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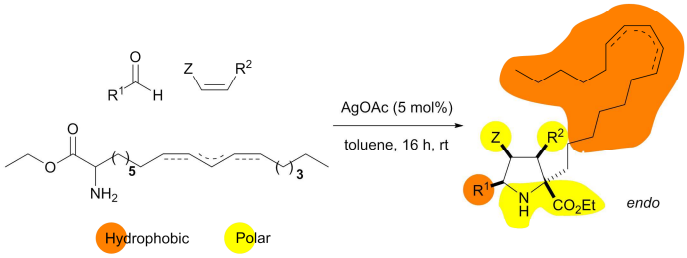

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Proline derivatives incorporating hydrophobic long-chain derived from natural and synthetic fatty acids

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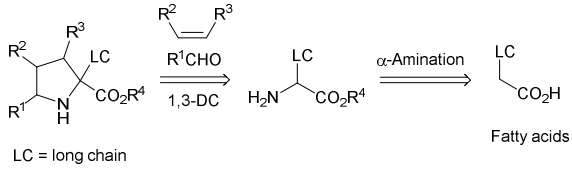
ABSTRACT

The α-hydrophobic long chain-α-amino esters are prepared by α-hydroxylation of a series of fatty acid esters [derived from oleic acid (OA), linolenic acid (LA), docosahexaenoic acid (DHA) and arachidonic acid (ARA)] followed by Mitsunobu reaction and hydrazinolysis of the phthalimide. These amino esters are mixed with aldehydes and electrophilic alkenes to give very good chemical yields and diastereoselectivities of prolinate derivatives incorporating a hydrophobic long chain at the α-position. This multicomponent 1,3-dipolar cycloaddition (1,3-DC) takes place at room temperature. The synthesis of the homologue hydrophobic chain of OA is performed by its oxidation to aldehyde/ racemic *N-tert*-butylsulfinyl imine/Neff reaction. Final 1,3-DC with benzaldehyde and *N*-methylmaleimide affords homologue prolinate derivative in good yield.

1. Introduction

Fatty acids possess many crucial functions in the organism. Apart from being constituents of cell membranes, energy source, inflammatory responses and exclusive building blocks for the synthesis of lipids and fats, they are employed in many interesting scientific applications. For example, they are used as dietary supplements to treat depressive symptoms,[1] as signaling probes in cancer development,[2] as cardiac biomarkers for early diagnosis of myocardial infarction,[3] as metabolic controllers of cardiac function,[4] in the treatment of neuropsychiatric disorders,[5] in pathogenesis and treatment of Alzheimer's disease and type 2 diabetic dementia,[6] in hormonal control,[7] etc.

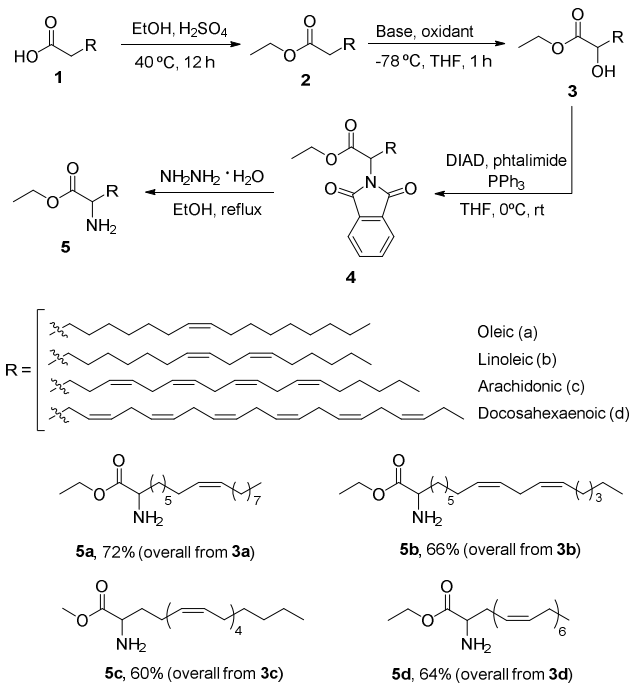
The synthetic transformations of fatty acid derivatives into valuable chemicals is desirable since the industrial point of view.[8] In addition, it has been demonstrated that an alteration in the polar part of these molecules produced changes in their activity as modulators of membrane structure, microdomain organization and cellular signaling.[9] With this idea, the employment of the fatty acids as starting materials was envisaged to prepare their corresponding α-amino esters and, in the final step, run the 1,3-dipolar cycloaddition (1,3-DC) between them and several representative dipolarophiles (Scheme 1). The main goal is to construct a polar unit (prolinate or proline) together with a long chain attached at the 2-position of the heterocycle.



Scheme 1. Retrosynthetic pathway to obtain long chain-substituted proline derivatives.

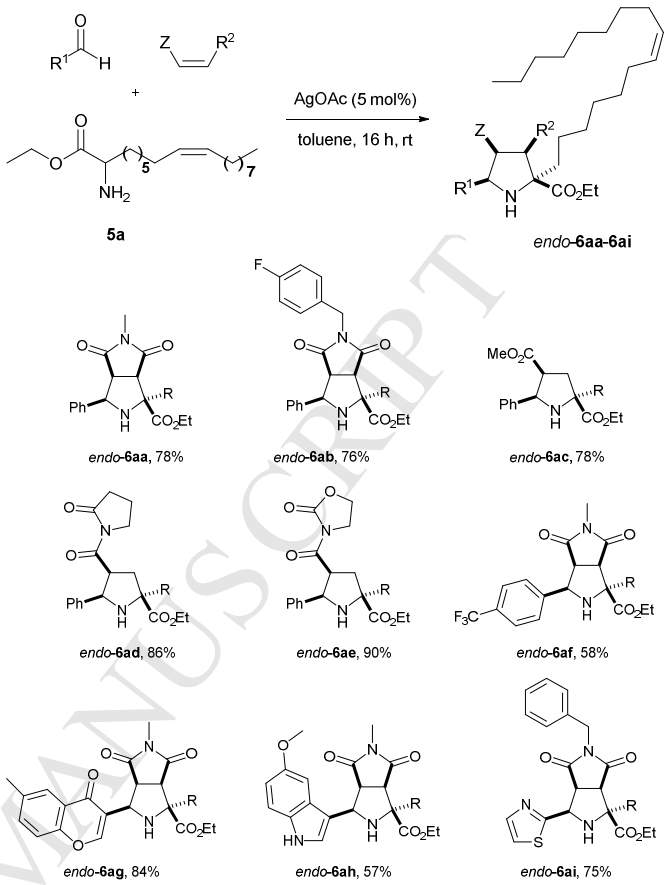
2. Results and Discussion

First of all, the synthesis of amines **5**, derived from fatty acids **1** was carried out due to they are not commercially available. They were synthesized following the procedure described in the literature.[10] The procedure consisted in an α-hydroxylation of the commercial fatty acids: oleic acid (OA), linolenic acid (LA), docosahexaenoic acid (DHA) and arachidonic acid (ARA). Next, the synthesis of the corresponding α-phthalimides **4** *via* Mitsunobu reaction of **3** and finally, the conventional Gabriel's synthesis using, in this last step, the Ing–Manske work-up (Scheme 2) was sequentially performed in this order. With this methodology the desired products **5** were achieved in good overall chemical yields from starting materials **3**.



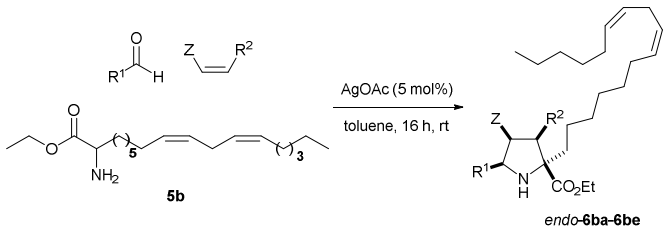
Scheme 2. Synthesis of long chain α-amino esters **5**.

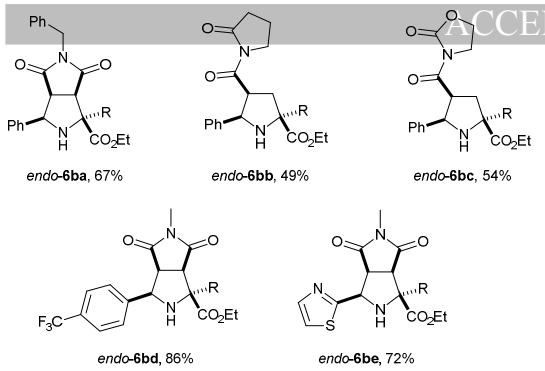
These α-amino esters **5** were allowed to participate in a multicomponent 1,3-dipolar cycloaddition (1,3-DC) with electrophilic alkenes and aldehydes. According to precedent surveys in our group,[11] toluene was selected as solvent and silver acetate as catalyst. After several optimization tests of the cycloaddition involving **5a**, benzaldehyde and *N*-methyl maleimide (NMM) took place at room temperature and no added base was necessary. The reaction was completed after 16 hours being crucial the presence of silver acetate (5 mol%). The absence of the silver salt supposed low conversions and very complex reaction mixtures in the crude material (analyzed by ^{1}H NMR spectroscopy). The final *endo*-cycloadduct **6aa** was isolated as pure compound in 78% yield (Scheme 3). This same procedure was extended to other maleimides and acrylic systems furnishing high yields of the corresponding cycloadducts **6a**. However, when acrylates were employed as dipolarophiles, the best results were obtained following the sequential order of addition: the amine (1 equiv.) and aldehyde (1 equiv.) were mixed in toluene during 2 h at 70 °C, then acrylate (1 equiv.) and the catalyst were added and stirred 16 h at this temperature. When the same sequential methodology was attempted, at room temperature, the conversion was very poor. *endo*-Cycloadduct **6ah** was prepared by the multicomponent route at 70 °C whilst *endo*-**6ag** was generated using ethanol[11] instead of toluene. The presence of chromenone, a 3-indolyl substituent and 2-thiazolyl residues in the molecule, as occurred in products **6ag**-**6ai** can increase their biological activity (Scheme 3) of the resulting cycloadducts.



