Organic & Biomolecular Chemistry

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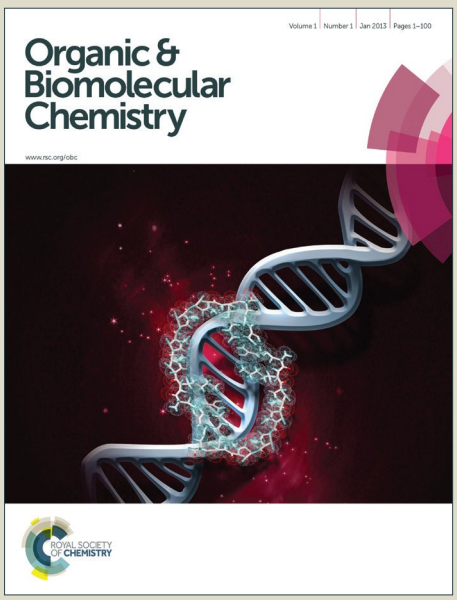

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PAPER

Total synthesis of the fellutamides, lipopeptide proteasome inhibitors. More sustainable peptide bond formation

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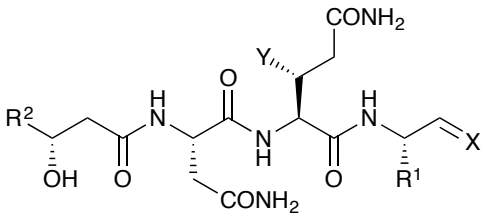
Solution-phase syntheses of three bioactive natural products of mixed polypeptide-polyketide biogenesis, fellutamides A, B, and C, have been achieved. Three peptide bonds are generated without the use of coupling reagents in each synthesis of the fellutamides, which act against the proteasome.

Introduction

The fellutamides are a small family of lipopeptide natural products (Table 1). Their structures vary mostly in the side chain at the *C*-terminus and in the hydroxylated fatty acyl chain at the *N*-terminus. Fellutamides A and B were originally discovered from a marine fungus found in fish, and newer representatives come from a range of fungi.[1] Peptide aldehydes like the fellutamides typically inhibit proteolytic enzymes, and the fellutamides expressly drew attention as proteasome inhibitors.[2] Fellutamide B stimulates transcription of the nerve growth factor (NGF) gene via proteasome inhibition and thereby promotes neurite outgrowth. Its complexation with the proteasome via covalent hemiacetal formation was characterized by X-ray crystallography.[2] It is also a strong inhibitor of the *Mycobacterium tuberculosis* proteasome.[3] Unfortunately, two different compounds have were named fellutamide C in the literature around the same time-frame. To resolve ambiguity between them, Singh's fellutamide C structure[1c] has been renamed in this work fellutamide E, an approach consistent with others.[1e] Fellutamide C is described as a potent cytotoxin vs. human cancer cells, which is a bit surprising as it is the only fellutamide that is not a *C*-terminal aldehyde. Fellutamides D and E have antifungal activity and inhibit the fungal proteasome. Fellutamide F shows strong cytotoxicity toward five cancer cell lines and is as potent as doxorubicin against two of them.

Table 1 The fellutamides



	R^1	R^2	X	Y
A	*i*Bu	C_9H_{19}	O	OH
B	*i*Bu	C_9H_{19}	O	H
C	*i*Bu	C_9H_{19}	H,OH	H
D	*i*Bu	$C_{11}H_{23}$	O	OH
E	*i*Pr	$C_{11}H_{23}$	O	OH
F	*i*Amyl	C_9H_{19}	OH,OH	H

Solid-phase or solution-phase syntheses of two members of this family, fellutamides B and C, have been reported.[4] While these are fairly simple compounds, the reported syntheses fall short in sustainability metrics for the production of an active pharmaceutical ingredient (API) as could emerge from these natural product leads. Most fellutamides also pose the challenge of the reactive α-amidoaldehyde that is key to their bioactivity.

Our goals in undertaking solution-phase synthesis of the fellutamides included improving the sustainability of peptide bond formation by minimizing protecting groups and avoiding classical, reagent-based condensation methods used in solid-phase peptide synthesis. Novel methods for peptide bond formation continue to be investigated, and here we exploited two we have practiced: aminoacylation with amino acid *N*-carboxyanhydrides (NCAs)[5] and ligation of aminoalcohols[6] (Scheme 1), both in organic media. A century-old approach to peptide synthesis by Leuchs[7] used NCAs (hence their common

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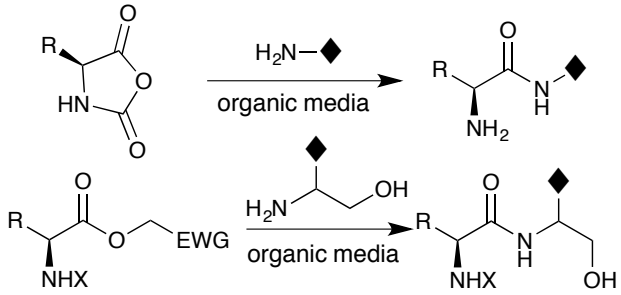
name, Leuchs' anhydrides). Another antecedent, by Hirschmann, used NCAs for peptide synthesis in rapidly stirred water.[8] NCAs are best known for their ring-opening polymerization. However, organic solvents enable their monoacylation reactions; several examples are known of the formation of single peptide bonds using NCAs.[9] The appeal of this method is enhanced by the commercial availability of many amino acid NCAs, as well as their easy 1-step preparations from amino acids or their *N*-carbamates. Aminoalcohol ligations are particularly pertinent to the hydroxyl-containing fellutamides and to serine-containing peptides (as also reported by others).[10] However, the latter technology is focused on ligations of native peptides in dilute, denaturing aqueous solvents, whereas our methods use protected peptides in concentrated organic media.

