at rt unless otherwise stated. The field was locked by external referencing to the relevant deuteron resonance. ¹H-¹H COSY, ¹H-¹³C HMQC, and ¹H-¹³C HMBC analyses were used to establish atom connectivity. Accurate mass measurements were run on a TOF spectrometer internally calibrated with polyalanine.

4.2.1 *tert*-Butyl (*E*)-oct-2-enoate **23**

6-Hexanal (6.42 mL, 52.2 mmol) was added to a stirred solution of **30** (19.8 g, 52.2 mmol) in CH₂Cl₂ (470 mL). The resultant mixture was stirred at rt for 48 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 98:2) gave **23** as a colourless oil (9.03 g, 87%, >99:1 dr [(*E*):(*Z*)]);¹⁸ δ_{H} (400 MHz, CDCl₃) 0.84–0.93 (3H, m, C(8)*H*₃), 1.22–1.38 (6H, m, C(5)*H*₂, C(6)*H*₂, C(7)*H*₂), 1.49 (9H, s, *CMe*₃), 2.10–2.18 (2H, m, C(4)*H*₂), 5.73 (1H, dt, *J* 15.6, 1.6, C(2)*H*), 6.86 (1H, dt, *J* 15.6, 7.0, C(3)*H*).

4.2.2 *tert*-Butyl (*E*)-8-chlorooct-2-enoate **25**

IBX (30.7 g, 110 mmol) was added to a stirred solution of **24** (4.88 mL, 36.6 mmol) in EtOAc (210 mL) at rt. The resultant mixture was then stirred at 70 °C for 24 h, then allowed to cool to rt and filtered (eluent EtOAc, 100 mL).

30 (13.8 g, 36.6 mmol) was added to a stirred solution of the resultant crude mixture in EtOAc (330 mL) at rt and the resultant mixture was stirred at rt for 18 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 98:2) gave **25** as a colourless oil (7.05 g, 83%, >99:1 dr [(E):(Z)]); ν_{\max} 1711 (C=O); δ_{H} (400 MHz, CDCl₃) 1.48 (9H, s, CMe₃), 1.44–1.52 (4H, m, C(5)H₂, C(6)H₂), 1.72–1.84 (2H, m, C(7)H₂), 2.10–2.20 (2H, m, C(4)H₂), 3.53 (2H, t, *J* 6.7, C(8)H₂), 5.74 (1H, dt, *J* 15.6, 1.6, C(2)H), 6.84 (1H, dt, *J* 15.6, 6.9, C(3)H); δ_{C} (100 MHz, CDCl₃) 26.4, 27.4 (C(5), C(6)), 28.1 (CMe₃), 31.8 (C(4)), 32.4 (C(7)), 44.9 (C(8)), 80.1 (CMe₃), 123.3 (C(2)), 147.5 (C(3)), 166.0 (C(1)); *m/z* (ESI⁺) 257 ([M(³⁷Cl)+Na]⁺, 32%), 255 ([M(³⁵Cl)+Na]⁺, 100%); HRMS (ESI⁺) C₁₂H₂₁³⁷ClNaO₂⁺ ([M(³⁷Cl)+Na]⁺) requires 257.1093; found 257.1093; C₁₂H₂₁³⁵ClNaO₂⁺ ([M(³⁵Cl)+Na]⁺) requires 255.1122; found 255.1122

4.2.3 *tert*-Butyl (E)-8-oxooct-2-enoate **28**

A solution of cyclohexene **26** (10.0 g, 122 mmol) in CH₂Cl₂ (240 mL) was cooled to –78 °C and degassed with N₂ and O₂ before O₃ was bubbled through the solution until a persistent blue colour appeared. O₂ was then bubbled through the solution until it became colourless. PPh₃ (32.0 g, 122 mmol) was then added and the reaction mixture was allowed to warm to rt and stirred at rt 4 h. Ylid **30** (13.7 g, 36.5 mmol) was added and the reaction mixture was stirred at rt for 18 h, then concentrated *in vacuo*. The resultant mixture was triturated with Et₂O (3 × 200 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 98:2 increased to 95:5) gave **28** as a colourless oil (5.09 g, 66%, >99:1 dr [(E):(Z)]); ν_{\max} 1653, 1709 (C=O); δ_{H} (400 MHz, CDCl₃) 1.41 (9H, s, CMe₃), 1.40–1.49 (2H, m, C(5)H₂), 1.58 (2H, app dt, *J* 9.2, 7.2, C(6)H₂), 2.13 (2H, td, *J* 6.9, 1.6, C(4)H₂), 2.38 (2H, td, *J* 7.2, 1.7, C(7)H₂), 5.68 (1H, dt, *J* 15.6, 1.6, C(2)H), 6.76 (1H, dt, *J* 15.6, 6.9, C(3)H), 9.70 (1H, t, *J* 1.7, C(8)H); δ_{C} (100 MHz, CDCl₃) 21.4 (C(6)), 27.4 (CMe₃), 28.0 (C(5)), 31.5 (C(4)), 43.4 (C(7)), 80.0 (CMe₃), 123.3 (C(2)), 146.8 (C(3)), 165.8 (C(1)), 202.0 (C(8)); *m/z* (ESI⁺) 235 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₁₂H₂₀NaO₃⁺ ([M+Na]⁺) requires 235.1305; found 235.1306.

4.2.4 *tert*-Butyl (E)-8,8-dichlorooct-2-enoate **29**

A solution of **28** (500 mg, 3.53 mmol, >99:1 dr) in CH₂Cl₂ (3 mL) was added to a stirred solution of ClPPH₂ (0.66 mL, 3.54 mmol) and NCS (470 mg, 3.53 mmol) in CH₂Cl₂ (9 mL) at rt and the resultant mixture was stirred at rt for 4 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 98:2) gave **29** as a colourless oil (630 mg, 48%, >99:1 dr); ν_{\max} 1791 (C=O); δ_{H} (400 MHz, CDCl₃) 1.48 (9H, s, CMe₃), 1.49–1.65 (4H, m, C(5)H₂, C(6)H₂), 2.15–2.31 (4H, m, C(4)H₂,

C(7)H₂), 5.68–5.80 (2H, m, C(2)H, C(8)H), 6.83 (1H, dt, *J* 15.5, 6.9, C(3)H); δ_{C} (100 MHz, CDCl₃) 25.3 (C(6)), 26.7 (C(5)), 28.0 (CMe₃), 31.5 (C(4)), 43.1 (C(7)), 73.1 (C(8)), 80.2 (CMe₃), 123.4 (C(2)), 146.8 (C(3)), 165.8 (C(1)); *m/z* (ESI⁺) 293 ([M(³⁷Cl₂)+Na]⁺, 10%), 291 ([M(³⁵Cl,³⁷Cl)+Na]⁺, 64%), 289 ([M(³⁵Cl₂)+Na]⁺, 100%); HRMS (ESI⁺) C₁₂H₂₀³⁷Cl₂NaO₂⁺ ([M(³⁷Cl₂)+Na]⁺) requires 293.0674; found 293.0679; C₁₂H₂₀³⁵Cl³⁷ClNaO₂⁺ ([M(³⁵Cl,³⁷Cl)+Na]⁺) requires 291.0703; found 291.0709; C₁₂H₂₀³⁵Cl₂NaO₂⁺ ([M(³⁵Cl₂)+Na]⁺) requires 289.0733; found 289.0744.