Scheme 3. 1,3-DC to obtain prolinates derived from α-amino ester **5a**.

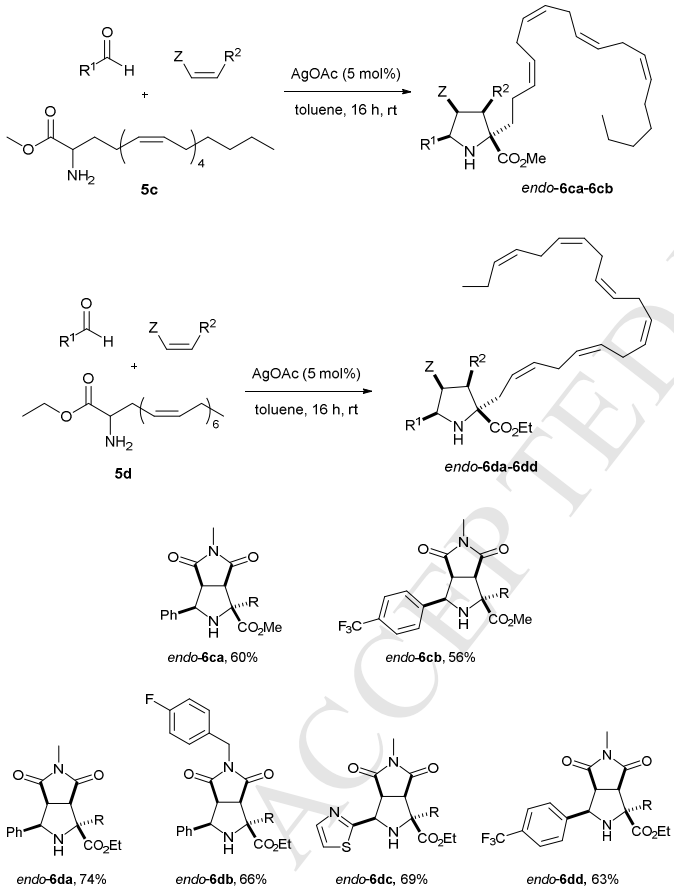
α-Amino ethyl ester **5b** derived from linoleic acid **1b** behaved similarly to α-amino ester **5a**. The cleanest reaction occurred in toluene at room temperature in presence of 5 mol% of silver acetate as catalyst. The reaction between benzaldehyde, **5b** and different dipolarophiles (**6ba**-**6bc**) was successfully performed. All of them were obtained in moderate to good yields and high *endo*-diastereoselectivity after flash column chromatography. It was also tested with different aldehydes bearing a pharmacophore unit as **6bd** and **6be** (Scheme 4).





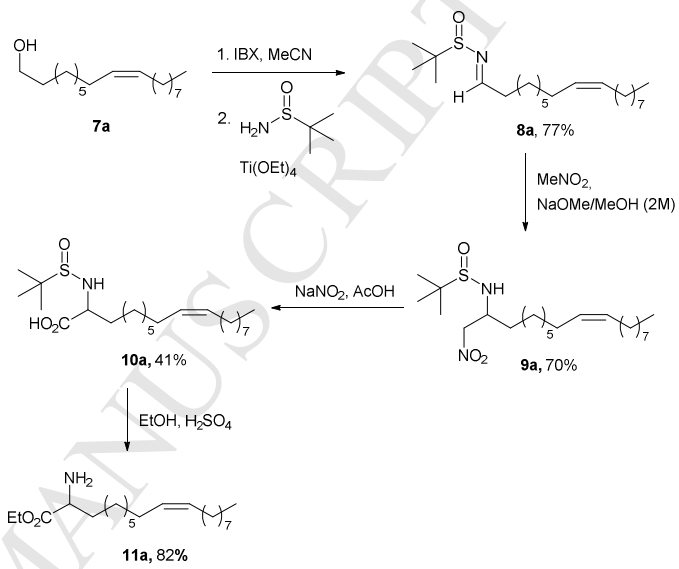
Scheme 4. 1,3-DC to obtain prolinates derived from α-amino ester **5b**

α-Amino esters **5c** and **5d**, obtained from ARA and DHA respectively, also were suitable precursors for this multicomponent 1,3-DC remaining unaltered all the conjugated insaturations. The high *endo*-diastereoselectivity was also kept and the chemical yields of compounds **6c** and **6d** were relatively good (Scheme 5).



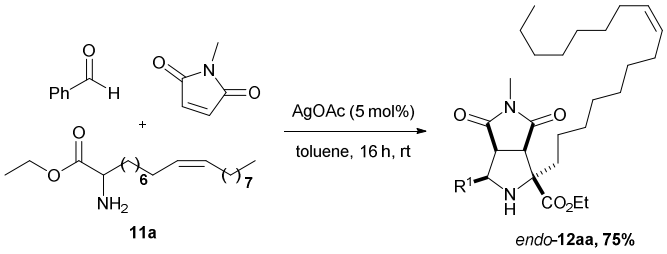
Scheme 5. Synthesis of prolinates *endo*-**6c** and *endo*-**6d** derived from α-amino ester **5c** and α-amino ester **5d**, respectively.

It is well known that a small change in the amino acid unit/protein is associated in biological engineering to evolution. Apparently, both of mutated entities are capable of exhibiting analogous biological properties acting as invariant residues, but in other scenarios a considerable variation of bioactivity can occur calling that variable residues.[12] Considering compounds **6** as synthetic surrogates of racemic prolinates, and expand the interest and utility of this methodology in general science, we focused on this study towards the preparation of the homologue α-amino acid **11a** (with respect to compound **5a**, derived from OA).[13] Thus, the preparation of racemic *N-tert*-butylsulfinyl imine **8a** was accomplished in very good yield from the corresponding alcohol **7a** (Scheme 6). Next, the addition of nitromethane-Neff reaction were successfully carried out in high conversions giving compound **10a** in moderate yields (41%).[14] Final one-pot esterification and removal of the sulfinyl group afforded the amino ester **11a** in 82% yield (Scheme 6).



Scheme 6. Synthesis of the homologue α-amino ester **11a**.

The multicomponent 1,3-dipolar reaction between **11a**, benzaldehyde and NMM was carried out following identical reaction conditions described in Schemes 3-5. Product *endo*-cycloadduct **12aa** was diastereoselectively formed and isolated in 75% yield (Scheme 7). So, this cycloadduct is integrated by from a non-natural side chain, which is homologous to the corresponding molecules *endo*-**6aa**.



Scheme 7. Synthesis of prolinate **12aa** derived from homologous α-amino ester **11a**.

In every reaction the *endo*-cycloadducts were obtained almost exclusively not only after chromatographic separation but in the raw material (observed by ^{1}H NMR spectroscopy). This relative configuration was supported by analysis of nOe experiments and by comparison of the coupling constant values with similar substances isolates in previous contributions.[11] At this moment the biological evaluation of them against tumor cells, bacteria and viruses are underway.

3. Conclusions

The preparation of new amino acid and prolinate derivatives, incorporating a long side chain at the α-position of the carbonyl group, was reported. These amino esters were also satisfactorily prepared in good yields and many of them are new compounds. The multicomponent cycloaddition operated under mild conditions, total atom economy and excellent diastereoselectivity. The stereochemical outcome of the novel prolinate derivatives provided an *all-cis*-arrangement [positions 2, 3 (for maleimides), 4 and 5). The biological interest of these amino esters and cycloadducts obtained through the multicomponent 1,3-DC are unpredictable. The efficient one atom elongation in the long side hydrophobic chain gave access to both homologous: a) new amino ester, and b) prolinate surrogate, which can be potentially interesting in many scientific areas.

4. Experimental section

4.1 General information.

All commercially available reagents and solvents were used without further purification, only aldehydes were also distilled prior to use. Analytical TLC was performed on Schleicher & Schuell F1400/LS 254 silica gel plates, and the spots were visualized under UV light (λ 254 nm). Flash chromatography was carried out on hand-packed columns of Merck silica gel 60 (0.040-0.063 mm). The structurally most important peaks of the IR spectra (recorded using a Nicolet 510 PFT) are listed and wave numbers are given in cm^{-1}. NMR spectra were obtained using a Bruker AC-300 or AC-400 and were recorded at 300 or 400 MHz for ^1H NMR and 75 or 100 MHz for ^{13}C NMR, using $CDCl_3$ as solvent and TMS as internal standard (0.00 ppm). The following abbreviations are used to describe peak patterns where appropriate: s ¼ singlet, d ¼ doublet, t ¼ triplet, q ¼ quartet, m¼ multiplet or unresolved and br s ¼ broad signal. All coupling constants (*J*) are given in Hz and chemical shifts in ppm. ^{13}C NMR spectra were referenced to $CDCl_3$ at 77.16 ppm. DEPT-135 experiments were performed to assign CH, CH_2 and CH_3. ^{19}F NMR were recorded at 282 MHz using $CDCl_3$ as solvent. Low resolution electron impact (EI) mass spectra were obtained at 70 eV using a Shimadzu QP-5000 by injection or DIP; fragment ions in *m/z* are given with relative intensities (%) in parentheses. High resolution mass spectra (HRMS) were measured on an instrument using a quadrupole time-of-flight mass spectrometer (QTOF) and also through the electron impact mode (EI) at 70 eV using a Finnigan VG Platform or a Finnigan MAT 95 S.

