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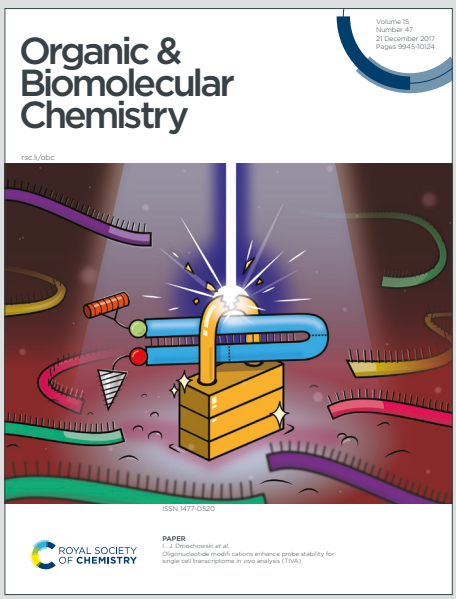

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ARTICLE

Total Synthesis and Absolute Structure of N55, a Positive Modulator of GLP-1 Signaling

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Glucagon-like peptide-1 (GLP-1) signaling is an established therapeutic target for type 2 diabetes mellitus (T2DM). We developed a 7-step synthesis of **N55**, a positive modulator of GLP-1 signaling isolated from fenugreek (*Trigonella foenum-graecum*) seeds, with 29% overall yield, and we determined the absolute structure of **N55** to be *N*-((3*R*,4*R*,5*S*)-4,5-dimethyl-2-oxotetrahydrofur-3-yl)linoleic amide.

Introduction

Glucagon-like peptide-1 (GLP-1) is an incretin peptide hormone secreted after nutrient intake that exhibits various important functions, such as enhancing glucose-dependent insulin secretion, protecting against inflammation, decreasing hypertension, and increasing cognitive function, as well as exhibiting cardio-protection and neuroprotection activities.[1] The physiological response to GLP-1 is mainly mediated through binding and activation of the GLP-1 receptor (GLP-1R).[1c,2] GLP-1R is a family B G-protein-coupled receptor (GPCR) and expressed in a wide array of tissues, including pancreatic islet β-cells, lungs, heart, kidneys, blood vessels, neurons, and lymphocytes.[1a,1c] The most potent actions of GLP-1 are the insulinotropic and glucagonostatic effects to lower the plasma glucose level.[3] After food intake, the plasma GLP-1 level rapidly rises 3-fold, contributing to normoglycemia.[4] GLP-1 is then quickly eliminated by the degradation of dipeptidyl peptidase-4 (DPP-4) and renal clearance. The short half-life (1.5-5 minutes) of GLP-1 can tightly regulate GLP-1 signaling and the insulin secretory response. The impaired secretion and reduced postprandial concentrations of GLP-1 observed in type 2 diabetic patients may contribute to their morbid insulin secretion and blood glucose hemostasis.[1e,4,5]

For treatment of type 2 diabetes mellitus (T2DM), several drugs have already been approved that act through the GLP-1 regulatory system.[6] Apart from the current therapeutic strategies aiming to constitutively activate GLP-1R by agonists or DPP-4 inhibitors,[7,8] positive modulators of GLP-1 signaling are foreseen as a promising alternative approach in the future.[9] The positive modulators are less likely to exhibit a chronic activation of GLP-1R and are favorable for the physiological spatiotemporal regulation of GLP-1. Some GLP-1 signaling positive modulators have already been reported that can enhance the degree of activation according to endogenous GLP-1 but do not activate the GLP-1R by themselves.[9,10]

We have discovered a positive modulator of GLP-1 signaling, **N55**, from the ethanol extract of fenugreek (*Trigonella foenum-graecum*) seeds.[10] Fenugreek is an edible plant that is utilized as food, spice, and traditional medicine worldwide. Extensive preclinical and clinical research have outlined the therapeutic utilities of fenugreek due to its anti-diabetic, anti-hyperlipidemic, anti-obesity, anti-cancer, anti-inflammatory, and antibiotic effects.[11] **N55** can specifically enhance GLP-1 potency by more than 40-fold in terms of GLP-1-dependent 3',5'-cyclic adenosine monophosphate (cAMP) production,[10] and its ability to lower plasma glucose base on physiological levels of GLP-1 was later revealed.[12] Considering the great anti-diabetic potential of **N55**, here we further expatiate its structure elucidation through the first total synthesis in 7 steps with an overall yield of 29%. The chirality of synthetic **N55** was created by a nearly enantio- and diastereo-specific D-proline catalyzed asymmetric anti-Mannich-type reaction to establish an asymmetric amino group and the vicinal tertiary carbon center at once.[13] Moreover, the chiral centers and substituents can be altered and replaced by the modification of reactions to obtain different **N55** analogues.

Results and discussion

4-Hydroxylisoleucine is a crucial component in fenugreek seeds.[14] According to the mass spectrometry analysis of the isolated sample of **N55** from fenugreek seeds, the *m/z* value of [**N55** + H]$^+$ is 392 with two major MS/MS fragments at *m/z* of 130 and 263 (Supporting Information, Figure S1). The compositions of the *m/z* 263 fragment may contain eighteen carbons, one oxygen, and three degrees of unsaturation, and these structural features were clearly observed in the ^{1}H and ^{13}C NMR spectra (Supporting Information, Figures S2 and S3). These results highly imply that the fragment should be an 18-carbon fatty acyl with two degrees of unsaturation. Linoleic acid is the only natural 18-carbon fatty acid with two degrees of unsaturation. On the other hand, the *m/z* value 130 ([M+H]$^+$) is potentially derived from dehydration of 4-hydroxylisoleucine

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(*m/z* 147), i.e., the lactone form of 4-hydroxylisoleucine. Together, we concluded that the structure of **N55** is 3-amino-4,5-dimethyl-γ-lactone linoleic amide. Possible assignments and atomic correlations in the ^{1}H, ^{13}C, HH-COSY, HSQC, and HMBC NMR spectra are all consistent with this proposed structure. However, the stereochemistry cannot be determined by these spectral data. In fenugreek seeds extract, the major 4-hydroxylisoleucine isoform possesses a (2*S*,3*R*,4*S*) configuration.[14,15] Therefore, we first aim to synthesize *N*-((3*S*,4*R*,5*S*)-4,5-dimethyl-2-oxotetrahydrofur-3-yl)linoleic amide (**2**) for the structure elucidation of **N55** (Fig. 1).

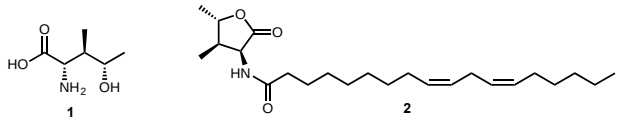


Fig. 1 (2*S*,3*R*,4*S*)-4-Hydroxylisoleucine (**1**) and *N*-((3*S*,4*R*,5*S*)-4,5-dimethyl-2-oxotetrahydrofur-3-yl)linoleic amide (**2**).

