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An improved synthesis of (2*S*, 4*S*)- and (2*S*, 4*R*)-2-amino-4-methyldecanoic acids: assignment of the stereochemistry of culicinins

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An improved synthesis of (2*S*, 4*S*)- and (2*S*, 4*R*)-2-amino-4-methyldecanoic acids was accomplished using a glutamate derivative as starting material and Evans' asymmetric alkylation as the decisive step. The NMR data of the two diastereomers were measured and compared with those of the natural product. As a result, the stereochemistry of this novel amino acid unit in culicinins was assigned as (2*S*, 4*R*).

Keywords: synthesis; 2-amino-4-methyldecanoic acid; culicinins; amino acid

Introduction

Peptaibiotics are known as a unique, constantly growing family of polypeptides which have amounted to more than 850 members during the past 50 years. Non-proteinogenic amino acids such as 4-hydroxyproline (Hyp), 2-amino-6-hydroxy-4-methyl-8-oxo-decanoic acid (AHMOD), β-Alanine (β-Ala) and others are quite widespread in these compounds. Among them, C^{α}-dialkylamino acids – most notably α-aminoisobutyric acid (Aib) and, if present, L- or D-isovaline (Iva) – , play a decisive role in determining physicochemical and biological activities of peptaibiotics. [1–4].

In 2006, He and co-workers [5] reported the isolation of four peptaibols culicinins A–D (Figure 1) with potent anticancer activity from the entomopathogenic fungus *Culicinomyces clavisporus* strain *LL*-12I252. These compounds contain a novel amino acid, (2*S*)-2-amino-4-methyldecanoic acid (AMD), which has been detected in peptaibols for the first time. However, the stereochemistry of this amino acid at C-4 was not determined. Recently, we have reported the preparation of (2*S*, 4*R*)-2-(benzyloxycarbonylamino)-4-methyldecanoic acid, based on Schöllkopf amino acid synthesis methodology [6]. However, there are some drawbacks in the initial route: (i) the use of expensive starting material and Schöllkopf chiral auxiliary; (ii) low yield in the asymmetric alkylation step; (iii) difficulties in separation of the desired Z-AMD-OEt from the by-product Z-DVal-OEt after cleavage of the chiral auxiliary; and (iv) inflexibility in the preparation of the two diastereoisomers. Herein, we would like to report an improved route for the synthesis of this amino acid and the assignment of its stereochemistry at C-4 position.

Results and Discussion

As shown in Scheme 1, the inexpensive commercially available reagent *N*-Boc-γ-benzyl L-glutamate (**1**) was transformed into the *N*,*O*-protected carboxylic acid (**2**) smoothly according to a published method [7]. Then the acid was linked to the chiral auxiliary (*R*)-4-benzyl-2-oxazolidinone under the very mild conditions developed by Ho and Mathre [8]. The resultant key intermediate **3** was then subjected to Evans' asymmetric alkylation under low temperature conditions. Initially, 1-iodohexane was used as an electrophilic reagent in this step (not shown in the scheme). However, no desired product was obtained. This might have resulted from the poor electrophilic intensity of the iodoalkane. Thus an 'auxiliary line' was introduced. In other words, a more efficient electrophile, 1-iodohex-2-ene, was used instead of 1-iodohexane. Compound **3** was enolized at low temperature. Addition of 1-iodohex-2-ene gave the alkylated *R*-adduct **4** as the major diastereomer, which could be easily separated from its diastereomer by column chromatography. Removal of the chiral auxiliary was accomplished under reductive conditions to give the alcohol **5**, which was subsequently transformed into its tosylate. Elimination of the – OTs group of **6** and thus release of the 4-methyl group gave compound **7** in a satisfactory yield. Now, it is time to erase the 'auxiliary line' – hydrogenation of the C=C double bond gave compound **8** in high yield. Next, both cleavage of the oxazalidine and oxidation of the newly released hydroxyl group could be smoothly achieved in a single step using excess of Jones' reagent. Acid **9** could not be separated from the traces of the unoxidized alcohol by means of silica gel chromatography. Thus, the mixture was treated with diazomethane in ether-methanol (1 : 1, *V* : *V*). The desired fully protected amino acid **10** was easily separated from the unoxidized alcohol by silica gel chromatography. Finally, in order to compare the NMR data with those of the residue in the natural product, compound **10** was transformed into the free amino acid **11** in refluxing hydrochloric acid.

