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Enantiospecific synthesis of α-amino acid semialdehydes: a key step for the synthesis of unnatural unsaturated and saturated α-amino acids

José M. Padrón,[a] George Kokotos,[b] Tomás Martín,[a] Theodoros Markidis,[b] William A. Gibbons [c] and Víctor S. Martín [a,*]

[a] *Instituto Universitario de Bio-Orgánica 'Antonio González', Unidad Asociada al CSIC, Universidad de La Laguna, C/Astrofísico Francisco Sánchez, 2, 38206 La Laguna, Tenerife, Spain*

[b] *Department of Chemistry, Laboratory of Organic Chemistry, University of Athens, Panepistimiopolis, 15771 Athens, Greece*

[c] *Department of Pharmaceutical Chemistry, The School of Pharmacy, University of London, 29–39 Brunswick Square, London, WC1N 1AX, UK*

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Abstract

The enantiospecific synthesis of unnatural unsaturated and saturated α-amino acids based on a Wittig type reaction is described. The versatile synthetic intermediates, L-glutamic and L-aspartic acid semialdehydes, are obtained from the corresponding *N*,*N*-di-Boc-diesters, by the selective reduction of the ω-ester with DIBAL® under controlled conditions. The semialdehydes are chemically stable for a prolonged time and react with various phosphorous ylides, under controlled conditions, to produce the enantiomerically pure unsaturated α-amino acids in high yields. The method is equally applicable to homologated diesters obtained by the presented methodology providing unsaturated amino acids with variable unsaturated positions and geometries. The corresponding saturated products can be obtained by simple hydrogenation.

1. Introduction

Optically active natural and unnatural α-amino acids are constituents of many biologically and pharmacologically important compounds, e.g. inhibitors of renin, angiotensin converting enzymes, immunomodulators, cytostatic drugs, peptide antibiotics, as well as important precursors for the synthesis of pharmaceuticals, agrochemical, and food ingredients. Modified amino acids have been widely used in medicinal chemistry and biochemistry to change the conformation, restrict the flexibility and enhance the potency of molecules. Moreover, the synthesis of new non-proteinogenic amino acids and their

* Corresponding author. E-mail: vmartin@ull.es

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incorporation into natural biologically active peptides might become a powerful method for the design of peptide and peptidomimetics therapeutics.

Of particular interest for us is a special class of non-natural α-amino acids, the lipidic α-amino acids (LAAs), which combine structural features of amino acids with those of lipids.[1] The LAAs and their derivatives are molecules with long aliphatic side chains exhibiting interesting biological properties. In particular, lipidic 2-amino alcohols and 1,2- and 1,3-diamines, derived from racemic LAAs, have been shown to exhibit in vivo anti-inflammatory activity[2] and in vitro cytotoxic activity,[3] while lipidic 2-amino alcohols have been proved to be potent immunosuppressants.[4]

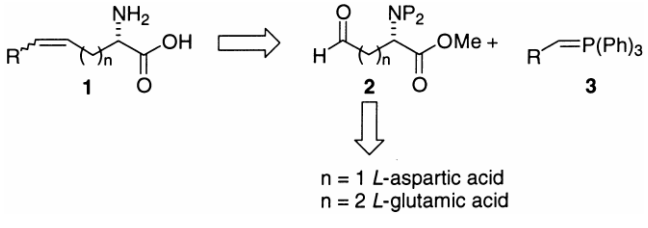
Many ingenious techniques have been devised for the efficient asymmetric synthesis of α-amino acids and have been extensively reviewed.[5] We have previously described the synthesis of saturated LAAs and their derivatives, based on the oxidative cleavage of 3-amino-1,2-diols obtained by the regioselective opening of enantiomerically enriched long chain 2,3-epoxy alcohols.[6] Unfortunately, this approach was not suitable for the preparation of the desired unsaturated LAAs.

