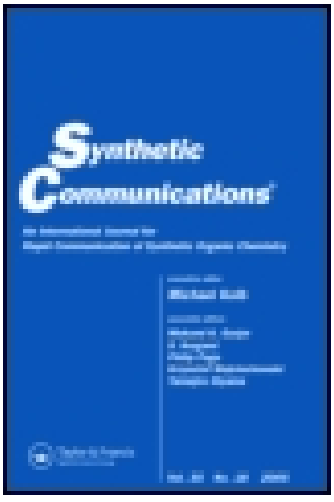

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Synthesis of β-Secretase Inhibitors Containing a Hydroxyethylene Dipeptide Isostere

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Synthesis of β-Secretase Inhibitors Containing a Hydroxyethylene Dipeptide Isostere

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Abstract: β-Secretase inhibitors with a Leu*Ala hydroxyethylene dipeptide (HED) isostere have been an especially interesting topic in recent years. In this study, a template compound **17** was synthesized, featuring truncation at the P_2' position and changes at P_2 and P_3, which differs from other reported potent inhibitors. The purpose was to explore optimal reaction conditions and construct an inhibitor library to investigate ideal protein–substrate interaction.

Keywords: hydroxyethylene dipeptide isostere, peptidomimetics, β-secretase, synthesis

INTRODUCTION

β-Amyloid plaques, a primary pathological characteristic of Alzheimer's disease, are generated through a sequential hydrolysis of APP (amyloid precursor protein), catalyzed by two proteases, β-secretase and γ-secretase. During this process, the hydrolysis via β-secretase was well known to be upstream to the cleavage induced by γ-secretase.[1,2] The inhibition of β-secretase is believed to be a desirable approach to preventing the formation of β-amyloid. Up to now, a great number of β-secretase inhibitors

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have been designed and synthesized, based on various transition-state analogs, such as hydroxyethylene dipeptide (HED),[3] HEA (hydroxyethylamine dipeptide),[4] statine,[5] and the like, of which the Leu*Ala hydroxyethylene dipeptide isostere was the most successful. Two potent inhibitors OM99-2 (EVNL*AAEF, $K_i = 1.4$ nM) and OM00-3 (ELDL*AVEF, $K_i = 0.3$ nM) were synthesized and reported first by Gosh et al. in 2001 and 2002.[3] Impenetration through the brain–blood barrier limited the compounds' further application in vivo because of the high molecular length and weight. Therefore, the emphasis was naturally directed to smaller molecular entities, which were shorter in length but retained their binding capability. The GT-1017 was a successful optimization, with a much shorter length and a K_i of 2.5 nM.[3]

In view of these facts, a template peptidomimetic compound (Fig. 1) in our project was designed and characterized by truncation of the P_2' side chain and variations at the P_2 and P_3 positions. The purpose was to maintain the interaction with β-secretase in the S_2 and S_3 pocket while removing the much weaker binding of the P_2' side chain. At the P_2 and P_3 positions, versatile structures were introduced, including non–amino acid scaffolds, especially P_3 capping. Considering the importance of Leu*Ala (L*A), our group followed the L*A modality in this work to detail the synthesis of such inhibitors and provide more information on the structural optimization and modification, which might accelerate finding of promising candidates.

RESULTS AND DISCUSSION

To common knowledge, the synthesis of HED has been published in more than 20 references over the past two decades,[6] and strategies include, the 3*S*,4*S*-γ-lactone strategy or using saccharides or other small molecules as a starting point. Because of a certain hindrance in the route described in Scheme 1, our group first adopted a relatively longer route to synthesize

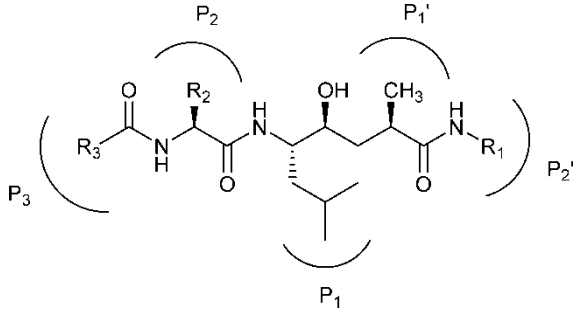
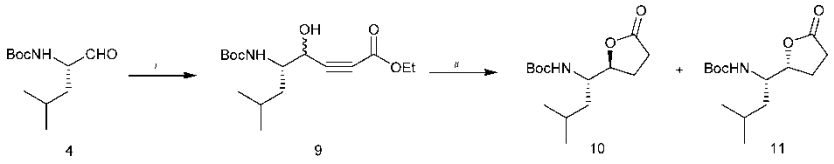


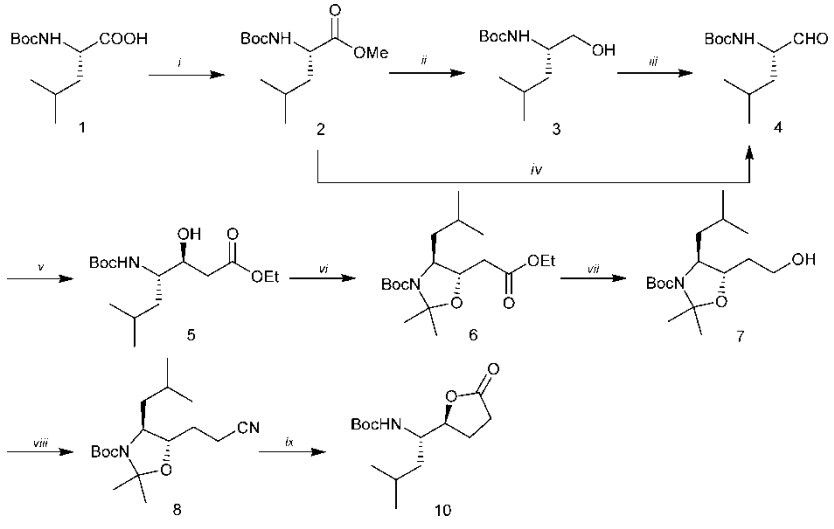
Figure 1. Template structure of target peptidomimetics.