Quite similarly, treatment of acid **2** with the (*S*)-4-benzyl-2-oxazolidinone instead of its enantiomer gave compound **3a**, which was converted into free amino acid **11a** over eight steps.

Next, the NMR data (Table 1) of **11**, **11a** and those of the natural product were carefully compared. No significant difference was

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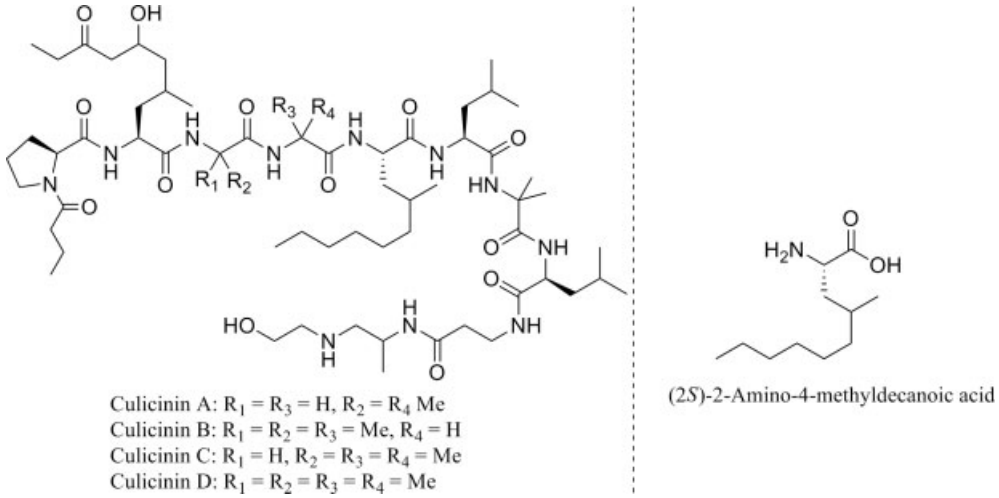
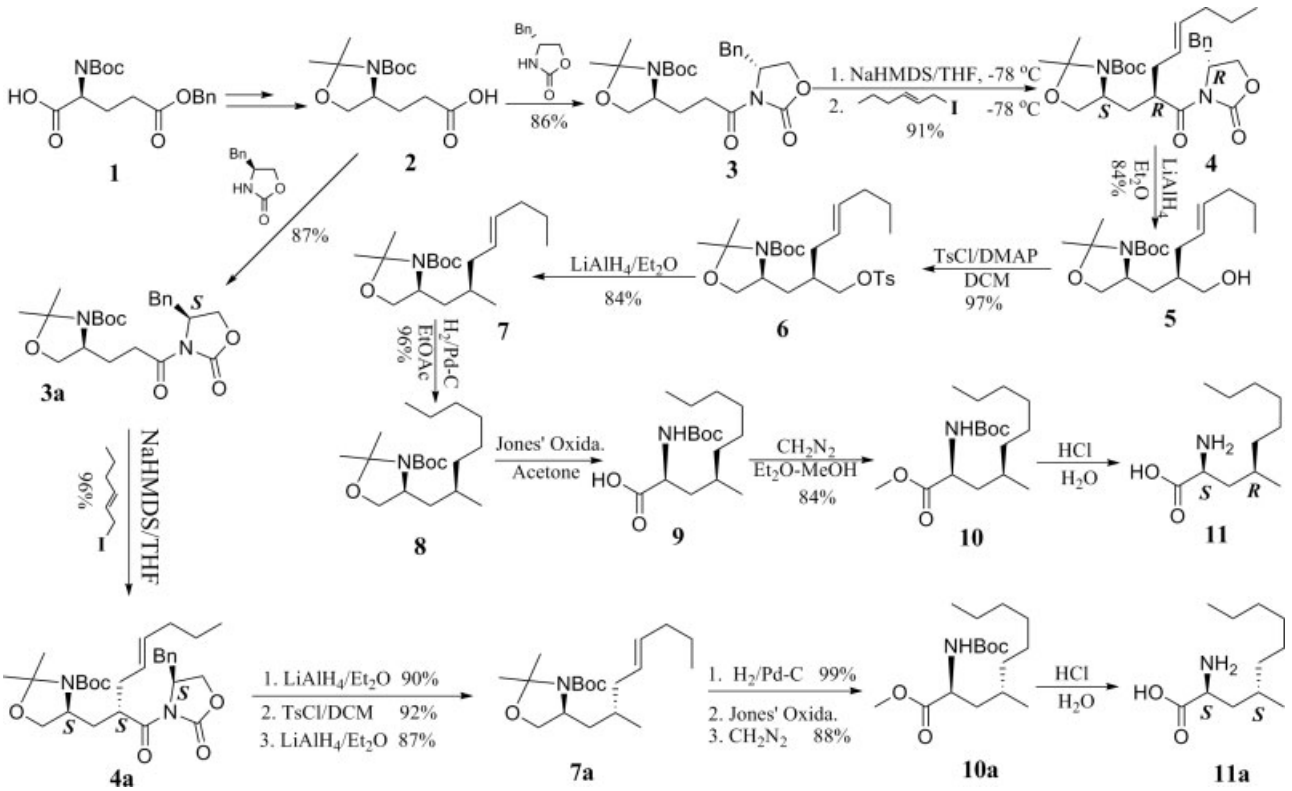


