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4-Formylazetidin-2-ones, synthon for the synthesis of (2*R*,3*S*) and (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid (AHDA)

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Abstract—An efficient synthesis of 3-amino-2-hydroxydecanoic acid (AHDA), a nonproteinogenic amino acid, using enantiopure 3-benzyloxy-4-formylazetidin-2-one as a building block is described. Both the enantiomers of AHDA have been synthesized from the corresponding enantiomer of 3-benzyloxy-4-formylazetidin-2-one in good yield and optical purity.

1. Introduction

Apart from the antibacterial agents,[1–3] azetidin-2-ones are increasingly used as synthons for the synthesis of variety of pharmaceutically useful products.[4] This is mainly because of the strain energy associated with the four membered azetidinone ring, that is responsible for selective bond cleavage, giving a variety of transformation products. Moreover, there are many methods available to prepare them in reasonable quantities required for synthetic purpose. One such synthon, 4-formylazetidin-2-one, has wide applications as a building block[5,6] for the synthesis of monobactams, isocephams, carbapenems and several other non-β-lactam compounds like α-hydroxy aspartate and hydroxybutanoic acids. As a part of our research program on asymmetric synthesis of β-lactams, we have developed an efficient method for the synthesis of enantiomerically pure 4-formylazetidin-2-ones[7a] and used them as building blocks for the synthesis of 4-aminopiperidin-2-ones,[8] important intermediates for the synthesis of biologically useful compounds.

2. Results and discussion

In continuation of our efforts towards the synthesis of substituted β-lactams via the Staudinger reaction[9] and their utility as synthons[7c,8,10] for the synthesis of various biologically important compounds, we were interested in the synthesis of 3-amino-2-hydroxydecanoic acid (AHDA) from the 4-formyl-β-lactam synthon. (2*S*,3*R*)-3-Amino-2-hydroxydecanoic acid (**1b**) is an unusual novel amino acid, which has been suggested as the N-terminal component of the recently isolated angiotensin-converting enzyme inhibitor microginin (**2**)[11] (Figs. 1 and 2).

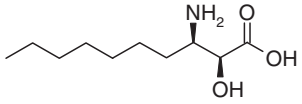

Figure 1. (2*S*,3*R*)-3-Amino-2-hydroxydecanoic acid (**1b**).

Microginin is a small linear peptide isolated from the blue-green alga *Microcystis aeruginosa* and its structure was established on the basis of degradation studies, spectral data and total synthesis.[11,12] It was shown that a linear α-hydroxy-β-aminodecanoic acid is at the N-terminal of the peptide chain. Subsequently it was also found that AHDA is common to other linear peptides isolated from the same species.[11b,c] There are several approaches[12,13] for the synthesis of AHDA. In most cases, asymmetric functionalization of alkenes[13c–e] via either asymmetric epoxidation or asymmetric dihydroxylation is the common strategy. There are few reports using 'chiral pool' strategies[13f,g] wherein a chiral starting material is used for the synthesis. The Lewis acid catalyzed addition of ketene acetals to chiral imines[13b] is another approach for the synthesis of α-hydroxy-β-amino acids.

Although β-amino acids are easily accessible by hydrolysis of the corresponding azetidin-2-ones,[4b,14] surprisingly there is no report on the synthesis of AHDA starting from an azetidin-2-one synthon. Therefore, we planned our

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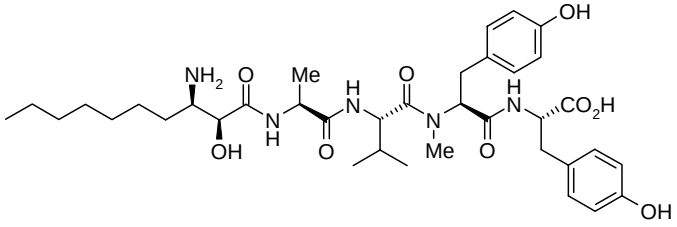
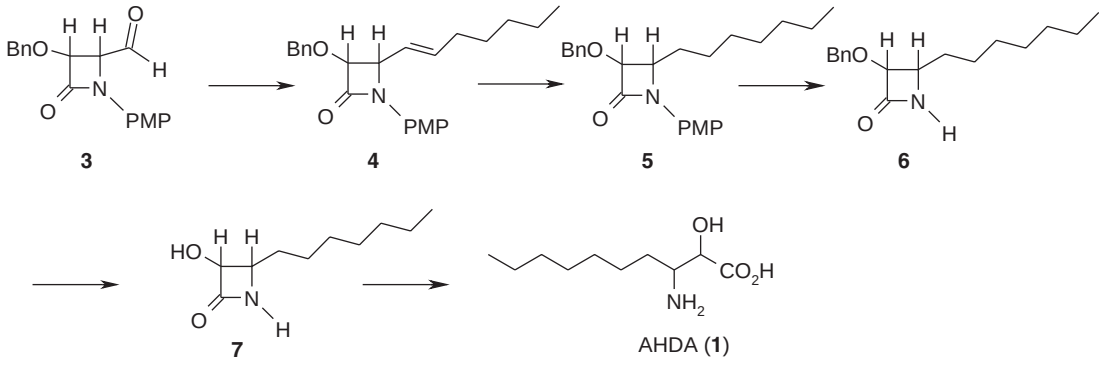