*4.2. General procedure for the preparation of α-hydroxy fatty esters **3a**.*

To a solution of the fatty ester **2a** (2.82 g, 10 mmol) in anhydrous THF (10 mL) was added lithium diisopropylamine 2.5 M (8 mL, 20 mmol) in tetrahydrofuran (15 mL) at -0 °C to provide the ester enolate. This ester enolate was bubbled with molecular oxygen (25 mmol) during 1 h. The mixture was hydrolyzed with 3M HCl and it was extracted with diethyl ether. The organic phase was dried ($MgSO_4$), filtered, evaporated under vacuum and purified by flash column chromatography on silica gel eluting with mixtures of *n*-hexane/AcOEt.

Ethyl (*Z*)-2-hydroxyoctadec-9-enoate **3a**.
Colorless oil, (2.45g, 75% yield). R_f 0.47 (hexane/ethyl acetate: 8/2). IR (neat) υ_{max}: 1106, 1213, 1464, 1731, 2854, 2925, 3500 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ) δ 5.36-5.33 (m, 2H), 4.25 (q, *J* = 7.2 Hz, 2H), 4.16 (dd, *J* = 7.2, 4.1 Hz, 1H), 2.73 (s, 1H), 2.05-1.99 (m, 4H), 1.83-1.74 (m, 1H), 1.68-1.59 (m, 1H), 1.48-1.21 (m, 23H), 0.90-0.87 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.4, 130.0, 129.7, 70.4, 61.5, 34.4, 31.9, 29.8, 29.6, 29.5, 29.3, 29.2, 29.1, 27.2, 27.1, 24.7, 22.7, 14.2, 14.1. LRMS (EI): *m/z* = 326 (M^+, <1%) 253 (100), 123 (23), 121 (27), 111 (27), 109 (41), 104 (53), 97 (49), 95 (73), 81 (70), 55 (80). HRMS (EI): calcd. for $C_{20}H_{38}O_3$ 326.2821; found 326.2826.

*4.3. General procedure for the preparation of α-hydroxy fatty esters **3b-d**.*

Fatty ester **2b-d** (10 mmol) was dissolved in anhydrous THF (10 mL) and treated with potassium bis(trimethylsilyl)amide 0.45 M (44 mL, 20 mmol) in tetrahydrofuran (15 mL), at -78 °C for 1 h. This ester enolate reacted with (phenylsulfonyl)-3-phenyloxaziridine (6.53 g, 25 mmol) giving α-hydroxy fatty esters **3b-d**. After 19 h at room temperature, the mixture was hydrolyzed with 3M HCl and it was extracted with diethyl ether. The organic phase was dried ($MgSO_4$), filtered, evaporated under vacuum and purified by flash column chromatography on silica gel eluting with *n*-hexane/AcOEt.

Ethyl (9*Z*,12*Z*)-2-hydroxyoctadeca-9,12-dienoate **3b**.
Yellow oil, (2.17g, 67% yield). R_f 0.52 (hexane/ethyl acetate: 8/2). IR (neat) υ_{max}: 1110, 1209, 1466, 1735, 2856, 2927, 3449 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.44-5.33 (m, 4H), 4.23 (qd, *J* = 7.2, 1.4 Hz, 2H), 4.15 (ddd, *J* = 7.2, 5.7, 4.2 Hz, 1H), 2.91 (dd, *J* = 5.7, 2.6 Hz, 1H), 2.76 (t, *J* = 6.4 Hz, 2H), 2.04 (q, *J* = 6.4 Hz, 4H), 1.80-1.73 (m, 1H), 1.64-1.58 (m, 1H), 1.47-1.17 (m, 17H), 0.88 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.4, 130.1, 129.9, 128.0, 127.9, 70.4, 61.5, 34.4, 31.5, 29.5, 29.3, 29.2, 29.1, 27.2, 27.1, 25.6, 24.7, 22.5, 14.1, 14.0. LRMS (EI): *m/z* = 324 (M^+, <1%) 251 (18), 110 (25), 109 (39), 96 (41), 95 (79), 93 (29), 81 (96), 69 (42), 67 (100), 55 (68), 41 (46). HRMS (EI): calcd. for $C_{20}H_{36}O_3$ 324.2664; found 324.2668.

Methyl (5*Z*,8*Z*,11*Z*,14*Z*)-2-hydroxyicosa-5,8,11,14-tetraenoate **3c**.
Yellow oil, (2.10g, 63% yield). R_f 0.50 (hexane/ethyl acetate: 8/2). IR (neat) υ_{max}: 1113, 1216, 1440, 1738, 2857, 2927, 2955, 3012, 3452 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.50-5.31 (m, 8H), 4.20 (dt, *J* = 8.3, 4.2 Hz, 1H), 3.79 (s, 3H), 2.86-2.81 (m, 6H), 2.30-2.18 (m, 2H), 2.09-2.04 (m, 2H), 1.91-1.83 (m, 1H), 1.76-1.67 (m, 1H), 1.39-1.26 (m, 6H), 0.90 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.7, 130.5, 129.2, 128.6, 128.5, 128.2, 128.1, 127.9, 127.5, 69.8, 52.5, 34.1, 31.5, 29.3, 27.2, 25.6, 25.6, 22.6, 22.5, 14.0. LRMS (EI): *m/z* = 334 (M^+, <1%) 129 (25), 109 (28), 101 (40), 99 (44), 97 (33), 95 (52), 85 (45), 83 (49), 79 (40), 71

(47), 69 (56), 57 (57), 55 (88), 43 (100), 41 (67). HRMS (EI): calcd. for $C_{21}H_{34}O_3$ 334.2508; found 334.2497.

Ethyl (4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-2-hydroxydocosa-4,7,10,13,16,19-hexaenoate **3d**.
Yellow oil, (2.53g, 68% yield). R_f 0.48 (hexane/ethyl acetate: 8/2). IR (neat) υ_{max}: 1110, 1206, 1445, 1735, 2964, 3013, 3412 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.60-5.32 (m, 12H), 4.27-4.20 (m, 3H), 2.89-2.79 (m, 10H), 2.59-2.47 (m, 2H), 2.12-2.02 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 1H), 0.97 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.6, 132.0, 131.6, 128.6, 128.4, 128.3, 128.1, 127.9, 127.8, 127.0, 123.4, 70.1, 61.7, 32.2, 25.8, 25.6, 25.5, 20.6, 14.3, 14.2. LRMS (EI): *m/z* = 372 (M^+, <1%), 145 (19), 131 (27), 119 (49), 117 (33), 108 (35), 105 (49), 93 (50), 91 (85), 79 (100), 67 (59), 55 (26). HRMS (EI): calcd. for $C_{24}H_{36}O_3$ 372.2664; found 372.2664.

*4.4. General procedure for the preparation of α-amino fatty esters **5**.*
A mixture of the α-hydroxylated ester 3 (7.00 mmol), phthalimide (1.24 g, 8.4 mmol) and triphenylphosphine (2.20 g, 8.4 mmol) in 50 mL of THF was cooled to 0 °C under N_2-atmosphere before diisopropyl azodicarboxylate (1.72 mL, 8.75 mmol) was added dropwise. The ice-bath was removed and the reaction mixture was stirred at room temperature for 18 h. Then, it was evaporated under vacuum and α-phthalimide alkyl ester **4** was isolated after flash column chromatography on silica gel. Then, a solution of compound **4** (5 mmol) in 15 mL of EtOH (for **4c**, MeOH), was added hydrazine (0.40 mL, 7.5 mmol) and the resulting mixture was refluxed under N_2-atmosphere for 48 h followed by evaporation under vacuum and purification by flash column chromatography on silica gel eluting with *n*-hexane/AcOEt .

Ethyl (*Z*)-2-aminooctadec-9-enoate **5a**.
Yellow oil, (1.64 g, 72% yield). R_f 0.26 (dichloromethane/methanol: 3/1). IR (neat) υ_{max}: 1180, 1465, 1736, 2853, 2922, 3196, 3311, 3371 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.32-5.28 (m, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.41 (td, *J* = 6.4, 5.3, 1.7 Hz, 1H), 2.00-1.94 (m, 5H), 1.78-1.59 (m, 1H), 1.63-1.46 (m, 1H), 1.45-1.06 (m, 23H), 0.84 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.2, 130.1, 129.8, 60.8, 54.5, 35.0, 32.0, 29.8, 29.7, 29.6, 29.4, 29.2, 27.3, 27.2, 25.7, 22.8, 14.3, 14.1. LRMS (EI): *m/z* = 325 (M^+, <1%), 254 (19), 253 (18), 252 (100), 56 (12). HRMS (EI): calcd. for $C_{20}H_{39}NO_2$ 325.2981; found 325.2983.

Ethyl (9*Z*,12*Z*)-2-aminooctadeca-9,12-dienoate **5b**.
Yellow oil, (1.49 g, 66% yield). R_f 0.25 (dichloromethane/methanol: 9/3). IR (neat) υ_{max}: 1181, 1465, 1736, 2854, 2925, 3301, 3375 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.38-5.25 (m, 4H), 4.16 (qd, *J* = 7.2, 1.7 Hz, 2H), 3.40 (dd, *J* = 7.4, 5.4 Hz, 1H), 2.73 (t, *J* = 6.3 Hz, 2H), 2.04-1.99 (m, 5H), 1.73-1.67 (m, 1H), 1.58-1.51 (m, 1H), 1.48-1.14 (m, 17H), 0.87-0.84 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.8, 129.9, 129.7, 127.8, 127.6, 60.5, 54.2, 34.6, 31.3, 29.3, 29.1, 28.9, 26.9 (2), 25.4, 25.3, 22.3, 14.0, 13.8. LRMS (EI): *m/z* = 323 (M^+, <1%), 252 (53), 250 (100), 67 (12), 56 (19). HRMS (EI): calcd. for $C_{20}H_{37}NO_2$ 323.2824; found 323.2830.