4.2.5 *tert*-Butyl (*R,R,R*)-2-hydroxy-3-[*N*-benzyl-*N*- α -(methylbenzyl)amino]octanoate **32**

BuLi (2.5 M in hexanes, 28.3 mL, 70.7 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α -methylbenzyl)amine (15.4 g, 73.0 mmol, >99:1 er) in THF (203 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min, then a solution of **23** (9.04 g, 45.6 mmol, >99:1 dr [(*E*):(*Z*)]) in THF (101 mL) was added dropwise at –78 °C and the resultant mixture was stirred at –78 °C for 2 h. (–)-CSO **9** (16.2 g, 70.7 mmol) was added and the resultant mixture was allowed to warm to rt and stirred at rt for 18 h. The reaction mixture was then concentrated *in vacuo* and partitioned between CH₂Cl₂ (100 mL) and 10% aq citric acid (100 mL). The aqueous layer was extracted with CH₂Cl₂ (3 \times 100 mL), and the combined organic extracts were washed with satd aq NaHCO₃ (200 mL), then dried and concentrated *in vacuo*. The residue was triturated with Et₂O (200 mL), then filtered and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 98:2) gave **32** as a colourless oil (16.3 g, 84%, >99:1 dr); $[\alpha]_{\text{D}}^{25}$ –27.0 (*c* 1.0 in CHCl₃); ν_{max} 3501 (br, O–H), 1719 (C=O); δ_{H} (400 MHz, CDCl₃) 0.80 (3H, t, *J* 7.3, C(8)H₃), 1.08 (3H, d, *J* 6.9, C(α)Me), 1.17–1.50 (6H, m, C(5)H₂, C(6)H₂, C(7)H₂), 1.34 (9H, s, CMe₃), 1.60–1.75 (2H, m, C(4)H₂), 2.84 (1H, d, *J* 6.1, OH), 3.12 (1H, ddd, *J* 8.6, 4.8, 1.8, C(3)H), 3.60 (1H, d, *J* 15.4, NCH_AH_BPh), 3.81–3.92 (2H, m, C(2)H, C(α)H), 4.18 (1H, d, *J* 15.4, NCH_AH_BPh), 7.10–7.40 (10H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 14.6 (C(8)), 19.9 (C(α)Me), 23.1, 26.8, 27.8 (C(5), C(6), C(7)), 28.5 (CMe₃), 32.4 (C(4)), 51.5 (NCH₂Ph), 59.0 (C(3)), 59.2 (C(α)), 71.6 (C(2)), 82.8 (CMe₃), 126.2, 126.8, 127.4, 128.5, 128.6, 128.7 (*o,m,p-Ph*), 144.0, 143.2 (*i-Ph*), 174.9 (C(1)); *m/z* (ESI⁺) 426 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₇H₄₀NO₃⁺ ([M+H]⁺) requires 426.3003; found 426.2996.

4.2.6 *tert*-Butyl (*R,R,R*)-2-hydroxy-3-[*N*-benzyl-*N*- α -(methylbenzyl)amino]-8-chlorooctanoate **33**

BuLi (2.5 M in hexanes, 12.9 mL, 32.4 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α -methylbenzyl)amine (7.05 g, 33.4 mmol, >99:1 er) in THF (93 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min, then a solution of **25** (4.41 g, 20.9 mmol, >99:1 dr [(*E*):(*Z*)]) in THF (46 mL) was added dropwise at –78 °C and the resultant mixture was stirred at –78 °C for 2 h. (–)-CSO **9** (7.42 g,

32.4 mmol) was added and the resultant mixture was allowed to warm to rt and stirred at rt for 18 h. The reaction mixture was then concentrated *in vacuo* and partitioned between CH₂Cl₂ (100 mL) and 10% aq citric acid (100 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 50 mL), and the combined organic extracts were washed with satd aq NaHCO₃ (200 mL), then dried and concentrated *in vacuo*. The residue was triturated with Et₂O (200 mL), then filtered and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 98:2) gave **33** as colourless oil (7.68 g, 80%, >99:1 dr); $[\alpha]_{\text{D}}^{25}$ –23.7 (*c* 1.0 in CHCl₃); ν_{max} 3084 (br, O–H), 1717 (C=O); δ_{H} (400 MHz, CDCl₃) 0.99–1.61 (6H, m, C(4)*H*₂, C(5)*H*₂, C(6)*H*₂), 1.21 (3H, d, *J* 7.0, C(α)*Me*), 1.36 (9H, s, *CMe*₃), 1.62–1.71 (2H, m, C(7)*H*₂), 2.83 (1H, d, *J* 5.9, OH), 3.12 (1H, ddd, *J* 8.9, 4.5, 1.7, C(3)*H*), 3.43 (2H, t, *J* 6.7, C(8)*H*₂), 3.60 (1H, d, *J* 15.6, NCH_AH_BPh), 3.86–3.90 (2H, m, C(2)*H*, C(α)*H*), 4.20 (1H, d, *J* 15.6, NCH_AH_BPh), 7.18–7.43 (10H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 19.7 (C(α)*Me*), 27.8 (*CMe*₃), 25.7, 26.8, 27.0 (C(4), C(5), C(6)), 32.4 (C(7)), 44.9 (C(8)), 50.8 (NCH₂Ph), 58.5, 58.7 (C(α), C(3)), 70.8 (C(2)), 82.3 (*CMe*₃), 126.2, 126.8, 127.8, 127.9, 127.9, 128.0 (*o,m,p-Ph*), 142.4, 143.5 (*i-Ph*), 174.2 (C(1)); *m/z* (ESI⁺) 462 ([M(³⁷Cl)+H]⁺, 32%); 460 ([M(³⁵Cl)+H]⁺, 100%); HRMS (ESI⁺) C₂₇H₃₉³⁷ClNO₃⁺ ([M(³⁷Cl)+H]⁺) requires 462.2583; found 462.2601; C₂₇H₃₉³⁵ClNO₃⁺ ([M(³⁵Cl)+H]⁺) requires 460.2613; found 460.2625.

4.2.7 *tert*-Butyl (*R,R,R*)-2-hydroxy-3-[*N*-benzyl-*N*- α -(methylbenzyl)amino]-8,8-dichlorooctanoate **34**

BuLi (2.5 M in hexanes, 5.98 mL, 5.90 mmol) was added dropwise to a stirred solution of (*R*)-*N*-benzyl-*N*-(α -methylbenzyl)amine (3.22 g, 15.3 mmol, >99:1 er) in THF (93 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 30 min, then a solution of **29** (1.24 g, 5.86 mmol, >99:1 dr [(*E*):(*Z*)] in THF (13 mL) was added dropwise at –78 °C and the resultant mixture was stirred at –78 °C for 2 h. (–)-CSO **9** (3.49 g, 15.3 mmol) was added and the resultant mixture was allowed to warm to rt and stirred at rt for 18 h. The reaction mixture was then concentrated *in vacuo* and partitioned between CH₂Cl₂ (40 mL) and 10% aq citric acid (40 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 50 mL), and the combined organic extracts were washed with satd aq NaHCO₃ (50 mL), then dried and concentrated *in vacuo*. The residue was triturated with Et₂O (50 mL), then filtered and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 98:2) gave **34** as colourless oil (1.73 g, 60%, >99:1 dr); $[\alpha]_{\text{D}}^{25}$ –19.0 (*c* 1.0 in CHCl₃); ν_{max} 3501 (br, O–H), 1719 (C=O); δ_{H} (400 MHz, CDCl₃) 1.21 (3H, d, *J* 7.1, C(α)*Me*), 1.23–1.34 (4H, m, C(5)*H*₂, C(6)*H*₂), 1.36 (9H, s, *CMe*₃), 1.40–1.63 (2H, m, C(4)*H*₂), 2.02–2.11 (2H, m, C(7)*H*₂), 2.84 (1H, d, *J* 5.7, OH), 3.12 (1H, ddd, *J* 9.3, 4.2, 1.6, C(3)*H*), 3.60 (1H, d, *J* 15.6, NCH_AH_BPh), 3.79–3.93 (2H, m, C(2)*H*, C(α)*H*), 4.22 (1H, d, *J* 15.6, NCH_AH_BPh), 5.60 (1H, t, *J* 6.0, C(8)*H*), 7.12–7.39 (10H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 20.3 (C(α)*Me*), 25.2, 26.2 (C(5), C(6)), 27.3 (C(4)),