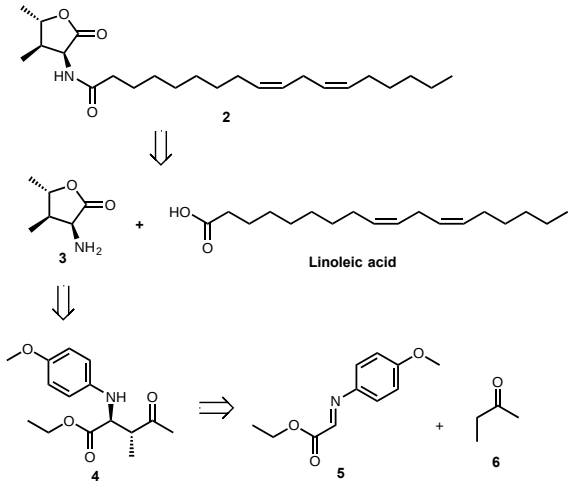
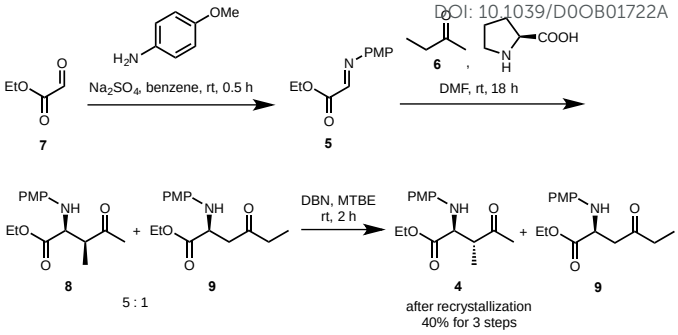


Fig. 2 The retrosynthesis of **2**.

A reterosynthetic analysis was proposed as shown in Fig. 2. The proposed compound **2** could be obtained from a simple coupling reaction of amino lactone **3** and commercially available linoleic acid. Although the synthesis of amino lactone **3** has been reported by several groups,[15,16] the efficiency could be further improved by developing a shorter and stereoselective synthetic route. Therefore, amino lactone **3** was planned to be acquired through an asymmetric ketone reduction-lactonization tandem reaction from amino-keto ester **4**, which can be prepared from PMP-protected imine **5** and 2-butanone (**6**) through known procedures.[13,15,17]

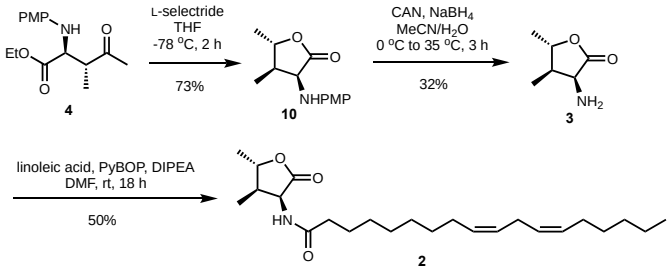
As shown in Scheme 1, commercially available ethyl 2-oxoacetate (**7**) was first transferred to inmine **5** and then submitted to an L-proline catalyzed asymmetric anti-Mannich-type reaction to give a 5:1 ratio of amino ketone **8** (> 99% ee) and regioisomer **9**. The inseparable mixture of **8** and **9** was further treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBN) in methyl *tert*-butyl ether (MTBE) to afford amino-keto ester **4** after recrystallization. The enantiomeric purity (> 99% ee) of amino ketone **4** was confirmed by HPLC analysis.

Scheme 1 Synthesis of **4** (PMP: *p*-methoxyphenyl).



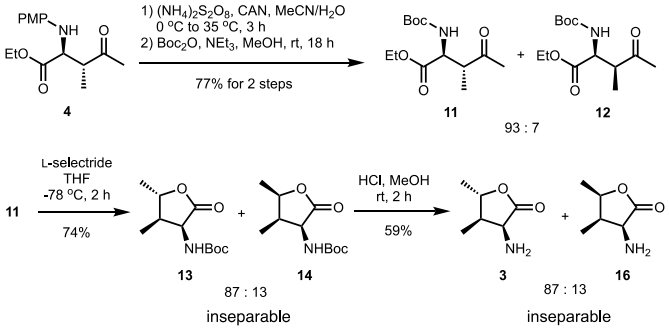
The reduction-lactonization tandem reaction from **4** to **10** (PMP-protected lactone) was stereospecifically accomplished by L-selcectride at -78 °C in 73% yield (Scheme 2).[13,16c] Although the yield of the PMP deprotection of **10** was lower than expected under various conditions,[18] compound **2** was easily obtained after an amide bond formation between free amine **3** and linoleic acid.

Scheme 2 Synthesis of **2** (PyBOP: benzotriazol-1-oxytripyrrolidinophosphonium hexafluorophosphate, CAN: ceric ammonium nitrate).



Other attempts to improve the synthetic efficiency are summarized as below: 1) In Scheme 3, the PMP group was replaced with a *tert*-butyloxycarbonyl (Boc) group to facilitate the deprotection. 2) In Scheme 4, linoleic acid was first conjugated to amino ketone **17** to circumvent the use of protecting group. However, both of the alternative strategies resulted in inseparable epimer and were excluded from further studies.

Scheme 3 Synthesis of **3** through Boc-protected aminoketone **11**.



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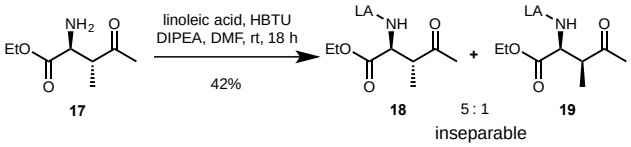
Scheme 4 Conjugation of **17** and linoleic acid (HBTU: 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, LA: linoleic acyl).



17 18 19

However, the ^{1}H NMR spectrum of synthetic compound **2** was not consistent with that of the isolated **N55**. We then revised the configuration of the amino lactone moiety from (3*S*,4*R*,5*S*) to (3*S*,4*S*,5*R*) **20**, which has been observed in other natural products, (–)-funebral and (–)-funebrine.[18c,19] The newly proposed structure was *N*-((3*S*,4*S*,5*R*)-4,5-dimethyl-2-oxotetrahydrofur-3-yl)linoleic amide (**21**) (Fig. 3).

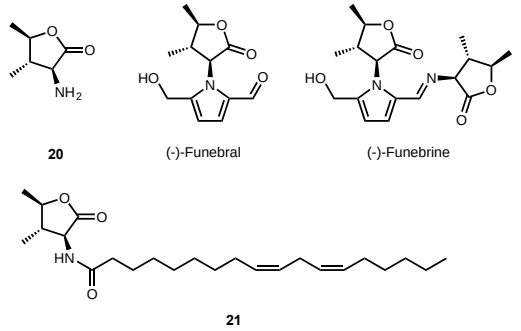
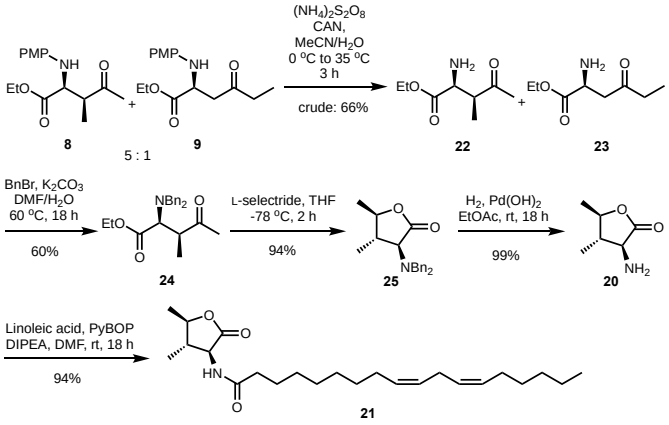


Fig. 3 The revised structure of **N55**.