Ethyl (4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-2-aminodocosa-4,7,10,13,16,19-hexaenoate **5d**.
Yellow oil, (1.60 g, 64% yield). R_f 0.29 (dichloromethane/methanol: 97/3). IR (neat) υ_{max}: 1185, 1392, 1445, 1735, 2964, 3012, 3309, 3377 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.43-5.32 (m, 12H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.52 (dd, *J* = 7.1, 5.2 Hz, 1H), 2.89-2.80 (m, 10H), 2.59-2.37 (m, 2H), 2.12-1.95 (m, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.4, 132.1, 131.6, 128.6, 128.5, 128.3, 128.0, 127.9, 127.8, 127.1, 124.6, 61.0, 54.3, 32.6, 25.7, 25.6, 20.6, 14.4, 14.3. LRMS (EI): *m/z* = 371 (M^+, <1%), 298 (17), 102 (100), 91 (15), 74 (16). HRMS (EI): calcd. for $C_{24}H_{37}NO_2$ 371.2824; found 371.2829.

*4.5. General procedure for the preparation of prolinates **6** and **12**.*
Synthesis of **6** and **12** with maleimides as dipolarophile: Multicomponent reaction: to a stirred solution of α-amino ester **5** or **11a** (0.5 mmol) in toluene (3 mL) or EtOH (for **6ag**), aldehyde (0.5 mmol) was added. After that, the maleimide (0.5 mmol) and AgOAc (4.2 mg, 5 mol%) were added in this order. The reaction mixture was stirred overnight at room temperature (at 70 °C for **6ag** and **6ah**). Then, it was extracted with ethyl acetate and washed with brine. The organic phase was dried ($MgSO_4$), filtrated and evaporated. The corresponding pyrrolidines were obtained in good yields after purification by flash chromatography (Hexane/AcOEt).

Synthesis of **6** with acrylates as dipolarophile: Sequential reaction: to a stirred solution of α-amino ester **5** (1 equiv., 0.5 mmol) in toluene (3 mL), aldehyde (1 equiv., 0.5 mmol) was added and the mixture was stirred during 2 h at 70 °C. Then acrylate (1 equiv., 0.5 mmol) and the catalyst AgOAc (4.2 mg, 5 mol%) were added and stirred 16 h at this temperature. The crude mixture was extracted with ethyl acetate and washed with brine. The organic phase was dried ($MgSO_4$), filtrated and evaporated. The corresponding pyrrolidines were obtained in good yields after purification by flash column chromatography (Hexane/AcOEt).

Ethyl (1*SR*,3*RS*,3*aSR*,6*aRS*)-1-[(*Z*)-hexadec-7-en-1-yl]-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate **6aa**.
Yellow oil, (205 mg, 78% yield). R_f 0.30 (hexane/ethyl acetate: 7/3). IR (neat) υ_{max}: 1287, 1383, 1435, 1705, 1779, 2854, 2925, 3343, 3466 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.38-7.31 (m, 5H), 5.45-5.20 (m, 2H), 4.66 (d, *J* = 9.1 Hz, 1H), 4.47-4.21 (m, 2H), 3.52 (dd, *J* = 9.1, 7.4 Hz, 1H), 3.27 (d, *J* = 7.4 Hz, 1H), 2.81 (s, 3H), 2.13-2.01 (m, 4H), 1.84-1.75 (m, 1H), 1.43-1.27 (m, 25H), 0.92-0.87 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.7, 174.8, 171.6, 137.1, 130.1, 129.6, 128.5, 128.4, 127.0, 70.7, 61.7, 55.4, 50.4, 35.0, 31.9, 29.7, 29.7, 29.5, 29.4, 29.3, 29.0, 27.2, 27.1, 24.8, 23.6, 22.7, 14.1. LRMS (EI): *m/z* = 524 (M^+, <1%), 454 (24), 453 (80), 452 (32), 451 (100), 301 (88), 205 (15), 144 (19). HRMS (EI): calcd. for $C_{32}H_{48}N_2O_4$ 524.3614; found 524.3621.

Ethyl (1*SR*,3*RS*,3*aSR*,6*aRS)*-5-(4-fluorobenzyl)-1-[(*Z*)-hexadec-7-en-1-yl]-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate **6ab**.
Yellow oil, (235 mg, 76% yield). R_f 0.52 (hexane/ethyl acetate: 7/3). IR (neat) υ_{max}: 1224, 1432, 1511, 1707, 2854, 2925, 3348, 3464 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.30-7.14 (m, 5H), 7.13-7.06 (m, 2H), 6.99 (t, *J* = 8.7 Hz, 2H),

5.45-5.29 (m, 2H), 4.63 (d, *J* = 9.0 Hz, 1H), 4.43 (dd, *J* = 7.4, 3.7 Hz, 2H), 4.37 (dd, *J* = 11.2, 7.1 Hz, 2H), 3.46 (dd, *J* = 9.1, 7.5 Hz, 1H), 3.25 (d, *J* = 7.5 Hz, 1H), 2.10-2.01 (m, 4H), 1.88-1.68 (m, 1H), 1.43-1.03 (m, 25H), 0.92-0.88 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.3, 174.3, 162.5 (d, $^1J_{C\text{-}F}$ = 246.7 Hz, *C*F), 131.6 (d, $^4J_{C\text{-}F}$ = 3.1 Hz, *C*CHCHCF), 131.1 (d, $^3J_{C\text{-}F}$ = 8.2 Hz, *C*HCHCF), 130.2, 129.7, 128.5, 128.3, 127.1, 115.4 (d, $^2J_{C\text{-}F}$ = 21.6 Hz, *C*HCF), 71.0, 61.9, 61.8, 55.6, 50.2, 41.8, 35.1, 32.0, 29.9 , 29.8, 29.7, 29.6, 29.5, 29.4, 29.2, 27.3, 27.2, 23.7, 22.8, 14.3, 14.2. ^{19}F NMR δ: -114.2. LRMS (EI): *m/z* = 618 (M^+, <1%), 545 (100), 395 (64), 144 (13), 109 (47), 91 (8). HRMS (EI): calcd. for $C_{38}H_{51}FN_2O_4$ 618.3833; found 618.3846.

2-Ethyl 4-methyl (2*SR*,4*SR*,5*RS*)-2-[(*Z*)-hexadec-7-en-1-yl]-5-phenylpyrrolidine-2,4-dicarboxylate **6ac**.
Colorless oil, (195 mg, 78% yield). R_f 0.30 (hexane/ethyl acetate: 7/3). IR (neat) υ_{max} : 1201, 1248, 1456, 1731, 2854, 2923, 3370, 3452 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.30 (m, 5H), 5.43-5.32 (m, 2H), 4.85 (d, *J* = 6.4 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.30-3.29 (m, 1H), 3.23 (s, 3H), 2.79 (dd, *J* = 13.9, 3.6 Hz, 1H), 2.17 (dd, *J* = 13.7, 7.6 Hz, 1H), 2.20-1.88 (m, 5H), 1.60-1.55 (m, 1H), 1.38-1.18 (m, 25H) 0.89-0.85 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.8, 169.1, 130.0, 129.7, 128.6, 128.2, 126.7, 65.6, 62.0, 51.4, 49.7, 39.6, 31.9, 29.8, 29.7, 29.5, 29.3, 29.1, 27.2, 27.2, 25.0, 22.7, 14.2, 14.1. LRMS (EI): *m/z* = 499 (M^+, <1%), 428 (27), 427(31), 426 (100), 276 (16), 105 (9). HRMS (EI): calcd. for $C_{31}H_{49}NO_4$ 499.3662; found 499.3647.

Ethyl (2*SR*,4*SR*,5*RS*)-2-[(*Z*)-hexadec-7-en-1-yl]-4-(2-oxopyrrolidine-1-carbonyl)-5-phenylpyrrolidine-2-carboxylate **6ad**.
Yellow oil, (237 mg, 86% yield). R_f 0.48 (hexane/ethyl acetate: 7/3). IR (neat) υ_{max}: 1252, 1362, 1457, 1686, 1736, 2853, 2924, 3312, 3359, 3452 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.28-7.26 (m, 5H), 5.36-5.32 (m, 2H), 4.83 (s, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 3.54-3.46 (m, 1H), 3.08-3.00 (m, 1H), 2.84 (d, *J* = 12.8 Hz, 1H), 2.34-2.19 (m, 2H), 2.17-2.07 (m, 2H) 2.09-1.94 (m, 5H), 1.93-1.90 (m, 2H), 1.79-1.67 (m, 1H), 1.61-1.47 (m, 1H), 1.50-1.09 (m, 23H), 0.91-0.86 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.5, 175.0, 173.8, 130.1, 129.9, 128.1, 127.4, 66.2, 61.7, 45.6, 40.0, 33.6, 32.0, 29.9, 29.8, 29.6, 29.4, 29.3, 27.3, 25.3, 22.8, 16.8, 14.5, 14.2. LRMS (EI): *m/z* = 552 (M^+, <1%), 481 (30), 480 (38), 479(100), 392 (12), 329 (21), 230 (11). HRMS (EI): calcd. for $C_{34}H_{52}N_2O_4$ 552.3927; found 552.3913.