Figure 1. Structures of culicins and (2*S*)-2-amino-4-methyldecanoic acid.



Scheme 1. Synthesis of (2*S*, 4*R*)- and (2*S*, 4*S*)-2-amino-4-methyldecanoic acids.

found between the ^{1}H NMR data of the two diastereomers and those of the natural product [5]. However, their ^{13}C NMR shifts were quite different. (Figure 2) The data of **11** (right) differ <0.2 ppm, whereas those of **11a** (left) exhibit larger differences (-0.34 to $+0.30$ ppm). Obviously, the stereochemistry of this amino acid residue in the natural products should be (2*S*, 4*R*).

Conclusion

In conclusion, an improved and efficient synthesis of AMD was accomplished using a glutamate derivative as starting material and Evans' asymmetric alkylation as key step. As a result, two diastereomers of this novel amino acid were prepared. The stereochemistry at C-4 of this amino acid was assigned as *R* by careful examination and comparison of their NMR data to that of the natural product. This approach is economic, efficient, flexible, and should be valuable for the total synthesis of culicinins.

Experimental

General Information

Solvents were purified by standard methods. *N*-Boc-γ-benzyl L-glutamate (**1**) was purchased from GL Shanghai, Co. Ltd. and

Table 1. NMR data of AMDs

	^{1}H NMR			^{13}C NMR		
	Lit.	(2*S*, 4*S*)	(2*S*, 4*R*)	Lit.	(2*S*, 4*S*)	(2*S*, 4*R*)
1	–	–	–	171.67	171.38	171.50
2	3.78 (m)	3.81–3.79 (m)	3.76–3.74 (m)	50.66	50.40	50.55
3	1.65–1.50 (m)	a. 1.76–1.72 (m) b. 1.57–1.52 (m)	a. 1.72–1.67 (m) b. 1.57–1.53 (m)	37.76	37.55	37.70
4	1.65–1.50 (m)	1.64–1.60 (m)	1.66–1.62 (m)	28.27	28.42	28.24
4-Me	0.86 (*t*, *J* = 6.5 Hz)	0.88 (*t*, *J* = 6.4 Hz)	0.87 (*t*, *J* = 5.5 Hz)	18.84	19.14	18.90
5	a. 1.23 (m) b. 1.12 (m)	a. 1.28–1.21 (m) b. 1.12–1.08 (m)	a. 1.28–1.21 (m) b. 1.14–1.10 (m)	36.36	36.02	36.26
6	1.23 (m)	1.28–1.21 (m)	1.28–1.21 (m)	26.09	25.96	26.04
7	1.23 (m)	1.28–1.21 (m)	1.28–1.21 (m)	28.90	28.89	28.88
8	1.23 (m)	1.28–1.21 (m)	1.28–1.21 (m)	31.32	31.27	31.27
9	1.23 (m)	1.28–1.21 (m)	1.28–1.21 (m)	22.13	22.07	22.09
10	0.84 (*t*, *J* = 6.5 Hz)	0.86 (*t*, *J* = 7.1 Hz)	0.86 (t, *J* = 6.8 Hz)	14.00	13.95	13.97