Scheme 1. Reagents and conditions: (i) ethyl propiolate, LDA (n-BuLi and i-Pr_2NH, −23°C in THF, 1 h), −78°C, N_2, 4.5 h; and (ii) H_2/Pd, 60 psi, EtOAc, then reflux in toluene/acetic acid (97.5:2.5 v/v).

lactone **10** (Scheme 2).[7] All the amino acids used herein had an L configuration.

Boc-Leu-OH **1** was initially reacted with CH_3I to afford methyl ester **2**.[8] Then **2** was reduced by $NaBH_4$ to give Boc-Leucinal **3**, which was further oxidized by Py·SO_3 to furnish Boc-Leucinal **4**.[9] We also tried to reduce **2** to **4** in one step by diisobutylaluminum hydride (DIBAL) as reported[10]; however, the solvent toluene was hard to be completely remove from the reaction mixture, and **4** would readily undergo racemization during distillation under reduced pressure at a temperature of more than 30°C.[11] The Boc-Leucinal **4** was then treated with anhydrous EtOAc to



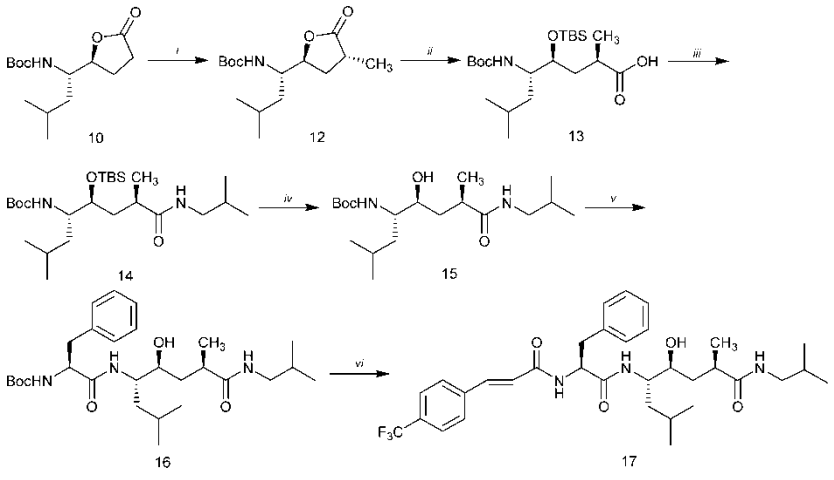
Scheme 2. Reagents and conditions: (i) $NaHCO_3$, CH_3I, DMF; (ii) $NaBH_4$, $CaCl_2$, THF/EtOH; (iii) Py·SO_3, TEA, DCM/DMSO; (iv) DIBAL, toluene, 0°C, 10 min; (v) n-BuLi, i-Pr_2NH, ethyl acetate, −78°C; (vi) 2-methoxy-propene, $POCl_3$, TEA, CH_2Cl_2; (vii) DIBAL, THF, 0°C; (viii) MsCl, TEA, CH_2Cl_2, then NaCN, DMSO, 50°C; and (ix) (1) H_2O_2, NaOH (1 N), ethanol, 0°C; (2) $Na_2S_2O_3$ (20%), −30°C; (3) water–acetic acid = 35:65, 3 days, reflux in toluene.

give the addition product *SS* hydroxyl ester **5** (less polar on thin-layer chromatography, TLC, according to Rich) and its diastereomer under the aid of lithium diisopropylamide (LDA).[10] However, because of lack of specificity, the 3*S*,4*S*- and 3*R*,4*S*-diastereomers were obtained in amounts that were not far from each other; therefore the low yield of the *SS* diastereomer rendered this reaction unfavorable en route to lactone **10**. Protection of **5** with 2-methoxy-propene allowed successful reduction of the ester group of **6** to alcohol **7** by DIBAL in a yield of 80%. The capillary holding the catalyst $POCl_3$ should be quickly dipped into the mixture before the liquid within turned brown (as a result of interaction of $POCl_3$ with 2-methoxy-propene vapor), which would otherwise result in unexpected side reactions and obstacles for isolation. Besides, to remove the DIBAL left after the reaction, Rochester salt (potassium sodium tartate, saturated in H_2O) should be added in excess and violently shaken with DIBAL for the complex to be formed, or else the reaction mixture would be extremely viscous and hard to extract. Then alcohol **7** was treated with MsCl to give the sulfonate, followed by further substitution by the CN group to generate nitrile **8**. The formation of 3*S*,4*S*-lactone **10** involved three consecutive steps: hydrolysis under NaOH with H_2O_2, removal of excessive H_2O_2 by $Na_2S_2O_3$, and deprotection followed by cyclization in benzene.[7] These three steps took more than 4 days to finish, and the overall yield was far from ideal, nearly the half of the procedure to be discussed in Scheme 1. C_4 of lactone **10** was identified as *S* configuration by lack of nuclear Overhauser effect (NOE) between protons of -NCH- and -OCH-.

Taking into account the unfavorable factors in Scheme 2, we made partial revisions and retried the route in Scheme 1 until it was put through. This approach was first reported by Fray et al. and modified by later researchers.[7] In this article, we documented several potential problems that were implicated (Scheme 1). Condensation of **4** with the lithium salt of ethyl propiolate, formed in situ by LDA (prepared via n-BuLi with diisopropylamine) with ethyl propiolate afforded hydroxyl acetylenic ester **9** as a stereo-mixture. During the nucleophilic addition, the lithium salt was found to be extremely sensitive to traces of O_2 and H_2O, which would turn the whole system almost black, probably resulting from its degradation or a succession of complex chain reactions, but it is interesting to note that sometimes the yields under such circumstances were a bit higher than that in normally treated reactions, up to approximately 47%. It remains to be determined whether these black substances played a positive or negative role in this step. Furthermore, because the aldehyde could be readily reduced by LDA,[12] sufficient time should be allowed for complete formation of the lithium salt of ethyl propiolate before **4** was added. Additionally, compound **9** was a light yellow solid after recrystallization in hexane, distinct from what has been reported in literature as an oil.[7] The structure of **9** ($mp = 72-74^{\circ}C$) was verified by ^1H NMR and MS. Subsequent reduction of ester **9** by H_2 on Pd/C at 60 psi and further lactonization in

toluene/acetic acid without separation of the reduced product gave lactone **10**, and the 3*R*,4*S*-diastereomer **11** was also obtained in a yield below 15%.