In principle, the selective chemical modification of the side chains of inexpensive proteinogenic amino acids offers attractive access to rare or unnatural α-amino acids, provided the original chirality can be preserved. Based on this approach we synthesized enantiomerically pure α-amino arachidonic acid from glutamic acid semialdehyde using Wittig type reactions.[7]

In the present paper[8] we wish to report in full the results concerning the synthesis of enantiomerically pure unsaturated α-amino acids, which eventually can be transformed into the saturated products by simple hydrogenation. The key steps in our methodology are the selective reduction with DIBAL® of *N*,*N*-di-Boc-glutamic or aspartic dialkyl esters and further Wittig reaction, both steps being performed under controlled conditions. Furthermore, it is possible to control the stereochemistry of the double bond in the final products. This method provides almost unlimited possibilities, with the only restriction being the synthesis of the suitable ylide and the corresponding Wittig reaction.

2. Results and discussion

The retrosynthetic pathway we have followed is outlined in Scheme 1. We based our strategy on the possibility of building the chain using Wittig type reactions from aldehydes such as **2** that could be obtained from glutamic or aspartic acid. These amino acids are inexpensive and available in both enantiomeric forms. In addition, this approach permits both convergence in the synthetic procedure and stereoselectivity in the formation of the double bond.



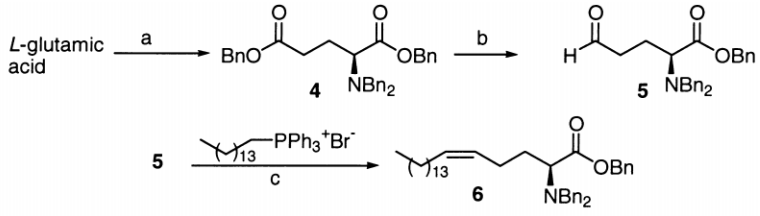
Scheme 1.

Glutamic and aspartic acid semialdehydes are configurationally stable compounds and were selected as chiral building blocks. Although these intermediates are known and their syntheses have been reported previously,[9] the strategies found in the literature afford only low chemical yield due to the number of steps and/or the use of expensive, impractical starting material or reagents. Our approach describes a new synthesis of protected derivatives of enantiomerically pure glutamic and aspartic acid semialdehydes in

a limited number of steps using readily available reagents. This procedure permitted us to easily increase the scale of the reaction.

2.1. Glutamic acid semialdehyde and derivatives

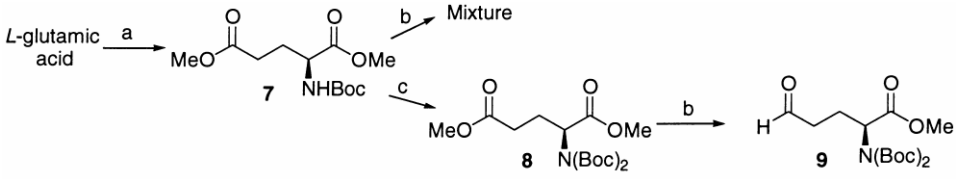
In a first attempt, commercial L-glutamic acid was submitted to perbenzylation under known conditions to afford the diester **4** in 70% yield.[10] Then, this compound was reduced with DIBAL® under controlled conditions (1.1 equivalents, −78°C, 15 min) to yield **5** as the only compound in 87% yield. Further homologation under usual Wittig conditions (*n*-BuLi, THF, −78°C) permitted us to obtain the protected LAA **6** with total stereoselection in the double bond formed and in a good yield (78%) (Scheme 2).[11] This method was, however, discarded because of the impossibility of cleavage of the benzyl protecting groups under non-hydrogenating conditions.[12]



(a) BnBr, K_2CO_3, H_2O, Δ; (b) (i) DIBAL®, ether, −78 °C, (ii) H_2O; (c) *n*-BuLi, THF, −78 °C

Scheme 2.