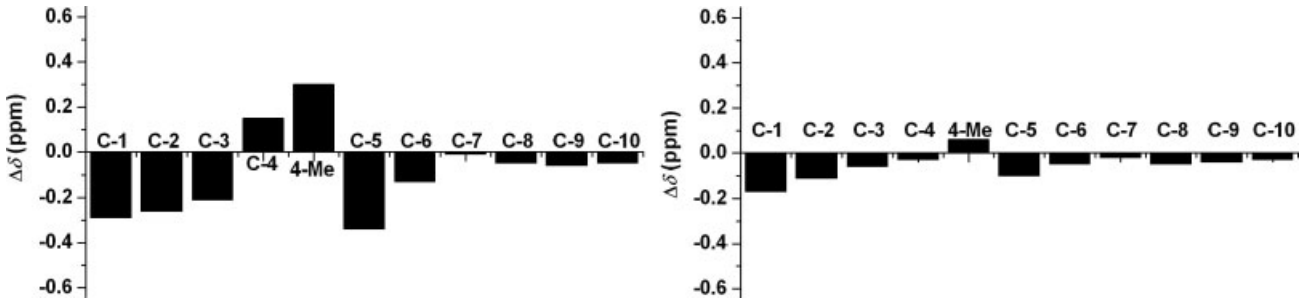


Figure 2. Difference in ^{13}C NMR chemical shifts. Left: (2*S*, 4*S*)-AMD; right: (2*S*, 4*R*)-AMD.

transformed into *N*,*O*-protected carboxylic acid (**2**) according to the published method [7]. TLCs were carried out on Merck 60 F_{254} silica gel plates and visualized by UV irradiation or by staining with iodine absorbed on silica gel, ninhydrin solution or with aqueous acidic ammonium molybdate solution as appropriate. Flash column chromatography was performed on silica gel (200–300 mesh, Qingdao, China). Petroleum ether used as eluting solvent in this paper refers to the fraction of boiling range 60–90 °C. Optical rotations were measured using a JASCO P-1020 digital polarimeter. NMR spectra were recorded on JEOL JNM-ECP 600 MHz spectrometers. Chemical shifts are reported in parts per million (ppm), relative to the signals due to the solvent. Data are described as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), integration, and assignment. Mass spectra were recorded on a Q-Tof Ultima Global mass spectrometer.

Compound ***3***

Acid **2** (58.73 g, 214.87 mmol) was dissolved in 1 L of anhydrous THF and cooled to −5 °C. Triethylamine (89.4 mL, 645 mmol) and pivaloyl chloride (28.7 mL, 236 mmol) were added sequentially after 30 min at that temperature. The cloudy mixture was stirred at 0 °C for 3 h, and then anhydrous LiCl (10.94 g, 258 mmol) and (*R*)-4-benzyl-2-oxazolidinone (38.07 g) were added sequentially. After warming to room temperature and being stirred for 24 h, the suspension was filtered through a pad of celite, washed with EtOAc (3 × 50 mL), and concentrated in vacuo. The residue was dissolved in 4 L EtOAc; washed with 0.5 M HCl, saturated $NaHCO_3$, and brine; dried over Na_2SO_4; and concentrated in vacuo to give the crude product as a pale yellow solid. Recrystallization from EtOAc–petroleum ether (1 : 1, *V* : *V*) gave pure **3** (79.90 g, 86%) as a white solid.

