Research Article

Journal of PeptideScience

Received: 28 July 2011 Revised: 28 October 2011 Accepted: 28 October 2011 Published online in Wiley Online Library: 16 January 2012

(wileyonlinelibrary.com) DOI 10.1002/psc.1433

Stereoselective synthesis of fully protected (2*S*,4*S*,6*S*)-2-amino-6-hydroxy-4-methyl-8-oxodecanoic acid (AHMOD)

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ABSTRACT: The stereocontrolled synthesis of fully protected (2*S*,4*S*,6*S*)-2-amino-6-hydroxy-4-methyl-8-oxodecanoic acid was accomplished using a glutamate derivative as starting material. The key steps of this stereochemical synthetic pathway involved an Evans asymmetric alkylation, a Sharpless asymmetric epoxidation, and a Grignard reaction. Copyright © 2012 European Peptide Society and John Wiley & Sons, Ltd.

Keywords: amino acids; peptaibiotics; AHMOD; synthesis; stereoselectivity

Introduction

Over the past half century, more than 850 peptaibiotics have been isolated from fungi. These special peptides, with high content of α-aminoisobutyric acid (Aib), have attracted considerable attention because of their broad bioactivities and particular structural properties. A special issue on these interesting molecules was published in the *Journal of Peptide Science* in 2003 [1]. Four years later, a similar topical issue with updated studies and overviews on peptaibiotics was published in *Chemistry & Biodiversity* [2]. Generally, peptaibiotics exhibit a broad range of biological activities such as antibacterial [3–7], antifungal [8–11], antiviral [12–14], and antimycoplasmic [15,16]. Inhibition of mitochondrial ATPase, immunosuppression, uncoupling of oxidative phosphorylation, and inhibition of platelet aggregation have also been reported [17–20]. Besides, peptaibiotics with sufficient chain length can form voltage-dependent ion channels in bilayer membranes [21–23].

Structurally, peptaibiotics can be divided into four subfamilies [24]: peptaibols, lipopeptaibols, lipoaminopeptides (also called aminolipopeptides), and others. Among them, the third subfamily has the most conservative structure. A proline or a modified proline (mainly *trans*-4-hydroxy-proline or *cis*-4-hydroxy-proline) is located in position 1, with C_4–C_{15} fatty acids at the N-terminus. In position 2, to our present knowledge, is 2-amino-6-hydroxy-4-methyl-8-oxodecanoic acid (AHMOD). This unique amino acid residue has only been detected in this subfamily up till now. Some lipoaminopeptides containing this unit are listed in Figure 1. However, none of these compounds bearing the AHMOD residue has been synthesized by chemical methods, which limits further biological and structure–activity relationship (SAR) research. Lack of practical preparing methods of this highly modified amino acid is one of the reasons that hampered so far the chemical synthesis of lipoaminopeptides. To the best of our knowledge, only one chemical synthetic route for this unit has been disclosed so far, by Hadrami *et al*. 20 years ago [29]. But this route has not been widely adopted until now because of some drawbacks: (i) the use of expensive starting materials, (ii) the use of foul sulfide and highly toxic mercuride, and (iii) non-stereoselectivity in the construction of the C-6 chiral center. Recently, we reported the preparation of (2*S*,4*S*)-2-amino-4-methyl decanoic and (2*S*,4*R*)-2-amino-4-methyl decanoic acids (AMDs) [30]. Based on this previous work, here we would like to report a novel, practical, and stereoselective synthetic route to the fully protected (2*S*,4*S*,6*S*)-AHMOD.

Results and Discussion

As displayed in Scheme 1, an inexpensive and commercially available glutamate derivative [Boc-Glu(OBn)-OH] was chosen as starting material, which was transformed into compound **1** smoothly according to reported procedures [31]. The resulting intermediate **1**, equipped with chiral auxiliary (*R*)-4-benzyl-2-oxazolidinone, was ready for Evans asymmetric alkylation. Notably, the structure of nucleophilic reagent **1a** was crucial to the following procedures. The *trans*-allylic alcohol was selected as it gives better results than its *cis*-isomer in the subsequent Sharpless asymmetric epoxidation. The *tert*-butyldimethylsilyl (TBS) protecting group for the hydroxyl group of **1a** was chosen as it is stable under the base-mediated enolization conditions and the reductive environment (to remove the auxiliary) and can be easily removed.

Compound **1** was enolized at low temperature, followed by the addition of nucleophilic reagent **1a**, giving the alkylated *R*-adduct **2** as the major product (*dr* = 19 : 1), which could be easily separated from its diastereomer by column chromatography. Reductive removal of the chiral auxiliary furnished the primary alcohol **3**, which was subsequently transformed to its tosylate. The tosylate, without purification, was treated with $LiAlH_4$, releasing a methyl group after displacement of the –OTs group with hydride. After simple washes, the new intermediate was treated with TBAF, removing the TBS group and then giving alcohol **4**. All

