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Asymmetric Synthesis of the *N*-terminal component of Microginin: (2*S*,3*R*)-3-Amino-2-Hydroxydecanoic Acid, its (2*R*,3*R*)-Epimer and (3*R*)-3-Aminodecanoic Acid.

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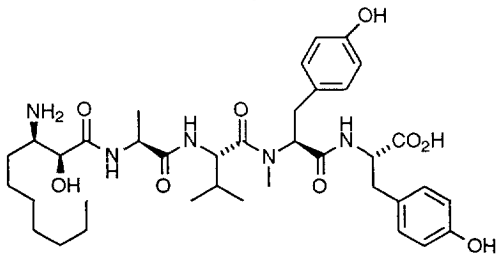
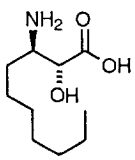
Abstract: 3-Amino-2-hydroxydecanoic acid (AHDA) is a novel amino acid which has been suggested as the *N*-terminal component of the recently isolated angiotensin-converting enzyme inhibitor microginin. The naturally occurring amino acid was found to possess *syn* relative stereochemistry and (2*S*,3*R*) absolute stereochemistry when the reported ^{1}H and ^{13}C nmr spectroscopic data and the CD data were compared to the spectroscopic data for synthetic (2*R*,3*R*)- and (2*S*,3*R*)-AHDA. These studies complete the stereochemical assignment of microginin.

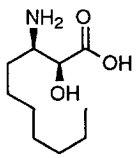
Microginin **1**, a linear pentapeptide, has recently been isolated from the freshwater blue-green alga *Microcystis aeruginosa*.[1] It was found to possess angiotensin-converting enzyme (ACE) inhibitory properties, which is of considerable medical interest since ACE inhibitors have been developed as antihypertensive agents.[2] A number of techniques, principally 2D nmr spectroscopy and chemical degradation, were employed to elucidate the partial structure of **1**. The degradative studies conducted upon this compound provided a novel 3-amino-2-hydroxydecanoic acid (AHDA) which was considered to be the *N*-terminal moiety. The structure of this AHDA was indicated by the ^{1}H and ^{13}C nmr spectra, and by a FAB mass spectrum. On the basis of a Cotton effect in the CD spectrum, it was further suggested that the α-stereogenic centre in this acid was of the *R* configuration, however, this has to be regarded as tentative, especially since there is a β-stereogenic centre of undefined stereochemistry present.[1] In a preliminary communication we have recently reported the completion of the stereochemical assignment of microginin,[3] through the comparison of spectroscopic data for the naturally occurring AHDA with the data for both of our synthetic homochiral stereoisomers, (2*R*,3*R*)-AHDA **2** and (2*S*,3*R*)-AHDA **3**. Thus it was established unambiguously that the naturally occurring acid possessed the (2*S*,3*R*) stereochemistry. We describe herein full details on the asymmetric synthesis of homochiral *anti*- and *syn*-stereoisomers of AHDA, namely (2*R*,3*R*)-AHDA **2** and (2*S*,3*R*)-AHDA **3**.[3]



1



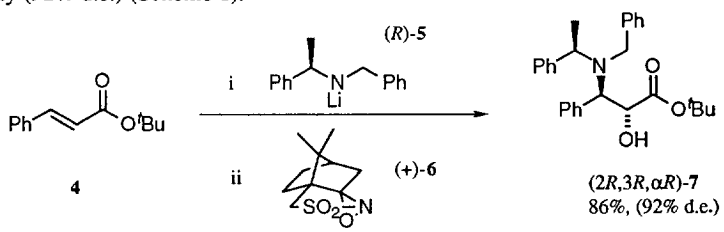
2



3

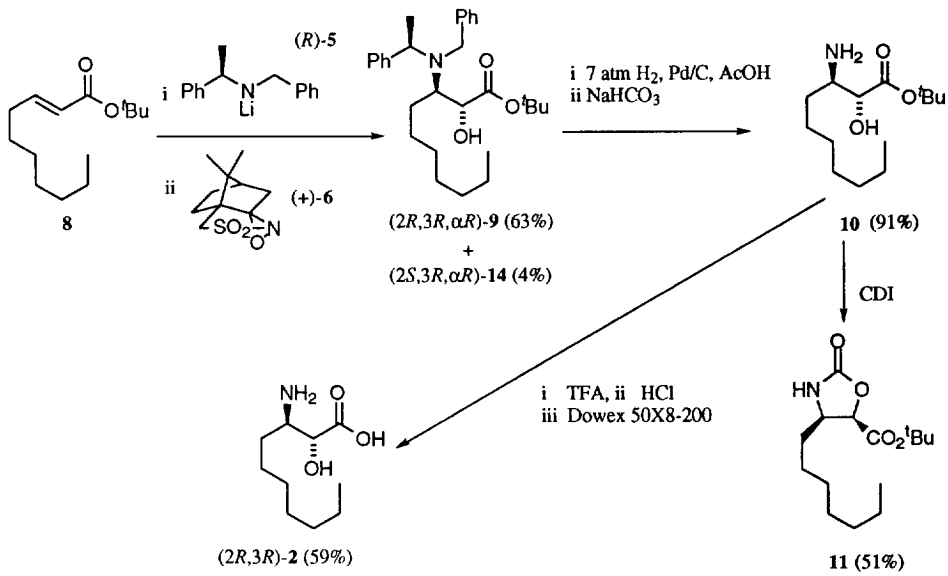
Earlier studies in this laboratory have shown that lithium amides derived from (*R*)- or (*S*)-(α-methylbenzyl)benzylamine have a tendency to undergo highly diastereoselective conjugate additions to a variety of enoate substrates, and this has been developed as a general protocol for the synthesis of homochiral β-amino acids.[4,5] Furthermore, it was demonstrated that *in situ* hydroxylation of the resultant β-amino enolates can occur

with excellent levels of 1,2-asymmetric induction to furnish the *anti* diastereoisomer of the corresponding β-amino-α-hydroxy acid derivative.[6,7] For example, it has previously been shown that the conjugate addition of lithium (*R*)-(α-methylbenzyl)benzylamide **5** to *tert*-butyl cinnamate **4**, followed by *in situ* hydroxylation with (+)-(camphorsulfonyl)oxaziridine **6**, provides the corresponding *anti*-β-amino-α-hydroxy ester **7** with excellent diastereoselectivity (92% d.e.) (Scheme 1).[6]