The methyl group was smoothly introduced at α-C of **10** in 80% yield using methyl iodide and lithium hexamethyldisilazide (LiHMDs, Scheme 3). On a larger scale, the reaction duration should be prolonged to 35–40 min instead of 30 min as reported,[3a] for exhaustion of the starting materials. However, longer duration would also in the meantime lead to a dimethylated product (a white crystal, determined by ^{1}H NMR and MS) in a small amount. The α-C of compound **12** was identified as *R* configuration on the basis of NOE between α-CH_3 and C_3-α-H, as well as nonexistence of NOE between -OCH- and α-CH-. Subsequent hydrolysis of 2*R*,4*S*,5*S*-lactone **12** gave the hydroxyl acid derivative, which was protected by *tert*-butyldimethylsilyl chloride (TBDMSCl) to furnish **13**, followed by coupling with diisobutylamine. The TBDMS group was then removed to afford hydroxyl amide **15** as an amorphous white solid, which proceeded from **16** to the model compound **17** through classic peptide condensation using *N*-Boc-L-Phenylalanine and then 3-(trifluoromethyl)cinnamic acid in turn. The reagents for condensation involved *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) or *N*,*N*′-dicyclohexylcarbodiimide (DCC), accompanied by 1-hydroxybenzotriazole (HOBt) and *N*,*N*′-diisopropyethylamine (DIPEA) or *N*-methylmorpholine (NMM) in THF or DMF at room temperature. The reaction duration varied along with different acids used.



Scheme 3. Reagents and conditions: (i) CH_3I, LiHMDS, −78°C; (1) LiOH (1 N), THF; (2) TBDMSCl, imidazole, DMF; (iii) isobutylamine, EDC, HOBt, DIPEA, DMF/CH_2Cl_2; (iv) n-$Bu_4N^+F^-$, THF; (v) N-Boc-L-phenylalanine, EDC, HOBt, NMM, DMF; and (vi) 3-(trifluoromethyl)cinnamic acid, EDC, HOBt, NMM, DMF.

CONCLUSION

A new series of potential peptidomimetic β-secretase inhibitors containing a Leu*Ala hydroxyethylene dipeptide isostere was designed, which is structurally altered at the P_2 side chain and P_3 capping, for further structure–activity relationship studies. In this work, compound **17** was selected as a model and synthesized first to build up a practically universal preparation method for the target molecules. Two synthetic pathways to compound **17** were performed, modified, and compared in reaction conditions, yields, and stereoselectivity. With these methods, a number of target compounds are being prepared and their bioactivity evaluation is under way.

EXPERIMENTAL

Unless otherwise mentioned, reagents were obtained commercially and used without further purification. The petroleum ether used had a boiling point range of 60–90°C. Melting points were taken with an X-4 apparatus and were uncorrected. IR (KBr), ^{1}H NMR, MS, element data, and optical rotations were taken with Perkin-Elmer 983, Inova-500, MDS SCIEX QSTAR, Flash EA 1112, and AA-10R Automatic Polarimeter instruments respectively.

(*S*)-Methyl 2-(*t*-boc-amino)-4-methylpentanoate (*N*-Boc-L-Leucine methyl ester) (2)

To a stirred solution of *N*-Boc-Leu-OH (30 g, 130 mmol) in DMF, 21.840 g (260 mmol) of $NaHCO_3$ and 13 mL (208 mmol) of CH_3I were successively added. After 48 h at room temperature, the reaction was quenched with H_2O (400 mL), and the mixture was extracted with ethyl acetate/benzene (1:1) (100 mL × 4). The organic layers were collected and washed with H_2O (100 mL × 2), 10% aqueous Na_2SO_3 (100 mL × 2), and saturated aqueous NaCl (100 mL) and dried over Na_2SO_4. Removal of ethyl acetate afforded 29.219 g (91.7%) of ester **2** as a colorless viscous oil and was used for the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.925 (d, 1H, BocNH-), 4.317 (m, 1H, N-CH-), 3.732 (s, 3H, -OCH_3), 1.688 (m, 1H, -CH-), 1.656–1.487 (m, 2H, -CH_2-), 1.444 (s, 9H, Boc), 0.959–0.929 (d, 6H, $J = 6.5$ Hz, 2CH_3-). MS (ESI): 246.20 (M^+).

(S)-2-(*t*-Boc-amino)-4-methylpentan-1-ol (*N*-Boc-L-Leucinol) (3)

At 0°C, 9.887 g (89.10 mmol) of $CaCl_2$ and 6.731 g (178.20 mmol) of $NaBH_4$ were successively put into a solution of 10.914 g (44.55 mmol) of ester **2** in ethanol/THF (80 mL/48 mL). The ice bath was removed after $NaBH_4$ was added. After 6 h, the mixture was poured into 250 mL of citric acid/ice,

followed by extraction with ethyl acetate (100 mL × 4), and was then washed with saturated aqueous $NaHCO_3$ (100 mL × 2) and NaCl (100 mL). The extracts were dried over $MgSO_4$, and removal of the solvent gave **3** as a colorless oil in 98% crude yield (9.495 g). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.560 (s, 1H, BocNH-), 3.719 (m, 1H, N-CH-), 3.677–3.489 (dd, 2H, $J = 6$ Hz and 11 Hz, -CH_2-O-), 2.326 (b-s, 1H, -OH), 1.668 (m, 1H, -CH-), 1.449 (s, 9H, Boc), 1.358–1.274 (m, 2H, -CH_2-), 0.942–0.924 (d, 6H, $J = 6.5$ Hz, 2CH_3-). MS (ESI): 218.20 (M^+).