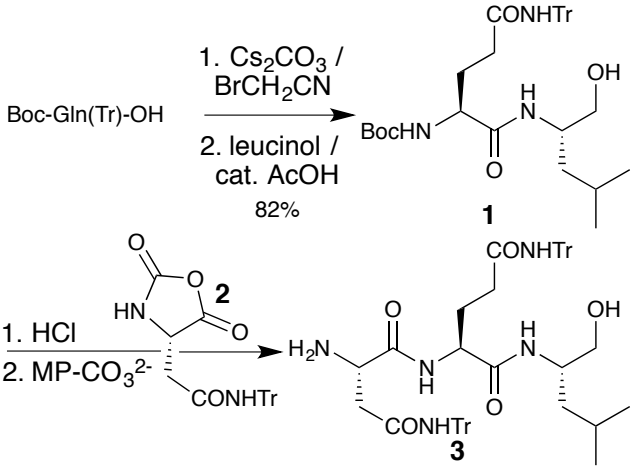


Scheme 1 Peptide synthesis via NCAs and ester ligations

Results and discussion

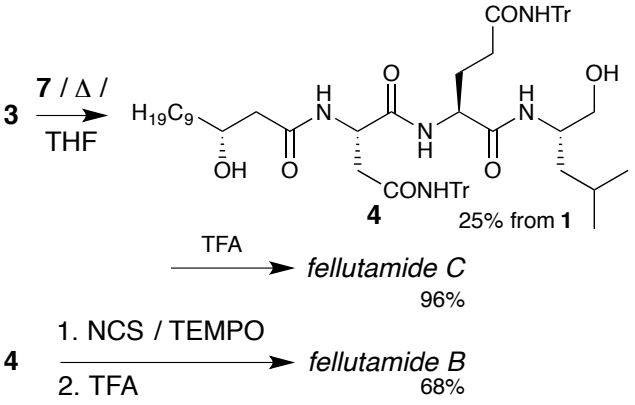
Synthesis of Fellutamides B and C

Commercial trityl-protected Boc-glutamine is converted quickly and efficiently in MeCN to the cyanomethyl ester (1 h, 90%). Its reaction with leucinol catalyzed by AcOH was investigated under a variety of conditions based on our previous study (Scheme 2).[6] Superior results were earlier seen in cyclohexane, but in this case solubility in cyclohexane was poor and conversion was low. Microwave heating improved the conversion and gave **1** in 85% yield. THF and ethyl acetate are better solvents for this transformation, though. It is interesting that ethyl acetate does not compete with the cyanomethyl ester for reaction with the aminoalcohol, despite the fact that it is in far higher concentration. We interpret this behaviour as a fortunate matching of the reactivity in transesterification reactions of aminoalcohols and mildly activated esters like lactones and cyanomethyl esters. This accounts for the fact that such ligations, despite their mechanistic obviousness and favourable thermodynamics, have been rarely reported. In our experience, many such ligations can be successfully performed in ethyl acetate. With 1.5 equiv leucinol at 1M in THF for 60 h, **1** is obtained in 91% yield; microwave heating enables complete reaction in 45 min. Removal of the Boc group was achieved with anhydrous HCl in ethyl acetate, which does not affect the trityl amide. It requires a stronger organic acid to remove, a difference that is also used later. The hydrochloride was neutralized using MP-carbonate ion exchange resin.[11] The NCA of *N*-trityl asparagine (**2**) was obtained in quantitative yield as white crystals by treatment of commercial *N*-Boc-*N*-β-trityl-Asn with PBr_3.[12] This NCA was heated with the peptide in NMP/THF at 60 °C for 24 h to produce **3**. These stringent conditions show the very low tendency of this NCA to undergo ring-opening polymerization in organic solvents. While asparagine NCA is known,[13] this is the first derivative with a modern protected amide grouping.



Scheme 2 Synthesis of a fellutamide advanced intermediate

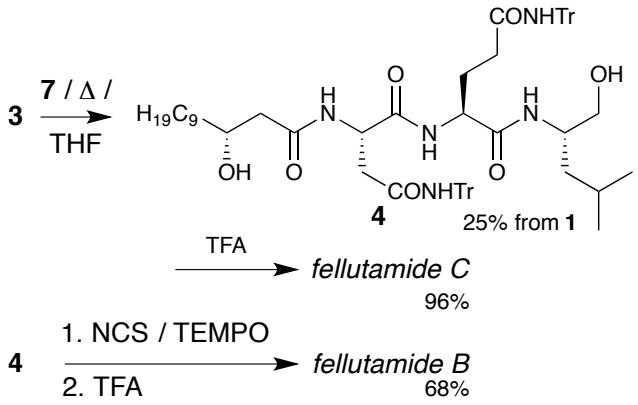
Without further treatment, **3** was coupled with a β-lactone **7** that is a simultaneously activated/protected synthon for (*R*)-3-hydroxydodecanoic acid. Compound **7** is available in two ways (Scheme 3), a 4-step sequence: hydrolytic kinetic resolution of 1-undecene oxide using the (*R,R*)-Jacobsen catalyst,[14] conversion to the β-hydroxyacid by Guaragna's route[15] (epoxide opening with cyanide and Radziszewski hydrolysis), and conversion to the β-lactone via the pyridyl thioester (Ph_3P, $(PyrS)_2$; $Hg(OMs)_2$);[16] or a 1-step route via asymmetric cycloaddition of decanal with ketene (89% yield, 98:2 *er*).[17] With **7** in hand, the final peptide bond is formed very simply by heating **3** with 1.2 equiv of β-lactone at 60 °C for 36 h (Scheme 4). The desired product **4** is obtained in 25% overall yield from **1** after chromatography.



Scheme 3 Synthesis of β-hydroxydodecanoic acid lactone

Further investigation of this route revealed the strengths of particular steps. Purifying only at the end gave the highest overall yield, but the best way to obtain a pristine sample of **3**

for characterization was a conventional peptide coupling. Compound **1** was deprotected, neutralized and coupled with *N*-Boc-*N*-β-trityl-asparagine using EDC/HOBt (~50% yield). After deprotection with HCl, the salt of **3** was washed several times with ethyl acetate/hexanes, which resulted in pure **3** following neutralization. Simply heating it with **7** in THF for 14 h delivers **4** in 72% yield.



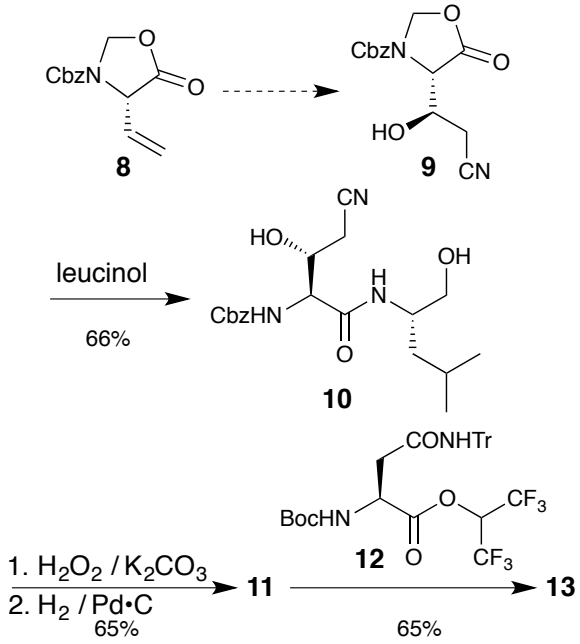
Scheme 4 Synthesis of fellutamides C and B

Completion of the fellutamide C synthesis from **4** exploited the method used by Crews for removing the peptide from the support in his fellutamide B synthesis, neat TFA. The synthetic natural product is easily isolated as a white solid following removal of the detritus of trityl deprotection by trituration with cold ether; fellutamide C is obtained in 96% yield. The so-produced compound was compared to literature spectroscopic data reported for the natural product.[1d] While most properties of the material we prepared, such as NMR data, match those reported for the natural product, some do not. Our material shows $[\alpha]_D^{25}$ -37.0 (*c* 0.12, MeOH) and -32.8 (*c* 0.3, MeOH), whereas the natural product (described as light violet in colour) is reported as -128 (*c* 0.18, MeOH). Optical rotations admittedly can be difficult to reproduce. Because **4** is converted to fellutamide B that is identical to the natural product, as we show following, it is certain that our synthetic fellutamide C has the structure assigned to the natural product.