Scheme 1

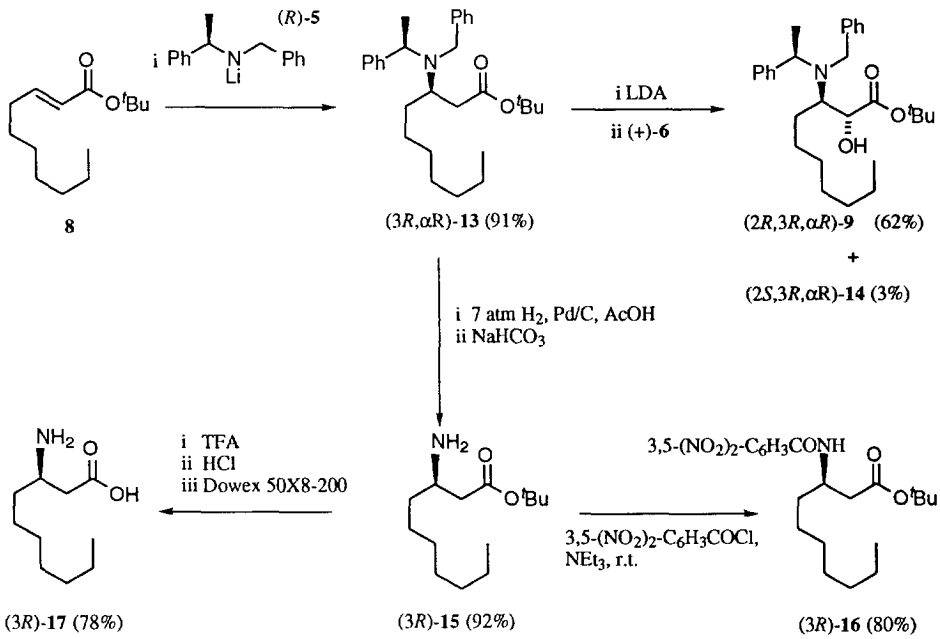
With such a methodology at our disposal, it was anticipated therefore that the corresponding reaction using the readily available enoate **8**[8] would lead to an efficient synthesis of **2**. Indeed, the tandem addition-hydroxylation of **8** using (*R*)-**5** and (+)-**6** provided the desired β-amino-α-hydroxy acid derivative (2*R*,3*R*,α*R*)-**9** with good diastereoselectivity (16:1, 88% d.e.) and this material was isolated as a single diastereoisomer in 63% yield after flash chromatography.[3] Subsequent catalytic debenzylation of **9** followed by hydrolysis of the *tert*-butyl ester, furnished the (2*R*,3*R*)-AHDA **2** (Scheme 2) in 34% overall yield starting from enoate **8**.



Scheme 2

The *anti* relative stereochemistry within **10** was confirmed[3] by conversion to the oxazolidinone **11** using carbonyl diimidazole (CDI). Analysis of the ring proton coupling constant in **11** ($J_{4,5}$ = 8.6 Hz) confirmed the *cis* stereochemistry[3] which follows directly from the *anti* arrangement in **10**, and hence **9**. The *absolute* stereochemistry of **9** follows from addition of (*R*)-**5** to the *Re*-face of **8** in an analogous manner to that previously elucidated for a number of related enoates.[3,4,5,6,7]

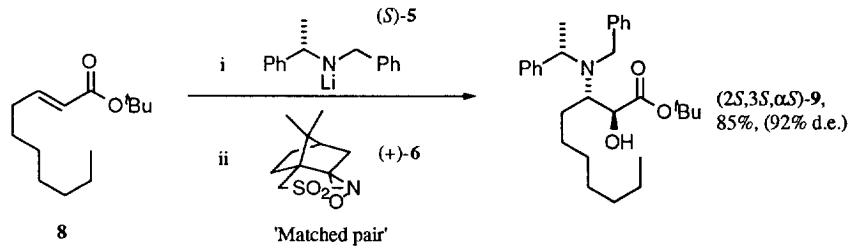
It is of note that when the tandem addition-hydroxylation of **8** was conducted in a stepwise manner as delineated in scheme 3, there was little difference in stereoselectivity. Addition of (*R*)-**5** to enoate **8** afforded the adduct **13** with excellent diastereoselectivity (≥ 95% d.e.). The β–amino acid derivative **13** was deprotonated with lithium diisopropylamide (LDA) and hydroxylated with (+)-**6** to give a mixture of (2*R*,3*R*,α*R*)-**9** and (2*S*,3*R*,α*R*)-**14** in a ratio of 15 : 1 (88% d.e.), from ^{1}H nmr spectroscopic analysis of the crude product. Purification of the crude product by flash chromatography provided (2*R*,3*R*,α*R*)-**9** in 62% yield. In this case therefore the tandem addition-hydroxylation approach to preparing (2*R*,3*R*,α*R*)-**9** offers no advantages over the stepwise approach.



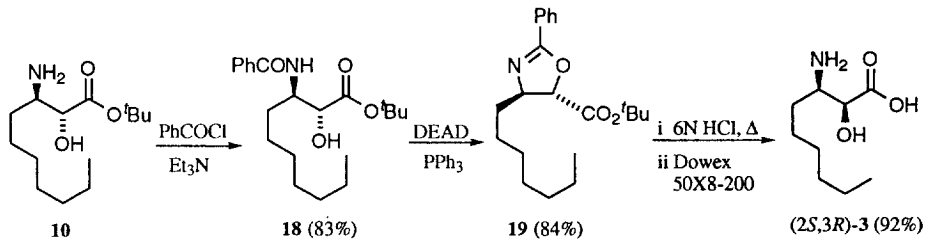
Scheme 3

The novel homochiral β-amino acid **17**, was prepared in 72% yield in two steps from the *N*-benzylated ester **13**, by debenzylation of **13** and subsequent hydrolysis of the free amino ester intermediate **15** as delineated in Scheme 3. It is noteworthy that 3-aminodecanoic acid **17** has only previously been prepared in racemic form[9,10], and the racemate has been found to have biological activity,[10] in that it inhibited the germination of sasanqua pollen. The intermediate β-amino ester **15** was also converted to the amide **16** by treating the former compound with 3,5-dinitrobenzoyl chloride.

In the tandem addition-hydroxylation reaction outlined in Scheme 2, it was hypothesised that the diastereoisomer distribution observed here was a consequence of employing the 'mismatched' pairing of homochiral reagents. This was inferred from previous work in this laboratory [6,7] where the diastereoselectivity arising from the complementary pairings of homochiral reagents were compared. This prediction was borne out when the complementary pair of reagents, namely (*S*)-**5** and (+)-**6**, was used in the tandem addition-hydroxylation of enoate **8**, as (2*S*,3*S*,α*S*)-**9** was obtained in 85% yield with an improved d.e. of 92%.



With the *anti*-diastereoisomer in hand and its relative and absolute stereochemistry established beyond doubt, the synthesis of the *syn* diastereoisomer **3** was undertaken,[3] as outlined in Scheme 4. The key step in this synthesis was the intramolecular cyclisation of amide **18** under Mitsunobu conditions to give the *trans*-oxazoline **19** ($J_{4,5}$ = 6.3 Hz) with inversion at the α-centre. The overall yield of amino acid **3** in five steps starting from enoate **8** was 37%. Comparison of the ^1H and ^{13}C nmr data of synthetic homochiral amino acids **2** and **3** with the data reported for the natural acid [1,3] (see Tables 1 and 2) confirmed that the natural amino acid component of microginin was indeed AHDA with the *syn* relative stereochemistry.