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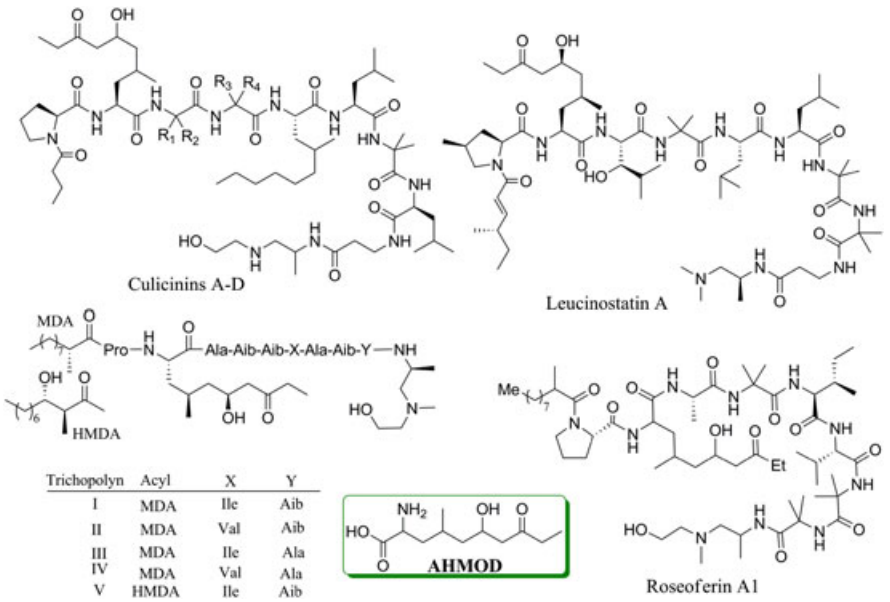

Figure 1. Structures of AHMOD and some AHMOD-containing lipoaminopeptides [25–28].

intermediates formed during the conversion of compound **3** to compound **4** were not subjected to column chromatography. The overall yield for these three steps was 90%. Allylic alcohol **4** was subjected to standard Sharpless asymmetric epoxidation conditions providing the epoxy alcohol **5** in 91% yield as a single diastereomer (by ^{1}H NMR). Direct epoxide ring opening of **5** and its transformation to the corresponding β-hydroxyl aldehyde (precursor of compound **9**) were found inefficient. Alternatively, epoxide **5** was converted to its iodide (Scheme 1) [32], followed by treatment with zinc dust in methanol at reflux, giving allylic alcohol **6** in satisfactory yields. The secondary hydroxyl group was masked with benzyl ether, giving compound **7**, which was then elaborated into alcohol **8** by treatment with BH_3 smoothly. Note that other hindered boranes, such as 9-borabicyclo[3.3.1]nonane, did not work in this hydroboration–oxidation reaction. Primary alcohol **8** was exposed to Swern conditions, and the resultant crude aldehyde was treated with Grignard reagent, lengthening the carbon chain to yield compound **9**. Oxidative cleavage of the oxazolidine, oxidation of the secondary alcohol and the newly released primary alcohol, could be smoothly achieved in a single step using freshly prepared Jones reagent, yielding 88% of carboxylic acid **10**. Finally, this acid was transformed to its methyl ester with diazomethane, giving the fully protected (2*S*,4*S*,6*S*)-AHMOD (**11**)[1] in 79% yields.

Conclusion

In conclusion, we have achieved a novel and stereoselective synthesis of fully protected (2*S*,4*S*,6*S*)-AHMOD in 9.2% yield over 14 steps. In this route, the chiral C-2 center originated from L-glutamates, the stereochemistry of C-4 was controlled by Evans asymmetric alkylation, and the C-6 chiral center was introduced by Sharpless asymmetric epoxidation. The approach is economic, stereoselective, and flexible, which will be beneficial for the chemical synthesis and SAR research of the peptaibiotics bearing AHMOD unit.

[1]This unusual amino acid unit shows quite different characters to other amino acids. It has been proved that the skeleton of this amino acid derivate can be destroyed by treatment with TFA (50% volume in CH_2Cl_2, 0 °C, 1 h) or aqueous solution of LiOH (0.2 mol/l, 0 °C, 1 h). But the structures of products have not been identified yet.

Experimental

General Information

Solvents were purified by standard methods. 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 was the fraction of boiling range 60–90 °C. Optical rotations were measured using a JASCO P-1020 digital polarimeter (JASCO, Tokyo, Japan). NMR spectra were recorded on JEOL JNM-ECP 600 MHz spectrometer (JEOL Ltd, Tokyo, Japan). 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. High resolution electrospray ionization mass spectroscopy (HRESIMS) were recorded on a Q-Tof Ultima Global mass spectrometer (Waters Asia Ltd, Singapore).

(S)-tert-Butyl 4-(3-((*R*)-4-benzyl-2-oxooxazolidin-3-yl)-3-oxopropyl)-2,2-dimethyloxazolidine-3-carboxylate (compound **1**)

This compound was prepared as reference [31] described. Starting from Boc-Glu(OBn)-OH, the title compound was obtained 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, $(CH_3)_3COC{=}O$ + ), 1.58 and 1.64 (s each, total 3H, ), 1.94–2.08 (brm, 2H, $CH_2CH_2C{=}O$), 2.74–2.81 (m, 1H, PhCHaHb), 2.85–3.10 (brm, 2H, $CH_2CH_2C{=}O$), 3.30–3.33 (m, 1H, PhCHaHb), 3.75 (d, *J* = 9.0 Hz, 1H, ), 3.91 and 4.08–4.12