Ethyl (2*SR*,4*SR*,5*RS)*-2-[(*Z*)-hexadec-7-en-1-yl)]-4-(2-oxooxazolidine-3-carbonyl)-5-phenylpyrrolidine-2-carboxylate **6ae**.
White solid, (250 mg, 90% yield). R_f 0.33 (hexane/ethyl acetate: 7/3). IR (neat) υ_{max}: 1222, 1386, 1698, 1736, 1774, 2853, 2924, 3361 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31-7.28 (m, 5H), 5.36-5.31 (m, 2H), 4.78 (d, *J* = 6.0 Hz, 1H), 4.32 (q, *J* = 7.0 Hz, 2H), 4.16-3.97 (m, 1H), 3.63 (q, *J* = 8.5, 8.0 Hz, 2H), 3.29-3.06 (m, 1H), 2.80 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.10 (dd, *J* = 13.6, 7.1 Hz, 1H), 2.09-1.91 (m, 4H), 1.88 (dd, *J* = 12.6, 4.5 Hz, 1H), 1.84-1.65 (m, 1H), 1.61-1.42 (m, 1H), 1.37-1.35 (m, 23H), 1.09-0.74 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.5, 172.9, 152.8, 129.9, 129.7, 128.2, 128.0, 127.0, 70.2, 65.8, 61.7, 48.4, 42.4, 39.6, 31.9, 29.7, 29.7, 29.5, 29.3, 29.1, 27.2, 25.2, 22.7, 14.3, 14.1. LRMS (EI): *m/z* = 554 (M^+, <1%), 483 (29), 482 (33), 481(100), 391 (11), 331 (30), 156 (10). HRMS (EI): calcd. for $C_{33}H_{50}N_2O_5$ 554.3720; found 554.3708.

Ethyl (1*SR*,3*RS)*-1-[(*Z*)-hexadec-7-en-1-yl]-5-methyl-4,6-dioxo-3-(4-(trifluoromethyl)phenyl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate **6af**.
Colorless oil, (172 mg, 58% yield). R_f 0.48 (hexane/ethyl acetate: 7/3). IR (neat) υ_{max}: 1128, 1325, 1435, 1620, 1704, 1780, 2855, 2925, 3342, 3467 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 5.41-5.28 (m, 2H), 4.66 (d, *J* = 8.9 Hz, 1H), 4.49-4.23 (m, 2H), 3.53 (dd, *J* = 8.9, 7.4 Hz, 1H), 3.26 (d, *J* = 7.4 Hz, 1H), 2.80 (s, 3H), 2.09-1.98 (m, 5H), 1.89-1.65 (m, 1H), 1.51-1.20 (m, 25H), 0.90-0.78 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.4, 174.5, 171.4, 141.5, 130.3 (d, $^2J_{C\text{-}F}$ = 34.5 Hz, *C*CF_3), 130.1, 129.5, 127.5, 125.8, 125.4, 125.3 (d, $^3J_{C\text{-}F}$ = 3.6 Hz, *C*HCHCF_3), 125.2, 124.0 (d, $^1J_{C\text{-}F}$ = 272.2 Hz, *C*F_3), 70.6, 61.67, 60.69, 55.0, 49.9, 34.9, 31.9, 29.7, 29.67, 29.6, 29.6, 29.5, 29.3, 29.3, 29.0, 27.2, 27.1, 24.8, 23.6, 22.7, 14.1, 14.1. ^{19}F NMR δ: -62.5. LRMS (EI): *m/z* = 592 (M^+, <1%), 521 (42), 520 (44), 519 (100), 369 (68), 323 (17), 212 (18). HRMS (EI): calcd. for $C_{33}H_{47}F_3N_2O_4$ 592.3488; found 592.3495.

Ethyl (1*SR*,*3RS*,3*aSR*,6*aRS*)-1-[(*Z*)-hexadec-7-en-1-yl]-5-methyl-3-(6-methyl-4-oxo-4*H*-chromen-3-yl)-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate **6ag**.
Yellow oil, (254 mg, 84% yield). R_f 0.21 (hexane/ethyl acetate: 7/3). IR (neat) υ_{max}: 1130, 1288, 1435, 1644, 1750, 2854, 2924, 3056, 3315, 3460 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.03 (s, 1H), 7.99 (d, *J* = 2.2 Hz, 1H), 7.49 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 1H), 5.35-5.32 (m, 2H), 4.66 (s, 1H), 4.35 (dqt, *J* = 17.8, 7.1, 3.6 Hz, 2H), 3.74 (t, *J* = 8.2 Hz, 1H), 3.32 (d, *J* = 7.4 Hz, 1H), 2.85 (s, 3H), 2.45 (s, 3H), 2.21-2.07 (m, 1H), 2.09-1.93 (m, 4H), 1.94-1.76 (m, 1H), 1.38-1.13 (m, 24H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 177.9, 175.3, 174.9, 170.8, 154.6, 135.4, 135.3, 130.0, 129.6, 125.1, 117.9, 71.6, 62.1, 55.4, 48.4, 35.0, 31.9, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 29.0, 27.2, 27.1, 25.1, 23.9, 22.7, 20.9, 14.1. LRMS (EI): *m/z* = 606 (M^+, <1%), 577 (19), 533 (100), 383 (24), 337 (30), 297 (24). HRMS (EI): calcd. for $C_{36}H_{50}N_2O_6$ 606.3669; found 606.3669.

Ethyl (1*SR*,3*RS*,3*aSR*,6*aRS*)-1-[(*Z*)-hexadec-7-en-1-yl]-3-(5-methoxy-1H-indol-2-yl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate **6ah**.
Red oil, (120 mg, 57% yield). R_f 0.43 (hexane/ethyl acetate: 7/3). IR (neat) υ_{max}: 1031, 1216, 1287, 1440, 1486, 1694, 1776, 2854, 2925, 3360 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.72 (s, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 7.04 (d, *J* = 3.0 Hz, 2H), 6.78 (dd, *J* = 8.8, 2.3 Hz, 1H), 5.38-5.28 (m, 2H), 4.97 (d, *J* = 9.2 Hz, 1H), 4.50-4.28 (m, 2H), 3.81 (s, 3H), 3.56 (t, *J* = 8.4 Hz, 1H), 3.34 (d, *J* = 7.5 Hz, 1H), 2.69 (s, 3H), 2.11 (td, *J* = 13.7, 13.1, 4.5 Hz, 1H), 2.02 (dt, *J* = 13.5, 7.1 Hz, 4H),

1.86 (t, *J* = 12.4 Hz, 1H), 1.40-1.20 (m, 25H), 0.89 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.9, 175.3, 171.7, 153.9, 131.7, 130.1, 130.0, 129.6, 126.2, 123.8, 112.5, 112.3, 100.7, 70.9, 61.9, 56.4, 55.9, 55.7, 50.0, 35.1, 31.9, 29.8, 29.7, 29.6, 29.5, 29.5, 29.3, 29.1, 27.2, 27.2, 25.0, 23.8, 22.7, 14.1. LRMS (EI): *m/z* = 593 (M^+, <1%), 520 (83), 482 (100), 371 (35), 329 (45), 323 (22), 273 (96), 175 (26), 160 (36), 55 (27). HRMS (EI): calcd. for $C_{35}H_{51}N_3O_5$ 593.3829; found 593.3815.

Ethyl (1*SR*,3*RS*,3*aSR*,6*aRS*)-5-benzyl-1-[(*Z*)-hexadec-7-en-1-yl]-4,6-dioxo-3-(thiazol-2-yl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate **6ai**.

Yellow oil, (228 mg, 75% yield). R_f 0.15 (hexane/ethyl acetate: 7/3). IR (neat) υ_{max}: 1397, 1705, 2854, 2925, 3312, 3465 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.71 (dd, *J* = 5.6, 3.2 Hz, 1H), 7.28-7.26 (m, 6H), 5.37-5.29 (m, 2H), 4.99 (d, *J* = 8.6 Hz, 1H), 4.47 (d, *J* = 2.0 Hz, 2H), 4.32 (qd, *J* = 7.2, 5.2 Hz, 2H), 3.64 (t, *J* = 8.1 Hz, 1H), 3.29 (d, *J* = 7.3 Hz, 1H), 2.01 (q, *J* = 6.7 Hz, 4H), 1.71-1.62 (m, 1H), 1.53-1.11 (m, 25H), 0.91-0.86 (m, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.8, 174.0, 170.6, 142.4, 135.3, 130.1, 129.6, 129.0, 128.5, 127.8, 71.3, 61.8, 59.5, 55.7, 50.1, 42.7, 35.7, 31.9, 29.8, 29.6, 29.5, 29.4, 29.3, 29.1, 27.3, 27.2, 23.8, 22.7, 14.2, 14.1. LRMS (EI): *m/z* = 607 (M^+, <1%), 534 (100), 384 (39), 347 (22), 151 (13), 91 (52), 86 (18). HRMS (EI): calcd. for $C_{35}H_{49}N_3O_4S$ 607.3444; found 607.3435.

Ethyl (1*SR*,3*RS*,3*aSR*,6*aRS*)-5-benzyl-1-[(7*Z*,10*Z*)-hexadeca-7,10-dien-1-yl]-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate **6ba**.