Completion of the fellutamide B synthesis (Scheme 4) from **4** requires selective oxidation of the primary alcohol in the presence of amides and the secondary alcohol. Reactions were investigated that had been reported to exhibit such selectivity, including Parikh–Doering oxidation and Dess-Martin reagent. However, in our hands a TEMPO-catalyzed oxidation[18] was uniquely successful. The aldehyde was obtained in 72% yield. Completion of the synthesis used trityl deprotection as performed earlier, with the natural product being obtained in 94% yield. In just seven operations from commercial materials, fellutamide B was assembled in 14% overall yield. Its identity was verified by comparison to an authentic sample (NMR, TLC, $[\alpha]_D^{25}$).

Synthesis of Fellutamide A

The additional hydroxylation in the glutamine of fellutamide A complicates its structure but actually facilitates its synthesis, since it creates an aminoalcohol that is amenable to ligation. For this synthesis, we used only one protected side-chain amide (owing to the accessibility of a key reagent) (Scheme 5). The vinyl glycine derivative **8** is known from the work of Hanessian,[19] and has been converted to **9**, which is essentially a threonine derivative with an added cyano group. This is done via stereoselective (4:1) epoxidation (separated by chromatography) and epoxide opening with TMSCN (36% overall).[20] Upon treatment of **9** with leucinol under conditions described earlier, ligation product **10** is obtained in 70% yield. Radziszewski hydrolysis of the nitrile (87%) and Cbz removal set up a ligation with the hexafluoroisopropyl (HIP) ester of Boc trityl asparagine (**12**). In work to be detailed elsewhere,[21] we find that HIP esters are the best of a family of mildly activated esters with significantly enhanced ligation ability compared to CM esters. This trait enables ligation at what is essentially a threonine residue.[10] The product **13** is obtained in 65% overall yield from **10** upon heating at reflux in THF. Despite potential concerns about these conditions in reactions of an activated amino acid, there is no evidence for racemization as manifest in stereoisomeric products in **13**.

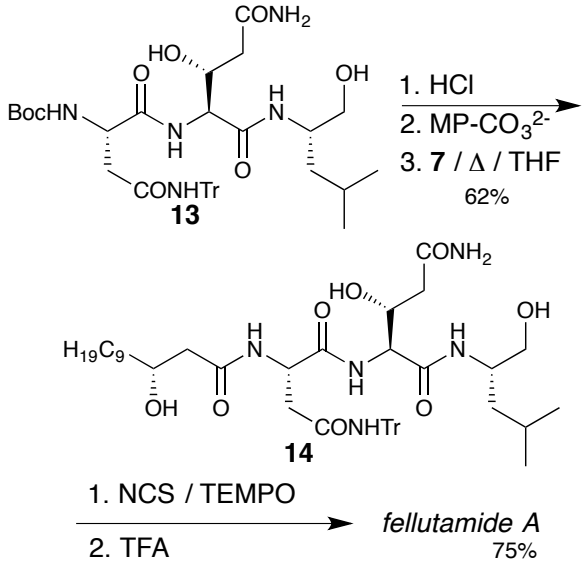


Scheme 5 Preparation of fellutamide A intermediate **13**

The selectivity in the initial transesterification for the last peptide bond formation is noteworthy. A secondary alcohol with two β-branches competes effectively against a primary alcohol with one β-branch. The structural feature that distinguishes them is the basic amine (that is eventually amidated), to which we have earlier ascribed an internal base effect.[6] This appears to be a phenomenon of kinetic control, not equilibrium transesterification at either alcohol and an irreversible, internal amidation. There is no indication of any reaction of **12** at the primary alcohol.

Intermediate **13** was carried forward via selective Boc deprotection and then reaction with the β-lactone **7**, giving **14** in 62% yield. Completion of the fellutamide A synthesis entails

initial primary alcohol oxidation as was applied to fellutamide B. Deprotection of the trityl group was also performed as before, giving synthetic fellutamide A in 75% yield for two steps, whose identity was shown by comparison to spectral data reported in the literature. In 10 operations from **8**, the natural product was assembled in 8% overall yield.



Scheme 6 Completion of the synthesis of fellutamide A

Conclusions

A structural theme in this work is reagents that simultaneously protect sites of undesired reactivity and activate a carboxyl group for coupling reactions. The β-lactone, oxazolidinone, and NCA are all examples of this principle.

Many metrics have been proposed to evaluate the sustainability of chemical processes.[22] A leading measure is process mass intensity (PMI), the ratio of the mass of all materials entering a synthesis (excluding aqueous solvents) to the mass of final product. The lower the PMI the better. A comparison of PMI and the other conventional synthesis metrics (Table 2) for reported fellutamide syntheses shows the utility in environmentally sensitive synthesis of the approaches to peptide bond formation applied here.

Table 2 Sustainability metrics for fellutamide syntheses

Author	Target	Steps	Yield	Stereoselectivity	PMI
Crews	Fellutamide B	13	42%[a]	100%	1980[b]
Payne	Fellutamide B	10	55%	100%	878
hoc opus	Fellutamide B	8	14%	100%	1014
Jung	Fellutamide C	9	3%	50%	5900
hoc opus	Fellutamide C	7	20%	100%	396

[a]yields for SPPS steps not provided; quantitative yields assumed

[b]includes only SPPS steps

In summary, these syntheses of lipopeptide natural products showcase three greener methods for peptide bond formation. An attractive feature is simultaneous internal protection/activation of the inherently multifunctional building blocks essential for biopolymer synthesis. As more environmentally benign peptide synthesis is a topic of significant current pursuit,[23] such methods could play an increased role in future preparative processes for peptide drugs, an area of burgeoning interest.[24]

Experimental

Boc-Gln(Tr)-O-cyanomethyl. A mixture of Boc-Gln(Trt)-OH (147 mg, 0.3 mmol), cesium carbonate (98 mg, 0.3 mmol), bromoacetonitrile (42 μL, 0.6 mmol), and acetonitrile (3 mL) was stirred at ambient temperature for 1 h. Ethyl acetate (50 mL) was added and the mixture was washed with water (20 mL × 2) and brine (20 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified with flash chromatography on silica gel with dichloromethane/methanol = 99/1 to give the product as a white solid (143 mg, 90 % yield). mp 171.4-172.7 °C (dichloromethane/hexanes). $[\alpha]_D^{23}$ + 2.6 (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.44 (s, 9H), 1.95-2.07 (m, 1H), 2.10-2.23 (m, 1H), 2.35-2.50 (m, 2H), 4.28-4.38 (m, 1H), 4.59 (d, J = 15.6 Hz, 1H), 4.65 (d, J = 16.0 Hz, 1H), 5.32 (d, J = 6.4 Hz, 1H), 6.83 (s, 1H), 7.18-7.32 (m, 15H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.3, 28.4, 32.9, 49.1, 53.1, 70.8, 80.6, 114.2, 127.2, 128.1, 128.8, 144.6, 155.8, 170.7, 171.2. IR (neat): 3388, 3263, 2973, 1765, 1719, 1638, 1540, 1141 cm^{-1}. HRMS (ESI-TOF): m/z calcd. for $C_{31}H_{34}N_3O_5$ $[M+H]^+$ 528.2493, found 528.2499.