Scheme 4

Both the epimeric homochiral acids **2** and **3** exhibited a negative cotton effect in their CD spectra (Figure 1) at 204 and 216nm, respectively. However, it was that of the synthetic homochiral **3** that showed greatest similarity with the CD spectrum reported[1] for the natural acid, which demonstrated a negative cotton effect at 215nm. This result shows the previous assumption that the α-stereogenic centre had the *R* configuration[1] to be incorrect,[11] obviously the β-stereogenic centre exerts more of an influence on the CD spectrum in both acids than the α–centre. Therefore the unknown amino acid component of microginin has in fact the (2*S*,3*R*)-configuration.

Table 1: ^1H nmr data for *anti* and *syn* 3-amino-2-hydroxydecanoic acid **2** and **3**

^1H nmr (DMSO-d_6)	**2**	**3**[12]	Natural Acid[1]
2-H	δ3.35, d, *J* 8.1 Hz	δ3.56, d, *J* 3.4 Hz	δ3.54, m
3-H	δ2.82, m	δ3.12, m	δ3.08, br
$CH_3(CH_2)_6$	δ1.71–1.26, m	δ1.60–1.20, m	δ1.3–1.2, m
$CH_3(CH_2)_6$	δ0.86, t, *J* 6.9 Hz	δ0.86, t, *J* 6.8 Hz	δ0.85, t

Table 2: ^{13}C nmr data for *anti* and *syn* 3-amino-2-hydroxydecanoic acid **2** and **3**

^{13}C nmr (DMSO-d_6)	**2**	**3**	Natural Acid[1]
1-C	-	δ173.4	-
2-C	δ70.3	δ69.5	δ69.60
3-C	δ53.9	δ53.0	δ52.30
$CH_3(\underline{C}H_2)_6$	δ31.3	δ31.4	δ31.17
	δ30.2	δ29.1	δ28.90
	δ29.0	δ28.8	δ28.90
	δ28.6	δ28.7	δ28.48
	δ24.8	δ25.3	δ25.20
	δ22.1	δ22.3	δ22.07
$\underline{C}H_3(CH_2)_6$	δ14.0	δ14.2	δ13.95

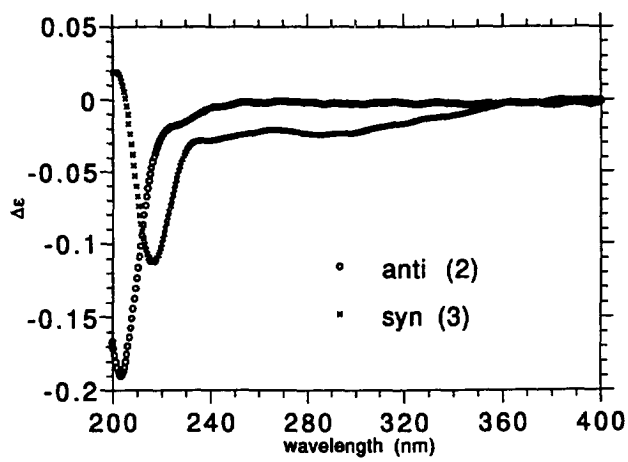
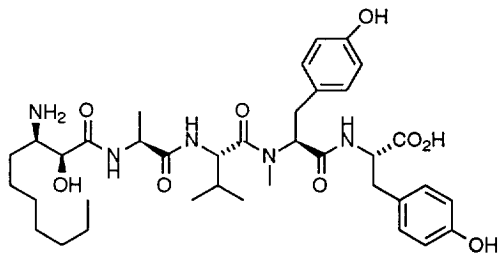


Figure 1: CD spectra of (2*R*,3*R*)-AHDA **2** and (2*S*,3*R*)-AHDA **3**.

In conclusion, we have successfully demonstrated that the unknown amino acid component of microginin is (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid **3** by an independent asymmetric synthesis and spectroscopic comparison with data reported for a sample secured by hydrolysis of the natural product.[3] These studies conclude the stereochemical assignment of microginin, for which the revised structure is depicted below.



Microginin

EXPERIMENTAL

General. Melting points were determined using either Gallenkamp or Koffler hot stage apparatus and are uncorrected. Specific rotations were recorded using a Perkin-Elmer 241 Polarimeter with a thermally jacketed 10 cm cell. IR spectra were obtained on a Perkin-Elmer 781 or Perkin-Elmer 1750 spectrophotometer with solution spectra generally being recorded in chloroform using 0.1 mm or 1.0 mm NaCl cells. Nmr spectra were generally recorded in deuteriochloroform and referenced with respect to residual protio solvent as internal standard. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ0.00 ppm), and coupling constants (*J*) are measured in Hertz. ^{1}H nmr spectra were recorded using Bruker AC200, Bruker WH300, Bruker AM500 or Bruker AMX500 spectrometers, and ^{13}C nmr spectra were recorded with DEPT editing as necessary using either Bruker AC200, Bruker AM500, Bruker AMX500 or Varian Gemini 200 spectrometers. CD spectra were recorded using a JASCO J 720 spectropolarimeter using a 1cm cell. Mass spectra were recorded on a VG MASSLAB VG 20-250 instrument using the chemical ionisation (CI) technique. Elemental analyses were performed by the Dyson Perrins Laboratory analytical department. Flash column chromatography was undertaken on silica gel (kieselgel 60). Tetrahydrofuran was distilled from sodium benzophenone ketyl under an atmosphere of dry nitrogen. Petrol refers to that fraction of petroleum ether which boils in the range 40-60°C and was redistilled before use. Reactions involving lithium amides were performed under an atmosphere of dry nitrogen and reaction diastereoselectivities were determined by integration of the appropriate peaks in the ^{1}H nmr spectrum of the crude reaction product.