Yellow oil, (200 mg, 67% yield). R_f 0.57 (hexane/ethyl acetate: 7/3). IR (neat) υ_{max}: 1168, 1346, 1431, 1707, 2855, 2926, 3343, 3465 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31-7.28 (m, 5H), 7.26-7.24 (m, 1H), 7.22-7.16 (m, 1H), 7.13-7.10 (m, 2H), 7.05-6.93 (m, 2H), 5.51-5.27 (m, 4H), 4.60 (d, *J* = 9.1 Hz, 1H), 4.48 (d, *J* = 10.7 Hz, 2H), 4.42-4.35 (m, 2H), 3.46 (dd, *J* = 9.1, 7.5 Hz, 1H), 3.26 (d, *J* = 7.5 Hz, 1H), 2.82-2.79 (m, 2H), 2.11-1.91 (m, 4H), 1.79 (t, *J* = 11.7 Hz, 1H), 1.48-1.04 (m, 19H), 0.94-0.89 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.3, 174.4, 171.5, 136.6, 135.7, 130.3, 130.0, 129.2, 128.6, 128.5 , 128.2, 128.2, 128.0, 127.9, 127.1, 71.1, 62.1, 61.8, 55.7, 50.3, 42.5, 35.1, 31.6, 29.6, 29.5, 29.4, 29.1, 27.3, 27.2, 25.7, 23.7, 22.7, 14.2. LRMS (EI): *m/z* = 598 (M^+, <1%), 527 (40), 525 (100), 377 (84), 144 (21), 91 (51). HRMS (EI): calcd. for $C_{38}H_{50}N_2O_4$ 598.3771; found 598.3776.

Ethyl (2*SR*,4*SR*,5*RS*)-2-[(7*Z*,10*Z*)-hexadeca-7,10-dien-1-yl]-4-(2-oxopyrrolidine-1-carbonyl)-5-phenylpyrrolidine-2-carboxylate **6bb**.

Yellow oil, (135 mg, 49% yield). R_f 0.46 (hexane/ethyl acetate: 7/3). IR (neat) υ_{max}: 1253, 1364, 1690, 1736, 2855, 2927, 3358, 3452 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48-7.27 (m, 5H), 5.41-5.28 (m, 4H), 4.87 (d, *J* = 8.7 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.55-3.46 (m, 1H), 3.10-3.01 (m, 1H), 2.86 (dd, *J* = 13.8, 2.9 Hz, 1H), 2.77 (t, *J* = 6.2 Hz, 2H), 2.32-2.21 (m, 2H), 2.08-1.87 (m, 7H), 1.76-1.64 (m, 1H), 1.61-1.52 (m, 1H), 1.48-1.16 (m, 17H), 0.90-0.88 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 175.0, 173.6, 130.3, 130.2, 130.0, 128.2, 128.1, 128.0, 127.4, 66.2, 62.1, 45.6, 39.9, 33.5, 33.0, 31.6, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 27.3, 25.7, 25.3, 22.8, 22.7, 16.8, 14.4, 14.2. LRMS (EI): *m/z* = 550 (M^+,<1%), 479 (80), 477 (100), 329 (36), 230 (17), 156 (22), 91 (17), 55 (18). HRMS (EI): calcd. for $C_{34}H_{50}N_2O_4$ 550.3771; found 550.3765.

Ethyl (2*SR*,4*SR*,5*RS*)-2-[(7*Z*,10*Z*)-hexadeca-7,10-dien-1-yl]-4-(2-oxooxazolidine-3-carbonyl)-5-phenylpyrrolidine-2-carboxylate **6bc**.

Red oil, (149 mg, 54% yield). R_f 0.37 (hexane/ethyl acetate: 7/3). IR (neat) υ_{max}: 1265, 1387, 1732, 1778, 2854, 2925, 3372 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31-7.28 (m, 5H), 5.43-5.28 (m, 4H), 4.80 (s, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.11- 4.05 (m, 1H), 3.69-3.62 (m, 2H), 3.25-3.12 (m, 1H), 3.13 (s, 1H), 2.86 -2.76 (m, 2H), 2.23-2.15 (m, 1H), 2.13-1.96 (m, 4H), 1.91 (dd, *J* = 12.4, 4.4 Hz, 1H), 1.83-1.70 (m, 1H), 1.63-1.46 (m, 1H), 1.55-1.16 (m, 17H), 0.92-0.88 (m, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.6, 168.2, 152.7, 138.5, 130.2, 130.0, 129.9, 128.5, 128.4, 128.0, 127.9, 127.3, 127.1, 71.2, 66.0, 61.8, 47.2, 42.4, 39.5, 31.9, 31.5, 29.8, 29.7, 29.5, 29.3, 29.1, 27.2, 25.62, 25.2, 22.7, 22.6, 14.3, 14.1. LRMS (EI): *m/z* = 552 (M^+, <1%), 481 (97), 479 (100), 392 (26), 331 (58), 198 (16), 170 (20), 156 (36), 91 (25), 55 (32). HRMS (EI): calcd. for $C_{33}H_{48}N_2O_5$ 552.3563; found 552.3557.

Ethyl (1*SR*,3*RS*,*3aSR*,6*aRS*)-1-[(7*Z*,10*Z*)-hexadeca-7,10-dien-1-yl]-5-methyl-4,6-dioxo-3-(4-(trifluoromethyl)phenyl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate **6bd**.

Yellow oil, (255 mg, 86% yield). R_f 0.43 (hexane/ethyl acetate: 7/3). IR (neat) υ_{max}: 1127, 1165, 1325, 1706, 2856, 2927, 3341, 3464 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.61 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 5.53-5.20 (m, 4H), 4.69 (d, *J* = 9.1 Hz, 1H), 4.36 (dd, *J* = 7.2, 4.6 Hz, 2H), 3.56 (dd, *J* = 9.1, 7.5 Hz, 1H), 3.29 (d, *J* = 7.5 Hz, 1H), 2.81 (s, 3H), 2.77 (t, *J* = 6.1 Hz, 1H), 2.06 (dd, *J* = 8.2, 5.2 Hz, 4H), 1.95-1.65 (m, 1H), 1.52-1.14 (m, 19H), 0.96-0.86 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.4, 174.4, 171.4, 141.4, 132.5 (d, $^1J_{C\text{-}F}$ = 271.7 Hz, CF_3), 130.5 (d, $^2J_{C\text{-}F}$ = 32.7 Hz, $CHCF_3$), 130.3 129.8, 128.2, 127.8, 127.5, 125.4 (d, $^3J_{C\text{-}F}$ = 3.7 Hz, $CHCHCF_3$), 70.6, 61.7, 60.7, 55.0, 49.9, 34.9, 31.5, 29.4, 29.3, 29.0, 27.2, 27.1, 25.6, 24.9, 23.6, 22.5, 14.1. ^{19}F NMR δ: -62.5. LRMS (EI): *m/z* = 590 (M^+, <1%), 519 (47), 517 (100), 369 (83), 323 (22), 212 (26). HRMS (EI): calcd. for $C_{33}H_{45}F_3N_2O_4$ 590.3331; found 590.3333.

Ethyl (1*SR*,3*RS*,3*aSR*,6*aRS*)-1-[(7*Z*,10*Z*)-hexadeca-7,10-dien-1-yl]-5-methyl-4,6-dioxo-3-(thiazol-2-yl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate **6be**.

Yellow oil, (190 mg, 72% yield). R_f 0.13 (hexane/ethyl acetate: 7/3). IR (neat) υ_{max}: 1287, 1436, 1705, 1736, 2254, 2855, 2927, 3007, 3314, 3464 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.81 (d, *J* = 3.2 Hz, 1H), 7.35 (d, *J* = 3.2 Hz, 1H), 5.44-5.29 (m, 4H), 5.05 (d, *J* = 9.0 Hz, 1H), 4.36 (dq, *J* = 7.1, 3.8 Hz, 2H), 3.69 (t, *J* = 8.3 Hz, 1H), 3.32 (d, *J* = 7.5 Hz, 1H), 2.84 (s, 3H), 2.77 (t, *J* = 6.0 Hz, 1H), 2.04 (q, *J* = 6.9, 5.0 Hz, 4H), 1.86-1.57 (m, 1H), 1.48-1.16 (m, 19H), 0.90 (td, *J* = 6.9, 5.9, 3.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.2, 174.4, 170.8, 167.4, 142.8, 130.2, 129.9, 128.1, 127.8, 119.6, 71.1, 61.7, 59.4, 55.7, 50.3, 35.6, 31.5, 29.5, 29.4, 29.3, 29.0, 27.2, 27.1, 25.6, 25.0, 23.7, 22.6, 14.1. LRMS (EI): *m/z* = 529 (M^+, <1%), 558 (48), 556 (100), 308 (47), 262 (15), 86 (26). HRMS (EI): calcd. for $C_{29}H_{43}N_3O_4S$ 529.2974; found 529.2979.

Methyl (1*SR*,3*RS*,3*aSR*,6*aRS*)-5-methyl-1-[(3*Z*,6*Z*,9*Z*,12*Z*)-octadeca-3,6,9,12-tetraen-1-yl]-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate **6ca**.
Yellow oil, (160 mg, 60% yield). R_f 0.28 (hexane/ethyl acetate: 8/2). IR (neat) υ_{max}: 1098, 1288, 1436, 1484, 1642, 1703, 1736, 2959 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.38-7.30 (m, 5H), 5.43-5.34 (m, 8H), 4.67 (d, *J* = 9.1 Hz, 1H), 3.91 (s, 3H), 3.52 (dd, *J* = 9.2, 7.4 Hz, 1H), 3.27 (d, *J* = 7.4 Hz, 1H), 2.82-2.77 (m, 9H), 2.19-2.16 (m, 1H), 2.11-1.99 (m, 3H), 2.08-1.25 (m, 10H), 0.92-0.88 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.8, 174.8, 172.1, 130.6, 129.3, 128.8, 128.6, 128.6, 128.5, 128.2, 127.9, 127.8, 127.6, 127.0, 70.8, 61.9, 55.8, 52.6, 50.6, 35.0, 31.6, 29.4, 27.3, 25.7, 25.6, 24.9, 22.7, 22.0, 14.2. LRMS (EI): *m/z* = 532 (M^+, <1%), 473 (35), 341 (28), 327 (22), 287 (100), 254 (26), 241 (21), 193 (23), 130 (29), 91 (21). HRMS (EI): calcd. for $C_{33}H_{44}N_2O_4$ 532.3301; found 532.3289.