Mp 123–124 °C; $[\alpha]_D^{26}$ = −37.0 (*c* = 1.3, MeOH); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.46 (s, 12H), 1.58 and 1.64 (s each, total 3H), 1.94–2.08 (brm, 2H), 2.74–2.81 (m, 1H), 2.85–3.10 (brm, 2H), 3.30–3.33 (m, 1H), 3.75 (d, *J* = 9.0 Hz, 1H), 3.91 and 4.08–4.12 (brm, 1H), 3.96 (dd, *J* = 9.0, 5.7 Hz, 1H), 4.15–4.23 (m, 2H), 4.68–4.72 (m, 1H), 7.22–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 24.3, 27.7, 28.4, 31.9, 38.1, 55.3, 56.0, 66.3, 67.3, 80.1, 93.5, 127.2, 128.9, 129.4, 135.5, 152.7, 153.7, 172.6; HRESIMS calculated for $C_{23}H_{32}N_2O_6Na$ 455.2153 $[M+Na]^+$, found 455.2116.

Compound ***3a***

Prepared as described above for **3**.

Yield 87%. White solid. Mp 86–88 °C. $[\alpha]_D^{26}$ = 103.3 (*c* = 1.0, MeOH). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.49 (s, 12H), 1.59 (s, 3H), 1.97–2.09 (m, 2H), 2.76 (dd, *J* = 13.3, 10.1 Hz, 1H), 2.83–3.12 (m, 2H), 3.32 and 3.39 (two br d, *J* = 12.6 Hz, 1H), 3.77 and 3.81 (two br d, *J* = 8.9 Hz, 1H), 3.89 (br m, 1H), 3.96 (dd, *J* = 9.0, 5.7 Hz, 1H), 4.66–4.69 (ddd, *J* = 13.5, 6.8, 2.8 Hz, 1H), 7.23–7.35 (m, 5H); HRESIMS calculated for $C_{23}H_{32}N_2O_6Na$ 455.2153 $[M+Na]^+$, found 455.2128.

Compound ***4***

NaHMDS (2.8 mL, 2.0 M solution in THF) was added slowly to a solution of **3** (2.16 g, 5.0 mmol) in anhydrous THF (25 mL) at −78 °C.

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The reaction mixture was stirred at that temperature for 20 min and then (*E*)-1-iodohex-2-ene (3.15 g, 15.0 mmol) was added via a syringe. After being stirred for 8 h at −78 °C, the reaction was quenched by addition of saturated aqueous NH_4Cl solution. The mixture was warmed to room temperature; diluted with Et_2O (200 mL); washed with 10% $Na_2S_2O_3$ and brine; dried over Na_2SO_4; and concentrated in vacuo. The residue was purified by flash column chromatography, eluting with EtOAc/petroleum ether (1 : 5 → 1 : 3) to give compound **4** (2.33 g, 91%) as a colorless oil.

$[\alpha]_D^{25} = -11.4$ (c = 1.4, MeOH); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.88 (t like, J = 6.9 Hz, 3H, $C\underline{H}_3CH_2$), 1.34–1.38 (m, 2H, $CH_3C\underline{H}_2CH_2$), 1.42 (s, 9H, Boc), 1.45 (s, 3H), 1.51 (s, 3H), 1.74–1.78 (m, 1H), 1.95–1.98 (m, 3H), 2.18–2.23 (m, 1H), 2.44–2.46 (m, 1H), 2.73–2.77 (m, 1H, PhC$\underline{H}$aHb), 3.25–3.27 (m, 1H, PhCHa$\underline{H}$b), 3.56–3.57 (m, 1H), 3.65–3.67 (m, 1H), 3.90–3.92 (m, 1H), 4.04–4.06 (m, 1H), 4.11–4.13 (m, 1H), 4.25–4.28 (m, 1H), 4.77–4.79 (m, 1H), 5.39–5.43 (m, 1H), 5.46–5.50 (m, 1H), 7.23–7.27 (m, 3H), 7.31–7.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.7, 22.5, 24.4, 28.1, 28.4, 29.4, 29.7, 34.6, 35.6, 35.9, 38.7, 39.9, 54.8, 55.4, 66.3, 68.5, 80.1, 93.6, 126.3, 127.1, 128.8, 129.4, 133.5, 135.8, 153.3, 175.3; HRESIMS calculated for $C_{29}H_{42}N_2O_6Na$ 537.2935 $[M+Na]^+$, found 537.2888.