Preparation of (2R,3R,αR)-tert-*Butyl* 3-(N-*benzyl*-N-α-*methylbenzyl*)*amino*-2-*hydroxydecanoate* **9** *by the* tandem addition *method.*

A solution of (*R*)-(α-methylbenzyl)benzylamine **5** (338 mg, 1.60 mmol) in anhydrous tetrahydrofuran (5 cm^3) was cooled to 0°C and 1.60 M n-butyllithium (0.9 cm^3, 1.50 mmol in hexane) was added dropwise *via* syringe. The resultant pink lithium amide solution was stirred at 0°C for 45 min., subsequently cooled to -78°C and (*E*)-*tert*-butyl 2-decenoate[8] (200 mg, 0.885 mmol) in anhydrous tetrahydrofuran (2 cm^3) was added. Stirring was continued for 2 h whereupon the resultant enolate solution was treated with solid (+)-(camphorsulfonyl)oxaziridine (367 mg, 1.60 mmol). After stirring for a further 1 h at -78°C, the mixture was warmed to 0°C for 15 min., and quenched by the addition of saturated aqueous ammonium chloride. The

solvent was evaporated under reduced pressure, the residue diluted with water (20 cm^3) and extracted with dichloromethane (3 x 30 cm^3). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated under reduced pressure to afford an oily solid residue. Analysis of this crude material by ^1H nmr spectroscopy indicated a 16 : 1 (88% d.e.) mixture of α-epimeric products in favour of the *anti*-diastereoisomer (2*R*,3*R*,α*R*)-**9**. Purification of the residue by flash chromatography on silica gel [petrol/diethyl ether (17 : 1)] provided the title compound as a colourless oil (253 mg, 63%) and the more polar minor *syn* diastereoisomer (2*S*,3*R*,α*R*)-**14** (16 mg, 4%), also as a colourless oil. (2*R*,3*R*,α*R*)-**9**: $[\alpha]_D^{25}$ -24.6 (*c* 1.02, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1716m (C=O); δ_H (300 MHz; $CDCl_3$) 7.50-7.21 (10H, m, Ph), 4.27, 3.70 (2H, AB system, J_{AB} 15.4, NCH_2Ph), 3.99-3.92 (2H, m, $NCHCH_3$, 2-H), 3.21 (1H, ddd, *J* 8.5, 4.7, 1.7, 3-H), 2.93 [1H, d, *J* 6.0, CH(OH)], 1.69-1.12 [12H, m, $CH_3(CH_2)_6$], 1.44 [9H, s, $CO_2C(CH_3)_3$], 1.31 (3H, d, *J* 7.0, $NCHCH_3$), 0.91 [3H, t, *J* 6.8, $CH_3(CH_2)_6$]; δ_C (125 MHz; $CDCl_3$) 174.5 (1-C), 143.8, 142.8 (1'-C), 128.2 (2'-, 6'-C), 128.1 (3'-, 5'-C), 126.9, 126.3 (4'-C), 82.3 [$CO_2C(CH_3)_3$], 71.4 (2-C), 59.0 ($NCHCH_3$), 58.7 (3-C), 51.1 (NCH_2Ph), 31.9, 29.8, 29.3, 27.5, 26.8, 22.7 [$CH_3(CH_2)_6$], 28.0 [$CO_2C(CH_3)_3$], 19.5, 14.1 [$NCHCH_3$, $CH_3(CH_2)_6$]; *m/z* (CI) 454 (MH^+, 100%), 322 (84), 218 (26); (Found: C, 76.56; H, 9.50; N, 3.21. $C_{29}H_{43}NO_3$ requires C, 76.78; H, 9.55; N, 3.09%);
(2*S*,3*R*,α*R*)-**14**: $[\alpha]_D^{21}$ -22.0 (*c* 0.54, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1719s (C=O); δ_H (300 MHz; $CDCl_3$) 7.32-7.22 (10H, m, Ph), 4.08 (1H, q, *J* 7.0, $NCHCH_3$), 3.88, 3.79 (2H, AB system, J_{AB} 14.5, NCH_2Ph), 3.80 (1H, d, obscured, 2-H) 3.48 [1H, br s, CH(OH)], 3.04 (1H, apparent q, *J* 6.3, 3-H), 1.53-1.26 [12H, m, $CH_3(CH_2)_6$], 1.44 [9H, s, $CO_2C(CH_3)_3$], 1.40 (3H, d, *J* 7.0, $NCHCH_3$), 1.33 [3H, t, *J* 6.7, $CH_3(CH_2)_6$]; δ_C (125 MHz; $CDCl_3$) 173.2 (1-C), 143.4, 141.3 (1'-C), 128.6, 128.3 (2'-, 6'-C), 128.2, 127.9 (3'-, 5'-C), 127.1, 126.8 (4'-C), 81.7 [$CO_2C(CH_3)_3$], 73.6 (2-C), 61.0 ($NCHCH_3$), 59.9 (3-C), 50.4 (NCH_2Ph), 31.8, 30.0, 29.2, 28.8, 27.7, 22.6 [$CH_3(CH_2)_6$], 28.0 [$CO_2C(CH_3)_3$], 17.7, 14.1 [$NCHCH_3$, $CH_3(CH_2)_6$]; *m/z* (CI) 454 (MH^+, 93%), 322 (100), 218 (67), 105 (77), 91 (79); (Found: C, 76.51; H, 9.72; N, 3.45. $C_{29}H_{43}NO_3$ requires C, 76.78; H, 9.55; N, 3.09%).

Preparation of (2R,3R)-tert-*Butyl* 3-*amino*-2-*hydroxydecanoate* **10**.

(2*R*,3*R*,α*R*)-*tert*-Butyl 3-(*N*-*benzyl*-*N*-α-methylbenzyl)amino-2-hydroxydecanoate **9** (150 mg, 0.331 mmol) was dissolved in acetic acid (5 cm^3) and treated with 10% palladium on activated charcoal (45 mg). The mixture was stirred at room temperature overnight under 7 atm of hydrogen. (However, on subsequent occassions a reaction time of 2-3 days at this temperature was required for total cleavage of the benzyl groups). After removal of the catalyst by filtration, the solvent was evaporated under reduced pressure to furnish the crude acetate salt of the title compound. The acetate salt was treated with saturated aqueous sodium bicarbonate (20 cm^3) and extracted with dichloromethane (3 x 20 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure to afford the title compound as a white solid (78 mg, 91%); m.p. 60-62°C; $[\alpha]_D^{21}$ -10.5 (*c* 0.52, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1719vs (C=O); δ_H (300 MHz; $CDCl_3$) 4.03 (1H, br s, 2-H), 2.99 (1H, br s, 3-H), 1.50 [9H, s, $CO_2C(CH_3)_3$], 1.48-1.28 [12H, m, $CH_3(CH_2)_6$], 0.89 [3H, t, *J* 6.6, $CH_3(CH_2)_6$]; δ_C (125 MHz; $CDCl_3$) 172.8 (1-C), 82.5 [$CO_2C(CH_3)_3$], 75.0 (2-C), 54.6 (3-C), 32.6, 31.8, 29.6, 29.2, 26.5, 22.6 [$CH_3(CH_2)_6$], 28.1 [$CO_2C(CH_3)_3$], 14.0 [$CH_3(CH_2)_6$]; *m/z* (CI) 260 (MH^+, 100%), 204 (69), 128 (74); (Found: C, 64.88; H, 11.37; N, 5.33. $C_{14}H_{29}NO_3$ requires C, 64.83; H, 11.27; N, 5.40%).