Boc-Gln(Tr)-Leucinol (1). To a solution of Boc-Gln(Trt)-OCH_2CN (114 mg, 0.220 mmol) in THF (2.2 mL) was added acetic acid (2.5 μL, 0.044 mmol) and *L*-leucinol (39 mg, 0.33 mmol). The reaction mixture was stirred at ambient temperature for 60 h. After evaporation, the residue was taken up in ethyl acetate (50 mL) and washed with sat ammonium chloride (20 mL), sat sodium bicarbonate (20 mL), and brine (20 mL). The organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with dichloromethane/methanol = 100/0 ~ 98/2 to give **1** as a white solid (116 mg, 91 % yield). mp 172.6-173.9 °C (dichloromethane/hexanes). $[\alpha]_D^{23}$ -1.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.87 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H), 1.19-1.33 (m, 2H), 1.43 (s, 9H), 1.50-1.60 (m, 1H), 1.89-1.99 (m, 1H), 2.00-2.10 (m, 1H), 2.40 (ddd, J = 15.6, 8.0, 5.2 Hz, 1H), 2.54 (ddd, J = 15.6, 8.0, 5.2 Hz, 1H), 2.79 (br s, 1H), 3.27-3.34 (m, 1H), 3.56-3.63 (m, 1H), 3.89-3.99 (m, 2H), 5.66 (br s, 1H), 6.06 (d, J = 8.4 Hz, 1H), 7.02 (s, 1H), 7.20-7.32 (m, 15H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.2, 23.2, 24.9, 28.4, 29.1, 33.8, 40.0, 50.2, 54.4, 65.6, 70.8, 80.1, 127.2, 128.1, 128.8, 144.6, 156.1, 172.0, 172.2. IR (neat): 3275 (br), 2959, 1698, 1652, 1632, 1525, 1493 cm^{-1}. HRMS (ESI-TOF): m/z calcd. for $C_{35}H_{46}N_3O_5$ $[M+H]^+$ 588.3432, found 588.3449.

***N*-Trityl 2-[(*S*)-2,5-dioxooxazolidin-4-yl]acetamide (2).** To a suspension of Boc-L-Asn(Trt)-OH (237 mg, 0.500 mmol) in dichloromethane (5 mL) under N_2 was added PBr_3 (28 μL, 0.30 mmol) drop-wise. Et_3N (70 μL, 0.50 mmol) was immediately

added drop-wise. The mixture was stirred at ambient temperature for 24 h. Filtration afforded the title compound as a light yellow solid (200 mg, 100% yield). mp 176.2 °C (dec, THF/hexanes). $[\alpha]_D^{23}$ -22.4 (*c* 0.16, acetone). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.75 (dd, J = 16.4, 4.0 Hz, 1H), 3.07 (dd, J = 16.4, 4.4 Hz, 1H), 4.55 (t, J = 4.0 Hz, 1H), 7.15-7.29 (m, 15H), 8.92 (s, 1H), 9.02 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 36.8, 54.0, 69.7, 126.5, 127.6, 128.6, 144.4, 152.4, 167.8, 171.6. IR (neat): 3416, 3359, 3061, 1858, 1786, 1666, 1508, 1495, 908, 901 cm^{-1}. HRMS (ESI/APCI): m/z calcd. for $C_{24}H_{24}N_3O_4$ $[M+NH_4]^+$ 418.1761, found 418.1772.

Asn(Tr)-Gln(Tr)-Leucinol (3). A 4N solution of HCl in ethyl acetate was prepared by bubbling HCl gas into cold solvent and measuring the mass increase. Dipeptide **1** (294 mg, 0.500 mmol) was deprotected by treatment with 4N HCl/ethyl acetate (2.5 mL) at 0 °C for 1 h. After concentration, the residue was taken up in methanol (5 mL) and neutralized with MP-carbonate ion exchange resin (514 mg, 1.50 mmol) at ambient temperature for 1 h. To a solution of the free amine in DMF/THF (6 mL, 2/1) was added Boc-Asn(Trt)-OH (237 mg, 0.500 mmol), HOBt (68 mg, 0.50 mmol), and EDC•HCl (96 mg, 0.50 mmol). The mixture was stirred at ambient temperature for 24 h. Water (100 mL) was added and the resulting mixture was extracted with ethyl acetate (30 mL × 3). The organic phases were combined and washed with water (30 mL × 3), sat NH_4Cl solution (30 mL), sat $NaHCO_3$ solution (30 mL) and brine (30 mL). The organic phase was dried over sodium sulfate, filtered and concentrated. The residue was purified with flash chromatography on silica gel eluting with dichloromethane/methanol = 99/1 ~ 97/3 to afford the product as a white solid (230 mg, 49 % yield over two steps). mp 95 °C (dec acetone/hexanes). $[\alpha]_D^{23}$ -11.9 (*c* 0.5, acetone). ^{1}H NMR (acetone-d_6, 400 MHz): δ 0.80 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 6.4 Hz, 3H), 1.07-1.14 (m, 2H), 1.40 (s, 9H), 1.48-1.56 (m, 1H), 1.85-1.94 (m, 1H), 1.98-2.02 (m, 1H), 2.45-2.59 (m, 2H), 2.67 (dd, J = 15.2, 5.2 Hz, 1H), 2.94 (dd, J = 15.2, 5.6 Hz, 1H), 3.08-3.20 (m, 2H), 3.82-3.92 (m, 1H), 4.05-4.15 (m, 1H), 4.21 (q, J = 5.2 Hz, 1H), 6.00 (d, J = 6.0 Hz, 1H), 7.09-7.11 (m, 1H), 7.19-7.27 (m, 30H), 8.01 (d, J = 4.1 Hz, 1H), 8.08 (brs, 1H), 8.14 (brs, 1H). ^{13}C NMR (acetone-d_6, 100 MHz): δ 22.4, 23.7, 25.4, 28.1, 28.6, 33.7, 39.1, 40.6, 50.5, 52.9, 55.3, 65.4, 71.0, 71.2, 79.8, 127.4, 127.5, 128.4, 128.4, 129.7, 145.7, 145.9, 156.2, 170.7, 171.7, 172.2, 173.6. IR (neat): 3302 (br), 2955, 1661, 1490 cm^{-1}. HRMS (ESI-TOF): m/z calcd. for $C_{58}H_{65}N_5NaO_7$ $[M+Na]^+$ 966.4776, found 966.4808.

Boc-Asn(Tr)-Gln(Tr)-Leucinol (150 mg, 0.159 mmol) was deprotected with 4 N HCl/ethyl acetate as stated earlier. The solvent was removed under reduced pressure. The resulting HCl salt was washed two times with ethyl acetate/hexanes before neutralization with MP-carbonate. Filtration and concentration afforded the free amine as a white foam (130 mg, 97% yield). mp 127.4 °C (dec, methanol/dichloromethane). $[\alpha]_D^{23}$ -17.2 (*c* 0.71, MeOH). ^{1}H NMR (CD_3OD, 400 MHz): δ 0.85 (d, J = 6.4 Hz, 6H), 1.15-1.19 (m, 2H), 1.51-1.58 (m, 1H), 1.79-1.88 (m, 1H), 2.03-2.12 (m, 1H), 2.29-2.46 (m, 2H), 2.69 (dd, J = 15.2, 6.0 Hz, 1H), 2.77 (dd, J = 15.2, 5.6 Hz, 1H), 3.22 (dd, J = 11.2, 6.4 Hz, 1H), 3.26 (dd, J = 11.2, 5.2 Hz, 1H), 3.57 (t, J = 5.6 Hz, 1H), 3.90-3.96 (m, 1H), 4.27-4.30 (m, 1H), 7.18-7. 23 (m, 30 H). ^{13}C NMR (CD_3OD, 100 MHz): δ 22.5, 23.7, 25.8, 29.0, 33.8, 40.8, 41.5, 50.9, 53.1, 54.6, 65.4, 71.5, 71.6, 127.7, 127.8, 128.6, 128.7, 130.0, 145.8, 172.1, 173.2, 174.6, 175.8. IR (neat): 3284 (br), 2953, 1653, 1520, 1491, 1027 cm^{-1}. HRMS (ESI-TOF): m/z calcd. for $C_{53}H_{57}N_5NaO_5$ $[M+Na]^+$ 866.4252, found 866.4274.