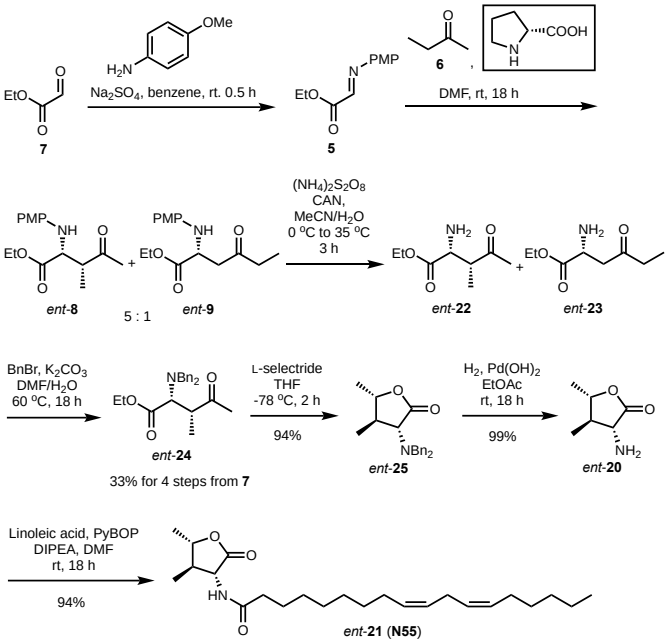
Starting from the aforementioned amino ketone **8** and **9**, the PMP protecting groups were removed by ceric ammonium nitrate. Free amine **22** was later isolated from the mixture after protected with di-benzyl (Bn) groups to form di-benzyl amino ketone **24**, which was reduced and cyclized after the treatment of L-selectride to afford lactone **25,** exclusively, in 94% yield (Scheme 5). The following deprotection of the di-benzyl group by a palladium-catalyzed hydrogenation and PyBOP mediated amide bond formation with linoleic acid were carried out successfully to produce *N*-((3*S*,4*S*,5*R*)-4,5-dimethyl-2-oxotetrahydrofur-3-yl)linoleic amide **21** in high yields.

Scheme 5 Synthesis of **21**.



8 9 22 23 24 25 20 21

Scheme 6 Synthesis of *ent*-**21** (**N55**).



7 5 6 *ent*-8 *ent*-9 *ent*-22 *ent*-23 *ent*-24 *ent*-25 *ent*-20 *ent*-21 (**N55**)

The ^{1}H and ^{13}C NMR spectra of **21** are exactly identical with those of **N55**, and the specific optical rotation of **21** ($[\alpha]_D^{19.8}$ = 20.7) is equal in magnitude but opposite in sign to that of **N55** ($[\alpha]_D^{21}$ = –23.0), which supports the enantiomeric relationship between **21** and **N55**. Finally, synthetic **N55** (*ent*-**21**) was obtained through the same synthetic route as **21** with only a replacement of L-proline to D-proline in the asymmetric anti-Mannich-type reaction (Scheme 6). This time, all the spectra of *ent*-**21** are consistent with the spectra of isolated **N55**. A comparison of ^{1}H NMR between *ent*-**21** and **N55** is given in Fig. 4. Thus, the chemical structure of **N55** was determined to be *N*-((3*R*,4*R*,5*S*)-4,5-dimethyl-2-oxotetrahydrofur-3-yl)linoleic amide.

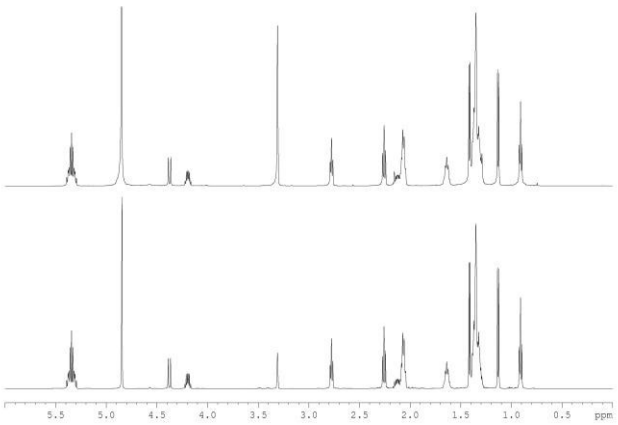


Fig. 4 Comparative 500 MHz ^{1}H NMR spectra between isolated **N55** (upper) and synthetic **N55** (lower) in d_4-methanol (δ_H = 3.31 ppm).

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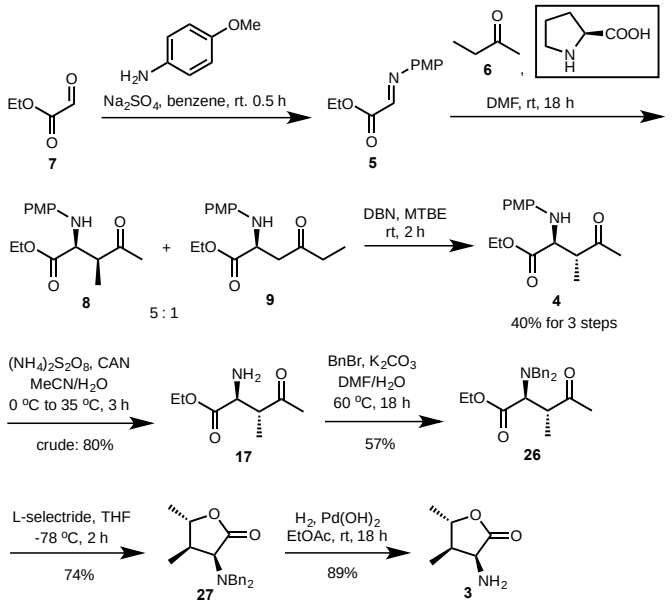
Inspired by the success of **N55**, we re-examined the synthesis of amino lactone **3** through the di-benzyl protected intermediates (Scheme 7). Amino lactone **3** was then successfully acquired with high selectivity and yield. The overall yield of **3** was 12% over 7 steps.

Scheme 7 Synthesis of **3**.



Conclusions

We performed the first total synthesis of **N55** isolated from fenugreek seeds with an overall yield of 29% over 7 steps and elucidated its absolute structure as a *N*-((3*R*,4*R*,5*S*)-4,5-dimethyl-2-oxotetrahydrofur-3-yl)linoleic amide. This study provides a comprehensive platform to further expand the scope of **N55** analogues for pharmaceutical applications.

Experimental

General Experimental Methods: All reactions were carried out under an inert nitrogen atmosphere with dry solvents under anhydrous conditions unless otherwise stated, and standard syringe–septa techniques were followed. Solvents were dried by conventional methods prior to use. Reagents were purchased and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) using glass-backed plates pre-coated with silica gel 60 (Merck, silica gel 60 F_{254}). Ultraviolet (UV) light was used as the visualizing agent. Ceric ammonium molybdate and heat, ninhydrin and heat, or iodine were used as developing agents. Flash silica gel chromatography was performed using silica gel 60 (Merck, F_{254} 230–400 mesh). Nuclear magnetic resonance (NMR) spectra were recorded on Bruker AV 400 MHz, AV-III 400 MHz and AV-500 MHz instruments and were calibrated using a residual undeuterated solvent as an internal reference (d-chloroform, 1H NMR δ 7.26 ppm, 13C NMR δ 77.1 ppm; d4-methanol, 1H NMR δ 3.31 ppm, 13C NMR δ 49.0 ppm). The abbreviations were used to interpret NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. HR MALDI-mass spectra were conducted on an Applied Biosystems 4800 Proteomics Analyzer equipped with an Nd/YAG laser (335 mm) operating at a repetition rate of 200 Hz. HR FAB and HR EI-mass spectra were conducted on a JEOL JMS-700 double-focusing mass spectrometer with a resolution of 8000 (5% valley definition). HR ESI-mass spectra were conducted on a dual ionization ESCi® (ESI/APCi) source options, Waters LCT premier XE (Waters Corp., Manchester, UK). Optical rotations were obtained on a Jasco P-2000 polarimeter (1-dm cell if not stated). Infrared (IR) spectra were recorded on a Thermo Nicolet iS-5 FT-IR spectrometer. Melting points were recorded on a BÜCHI M-565 melting point apparatus.