*Compound **4a***

Prepared as described above for **4**.

Yield 96%. Colorless oil. $[\alpha]_D^{26} = 283.6$ (c = 0.4, MeOH). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.87 (t, J = 7.3 Hz, 3H, $C\underline{H}_3CH_2$), 1.35 (sex., J = 7.3 Hz, 2H, $CH_3C\underline{H}_2CH_2$), 1.45 (s, 3H), 1.49 (s, 9H, Boc), 1.60 (s, 3H), 1.72–1.77 and 2.15 (two brm, 2H), 1.94–1.97 (brm, 2H, $C\underline{H}_2CH{=}CH$), 2.25–2.45 (brm, 2H, $CH{=}CHC\underline{H}_2$), 2.60–2.70 (m, 1H, PhC$\underline{H}$aHb), 3.31 (dd, J = 13.3, 2.7 Hz, 1H, PhCHa$\underline{H}$b), 3.68–3.89 (brm, 3H), 4.10–4.18 (brm, 2H, Oxa H-3), 4.66–4.75 (brm, 1H, Oxa H-4), 5.38–5.41 (m, 1H, C$\underline{H}$=CH), 5.50–5.51 (m, 1H, CH=C$\underline{H}$), 7.21–7.34 (m, 5H, Ar H); HRESIMS calculated for $C_{29}H_{42}N_2O_6Na$ 537.2935 $[M+Na]^+$, found 537.2890.

*Compound **5***

$LiAlH_4$ (1.14 g, 30 mmol) was added in small portions to a solution of oxazolidinone **4** (5.15 g, 10 mmol) in Et_2O at 0 °C. The reaction mixture was stirred for 3 h at room temperature, quenched by dropwise addition of water (1 mL), 15% aqueous NaOH (1 mL), and water (3 mL). The mixture was stirred for 1 h at room temperature, and then $MgSO_4$ (5 g) was added. The suspension was filtered through a pad of celite, washed with Et_2O and concentrated in vacuo. The residue was purified by flash silica gel chromatography, eluting with EtOAc/petroleum (2 : 1) ether to give alcohol **5** as a colorless oil (2.85 g, 84%).

^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.88 (t, J = 7.5 Hz, 3H), 1.35–1.38 (m, 2H), 1.49 (brs 12H), 1.55 (s, 3H), 1.60–1.69 (brm, 3H), 1.84–1.99 (m, 4H), 3.47–4.22 (brm overlapped, 5H), 5.33–5.37 (m, 1H), 5.41–5.49 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.7, 22.6, 24.5, 28.4, 28.6, 29.4, 34.6, 36.3, 37.9, 55.2, 66.6, 68.4, 80.5, 93.3, 127.9, 132.5, 152.7; HRESIMS calculated for $C_{19}H_{35}NO_4Na$ 364.2458 $[M+Na]^+$, found 364.2449.

*Compound **5a***

Prepared as described above for **5**.

Yield 90%. Colorless oil. $[\alpha]_D^{26} = 88.2$ (c = 0.4, MeOH); ^{1}H NMR ($CDCl_3$, 600 MHz, mixture of rotamers) δ 0.88 (t, J = 7.3 Hz, 3H, $C\underline{H}_3CH_2$), 1.37 (sex., J = 7.2 Hz, 2H, $CH_3C\underline{H}_2CH_2$), 1.44, 1.48 (brs, 15H, Boc+$(CH_3)_2$), 1.55–1.72 (brm, 3H), 1.89–2.13 (brm, 4H, $C\underline{H}_2CH{=}CHC\underline{H}_2$), 3.34–4.04 (brm, overlapped, 5H), 5.33–5.50 (m, 2H, CH=CH); HRESIMS calculated for $C_{19}H_{35}NO_4Na$ 364.2458 $[M+Na]^+$, found 364.2432.

*Compound **7***

Triethylamine (4.2 mL, 30 mmol) was added to a solution of **5** in dichloromethane at 0 °C. TsCl (3.81 g, 20 mmol) and DMAP (244 mg, 2 mmol) were then added at the same temperature and stirred overnight. The mixture was diluted with dichloromethane and then washed with 1 M HCl, H_2O, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash silica gel chromatography, eluting with EtOAc/petroleum ether to give compound **6** as a colorless oil (4.81 g, 97%).