We thus decided to employ other, more easily removed protecting groups. As an alternative approach for the protection of free L-glutamic acid we designed a one-pot procedure for the esterification of both carboxyl groups and further *N*-Boc protection. Thus, L-glutamic acid was treated for 12 h with Me_3SiCl in dry MeOH[13] followed by the addition of Et_3N and di-*tert*-butyl dicarbonate,[14] to obtain **7** in high yields (95%). Disappointingly, we were unable to obtain the desired aldehyde when **7** was submitted to reduction with DIBAL® under our conditions, presumably because of some participation of the nitrogen. This result induced us to minimize the nucleophilic power of the nitrogen by the introduction of a second *N*-Boc group. The dimethyl *N*-Boc-glutamate **7** was treated with di-*tert*-butyl dicarbonate under known conditions to afford **8** in almost quantitative yield.[15] In this case, fortunately, when **8** was submitted to reduction with DIBAL® under our conditions the aldehyde **9** was obtained in 85% yield (Scheme 3).

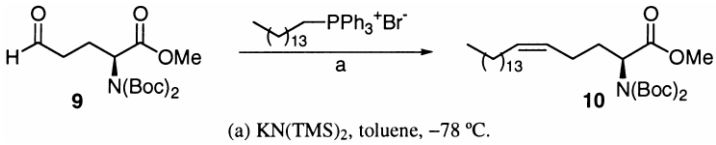


(a) (i) Me_3SiCl, MeOH, (ii) $(Boc)_2O$, Et_3N; (b) (i) DIBAL®, ether, −78 °C, (ii) H_2O; (c) $(Boc)_2O$, DMAP, CH_3CN.

Scheme 3.

Unsuccessful results were obtained when the aldehyde **9** was submitted to usual Wittig conditions (*n*-BuLi, THF, −78°C). We therefore changed the reaction conditions. In fact, when $NaN(TMS)_2$ was used as base, in THF, the unsaturated LAA derivative **10** was obtained in 10% yield. In addition, when the generation of the ylide was performed with $KN(TMS)_2$, in toluene, at 0°C and the Wittig reaction performed at −78°C, the *Z*-ester **10** was obtained in 92% isolated yield (Scheme 4).[16]

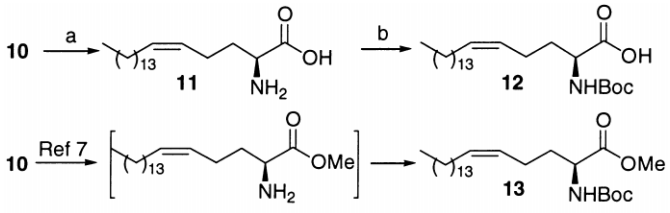
The saponification of the methyl esters must be carried out under controlled conditions in order to avoid any epimerization.[17] Although a procedure based on di-*N*-Boc cleavage, *N*-Boc protection and saponification[18] is plausible, we found that depending on the reaction conditions such as rate of



(a) $KN(TMS)_2$, toluene, −78 °C.

Scheme 4.

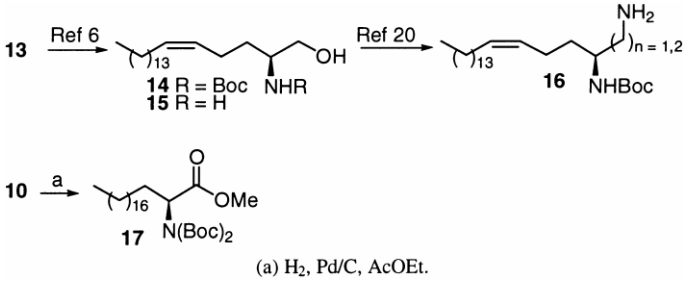
stirring, concentration and reaction time, on occasion, racemization may occur. Therefore, we strongly recommend the alternative sequence based on Scheme 5 to obtain the free acid without racemization. Firstly, we removed the two *N*-Boc groups under acid conditions. Then, we hydrolyzed the methyl ester under alkaline conditions during a relatively short period of time. In order to obtain the *N*-Boc derivative, the free amino compound was *N*-Boc-protected to **12**. These steps proceeded with a very good overall yield. In contrast, if the methyl *N*-Boc-ester **13** is the desired product, the best method is the one based on the cleavage of the two *N*-Boc groups in **10**, under acid conditions, and consecutive *N*-Boc protection to afford **13**.