Figure 2. Microginin (**2**).

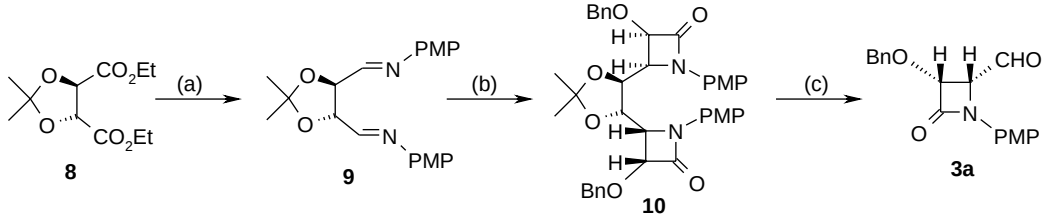


Scheme 1.

synthesis from suitably substituted 4-formylazetidin-2-one. Our synthesis is based on the application of well-defined stereochemistry at both the stereocentres of *cis*-3-benzyloxy-4-formylazetidin-2-one ring, which is required for the synthesis of natural AHDA. The synthesis involves Wittig olefination of *cis*-3-benzyloxy-4-formylazetidin-2-one, followed by hydrogenation and careful hydrolysis of the azetidinone ring to get the desired AHDA (Scheme 1). The Scheme is simple and it can be applied for the synthesis of both the enantiomers of AHDA, since both the enantiomers of starting *cis*-4-formylazetidin-2-one can be prepared in reasonable yields and good optical purities. Also by following the synthetic protocol, one can easily prepare other analogues of AHDA.

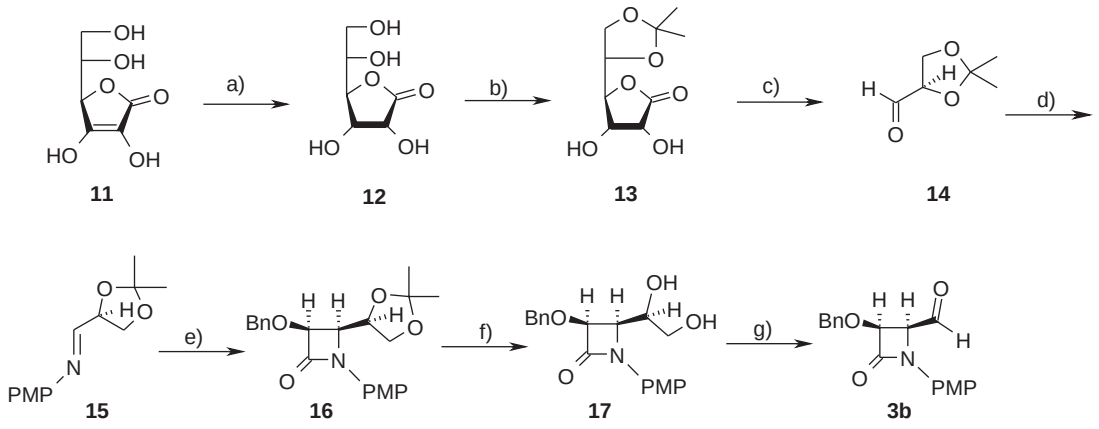
Enantiomerically pure (3*R*,4*R*)-3-benzyloxy-4-formylazetidin-2-one (**3a**) was prepared from L-diethyl tartrate using a synthetic method developed by our group.[7a] C_2-Symmetry of natural tartaric acid has been exploited to achieve the synthesis of 2 mol of *cis*-4-formylazetidin-2-ones from 1 mol of diethyl tartrate acetonide (Scheme 2). Alternatively enantiopure **3a** can also be prepared from D-mannitol diacetonide in four steps.[15] The other enantiomer (3*S*,4*S*)-3-benzyloxy-4-formylazetidin-2-one (**3b**) was also synthesized (Scheme 3) from L-glyceraldehyde acetonide, which was easily prepared from L-ascorbic acid in three steps.[16]