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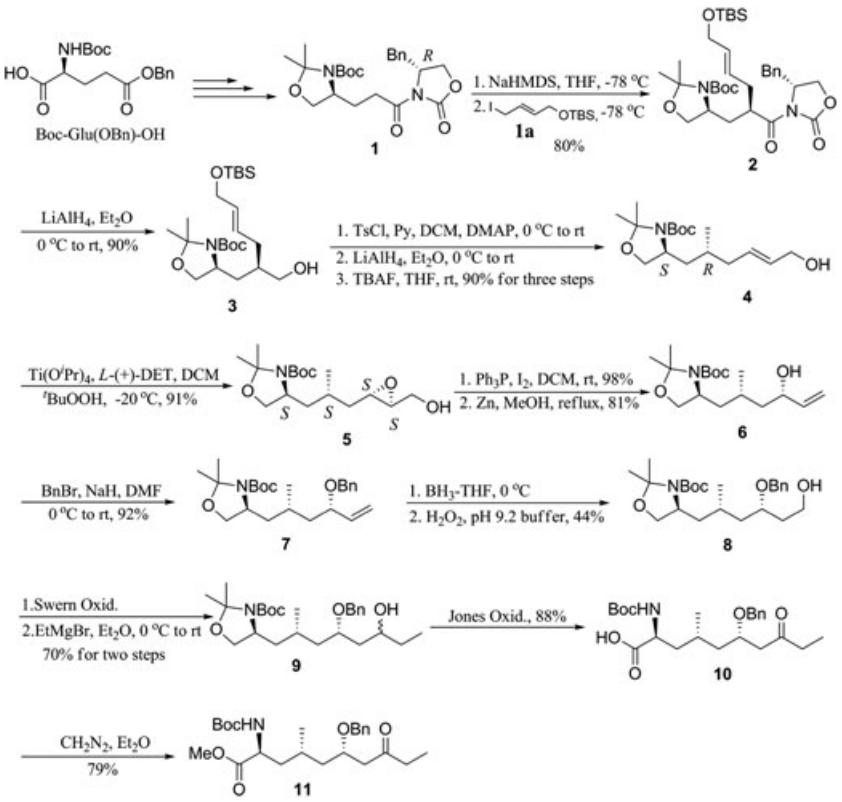
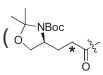


Scheme 1. Stereoselective synthesis of fully protected (2*S*,4*S*,6*S*)-AHMOD. Boc, *tert*-butoxycarbonyl; Bn, benzyl; NaHMDS, sodium bis(trimethylsilyl)amide; TBS, *tert*-butyldimethylsilyl; TsCl, *p*-toluenesulfonyl chloride; DMAP, 4-dimethylaminopyridine; TBAF, tetrabutylammonium fluoride; DET, diethyl tartrate.

(brm, 1H, ), 3.96 (dd, $J = 9.0$, 5.7 Hz, 1H, ), 4.15–4.23 (m, 2H, oxazolidinone H-5), 4.68–4.72 (m, 1H, oxazolidinone H-4), 7.22–7.35 (m, 5H, Ar H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 24.3 (), 27.7 (), 28.1 (), 28.4 ((CH_3)$_3$COC=O), 31.9 (), 38.1 (PhCH_2), 55.3 (oxazolidinone C-4), 56.0 (), 66.3 (oxazolidinone C-5), 67.3 (), 80.1 ((CH$_3$)$_3$COC=O), 93.5 (), 127.2 (Ar CH), 128.9 (Ar CH), 129.4 (Ar CH), 135.5 (Ar C), 152.7 (C=O), 153.7 (C=O), 172.6 (C=O); HRESIMS calcd for $C_{23}H_{32}N_2O_6Na$ 455.2153 $[M + Na]^+$, found 455.2116.

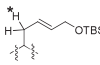
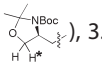
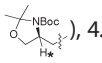
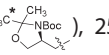
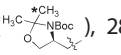
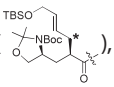
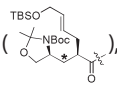
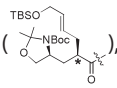
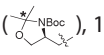
(*E*)-1-Iodo-4-(*tert*-butyldimethylsilyloxy)-2-butene (**1a**)

Sodium hydride (60% dispersion in mineral oil, 2.88 g, 72.0 mmol) was added in portions to a solution of (*E*)-2-butene-1,4-diol [33] (5.29 g, 60.0 mmol) in 70 ml of anhydrous THF at 0 °C. The mixture was stirred at 0 °C for 1 h, followed by dropwise addition of TBSCl (9.05 g, 60.0 mmol) in 50 ml of THF. The reaction was stirred at 0 °C for 1 h and then warmed to room temperature for another 2 h. The reaction was quenched carefully with crushed ice, diluted with 300 ml of Et_2O, and washed with saturated $NaHCO_3$ and brine, respectively. The organic phase was dried over Na_2SO_4, concentrated *in vacuo* and purified by flash column chromatography, giving the monoprotected silyl ether (10.44 g, 86%) as a colorless oil: ^{1}H NMR (DMSO-d_6, 600 MHz) δ 0.039 (s, 6H, (CH_3)$_3$CSi(CH_3)$_2$), 0.87 (s, 9H, (CH_3)$_3$CSi(CH$_3$)$_2$), 3.92–3.93 (m, 2H, H-1), 4.12 (d, $J = 4.2$ Hz, H-4), 4.69 (t, $J = 5.7$ Hz, 1H, OH), 5.66 (dt, $J = 15.6$, 4.6 Hz, 1H, C*H*=CH), 5.72 (dt, $J = 15.5$, 4.6 Hz, 1H, CH=C*H*); ^{13}C NMR (DMSO-d_6, 150 MHz) δ −5.3 (Me$_2$SiC(CH$_3$)$_3$), 17.9 (Me$_2$SiC(CH$_3$)$_3$), 25.8 (Me$_2$SiC(CH_3)$_3$), 60.8 (C-4), 62.6 (C-1), 128.4 (C*H*=CH), 130.3 (CH=C*H*).