28.2 (CMe₃), 43.6 (C(7)), 51.0 (NCH₂Ph), 58.8 (C(3)), 59.2 (C(α)), 71.0 (C(2)), 73.7 (C(8)), 82.8 (CMe₃), 126.5, 127.2, 128.0, 128.2, 128.3, 128.4 (*o,m,p-Ph*), 143.8, 142.9 (*i-Ph*), 174.5 (C(1)); *m/z* (ESI⁺) 498 ([M(³⁷Cl₂)+H]⁺, 10%), 496 ([M(³⁵Cl,³⁷Cl)+H]⁺, 64%), 494 ([M(³⁵Cl₂)+H]⁺, 100%); HRMS (ESI⁺) C₂₇H₃₈³⁷Cl₂NO₃⁺ ([M(³⁷Cl₂)+H]⁺) requires 498.2164; found 494.2188; C₂₇H₃₈³⁵Cl³⁷ClNO₃⁺ ([M(³⁵Cl,³⁷Cl)+H]⁺) requires 496.2194; found 494.2206; C₂₇H₃₈³⁵Cl₂NO₃⁺ ([M(³⁵Cl₂)+H]⁺) requires 494.2223; found 494.2231.

4.2.8 *tert*-Butyl (2*S*,3*R*,α*R*)-2-hydroxy-3-[*N*-benzyl-*N*-α-(methylbenzyl)amino]octanoate **38**

Step 1: DMSO (1.50 mL, 18.8 mmol) was added to a stirred solution of (COCl)₂ (0.80 mL, 9.41 mmol) in CH₂Cl₂ (16 mL) and the resultant mixture was stirred at −78 °C for 20 min. A solution of **32** (2.00 g, 4.70 mmol, >99:1 dr) in CH₂Cl₂ (8.0 mL) was then added dropwise at −78 °C and the resultant mixture was stirred at −78 °C for 30 min. Et₃N (3.95 mL, 28.2 mmol) was then added and the resultant mixture was stirred at −78 °C for 30 min then allowed to warm rt. H₂O (15 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (3 × 15 mL). The combined organic extracts were then dried and concentrated *in vacuo*.

Step 2: NaBH₄ (178 mg, 4.70 mmol) was added to a stirred solution of the residue of **35** in MeOH (23.5 mL) at −20 °C and the resultant mixture was stirred at −20 °C for 2 h, then allowed to warm to rt. The reaction mixture was then concentrated *in vacuo* and partitioned between CH₂Cl₂ (20 mL) and H₂O (20 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL), and the combined organic extracts were dried and concentrated *in vacuo* to give an 85:15 mixture of **38** and **32**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et₂O, 95:5) gave **38** as a colourless oil (1.14 g, 57%, >99:1 dr); [α]_D²⁵ −24.4 (*c* 1.0 in CHCl₃); *v*_{max} 3658 (br, O–H), 1720 (C=O); δ_H (400 MHz, CDCl₃) 0.85 (3H, t, *J* 7.0, C(8)H₃), 1.31 (3H, d, *J* 7.0, C(α)Me), 1.36 (9H, s, CMe₃), 1.11–1.58 (8H, m, C(4)H₂, C(5)H₂, C(6)H₂, C(7)H₂), 2.99 (1H, app q, *J* 6.3, C(3)H), 3.41 (1H, br s, OH), 3.70–3.80 (2H, m, C(2)H, NCH_AH_BPh), 3.84 (1H, d, *J* 14.5, NCH_AH_BPh), 4.03 (1H, q, *J* 7.0, C(α)H), 7.14–7.35 (10H, m, *Ph*); δ_C (100 MHz, CDCl₃) 14.6 (C(8)), 18.0 (C(α)Me), 23.0, 27.9, 29.2, 32.7 (C(4), C(5), C(6), C(7)), 28.5 (CMe₃), 50.8 (NCH₂Ph), 61.2 (C(α)), 61.3 (C(3)), 73.9 (C(2)), 82.2 (CMe₃), 127.2, 127.6, 128.3, 128.7, 128.8, 129.0 (*o,m,p-Ph*), 143.8, 142.7 (*i-Ph*), 174.6 (C(1)); *m/z* (ESI⁺) 426 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₇H₄₀NO₃⁺ ([M+H]⁺) requires 426.3003; found 426.2996.

4.2.9 *tert*-Butyl (2*S*,3*R*,α*R*)-2-hydroxy-3-[*N*-benzyl-*N*-α-(methylbenzyl)amino]-8-chlorooctanoate **39**

Step 1: DMSO (1.73 mL, 24.2 mmol) was added to a stirred solution of (COCl)₂ (1.02 mL, 12.1 mmol) in

CH₂Cl₂ (10 mL) and the resultant mixture was stirred at –78 °C for 20 min. A solution of **33** (2.78 g, 6.05 mmol, >99:1 dr) in CH₂Cl₂ (22 mL) was then added dropwise at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. Et₃N (5.09 mL, 36.3 mmol) was then added and the resultant mixture was stirred at –78 °C for 30 min then allowed to warm rt. H₂O (30 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic extracts were then dried and concentrated *in vacuo*.

Step 2: NaBH₄ (229 mg, 6.05 mmol) was added to a stirred solution of the residue of **36** in MeOH (24 mL) at –20 °C and the resultant mixture was stirred at –20 °C for 2 h, then allowed to warm to rt. The reaction mixture was then concentrated *in vacuo* and partitioned between CH₂Cl₂ (20 mL) and H₂O (20 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL), and the combined organic extracts were dried and concentrated *in vacuo* to give an 93:7 mixture of **39** and **33**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et₂O, 95:5) gave **39** as a colourless oil (1.70 g, 61%, >99:1 dr); [α]_D²⁵ –20.8 (*c* 1.0 in CHCl₃); ν_{max} 3062 (br, O–H), 1721 (C=O); δ_H (400 MHz, CDCl₃) 1.31 (3H, d, *J* 7.0, C(α)*Me*), 1.39 (9H, s, *CMe*₃), 1.17–1.55 (6H, m, C(4)*H*₂, C(5)*H*₂, C(6)*H*₂), 1.60–1.72 (2H, m, C(7)*H*₂), 2.98 (1H, ddd, *J* 7.8, 6.1, 4.6, C(3)*H*), 3.28 (1H, d, *J* 3.3, OH), 3.45 (2H, t, *J* 6.7, C(8)*H*₂), 3.71–3.77 (2H, m, C(2)*H*, NCH_AH_BPh), 3.82 (1H, d, *J* 14.6, NCH_AH_BPh), 4.02 (1H, q, *J* 7.0, C(α)*H*), 7.12–7.30 (10H, m, *Ph*); δ_C (100 MHz, CDCl₃) 18.0 (*CMe*₃), 28.0 (C(α)*Me*), 26.9, 27.2, 28.5 (C(4), C(5), C(6)), 32.4 (C(7)), 45.0 (C(8)), 50.2 (NCH₂Ph), 60.3 (C(α)), 61.0 (C(3)), 73.5 (C(2)), 81.9 (*CMe*₃), 127.2, 126.8, 128.29, 127.9, 128.5, 128.3 (*o,m,p-Ph*), 143.3, 141.4 (*i-Ph*), 173.2 (C(1)); *m/z* (ESI⁺) 462 ([M(³⁷Cl)+H]⁺, 32%), 460 ([M(³⁵Cl)+H]⁺, 100%); HRMS (ESI⁺) C₂₇H₃₉³⁷ClNO₃⁺ ([M(³⁷Cl)+H]⁺) requires 462.2583; found 462.2592; C₂₇H₃₉³⁵ClNO₃⁺ ([M(³⁵Cl)+H]⁺) requires 460.2613; found 460.2605.