Preparation of (4R,5R)-5-(tert-*butoxycarbonyl*)-4-*heptyl*-2-*oxazolidinone* **11**.

A solution of (2*R*,3*R*)-*tert*-butyl 3-amino-2-hydroxydecanoate **10** (68 mg, 0.263 mmol) in dichloromethane (4 cm^3) was treated with solid carbonyldiimidazole (64 mg, 0.395 mmol) and stirred at room temperature overnight. The solution was subsequently diluted with dichloromethane (20 cm^3) and 1.0M aqueous hydrochloric acid (15 cm^3) was added. After thorough mixing, the organic layer was separated and the aqueous layer extracted with further dichloromethane (20 cm^3). The combined organic extracts were then dried ($MgSO_4$), filtered, and the solvent evaporated under reduced pressure. Purification of the residue by flash chromatography on silica gel [petrol/diethyl ether] afforded the title compound as a white hygroscopic solid (38 mg, 51%); $[\alpha]_D^{22}$ +15.9 (*c* 0.61, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3461w (N-H), 1770vs (C=O oxazolidinone), 1732m (C=O ester); δ_H (300 MHz; $CDCl_3$) 5.92 (1H, br s, CONH), 4.90 (1H, d, *J* 8.6, 5-H), 4.06 (1H, m, 4-H), 1.57-1.28 [12H, m, $CH_3(CH_2)_6$], 1.52 [9H, s, $CO_2C(CH_3)_3$], 0.89 [3H, br t, *J* 6.6, $CH_3(CH_2)_6$]; δ_C (125 MHz; $CDCl_3$) 166.2 (1-C), 158.3 (2-C), 83.6 [$CO_2C(CH_3)_3$], 77.0 (5-C), 54.8 (4-C), 31.6, 30.9, 29.2, 28.9, 26.1, 22.5, [$CH_3(CH_2)_6$], 28.0 [$CO_2C(CH_3)_3$], 14.0 [$CH_3(CH_2)_6$]; *m/z* (CI) 303 (MNH_4^+, 100%), 286 (MH^+, 49), 247 (19); (Found: C, 62.82; H, 9.79; N, 4.65. $C_{15}H_{27}NO_4$ requires C, 63.13 H, 9.54; N, 4.91%).

Preparation of (3R,2R)-3-*Amino*-2-*hydroxydecanoic acid* **2**.

(2*R*,3*R*)-*tert*-Butyl 3-amino-2-hydroxydecanoate **10** (259 mg, 0.417 mmol) was treated with trifluoroacetic acid (2 cm^3) and the resultant solution stirred at room temperature overnight. The solvent was subsequently evaporated under reduced pressure and the residue dissolved in 1.0M aqueous hydrochloric acid (5 cm^3). After stirring for 5 min, the solvent was removed *in vacuo* and the residue submitted to ion exchange chromatography (Dowex 50X8-200) to afford the desired amino acid **2** as a white hygroscopic solid which was dried *in vacuo* at 70°C overnight (50 mg, 59%); m.p 225°C ;$[\alpha]_D^{25}$ +3.4 (*c* 0.7, 1N HCl); CD λ (H_2O)/nm 204, $\Delta\varepsilon$ -1.893 x 10^{-1} dm^3 mol^{-1} cm^{-1} (5.80 x 10^{-3}M); ν_{max}(KBr)/cm^{-1} 1629s (C=O), 1589vs (C=O); δ_H (500 MHz; D_2O) 4.07 (1H, d, *J* 3.6, 2-H), 3.40 (1H, m, 3-H), 1.50-1.42 (2H, m, 4-H), 1.31-1.15 [10H, m, $CH_3(CH_2)_5CH_2$], 0.74 [3H, t, *J* 6.7, $CH_3(CH_2)_6$]; δ_H [500 MHz; $(CD_3)_2SO$] 3.35 (1H, d, *J* 8.1, 2-H), 2.82 (1H, m, 3-H), 1.71-1.26 [12H, m, $CH_3(CH_2)_6$], 0.86 [3H, t, *J* 6.9, $CH_3(CH_2)_6$]; δ_C (125 MHz; D_2O) 177.8 (1-C), 73.0 (2-C), 55.1 (3-C), 32.0, 29.4, 29.0, 28.3, 25.8, 23.0 [$CH_3(CH_2)_6$], 14.4 [$CH_3(CH_2)_6$]; δ_C [125 MHz; $(CD_3)_2SO$] 70.3 (2-C), 53.9 (3-C), 31.3, 30.2, 29.0, 28.6, 24.8, 22.1 [$CH_3(CH_2)_6$], 14.0 [$CH_3(CH_2)_6$]; *m/z* (CI) 204 (MH^+, 100%), 128 (MH^+-$C_2H_4O_3$+, 33); (Found: C, 58.95; H, 10.68; N, 6.55. $C_{10}H_{21}NO_3$ requires C, 59.07; H, 10.43; N, 6.89%).

Preparation of (3R,αR)-tert-*Butyl* 3-(N-*benzyl*-N-α-*methylbenzyl*)*aminodecanoate* **13**.

A solution of (*R*)-(α-methylbenzyl)benzylamine **5** (896 mg, 4.25 mmol) in anhydrous tetrahydrofuran (15 cm^3) was cooled to -78°C and treated with 1.49M n-butyllithium (2.7 cm^3, 3.98 mmol in hexane). The resultant pink solution was stirred at -78°C for 30 min. whereupon (*E*)-*tert*-butyl 2-decenoate **8** (600 mg, 2.65 mmol) in anhydrous tetrahydrofuran (2 cm^3) was added. After stirring for a further 2 h, the reaction was quenched by the addition of saturated aqueous ammonium chloride (5 cm^3), then warmed to room temperature, and the solvent was evaporated under reduced pressure. The residue was diluted with water (30 cm^3) and extracted with dichloromethane (3 x 40 cm^3). The combined organic extracts were then dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Analysis of the crude product by ^1H nmr spectroscopy (500 MHz) indicated the successful formation of (3*R*,α*R*)-**13** with excellent diastereoselectivity (≥95% d.e.). Purification by flash chromatography on silica gel [petrol/diethyl ether (19:1)] gave the title compound as a colourless oil (1.05 g,