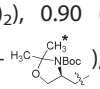
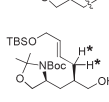
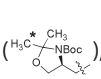
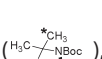
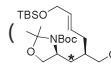
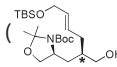
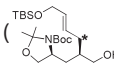
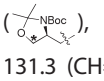
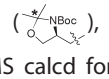
To a stirred solution of the mono protected silyl ether obtained above (9.78 g, 48.3 mmol) in DCM (250 ml) at 0 °C were added imidazole (8.22 g, 120.7 mmol), Ph_3P (16.47 g, 62.8 mmol), and iodine (13.50 g, 53.2 mmol), respectively. After being stirred at 0 °C for 1 h, the reaction was quenched with 10% $Na_2S_2O_3$ (100 ml) and concentrated at low temperature. The residue was extracted with petroleum ether for three times. The extracts were combined, washed with 10% $Na_2S_2O_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (100% petroleum ether) to give iodide **1a** (9.80 g, 65%) as a pale yellow oil [R_f 0.69 (10 : 1, petroleum ether/EtOAc)]. This compound was unstable at room temperature and was used immediately for the next step.

(*S*)-*tert*-Butyl 4-((*R*,*E*)-2-((*R*)-4-benzyl-2-oxooxazolidine-3-carbonyl)-6-(*tert*-butyldimethylsilyloxy)hex-4-enyl)-2,2-dimethyloxazolidine-3-carboxylate (compound **2**)

To a solution of oxazolidinone **1** (8.65 g, 20.0 mmol) in anhydrous THF (80 ml) at −78 °C was added sodium bis(trimethylsilyl)amide (2.0 M in THF, 10.0 ml, 20.0 mmol) via syringe. After stirring for 30 min at that temperature, iodide **1a** (9.80 g, 31.4 mmol) in 20 ml of THF was added slowly via syringe. The mixture was stirred in the dark at −78 °C for 6 h, then quenched with saturated NH_4Cl and warmed to room temperature. The mixture was diluted with Et_2O (300 ml) and washed with 10% $Na_2S_2O_3$ and brine. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography providing

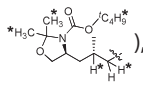
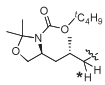
9.87 g (80%) of compound **2** as a colorless oil: $[\alpha]_D^{20} = -6.2$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 0.05 (s, 6H, $(CH_3)_2SiC(CH_3)_3$), 0.89 (s, 9H, $(CH_3)_2SiC(CH_3)_3$), 1.42 (s, 9H, $(CH_3)_3COC=O$), 1.45 (s, 3H, ), 1.51 (s, 3H, ), 1.73–1.78 (m, 1H, ), 1.93–1.97 (m, 1H, ), 2.25–2.30 (m, 1H, ), 2.48–2.51 (m, 1H, ), 2.75 (dd, $J = 13.2$, 10.2 Hz, 1H, PhCHaHb), 3.26 (dd, $J = 13.5$, 3.3 Hz, 1H, PhCHaHb), 3.59–3.63 (m, 1H, ), 3.66 (d, $J = 9.0$ Hz, 1H, ), 3.91 (dd, $J = 8.7$, 5.7 Hz, 1H, ), 4.03–4.06 (m, 1H, ), 4.10–4.14 (m, 3H, oxazolidinone H-5a + CH_2OTBS), 4.27 (t, $J = 8.4$ Hz, 1H, oxazolidinone H-5b), 4.77–4.80 (m, 1H, oxazolidinone H-4), 5.62–5.67 (m, 2H, ), 7.22–7.25 (m, 2H, Ar H), 7.31–7.34 (m, 3H, Ar H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ −5.2 ($(CH_3)_3CSi(CH_3)_2$), 18.4 ($Me_2SiC(CH_3)_3$), 24.4 (), 25.9 ($Me_2SiC(CH_3)_3$), 28.2 (), 28.4 ($(CH_3)_3COC=O$), 35.4 (), 35.7 (), 38.7 ($PhCH_2$), 39.7 (), 54.8 (), 55.4 (oxazolidinone C-4), 63.6 (CH_2OTBS), 66.3 (oxazolidinone C-5), 68.4 (), 80.1 ($(CH_3)_3COC=O$), 93.6 (), 126.9 (Ar CH), 127.1 (CH=CH), 128.8 (Ar CH), 129.4 (Ar CH), 132.4 (CH=CH), 135.8 (Ar C), 153.3 (C=O), 153.4 (C=O), 175.1 (C=O); HRESIMS calcd for $C_{33}H_{52}N_2O_7NaSi$ 639.3442 $[M + Na]^+$, found 639.3452.