Having both the enantiomers in hand, we initially started our work with (3*R*,4*R*)-3-benzyloxy-4-formylazetidin-2-one (**3a**) since it can be easily prepared in large quantities from L-diethyl tartrate.[7a] The aldehyde **3a**, on Wittig olefination reaction with the Wittig reagent derived from triphenylphosphine and *n*-1-bromohexane, gave olefin **4a** in good yield. The olefin **4a** on catalytic hydrogenation with Pd/C (10%) gave 4-heptanyl-β-lactam **5a**, in very good yield (90%). A small amount of debenzylated compound **18a** (6%) was also obtained along with **5a**, which was separated by flash column chromatography. The oxidative removal of the *p*-methoxyphenyl (PMP) group from **5a** was achieved by cerric ammonium nitrate (CAN)[17] to get (3*R*,4*S*)-3-benzyloxy-4-heptanyl-azetidin-2-one (**6a**) in 85% yield. The benzyl group was removed by transfer hydrogenation[18] using Pd/C (10%) to afford 3-hydroxy-β-lactam **7a** in quantitative yield. Hydrolysis of **7a** was achieved by heating with 3 M HCl at 60 °C for 6 h and the product was purified by ion-exchange chromatography (Dowex 50 W×2-400) using 5% NH_4OH as the eluent to afford pure (2*R*,3*S*)-AHDA (**1a**) in 70% yield (Scheme 4).



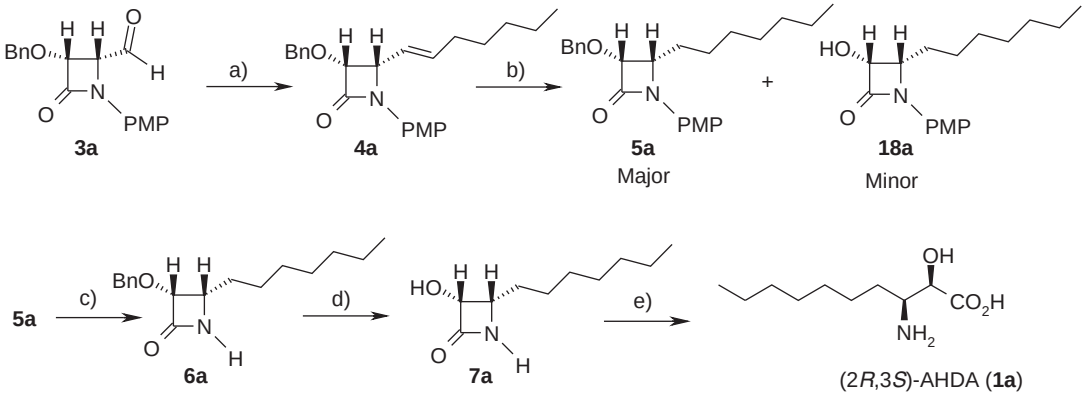
Reagents and conditions: (a) DIBAL-H, PMP-NH_2, toluene, -78°C to rt, 15 h (b) $BnOCH_2COCl$, Et_3N, CH_2Cl_2, –23°C to rt, 14 h (c) i) 2.5 M $HClO_4$, THF, rt, 4-8 h; ii) $NaIO_4$, acetone-H_2O, rt, 4-12 h

Scheme 2.



Reagents and conditions: a) H_2, Pd/C (10%), 50 Psi, 50 °C, H_2O, 95% b) 2-Methoxypropene, DMF, PTSA, 24 h, rt, 70% c) $NaIO_4$, H_2O, 0 °C to rt, 2h d) PMP-NH_2, CH_2Cl_2, 2 h, rt e) $BnOCH_2COCl$, Et_3N, CH_2Cl_2, 0 °C to rt, 12h, 50% f) PTSA, THF/H_2O, reflux, 18h, 98% g) $NaIO_4$, Acetone/H_2O, 85%.

Scheme 3.



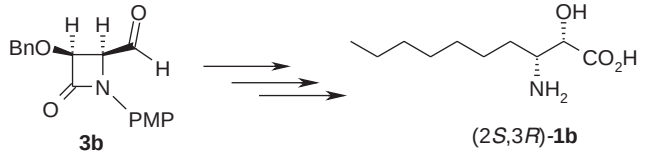
Reagents and conditions: a) $CH_3(CH_2)_5PPh_3^+ Br^-$, *n*-BuLi, 0 °C, 6h, dry THF, 75% b) H_2, Pd/C (10%), 50 psi, 6h, EtOAc, 90% c) CAN, CH_3CN/H_2O, 0 °C, 25 min, 85% d) $HCOONH_4$, Pd/C (10%), MeOH, reflux, 6h, 95% e) 3M HCl, 60 °C, 6h, Ion-exchange resin, Dowex 50W x 2-400, 5% NH_4OH, 70%.