4.2.10 *tert*-Butyl (2*S*,3*R*,α*R*)-2-hydroxy-3-[*N*-benzyl-*N*-α-(methylbenzyl)amino]-8,8-dichlorooctanoate **40**

Step 1: DMSO (1.50 mL, 18.8 mmol) was added to a stirred solution of (COCl)₂ (0.80 mL, 9.41 mmol) in CH₂Cl₂ (0.3 mL) and the resultant mixture was stirred at –78 °C for 20 min. A solution of **34** (100 mg, 0.238 mmol, >99:1 dr) in CH₂Cl₂ (0.9 mL) was then added dropwise at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. Et₃N (0.19 mL, 1.39 mmol) was then added and the resultant mixture was stirred at –78 °C for 30 min then allowed to warm rt. H₂O (5 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (3 × 5 mL). The combined organic extracts were then dried and concentrated *in vacuo*.

Step 2: NaBH₄ (9 mg, 0.238 mmol) was added to a stirred solution of the residue of **36** in MeOH (23.5 mL) at –20 °C and the resultant mixture was stirred at –20 °C for 2 h, then allowed to warm to rt. The reaction

mixture was then concentrated *in vacuo* and partitioned between CH₂Cl₂ (5 mL) and H₂O (5 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 5 mL), and the combined organic extracts were dried and concentrated *in vacuo* to give an 95:5 mixture of **40** and **34**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 98:2) gave **40** as a colourless oil (60 mg, 60%, >99:1 dr); $[\alpha]_{\text{D}}^{25}$ –15.0 (*c* 1.0 in CHCl₃); ν_{max} 3503 (br, O–H), 1722 (C=O); δ_{H} (400 MHz, CDCl₃) 1.29 (3H, d, *J* 7.0, C(α)Me), 1.35 (9H, s, CMe₃), 1.14–1.61 (6H, m, C(4)H₂, C(5)H₂, C(6)H₂), 1.99–2.10 (2H, m, C(7)H₂), 2.96–2.99 (1H, m, C(3)H), 3.20 (1H, br s, OH), 3.70–3.79 (2H, m, NCH₂Ph), 3.82 (1H, d, *J* 14.7, C(2)H), 3.98–4.05 (1H, m, C(α)H), 5.62 (1H, t, *J* 6.0, C(8)H), 7.12–7.25 (10H, m, Ph); δ_{C} (100 MHz, CDCl₃) 18.3 (C(α)Me), 26.2, 26.5, 28.4 (C(4), C(5), C(6)), 28.1 (CMe₃), 43.3 (C(7)), 50.2 (NCH₂Ph), 60.7 (C(α)), 61.2 (C(3)), 73.4 (C(2)), 73.5 (C(8)), 82.0 (CMe₃), 126.8, 127.3 (*p*-Ph), 127.9, 128.3, 128.4, 128.5 (*o,m,p*-Ph), 141.5, 143.2 (*i*-Ph), 173.18 (C(1)); *m/z* (ESI⁺) 498 ([M(³⁷Cl₂)+H]⁺, 10%), 496 ([M(³⁵Cl,³⁷Cl)+H]⁺, 64%), 494 ([M(³⁵Cl₂)+H]⁺, 100%); HRMS (ESI⁺) C₂₇H₃₈³⁷Cl₂NO₃⁺ ([M(³⁷Cl₂)+H]⁺) requires 498.2164; found 494.2188; C₂₇H₃₈³⁵Cl³⁷ClNO₃⁺ ([M(³⁵Cl,³⁷Cl)+H]⁺) requires 496.2194; found 494.2206; C₂₇H₃₈³⁵Cl₂NO₃⁺ ([M(³⁵Cl₂)+H]⁺) requires 494.2223; found 494.2230.

4.2.11 *tert*-Butyl (*R,R*)-2-hydroxy-3-aminooctanoate **41**

Pd(OH)₂/C (13 mg, 25% w/w) was added to a degassed solution of **32** (54 mg, 0.13 mmol, >99:1 dr) in MeOH (1.3 mL). The resultant mixture was stirred under H₂ (1 atm) at rt for 18 h. The reaction mixture was then filtered through Celite[®] (eluent MeOH) and concentrated *in vacuo* to give **41** as a yellow oil (28 mg, 96%, >99:1 dr); $[\alpha]_{\text{D}}^{25}$ +8.3 (*c* 1.0 in CHCl₃); ν_{max} 3672 (br, N–H, O–H), 1728 (C=O); δ_{H} (400 MHz, CDCl₃) 0.88 (3H, t, *J* 6.9, C(8)H₃), 1.22–1.48 (6H, m, C(5)H₂, C(6)H₂, C(7)H₂), 1.49 (9H, s, CMe₃), 1.51–1.55 (2H, m, C(4)H₂), 2.97–3.00 (1H, m, C(3)H), 4.01–4.06 (1H, m, C(2)H); δ_{C} (100 MHz, CDCl₃) 14.5 (C(8)), 28.5 (CMe₃), 23.0, 26.6, 32.3 (C(5), C(6), C(7)), 34.8 (C(4)), 54.9 (C(3)), 75.3 (C(2)), 83.0 (CMe₃), 173.2 (C(1)); *m/z* (ESI⁺) 232 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₂H₂₆NO₃⁺ ([M+H]⁺) requires 232.1907; found 232.1906.

4.2.12 (*R,R*)-2-Hydroxy-3-aminooctanoic acid [(*R,R*)-ahoa] **19**

A solution of **41** (261 mg, 1.13 mmol, >99:1 dr) in 6.0 M aq HCl (10 mL) was stirred at rt for 3 h, then concentrated *in vacuo*. Purification *via* ion-exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH₄OH) gave **19** as a white solid (119 mg, 60%, >99:1 dr);⁶ mp 243–244 °C; $[\alpha]_{\text{D}}^{25}$ +3.6 (*c* 1.0 in MeOH); ν_{max} 3672 (br, N–H, O–H), 2997 (C–H), 1583 (C=O); δ_{H} (400 MHz, D₂O) 0.83 (3H, t, *J* 7.0, C(8)H₃), 1.24–1.45 (6H, m, C(5)H₂, C(6)H₂, C(7)H₂), 1.42–1.68 (2H, m, C(4)H), 3.54–3.56 (1H, m, C(3)H), 4.21 (1H, d, *J* 3.6, C(2)H); δ_{C} (100 MHz, CDCl₃) 13.1 (C(8)), 21.6, 24.4, 26.9 (C(5), C(6), C(7)), 32.0 (C(4)), 54.0 (C(3)),

71.6 (C(2)), 176.7 (C(1)); m/z (ESI⁺) 176 ([M+H]⁺, 100%); HRMS (ESI⁺) C₈H₁₈NO₃⁺ ([M+H]⁺) requires 176.12812; found 176.12824.