(*R*)-3-Hydroxydodecanoyl-Asn(Tr)-Gln(Tr)-Leucinol (4). Compound **1** (294 mg, 0.500 mmol) was deprotected and neutralized as detailed above. To a solution of the resulting free amine in NMP/THF (2:1, 6 mL) was added **2** (200 mg, 0.500 mmol). The mixture was stirred at 60 °C for 24 h. After addition of β-lactone **7** (119 mg, 0.600 mmol), the mixture was kept at 60 °C for another 36 h. Water (300 mL) was added and the resulting mixture was extracted with ethyl acetate (100 mL × 3). The organic phases were combined and washed with water (100 mL × 3), sat NH_4Cl (100 mL), and brine (100 mL). The organic phase was dried over sodium sulfate, filtered and concentrated. The residue was purified with flash chromatography on silica gel eluting with dichloromethane/methanol = 98/2 ~ 96/4 to afford the product as a white solid (132 mg, 25% yield over three steps). mp 103.5-105.1 °C (acetone/hexanes). $[\alpha]_D^{23}$ -10.8 (*c* 0.4, acetone). ^{1}H NMR (acetone-d_6, 400 MHz): δ 0.82-0.90 (m, 9H), 1.16-1.36 (m, 18H), 1.53-1.59 (m, 2H), 1.81-1.89 (m, 2H), 1.98-2.01 (m, 1H), 2.06-2.09 (m, 1H), 2.25 (dd, J = 14.4, 3.6 Hz, 1H), 2.36-2.45 (m, 1H), 2.47-2.53 (m, 1H), 3.20-3.29 (m, 2H), 3.49 (br s, 1H), 3.80-3.92 (m, 2H), 4.08-4.14 (m, 1H), 4.30 (br s, 1H), 4.49 (dd, J = 12.4, 5.6 Hz, 1H), 7.00 (d, J = 9.2 Hz, 1H), 7.18-7.27 (m, 30H), 7.41 (d, J = 7.2 Hz, 1H), 8.09 (s, 1H), 8.10 (d, J = 4.4 Hz, 1H), 8.19 (s, 1H). ^{13}C NMR (acetone-d_6, 100 MHz): δ 14.4, 22.5, 23.3, 23.7, 25.4, 26.3, 28.0, 30.3, 30.4, 32.6, 33.7, 37.9, 38.6, 40.6, 43.7, 50.5, 51.9, 55.2, 65.4, 69.1, 71.0, 71.2, 127.4, 128.4, 129.7, 145.7, 145.9, 170.9, 171.9, 172.3, 173.3, 173.8. IR (neat): 3301 (br), 2926, 1635, 1492, 1447, 1412 cm^{-1}. HRMS (ESI-TOF): m/z calcd. for $C_{65}H_{79}N_5O_7Na$ $[M+Na]^+$ 1064.5872, found 1064.5925.

(*R*)-3-Hydroxydodecanoyl-Asn(Tr)-Gln(Tr)-Leucinol (4). A solution of free amine **3** (63 mg, 0.075 mmol) and β-lactone **7** (30 mg, 0.15 mmol) in THF (1.5 mL) was heated at reflux for 14 h. The solvent was removed by rotary evaporation. Purification by flash chromatography on silica gel with dichloromethane/methanol = 98/2 ~ 96/4 afforded the product as white foam (59 mg, 72 % yield).

(*R*)-2-Nonyloxirane (5). AcOH (0.11 mL, 2.0 mmol) was added to a suspension of (*R,R*)-Jacobsen catalyst (0.12 g, 0.2 mmol) in toluene (5 mL) and the mixture was stirred for 1 h at ambient temperature. The solvent was removed by rotary evaporation followed by high vacuum, and the residue was cooled to 0 °C. Neat racemic epoxide (6.9 g, 40 mmol) was added with stirring. Water (0.40 mL, 22 mmol) was added drop-wise to the cooled reaction mixture over 25 min and the mixture was stirred at ambient temperature for 13 h. The reaction mixture was purified by Kugelrohr distillation (75 °C, 5 torr) to give the title compound (3.04 g, 44%, 93% *ee*). $[\alpha]_D^{25}$ − 9.05 (*c* = 1.0, $CHCl_3$). This material gave spectroscopic data identical to the known compound.

(*R*)-3-hydroxydodecanenitrile. A suspension of KCN (9.18 g, 141 mmol) and epoxide **5** (3.00 g, 17.6 mmol) in MeOH (50 mL) was heated at reflux (70 °C) for 16 h. The reaction mixture was diluted with chloroform (100 mL) and the organic phase was washed with water (3 × 75 mL). The organic phase was dried with sodium sulfate and concentrated, and the residue was purified by flash chromatography to give the title compound (2.4 g, 69%). R_f 0.4 (20% ethyl acetate/hexanes). IR (neat): 3439, 2923, 2854, 2253, 1465, 1084 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.90 (m, 1H), 2.50 (m, 3H), 1.68 – 1.11 (m, 16H), 0.86 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 117.9, 67.8, 36.6, 31.9, 31.0, 29.6, 29.4, 29.3, 26.2, 25.5, 22.7, 14.2. $[\alpha]_D^{25}$ – 3.8 (*c* = 1.0, $CHCl_3$). This was identical to the known compound.

(*R*)-3-hydroxydodecanoic acid (6). A mixture of the foregoing compound (2.18 g, 11.0 mmol), 48% NaOH (3.7 mL) and 30% H_2O_2 (3.4 mL) in MeOH (25 mL) was heated at reflux overnight. The reaction mixture was acidified with 2N HCl at ambient temperature and extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried with sodium sulfate and concentrated. The resultant residue was purified by flash chromatography to give the pure title compound (1.82 g, 76%). R_f 0.2 (50% ethyl acetate/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 6.91 (s, 1H), 4.00–4.07 (m, 1H), 2.64-2.35 (m, 2H), 1.79–1.05 (m, 16H), 0.87 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.0, 68.3, 41.3, 36.6, 32.0, 29.7, 29.6, 29.4, 25.6, 22.8, 14.2. $[\alpha]_D^{25}$ – 16.9 (*c* = 1.0, $CHCl_3$). This was identical to the known compound.