(*S*)-2-(*t*-Boc-amino)-4-methylpentanal (*N*-Boc-L-Leucinal) (4)

Method A

N-Boc-L-Leucinol **3** (651 mg, 3 mmol) and 1.27 mL (9 mmol) of TEA were dissolved in 5 mL of CH_2Cl_2 and cooled to 0°C, to which a solution of 1.440 g (9 mmol) of Py·SO_3 in 5 mL of DMSO was added, followed by removal of the ice bath. After 35 min (prolonged accordingly on larger scales and monitored by TLC), the mixture turned light brown and was quenched with 25 mL of water/ice. Then the mixture was extracted with ether (30 mL × 3), which was washed successively with 10% citric acid (30 mL × 2), H_2O (30 mL × 2), saturated $NaHCO_3$ (30 mL), and brine (30 mL) and dried over $MgSO_4$ Crude aldehyde **4** (602 mg, 93%) was obtained after removal of the solvent (below 30°C), which was used for the next step without isolation. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.589 (s, 1H, -CHO), 5.047 (d, 1H, BocNH-), 4.251 (m, 1H, N-CH-), 1.449 (s, 9H, Boc), 0.979–0.919 (d, 6H, 2CH_3-).

Method B

At −78°C under a nitrogen atmosphere, were added 2.07 mL of DIBAL (2.5 mmol, 20 wt% in toluene) to a stirred solution of 245 mg (1 mmol) of ester **2** in 3 mL of dry toluene. After 10 min, the reaction was quenched with 1.5 mL of CH_3OH, followed by 10 mL of saturated aqueous Rochelle salt. The mixture was allowed to warm to room temperature, and 10 mL of ether was added. After violent shaking for 3 min, until the mixture turned transparent, the organic layer was separated. The aqueous layer was extracted with ether (10 mL × 3). The layers were combined and dried over $MgSO_4$. Crude aldehyde **4** (190 mg, 88%) was obtained under reduced pressure.

(3*S*,4*S*)-(*N*-Boc-4-amino)-3-hydroxy-6-methylheptanioc Acid Ethyl Ester (5)

At −23°C under a N_2 atmosphere, 8 mL (12.75 mmol, 1.6 M in THF) *n*-BuLi were added to a stirred solution of 2.16 mL (15.3 mmol)

diisopropylamine in 5 mL of anhydrous THF. After 1 h, the mixture was cooled to $-78^{\circ}C$ and for 30 min, followed by the addition of 1.20 mL anhydrous EtOAc in 1 mL of THF, which was then stirred for another 20 min. Then, 1.85 g of crude aldehyde **4** in 2 mL of THF was added, and the mixture was stirred for 40 min before 36 mL of HCl (in excess, 1N) were added. The mixture was warmed to room temperature and extracted with EtOAc (50 mL × 3). The extracts were washed with brine and dried over $MgSO_4$. After silica-gel column chromatography, 757 mg (29%) of 3*S*,4*S*-N-Boc-Leu-statine-OEt (oil, less polar), 404 mg (15%) of 3*R*,4*S*-diastereomer (white solid, mp: 48–50°C), and 274 mg of the mixture were obtained. ^{1}H NMR ($CDCl_3$, 500 MHz) for 3*S*,4*S*-diastereomer: δ 4.708 (d, 1H, $J = 9.5$ Hz, BocNH-), 4.172 (m, 2H, $J = 7$ Hz, -CO_2CH_2-), 4.018 (d, 1H, -CH-O), 3.617 (m, 1H, N-CH-), 3.276 (b-s, 1H, -OH), 2.468–2.571 (m, 2H, -CH_2CO_2-), 1.661 (m, 1H, -CH-), 1.527 (m, 1H, -CH_2-), 1.440 (s, 9H, Boc), 1.348 (m, 1H, -CH_2-), 1.274 (t, 3H, $J = 7$ Hz, -CO_2-C-CH_3),0.936 (d, 3H, $J = 1.5$ Hz, -CH_3), 0.922 (d, 3H, $J = 1$ Hz, -CH_3). MS (ESI): 304.27 (M^+). ^{1}H NMR ($CDCl_3$, 500 MHz) for 3*R*, 4*S*-diastereomer: δ 4.577 (d, 1H, $J = 8$ Hz, BocNH-), 4.170 (m, 2H, J= 7 Hz, -OCH_2-), 4.003 (m, 1H, -CH-O), 3.666 (m, 1H, N-CH-), 3.442 (b-s, 1H, -OH), 2.495–2.422 (m, 2H, -CH_2CO_2-), 1.669 (m, 1H, -CH-), 1.438 (s, 9H, Boc), 1.325 (t, 2H, -CH_2-), 1.271 (t, 3H, $J = 7.5$ Hz, -CO_2-C-CH_3), 0.934 (d, 3H, $J = 6.5$ Hz, -CH_3), 0.910 (d, 3H, $J = 6.5$ Hz, -CH_3). MS (ESI): 304.24 (M^+).

(4*S*,5*S*)-*N*-Boc-5-(carbethoxymethyl)-2,2-dimethyl-4-(2-methylpropyl)-1,3-oxazolidine (6)

3*S*,4*S*-*N*-Boc-Leu-Statine-OEt (977 mg, 3.23 mmol) and 1.30 mL (13 mmol) of 2-methoxy-propene were dissolved in 2 mL of CH_2Cl_2, to which was added a trace of phosphorous oxychloride using a capillary, dipping quickly into the mixture before $POCl_3$ turned brown. The mixture was allowed to react for 15 h, and 4 drops of Et_3N was added to remove $POCl_3$, which was concentrated under reduced pressure, followed by dilution with 25 mL of EtOAc. The mixture was washed with aqueous 10% citric acid (20 mL × 2), saturated aqueous $NaHCO_3$ (20 mL × 2), and brine (20 mL) and dried over $MgSO_4$. Silica-gel column chromatography gave 1.01 g (91%) of protected statine **6** as a light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.324 (b-s, 1H, -OCH-), 4.164 (m, 2H, $J = 7$ Hz, -CH_2-), 3.835–3.722 (m, 1H, -NCH-), 2.680–2.566 (m, 2H, -CH_2CO_2-), 1.602 (m, 1H, -CH-), 1.511 (s, 6H, 2CH_3-), 1.499 (s, 1H, -CH_2-), 1.484 (s, 9H, Boc), 1.441 (s, 1H, -CH_2-), 1.273 (t, 3H, $J = 7$ Hz, -CH_3), 0.946 (d, 3H, $J = 6.5$ Hz, -CH_3), 0.925 (d, 3H, $J = 6.5$ Hz, -CH_3). MS (FAB): 344.30 (M^+).