Scheme 4.

The other enantiomer, (2*S*,3*R*)-AHDA (**1b**) was also synthesized (Scheme 5) from (3*S*,4*S*)-3-benzyloxy-4-formyl-azetidin-2-one (**3b**) by following a similar synthetic protocol as shown in Scheme 4. The spectral data and the specific rotations are comparable with that of the reported in the literature.[12ab,13a]

3. Conclusion

In conclusion, we have accomplished the synthesis of both the enantiomers of 3-amino-2-hydroxydecanoic acid (AHDA), from corresponding enantiomer of 4-formyl-3-benzyloxyazetidin-2-one. (2*S*,3*R*)-AHDA is a nonproteinogenic amino acid, an important constituent of natural product microginin (**2**).



Scheme 5.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions on Brüker AC 200, AV 400 spectrometers, and chemical shifts are reported in ppm downfield from tetramethylsilane for ^1H NMR. Infrared spectra were recorded on Perkin-Elmer Infrared Spectrophotometer, Model 599-B or Shimadzu FTIR-8400 using sodium chloride optics. Melting points were determined on a Thermonik Campbell melting point apparatus and are uncorrected. The microanalyses were performed on a Carlo-Erba, CHNS-O EA 1108

elemental analyzer. Optical rotations were recorded on ADP 220 polarimeter Bellingham + Stanley Ltd. under standard conditions. Mass spectra were recorded on API QSTAR PULSAR using electron spray ionization (ESI) method.

4.1.1. (3*R*,4*S*)-3-Benzyloxy-4-hept-1-enyl-1-(4-methoxyphenyl)-azetidin-2-one (4a). To a solution of a *n*-hexyltriphenylphosphonium bromide (1.538 g, 3.6 mmol) in anhydrous THF at 0 °C was added *n*-butyl lithium (2.20 mL, 3.3 mmol, 1.5 M, colour change from yellow to orange red was observed). Reaction mixture was stirred at this temperature for 45 min. A solution of azetidin-2-one **3a** (0.934 g, 3 mmol) in anhydrous THF (20 mL) was added drop-wise at 0 °C to the reaction mixture and then allowed to warm up to room temperature. After 6 h, the reaction mixture was quenched with saturated solution of NH_4Cl (5 mL). The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (20 mL), washed with water (10 mL) and then with saturated brine solution (5 mL) to afford the crude **4a**, which was then purified by flash column on silica gel (EtOAc/pet ether 1:9 as eluent), to get *E*/*Z* isomeric mixture of **4a** (0.853 g, 75%) as a viscous oil. The geometrical isomers were difficult to separate by flash column chromatography and used as such for further reaction. [Found C, 75.65; H, 7.52; N, 3.80. $C_{24}H_{29}NO_3$ requires C, 75.95; H, 7.72; N, 3.69%]; ν_{max} ($CHCl_3$) 1747 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.94 (m, 3H), $CH_3(CH_2)_6$), 1.28–1.51 (m, 6 H, =CH–CH_2 (CH_2)$_3$–CH_3), 2.08–2.40 (m, 2H, CH=CH–CH_2), 3.79 (s, 3H, Ar-OCH_3), 4.54–4.95 (m, 4H, C3*H*, C4*H*, OCH_2Ph), 5.56–5.68 (m, 1H, CH=C*H*–CH_2–(CH_2)$_3$–CH_3), 5.83–6.06 (m, 1H, C*H*=CH–CH_2–(CH_2)$_3$–CH_3), 6.85 (d, J=9.1 Hz, 2H, Ar), 7.28–7.43 (m, 7H, Ar); δ_C (75.48 MHz) 14.0, 22.5, 27.9, 28.5, 29.1, 31.2, 31.6, 32.4, 55.4, 55.5, 60.9, 72.6, 72.7, 82.2, 82.4, 114.4, 118.6, 118.7, 124.0, 124.3, 128.0, 128.4, 131.1, 137.0, 137.5, 138.8, 156.4, 163.5; MS (*m*/*z*): 380 ($M^+ + 1$).