(*R*)-3-hydroxydodecanoic acid (6). A mixture of epoxide **5** (105 mg, 0.617 mmol) and KCN (112 mg, 1.726 mmol) in MeOH/H_2O (1.5 mL, 9/1) was stirred at ambient temperature for 16 h. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with H_2O (30 mL × 3) and brine (30 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified with flash chromatography on silica gel eluting with hexanes / ethyl acetate = 85/15 ~ 70/30 to give (*R*)-3-hydroxydodecanenitrile as a colorless oil (117 mg, 0.593 mmol, 96 % yield). To a solution of (*R*)-3-hydroxydodecanenitrile (110 mg, 0.557 mmol) in MeOH (3 mL) was added 48 % NaOH aqueous solution (186 μL, 2.23 mmol) and 30 % H_2O_2 solution (246 μL, 2.17 mmol). The mixture was heated at reflux for 20 h, acidified with 2 N HCl (1.2 mL), and extracted with ethyl acetate (30 mL × 2). The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated. Recrystallization from hexanes/ethyl acetate gave the title compound as a white solid (93 mg, 77 % yield). $[\alpha]_D^{23}$ -18.5 (*c* 1.0, $CHCl_3$) ($[\alpha]_D^{25}$ = -17.8 (*c* 1.2, MeOH). ^1H NMR data match previously reported data.

(*R*)-4-Nonyloxetan-2-one (7). In an oven-dried flask 2,2'-pyridine disulfide (66 mg, 0.30 mmol) and triphenylphosphine (84 mg, 0.32 mmol) were dissolved in anhydrous chloroform (2 mL) at ambient temperature under nitrogen. Acid **6** (43 mg, 0.20 mmol) was slowly added. After 30 min, the resulting yellow solution was added drop-wise to a vigorously stirred suspension of mercury(II) methanesulfonate (156 mg, 0.400 mmol) in anhydrous acetonitrile (4.8 mL) at 50 °C under nitrogen. After 20 min at 50 °C, the reaction mixture was filtered and the white precipitate was washed several times with chloroform. After evaporation of the solvent, the residue was purified by a very short column on silica gel eluting with hexanes/ethyl acetate = 2/1 to give the β-lactone as light yellow oil (34 mg, 86 % yield). $[\alpha]_D^{23}$ +21.4 (*c* 0.6, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.87 (t, J = 6.9 Hz, 3H), 1.20-1.50 (m, 14H), 1.67-1.89 (m, 2H), 3.04 (dd, J = 16.2, 4.5 Hz, 1H), 3.49 (dd, J = 16.2, 5.7 Hz, 1H), 4.45-4.53 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.2, 22.8, 25.0, 29.3, 29.4, 29.5, 32.0, 34.8, 43.0, 71.4, 168.5. IR (neat): 2924, 2854, 1825 cm^{-1}. HRMS (ESI-TOF): m/z calcd. for $C_{12}H_{23}O_2$ $[M+H]^+$ 199.1693, found 199.1702.

Fellutamide C. Diol **4** (33 mg, 0.032 mmol) in TFA (0.5 mL) was stirred at ambient temperature for 30 min, then the mixture was evaporated to give a light yellow solid. This was washed with cold ether (1.5 mL × 3) to afford the desired product as a white solid (17 mg, 96 % yield). mp 157.0 °C (dec, acetone/hexanes). $[\alpha]_D^{23}$ -37.0 (*c* 0.12, MeOH) $[\alpha]_D^{23}$ -32.8 (*c* 0.3, MeOH) (lit.[1d] $[\alpha]_D$ = -128 (*c* 0.18, MeOH), $[\alpha]_D$ -112 (*c* 0.15, MeOH). ^1H NMR (CD_3OD, 400 MHz): δ 0.89-0.94 (m, 9H), 1.27-1.37 (m, 14H), 1.42-1.55 (m, 4H), 1.64 (m, 1H), 1.92 (m, 1H), 2.18 (m 1H), 2.30-2.36 (m, 3H), 2.44 (dd, J = 14.4, 4 Hz, 1H), 2.73 (dd, J = 15.6, 6.8 Hz, 1H), 2.79 (dd, J = 15.6, 6.8 Hz, 1H), 3.47 (d, J = 5.2 Hz, 2H), 3.98 (m, 2H), 4.29 (dd, J = 9.6, 4 Hz, 1H), 4.64 (t, J = 6.4 Hz, 1H). ^{13}C NMR (CD_3OD, 100 MHz): δ 14.4, 22.4, 23.7, 25.9, 26.7, 28.7, 30.5, 30.7, 30.8, 32.7, 33.1, 37.4, 38.4, 40.9, 44.5, 51.0, 51.9, 54.8, 65.5, 69.8, 173.3, 173.6, 174.5, 174.9, 178.0. The ^{13}C NMR data show a consistent shift difference of ~2 ppm compared to the literature, which may be due to a faulty spectral calibration therein. IR (neat): 3278 (br), 2924, 2854, 2419, 1653, 1621, 1546 cm^{-1}. HRMS (ESI-TOF): m/z calcd. for $C_{27}H_{51}N_5O_7Na$ $[M+Na]^+$ 580.3681, found 580.3700.

Fellutamide B. Diol **4** (28 mg, 0.027 mmol) was dissolved in dichloromethane (2.7 mL) and pH 8.6 buffer ($NaHCO_3/K_2CO_3$, 2.7 mL). The biphasic mixture was cooled to 0 °C and KBr (0.1 mL of a 0.27 M solution, 0.027 mmol), $n$$Bu_4NBr$ (0.1 mL of a 0.18 M solution, 0.018 mmol) and TEMPO (0.1 mL of a 0.03 M solution in dichloromethane, 0.003 mmol) were added. NCS (3.6 mg, 0.027 mmol) was added to the vigorously stirred mixture. After stirring at 0 °C for 1.5 h, the reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (20 mL × 3). The organic layers were combined and washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated. The crude product was purified with flash chromatography on silica gel eluting with dichloromethane/methanol = 99/1 ~ 96/4 to afford the aldehyde as a white solid (20 mg, 72 % yield). mp 195.0 °C (dec, acetone/hexanes). $[\alpha]_D^{23}$ -11.7 (*c* 0.9, acetone). ^1H NMR (acetone-d_6, 400 MHz): δ 0.78-0.90 (m, 9H), 1.20-1.42 (m, 18H), 1.57-1.70 (m, 2H), 1.80-1.90 (m, 1H), 1.95-2.02 (m, 1H), 2.07-2.11 (m, 1H), 2.27 (dd, J = 14.4, 3.6 Hz, 1H), 2.38-2.56 (m, 2H), 3.22-3.26 (m, 1H), 3.78-3.87 (m, 1H), 3.89-3.97 (m, 1H), 4.10-4.40 (m, 2H), 4.48-4.60 (m, 1H), 7.16-7.32 (m, 30H), 7.49 (d, J = 6.8 Hz, 1H), 7.84 (d, J = 7.6 Hz, 1H), 8.08 (s, 1H), 8.09 (d, J = 6.4 Hz, 1H), 8.21 (s, 1H), 9.35 (s, 1H). ^{13}C NMR (acetone-d_6, 100 MHz): δ 14.4, 21.9, 23.3, 23.5, 25.0, 26.3, 27.8, 30.3, 30.4, 32.6, 33.6, 37.6, 37.9, 38.9, 43.7, 51.7, 54.5, 57.9, 69.1, 71.1, 71.2, 127.5, 128.4, 129.8, 145.8, 145.9, 171.0, 171.9, 172.6,

173.1, 173.7, 202.1. IR (neat): 3264 (br), 2927, 1733, 1662, 1632, 1521, 1490 cm^{-1}. HRMS (FAB): m/z calcd. for $C_{65}H_{77}N_5O_7Na$ $[M+Na]^+$ 1062.5715, found 1062.5720.