(9*Z*,12*Z*)-*N*-((3*R*,4*R*,5*S*)-4,5-Dimethyl-2-oxotetrahydrofur-3-yl) octadeca-9,12-dienamide (**N55**):[10]

Data of **N55** from isolated sample purified by high-performance liquid chromatography (HPLC): R_f = 0.28 [ethyl acetate (EtOAc)/hexane = 1/2, I_2]; $[\alpha]_D^{21}$ = –23.0 (c 0.30, $CHCl_3$, 5-cm cell); IR (film) ṽ = 3303, 3008, 2956, 2926, 2854, 1782, 1657, 1650, 1536, 1461, 1453, 1388, 1183, 1047, 908, 723 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 5.39–5.29 (m, 4 H, $CH_2CHCHCH_2$), 4.38 (d, *J* =11.8 Hz, 1 H, C*H*NH), 4.19 (dt, *J* = 9.8, 6.1 Hz, 1H, COOC*H*), 2.78 (t, *J* = 6.5 Hz, 2 H, CHCH_2CH), 2.26 (t, *J* = 7.4 Hz, 2 H, CH_2CONH), 2.17–2.04 (m, 5 H, C*H*CH_3, CH_2CH_2CH), 1.66–1.60 (m, 2 H, CH_2CH_2CONH), 1.41 (d, *J* = 6.1 Hz, 3 H, COOCHCH_3), 1.40–1.28 (m, 14 H, CH_2CH_2), 1.13 (d, *J* = 6.6 Hz, 3H, CHCH_3), 0.91 (t, *J* = 6.8 Hz, 3H, CH_2CH_3); ^{13}C NMR (125 MHz, CD_3OD) δ 176.5 (s, *C*ONH), 176.2 (s, *C*OOCH), 130.9 (d, $CH_2CHCHCH_2$), 130.9 (d, $CH_2CHCHCH_2$), 129.1 (d, $CH_2CHCHCH_2$), 129.1 (d, $CH_2CHCHCH_2$), 81.4 (d, COO*C*H), 57.5 (d, *C*HNH), 45.6 (d, *C*HCH_3), 36.9 (t, *C*H_2CONH), 32.7 (t, *C*H_2CH_2), 30.7 (t, *C*H_2CH_2), 30.5 (t, *C*H_2CH_2), 30.3 (t, *C*H_2CH_2), 30.3 (t, *C*H_2CH_2), 30.2 (t, *C*H_2CH_2), 28.2 (t, CH_2CH_2CH), 26.8 (t, *C*H_2CH_2CONH), 26.5 (t, CH*C*H_2CH), 23.6 (t, *C*H_2CH_2), 18.8 (q, COOCH*C*H_3), 14.4 (q, CH_2CH_3), 14.0 (q, CH*C*H_3); HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd. for $C_{24}H_{42}O_3N$ 392.3165, found 392.3160.

Data of synthetic **N55**: R_f = 0.28 (EtOAc/hexane = 1/2, I_2); $[\alpha]_D^{21}$ = –21.8 (c 0.30, $CHCl_3$, 5-cm cell); IR (film) ṽ = 3303, 3009, 2957, 2927, 2855, 1782, 1657, 1650, 1533, 1461, 1454, 1389, 1187, 1047, 908, 723 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 5.39–5.29 (m, 4 H, $CH_2CHCHCH_2$), 4.38 (d, *J* =11.8 Hz, 1 H, C*H*NH), 4.19 (dt, *J* = 9.8, 6.1 Hz, 1 H, COOC*H*), 2.78 (t, *J* = 6.5 Hz, 2 H, CHCH_2CH), 2.26 (t, *J* = 7.5 Hz, 2 H, CH_2CONH), 2.17–2.04 (m, 5 H, C*H*CH_3, CH_2CH_2CH), 1.66–1.60 (m, 2 H, CH_2CH_2CONH), 1.41 (d, *J* = 6.1 Hz, 3 H, COOCHCH_3), 1.40–1.28 (m, 14 H, CH_2CH_2), 1.13 (d, *J* = 6.6 Hz, 3H, CHCH_3), 0.91 (t, *J* = 6.9 Hz, 3H, CH_2CH_3); ^{13}C NMR (125 MHz, CD_3OD) δ 176.5 (s, *C*ONH), 176.2 (s, *C*OOCH), 130.9 (d, $CH_2CHCHCH_2$), 130.9 (d, $CH_2CHCHCH_2$), 129.1 (d, $CH_2CHCHCH_2$), 129.1 (d, $CH_2CHCHCH_2$), 81.4 (d, COO*C*H), 57.5 (d, *C*HNH), 45.6 (d, *C*HCH_3), 36.9 (t, *C*H_2CONH), 32.7 (t, *C*H_2CH_2), 30.7 (t, *C*H_2CH_2), 30.5 (t, *C*H_2CH_2), 30.3 (t, *C*H_2CH_2), 30.3 (t, *C*H_2CH_2), 30.2 (t, *C*H_2CH_2), 28.2 (t, CH_2CH_2CH), 26.8 (t, *C*H_2CH_2CONH), 26.5 (t, CH*C*H_2CH), 23.6 (t, *C*H_2CH_2), 18.8 (q, COOCH*C*H_3), 14.4 (q, CH_2CH_3), 14.0 (q, CH*C*H_3); HRMS (MALDI-TOF) *m/z* $[M + Na]^+$ calcd. for $C_{24}H_{41}O_3NNa$ 414.2979, found 414.2963.

Ethyl (2*R*,3*R*)-2-(4-Methoxyphenylamino)-3-methyl-4-oxopentanoate (*ent*-8):[13,15] Na_2SO_4 (10.7 g, 75.0 mmol) was added to a stirred solution of 4-anisidine (3.69 g, 30.0 mmol) in toluene (PhMe) (30.0 mL), followed by the addition of ethyl glyoxalate (**7**)

(6.13 mL, 30.0 mmol, 50% in toluene) within 10 to 20 minutes. The reaction mixture was stirred at room temperature for 30 minutes. After the starting material was consumed, Na_2SO_4 was filtered out by Celite, and the filtrate was concentrated under reduced pressure to give a brown oil containing **5** that was used immediately for the next step without further purification. A solution of **5** in dry dimethylformamide (DMF) (15.5 mL) was slowly added to a stirred solution of butanone (**6**) (59.0 mL, 660 mmol) and D-proline (1.21 g, 10.5 mmol) in dry DMF (46.6 mL) over 30 minutes at room temperature, and the resulting mixture was stirred at room temperature for 12 hours. After the starting material was consumed, the reaction mixture was filtered through a pad of sieve and concentrated under reduced pressure. The resulting yellow oil containing *ent*-**8** and its regioisomer (*ent*-**9**; 5 : 1) was directly used for the next reaction without further purification. A small amount of mixture was applied to column chromatography (silica gel, EtOAc/hexane = 1/4) and then HPLC for the characterization of *ent*-**8**. R_f = 0.25 (EtOAc/hexane = 1/5, UV); $[\alpha]_D^{23.1}$ = 47.3 (c 1.05, $CHCl_3$, >99% ee); IR (film) ṽ = 3379, 2981, 2936, 1729, 1713, 1514, 1235, 1200, 1180, 1035, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, *J* = 8.8 Hz, 2 H, *Ar*), 6.66 (d, *J* = 8.8 Hz, 2 H, *Ar*), 4.31 (d, *J* = 5.8 Hz, 1 H, C*H*NH), 4.19–4.13 (m, 2 H, COOCH_2), 3.74 (s, 3 H, OCH_3), 3.03 (m, 1 H, C*H*CH$_3$), 2.23 (s, 3 H, COCH_3), 1.25 (d, *J* = 7.1 Hz, 3 H, CHCH_3), 1.22 (t, *J* = 7.2, 3 H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.3 (s, *C*OCH$_3$), 172.9 (s, *C*OOCH$_2$), 153.3 (s, *Ar*), 140.9 (s, *Ar*), 116.0 (d, *Ar*), 115.0 (d, *Ar*), 61.5 (t, COO*C*H$_2$), 59.8 (d, *C*HNH), 55.8 (q, O*C*H$_3$), 49.4 (d, *C*HCH$_3$), 28.6 (q, CO*C*H$_3$), 14.3 (q, CH_2CH_3), 12.4 (q, CH*C*H$_3$); enantioselectivity was determined by HPLC analysis (Chiralpak-AS, 1.0 mL/minute, 220 nm, hexane/*i*-PrOH 97/3); retention times were 21.7 (enantiomer) and 30.9 minutes (major).