$LiAlH_4$ (1.10 g, 29 mmol) was added in small portions to a solution of tosylate **6** (4.81 g, 9.7 mmol) in Et_2O at 0 °C. The reaction mixture was stirred for 3 h at room temperature, quenched by dropwise addition of water (1 mL), 15% aqueous NaOH (1 mL), and water (3 mL). The mixture was stirred for 1 h at room temperature, and then $MgSO_4$ (5 g) was added. The suspension was filtered through a pad of celite, washed with Et_2O, and concentrated in vacuo. The residue was purified by flash silica gel chromatography, eluting with EtOAc/petroleum ether to give compound **7** as a colorless oil (2.65 g, 84%).

$[\alpha]_D^{25} = 36.2$ (c = 0.5, MeOH). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.86–0.92 (t and d, overlapped, 6H), 1.32–1.40 (brm, overlapped, 3H), 1.48–1.81(brm, 17H), 1.96–2.17 (brm, 4H), 3.72–4.01 (brm, overlapped, 3H), 5.33–5.42 (brm, 2H, C$\underline{H}$=C$\underline{H}$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.7, 22.7, 23.3, 27.0, 28.6, 29.4, 34.7, 39.3, 41.2, 56.0, 67.7, 79.8, 93.6, 128.5, 132.2, 152.4; HRESIMS calculated for $C_{19}H_{35}NO_3Na$ 348.2509 $[M+Na]^+$, found 348.2511.

*Compound **7a***

Prepared as described above for **7**.

Yield 87%. Colorless oil. $[\alpha]_D^{26} = 67.2$ (c = 1.2, MeOH). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.89 (t, J = 7.3 Hz, 3H, $CH_2C\underline{H}_3$), 0.90 (d, overlapped, 3H, $CHC\underline{H}_3$), 1.35–1.40 (brm, 3H), 1.47 and 1.59 (brs, 15H, Boc+$(CH_3)_2$), 1.87–2.01 (brm, 4H), 3.71 (t, J = 8.2 Hz, 1H), 3.84 and 3.99 (brm, 1H), 3.90 (dd, J = 8.2, 5.9 Hz, 1H), 5.32–5.45 (m, 2H, C$\underline{H}$=C$\underline{H}$); HRESIMS calculated for $C_{19}H_{35}NO_3Na$ 348.2509 $[M+Na]^+$, found 348.2504.

*Compound **8***

Palladium on charcoal (65 mg, 10% weight) was added to a solution of compound **7** (651 mg, 2 mmol) in EtOAc (10 mL). The reaction mixture was purged with hydrogen three times and stirred for 2 h at room temperature. The suspension was filtered through a pad of celite, washed with EtOAc (3 × 5 mL), and concentrated in vacuo, to give compound **8** as a colorless oil (629 mg, 96%).

$[\alpha]_D^{26} = 24.9$ (c = 1.3, MeOH). ^{1}H NMR ($CDCl_3$, 600 MHz, mixture of rotamers) δ 0.88 (t, J = 6.6 Hz, 3H, $C\underline{H}_3CH_2$), 0.90 (d, J = 6.6 Hz, 3H, $C\underline{H}_3CH$), 1.06–1.73 (brm, total 28H), 3.73 (brd, J = 8.4 Hz, 1H), 3.83 and 3.99 (brm, total 1H), 3.91–3.93 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.1, 20.8, 22.7, 28.6, 29.6, 30.8, 31.9, 36.1, 41.6, 56.0, 67.6, 79.8, 93.5, 151.7; HRESIMS calculated for $C_{19}H_{37}NO_3Na$ 350.2666 $[M+Na]^+$, found 350.2659.

*Compound **8a***

Prepared as described above for **8**.