(4*S*,5*S*)-*N*-Boc-2,2-dimethyl-5-(2-hydroxyethyl)-4-(2-methylpropyl)-1,3-oxazolidine (7)

To a stirred solution of 1.01 g (2.94 mmol) of ester **6** in 3 mL of THF, 6.18 mL (7.37 mmol) of DIBAL were added at 0°C. After 45 min, the reaction was quenched by pouring onto ice, which was then diluted with 50 mL of ether. The mixture was warmed to 30°C, and 50 mL of saturated aqueous Rochester salt was added, which was shaken violently to remove excessive aluminum in the system. After both the organic and aqueous layers turned clear, the upper layer was separated and subjected to silica-gel column chromatography to furnish 802 mg (91%) of **7** as a light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.910–3.809 (m, 3H, -OCH-, -CH_2O-), 3.614 (m, 1H, -NCH-), 3.000–2.500 (b-s, 1H, -OH), 2.192–2.164 (m, 2H, -CH_2-C-O-), 1.826–1.791 (m, 1H, -CH-), 1.687–1.604 (m, 2H, -CH_2-), 1.482 (s, 6H, 2CH_3-), 1.445 (s, 9H, Boc), 0.937–0.910 (d, 6H, $J = 6.5$ Hz, 2CH_3-). MS (FAB): 302.4 (M^+).

(4*S*,5*S*)-*N*-Boc-5-(2-cyanoethyl)-2,2-dimethyl-4-(2-methylpropyl)-1,3-oxazolidine (8)

At 0°C, 0.31 mL (4.00 mmol) of MsCl was added to a solution of 802 mg (2.66 mmol) of alcohol **7** and 0.56 mL (3.88 mmol) Et_3N in 4 mL of CH_2Cl_2. After 2.5 h, the mixture was washed successively with aqueous 10% citric acid (10 mL × 2), saturated aqueous $NaHCO_3$ (10 mL × 2), and brine (10 mL). The organic layer was dried over $MgSO_4$ and evaporated to 846 mg of mesylate as a yellow oil, which was used for the next step without further purification. Then the residue was dissolved in 8 mL of DMSO and treated with 150 mg of NaCN (3.06 mmol). The reaction was allowed to proceed at 50°C for 10 h before another 150 mg of NaCN was added, which was allowed to react for an additional 10 h. The mixture was diluted with 25 mL of water and extracted with ether (25 mL × 4). The combined organic layer was washed with water (25 mL × 3) and dried over $MgSO_4$. Silica-gel purification afforded 588 mg (71%) of nitrile **8** as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.948–3.914 (m, 1H, -OCH-), 3.740–3.650 (m, 1H, -NCH-), 2.553–2.440 (m, 2H, -CH_2CN), 1.983–1.867 (m, 2H, -CH_2-C-CN), 1.581 (s, 6H, 2CH_3-), 1.604–1.440 (m, 3H, -CH-, -CH_2-), 1.481 (s, 9H, Boc), 0.955–0.942 (d, 6H, $J = 6.5$ Hz, 2CH_3-). IR (CH_3Cl): 2247.46, 1696.94 cm^{-1}. MS (ESI): 311.27 (M^+).

(4*RS*,5*S*)-*N*-Boc-5-amino-4-hydroxy-7-methyloct-2-ynoic Acid Ethyl Ester (9)

To a stirred solution of 17.60 mL (67.74 mmol) diisopropylamine in 40 mL of anhydrous THF, 35.52 mL (56.45 mmol, 1.6 M in THF) of *n*-BuLi were added

at $-23^{\circ}C$ under an N_2 atmosphere. After 1 h, the mixture was cooled to $-78^{\circ}C$ for 30 min, when 5.86 mL (56.45 mmol) of ethyl propiolate in 5 mL of THF were added in a dropwise fashion and stirred for 1 h. Then, 8.164 g of crude aldehyde **4** (precooled at $-78^{\circ}C$) in 10 mL of THF was added, and the mixture was stirred for 4.5 h before 16 mL of acetic acid (in excess) was added. The mixture was warmed to room temperature, diluted with 250 mL of ether, washed sequentially with aqueous 10% citric acid (100 mL × 2) and saturated aqueous $NaHCO_3$ (100 mL × 2), and dried over $MgSO_4$. After silica-gel column chromatography, 6.200 g (47%) of acetylenic alcohols **9** were obtained as a light yellow solid. Mp: 72–74°C. ^1H NMR ($CDCl_3$, 500 MHz): δ 4.665 (broad s, 1H, BocNH-), 4.500 (m, 1H, -OCH-), 4.267–4.216 (m, 2H, $J = 7$ Hz, -CH_2-), 3.847–3.790 (m, 1H, -NCH-), 3.221 (b-s, 1H, -OH), 1.730–1.626 (m, 1H, $J =$ 6.5 Hz, -CH-), 1.514–1.477 (m, 1H, -CH_2-), 1.449 (s, 9H, Boc), 1.379–1.342 (m, 1H, -CH_2-), 1.310 (t, 3H, $J = 7$ Hz, -CH_3), 0.964–0.924 (d, 6H, $J = 6.5$ Hz, 2CH_3-). MS (FAB): 313.8 (M^+).