4.1.2. (3*R*,4*S*)-3-Benzyloxy-4-heptyl-1-(4-methoxyphenyl)azetidine-2-one (5a) and (3*R*,4*S*)-4-heptyl-3-hydroxy-1-(4-methoxyphenyl)-azetidine-2-one (18a). Compound **4a** (0.760 g, 2 mmol) was dissolved in EtOAc (20 mL) and Pd/C (10%) (70 mg) was added. The mixture was hydrogenated at 50 psi of H_2 in a Parr hydrogenator for 6 h at room temperature. The catalyst was removed by filtration through Celite and washed with EtOAc. The solvent was distilled off under reduced pressure and the crude product was purified by flash column chromatography on silica gel (EtOAc/pet ether 15:85 as eluent) to afford compound **5a**; (0.688 g, 90%) as viscous oil. [Found C, 75.47; H, 8.35; N, 3.61. $C_{24}H_{31}NO_3$ requires C, 75.57; H, 8.21; N, 3.67%]; R_f (40% EtOAc/pet ether) 0.56; $[\alpha]_D^{30}$ +112.38 (*c* 1.05, $CHCl_3$); ν_{max} ($CHCl_3$) 1742 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.89 (t, J=6.5 Hz, 3H, $(CH_2)_6CH_3$), 1.2–1.5 (m, 10H, $CH_2(CH_2)_5CH_3$), 1.83–1.94 (m, 2H, $CH_2(CH_2)_5CH_3$), 3.80 (m, 3H, Ar-OCH_3), 4.11–4.19 (m, 1H, C4*H*), 4.74–4.80 (m, 2H, C3*H*, CH_aH_bPh), 4.98 (d, J= 11.9 Hz, 1H, CH_aH_bPh), 6.89 (d, J=9.1 Hz, 2H, Ar), 7.28–7.43 (m, 7H, Ar); δ_C (50.32 MHz) 13.7, 22.2, 25.3, 27.0, 28.7, 29.3, 31.3, 54.9, 57.5, 72.7, 80.7, 114.1, 118.3, 127.3, 127.4, 128.0, 130.5, 137.1, 156.0, 164.4; MS (*m*/*z*): 382 ($M^+ + 1$).

The compound **18a** (0.035 g, 6%) was obtained as a white crystalline solid; mp 105–107 °C; [Found C, 70.20; H, 8.70; N, 4.93. $C_{17}H_{25}NO_3$ requires C, 70.06, H, 8.66; N, 4.81%]; R_f (40% EtOAc/pet ether) 0.27; $[\alpha]_D^{30}$ +107.50 (*c* 0.4, $CHCl_3$); ν_{max} ($CHCl_3$) 1724, 3365 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.89 (t, J=6.8 Hz, 3H, $(CH_2)_6CH_3$), 1.28–1.50 (m, 10H, CH_2 (CH_2)$_5CH_3$), 1.80–2.00 (m, 2H, $CH_2(CH_2)_5CH_3$), 2.88 (br s, 1H, O*H*), 3.81 (s, 3H, Ar-OCH_3), 4.14–4.20 (m, 1H, C4*H*), 5.05 (d, J=5.2 Hz, 1H, C3*H*), 6.85 (d, J=9.0 Hz, 2H, Ar), 7.32 (d, J=9.0 Hz, 2H, Ar); δ_C (50.32 MHz) 13.9, 22.5, 25.7, 27.1, 29.1, 29.6, 31.7, 55.4, 59.1, 75.1, 114.4, 119.0, 130.5, 156.5, 167.2; MS (*m*/*z*): 292 ($M^+ + 1$).