Yield 99%. Colorless oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.88 (t, J = 6.9 Hz, 3H, $CH_2C\underline{H}_3$), 0.90 (d, J = 6.9 Hz, 3H, $CHC\underline{H}_3$), 1.26 (brm, 10H), 1.47 (brs, 15H, Boc+$(C\underline{H}_3)_2$), 1.55–1.60 (brm, 3H), 3.72 (t, J = 8.5 Hz, 1H), 3.84 and 3.98 (brm, total 1H), 3.90 (dd, J = 8.7, 5.5 Hz, 1H); HRESIMS calculated for $C_{19}H_{37}NO_3Na$ 350.2666 $[M+Na]^+$, found 350.2655.

*Ester **10***

Freshly prepared Jones' reagent (1.2 ml, ~2.67 M) was added at 0 °C to a solution of the oxazolidine **8** (328 mg, 1 mmol) in 5 mL acetone. After stirring for 2 h at 0 °C, the reaction mixture stirring was continued overnight at room temperature. A saturated solution of $NaHCO_3$ was added to obtain a pH value of 5 ~ 6. The aqueous phase was then extracted with Et_2O, and the combined organic extracts were washed with brine, dried, and concentrated to give the crude carboxylic acid along with traces of unoxidized alcohol, which could not be separated by silica gel chromatography.

The crude acid obtained above was treated with 2 eq. of diazomethane (*Caution! Diazomethane is highly toxic and must be operated in a fume hood.*) in dichloromethane. A few drops of HOAc were added carefully when TLC showed all the acid was consumed. The reaction mixture was diluted with Et_2O; washed with H_2O, saturated aqueous $NaHCO_3$, and brine; dried over Na_2SO_4; and concentrated in vacuo. The residue was purified by flash silica gel chromatography, eluting with EtOAc/petroleum ether (1 : 10) to give ester **10** as a colorless oil (265 mg, 84%).

$[\alpha]_D^{26}$ = −17.0 (c = 1.1, MeOH). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.88 (t, J = 6.9 Hz, 3H, H-10), 0.93 (d, J = 5.4 Hz, 3H, 4-Me), 1.25–1.30 (brm, 10H), 1.44 (s, 9H, Boc), 1.53–1.58 (brm, 3H, H-3 and H-4), 3.73 (s, 3H, $CO_2C\underline{H}_3$), 4.33 (brm, 1H, H-2), 4.84 (d, J = 9.0 Hz, 1H, NH); ^{13}C NMR (600 MHz, CDCl3) δ 14.1 (C-10), 19.0 (4-Me), 22.6, 26.8, 28.3 ($(\underline{C}H_3)_3COC{=}O$), 29.4, 29.5, 31.8, 37.2 (C-5), 40.0 (C-4), 51.8 (C-2), 52.2 (CO2Me), 79.8 ($(CH_3)_3\underline{C}OC{=}O$), 155.5 ($(CH_3)_3CO\underline{C}{=}O$), 174.2 (C-1); HRESIMS calculated for $C_{17}H_{33}NO_4Na$ 338.2302 $[M+Na]^+$, found 338.2282.

*Ester **10a***

Prepared as described above for **10**.

Yield 88%. Colorless oil. $[\alpha]_D^{26}$ = −13.5 (c = 1.2, MeOH). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.88 (t, J = 7.1 Hz, 3H, H-10), 0.91 (d, J = 6.4 Hz, 3H, 4-Me), 1.10–1.14 (m, 1H), 1.26–1.30 (m, 10H), 1.44 (s, 9H), 1.50–1.55 (m, 1H), 1.69–1.74 (m, 1H), 3.73 (s, 3H), 4.31–4.35 (m, 1H), 4.91 (d, J = 8.2 Hz, 1H, NH); HRESIMS calculated for $C_{17}H_{33}NO_4Na$ 338.2302 $[M+Na]^+$, found 338.2281.

*(2S, 4R)-2-amino-4-methyldecanoic acids (**11**)*

Methyl ester **10** (95 mg, 0.3 mmol) was dissolved in 20 mL of 6 M HCl and refluxed for 12 h. The reaction mixture was cooled and extracted with *n*-BuOH. The organic layer was dried and concentrated to yield the title compound. The NMR data of **11** are shown in Table 1.

*(2S, 4S)- 2-amino-4-methyldecanoic acids (**11a**)*

Using the same conditions as described above for **11**, the NMR data of **11a** are shown in Table 1.

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