4.2.13 *tert*-Butyl (2*S*,3*R*)-2-hydroxy-3-aminooctanoate **42**

Pd(OH)₂/C (116 mg, 25% w/w) was added to a degassed solution of **38** (465 mg, 1.09 mmol, >99:1 dr) in MeOH (11 mL). The resultant mixture was stirred under H₂ (1 atm) at rt for 18 h. The reaction mixture was then filtered through Celite[®] (eluent MeOH) and concentrated *in vacuo* to give **42** as a yellow oil (229 mg, 91%, >99:1 dr); $[\alpha]_D^{25}$ -11.0 (*c* 1.0 in CHCl₃); ν_{\max} 3673 (br, O-H, N-H), 1734 (C=O); δ_H (400 MHz, CDCl₃) 0.90 (3H, t, *J* 6.9, C(8)H₃), 1.18–1.42 (6H, m, C(5)H₂, C(6)H₂, C(7)H₂), 1.43 (9H, s, CMe₃), 1.45–1.54 (2H, m, C(4)H₂), 2.99–3.04 (1H, m, C(3)H), 3.95–4.01 (1H, m, C(2)H); δ_C (100 MHz, CDCl₃) 14.2 (C(8)), 22.8, 26.3, 32.0 (C(5), C(6), C(7)), 34.7 (C(4)), 28.2 (CMe₃), 54.0 (C(3)), 73.8 (C(2)), 82.6 (CMe₃), 173.9 (C(1)); m/z (ESI⁺) 232 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₂H₂₆NO₃⁺ ([M+H]⁺) requires 232.1907; found 232.1907.

4.2.14 (2*S*,3*R*)-2-Hydroxy-3-aminooctanoic acid [(2*S*,3*R*)-ahoa] **16**

A solution of **42** (150 mg, 0.649 mmol, >99:1 dr) in 6.0 M aq HCl (5 mL) was stirred at rt for 3 then concentrated *in vacuo*. Purification *via* ion-exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH₄OH) gave **16** as a white solid (90 mg, 79%, >99:1 dr);⁶ mp 242.5–243.5 °C; $[\alpha]_D^{25}$ -6.0 (*c* 1.0 in H₂O/MeOH (v/v, 1:1)); ν_{\max} 3672 (br, N-H, O-H), 2998 (C-H), 1591 (C=O); δ_H (400 MHz, D₂O) 0.75 (3H, t, *J* 7.1, C(8)H₃), 1.71–1.41 (6H, m, C(5)H₂, C(6)H₂, C(7)H₂), 1.48–1.67 (2H, m, C(4)H₂), 3.33–3.37 (1H, m, C(3)H), 3.97 (1H, d, *J* 3.9, C(2)H); δ_C (100 MHz, CDCl₃) 13.1 (C(8)), 21.6, 24.3, 30.5 (C(5), C(6), C(7)), 29.0 (C(4)), 54.0 (C(3)), 70.9 (C(2)), 177.7 (C(1)); m/z (ESI⁺) 176 ([M+H]⁺, 100%); HRMS (ESI⁺) C₈H₁₈NO₃⁺ ([M+H]⁺) requires 176.12812; found 176.12816.

4.2.15 *tert*-Butyl (*R,R,R*)-2-acetoxy-3-[*N*-benzyl-*N*- α -(methylbenzyl)amino]-8-chlorooctanoate **143**

Ac₂O (1.15 mL, 12.3 mmol) and DMAP (14 mg, 0.123 mmol) were added to a stirred solution of **33** (543 mg, 1.23 mmol, >99:1 dr) in pyridine (5.0 mL) at 0 °C. The resultant mixture was allowed to warm to rt and stirred at rt for 18 h. The reaction mixture was then diluted with H₂O (6 mL) and EtOAc (6 mL), and the aqueous layer was extracted with EtOAc (3 × 6 mL). The combined organic extracts were washed with brine (20 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography gave **43** as a white solid (573 mg, 93%, >99:1 dr); mp 85.5–86.5 °C; $[\alpha]_D^{25}$ +1.8 (*c* 1.0 in CHCl₃); ν_{\max} 1742 (C=O); δ_H (400 MHz, CDCl₃) 1.16 (3H, d, *J* 7.0, C(α)Me), 1.31 (9H, s, CMe₃), 1.10–1.54 (6H, m, C(4)H₂, C(5)H₂,

C(6) H_2), 1.56–1.72 (2H, m, C(7) H_2), 1.99 (3H, s, COMe), 3.22 (1H, ddd, J 9.9, 3.8, 1.4, C(3) H), 3.40 (2H, t, J 6.8, C(8) H_2), 3.49 (1H, d, J 15.6, NCH_AH_BPh), 3.86 (1H, q, J 7.0, C(α) H), 4.12 (1H, d, J 15.6, NCH_AH_BPh), 4.95 (1H, d, J 3.8, C(2) H), 7.13–7.38 (10H, m, *Ph*); δ_c (100 MHz, CDCl₃) 21.1 (C(α)Me), 21.6 (COMe), 26.2, 26.9, 28.0, 32.6 (C(4), C(5), C(6), C(7)), 28.1 (CMe₃), 45.1 (C(8)), 50.6 (NCH₂Ph), 57.7 (C(3)), 60.2 (C(α)), 73.0 (C(2)), 82.3 (CMe₃), 126.7, 127.2, 127.8, 128.0, 128.4, 128.5 (*o,m,p-Ph*), 142.9, 144.1 (*i-Ph*), 168.8, 170.4 (C(1), COMe); m/z (ESI⁺) 504 ([M(³⁷Cl)+H]⁺, 32%), 502 ([M(³⁵Cl)+H]⁺, 100%); HRMS (ESI⁺) C₂₉H₄₁³⁷ClNO₄⁺ ([M(³⁷Cl)+H]⁺) requires 504.2689; found 504.2715; C₂₉H₄₁³⁵ClNO₄⁺ ([M(³⁵Cl)+H]⁺) requires 502.2719; found 502.2733.

4.2.16 *tert*-Butyl (*R,R*)-2-hydroxy-3-acetamido-8-chlorooctanoate **45**

A solution of NaBrO₃ (398 mg, 2.63 mmol) in H₂O (9.0 mL) was added to a stirred solution of **43** (440 mg, 0.878 mmol, >99:1 dr) in EtOAc (12 mL) at rt and the resultant mixture was stirred at rt for 10 min. A solution of Na₂S₂O₄ (382 mg, 2.19 mmol) in H₂O (16 mL) was added dropwise at rt over 5 min then the reaction mixture was stirred at rt for 4 h. EtOAc (15 mL) was added and the resultant mixture was washed with satd aq Na₂S₂O₃ (15 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL) and the combined organic extracts were washed with brine (35 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 40:60) gave **45** as a yellow oil (213 mg, 79%, >99:1 dr); $[\alpha]_D^{25}$ –3.2 (*c* 1.0 in CHCl₃); ν_{\max} 3294 (br, O–H, N–H), 1733 (C=O, ester), 1653 (C=O, amide); δ_H (400 MHz, CDCl₃) 1.51 (9H, s, CMe₃), 1.16–1.58 (6H, m, C(4) H_2 , C(5) H_2 , C(6) H_2), 1.75 (2H, m, C(7) H_2), 2.02 (3H, s, COMe), 3.08 (1H, d, J 5.2, OH), 3.52 (2H, t, J 6.0, C(8) H_2), 4.16 (1H, dd, J 5.2, 3.1, C(2) H), 4.25–4.39 (1H, m, C(3) H), 5.68 (1H, d, J 9.6, NH); δ_c (100 MHz, CDCl₃) 23.5 (COMe), 25.2, 26.8, 28.8 (C(4), C(5), C(6)), 28.1 (CMe₃), 32.5 (C(7)), 45.0 (C(8)), 51.0 (C(3)), 73.0 (C(2)), 83.6 (CMe₃), 170.0, 172.1 (C(1), COMe); m/z (ESI⁺) 332 ([M(³⁷Cl)+Na]⁺, 32%), 330 ([M(³⁵Cl)+Na]⁺, 100%); HRMS (ESI⁺) C₁₄H₂₆³⁷ClNNaO₄⁺ ([M(³⁷Cl)+Na]⁺) requires 332.1413; found 332.1408; C₁₄H₂₆³⁵ClNNaO₄⁺ ([M(³⁵Cl)+Na]⁺) requires 330.1443; found 330.1458.