91%); $[\alpha]_D^{22}$ +5.3 (*c* 1.03, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 1713m (C=O); δ_H (300 MHz; $CDCl_3$) 7.44-7.24 (10H, m, Ph), 3.89-3.77 (2H, m, NC<u>H</u>CH_3, NC<u>H</u>HPh), 3.48 (1H, part AB system, J_{AB} 15.0, NCH<u>H</u>Ph), 3.30 (1H, m, 3-H), 1.95, 1.87 (2H, ABX system, J_{AB} 14.5, J_{AX} 3.8, J_{BX} 9.2, 2-H), 1.66-1.18 [12H, m, $CH_3(C\underline{H}_2)_6$], 1.40 [9H, s, $CO_2C(C\underline{H}_3)_3$], 1.33 (3H, d, *J* 7.0, NCHC<u>H</u>$_3$), 0.90 [3H, m, $C\underline{H}_3(CH_2)_6$]; δ_C (125 MHz; $CDCl_3$) 172.3 (1-C), 143.4, 142.2, (1'-C), 128.2, 128.1, 128.0 (2'-, 6'-C and 3'-, 5'-C), 126.9, 126.5 (4'-C), 80.1 [$CO_2\underline{C}(CH_3)_3$], 58.5, 54.2 (N<u>C</u>HCH_3, 3-C), 50.2 (N<u>C</u>H_2Ph), 38.0 (2-C), 33.6, 31.9, 29.6, 29.3, 27.0, 22.7 [$CH_3(\underline{C}H_2)_6$], 28.1 [$CO_2C(\underline{C}H_3)_3$], 20.5, 14.1 [NCH<u>C</u>H_3, <u>C</u>$H_3(CH_2)_6$]; *m/z* (CI) 438 (MH^+, 100%), 338 (90), 322 (96), 218 (38), 178 (31), 105 (61), 91 (48), 57 (30); (Found: C, 79.63; H, 9.87; N, 3.28. $C_{29}H_{43}NO_2$ requires C, 79.56; H, 9.90; N, 3.20%).

Preparation of (2R,3R,αR)-tert-*Butyl* 3-(N-*benzyl*-N-α-*methylbenzyl*)*amino*-2-*hydroxydecanoate* **9** *by the* stepwise *approach.*

A solution of diisopropylamine (0.22 cm^3, 1.60 mmol) in anhydrous tetrahydrofuran (5 cm^3) was cooled to 0°C and 1.60M n-butyllithium (0.9 cm^3, 1.50 mmol in hexane) was added dropwise *via* syringe. After stirring for 20 min. the colourless lithium diisopropylamide (LDA) solution was cooled to -78°C and (3*R*,α*R*)-*tert*-Butyl 3-(*N*-benzyl-*N*-α-methylbenzyl)aminodecanonate **13** (459 mg, 1.06 mmol) in anhydrous tetrahydrofuran (2 cm^3) was added. The resultant enolate solution was stirred for 30 min. and solid (+)-(camphorsulfonyl)oxaziridine **6** (459 mg, 2.00 mmol) was added. The mixture was then stirred for 1.5 h at -78°C, warmed to 0°C over 15 min. and quenched by the addition of saturated aqueous ammonium chloride. The solvent was evaporated under reduced pressure, the residue diluted with water (20 cm^3) and extracted with dichloromethane (3 x 30 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent evaporated under reduced pressure to provide an oily solid residue. Analysis of the crude product by ^1H nmr spectroscopy indicated a 15:1 (88% d.e.) mixture of α-epimeric products in favour of the *anti* diastereoisomer (2*R*,3*R*,α*R*)-**9**. Purification of the residue by flash chromatography on silica gel [petrol/diethyl ether (17 : 1)] afforded the title compound as a colourless oil (297 mg, 62%) and a more polar fraction of the minor *syn* diastereoisomer (2*S*,3*R*,α*R*)-**14**, also as a colourless oil (16 mg, 3%).

Preparation of (3R)-tert-*Butyl* 3-*aminodecanoate* **15**.

A solution of (3*R*,α*R*)-3-aminodecanoate **13** (515 mg, 1.175 mmol) in glacial acetic acid (5 cm^3) was treated with 10% palladium on activated carbon (175 mg). The mixture was stirred for 3 days under 7 atm of hydrogen. After removal of the catalyst by filtration, followed by successive washing with acetic acid, the solvent was evaporated under reduced pressure to afford the acetate salt of the title compound. The acetate salt was treated with saturated aqueous sodium bicarbonate (20 cm^3) and then extracted with dichloromethane (3 x 25 cm^3), the combined organic extracts were dried (K_2CO_3), and evaporation under reduced pressure provided a yellow oil. Purification of this oil by flash chromatography on silica gel (diethyl ether; R_f 0.21) gave (3*R*)-**15** as a pale yellow oil (263 mg, 92%); $[\alpha]_D^{25}$ -6.5 (*c* 0.88, $CHCl_3$); $\nu_{max}(NaCl)/cm^{-1}$ 3295 (N-H), 1718 (C=O); δ_H (200 MHz; $CDCl_3$) 3.10 (1H, br s, 3-H), 2.35, 2.15 (2H, ABX system, J_{AB} 15.5, J_{AX} 4.0, J_{BX} 8.0, 2-H), 1.60-1.20 [12H, m, $CH_3(C\underline{H}_2)_6$], 1.39 [9H, s, $CO_2C(\underline{C}H_3)_3$], 0.87 [3H, br s, $C\underline{H}_3(CH_2)_6$]; δ_C (50 MHz; $CDCl_3$) 172.0 (1-C), 80.4 [$CO_2\underline{C}(CH_3)_3$], 48.3 (3-C), 43.9 (2-C), 37.5, 31.7, 29.5, 29.2, 26.0, 22.6 [$CH_3(\underline{C}H_2)_6$], 28.1 [$CO_2C(\underline{C}H_3)_3$], 14.0 [$\underline{C}H_3(CH_2)_6$]; *m/z* (CI) 244 ($MH^+$, 15%), 188 ($MH^+$-$C_4H_8$, 100).

Preparation of (3R)-tert-*Butyl* 3-N-(3,5-*dinitrobenzoyl*)*aminodecanoate* **16**.

3,5-Dinitrobenzoyl chloride (86 mg, 0.374 mmol) was added to a solution of (3*R*)-*tert*-butyl-3-aminodecanoate **15** (91 mg, 0.374 mmol) and triethylamine (95 mg, 0.935 mmol) in anhydrous dichloromethane (10 cm^3) at room temperature. The mixture was stirred for 22 h and the solvent was evaporated *in vacuo* to afford an amber coloured solid which upon purification by flash chromatography on silica gel [petrol/diethyl ether (19 : 1)] furnished the title compound as a white solid (132 mg, 80%). This compound recrystallised from cyclohexane-benzene as colourless needles, m.p. 78-79°C; $[\alpha]_D^{25}$ +33.0 (*c* 1.06, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3364s (N-H), 1715s (C=O ester), 1654s (C=O amide); δ_H (500 MHz; $CDCl_3$) 9.18 (1H, d *J* 2.1, 4'-H), 8.98 (2H, d *J* 2.1, 2'-, 6'-H), 7.53 (1H, d *J* 6.9, CONH), 4.45 (1H, m, 3-H), 2.65, 2.58 (2H, ABX system, J_{AB} 15.9, J_{AX} 4.7, J_{BX} 4.8, 2-H), 1.50 [9H, s, $CO_2C(CH_3)_3$], 1.42-1.22 [12H, m, $CH_3(CH_2)_6$], 0.89 [3H, t, *J* 6.9, $CH_3(CH_2)_6$]; δ_C (125 MHz; $CDCl_3$) 171.7 (1-C), 161.9 (CONH), 148.7 (3'-, 5'-C), 138.3 (1'-C), 127.1 (2'-, 6'-C), 120.9 (4'-C), 82.0 [$CO_2C(CH_3)_3$], 47.5 (3-C), 38.8 (2-C), 28.1 [$(CH_3)_3CO$], 34.0, 31.7, 29.3, 29.1, 26.3, 22.6 [$CH_3(CH_2)_6$], 14.0 [$CH_3(CH_2)_6$]; *m/z* (CI) 438 (MH^+, 18%), 382 (MH^+-C_4H_8, 100), 352 (36); (Found: C, 57.36; H, 7.13; N, 9.27. $C_{21}H_{31}N_3O_7$ requires C, 57.64; H, 7.16; N, 9.61%).