4.1.3. (3*R*,4*S*)-3-Benzyloxy-4-heptylazetidin-2-one (6a). A solution of **5a** (0.572 g, 1.5 mmol) in acetonitrile (15 mL) was cooled to 0 °C and treated with a solution of CAN (2.469 g, 4.51 mmol) in water (20 mL) over 3 min. The reaction mixture was stirred at −5 to 0 °C for 25 min and diluted with water (110 mL). The mixture was extracted with EtOAc (3×25 mL). The organic extracts were washed with 5% $NaHCO_3$ (2×25 mL) and the aqueous extracts back washed with EtOAc (10 mL). The combined organic layer was washed with 10% sodium sulfite (until the aqueous layer remained colourless), 5% $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was then dried over anhydrous Na_2SO_4, evaporated under reduced pressure to yield the crude product **6a**, which was then purified by flash column chromatography on silica gel (EtOAc/pet ether 3:7 as eluent) to get pure **6a** (0.351 g, 85%) as a white solid; mp 53–55 °C; [Found C, 74.13; H, 8.93; N, 4.95. $C_{17}H_{25}NO_2$ requires C, 74.13; H, 9.17; N, 5.08%]; R_f (40% EtOAc/pet ether) 0.18; $[\alpha]_D^{30}$ +40.57 (*c* 0.30, $CHCl_3$); ν_{max} ($CHCl_3$) 1757 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.89 (t, J=6.4 Hz, 3H, $CH_3(CH_2)_6$), 1.05–1.45 (m, 10 H, $CH_2(CH_2)_5CH_3$), 1.50–1.75 (m, 2H, $CH_2(CH_2)_5CH_3$), 3.67–3.77 (m, 1H, C4*H*), 4.66–4.72 (m, 2H, C3H, CH_aH_bPh,), 4.87 (d, J=11.9 Hz, 1H, CH_aH_bPh), 6.21 (br s, 1H, N–*H*), 7.25–7.45 (m, 5H, Ar); δ_C (50.32 MHz) 13.8, 22.3, 25.7, 28.9, 29.2, 29.4, 29.7, 31.5, 55.0, 72.5, 82.2, 127.4, 127.6, 128.1, 137.1, 169.4; MS (*m*/*z*): 276 ($M^+ + 1$).

4.1.4. (3*R*,4*S*)-4-Heptyl-3-hydroxyazetidin-2-one (7a). To a solution of **6a** (0.275 g, 1 mmol) in methanol (10 mL), 10% Pd/C (30 mg) was added followed by ammonium formate (0.315 g, 5 mmol) and the reaction mixture was heated at reflux under argon for 6 h. After completion of the reaction (TLC), the reaction mixture was allowed to cool to room temperature and filtered through Celite. The solvent was distilled off under reduced pressure and the residue was dissolved in CH_2Cl_2 (20 mL), washed with water (5 mL), brine (5 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave crude product, which was then purified by flash column chromatography on silica gel (EtOAc/pet ether 6:4 as eluent) to get pure **7a** (0.176 g, 95%) as a white solid, mp 112–113 °C; [Found C, 64.91; H, 10.40; N, 7.77. $C_{10}H_{19}NO_2$ requires C, 64.81; H, 10.36; N, 7.56%]; R_f (60% EtOAc/pet ether) 0.22; $[\alpha]_D^{30}$ +40 (*c* 0.25, $CHCl_3$); ν_{max} ($CHCl_3$) 1751 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.88 (t, J=6.3 Hz, 3H, $CH_3(CH_2)_6$), 1.15–1.65 (m, 12H, $(CH_2)_6CH_3$), 3.65–3.85 (m, 1H, C4*H*), 4.55–4.85 (m, 1H, C3*H*), 4.91 (br s, 1H, O*H*), 6.80 (br s, 1H, N–*H*); δ_C

(50.32 MHz) 14.1, 22.6, 25.9, 29.2, 29.5, 29.7, 31.7, 56.7, 76.5, 172.0; MS (*m*/*z*): 186 ($M^+ + 1$).

4.1.5. (2*R*,3*S*)-3-Amino-2-hydroxydecanoic acid (1a). A solution of **7a** (93 mg, 0.5 mmol) in 3 M HCl (5 mL) was heated at 60 °C for 6 h. After completion of the reaction (TLC), the solution was cooled to room temperature and extracted with CH_2Cl_2 (3 mL). The aqueous layer was evaporated to dryness under reduced pressure and the residue was further subjected to ion exchange chromatography (Dowex 50 W×2-400) using 5% NH_4OH as the eluent to afford **1a** (71 mg, 70%) as a white solid, mp 220–223 °C (dec), lit. mp 152–156 °C (dec);[12a] [Found C, 59.28; H, 10.53; N, 7.10. $C_{10}H_{21}NO_3$ requires C, 59.07; H, 10.43; N, 6.89%]; $[\alpha]_D^{30}$ −6.2 (*c* 0.40, 1 M HCl); δ_H (200 MHz, D_2O) 0.84 (t, *J*=6.7 Hz, 3H, C*H*$_3$(CH$_2$)$_6$), 1.19–1.45 (m, 10H, CH$_2$(C*H*$_2$)$_5$-CH$_3$), 1.50–1.83 (m, 2H, C*H*$_2$(CH$_2$)$_5$CH$_3$), 3.38–3.50 (m, 1H, C3*H*), 4.08 (d, *J*=3.8 Hz, 1H, C2*H*); δ_C (50.32 MHz, DMSO-d_6) 14.0, 22.1, 24.7, 28.4, 28.7, 29.1, 31.2, 52.7, 69.3, 172.9; MS (*m*/*z*): 204 (M+1).