Ethyl (2*S*,3*S*)-2-(4-Methoxyphenylamino)-3-methyl-4-oxopentanoate (8): Compound **8**, the enantiomer of *ent*-**8**, was prepared and characterized by the same methods as *ent*-**8** except a replacement of D-proline with L-proline with identical selectivity and yield.

Ethyl (2*R*,3*R*)-2-Amino-3-methyl-4-oxopentanoate (*ent*-22): A solution of $(NH_4)_2S_2O_8$ (913 mg, 4.0 mmol) and cerium ammonium nitrate (CAN) (110 mg, 0.2 mmol) in H_2O (5.8 mL) was slowly added to a stirred solution of the mixture of *ent*-**8** and its regeoisomer (*ent*-**9**; 5 : 1, 547 mg, ~2.0 mmol) in MeCN (1.0 mL) at 0 °C. The resulting mixture was then heated to 35 °C and stirred for 3 hours. Upon the completion of the reaction, the reaction mixture was diluted with H_2O (5.8 mL) and washed with CH_2Cl_2 (5 mL × 4). The aqueous layer was basified with 1 M Na_2CO_3 aqueous solution to pH ~ 8 and then extracted with CH_2Cl_2 (15 mL × 5). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a brown liquid that contains *ent*-**22** and its regioisomer (*ent*-**23**, 5 : 1, 229 mg). The crude mixture was used immediately for the next reaction without further purification. Data of crude *ent*-**22** from pure *ent*-**8**: R_f = 0.40 (methanol/CH_2Cl_2 = 1/10, ninhydrin); ^1H NMR (400 MHz, $CDCl_3$) δ 4.19–4.13 (m, 2 H, COOCH_2), 3.86 (d , *J* = 4.8 Hz, 1 H, C*H*NH$_2$), 2.91 (m, 1 H, C*H*CH$_3$), 2.19 (s, 3 H, COCH_3), 1.25 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.11 (d, *J* = 7.2 Hz, 3 H, CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9 (s, *C*OCH$_3$), 174.3 (s, *C*OOCH$_2$), 61.3 (t, COO*C*H$_2$), 55.4 (d, *C*HNH$_2$), 49.8 (d, *C*HCH$_3$), 28.4 (q, CO*C*H$_3$), 14.2 (q, CH_2CH_3), 11.0 (q, CH*C*H$_3$); HRMS (APCI-TOF) *m/z* $[M + H]^+$ calcd. for $C_8H_{16}O_3N$ 174.1130, found 174.1127.

Ethyl (2*S*,3*S*)-2-Amino-3-methyl-4-oxopentanoate (22): Compound **22**, the enantiomer of *ent*-**22**, was prepared and characterized by the same methods as *ent*-**22** except a replacement of substrate *ent*-**8** to **8** with identical selectivity and yield.

Ethyl (2*R*,3*R*)-2-(Dibenzylamino)-3-methyl-4-oxopentanoate (*ent*-24): A suspension of the crude *ent*-**22**, its regeoisomer (*ent*-**23**, 5 : 1, 98 mg, ~0.57 mmol) and K_2CO_3 (235 mg, 1.7 mmol) in DMF/H_2O (1.1 mL/0.11 mL) was stirred at room temperature for 15 minutes, followed by the dropwise addition of benzyl bromide (BnBr) (0.34 mL, 2.8 mmol). After stirring at 60 °C for 18 hours, H_2O (5 mL) was added, and the reaction mixture was then extracted with EtOAc (10 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1/15) to give *ent*-**24** as a white solid (120 mg, 0.34 mmol, 60%). R_f = 0.45 (EtOAc/hexane = 1/5, UV); mp 58.8–62.3 °C; $[\alpha]_D^{23}$ = 186 (c 1.03, $CHCl_3$); IR (film) ṽ = 3062, 3029, 2977, 2929, 2852, 1723, 1602, 1495, 1454, 1370, 1201, 1169, 1026, 961, 748, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.22 (m, 10 H, *Ar*), 4.34–4.16 (m, 2 H, COOCH_2), 3.86 (d, *J* = 13.5 Hz, 2 H, PhCH_2), 3.49 (d, *J* = 10.9 Hz, 1 H, C*H*NBn$_2$), 3.45 (d, *J* = 13.4 Hz, 2 H, PhCH_2), 3.08 (dt, *J* = 10.9, 7.2 Hz, 1 H, C*H*CH$_3$), 2.15 (s, 3 H, COCH_3), 1.38 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.10 (d, *J* = 7.3 Hz, 3 H, CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.5 (s, *C*OCH$_3$), 171.9 (s, *C*OOCH$_2$), 138.9 (s, *Ar*), 129.2 (d, *Ar*), 128.4 (d, *Ar*), 127.3 (d, *Ar*), 62.6 (d, *C*HNBn$_2$), 60.5 (t, COO*C*H$_2$), 55.2 (t, Ph*C*H$_2$), 46.0 (d, *C*HCH$_3$), 29.2 (q, CO*C*H$_3$), 14.7 (q, CH_2CH_3), 14.5 (q, CH*C*H$_3$); HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd. for $C_{22}H_{28}O_3N$ 354.2069, found 354.2061.

Ethyl (2*S*,3*S*)-2-(Dibenzylamino)-3-methyl-4-oxopentanoate (24): Compound **24**, the enantiomer of *ent*-**24**, was prepared and characterized by the same methods as *ent*-**24** except a replacement of substrate *ent*-**22** to **22** with identical selectivity and yield.