(5*S*)-5-[(1′*S*)-1-(*N*-Boc-amino)-3-methylbutyl]dihydrofuran-2(3*H*)-one (10) and (5*R*)-5-[(1′*S*)-1-(*N*-Boc-amino)-3-methylbutyl]dihydrofuran-2(3*H*)-one (11)

Method A

Acetylenic alcohol **9** (6.200 g, 19.79 mmol) dissolved in 100 mL of EtOAc, which underwent hydrogenation at 60 psi over 3.72 g of 10% Pd/C for 2.5 h. After filtration of Pd/C, the solvent was evaporated, and the residue was redissolved in 250 mL of toluene/acetic acid (97.5:2.5) for reflux at 120°C for 3 h. The mixture was concentrated and subjected to silica-gel purification. The less polar lactone **10** (3.269 g, 61%) and 751 mg (14%) of the more polar lactone **11** were obtained as white solids. ^1H NMR ($CDCl_3$, 500 MHz) for **10**: δ 4.511 (t, 1H, -OCH-), 4.432 (d, 1H, $J = 9.5$ Hz, BocNH-), 3.877–3.830 (m, 1H, -NCH-), 2.542–2.507 (m, 2H, -$COCH_2$-), 2.255–2.200 (m, 1H, -CH_2-C-CO-), 2.170–2.109 (m, 1H, -CH_2-C-CO-), 1.696–1.642 (m, 1H, -CH-), 1.602–1.543 (m, 1H, -CH_2-), 1.439 (s, 9H, Boc), 1.384–1.329 (m, 1H, -CH_2-), 0.940 (d, 3H, $J = 6.5$ Hz, -CH_3), 0.927 (d, 3H, $J = 6.5$ Hz, -CH_3). MS (FAB): 271.4 (M^+). $[\alpha]_D$ -32° (*c* 1.0 CH_3OH). Mp: 77–79°C. ^1H NMR ($CDCl_3$, 500 MHz) for **11**: δ 4.456–4.432 (m, 2H, -OCH-, BocNH-), 3.759 (s, 1H, -NCH-), 2.611–2.418 (m, 2H, -$COCH_2$-), 2.322–2.250 (m, 1H, -CH_2-C-CO-), 2.102–2.024 (m, 1H, -CH_2-C-CO-), 1.719–1.707 (m, 1H, -CH-), 1.442 (s, 9H, Boc), 1.423–1.283 (m, 2H, -CH_2-), 0.944 (d, 3H, $J = 6.5$ Hz, -CH_3), 0.919 (d, 3H, $J = 6.0$ Hz, -CH_3). MS (ESI): 272.22 (M^+). $[\alpha]_D$ -44.8° (*c* 0.625 CH_3OH). Mp: 119–120°C.

Method B

Nitrile **8** (278 mg, 0.90 mmol) was dissolved in 6 mL of EtOH at 0°C, followed by the addition of 1.56 mL of aqueous NaOH (1 N) and 5.13 mL of H_2O_2 (30%). The mixture was stirred at 0°C overnight, which was then cooled to −30°C, and 12 mL of aqueous $Na_2S_2O_3$ (20%) were added. After removal of ethanol under reduced pressure at 40°C, the aqueous layer (with small drops of oil on the surface) was extracted with EtOAc (20 mL × 4). The layers were combined, washed with brine (20 mL), and dried over $MgSO_4$. The solvent was then evaporated, and the residue was stirred in acetic acid/water (65:35) for 3 days at room temperature. Then the solvent was removed, and 10 mL benzene and 10 mL CH_2Cl_2 were used to remove the small amount of water left. The residue was refluxed in benzene for 1 h and then purified by silica-gel column chromatography, which furnished 211 mg (86%) of lactone **10**.

(3*R*,5*S*)-5-[(1′*S*)-1-(*N*-Boc-amino)-3-methylbutyl]-3-methyl-dihydrofuran-2(3*H*)-one (12)

To a stirred solution of 2.012 g (7.42 mmol) of lactone **10** in 25 mL of anhydrous THF, 16.33 mL of LiHMDS (1.0 M in THF) were added and stirred at −78°C under a nitrogen atmosphere for 1 h. CH_3I (0.51 mL, 8.17 mmol) was then added, and the mixture was allowed to react for 35 min before 40 mL of saturated aqueous NH_4Cl solution was added. The mixture was warmed to room temperature and underwent evaporation to remove THF. The residue was extracted with EtOAc (25 mL × 3) and the combined organic layers were washed with 25 mL of brine and then dried over $MgSO_4$. Silica-gel chromatography gave 1.465 g (69%) of the alkylated lactone **12** as a colorless solid. Dimethylated product (180 mg) was also obtained. ^{1}H NMR ($CDCl_3$, 500 MHz) for **12**: δ 4.492 (t, 1H, -OCH-), 4.367 (d, 1H, $J = 9.5$ Hz, BocNH-), 3.839 (m, 1H, -NCH-), 2.684 (m, 1H, -CHCO-), 2.413 (m, 1H, β-H, -CH_2-C-CO-), 1.922 (m, 1H, α-H, -CH_2-C-CO-), 1.655 (m, 1H, -CH-), 1.546 (m, 1H, -CH_2-), 1.440 (s, 9H, Boc), 1.359 (m, 1H, -CH_2-), 1.272 (d, 3H, $J = 7.5$ Hz, -CH_3), 0.937–0.915 (d, 6H, $J = 6.5$ Hz, 2CH_3-). MS (ESI): 286.22 (M^+). Mp: 90–91°C. $[\alpha]_D$ -28.6° (*c* 0.7 CH_3OH). ^{1}H NMR ($CDCl_3$, 500 MHz) for dimethylated lactone: δ 4.465–4.433 (m, 2H, BocNH-, -OCH-), 3.821–3.774 (m, 1H, -NCH-), 2.060–2.021 (dd, 1H, $J = 13$ Hz, 6.5 Hz, -CH_2-C-CO), 1.959–1.914 (dd, 1H, $J = 9.5$ Hz, 12.5 Hz, -CH_2-C-CO-), 1.709–1.655 (m, 1H, -CH-), 1.629–1.571 (m, 1H, -CH_2-), 1.432 (s, 9H,), 1.387–1.332 (m, 1H, -CH_2-), 1.266 (s, 3H, -CH_3), 1.263 (s, 3H, -CH_3), 0.943–0.926 (dd, 6H, $J = 2$ Hz, 6.5 Hz, 2CH_3-). MS (EI): 300.1 (M^+). Anal. calcd. for $C_{15}H_{27}NO_4$: C, 64.18; H, 9.76; N, 4.68. Found: C, 64.33; H, 9.48; N, 4.67. Mp: 154–156°C.