4.1.6. (3*S*,4*R*)-3-Benzyloxy-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-1-(4-methoxyphenyl)azetidine-2-one (16). To a stirred solution of 5,6-*O*-isopropylidene-L-gulono-1,4-lactone **13** (10.90 g, 50 mmol) in water (150 mL), $NaIO_4$ (21.37 g, 100 mmol) was added portion-wise at 0 °C, over 30 min, at pH 5.5 (adjusted by addition of 2 M NaOH). The suspension was further stirred at room temperature for 2 h, and filtered through filter paper to get a crude aqueous solution of L-(*S*)-glyceraldehyde acetonide (**14**), which was then cooled to 10 °C under argon and vigorously stirred with a solution of *p*-anisidine (5.72 g, 46.5 mmol) in CH_2Cl_2 (150 mL) for 30 min. The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (2×50 mL). The combined organic layers dried over anhydrous Na_2SO_4 under argon. The organic layers were collected and reduced in volume to 30 mL. To this solution dry triethylamine (6.22 g, 61.5 mmol) was added and the reaction mixture was then cooled to 0 °C. A solution of benzyloxyacetyl chloride (8.59 g, 46.5 mmol) in dry CH_2Cl_2 (100 mL) was added drop-wise to the above reaction mixture. The reaction mixture was further stirred for 12 h at room temperature and then washed with water (3×15 mL), 1 N hydrochloric acid (10 mL), saturated $NaHCO_3$ (25 mL), water (25 mL) and brine solution (20 mL). The organic phase dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/pet ether 15:85 as eluent) to get a pure product **16** (8.90 g, 50%) as a white solid, mp 117 °C; [Found C, 68.98; H, 6.73; N, 3.61. $C_{22}H_{25}NO_5$ requires C, 68.90; H, 6.58; N, 3.65%]; R_f (30% EtOAc/pet ether) 0.57; $[\alpha]_D^{30}$ = −113.4 (*c* 0.70, $CHCl_3$); ν_{max} ($CHCl_3$) 1735 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.35 (s, 3H, C*H*$_3$), 1.54 (s, 3H, C*H*$_3$), 3.73–3.89 (m, 1H, OC*H*CH$_2$), 3.75 (s, 3H, Ar-OC*H*$_3$), 4.10–4.50 (m, 3H, C4*H*, OC*H*$_2$CHO), 4.70–4.80 (m, 2H, C3*H*, OC*H*$_a$H$_b$Ph), 5.00 (d, *J*=11.8 Hz, 1H, OCH$_a$*H*$_b$Ph), 6.85 (d, *J*=9.2 Hz, 2H, Ar), 7.30–7.45 (m, 5H, Ar), 7.70 (d, *J*=9.2 Hz, 2H, Ar); δ_C (50.32 MHz) 24.8, 26.5, 55.3, 61.6, 66.9, 73.1, 79.6, 109.6, 113.8, 119.4, 127.8, 128.1, 128.4, 131.1, 136.6, 156.3, 164.8; MS (*m*/*z*): 383 ($M^+ + 1$).

4.1.7. (3*S*,4*S*)-3-Benzyloxy-1-(4-methoxyphenyl)-4-oxoazetidin-2-carbaldehyde (3b). A mixture of azetidin-2-one **16** (3.83 g, 10 mmol) and PTSA (0.570 g, 3 mmol) in THF (40 mL) and water (15 mL) was refluxed for 24 h. After completion of reaction (TLC), the reaction mixture was neutralized with $NaHCO_3$ and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (25 mL) and the organic layer was washed with saturated brine solution (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford diol **17**, which was then dissolved in acetone (50 mL) and water (25 mL) and cooled to 0 °C. To the cooled diol solution, $NaIO_4$ (2.60 g, 12 mmol) was added in portions. After completion of addition, the reaction mixture was stirred at room temperature for 1 h. After completion of reaction (TLC), the solid was filtered off and washed with acetone. The solvent was removed and the residue was dissolved in CH_2Cl_2 (30 mL), washed with water (2×10 mL), saturated $NaHCO_3$ (2×10 mL), brine solution (15 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford **3b** (2.65 g, 85%) as a white solid, mp 157–158 °C; [Found C, 69.33; H, 5.58; N, 4.63. $C_{18}H_{17}NO_4$ requires C, 69.43; H, 5.51; N, 4.50%]; R_f (30% EtOAc/pet ether) 0.28; $[\alpha]_D^{30}$ = −176.19 (*c* 0.42, $CHCl_3$); ν_{max} ($CHCl_3$) 1753 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.79 (s, 3H, Ar-OC*H*$_3$), 4.51 (dd, *J*=5.3, 3.7 Hz, 1H, C4*H*), 4.71 (d, *J*=11.3 Hz, 1H, OC*H*$_a$H$_b$Ph), 4.84 (d, *J*=11.3 Hz, 1H, OCH$_a$*H*$_b$Ph), 5.05 (d, *J*=5.3 Hz, 1H, C$_3$*H*), 6.88 (d, *J*=9.1 Hz, 2H, Ar), 7.26 (d, *J*=9.1 Hz, 2H, Ar), 7.30–7.50 (m, 5H, Ar), 9.72 (d, *J*=3.7 Hz, 1H, C*H*O); δ_C (50.32 MHz) 55.5, 63.2, 73.5, 82.6, 114.6, 118.1, 128.3, 128.5, 128.6, 130.5, 135.8, 156.9, 162.9, 198.9; MS (*m*/*z*): 312 ($M^+ + 1$).