(S)-tert-Butyl 4-((*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-2-(hydroxymethyl)hex-4-enyl)-2,2-dimethyloxazolidine-3-carboxylate (compound **3**)

$LiAlH_4$ (1.14 g, 30 mmol) was added in small portions to a solution of oxazolidinone **2** (6.17 g, 10 mmol) in Et_2O (100 ml) at 0 °C. The reaction mixture was stirred for 3 h at room temperature and quenched by dropwise addition of iced 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 (1 : 3) to give alcohol **3** as a colorless oil (4.00 g, 90%): $[\alpha]_D^{20} = 51.4$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 0.062 (s, 6H, $^tBuSi(CH_3)_2$), 0.90 (s, 9H, $^tBuSi(CH_3)_2$), 1.48 (brs, 12H, $(CH_3)_3COC=O$ + ), 1.54 (s, 3H, ), 1.60–1.86 (brm, 3H, ), 1.99–2.21 (m, 2H, ), 3.39–3.57 (m, 2H, CH_2OH), 3.65–3.76 (m, 1H, ), 3.88–4.20 (brm, 1H, ), 3.94 (dd, $J = 8.4$, 5.4 Hz, 1H, ), 4.12 (d, $J = 4.2$ Hz, 2H, CH_2OTBS), 5.58–5.62 (brm, 2H, CH=CH); ^{13}C NMR ($CDCl_3$, 150 MHz) δ −5.2 ($(CH_3)_3CSi(CH_3)_2$), 18.4 ($Me_2SiC(CH_3)_3$), 24.5 (), 25.9 ($Me_2SiC(CH_3)_3$), 27.7 (), 28.4 ($(CH_3)_3COC=O$), 34.3 (), 36.4 (), 37.7 (), 55.2 (), 63.6 (CH_2OTBS), 66.5 (CH_2OH), 68.3 (), 80.5 ($(CH_3)_3COC=O$), 93.3 (), 128.5 (CH=CH), 131.3 (CH=CH), 153.0 (C=O); HRESIMS calcd for $C_{23}H_{45}NO_5NaSi$ 466.2965 $[M + Na]^+$, found 466.2953.

(S)-tert-Butyl 4-((*R*,*E*)-6-hydroxy-2-methylhex-4-enyl)-2,2-dimethyloxazolidine-3-carboxylate (allylic alcohol **4**)

Triethylamine (TEA) (4.2 ml, 30.0 mmol) was added to a solution of **3** (4.44 g, 10.0 mmol) in DCM (100 ml) at 0 °C. TsCl (3.81 g, 20.0 mmol) and 4-dimethylaminopyridine (244 mg, 2.0 mmol) were then added at the same temperature and stirred overnight. The mixture was diluted with DCM (100 ml) and then washed with 1 M HCl, water, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo*, giving the crude tosylate. This intermediate was used for the next step without further purification.

$LiAlH_4$ (1.14 g, 30.0 mmol) was added in small portions to a solution of the crude tosylate obtained above in Et_2O (100 ml) at 0 °C. The reaction mixture was stirred for 3 h at room temperature. TLCs showed that the starting material was completely consumed. Partly cleavage of the TBS ether was also observed at the same time. The reaction was 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 then dissolved in 20 ml of THF, followed by the addition of TBAF (1.0 M in THF, 10 ml, 10.0 mmol). The reaction was stirred at room temperature for another 2 h and quenched with saturated NH_4Cl. The mixture was diluted with EtOAc (150 ml), washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The oily residue was purified by flash silica gel chromatography, eluting with EtOAc/petroleum ether (1 : 3) to give allylic alcohol **4** as a colorless oil (2.82 g, 90% for three steps): $[\alpha]_D^{20} = 5.1$ (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 0.97 (d, $J = 6.6$ Hz, 3H, CH_3CH), 1.31–1.36 (m, 1H, ), 1.45–1.59 (brm, overlapped, total 17H, ), 1.77–1.86 (m, 1H, ), 2.04–2.07 (m, 1H, ), 3.72–3.96 (brm, overlapped, total 3H, ), 4.08–4.10 (m, 2H, CH_2OH), 5.66–5.76 (m, 2H, CH=CH); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.3 (CH_3CH), 24.5 (), 27.7 (), 28.4 ($(CH_3)_3COC=O$), 30.2 (CH_3CH), 38.5 (), 38.6 (), 56.2 (), 63.9 (), 66.6 (), 80.2 ($(CH_3)_3COC=O$), 93.0 (), 130.5 (CH=CH), 131.4 (CH=CH),

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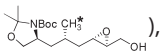
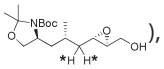
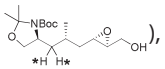
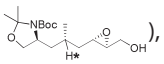
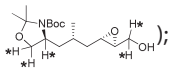
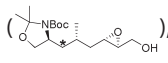
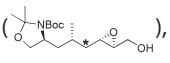
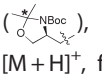
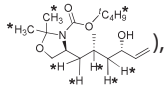
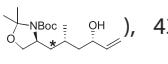
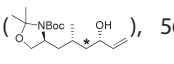
152.0 (C=O); HRESIMS calcd for $C_{17}H_{31}NO_4Na$ 336.2151 $[M+Na]^+$, found 336.2136.