(3*R*,4*R*,5*S*)-3-(Dibenzylamino)-4,5-dimethyldihydrofuran-2(3H)-one (*ent*-25): L-selectride [0.54 mL, 1.0 M in tetrahydrofuran (THF), 0.54 mmol] was added to a stirred solution of *ent*-**24** (173 mg, 0.49 mmol) in dry THF (4.9 mL) at -78 °C under nitrogen. After stirring for 2 hours at -78 °C, the reaction mixture was poured into a vigorously stirred mixture of EtOAc/1 M HCl aqueous solution (10.0 mL/10.0 mL). The aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with H_2O (5 mL × 3–5) until pH ~ 6 (pH paper) and then washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1/20, UV) to give *ent*-**25** as a white solid (143 mg, 0.46 mmol, 94%). R_f = 0.33 (EtOAc/hexane = 1/10, UV); mp 66.5–69.7 °C; $[\alpha]_D^{21}$ = 89.8 (c 1.06, $CHCl_3$); IR (film) ṽ = 3062, 3028, 2972, 2928, 2850, 1769, 1601, 1493, 1454, 1385, 1325, 1236, 1185, 1171, 1141, 1050, 995, 953, 745, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.40 (m, 4 H, *Ar*), 7.35–7.31 (m, 4 H, *Ar*), 7.28–7.23 (m, 2 H, *Ar*), 4.00 (d, *J* = 13.8 Hz, 2 H, PhCH_2), 3.91–3.83 (m, 3 H, COOC*H*, PhCH_2), 3.29 (d, *J* = 11.8 Hz, 1 H, C*H*NBn$_2$), 2.05 (m, 1 H, C*H*CH$_3$), 1.35 (d, *J* = 6.1 Hz, 3 H, COOCHCH_3), 1.02 (d, *J* = 6.5 Hz, 3 H, CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3 (s, *C*OOCH), 139.4 (s, *Ar*), 128.8 (d, *Ar*), 128.4 (d, *Ar*), 127.3 (d, *Ar*), 79.6 (d, COO*C*H), 65.4 (d, *C*HNBn$_2$), 54.9 (t, Ph*C*H$_2$), 42.1 (d, *C*HCH$_3$), 18.9 (q, COOCH*C*H$_3$), 14.1 (q, CH*C*H$_3$); HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd. for $C_{20}H_{23}O_2NNa$ 332.1626, found 332.1623.

(3*S*,4*S*,5*R*)-3-(Dibenzylamino)-4,5-dimethyldihydrofuran-2(3H)-one (25): Compound **25**, the enantiomer of *ent*-**25**, was prepared and

characterized by the same methods as *ent*-**25** except a replacement of substrate *ent*-**24** to **24** with identical selectivity and yield.

(3*R*,4*R*,5*S*)-3-Amino-4,5-dimethyldihydrofuran-2(3H)-one (*ent*-20):[18c,19] $Pd(OH)_2/C$ (6.2 mg, 20%) was added to a stirred solution of *ent*-**25** (61.9 mg, 0.20 mmol) in EtOAc (4.0 mL) under nitrogen and then purged with hydrogen (1 atm, balloon) for an hour at room temperature. After stirring at room temperature under hydrogen for 18 hours, the reaction mixture was filtered through Celite and concentrated under reduced pressure to give *ent*-**20** as a colorless oil (25.8 mg, 0.20 mmol, >99%) without further purification. R_f = 0.4 (methanol/CH_2Cl_2 = 1/10, ninhydrin); $[\alpha]_D^{24}$ = 29.0 (c 0.98, $CHCl_3$); IR (film) $\tilde{\nu}$ = 3374, 3310, 2973, 2927, 2878, 2852, 1771, 1456, 1389, 1330, 1192, 1145, 1044, 983, 946, 918, 735, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.05 (dq, *J* = 9.9, 6.1 Hz, 1 H, COOC*H*), 3.25 (d, *J* = 5.2 Hz, 1 H, C*H*NH_2), 1.80 (m, 1 H, C*H*CH_3), 1.42 (d, *J* = 6.2 Hz, 3 H, COOCHC*H*$_3$), 1.21 (d, *J* = 6.6 Hz, 3 H, CHC*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2 (s, *C*OOCH), 79.8 (d, COO*C*H), 58.9 (d, *C*HNH_2), 47.5 (d, *C*HCH_3), 18.6 (q, COOCH*C*H_3), 14.2 (q, CH*C*H_3); HRMS (EI+) *m/z* M^+ calcd. for $C_6H_{11}O_2N$ 129.0790, found 129.0791.

(3*S*,4*S*,5*R*)-3-Amino-4,5-dimethyldihydrofuran-2(3H)-one (20): Compound **20**, the enantiomer of *ent*-**20**, was prepared and characterized by the same methods as *ent*-**20** except a replacement of substrate *ent*-**25** to **25** with identical selectivity and yield.

(9*Z*,12*Z*)-*N*-((3*R*,4*R*,5*S*)-4,5-Dimethyl-2-oxotetrahydrofur-3-yl)octadeca-9,12-dienamide (*ent*-21, N55): PyBOP (62.5 mg, 0.12 mmol) was added to a stirred solution of *ent*-**20** (12.9 mg, 0.10 mmol) and linoleic acid (31 µL, 0.10 mmol) in dry DMF (1.0 mL), followed by freshly distilled *N*,*N*-diisopropylethylamine (DIPEA) (21 µL, 0.12 mmol) at room temperature under nitrogen. The reaction mixture was stirred for 18 hours. After the starting material was consumed, the reaction mixture was diluted with EtOAc (10 mL) and washed with H_2O (5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1/4) to give *ent*-**21** (**N55**) as a colorless oil (36.9 mg, 0.094 mmol, 94%). R_f = 0.28 (EtOAc/hexane = 1/2, I_2); $[\alpha]_D^{21}$ = –21.8 (c 0.30, $CHCl_3$, 5-cm cell); IR (film) $\tilde{\nu}$ = 3303, 3009, 2957, 2927, 2855, 1782, 1657, 1650, 1533, 1461, 1454, 1389, 1187, 1047, 908, 723 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 5.39–5.29 (m, 4 H, $CH_2CHCHCH_2$), 4.38 (d, *J* =11.8 Hz, 1 H, C*H*NH), 4.19 (dt, *J* = 9.8, 6.1 Hz, 1 H, COOC*H*), 2.78 (t, *J* = 6.5 Hz, 2 H, CHCH_2CH), 2.26 (t, *J* = 7.5 Hz, 2 H, CH_2CONH), 2.17–2.04 (m, 5 H, C*H*CH_3, CH_2CH_2CH), 1.66–1.60 (m, 2 H, CH_2CH_2CONH), 1.41 (d, *J* = 6.1 Hz, 3 H, COOCHC*H*$_3$), 1.40–1.28 (m, 14 H, CH_2CH_2), 1.13 (d, *J* = 6.6 Hz, 3H, CHC*H*$_3$), 0.91 (t, *J* = 6.9 Hz, 3H, CH_2CH_3); ^{13}C NMR (125 MHz, CD_3OD) δ 176.5 (s, *C*ONH), 176.2 (s, *C*OOCH), 130.9 (d, $CH_2CHCHCH_2$), 130.9 (d, $CH_2CHCHCH_2$), 129.1 (d, $CH_2CHCHCH_2$), 129.1 (d, $CH_2CHCHCH_2$), 81.4 (d, COO*C*H), 57.5 (d, *C*HNH), 45.6 (d, *C*HCH_3), 36.9 (t, *C*H_2CONH), 32.7 (t, *C*H_2CH_2), 30.7 (t, *C*H_2CH_2), 30.5 (t, *C*H_2CH_2), 30.3 (t, *C*H_2CH_2), 30.3 (t, *C*H_2CH_2), 30.2 (t, *C*H_2CH_2), 28.2 (t, CH_2CH_2CH), 26.8 (t, *C*H_2CH_2CONH), 26.5 (t, CH*C*H_2CH), 23.6 (t, *C*H_2CH_2), 18.8 (q, COOCH*C*H_3), 14.4 (q, CH_2CH_3), 14.0 (q, CH*C*H_3); HRMS (MALDI-TOF) *m/z* $[M + Na]^+$ calcd. for $C_{24}H_{41}O_3NNa$ 414.2979, found 414.2963.