4.2.17 (*R,R*)-2-Hydroxy-3-amino-8-chlorooctanoic acid [(*R,R*)-chloro-ahoa] **20**

A solution of **45** (224 mg, 0.729 mmol, >99:1 dr) in 6.0 M aq HCl (7.0 mL) was stirred at 100 °C for 3 h, then concentrated *in vacuo*. Purification *via* ion-exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH₄OH) gave **20** as a white solid (139 mg, 91%, >99:1 dr); mp 185.5–186.5 °C; $[\alpha]_D^{25}$ +20.4 (*c* 1.0 in MeOH); ν_{\max} 3420 (br, O–H, N–H), 1590 (C=O); δ_H (400 MHz, MeOH-*d*₄) 1.37–1.53 (4H, m, C(5) H_2 , C(6) H_2), 1.54–1.74 (2H, m, C(4) H_2), 1.73–1.82 (2H, m, C(7) H_2), 3.30–3.36 (1H, m, C(3) H), 3.56 (2H, t, J

6.6, C(8)*H*), 3.99 (1H, d, *J* 3.0, C(2)*H*); δ_c (100 MHz, MeOH-*d*₄) 25.8, 27.7 (C(5), C(6)), 30.8 (C(4)), 33.5 (C(7)), 45.5 (C(8)), 55.2 (C(3)), 71.6 (C(2)), 177.1 (C(1)); *m/z* (ESI⁺) 212 ([M(³⁷Cl)+H]⁺, 32%); 210 ([M(³⁵Cl)+H]⁺, 100%); HRMS (ESI⁺) C₈H₁₇³⁷ClNO₃⁺ ([M(³⁷Cl)+H]⁺) requires 212.0862; found 212.0871; C₈H₁₇³⁵ClNO₃⁺ ([M(³⁵Cl)+H]⁺) requires 210.0891; found 210.0900.

4.2.18 *tert*-Butyl (2*S*,3*R*, α *R*)-2-acetoxy-3-[*N*-benzyl-*N*- α -(methylbenzyl)amino]-8-chlorooctanoate **46**

Ac₂O (1.08 mL, 11.2 mmol) and DMAP (13 mg, 0.112 mmol) were added to a stirred solution of **39** (523 mg, 1.14 mmol, >99:1 dr) in pyridine (4.8 mL) at 0 °C. The resultant mixture was allowed to warm and stirred at rt for 18 h. The reaction mixture was then diluted with H₂O (5 mL) and EtOAc (5 mL), and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with brine (15 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 40–60 °C petroleum ether/Et₂O, 90:10) gave **46** as a colourless oil (509 mg, 89%, >99:1 dr); $[\alpha]_D^{25} +1.1$ (*c* 1.0 in CHCl₃); ν_{\max} 1741 (C=O); δ_H (400 MHz, CDCl₃) 1.10–1.40 (6H, m, C(4)*H*₂, C(5)*H*₂, C(6)*H*₂), 1.21 (3H, d, *J* 6.9, C(α)*Me*), 1.38 (9H, s, *CMe*₃), 1.56–1.67 (2H, m, C(7)*H*₂), 1.93 (3H, s, *COMe*), 3.21 (1H, td, *J* 6.8, 4.6, C(3)*H*), 3.40 (2H, t, *J* 6.7, C(8)*H*₂), 3.83–3.90 (2H, m, NCH₂Ph), 4.04 (1H, q, *J* 6.9, C(α)*H*), 4.78 (1H, d, *J* 4.6, C(2)*H*), 7.10–7.36 (10H, m, *Ph*); δ_c (100 MHz, CDCl₃) 20.0 (C(α)*Me*), 20.8 (*COMe*), 26.5, 26.9, 28.6, 32.5 (C(4), C(5), C(6), C(7)), 28.1 (*CMe*₃), 45.1 (C(8)), 50.9 (NCH₂Ph), 59.6 (C(3)), 60.1 (C(α)), 75.9 (C(2)), 82.2 (*CMe*₃), 126.5, 127.1, 127.8, 128.1, 128.2, 128.4 (*o,m,p-Ph*), 142.5, 143.9 (*i-Ph*), 168.7, 170.5 (C(1), *COMe*); *m/z* (ESI⁺) 504 ([M(³⁷Cl)+H]⁺, 32%), 502 ([M(³⁵Cl)+H]⁺, 100%); HRMS (ESI⁺) C₂₉H₄₁³⁷ClNO₄⁺ ([M(³⁷Cl)+H]⁺) requires 504.2689; found 504.2708; C₂₉H₄₁³⁵ClNO₄⁺ ([M(³⁵Cl)+H]⁺) requires 502.2719; found 502.2748.

4.2.19 (2*S*,3*R*)-2-Hydroxy-3-amino-8-chlorooctanoic acid [(2*S*,3*R*)-chloro-ahoa] **17**

Step 1: A solution of NaBrO₃ (1.09 g, 7.24 mmol) in H₂O (25 mL) was added to a stirred solution of **46** (1.21 g, 2.41 mmol, >99:1 dr) in EtOAc (33 mL) at rt and the resultant mixture was stirred at rt for 10 min. A solution of Na₂S₂O₄ (1.05 g, 6.03 mmol) in H₂O (44 mL) was added dropwise at rt over 5 min then the reaction mixture was stirred at rt for 4 h. EtOAc (30 mL) was added and the resultant mixture was washed with satd aq Na₂S₂O₃ (50 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL) and the combined organic extracts were washed with brine (100 mL), then dried and concentrated *in vacuo*.

Step 2: The residue from the previous step was dissolved in 6.0 M aq HCl (19 mL) and the resultant mixture was stirred at 100 °C for 3 h then allowed to cool to rt. CH₂Cl₂ (20 mL) was added and the resultant solution was washed with 1.0 M aq HCl (2 × 20 mL). The combined aqueous layers were concentrated *in vacuo*.

Purification *via* ion-exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH₄OH) gave **17** as a white solid (448 mg, 89%, >99:1 dr); mp 181.5–182.5 °C; [α]_D²⁵ –4.9 (*c* 0.5 in MeOH); ν_{max} 3427 (br, O–H, N–H), 1615 (C=O); δ_{H} (500 MHz, MeOH-*d*₄) 1.39–1.65 (4H, m, C(5)*H*₂, C(6)*H*₂), 1.74–1.80 (2H, m, C(4)*H*₂), 1.81–1.87 (2H, m, C(7)*H*₂), 3.37 (1H, td, *J* 7.0, 3.1, C(3)*H*), 3.58 (2H, t, *J* 6.6, C(8)*H*₂), 3.96 (1H, d, *J* 3.1, C(2)*H*); δ_{C} (125 MHz, MeOH-*d*₄) 25.8, 27.7 (C(5), C(6)), 30.8 (C(4)), 33.5 (C(7)), 45.5 (C(8)), 55.2 (C(3)), 71.7 (C(2)), 177.4 (C(1)); *m/z* (ESI⁺) 212 ([M(³⁷Cl)+H]⁺, 32%), 210 ([M(³⁵Cl)+H]⁺, 100%); HRMS (ESI⁺) C₈H₁₇³⁷ClNO₃⁺ ([M(³⁷Cl)+H]⁺) requires 212.0862; found 212.0870; C₈H₁₇³⁵ClNO₃⁺ ([M(³⁵Cl)+H]⁺) requires 210.0891; found 210.0899.