(S)-tert-Butyl 4-((*S*)-3-((2*S*,3*S*)-3-(hydroxymethyl)oxiran-2-yl)-2-methylpropyl)-2,2-dimethyloxazolidine-3-carboxylate (epoxy alcohol **5**)

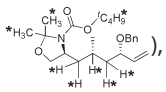
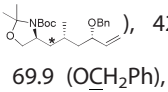
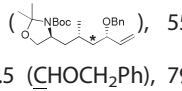
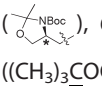
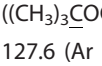
Activated 4 Å molecular sieves powder (~2 g) was added to 100 ml of dry DCM and cooled to −20 °C. Fifteen minutes later, 0.6 ml (2.0 mmol) of $Ti(O^iPr)_4$ was added, followed by the addition of L-(+)-diethyltartrate (600 mg, 2.9 mmol, in 5 ml of DCM) via syringe. The mixture was stirred for 15 min before *tert*-butyl hydroperoxide was added (7.67 M in DCM, 61.4 mmol, 8.0 ml). Thirty minutes later, allylic alcohol **4** (7.84 g, 25.0 mmol) in 50 ml of DCM was added dropwise via syringe. The mixture was allowed to stir at −20 °C for 30 h. When TLCs showed that all of the allylic alcohol **4** was consumed, the mixture was treated with 10 ml of 30% NaOH and then warmed to room temperature. The suspension was filtered through a pad of celite. The filtered liquid was treated with citric acid–ferrous sulfate solution. After stirring at room temperature for 30 min, the mixture was extracted with DCM for three times. The combined organic layers were washed with 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 : 5 → 1 : 1) to give epoxy alcohol **5** as a colorless oil (7.50 g, 91%): $[\alpha]_D^{20} = 10.6$ (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 1.04 (d, $J = 6.6$ Hz, 3H, ), 1.37 (brm, 2H, ), 1.48 (brs, 12H, Boc + CH_3), 1.54 and 1.42 (s, total 3H, CH_3), 1.65–1.67 (m, 2H, ), 1.83 (brm, 1H, ), 2.87–2.91 (m, 1H, epoxy H), 3.00 (brm, 1H, epoxy H), 3.64–3.96 (brm, overlapped, 5H, ); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.7 ($\underline{C}H_3CH$), 24.5 (), 27.7 (), 28.4 (($\underline{C}H_3)_3COC$=O), 29.5 ($CH_3\underline{C}H$), 38.6 (), 40.3 (), 55.3 (epoxy C), 56.6 (), 58.3 (epoxy C), 61.8 ($\underline{C}H_2OH$), 67.3 (), 80.2 (($CH_3)_3\underline{C}OC$=O), 93.1 (), 152.3 (C=O). HRESIMS calcd for $C_{17}H_{32}NO_5$ 330.2281 $[M+H]^+$, found 330.2288.

(S)-tert-Butyl 4-((2*S*,4*S*)-4-hydroxy-2-methylhex-5-enyl)-2,2-dimethyloxazolidine-3-carboxylate (compound **6**)

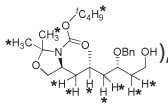
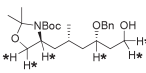
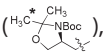
Ph_3P (4.04 g, 15.4 mmol) was dissolved in DCM (100 ml) and cooled to 0 °C. Imidazole (1.62 g, 23.8 mmol) and iodine (3.92 g, 15.4 mmol) were added to the mixture, respectively. Ten minutes later, epoxy alcohol **5** (3.91 g, 11.9 mmol) in 30 ml of DCM was added. The mixture was then allowed to be stirred in the dark at 0 °C for 2 h, diluted with Et_2O, washed with 20% $Na_2S_2O_3$ and brine, and concentrated *in vacuo*. The oily residue was purified by flash silica gel chromatography, eluting with EtOAc/petroleum ether (1 : 5) to give corresponding iodide (5.15 g, 98%) as pale yellow oil: ^1H NMR ($CDCl_3$, 600 MHz) δ 1.04 (d, $J = 6.6$ Hz, 3H), 1.04 (brm, 2H), 1.48 (brs, 12H), 1.54 and 1.42 (s, total 3H), 1.65–1.67 (m, 2H), 1.83 (brm, 1H), 2.87–2.91 (m, 1H), 3.00 (brm, 1H), 3.64–3.96 (brm, overlapped, 5H).

The iodide (1.33 g, 3.0 mmol) obtained above was dissolved in 50 ml of methanol, followed by the addition of zinc dust (1.97 g, 30 mmol). The suspension was refluxed for 2 h and then cooled to room temperature, filtered through a pad of celite, and washed with EtOAc. After concentration, the residue was redissolved in EtOAc (80 ml), washed with 20% $Na_2S_2O_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The oily residue was purified by flash silica gel chromatography, eluting with EtOAc/petroleum ether (1 : 3) to give alcohol **6** (765 mg, 81%) as a colorless oil: $[\alpha]_D^{20} = 16.5$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 0.98 (br, 3H, $\underline{C}H_3CH$), 1.37–1.85 (brm, overlapped, total 20H, ), 3.71 (d, $J = 7.8$ Hz, 1H, ), 3.83 (brm, 1H, ), 3.92–3.95 (m, 1H, ), 4.18–4.24 (m, 1H, $\underline{C}HOH$), 5.07–5.13 (m, 1H, $CH=CH_2$), 5.23 (d, $J = 17.4$ Hz, 1H, $CH=CH_2$), 5.78–5.87 (m, 1H, $CH=CH_2$); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.3 ($\underline{C}H_3CH$), 23.2 ($CH_3\underline{C}H$), 26.9 (), 27.8 (), 28.4 (($\underline{C}H_3)_3COC$=O), 40.3 (), 43.2 (), 56.2 (), 67.6 (), 71.8 ($\underline{C}HOH$), 80.1 (($CH_3)_3\underline{C}OC$=O), 93.1 (), 114.2 ($CH=\underline{C}H_2$), 141.0 ($\underline{C}H=CH_2$), 152.3 (C=O); HRESIMS calcd for $C_{17}H_{32}NO_4$ 314.2331 $[M+H]^+$, found 314.2344.