(a) (i) HCl, THF, (ii) NaOH, dioxane; (b) $(Boc)_2O$, Et_3N, MeOH.

Scheme 5.

Interestingly, the simple reduction of **13** with DIBAL® can then be considered to be a general method to obtain unsaturated lipidic 2-amino-1-alcohols **14** or **15** which can be further converted to 1,2- and 1,3-diamines **16**.[6,19] In addition, the catalytic hydrogenation of compound **10** led us to the saturated derivative **17** in high yields (Scheme 6). Thus, this approach offers an alternative, and perhaps more convenient, method for the preparation of saturated LAAs.

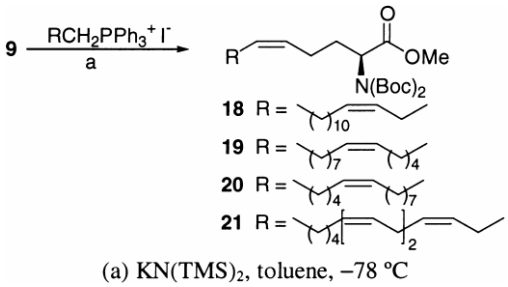


(a) H_2, Pd/C, AcOEt.

Scheme 6.

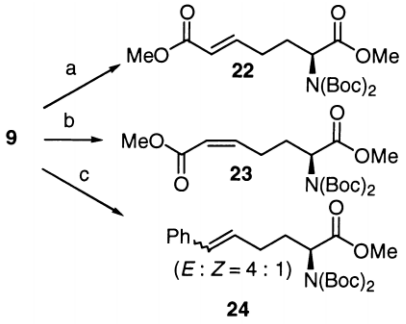
Once the methodology was set up, we were able to achieve the synthesis of different LAAs analogues and, importantly, the analysis of structure–activity relationships. Thus, by performing the Wittig reaction over (Scheme 7) with different phosphorous ylides[20] we prepared in high yields a series of derivatives, which presented various *Z*-unsaturations in the aliphatic chain, such as **18**, **19**, **20** and **21**.

In order to explore the scope and limitations of the aldehyde **9** we extended the Wittig reaction to the use of stabilized phosphoranes and phosphonates. We attempted the synthesis of compounds that presented either *E* or *Z* geometry in the double bond formed. Thus, the use of methyl (triphenylphosphoranylidene)acetate provided the *E*-olefin **22** as the sole stereoisomer. Complementarily, the treatment of **9** with the anion of methyl diphenoxyphosphorylacetate provided cleanly the *Z*-isomer **23**.[21] However,



Scheme 7.

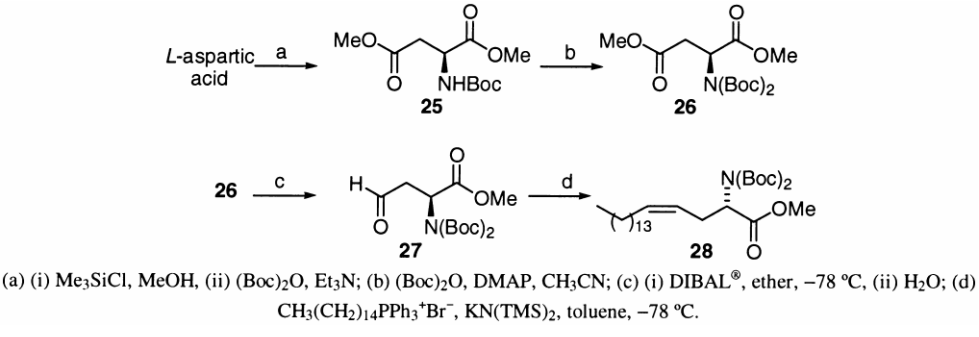
the use of ylide derived from benzyl triphenylphosphonium bromide provided a 4:1 *E*:*Z* mixture of the unsaturated compounds **24** (Scheme 8).