Methyl (1*SR*,3*RS*,3*aSR*,6*aRS*)-5-methyl-1-[(3*Z*,6*Z*,9*Z*,12*Z*)-octadeca-3,6,9,12-tetraen-1-yl]-4,6-dioxo-3-(4-(trifluoromethyl)phenyl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate **6cb**.
Yellow oil, (168 mg, 56% yield). R_f 0.45 (hexane/ethyl acetate: 8/2). IR (neat) υ_{max}: 1128, 1436, 1620, 1701, 1779, 2858, 2929, 3012, 3349, 3460 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 5.57-5.19 (m, 8H), 4.69 (d, *J* = 8.6 Hz, 1H), 3.88 (s, 3H), 3.54 (t, *J* = 8.2 Hz, 1H), 3.28 (d, *J* = 7.0 Hz, 1H), 2.88-2.61 (m, 9H), 2.18-1.84 (m, 5H), 1.51-1.11 (m, 8H), 0.99-0.70 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.4, 174.4, 171.8, 141.2, 130.4 (d, $^2J_{C\text{-}F}$ = 32.9 Hz, *C*HCF_3), 129.4, 128.7, 128.5, 127.9, 127.7, 127.6, 127.45, 127.4, 125.4 (d, $^3J_{C\text{-}F}$ = 4.1 Hz, *C*$HCHCF_3$), 70.7, 60.9, 55.3, 52.6, 50.0, 34.7, 31.5, 29.3, 27.2, 25.6, 25.5, 24.9, 22.5, 21.9, 14.1. ^{19}F NMR δ: -63.0. LRMS (EI): *m/z* = 600 (M^+, <1%), 541 (27), 395 (23), 355 (100), 322 (25), 210 (25), 91 (18), 67 (23). HRMS (EI): calcd. for $C_{34}H_{43}F_3N_2O_4$ 600.3175; found 600.3167.

Ethyl (1*SR*,3*SR*,3*aSR*,6*aRS*)-1-[(2*Z*,5*Z*,8*Z*,11*Z*,14*Z*,17*Z*)-icosa-2,5,8,11,14,17-hexaen-1-yl]-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate **6da**.
Yellow oil, (210 mg, 74% yield). R_f 0.40 (hexane/ethyl acetate: 7/3). IR (neat) υ_{max}: 1130, 1288, 1382, 1438, 1702, 2965, 3060, 3454 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.36-7.34 (m, 5H), 5.62-5.31 (m, 12H), 4.68 (d, *J* = 9.1 Hz, 1H), 4.35 (qd, *J* = 7.1, 0.9 Hz, 2H), 3.54 (dd, *J* = 9.2, 7.5 Hz, 1H), 3.33 (d, *J* = 7.4 Hz, 1H), 3.06-2.76 (m, 13H), 2.66 (dd, *J* = 14.5, 7.8 Hz, 1H), 2.09 (tt, *J* = 8.2, 1.2 Hz, 3H), 1.40 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.6, 174.7, 171.3, 137.3, 132.8, 132.1, 130.2, 129.8, 129.1, 128.8, 128.6, 128.4, 128.4, 127.9, 127.8, 127.8, 127.5, 127.1, 127.0, 122.5, 70.2, 61.8, 61.6, 54.5, 50.1, 33.1, 26.0, 25.7, 25.6, 25.5, 24.8, 20.6, 14.3, 14.1, 13.9. LRMS (EI): *m/z* = 570 (M^+, <1%), 370 (17), 369 (89), 301 (100), 211 (14), 144 (11). HRMS (EI): calcd. for $C_{36}H_{46}N_2O_4$ 570.3458; found 570.3435.

Ethyl (1*SR*,3*RS*,3*aSR*,6*aRS*)-5-(4-fluorobenzyl)-1-[(2*Z*,5*Z*,8*Z*,11*Z*,14*Z*,17*Z*)-icosa-2,5,8,11,14,17-hexaen-1-yl]-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate **6db**.
Yellow oil, (220 mg, 66% yield). R_f 0.54 (hexane/ethyl acetate: 7/3). IR (neat) υ_{max}: 1224, 1396, 1510, 1707, 2932, 2964, 3012, 3345, 3467 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.34-7.07 (m, 7H), 6.99 (t, *J* = 8.7 Hz, 2H), 5.52-5.22 (m, 12H), 4.63 (d, *J* = 9.2 Hz, 1H), 4.44 (d, *J* = 7.1 Hz, 2H), 4.39-4.32 (m, 2H), 3.47 (dt, *J* = 8.7, 6.2 Hz, 1H), 3.31 (d, *J* = 7.6 Hz, 1H), 3.10-2.63 (m, 10H), 2.64 (dd, *J* = 14.5, 7.8 Hz, 1H), 2.17-1.97 (m, 3H) 2.20-1.92 (m, 3H), 1.39 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.1, 174.2, 171.1, 162.44 (d, $^1J_{C\text{-}F}$ = 246.5 Hz, *C*F), 136.8, 132.8, 132.1, 131.5 (d, $^4J_{C\text{-}F}$ = 3.3 Hz, *C*CHCHCF), 131.0 (d, $^3J_{C\text{-}F}$ = 8.2 Hz, *C*HCHCF) , 129.7, 129.0, 128.8, 128.6, 128.4, 128.4, 128.3, 128.2, 127.9, 127.8, 127.8, 127.5, 127.1, 127.0, 122.5, 115.3 (d, $^2J_{C\text{-}F}$ = 21.4 Hz, *C*HCF), 70.4, 61.8, 61.7, 54.6, 49.8, 41.7, 33.0, 26.0, 25.7, 25.6, 25.5, 20.5, 14.3, 14.1. ^{19}F NMR δ: -114.2. LRMS (EI): *m/z* = 664 (M^+, <1%), 396 (24), 395 (100), 144 (15), 109 (41), 91 (15), 79 (13). HRMS (EI): calcd. for $C_{42}H_{49}FN_2O_4$ 664.3676; found 664.3666.

Ethyl (1*SR*,3*RS*,3*aSR*,6*aRS*)-1-[(2*Z*,5*Z*,8*Z*,11*Z*,14*Z*,17*Z*)-icosa-2,5,8,11,14,17-hexaen-1-yl]-5-methyl-4,6-dioxo-3-(thiazol-2-yl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate **6dc**.
Yellow oil, (200 mg, 69% yield). R_f 0.17 (hexane/ethyl acetate: 7/3). IR (neat) υ_{max}: 1098, 1288, 1381, 1435, 1705, 2934, 2967, 3401 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 3.2 Hz, 1H), 7.31 (d, *J* = 3.2 Hz, 1H), 5.59-5.19 (m, 12H), 5.02 (d, *J* = 9.1 Hz, 1H), 4.31 (qd, *J* = 7.2, 1.2 Hz, 2H), 3.76-3.57 (m, 1H), 3.35 (d, *J* = 7.5 Hz, 1H), 3.30 (dd, *J* = 7.6, 3.0 Hz, 1H), 3.02-2.59 (m, 13H), 2.52 (dd, *J* = 14.4, 7.5 Hz, 1H), 1.36 (t, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.1, 174.3, 170.5, 167.8, 143.0, 133.0, 132.1, 128.9, 128.7, 128.5, 128.4, 128.1, 128.0, 127.9, 127.5, 127.1, 122.5, 119.7, 70.9, 62.0, 59.6, 54.9, 50.2, 33.7, 26.1, 25.8, 25.7, 25.6, 25.2, 20.7, 14.4, 14.2. LRMS (EI): *m/z* = 577 (M^+, <1%), 308 (100), 262 (6), 177 (7), 91 (5). HRMS (EI): calcd. for $C_{33}H_{43}N_3O_4S$ 577.2974; found 577.2963.

Ethyl (1*SR*,3*SR*,3*aSR*,6*aSR*)-1-[(2*Z*,5*Z*,8*Z*,11*Z*,14*Z*,17*Z*)-icosa-2,5,8,11,14,17-hexaen-1-yl]-5-methyl-4,6-dioxo-3-(4-(trifluoromethyl)phenyl)octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate **6dd**.
Yellow oil, (200 mg, 63% yield). R_f 0.43 (hexane/ethyl acetate: 7/3). IR (neat) υ_{max}: 1127, 1325, 1707, 2930, 2962, 3013, 3342, 3471 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.59 (dd, *J* = 5.7, 3.3 Hz, 2H), 7.46 (dd, *J* = 5.7, 3.3 Hz, 2H), 5.47-5.12 (m, 12H), 4.72 (d, *J* = 9.2 Hz, 1H), 4.33 (qd, *J* = 7.2, 0.9 Hz, 2H), 3.57 (dd, *J* = 9.2, 7.4 Hz, 1H), 3.33 (d, *J* = 7.2 Hz, 1H), 2.91-2.79 (m, 13H), 2.65 (dd, *J* = 14.5, 7.8 Hz, 1H), 2.12-2.01 (m, 3H), 1.38 (t, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.3, 174.3, 171.0, 141.5, 134.1, 132.1, 132.0 (d, $^1J_{C\text{-}F}$ = 271.7 Hz, *C*F_3), 130.5, (d, $^2J_{C\text{-}F}$ = 32.3 Hz, *C*HCF_3), 128.9, 128.6, 128.6, 128.5, 128.4, 127.9, 127.8, 127.7, 127.6, 127.5, 127.3, 126.9, 125.4, 125.3 (d, $^3J_{C\text{-}F}$ = 3.9 Hz, *C*$HCHCF_3$) 122.2 (d, $^4J_{C\text{-}F}$ = 1.3 Hz, *C*$CHCHCF_3$), 70.1, 61.9, 60.8, 54.1, 49.7, 49.4, 33.0, 27.0, 25.9, 25.71, 25.65, 25.6, 25.5, 24.9, 20.5, 14.2, 14.1. ^{19}F NMR

δ: -62.5. LRMS (EI): *m/z* = 638 (M^+, <1%), 370 (20), 369 (100), 301 (43), 212 (16), 91 (7). HRMS (EI): calcd. for $C_{37}H_{45}F_3N_2O_4$ 638.3331; found 638.3334.