(S)-tert-Butyl 4-((2*S*,4*S*)-4-(benzyloxy)-2-methylhex-5-enyl)-2,2-dimethyloxazolidine-3-carboxylate (compound **7**)

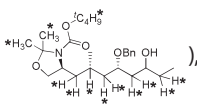
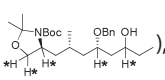
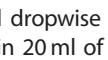
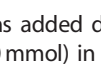
To a stirred solution of alcohol **6** (3.77 g, 12 mmol) in 50 ml of DMF at 0 °C was added NaH (60% dispersion in mineral oil, 960 mg, 24 mmol) in portions. The mixture was stirred at 0 °C for 30 min and another 30 min at room temperature. After that, the mixture was re-cooled to 0 °C, followed by the addition of BnBr (3.6 ml, 30 mmol). The reaction was stirred at 0 °C for 30 min and then warmed to room temperature. One hour later, the reaction was quenched by addition of crushed ice and diluted with Et_2O (400 ml). The mixture was washed with water and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography, giving compound **7** (4.45 g, 92%) as a colorless oil: $[\alpha]_D^{20} = 11.1$ (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 0.94 (d, $J = 5.4$ Hz, 3H, $\underline{C}H_3CH$), 1.46–1.78 (brm, overlapped, total 20 H, ), 3.66 (d, $J = 8.4$ Hz, 1H, ), 3.80–3.96 (brm, overlapped, total 3H,  + $\underline{C}HOBn$), 4.34 (d, $J = 11.4$ Hz, 1H, $PhC\underline{H}aHb$), 4.58 (d, $J = 11.4$ Hz, 1H, $PhCHa\underline{H}b$), 5.21–5.26 (m, 2H, $CH=\underline{C}H_2$), 5.64–5.71 (m, 1H, $\underline{C}H=CH_2$), 7.28–7.38 (m, 5H, Ar H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.3 ($\underline{C}H_3CH$), 23.2 ($CH_3\underline{C}H$), 27.0 (), 27.2 (), 28.6 (($\underline{C}H_3)_3COC$=O), 41.0 (), 42.0 (), 55.6 (), 67.6 (), 69.9 ($O\underline{C}H_2Ph$), 79.5 ($\underline{C}HOCH_2Ph$), 79.7 (($CH_3)_3\underline{C}OC$=O), 93.5 (), 117.7 ($CH=\underline{C}H_2$), 127.4 (Ar $\underline{C}H$), 127.6 (Ar $\underline{C}H$), 128.3 (Ar $\underline{C}H$), 138.6 (Ar C), 138.8($\underline{C}H=CH_2$), 151.7 (C=O); HRESIMS calcd for $C_{24}H_{37}NO_4Na$ 426.2620 $[M+Na]^+$, found 426.2633.

(S)-tert-Butyl 4-((2*S*,4*S*)-4-(benzyloxy)-6-hydroxy-2-methylhexyl)-2,2-dimethyloxazolidine-3-carboxylate (compound **8**)

BH_3-THF (1.0 M in THF, 20 ml, 20 mmol) was added dropwise to a stirred solution of compound **7** (4.04 g, 10 mmol) in 20 ml of THF at 0 °C. After the reaction mixture had been stirred at room temperature for 2 h, phosphate buffer solution (pH = 9.2) was added until the pH was 9.0. Then 15 ml of H_2O_2 (30%) was added, and the mixture was stirred at room temperature overnight. The reaction mixture was extracted with EtOAc. The combined organic phase was washed with saturated $Na_2S_2O_3$ and brine, dried over Na_2SO_4, and concentrated. Flash chromatography (EtOAc : petroleum ether = 1 : 4 → 1 : 2) gave primary alcohol **8** (1.87 g, 44%) as a colorless oil: $[\alpha]_D^{20} = 39.1$ (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.95 (d, J = 6.6 Hz, 3H, CH_3CH), 1.45–1.85 (brm, overlapped, 22H, ), 3.66–3.89 (brm, 6H, ), 4.48 (d, J = 11.4 Hz, 1H, PhCHaHb), 4.59 (d, J = 11.4 Hz, 1H, PhCHaHb), 7.28–7.34 (m, 5H, Ar H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.5 (CH_3CH), 23.2 (CH_3CH), 27.0 (), 27.5 (), 28.4 ((CH_3)$_3$COC=O), 36.0 ($CHCH_2CH$), 40.7 ($CHCH_2CH$), 42.4 ($CHCH_2CH$), 55.6 (), 60.5 (CH_2OH), 67.5 (), 70.7 (OCH_2Ph), 76.5 ($CHOCH_2Ph$), 80.0 ((CH_3)$_3$COC=O), 93.6 (), 127.8 (Ar CH), 128.0 (Ar CH), 128.5 (Ar CH), 138.4 (Ar C), 152.1 (C=O); HRESIMS calcd for $C_{24}H_{39}NO_5Na$ 444.2726 $[M + Na]^+$, found 444.2743.