4.2.20 *tert*-Butyl (*R,R,R*)-2-acetoxy-3-[*N*-benzyl-*N*- α -(methylbenzyl)amino]-8,8-dichlorooctanoate **48**

Ac₂O (0.47 mL, 5.0 mmol) and DMAP (6 mg, 0.05 mmol) were added to a stirred solution of **34** (246 mg, 0.497 mmol) in pyridine (2.1 mL) at 0 °C. The resultant mixture was allowed to warm to rt and stirred at rt for 18 h. The reaction mixture was diluted with H₂O (5 mL) and EtOAc (5 mL), and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (35 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 98:2) gave **48** as a colourless oil (261 mg, 98%, >99:1 dr); [α]_D²⁵ –1.8 (*c* 1.0 in CHCl₃); ν_{max} 1742 (C=O); δ_{H} (400 MHz, CDCl₃) 1.11 (3H, d, *J* 7.0, C(α)*Me*), 1.30 (9H, s, CMe₃), 1.17–1.78 (6H, m, C(4)*H*₂, C(5)*H*₂, C(6)*H*₂), 1.87–2.07 (2H, m, C(7)*H*₂), 1.94 (3H, s, C*OMe*), 3.18–3.26 (1H, m, C(3)*H*), 3.48 (1H, d, *J* 15.5, NCH_AH_BPh), 3.82–3.89 (1H, m, C(α)*H*), 4.12 (1H, d, *J* 15.5, NCH_AH_BPh), 4.88–5.00 (1H, m, C(2)*H*), 5.56 (1H, t, *J* 6.1, C(8)*H*), 7.12–7.39 (10H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 18.6 (C*OMe*), 21.3 (C(α)*Me*), 22.0, 26.0, 26.2 (C(4), C(5), C(6)), 28.4 (CMe₃), 43.8 (C(7)), 50.8 (NCH₂Ph), 57.9 (C(3)), 60.2 (C(α)), 73.2 (C(2)), 73.9 (C(8)), 82.2 (CMe₃), 126.6, 127.2, 127.7, 127.8, 127.9, 128.4 (*o,m,p-Ph*), 142.8, 144.1 (*i-Ph*), 168.8, 170.6 (C(1), C*OMe*); *m/z* (ESI⁺) 540 ([M(³⁷Cl₂)+H]⁺, 10%), 538 ([M(³⁵Cl,³⁷Cl)+H]⁺, 64%), 536 ([M(³⁵Cl₂)+H]⁺, 100%); HRMS (ESI⁺) C₂₉H₄₀³⁷Cl₂NO₄⁺ ([M(³⁷Cl₂)+H]⁺) requires 540.2270; found 540.2252; C₂₉H₄₀³⁵Cl³⁷ClNO₄⁺ ([M(³⁵Cl,³⁷Cl)+H]⁺) requires 538.2299; found 538.2291; C₂₉H₄₀³⁵Cl₂NO₄⁺ ([M(³⁵Cl₂)+H]⁺) requires 536.2329; found 536.2326.

4.2.21 (*R,R*)-2-Hydroxy-3-amino-8,8-dichlorooctanoic acid [(*R,R*)-dichloro-ahoa] **21**

Step 1: A solution of NaBrO₃ (179 mg, 1.29 mmol) in H₂O (4.0 mL) was added to a stirred solution of **48** (212 mg, 0.396 mmol, >99:1 dr) in EtOAc (5.4 mL) at rt and the resultant mixture was stirred at rt for 10 min. A solution of Na₂S₂O₄ (172 mg, 0.991 mmol) in H₂O (7.2 mL) was added dropwise at rt over 5 min then the reaction mixture was stirred at rt for 4 h. EtOAc (10 mL) was added and the resultant mixture was

washed with satd aq Na₂S₂O₃ (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic extracts were washed with brine (35 mL), then dried and concentrated *in vacuo*.

Step 2: The residue from the previous step was dissolved in 6.0 M aq HCl (5 mL) and the resultant mixture was stirred at rt for 18 h, then concentrated *in vacuo*. Purification *via* ion-exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH₄OH) gave **21** as a white solid (45 mg, 47%, >99:1 dr); mp 196–197 °C; $[\alpha]_{\text{D}}^{25} +32.7$ (*c* 0.5 in MeOH); ν_{max} 3401 (br, O–H, N–H), 1596 (C=O); δ_{H} (500 MHz, D₂O) 1.26–1.47 (2H, m, C(5)*H*₂), 1.47–1.51 (2H, m, C(6)*H*₂), 1.51–1.63 (2H, m, C(4)*H*₂), 2.14–2.18 (2H, m, C(7)*H*₂), 3.49 (1H, ddd, *J* 8.6, 5.7, 3.5, C(3)*H*), 4.12 (1H, d, *J* 3.5, C(2)*H*), 5.91 (1H, t, *J* 6.0, C(8)*H*); δ_{C} (125 MHz, D₂O) 23.9 (C(5)), 24.9 (C(6)), 26.9 (C(4)), 42.2 (C(7)), 53.8 (C(3)), 71.5 (C(2)), 73.9 (C(8)), 176.6 (C(1)); *m/z* (ESI[−]) 246 ([M(³⁷Cl₂)–H][−], 10%), 244 ([M(³⁵Cl,³⁷Cl)–H][−], 64%), 242 ([M(³⁵Cl₂)–H][−], 100%); HRMS (ESI[−]) C₈H₁₄³⁷Cl₂NO₃[−] ([M(³⁷Cl₂)–H][−]) requires 246.0297; found 246.0293; C₈H₁₄³⁵Cl³⁷ClNO₃[−] ([M(³⁵Cl,³⁷Cl)–H][−]) requires 244.0327; found 244.0323; C₈H₁₄³⁵Cl₂NO₄[−] ([M(³⁵Cl₂)–H][−]) requires 242.0356; found 242.0358.

4.2.22 *tert*-Butyl (2*S*,3*R*,*aR*)-2-acetoxy-3-[*N*-benzyl-*N*-*a*-(methylbenzyl)amino]-8,8-dichlorooctanoate **52**

Ac₂O (1.05 mL, 11.2 mmol) and DMAP (13 mg, 0.13 mmol) were added to a stirred solution of **40** (551 mg, 1.12 mmol, >99:1 dr) in pyridine (4.7 mL) at 0 °C. The resultant mixture was allowed to warm to rt and stirred at rt for 18 h. The reaction mixture was diluted with H₂O (10 mL) and EtOAc (10 mL), and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (20 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 94:6) gave **52** as a colourless oil (551 mg, 92%, >99:1 dr); $[\alpha]_{\text{D}}^{25} -1.5$ (*c* 1.0 in CHCl₃); ν_{max} 1741 (2 × C=O); δ_{H} (400 MHz, CDCl₃) 1.21 (3H, d, *J* 7.0, C(*α*)*Me*), 1.38 (9H, s, *CMe*₃), 1.12–1.56 (6H, m, C(4)*H*₂, C(5)*H*₂, C(6)*H*₂), 1.92 (3H, s, *COMe*), 1.96–2.05 (2H, m, C(7)*H*₂), 3.17–3.23 (1H, m, C(3)*H*), 3.82–3.84 (2H, m, NCH₂Ph), 4.05 (1H, q, *J* 7.0, C(*α*)*H*), 4.73–4.81 (1H, m, C(2)*H*), 5.58 (1H, t, *J* 6.1, C(8)*H*), 7.12–7.35 (10H, m, *Ph*); δ_{C} (100 MHz, CDCl₃) 20.2 (*COMe*), 20.8 (C(*α*)*Me*), 26.0, 26.1, 28.6 (C(4), C(5), C(6)), 28.1 (*CMe*₃), 43.5 (C(7)), 50.9 (NCH₂Ph), 59.3 (C(3)), 60.9 (C(*α*)), 73.6 (C(2)), 75.9 (C(8)), 82.3 (*CMe*₃), 126.6, 127.2, 127.6, 128.1, 128.2, 128.4 (*o,m,p-Ph*), 142.2, 143.9 (*i-Ph*), 168.7, 170.5 (C(1), *COMe*); *m/z* (ESI⁺) 540 ([M(³⁷Cl₂)+H]⁺, 10%), 538 ([M(³⁵Cl,³⁷Cl)+H]⁺, 64%), 536 ([M(³⁵Cl₂)+H]⁺, 100%); HRMS (ESI⁺) C₂₉H₄₀³⁷Cl₂NO₄⁺ ([M(³⁷Cl₂)+H]⁺) requires 540.2270; found 540.2256; C₂₉H₄₀³⁵Cl³⁷ClNO₄⁺ ([M(³⁵Cl,³⁷Cl)+H]⁺) requires 538.2299; found 538.2299; C₂₉H₄₀³⁵Cl₂NO₄⁺ ([M(³⁵Cl₂)+H]⁺) requires 536.2329; found 536.2327.