(2*R*,4*S*,5*S*)-5-(*N*-Boc-amino)-4-[(*tert*-butyldimethylsilyl)oxy]-2,7-dimethyloctanoic Acid (13)

Methylated lactone **12** (940 mg, 3.30 mmol) was dissolved in 15 mL of THF and then treated with 16.5 mL of aqueous LiOH (1 N), which was stirred overnight at room temperature. The mixture was concentrated under reduced pressure and acidified with 25% aqueous citric acid to pH 3–4, followed by extraction with EtOAc (20 mL × 4). The extracts were combined, washed with 20 mL of brine, and dried over $MgSO_4$. Evaporation of the solvent gave 920 mg of hydroxyl acid intermediate as a white solid. Then the intermediate was dissolved in 15 mL of anhydrous DMF, and 4.528 g (66.46 mmol) of imidazole and 5.012 g (33.23 mmol) of TBDMSCl (*tert*-butyldimethylchlorosilane) were added. The mixture was stirred at room temperature for 24 h and then quenched by 12 mL of MeOH, which was allowed to be stirred for 1 h to remove the residual TBDMSCl. The mixture was then acidified with excessive 25% aqueous citric acid and extracted with EtOAc (40 mL × 4). The organic layers were collected, washed with 50 mL of water and 50 mL of saturated aqueous NaCl solution, and then dried over Na_2SO_4. Removal of the solvent and silica-gel column chromatography afforded 1.250 g (91%) of the protected acid **13** as a colorless solid, mp: 132–134°C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.340 (b-s, 1H, -COOH), 4.576 (d, 1H, $J = 9.5$ Hz, BocNH-), 3.736–3.719 (m, 1H, -OCH-), 3.707–3.696 (m, 1H, -NCH-), 2.665–2.596 (m, 1H, $J = 7$ Hz, -CHCO-), 1.927–1.864 (m, 1H, -CH-), 1.655–1.615 (m, 1H, -CH_2-C-CO-), 1.445 (s, 9H, Boc), 1.401–1.332 (m, 1H, -CH_2-C-CO-), 1.299–1.256 (m, 2H, -CH_2-), 1.190 (d, 3H, $J = 7$ Hz, -CH_3), 0.932 (d, 3H, -CH_3), 0.919 (d, 3H, -CH_3), 0.896 [s, 9H, $(CH_3)_3$-], 0.082 (s, 6H, 2CH_3Si-). MS (EI): 418.2 (M^+).

[(2*R*,4*S*,5*S*)-5-(*N*-Boc-amino)-4-[(*tert*-butyldimethylsilyl)oxy]-2,7-dimethyloctal] *N*′-Isobutyl Amide (14)

HOBt (350 mg, 2.5 mmol), 485 mg (2.5 mmol) of EDC, 0.45 mL (4.40 mmol) of isobutylamine, and 1.50 mL (13.2 mmol) of NMM were successively added to a stirred solution of 918 mg (2.20 mmol) of acid **13** in DMF/CH_2Cl_2 (5 mL/30 mL) at room temperature. The mixture was stirred for 36 h and then poured into 50 mL of saturated aqueous $NaHCO_3$, followed by extraction with EtOAc (40 mL × 4). The organic layer was washed with 50 mL of brine and dried over Na_2SO_4. Silica-gel chromatography with an eluant of EtOAc/petroleum ether (1/5) afforded 923 mg (89%) of amide **14** as a light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.227 (s, 1H, -C-CONH-), 4.563 (d, 1H, $J = 10$ Hz, BocNH-), 3.804–3.755 (m, 1H, -OCH-), 3.648–3.621 (m, 1H, BocN-CH-), 3.284–3.229 (m, 1H, -CON-CH_2-), 2.769–2.719 (m, 1H, -CON-CH_2-), 2.447–2.406 (m, 1H, -CH-CO-), 1.767–1.688 (m, 2H, 2-CH-),

1.659–1.604 (m, 1H, -CH_2-C-CO), 1.518–1.468 (m, 1H, -CH_2-C-CO), 1.446 (s, 9H, Boc), 1.287–1.186 (m, 2H, -CH_2-), 1.120 (d, 3H, $J = 6.5$ Hz, -CH_3), 0.937–0.923 (s, 6H, 2CH_3-), 0.898–0.895 (d, 6H, 2CH_3-), 0.881 (s, 9H, $(CH_3)_3$-), 0.070 (s, 3H, -$SiCH_3$), 0.055 (s, 3H, -$SiCH_3$). MS (ESI): 473.36 (M^+).

[(2*R*,4*S*,5*S*)-5-(*N*-Boc-amino)-4-hydroxy-2,7-dimethyloctal] *N*′-Isobutyl Amide (15)

At room temperature, 1.388 g (2.93 mmol) of amide **14** was dissolved in 15 mL of THF, which was treated with 8.80 mL (8.80 mmol) of n-$Bu_4N^+F^-$ (1 M in THF). The mixture was stirred for 12 h and then concentrated for separation. Silica-gel chromatography purification furnished 798 mg (76%) of the deprotected amide **15** as a white solid, mp: 137–138°C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.937 (s, 1H, -CONH-), 4.696 (d, 1H, $J = 9.5$ Hz, BocNH-), 3.602 (s, 1H, -OCH-), 3.541 (m, 1H, -NCH-), 3.602–3.541 (s, 1H, -OH), 3.164–3.111 (m, 1H, -$CONCH_2$-), 3.012–3.296 (m, 1H, -$CONCH_2$-), 2.608–2.570 (m, 1H, -CHCO-), 1.792–1.739 (m, 1H, -N-C-CH), 1.693–1.623 (m, 3H, -CH-, -CH_2-C-CO-), 1.531–1.483 (m, 1H, -CH_2-), 1.435 (s, 9H, Boc), 1.323–1.283 (m, 1H, -CH_2-), 1.195 (d, 3H, $J = 7$ Hz, -CH_3), 0.925–0.902 (d, 12H, 4CH_3-). MS (ESI) (M^+ 359.28). Anal. calcd. for $C_{19}H_{38}N_2O_4$: C, 63.65; H, 10.68; N, 7.81. Found: C, 63.97; H, 10.43; N, 7.65. $[\alpha]_D$ −55.4° (*c* 0.65 CH_3OH).