4.1.8. (3*R*,4*S*)-3-Benzyloxy-4-hept-1-enyl-1-(4-methoxyphenyl)azetidin-2-one (4b). Following the similar procedure described for **4a**, an inseparable mixture of *E* and *Z* isomers of **4b** was obtained from **3b** as a viscous oil.

4.1.9. (3*S*,4*R*)-3-Benzyloxy-4-heptyl-1-(4-methoxyphenyl)azetidine-2-one (5b) and (3*S*,4*R*)-4-heptyl-3-hydroxy-1-(4-methoxyphenyl)azetidine-2-one (18b). Following the similar procedure described for **5a** and **18a**, compound **5b** and **18b** were prepared from **4b**.

Compound **5b** was obtained as viscous oil, [Found C, 75.57; H, 8.35; N, 3.61. $C_{24}H_{31}NO_3$ requires C, 75.57; H, 8.21; N, 3.67%]; $[\alpha]_D^{30}$ −113.42 (*c* 0.80, $CHCl_3$); MS (*m*/*z*): 382 ($M^+ + 1$); spectral data same as for **5a**.

Compound **18b** was obtained as white crystals, mp 106–107 °C; [Found C, 70.33; H, 8.79; N, 4.95. $C_{17}H_{25}NO_3$ requires C, 70.06, H, 8.66; N, 4.81%]; $[\alpha]_D^{30}$ −110.30 (*c* 0.52, $CHCl_3$); MS (*m*/*z*): 292 ($M^+ + 1$); spectral data same as for **18a**.

4.1.10. (3*S*,4*R*)-3-Benzyloxy-4-heptylazetidin-2-one (6b). Following the similar procedure described for **6a**, compound **6b** was prepared from **5b**. It was obtained as a white solid, mp 55–56 °C; [Found C, 74.18; H, 9.09; N, 4.96. $C_{17}H_{25}NO_2$ requires C, 74.13; H, 9.17; N, 5.08%]; $[\alpha]_D^{30}$ −38.57 (*c* 0.7, $CHCl_3$); MS (*m*/*z*): 276 ($M^+ + 1$); spectral data same as for **6a**.

4.1.11. (3*S*,4*R*)-4-Heptyl-3-hydroxyazetidin-2-one (7b). Following the similar procedure described for **7a**, compound **7b** was prepared from **6b**. It was obtained as a white crystalline solid, mp 111–113 °C; [Found C, 64.97; H, 10.33; N, 7.73. $C_{10}H_{19}NO_2$ requires C, 64.81; H, 10.36; N, 7.56%]; $[\alpha]_D^{30}$ −40.5 (*c* 0.25, $CHCl_3$); (*m*/*z*): 186 ($M^+ + 1$); spectral data same as for **7a**.

4.1.12. (2*S*,3*R*)-3-Amino-2-hydroxydecanoic acid (1b). Following the similar procedure described for **1a**, compound **1b** was prepared from **7b**. It was obtained as a white solid, mp 219–220 °C (dec), lit. mp 218.4–219.7 °C (dec);[9a] [Found C, 59.33; H, 10.48; N, 6.95. $C_{10}H_{21}NO_3$ requires C, 59.07; H, 10.43; N, 6.89%]; $[\alpha]_D^{30}$ +6.5 (*c* 0.47, 1 N HCl), lit. $[\alpha]_D^{22}$ +7.3 (*c* 0.34, 1 N HCl),[13a] $[\alpha]_D^{25}$ +5.4 (*c* 0.59, 1 M HCl);[12b] MS (*m*/*z*): 204 ($M^+ + 1$); spectral data same as for **1a**.

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