4.2.23 (2S,3R)-2-Hydroxy-3-amino-8,8-dichlorooctanoic acid [(2S,3R)-dichloro-ahoa] **18**

Step 1: A solution of NaBrO₃ (235 mg, 1.56 mmol) in H₂O (5.0 mL) was added to a stirred solution of **52** (279 mg, 0.521 mmol, >99:1 dr) in EtOAc (7.0 mL) at rt and the resultant mixture was stirred at rt for 10 min. A solution of Na₂S₂O₄ (227 mg, 1.302 mmol) in H₂O (9.4 mL) was added dropwise at rt over 5 min then the reaction mixture was stirred at rt for 4 h. EtOAc (10 mL) was added and the resultant mixture was washed with satd aq Na₂S₂O₃ (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic extracts were washed with brine (35 mL), then dried and concentrated *in vacuo*.

Step 2: The residue from the previous step was dissolved in 6.0 M aq HCl (5 mL) was stirred at rt for 80 h, then concentrated *in vacuo*. Purification *via* ion-exchange chromatography (Dowex 50WX8-100, eluent 1.0 M aq NH₄OH) gave **18** as a white solid (66 mg, 52%, >99:1 dr); mp 209.5–210.5 °C; [α]_D²⁵ –7.7 (*c* 0.5 in MeOH); ν_{\max} 3395 (br, O–H, N–H), 1617 (C=O); δ_{H} (500 MHz, D₂O) 1.26–1.52 (2H, m, C(5)*H*₂), 1.53–1.69 (2H, m, C(6)*H*₂), 1.76 (2H, ddd, *J* 13.9, 7.0, 6.8, C(4)*H*₂), 2.10–2.23 (2H, m, C(7)*H*₂), 3.44 (1H, td, *J* 7.0, 3.8, C(3)*H*), 4.06 (1H, d, *J* 3.8, C(2)*H*), 5.97 (1H, t, *J* 6.0, C(8)*H*); δ_{C} (125 MHz, D₂O) 23.5 (C(5)), 24.9 (C(6)), 28.6 (C(4)), 42.1 (C(7)), 53.8 (C(3)), 70.6 (C(2)), 73.8 (C(8)), 176.8 (C(1)); *m/z* (ESI⁺) 248 ([M(³⁷Cl₂)+H]⁺, 10%), 246 ([M(³⁵Cl,³⁷Cl)+H]⁺, 64%), 244 ([M(³⁵Cl₂)+H]⁺, 100%); HRMS (ESI⁺) C₈H₁₆³⁷Cl₂NO₃⁺ ([M(³⁷Cl₂)+H]⁺) requires 248.0443; found 248.0443; C₈H₁₆³⁵Cl³⁷ClNO₃⁺ ([M(³⁵Cl,³⁷Cl)+H]⁺) requires 246.0472; found 246.04737; C₈H₁₆³⁵Cl₂NO₄⁺ ([M(³⁵Cl₂)+H]⁺) requires 244.0502; found 244.0504.

References and Notes

- ¹ Namikoshi, M.; Rinehart, K. L. *J. Indust. Microbiol.* **1996**, *17*, 373.
- ² Ishida, K.; Kato, T.; Murakami, M.; Watanabe, M.; Watanabe, M. F. *Tetrahedron* **2000**, *56*, 8643.
- ³ Ishida, K.; Matsuda, H.; Murakami, M. *Tetrahedron* **1998**, *54*, 13475.
- ⁴ Okino, T.; Matsuda, H.; Murakami, M.; Yamaguchi, K. *Tetrahedron Lett.* **1993**, *34*, 501.
- ⁵ Strangman, W. K.; Wright, J. L. C. *Tetrahedron Lett.* **2016**, *57*, 1801.
- ⁶ The other examples include valinotins A and B; see: Sekizawa, R.; Iinuma, H.; Muraoka, Y.; Naganawa, H.; Kinoshita, N.; Nakamura, H.; Hamada, M.; Takeuchi, T.; Umezawa, K. *J. Nat. Prod.* **1996**, *59*, 232.
- ⁷ (a) Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Goodwin, C. J. *Tetrahedron: Asymmetry* **1994**, *5*, 203; (b) Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Goodwin, C. J. *Tetrahedron: Asymmetry* **1995**, *6*, 165.
- ⁸ Aghapour, G.; Afzali, A. *Synth. Commun.* **2008**, *38*, 4023.
- ⁹ Optimal conditions for the synthesis of **34** required the use of 2.6 equiv of (*R*)-**8** and 2.7 equiv of (–)-CSO **9**.
- ¹⁰ Costello, J. F.; Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1994**, *5*, 1999.

- ¹¹ (a) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833; (b) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron: Asymmetry* **2012**, *23*, 1111.
- ¹² (a) Davies, S. G.; Fletcher, A. M.; Foster, E. M.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2013**, *78*, 2500; (b) Davies, S. G.; Fletcher, A. M.; Frost, A. B.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2013**, *69*, 8885; (c) Brambilla, M.; Davies, S. G.; Fletcher, A. M.; Hao, L.; Lv, L.; Roberts, P. M.; Thomson, J. E. *Tetrahedron* **2014**, *70*, 3491; (d) Archer, S. G.; Csatayová, K.; Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Tetrahedron Lett.* **2016**, *57*, 1270; (e) Buchman, M.; Csatayová, K.; Davies, S. G.; Fletcher, A. M.; Houlsby, I. T. T.; Roberts, P. M.; Rowe, S.; Thomson, J. E. *J. Org. Chem.* **2016**, *81*, 4907.
- ¹³ Reduction of halides during the catalytic hydrogenation has been reported in the literature. For example, see: (a) Davies, S. G.; Fletcher, A. M.; Lv, L.; Roberts, P. M.; Thomson, J. E. *Tetrahedron: Asymmetry* **2012**, *23*, 910; (b) Kawata, S.; Ashizawa, S.; Hirama, M. *J. Am. Chem. Soc.* **1997**, *119*, 12012.
- ¹⁴ Adinolfi, M.; Barone, G.; Guariniello, L.; Iadonisi, A. *Tetrahedron Lett.* **1999**, *40*, 8439.
- ¹⁵ Davies, S. G.; Fletcher, A. M.; Frost, A. B.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2015**, *17*, 2254.
- ¹⁶ A prolonged reaction time was required in this case to effect complete hydrolysis of the acetyl group.
- ¹⁷ Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
- ¹⁸ Dixon, D. J.; Scott, M. S.; Luckhurst, C. A. *Synlett* **2003**, 2317.