Ethyl (1*SR*,3*RS*,3*aSR*,6*aRS*)-1-[(*Z*)-heptadec-8-en-1-yl]-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate **12aa**.

Yellow oil, (205 mg, 75% yield). R_f 0.45 (hexane/ethyl acetate: 7/3). IR (neat) υ_{max}: 1287, 1383, 1435, 1705, 1779, 2854, 2925, 3343, 3466 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.40-7.30 (m, 5H), 5.42-5.30 (m, 2H), 4.67 (d, *J* = 9.2 Hz, 1H), 4.43-4.24 (m, 2H), 3.53 (dd, *J* = 9.2, 7.4 Hz, 1H), 3.27 (d, *J* = 7.5 Hz, 1H), 2.82 (s, 3H), 2.12-1.94 (m, 4H), 1.84-1.76 (m, 1H), 1.531.17 (m, 27H), 0.99-0.87 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.7, 174.9, 171.7, 137.2, 130.2, 129.7, 128.6, 128.5, 127.1, 70.8, 61.8, 55.5, 50.5, 35.1, 32.0, 29.8, 29.8, 29.6, 29.5, 29.4, 29.1, 27.3, 27.2, 24.9, 23.7, 22.8, 14.2, 14.2. LRMS (EI): *m/z* = 538 (M^+, <1%), 465 (100), 439 (19), 301 (83), 254 (34), 241 (22), 156 (27), 55(17). HRMS (EI): calcd. for $C_{33}H_{50}N_2O_4$ 538.3771; found 538.3763.

*4.6. General procedure for preparation of α-amino ester **11a**.*

Synthesis of *N-tert*-butylsulfinyl imine **8**: powdered IBX (4.20 g, 15 mmol) was added to a solution of alcohol **7a** (2.68 g, 5 mmol) with acetonitrile. It was stirred 4 h at 80 °C. Filtration of the reaction mixture over a short-pad of silica give the corresponding pure aldehyde.[15] Then, a solution of *tert*-butanesulfinamide (0.67 g, 5.5 mmol) was added to the corresponding aldehyde (1.33 g, 5 mmol) in dry THF (20 mL) under argon atmosphere at 23 °C. Titanium tetraethoxide (2.23 g, 2.09 mL, 10 mmol) was slowly added and it was stirred for 12 h at the room temperature. The resulting mixture was hydrolyzed with brine, extracted with ethyl acetate, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by column chromatography (Hexane/AcOEt) to yield pure compound **8**.

2-Methyl-*N*-[(1*E*,9*Z*)-octadec-9-en-1-ylidene]propane-2-sulfinamide **8a**.

Yellow oil, (1.42 g, 77% yield). R_f 0.28 (hexane/ethyl acetate: 9/1). IR (neat) υ_{max}: 1088, 1363, 1458, 1622, 2854, 2924 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (t, *J* = 4.8 Hz, 1H), 5.40-5.32 (m, 2H), 2.52 (td, *J* = 7.4, 4.7 Hz, 2H), 2.02 (q, *J* = 5.9 Hz, 4H), 1.66-1.59 (m, 2H), 1.42-1.20 (m, 29H), 1.20 (s, 9H), 0.95-0.78 (m, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.8, 130.0, 129.7, 56.5, 36.1, 31.9, 29.8, 29.7, 29.6, 29.5, 29.3, 29.2, 29.2, 29.1, 27.2, 27.1, 25.5, 22.7, 22.3, 14.1. LRMS (EI): *m/z* = 369 (M^+, <1%), 313 (34), 264 (12), 57 (100), 41 (17). HRMS (EI): calcd. for $C_{22}H_{43}NOS$ (M^+ - C_4H_9SO) 264.2691; found 264.2697.

Synthesis of β-nitroamine derivative **9a**: a heterogeneous mixture of nitromethane (0.56 g, 0.50 mL, 9.0 mmol) and the corresponding *N-tert*-butylsulfinyl imine **8a** (1.11 g, 3.0 mmol) was added NaOMe/MeOH (10 mol%) dropwise and the mixture was stirred at room temperature 12 h. The resulting mixture was hydrolyzed with water, acidified with 1M hydrochloric acid, extracted with ethyl acetate, dried over anhydrous MgSO4, and evaporated. The residue was purified by column chromatography (silica gel, Hexane/AcOEt) to yield pure compound.

(*Z*)-2-Methyl-*N*-(1-nitrononadec-10-en-2-yl)propane-2-sulfinamide **9a**.

Yellow oil, (0.90 g, 70% yield). R_f 0.50 (hexane/ethyl acetate: 1/1). IR (neat) υ_{max}: 1048, 1378, 1465, 1553, 1740, 2854, 2925, 3199, 3402 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.37-5.28 (m, 2H), 4.70-4.63 (m, 2H), 4.12 (d, *J* = 9.3 Hz, 1H), 3.76 (dq, *J* = 8.9, 4.8 Hz, 1H), 1.99 (q, *J* = 6.5 Hz, 4H), 1.60-1.50 (m, 2H), 1.48-1.41 (m, 1H), 1.39-1.16 (m, 31H), 0.92-0.74 (m, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 130.0, 129.6, 79.8, 55.2, 33.1, 31.9, 29.7, 29.7, 29.6, 29.5, 29.3, 29.1, 29.0, 27.2, 27.1, 25.8, 22.7, 22.6, 14.1. LRMS (EI): *m/z* = 430 (M^+, <1%), 313 (16), 374 (7), 264 (10), 69 (10), 57 (100), 41 (16). HRMS (EI): calcd. for $C_{23}H_{46}N_2O_3S$ 430.3229; found 430.3233.

Synthesis of α-amino acid derivative **10a**: solid $NaNO_2$ (414 mg, 6.0 mmol) was added to a stirred solution of compound **9a** (0.39 g, 1 mmol) and AcOH (0.30 mg, 0.29 mL, 5 mmol) in a 7:1 mixture of DMF and water (2.5 mL) at 23 °C. The reaction was heated at 45 °C for 12 h, after which it was quenched with a 2 M NaOH water solution until pH = 6 and extracted with MTBE, dried over anhydrous $MgSO_4$ and evaporated to give pure compound.

(*Z*)-2-[(*tert*-butylsulfinyl)amino]nonadec-10-enoic acid **10a**.

Yellow oil, (170 mg, 41% yield). R_f 0.47 (dichloromethane/methanol: 9/1). IR (neat) υ_{max}: 1029, 1254, 1463, 1651, 1725, 2854, 2925, 3270, 3417. ^1H NMR (300 MHz, $CDCl_3$) δ 5.37-5.30 (m, 2H), 4.54 (s, 1H), 3.84 (d, *J* = 9.3 Hz, 1H), 1.99 (q, *J* = 6.5 Hz, 4H), 1.77 (d, *J* = 5.5 Hz, 1H), 1.65 (dd, *J* = 13.1, 5.7 Hz, 1H), 1.44-1.05 (m, 31H), 0.90-0.85 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.2, 130.4, 130.2, 59.0, 56.6, 34.0, 32.6, 31.9, 29.7, 29.6, 29.5, 29.3, 29.2, 29.0, 25.3, 22.8, 22.6, 14.1. LRMS (EI): *m/z* = 415 (M^+, <1%), 359 (19), 310 (18), 287 (19), 266 (33), 57 (100). HRMS (EI): calcd. for $C_{23}H_{45}NO_3S$ 415.3120; found 415.3109.

Synthesis of α-amino ester **11a**: a solution of **10a** (0.083 g, 0.2 mmol) in EtOH was added H_2SO_4. The mixture was stirred overnight at 40 °C. It was quenched with $NaHCO_3$ until pH=7 and solvent was evaporated. It was extracted with AcOEt, dried over anhydrous $MgSO_4$ and evaporated to give pure compound.

Ethyl (Z)-2-aminononadec-10-enoate **11a**.

Yellow oil, (56 mg, 82% yield). R_f 0.50 (dichloromethane/methanol: 9/1). IR (neat) υ_{max}: 1180, 1465, 1736, 2853, 2922, 3196, 3311, 3371 cm^{-1} .^1H NMR (300 MHz, $CDCl_3$) δ: 5.38 (dt, *J* = 4.9, 2.5 Hz, 2H), 4.37-3.82 (m, 2H), 2.06-1.87 (m, 4H), 1.83-1.70 (m, 1H), 1.63 (d, *J* = 6.3 Hz, 1H), 1.27 (d, *J* = 45.9 Hz, 3H), 0.94-0.80 (m, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 175.4, 130.4, 130.1,65.7, 62.1, 32.6, 31.9, 29.6, 29.4, 29.3, 29.1, 29.1, 27.2, 22.6, 21.5, 15.8, 14.1. LRMS (EI): *m/z* = 339 (M^+, <1%), 268 (16), 267(27), 266 (100), 240 (14), 57(19), 55(20). HRMS (EI): calcd. for $C_{21}H_{41}NO$ 339.3137; found 339.3132.

Conflicts of interest

There are no conflicts to declare.

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NMR spectra are available in ESI.

Dedicated to Professor Kiyoshi Tomioka on the occasion of his 70th Birthday

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