(9*Z*,12*Z*)-*N*-((3*S*,4*S*,5*R*)-4,5-Dimethyl-2-oxotetrahydrofur-3-yl)octadeca-9,12-dienamide (21): Compound **21**, the enantiomer of *ent*-**21**, was prepared and characterized by the same methods as *ent*-**21** except a replacement of substrate *ent*-**20** to **20** with identical selectivity and yield.

(2*S*,3*R*)-Ethyl 2-((4-Methoxyphenyl)amino)-3-methyl-4-oxopentanoate (4):[15,17] DBN (0.15 mL, 1.2 mmol) was added to a solution of the mixture of **8** and its regeoisomer (**9**; 5 : 1, 30.0 mmol) in MTBE (1.62 mL, 18.5 M) at room temperature under nitrogen. After the reaction mixture was stirred for 2 hours, the MTBE was evaporated slowly for 18 hours at room temperature. A solid cake was obtained and recrystallized from a layered EtOAc/Hexane solution to give a white needle crystal **4** (overall yield from *p*-anisidine: up to 40%). R_f = 0.25 (EtOAc/hexane = 1/5, UV); $[\alpha]_D^{22.7}$ = -34.6 (c = 0.99, $CHCl_3$); mp 98.7–99.3 °C; IR (neat, NaCl plate) $\tilde{\nu}$ = 3341, 2978, 2937, 1731, 1707, 1514, 1235, 1162, 1034, 819 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.76 (m, 2 H, *Ar*), 6.66 (m, 2 H, *Ar*), 4.21–4.09 (m, 4 H, C*H*NH, COOCH_2, CHN*H*), 3.74 (s, 3 H, OCH_3), 3.02 (m, 1 H, C*H*CH_3), 2.23 (s, 3 H, COCH_3), 1.23–1.18 (m, 6 H, CHCH_3, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6 (s, *C*OCH_3), 172.7 (s, *C*$OOCH_2$), 153.2 (s, *Ar*), 140.8 (s, *Ar*), 115.9 (d, *Ar*), 115.0 (d, *Ar*), 61.4 (t, COO*C*H_2), 60.6 (d, *C*HNH), 55.8 (q, O*C*H_3), 49.5 (d, *C*HCH_3), 28.7 (q, CO*C*H_3), 14.3 (q, CH_2CH_3), 13.1 (q, CH*C*H_3); HPLC (Daicel Chiralpak AS-H, hexane/*i*-PrOH = 96:4, flow rate 1.0 mL/minute, λ= 254 nm): t_R = 12.7 minutes.

(3*S*,4*R*,5*S*)-3-(4-Methoxyphenylamino)-4,5-dimethyldihydrofuran-2(3H)-one (10): L-selectride (1.10 mL, 1.0 M in THF, 1.10 mmol) was added to a stirred solution of **4** (279 mg, 1.00 mmol, 1.00 equiv.) in dry THF (10.0 mL, 0.10 M) at -78 °C under nitrogen. After stirred for 2 hours at -78 °C and the starting material was consumed, the reaction mixture was poured into a vigorously stirred mixture of EtOAc/1 M HCl aqueous solution (10.0 mL/10.0 mL). The aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layers were washed with H_2O (5 mL) until pH ~ 6 (pH paper) and then washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (Hexanes/EtOAc = 1/8, UV) to give pale yellow solid **10** (172 mg, 0.73 mmol, 73%). R_f = 0.50 (EtOAc/hexane = 1/2); mp 50–52 °C; $[\alpha]_D^{19.5}$ = +105.7 (c = 0.50, $CHCl_3$); IR (neat, NaCl plate) $\tilde{\nu}$ = 3378, 2976, 2934, 2833, 1769, 1515, 1313, 1179, 1146, 1036, 1024, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, *J* = 8.8 Hz, 2 H, *Ar*), 6.61 (d, *J* = 8.8 Hz, 2 H, *Ar*), 4.42 (q, *J* = 6.7 Hz, 1 H, COOC*H*), 4.24 (d, *J* = 7.5 Hz, 1 H, C*H*NH), 3.76 (s, 3 H, OCH_3), 2.66 (dt, *J* = 7.3, 7.3 Hz, 1 H, C*H*CH_3), 1.50 (d, *J* = 6.7 Hz, 3 H, COOCHCH_3), 1.00 (d, J = 7.3 Hz, 3 H, CHCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8 (s, *C*OOCH), 152.9 (s, *Ar*), 140.9 (s, *Ar*), 115.0 (d, *Ar*), 114.3 (d, *Ar*), 81.9 (d, COO*C*H), 56.1 (d, *C*HNH), 55.7 (q, O*C*H_3), 40.4 (d, *C*HCH_3), 20.4 (q, COOCHCH_3), 13.5 (q, CHCH_3); HRMS (ESI-TOF) calcd. for $C_{13}H_{17}O_3NNa^+$ $[M+Na^+]$ 258.1106, found 258.1107.

(3*S*,4*R*,5*S*)-3-Amino-4,5-dimethyldihydrofuran-2(3H)-one (3):[15] A solution of CAN (959 mg, 1.75 mmol) in H_2O (3.50 mL, 0.50 M) was slowly added to a stirred solution of **10** (165 mg, 0.70 mmol) in MeCN (3.50 mL, 0.20 M) followed by $NaBH_4$ (53.0 mg, 1.40 mmol) portionwise at 0 °C. After stirred for an hour and the starting material was consumed, the reaction mixture was diluted with H_2O (3.50 mL) and washed with CH_2Cl_2 (3.50 mL × 4). The aqueous layer was basified with 1 M Na_2CO_3 to pH ~ 8 (pH paper) and then extracted with CH_2Cl_2 (20 mL × 5). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The brown liquid crude containing **3** (29 mg, 32%) was directly used without purification. Compound **3** can also be prepared by the same method as *ent*-**20** except a replacement of substrate *ent*-**25** to **27** to give colorless oil **3** (89%). R_f = 0.50 (MeOH/CH_2Cl_2 = 1/20, ninhydrin); ^1H NMR (400 MHz,

$CDCl_3$) δ 4.31 (dq, *J* = 3.8, 6.4 Hz, 1 H, COOC*H*), 3.78 (d, *J* = 7.5 Hz, 1 H, C*H*NH_2), 2.28 (ddq, *J* = 3.7, 7.2, 7.2 Hz, 1 H, C*H*CH_3), 1.39 (d, *J* = 6.5 Hz, 3 H, COOCHC*H*$_3$), 1.08 (d, *J* = 7.2 Hz, 3 H, CHC*H*$_3$).