A solution of protected aldehyde (44 mg, 0.042 mmol) in trifluoroacetic acid (2.2 mL) was stirred at ambient temperature for 30 min. Upon completion of the deprotection, the trifluoroacetic acid was evaporated. The resultant light yellow solid was washed with cold diethyl ether (1.5 mL × 3) to give the title compound as a white solid (22 mg, 94 % yield). mp 165.2 °C (dec, acetone/hexanes). $[\alpha]_D^{23}$ -29.2 (*c* 0.3, MeOH) ($[\alpha]_D^{21}$ -24.7 (*c* 0.5, MeOH)). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.7-0.9 (m, 9H), 1.2-1.4 (m, 16H), 1.49 (m, 2H), 1.65 (m, 1H), 1.76 (m, 1H), 1.97 (m, 1H), 2.11 (m, 2H), 2.21 (m, 2H), 2.45 (m, 1H), 2.57 (m, 1H), 3.78 (m, 1H), 4.03 (m, 1H), 4.19 (m, 1H), 4.51 (m, 1H), 4.63 (m, 1H, exchangeable with D_2O), 6.76 (br s, 1H, exchangeable with D_2O), 6.93 (br s, 1H, exchangeable with D_2O), 7.21 (br s, 1H, exchangeable with D_2O), 7.43 (br s, 1H, exchangeable with D_2O), 8.10 (br s, 2H, slowly exchangeable with D_2O), 8.28 (d, J = 7.2 Hz, 1H, slowly exchangeable with D_2O), 9.35 (1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 13.9, 21.3, 22.1, 23.1, 23.9, 28.7, 29.0, 29.1, 31.3, 36.9, 37.0, 43.5, 49.8, 52.4, 56.6, 67.4, 171.1, 171.2, 171.8, 171.8, 173.8, 201.6. IR (neat): 3277 (br), 2924, 1732, 1662, 1627, 1544 cm^{-1}. HRMS (FAB): m/z calcd. for $C_{27}H_{49}N_5O_7Na$ $[M+Na]^+$ 578.3524, found 578.3531.

Cbz-4-cyanoThr-Leucinol (10). A solution of **9** (22 mg, 0.076 mmol) and L-leucinol (13 mg, 0.114 mmol) in anhydrous dichloromethane (760 μL) was stirred at ambient temperature for 2 d. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with 0.1 N HCl solution (10 mL) and brine (10 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified with flash chromatography on silica gel eluting with dichloromethane / methanol = 96/4 to give compound **10** as colorless oil (19 mg, 66 % yield). $[\alpha]_D^{23}$ = -25.6 (*c* 0.32, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.88 (d, J = 6.4 Hz, 3H), 0.90 (d, J = 6.0 Hz, 3H), 1.29 – 1.40 (m, 2H), 1.54 – 1.60 (m, 1H), 2.58 (d, J = 6.4 Hz, 2H), 2.85 (brs, 1H), 3.47 (dd, J = 10.8, 6.8 Hz, 1H), 3.69 (d, J = 9.2 Hz, 1H), 4.05 (brs, 1H), 4.34 (d, J= 7.6 Hz, 1H), 4.48 (brs, 1H), 4.55 (brs, 1H), 5.10 (d, J = 12.4 Hz, 1H), 5.14 (d, J = 11.6 Hz, 1H), 5.96 (brs, 1H), 6.58 (brs, 1H), 7.30 – 7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.0, 22.2, 23.1, 24.9, 39.9, 50.4, 57.5, 65.3, 67.6, 67.8, 118.1, 128.3, 128.6, 128.8, 135.8, 156.9, 169.7. IR (neat): 3318 (br), 2957, 2871, 2253, 1706, 1653, 1521, 1239, 1050 cm^{-1}. HRMS (ESI-TOF): m/z calcd. for $C_{19}H_{28}N_3O_5$ $[M+H]^+$ 378.2023, found 378.2038.

3-OHGln-Leucinol (11). To a solution of **10** (200 mg, 0.53 mmol) in 1,4 dioxane and water (2:1 5mL) was added K_2CO_3 (87 mg, 0.6 mmol) followed by H_2O_2 (270 mg, 7.95 mmol)at room temperature. After stirring for 2 hr the reaction mixture was heated to 40 °C for 30 min. The product was extracted with ethyl acetate and organic phases were washed with water and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure to afford crude free amide, which was dissolved in ethanol and a catalytic amount of Pd/C was added. This reaction mixture was stirred overnight in a hydrogen atmosphere to give the free amine. The reaction mixture was filtered and the crude product isolated by evaporation. This amine and active ester **12** (331 mg, 0.53 mmol) were dissolved in dry THF and heated at reflux for 18 h. The solvent was evaporated under reduced pressure to give the crude product, which was purified by column chromatography to furnish white solid (247 mg, 65 % yield). mp 135–138 °C. $[\alpha]_D^{23}$ +10.2 (*c* 0.1 CH_3OH). ^{1}H NMR (300 MHz, CD_3OD): δ 0.86 (d, *J* = 6.3 Hz, 6H), 1.32 – 1.13 (m, 2H), 1.46 (s, 9H), 1.58 (m, 1H), 2.23– 2.41 (m, 2H), 2.74– 2.95 (m, 2H), 3.86– 4.04 (m, 2H), 4.26– 4.42 (m, 2H), 4.44– 4.55 (m, 1H), 7.11–7.40 (s, 15H). ^{13}C NMR (100 MHz, CD_3OD); δ 174.9, 172.5, 171.1, 170.1, 156.2, 144.6, 128.8, 127.5, 126.3, 70.5, 68.0, 64.0, 57.5, 51.9, 49.8, 39.5, 39.1, 37.7, 27.8, 24.2, 22.3, 20.6. IR (neat): 3351, 2983, 1775, 1657, 1530, 1178 cm^{-1}. HRMS (ESI-TOF): m/z calcd. for $C_{39}H_{55}N_6O_8$ $[M+NH_4]^+$ 735.4076, found 735.4080.

Boc-Asn(Tr)-O-hexafluoroisopropyl (12). Boc-Asn(Tr)-OH (1.0 g, 2.1 mmol) was dissolved in dichloromethane and stirred at 0 °C. EDC (0.48 g, 2.53 mmol) and DMAP (0.051 g, 0.42 mmol) were added at 0 °C and stirred for 10 min, then hexafluoroisopropanol (0.42 g, 2.53 mmol) was added at the same temperature and stirred for 2 h. The reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was washed with sat $NaHCO_3$ and brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified with flash chromatography on silica gel eluting with hexane / ethyl acetate = 90/10 to give **12** as white solid (0.982 g, 75 % yield). mp 187–188 °C. $[\alpha]_D^{23}$ -14.3 (*c* 1.0, CH_3OH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.92 (dd, *J* = 15.8, 4.4 Hz, 1H), 3.11 (dd, *J* = 16.4, 4.7 Hz, 1H), 5.61– 5.84 (m, 1H), 6.64 (s, 1H), 4.56– 4.69 (m, 1H), 7.15 (dd, *J* = 7.5, 1.9 Hz, 5H), 7.20– 7.56 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.9, 168.7, 155.5, 144.4, 128.5, 128.5, 1275, 80.6, 71.3, 50.5, 38.36, 28.4. IR (neat): 3361 (br), 2982, 1780, 1686, 1660, 1519, 1198 cm^{-1}. HRMS (ESI-TOF): m/z calcd. for $C_{31}H_{30}F_6N_2NaO_5$ $[M+Na]^+$ 647.1951, found 647.1982.