(S)-tert-Butyl 4-((2*S*,4*S*)-4-(benzyloxy)-6-hydroxy-2-methyloctyl)-2,2-dimethyloxazolidine-3-carboxylate (compound **9**)

A solution of DMSO (1.1 ml, 15.6 mmol) in DCM (10 ml) was added dropwise to a stirred solution of $(COCl)_2$ (660 µl, 7.8 mmol) in DCM (90 ml) at −78 °C. Twenty minutes later, a solution of the primary alcohol **8** (1.63 g, 3.9 mmol) in 15 ml of DCM was added dropwise via syringe. The mixture was stirred for 2 h, and then TEA (3.0 ml, 21.6 mmol) was added. The reaction mixture was stirred at −78 °C for 15 min and then warmed to room temperature. The mixture was diluted with 80 ml of 10% $NaHSO_4$ solution and then extracted with Et_2O. The combined organic layers were washed with water and brine and concentrated to give the crude aldehyde, which was used for the next steps without further purification.

To the solution of the aldehyde obtained above in dry Et_2O (20 ml) at 0 °C was added ethylmagnesium bromide (3.0 M in Et_2O, 2.6 ml, 7.8 mmol). The mixture was stirred at 0 °C for 30 min and then at room temperature for 1 h. The reaction was quenched by the addition of saturated NH_4Cl solution and diluted with Et_2O. After washing with brine and drying over Na_2SO_4, the ether layer was concentrated. Flash chromatography gave compound **9** (1.22 g, 70% for two steps) as a colorless oil: $[\alpha]_D^{20} = 12.7$ (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.92 (t, J = 7.5 Hz, 3H, CH_3CH_2), 0.95 (d, J = 6.6 Hz, 3H, CH_3CH), 1.37–1.80 (brm, overlapped, 24H, ), 3.65–3.97 (brm, overlapped, 5H, ), 4.44–4.64 (m, 2H, $PhCH_2O$), 7.29–7.35 (m, 5H, Ar H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 10.1 (CH_2CH_3), 21.0 (CH_3CH), 23.2 (CH_3CH), 24.5 (), 27.7 (), 28.4 ((CH_3)$_3$COC=O), 30.4 (CH_2CH_3), 38.8 (), 39.7 (), 42.4 (), 55.6 (), 67.2 ($CHOH$), 67.5 (), 69.8 ($CHOBn$), 70.9 ($PhCH_2O$), 79.6 ((CH_3)$_3$COC=O), 93.6 (), 127.9 (Ar CH), 128.1 (Ar CH), 128.4 (Ar CH), 138.1 (Ar C), 151.6 (C=O); HRESIMS calcd for $C_{26}H_{44}NO_5$ 450.3220 $[M + H]^+$, found 450.3237.

(2*S*,4*S*,6*S*)-Methyl 6-(benzyloxy)-2-(*tert*-butoxycarbonylamino)-4-methyl-8-oxodecanoate (compound **11**)

Freshly prepared Jones reagent (~2.67 M, 3.6 ml, 9.6 mmol) was added at 0 °C to a solution of compound **9** (1.10 g, 2.4 mmol) in 25 ml of acetone. The reaction mixture was stirred at 0 °C for 2 h and then stirred 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 over Na_2SO_4, and concentrated to give the crude carboxylic acid **10** (890 mg, 88%), which was used for the next step directly.

The crude acid obtained above was treated with 2 eq. of diazomethane in Et_2O for 30 min. A few drops of HOAc were added carefully when TLCs showed that all of the acid was consumed. The reaction mixture was diluted with Et_2O, washed with water, 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 **11** (727 mg, 79%) as a colorless oil: $[\alpha]_D^{20} = 55.2$ (*c* 0.07, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.96 (d, J = 6.6 Hz, 3H, 4-CH_3), 1.05 (t, J = 7.2 Hz, 3H, H-10), 1.33–1.38 (m, 1H, H-5a), 1.44 (s, 9H, Boc), 1.49–1.58 (m, 3H, H-5b + H-3), 1.68–1.74 (m, 1H, H-4), 2.449 (q, J = 7.2 Hz, 1H, H-9a), 2.453 (q, J = 7.2 Hz, 1H, H-9b), 2.49 (dd, J = 15.6, 5.4 Hz, 1H, H-7a), 2.75 (dd, J = 16.2, 6.6 Hz, 1H, H-7b), 3.71 (s, 3H, CO_2CH_3), 3.98 (quintet, J = 6.2 Hz, 1H, H-6), 4.30 (dt, J = 9.6, 3.8 Hz, 1H, H-2), 4.45 (d, J = 11.4 Hz, 1H, PhCHaHbO), 4.50 (d, J = 11.4 Hz, 1H, PhCHaHbO), 4.74 (d, J = 9.0 Hz, 1H, NH), 7.29–7.37 (m, 5H, Ar H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 7.6 (C-10), 19.6 (4-Me), 26.1 (C-4), 28.3 ((CH_3)$_3$COC=O), 37.3 (C-9), 39.3 (C-3), 42.6 (C-5), 47.4 (C-7), 51.5 (C-2), 52.2 (CO_2CH_3), 71.4 ($PhCH_2O$), 73.2 (C-6), 79.8 ((CH_3)$_3$COC=O), 127.8 (Ar CH), 128.0 (Ar CH), 128.4 (Ar CH), 138.2 (Ar C), 155.6 ((CH_3)$_3$COC=O), 173.8 (C-1), 210.2 (C-8); HRESIMS calcd for $C_{24}H_{37}NO_6Na$ 458.2519 $[M + Na]^+$, found 458.2535.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (81001392), the Fundamental Research Funds for the Central Universities (10FX070), and the School of Pharmacy, Fudan University.

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