(9*Z*,12*Z*)-*N*-((3*S*,4*R*,5*S*)-4,5-Dimethyl-2-oxotetrahydrofur-3-yl)octadeca-9,12-dienamide (2): PyBOP (102 mg, 0.195 mmol) was added to a stirred solution of crude **3** (21 mg, 0.163 mmol,) and linoleic acid (50.8 µL, 0.163 mmol) in dry DMF (1.63 mL, 0.1 M) at room temperature under nitrogen followed by freshly distilled DIPEA (34.0 µL, 0.195 mmol,) and stirred for 18 hours. After the starting material was consumed, the reaction mixture was diluted with EtOAc (10 mL) and washed with H_2O (5 mL) and then brine (5 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/hexane = 1/4) to give white low melting point or hygroscopic solid **2** (32 mg, 0.082 mmol, 50%). R_f = 0.3 (EtOAc/hexane = 1/2, I_2); $[\alpha]_D^{20.9}$ = 38.5 (c = 1.03, $CHCl_3$), $[\alpha]_D^{24.1}$ = 38.8 (c = 0.50, $CHCl_3$); IR (neat, NaCl plate) ṽ = 3304, 3008, 2926, 2854, 1781, 1655, 1649, 1543, 1535, 1458, 1383, 1205, 1144 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (s, 1 H, N*H*), 5.42–5.29 (m, 4 H, $CH_2CHCHCH_2$), 4.73 (dd, *J* = 4.7, 5.5 Hz, 1 H, C*H*NH), 4.40 (dt, *J* = 6.6, 6.6, Hz, 1 H, COOC*H*), 2.77 (t, *J* = 6.4 Hz, 2 H, CHCH_2CH), 2.69 (ddt, J = 7.3, 7.3, 7.3 Hz, 1 H, C*H*CH_3), 2.27 (dd, *J* = 7.1, 8.3 Hz, 2 H, CH_2CONH), 2.05 (dt, *J* = 6.8, 6.8 Hz, 4 H, CH_2CH_2CH), 1.65 (m, 2 H, CH_2CH_2CONH), 1.45 (d, *J* = 6.7 Hz, 3 H, COOCHCH_3), 1.38–1.25 (m, 14 H, CH_2CH_2), 0.94 (d, *J* = 7.2 Hz, 3 H, CHCH_3), 0.88 (t, *J* = 6.7 Hz, 3 H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3 (s, *C*ONH), 173.9 (s, *C*OOCH), 130.3 (d, $CH_2CHCHCH_2$), 130.1 (d, $CH_2CHCHCH_2$), 128.2 (d, $CH_2CHCHCH_2$), 128.0 (d, $CH_2CHCHCH_2$), 82.7 (d, COO*C*H), 52.2 (d, *C*HNH), 39.2 (d, *C*HCH_3), 36.2 (t, *C*H_2CONH), 31.6 (t, *C*H_2CH_2), 29.7 (t, *C*H_2CH_2), 29.4 (t, *C*H_2CH_2), 29.3 (t, *C*H_2CH_2), 29.2 (t, *C*H_2CH_2), 27.3 (t, *C*H_2CH_2), 25.7 (t, *C*H_2CH_2CONH), 25.7 (t, CH*C*H_2CH), 22.7 (t, *C*H_2CH_2), 20.2 (q, COOCH*C*H_3), 14.2 (q, CH_2CH_3), 13.7 (q, CH*C*H_3); HRMS (ESI-TOF) calcd. for $C_{24}H_{41}O_2NNa^+$ [M+Na$^+$] 414.2984, found 414.2980.

Ethyl (2*S*,3*R*)-2-Amino-3-methyl-4-oxopentanoate (17): $(NH_4)_2S_2O_8$ (456 mg, 2.00 mmol) and CAN (54.8 mg, 0.10 mmol) in H_2O (2.90 mL, 0.69 M) was dropwise added to a stirred solution of **4** (279 mg, 1.00 mmol) in MeCN (1.00 mL, 0.1 M) at 0 °C and then the reaction mixture was allowed to warm to 35 °C and stirred for 3 hours. After the starting material was consumed, the reaction mixture was diluted with H_2O (2.9 mL) and washed with CH_2Cl_2 (3 mL × 4). The aqueous layer was basified with 1 M Na_2CO_3 to pH ~ 8 (pH paper) and then extracted with CH_2Cl_2 (10 mL × 5). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The brown liquid crude containing **17** (139 mg, 80%) was directly used without purification. R_f = 0.40 (MeOH/CH_2Cl_2 = 1/10, ninhydrin); ^1H NMR (400 MHz, $CDCl_3$) δ 4.16 (m, 2H, COOCH_2), 3.54 (d, *J* = 6.4 Hz, 1 H, C*H*NH_2), 2.94 (dt, *J* = 7.0, 7.0 Hz, 1 H, C*H*CH_3), 2.18 (s, 3 H, COCH_3), 1.25 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 1.18 (d, *J* = 7.2 Hz, 3 H, CHCH_3).

Ethyl (2*S*,3*R*)-2-(Dibenzylamino)-3-methyl-4-oxopentanoate (26): Compound **26** was prepared by the same method as *ent*-**24** except a replacement of substrate *ent*-**22** to **17** to give colorless oil **26** (57%). R_f = 0.43 (EtOAc/hexane = 1/5, UV); $[\alpha]_D^{20.5}$ = -99.2 (c = 1.00, $CHCl_3$); IR (neat, NaCl plate) ṽ = 3086, 3062, 3029, 2977, 2936, 2848, 1727, 1603, 1495, 1454, 1368, 1182, 1147, 1027, 970, 751, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.22 (m, 10 H, *Ar*), 4.40–4.22 (m, 2 H, COOCH_2), 3.97 (d, *J* = 13.5 Hz, 2 H, PhCH_2), 3.54 (d, *J* = 11.6 Hz, 1 H, C*H*NBn_2), 3.29 (d, *J* = 13.4 Hz, 2 H, PhCH_2), 3.15 (m, 1 H, C*H*CH_3), 1.74 (s, 3 H, COCH_3), 1.40 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3), 0.99 (d, *J* = 6.8 Hz, 3 H, CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7 (s, *C*OCH$_3$), 169.8 (s, *C*OOCH_2), 138.7 (s, *Ar*), 129.5 (d, *Ar*), 128.3 (d, *Ar*), 127.3 (d, *Ar*), 64.1 (d, *C*HNBn_2), 60.5 (t, COO*C*H_2), 54.7 (t, Ph*C*H_2), 47.6 (d, *C*HCH_3), 25.8 (q, CO*C*H_3), 14.8 (q, CH_2CH_3), 14.3 (q, CH*C*H_3); HRMS (ESI-TOF) calcd. for $C_{22}H_{28}O_3^+$ [M+H$^+$] 354.2069, found 354.2061.

(3*S*,4*R*,5*S*)-3-(Dibenzylamino)-4,5-dimethyldihydrofuran-2(3H)-one (27): Compound **27** was prepared by the same method as *ent*-**25** except a replacement of substrate *ent*-**24** to **26** to give colorless oil **27** (74%). R_f = 0.45 (EtOAc/hexane = 1/5, UV); $[\alpha]_D^{19.7}$ = -84.6 (c = 0.98, $CHCl_3$); IR (neat, NaCl plate) ṽ = 3085, 3062, 3028, 2973, 2930, 2849,1763, 1603, 1492, 1454, 1383, 1298, 1194, 1144, 1055, 1028, 990, 952, 746, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.4 Hz, 4 H, *Ar*), 7.33 (t, *J* = 7.4 Hz, 4 H, *Ar*), 7.26 (t, *J* = 7.4 Hz, 2 H, *Ar*), 4.25 (dq, *J* = 6.1, 8.7 Hz, 1 H, COOC*H*), 3.78 (s, 4 H, PhCH_2), 3.59 (d, *J* = 10.1 Hz, 1 H, C*H*NBn_2), 2.11 (m, 1 H, C*H*CH_3), 1.34 (d, *J* = 6.1 Hz, 3 H, COOCHCH_3), 1.23 (d, *J* = 7.1 Hz, 3 H, CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7 (s, *C*OOCH), 138.8 (s, *Ar*), 128.8 (d, *Ar*), 128.7 (d, *Ar*), 128.6 (d, *Ar*), 128.4 (d, *Ar*), 127.4 (d, *Ar*), 83.2 (d, COO*C*H), 59.7 (d, *C*HNBn_2), 55.9 (t, PhCH_2), 41.4 (d, *C*HCH_3), 20.6 (q, COOCHCH_3), 11.6 (q, CH*C*H_3); HRMS (ESI-TOF) calcd. for $C_{20}H_{24}O_2N^+$ [M+H$^+$] 310.1807, found 310.1808.

Conflicts of interest

There are no conflicts to declare.

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