[(2*R*,4*S*,5*S*)-5-(*N*-Boc-L-phenylalanylamido)-4-hydroxy-2,7-dimethyloctal] *N*′-Isobutyl Amide (16)

Amide **15** (294 mg, 0.82 mmol) was dissolved in 3 mL of CH_2Cl_2 at room temperature, followed by the addition of 1 mL of CF_3COOH, which was stirred for 30 min to remove the Boc group. The solvent and TFA were removed under reduced pressure. In another flask, 239 mg (0.90 mmol) of N-Boc-L-phenylalanine, 174 mg (0.90 mmol) of EDC, and 123 mg (0.90 mmol) of HOBt in 10 mL of anhydrous DMF was allowed to react for 10 min, to which the concentrated residue of amine (neutralized with 0.1 mL of NMM) and 0.2 mL (1.8 mmol) of NMM were added. The mixture was stirred for 24 h at room temperature and then washed successively with 10% aqueous citric acid (10 mL × 2), saturated aqueous $NaHCO_3$ (10 mL × 2), and brine. Silica-gel chromatography gave 245 mg (60%) of amide **16** as a white solid, mp: 200–201°C. The analytic sample can be prepared by crystallization in EtOAc/petroleum ether (1:4) at 60°C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.615 (m, 1H, -CONH-), 7.247–7.191 (m, 5H, Ph-), 7.170 (d, 1H, -CONH-), 6.968 (d, 1H, BocNH-), 4.638 (d, 1H,-OH), 4.130–4.085 (m, 1H, -NCHCO-), 3.706 (b-s, 1H, -OCH-), 3.273–3.254 (d, 1H, -NCH-), 2.974–2.938 (dd, 1H, $J = 4$ Hz and 14 Hz,

$PhCH_2$-), 2.832 (m, 2H, -CON-CH_2-), 2.723–2.675 (dd, 1H, $J = 10.5$ Hz and 13.5 Hz, $PhCH_2$-), 2.446 (m, 1H, -CHCO-), 1.675–1.608 (m, 1H, -CON-C-CH-), 1.535–1.369 (m, 3H, -CH-, -CH_2-C-CO-), 1.295 (s, 9H, Boc), 1.191–1.081 (m, 2H, -CH_2-), 0.949 (d, 3H, $J = 6.5$ Hz, -CH_3), 0.841–0.797 (d, 12H, 4CH_3-). MS (ESI): 506.42 (M^+). Anal. calcd. for $C_{28}H_{47}N_3O_5$: C, 66.50; H, 9.37; N, 8.31. Found: C, 66.80; H, 9.28; N, 8.14. $[\alpha]_D$ −51.2° (*c* 0.625 CH_3OH).

Model Compound 17

To a stirred solution of 65 mg (0.13 mmol) of amide **16** in CH_2Cl_2, 1 mL of TFA was added. After 30 min, the solvent and most of the TFA were removed by evaporation. In another flask, 33 mg (0.15 mmol) of 3-(trifluoromethyl)cinnamic acid, 30 mg (0.15 mmol) of EDC, and 21 mg (0.15 mmol) of HOBt were dissolved in 4 mL of DMF, to which were added the deprotected amine (neutralized with NMM) and 0.1 mL (0.3 mmol) of NMM. The mixture was stirred at room temperature for 48 h. After this period, the mixture was poured into 10 mL of aqueous $NaHCO_3$, extracted with EtOAc (30 mL × 3); washed successively with 10% aqueous citric acid (10 mL × 2), saturated aqueous $NaHCO_3$ (10 mL × 2), and brine; and dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved in MeOH at 65°C, to which ether and petroleum ether were added slowly. After 5 h at room temperature (lower temperature is desirable), 20 mg (26%) of compound **17**, a white crystal, were obtained. Recrystallization can be repeated for several times. Mp: 246–247°C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.413 (d, 1H, -CONH-), 7.761–7.722 (m, 4H, CF_3Ph-), 7.688–7.645 (m, 1H, -CONH-), 7.600 (d, 1H, $J = 9.5$ Hz, -CONH-), 7.402 (d, 1H, $J = 16$ Hz, CF_3PhCH═), 7.293–7.141 (m, 5H, Ph-), 6.818 (d, 1H, $J = 16$ Hz, ═CHCO-), 4.708–4.663 (m, 1H, -NCHCO-), 4.578 (d, 1H, $J = 5.5$ Hz, -OCH-), 3.727 (m, 1H, -NCH-), 3.114–3.077 (dd, 1H, $J = 4.5$ Hz and 14 Hz, $PhCH_2$-), 2.844–2.814 (m, 2H, -CON-CH_2-), 2.797–2.749 (dd, 1H, J = 10 Hz and 14 Hz, $PhCH_2$-), 2.460 (m, 1H, -CHCO-), 1.672–1.618 (m, 1H, -N-C-CH-), 1.604–1.555 (m, 1H, -CH-), 1.540–1.469 (m, 1H, -CH_2-C-CO-), 1.379–1.322 (m, 1H, -CH_2-C-CO-), 1.253–1.199 (m, 1H, -CH_2-), 1.124–1.069 (m, 1H, -CH_2-), 0.966 (d, 3H, $J = 6.5$ Hz, -CH_3), 0.841–0.791 (d, 12H, 4CH_3-). MS (ESI): 604.41 (M^+). Anal. calcd. for $C_{33}H_{44}F_3N_3O_4$: C, 65.65; H, 7.57; N, 6.86. Found: C, 65.65; H, 7.35; N, 6.96.

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