Boc-Asn(Tr)- 3-OHGln-Leucinol (13). To a solution of **10** (200 mg, 0.53 mmol) in 1,4-dioxane and water (2:1 5mL) was added K_2CO_3 (87 mg, 0.6 mmol) followed by H_2O_2 (270 mg, 7.95 mmol) at ambient temperature. After stirring for 2 h the reaction mixture was heated to 40 °C for 30 min. The mixture was extracted with ethyl acetate and the organic phases were washed with water and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure to afford crude free amide, which was dissolved in ethanol and a catalytic amount of Pd/C was added. This mixture was stirred overnight under a hydrogen atmosphere to give **11**. This amine and active ester **12** (331 mg, 0.53 mmol) were dissolved in dry THF and refluxed for 18 hr. then the solvent was evaporated under reduced pressure to give a residue that was purified by column chromatography to furnish a white solid (247 mg, 65 % yield). mp 135–138 °C. $[\alpha]_D^{23}$ +10.2 (*c* 0.1 CH_3OH). ^{1}H NMR (300 MHz, CD_3OD): δ 0.86 (d, *J* = 6.3 Hz, 6H), 1.13–1.32 (m, 2H), 1.46 (s, 9H), 1.58 (m, 1H), 2.23 – 2.41 (m, 2H), 2.74– 2.95 (m, 2H), 3.86 – 4.04 (m, 2H), 4.26 – 4.42 (m, 2H), 4.44 - 4.55 (m, 1H), 7.11– 7.40 (s, 15H). ^{13}C NMR (100 MHz, CD_3OD): δ 174.9, 172.5, 171.1, 170.1, 156.2, 144.6, 128.8, 127.5, 126.3, 70.5, 68.0, 64.0, 57.5, 51.9, 49.8, 39.5, 39.1, 37.7, 27.8, 24.2, 22.3, 20.6.

HRMS (ESI-TOF): m/z calcd. for $C_{39}H_{55}N_6O_8$ $[M+NH_4]^+$ 735.4076, found 735.4080. IR (neat): 3351, 2983, 1775, 1657, 1530, 1178 cm^{-1}.

(*R*)-3-Hydroxydodecanoyl-Asn(Tr)-3-OHGln-Leucinol (14). Boc-Asn(Tr)-OHGn-Leucinol (50 mg, 0.069 mmol) was deprotected with 4 N HCl/ethyl acetate as described earlier. The solvent was removed under reduced pressure. The resulting HCl salt was washed two times with ethyl acetate/hexanes before neutralization with MP-carbonate. Filtration and concentration afforded the crude free amine. A solution of the free amine and β-lactone **7** (27 mg, 0.139 mmol) in THF (1.5 mL) was heated at reflux for 14 h. The solvent was removed under reduced pressure. The residue was purified with flash chromatography on silica gel eluting with dichloromethane/methanol = 96/4 ~ 90/10 to afford the product as a white solid (35 mg, 62%). mp 155-157 °C. $[\alpha]_D^{23}$ -16.8 (*c* 0.1, MeOH). ^{1}H NMR (300 MHz, CD_3OD): δ 0.76– 1.01 (m, 9H), 1.18– 1.56 (m, 23H), 2.25– 2.50 (m, 2H), 2.87 (dd, *J* = 22.9, 14.6 Hz, 2H), 3.49 (d, *J* = 5.3 Hz, 1H), 3.73 (dt, *J* = 13.2, 6.6 Hz, 1H), 3.93 (m, 2H), 4.22 (d, *J* = 5.6 Hz, 1H), 4.40 (m, 1H), 4.48 (m, 1H), 7.24 (s, 15H). ^{13}C NMR (100 MHz, CD_3OD): δ 176.0, 174.5, 173.1, 170.1, 169.9, 144.6, 128.8, 127.5, 126.6, 70.5, 68.4, 66.0, 58.4, 57.5, 47.8, 42.9, 37.0, 31.8, 29.5, 29.2, 25.4, 22,5 13.2, 12.7. IR (neat): 3348 (br), 2955, 1765, 1652, 1547, 1412 cm^{-1}. HRMS (ESI-TOF): m/z calcd. for $C_{46}H_{65}N_5O_8Na$ $[M+Na]^+$ 838.4725,found 838.4727.

Fellutamide A. Triol **14** (20 mg, 0.024 mmol) was dissolved in dichloromethane (2.5 mL). A biphasic system was formed with pH 8.6 buffer ($NaHCO_3/K_2CO_3$, 2.5 mL), which was cooled to 0 °C. KBr (3 mg, 0.024 mmol), $n$$Bu_4NBr$ (4 mg, 0.012 mmol) and TEMPO (4 mg, 0.0024 mmol) were added. NCS (3.2 mg, 0.024 mmol) was added to the vigorously stirred mixture. After stirring at 0 °C for 1.5 h, the reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (20 mL × 3). The organic layers were combined and washed with brine (20 mL), dried over sodium sulfate, filtered and concentrated to get the crude protected aldehyde. A solution of this aldehyde in TFA (2 mL) was stirred at ambient temperature for 30 min. Upon completion of deprotection, the TFA was evaporated. The resultant solid was washed with cold diethyl ether (1.5 mL ×3) to give the title compound as a white solid (10 mg, 75% yield). mp 195.5 °C (dec, acetone/hexanes). $[\alpha]_D^{23}$-13.5 (*c* 0.1, MeOH). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.85 (m, 9H), 1.35 (m, 24H), 1.65 (m, 1H), 2.22 (m, 4H), 2.49 (m, 1H), 3.01 (m, 1H), 3.74 (m, 1H), 4.07 (m, 1H), 4.24 (m, 1H), 4.32 (m, 1H), 4.59 (m, 1H), 5.05 (m, 1H), 6.79 (m, 1H), 6.95 (m, 1H), 7.42 (m, 1H), 7.72 (m, 1H), 7.80 (m, 1H), 8.17 (m, 1H), 9.49 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 202.1, 173.5, 172.1, 171.7, 171.3, 171.0, 67.6, 67.3, 55.0, 51.2, 44.3, 39.6, 36.9, 36.8, 34.4, 31.2, 29.9, 29.0, 28.6, 23.7, 22.3, 22.5, 21.3, 14.8. IR (neat): 3410, 2975, 1710, 1676, 1519, 1188 cm^{-1}. HRMS (FAB): m/z calcd. for $C_{27}H_{53}N_6O_8$ $[M+NH_4]^+$ 589.3919,found 589.3945.

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