Preparation of (3R)-3-*aminodecanoic acid* **17**.

tert-Butyl (3*R*)-3-aminodecanoate **15** (82 mg, 0.337 mmol) was treated with trifluoroacetic acid (3 cm^3) and the resultant solution stirred for 27.5 h at room temperature. The solvent was subsequently evaporated under reduced pressure and the residue dissolved in 1.0 M aqueous hydrochloric acid (5 cm^3). This mixture was left standing with occassional shaking at room temperature for 1.5 h. The solvent was then evaporated and the resultant white solid residue subjected to ion exchange chromatography (Dowex 50X8-200) furnishing a white powdery solid, which was carefully dried *in vacuo* (49 mg, 78%), m.p. 202-204°C {(EtOH), [lit.[9] m.p. 206°C (racemate)]}; $[\alpha]_D^{24}$ -13.1 (*c* 0.41, 1N HCl); ν_{max}(KBr)/cm^{-1} 2926 (N-H), 1640 and 1553 (C=O); δ_H (200 MHz; D_2O) 3.40 (1H, m, 3-H), 2.51, 2.36 (2H, ABX system, J_{AB} 16.6, J_{AX} 4.8, J_{BX} 8.2, 2-H), 1.65-1.50 (2H, m, 4-H), 1.40-1.10 [10H, m, $CH_3(CH_2)_5CH_2$], 0.70 [3H, br s, $CH_3(CH_2)_6$]; δ_C (125 MHz; D_2O) 178.7 (1-C), 49.8 (3-C), 39.0 (2-C), 32.5, 31.3, 28.7, 28.5, 24.8, 22.3 [$CH_3(CH_2)_6$], 13.7 [$CH_3(CH_2)_6$]; *m/z* (CI) 188 (MH^+, 100%), 128 (MH^+-$C_2H_4O_2$, 17); (Found: C, 63.93; H, 11.79; N, 7.18. $C_{10}H_{21}NO_2$ requires C, 64.11; H, 11.32; N, 7.48%).

Preparation of (2S,3S,αS)-tert-*Butyl* 3-(N-*benzyl*-N-α-*methylbenzyl*)*amino*-2-*hydroxydecanoate* **9**.

A solution of (*S*)-(α-methylbenzyl)benzylamine **5** (106 mg, 0.5 mmol) in anhydrous tetrahydrofuran (5 cm^3) was cooled to 0°C and 1.44 M n-buthyllithium (0.35 cm^3, 0.5 mmol in hexane) was added dropwise *via* syringe. The resultant pink lithium amide solution was stirred at 0°C for 45 min., subsequently cooled to -78°C and (*E*)-*tert*-butyl 2-decenoate (126 mg, 0.335 mmol) in anhydrous tetrahydrofuran (20 cm^3) was added. Stirring was continued for 2 h whereupon the resultant enolate solution was treated with solid (+)-(camphorsulfonyl)oxaziridine (115 mg, 0.5 mmol). After stirring for a further 1 h at -78°C, the mixture was warmed to 0°C for 15 min., and quenched by the addition of saturated aqueous ammonium chloride. The solvent was evaporated under reduced pressure, the residue diluted with water (20 cm^3) and extracted with dichloromethane (3 x 50 cm^3). The combined organic extracts were dried (K_2CO_3) and the solvent evaporated under reduced pressure to afford an oily solid residue. Analysis of this crude material by ^1H nmr spectroscopy indicated a 22 : 1 (92% d.e.) mixture of α-epimeric products in favour of the *anti*-diastereoisomer (2*S*,3*S*,α*S*)-**9**. Purification of the residue by flash chromatography on silica gel [petrol/diethyl ether (17 : 1)] provided the

title compound as a colourless oil (129 mg, 85%); $[\alpha]_D^{26}$ +23.4 (*c* 2.28, $CHCl_3$); (Found: C, 76.53; H, 9.90; N, 2.77. $C_{29}H_{43}NO_3$ requires C, 76.78; H, 9.55; N, 3.09%).

Preparation of tert-*Butyl* (2*R*,3*R*)-3-N-*benzoylamino*-2-*hydroxydecanoate* **18.**

A solution of *tert*-Butyl (2*R*,3*R*)-3-amino-2-hydroxydecanoate **10** (100 mg, 0.407 mmol) in anhydrous dichloromethane (10 cm^3) was treated with freshly distilled triethylamine (100 mg, 1.02 mmol) at 0°C under an atmosphere of nitrogen. A solution of benzoyl chloride (60 mg, 0.399 mmol) in anhydrous dichloromethane (10 cm^3) was added and the mixture stirred at 0°C for 10 min. before being warmed to room temperature and stirred for a further 6 h. The reaction was quenched by the addition of *ca.* 7% aqueous hydrochloric acid, the organic layer was separared, dried (K_2CO_3) and evaporation to dryness under reduced pressure furnished an oil which later solidified into a soft white solid. Purification of the residue by flash chromatography on silica gel [petrol/diethyl ether (17 : 1), (R_f, 0.25)] afforded the title compound as a white solid [(116 mg, 83%)]; m.p. 74-76°C [petrol/diethyl ether (*ca.* 50 : 1), colourless needles]; $[\alpha]_D^{23}$ +11.1 (*c*, 0.27, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3300 (N-H), 1741 and 1729 (C=O ester), 1640 (C=O amide); δ_H (200 MHz; $CDCl_3$) 7.81 (2H, d, *J* 7.8, 2'-, 6'-H), 7.40 (3H, m, 3'-, 4'-, 5'-H), 6.42 (1H, d, *J* 9.3, CONH), 4.55 (1H, m, 3-H), 4.29 (1H, d, *J* 3.0, 2-H), 1.52 [9H, s, $(CH_3)_3CO$], 1.37-1.10 [12H, m, $CH_3(CH_2)_6$], 0.87 [3H, m, $CH_3(CH_2)_6$]; δ_C (125 MHz; $CDCl_3$) 172.1 (1-C), 167.2 (PhCONH), 134.4 (1'-C), 131.5 (4'-C), 128.5 (2'-, 6'-C), 127.0 (3', 5'-C), 83.4 [$(CH_3)_3CO$], 73.0 (2-C), 51.6 (3-C), 31.7, 29.3, 29.1, 28.9, 25.8, 22.6 [$CH_3(CH_2)_6$], 28.0 [$(CH_3)_3CO$], 14.0 [$CH_3(CH_2)_6$]; *m/z* (CI) 364 (MH^+, 17%), 308 (MH^+-C_4H_8, 100), 232 (19), 105 ($C_7H_5O^+$, 52); (Found: C, 69.30; H, 9.04; N, 3.69. $C_{21}H_{33}NO_4$ requires C, 69.37; H, 9.17; N, 3.85%).

Preparation of (4R,5S)-5-(tert-*Butylcarbonyl*)-4-*heptyl*-2-*phenyl*-2-*oxazoline* **19.**

A solution of *tert*-Butyl (2*R*,3*R*)-3-*N*-benzoylamino-2-hydroxydecanoate **18** (124 mg, 0.341 mmol) in anhydrous tetrahydrofuran (15 cm^3) was treated dropwise with a solution of triphenylphosphine (206 mg, 0.784 mmol) and diethylazodicaboxylate (137 mg, 0.784 mmol) in anhydrous tetrahydrofuran (20 cm^3) at 0°C. When addition of the latter mixture was complete, the reaction mixture was allowed to warm to room temperature and stirred at this temperature for 26 h. The yellow solution was subsequently evaporated to dryness under reduced pressure to furnish a pale-yellow solid. Purification of the residue by flash chromatography on silica gel [petrol/diethyl ether (10 : 1)] gave the title compound as a colourless oil (99 mg, 84%); $[\alpha]_D^{25}$ -9.7 (*c* 0.61, $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 1754vs (C=O), 1657vs (N=C); δ_H (200 MHz; $CDCl_3$) 7.99 (2H, dd, *J* 7.3, 1.6, 2'-, 6'-H), 7.40 (3H, m, 3'-, 4'-, 5'-H), 4.57 (1H, d, *J* 6.3, 5-H), 4.24 (1H, q, *J* 6.3, 4-H), 1.65 [2H, m, $CH_3(CH_2)_5CH_2$], 1.50 [9H, s, $(CH_3)_3CO$], 1.45-1.20 [10H, m, $CH_3(CH_2)_5CH_2$], 0.87 [3H, m, $CH_3(CH_2)_6$]; δ_C (125 MHz; $CHCl_3$) 169.8 (1-C), 162.8 (2-C), 131.5 (1'-C), 128.4 (4'-C), 128.3 (3'-, 5'-C), 127.3 (2'-, 6'-C), 82.4 [$(CH_3)_3CO$], 80.9 (5-C), 72.1 (4-C), 36.1, 31.8, 29.4, 29.2, 25.4, 22.7 [$CH_3(CH_2)_6$], 28.0 [$(CH_3)_3CO$], 14.1 [$CH_3(CH_2)_6$]; *m/z* (CI) 346 (MH^+, 100%), 290 (MH^+-C_4H_8, 58), 244 (MH^+-$C_5H_{10}O_2$, 23).

Preparation of (2S,3R)-3-*Amino*-2-*hydroxydecanoic acid* **3.**

(4*R*,5*S*)-5-(*tert*-Butylcarbonyl)-4-heptyl-2-phenyl-2-oxazoline **19** (87 mg, 0.252 mmol) was treated with 6M aqueous hydrochloric acid (10 cm^3) at 0°C. Stirring was continued at this temperature for 10 min. before gradually raising the temperature to reflux and heating it at this temperature for 7 h. This was followed by

stirring at room temperature overnight, diluting with water (10 cm^3) and washing with diethyl ether (3 x 20 cm^3). The aqueous layer was evaporated to dryness under reduced pressure and the residue submitted to ion exchange chromatography (Dowex 50X8-200) furnishing the title compound as a white solid which was dried *in vacuo* at *ca.* 70°C overnight (47 mg, 92%); m.p. 219-220°C (decomp.); $[\alpha]_D^{25}$ +5.4 (*c* 0.59, 1N HCl); CD λ (H_2O)/nm 216, $\Delta\varepsilon$ -1.129 x 10^{-1} dm^3 mol^{-1} cm^{-1} (4.92 x 10^{-3}M); ν_{max}(KBr)/cm^{-1} 3449 (O-H, carboxyl), 2924s (N-H), 1622s and 1592vs (C=O); δ_H (200 MHz; D_2O) 4.03 (1H, d, *J* 3.7, 2-H), 3.33 (1H, m, 3-H), 1.70-1.20 (12H, m, $CH_3(C\underline{H}_2)_6$], 0.82 [3H, m, $C\underline{H}_3(CH_2)_6$]; δ_H [500 MHz; $(CD_3)_2SO$] 3.56 (1H, d, *J* 3.4, 2-H), 3.12 (1H, m, 3-H) 1.60-1.20 [12H, m, $CH_3(C\underline{H}_2)_6$], 0.86 [3H, t, *J* 6.8, $C\underline{H}_3(CH_2)_6$]; δ_C [125 MHz; $(CD_3)_2SO$] 173.4 (1-C), 69.5 (2-C), 53.0 (3-C), 31.4, 29.1, 28.8, 28.7, 25.3, 22.3 [$CH_3(\underline{C}H_2)_6$], 14.2 [$\underline{C}H_3(CH_2)_6$]; *m/z* (CI) 204 (MH^+, 100%), 158 (MH^+-$CH_2O_2^+$, 37), 128 (MH^+-$C_2H_4O_3^+$, 66); (Found: C, 58.91; H, 10.64; N, 6.85. $C_{10}H_{21}NO_3$ requires C, 59.07; H, 10.43; N, 6.89%).

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11. Dr. Murakami informed us that he has independently reassessed the configuration of the 3-amino-2-hydroxydecanoic acid found in microginin also as (2*S*,3*R*). We thank him for advising us of the solvent (DMSO-d_6) and instruments (600MHz ^1H nmr ; 75MHz ^{13}C nmr) employed in the characterisation of the naturally occurring acid.
12. ^1H nmr data for a sample of synthetic (2*S*,3*R*)-AHDA which had been scrupulously dried compared to that of the sample used in our original communication[3].

Note added in proof: The recent total synthesis of Microginin by Shioiri *et al* confirms our configurational assignment of natural AHDA: Matsuura, F.; Hamada, Y.; Shioiri T. *Tetrahedron,* **1994**, *50*, 11303.

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