Scheme 8.

2.2. *Aspartic acid semialdehyde and derivatives.*

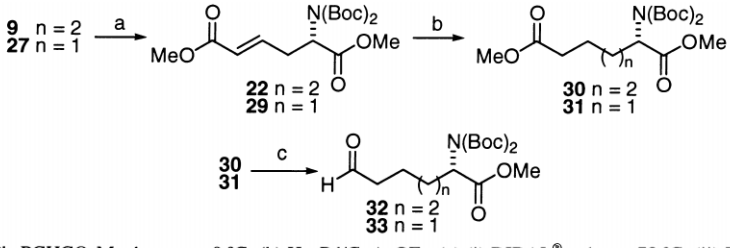
All the above compounds can be obtained from glutamic acid and therefore present the formed double bond at C-5. Because of our aforementioned interest in structure–activity relationships and search for a general methodology to place a double bond at any position of the chain, we thought about the possibility of using aspartic acid in the same manner in order to obtain LAA derivatives with the unsaturation at C-4. Thus, when commercially available L-aspartic acid was submitted to the sequence described earlier we could obtain, in similar yields, not only the aspartic acid semialdehyde **27**, but also the corresponding unsaturated LAA derivative **28**, in a similar manner to that using glutamic acid (Scheme 9).



Scheme 9.

2.3. α-Amino diacid ω-semialdehydes

The similarity in the methodology to obtain semialdehydes such as **9** and **27** derived from glutamic and aspartic acids, respectively, induced us to envisage that the reduction of any ester located in a longer chain should lead to the suitable aldehyde in a similar manner. In order to explore such an idea, we decided to prepare new α-amino diacids with a longer carbon chain. Thus, semialdehydes **9** and **27**, respectively, were submitted to Wittig reaction using methyl (triphenylphosphoranylidene)acetate to obtain the corresponding *E*-unsaturated esters. The simple hydrogenation of the double bond led us again to the saturated *N*,*N*-di-Boc dialkyl esters, **30** and **31**. Gratifyingly, the reduction of these compounds using the earlier described reduction procedure led to the desired aldehydes **32** and **33** in a straightforward manner. Thus, the use of these compounds and/or the iteration of the procedure permit tailoring the location of a new double bond at any position of the chain (Scheme 10).



(a) Ph_3PCHCO_2Me, benzene, 0 °C; (b) H_2, Pd/C, AcOEt; (c) (i) DIBAL®, ether, −78 °C, (ii) H_2O.

Scheme 10.

2.4. Conclusions

In summary, we have reported on a simple, efficient and general method to prepare unsaturated α-amino acids and derivatives in their enantiomeric forms, which can eventually be transformed into the saturated products by simple hydrogenation. The use of this methodology opens the way to the synthesis of almost unlimited types of non-proteinic α-amino acids. Although the presented methodology has been described only for one enantiomer series, the choice of the proper enantiomer of glutamic or aspartic acid permits the control of the absolute configuration in the final products.

3. Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 and/or Bruker AC 200 spectrometer in $CDCl_3$ as solvent, and chemical shifts are reported relative to Me_4Si. Low-resolution mass spectra were taken using a Hewlett–Packard model 257. Elemental analyses were performed on a Carlo–Erba model 1106. Optical rotations were determined for solutions in chloroform with a Perkin–Elmer model 241 polarimeter. Infrared spectra were recorded on a Bruker model IFS55. Melting points were determined on a Büchi model 535 melting point apparatus and are uncorrected. HPLC chromatography was performed using a Waters pump model 515 with a Waters 2487 dual λ absorbance detector using a μ-Porasil silica 10 μm Waters column. Column chromatography was performed on silica gel, 0.015–0.04 and 0.04–0.063 mm, and TLC and PLC were performed on silica gel, all Merck products. Visualization of spots was effected with UV light and/or phosphomolybdic acid and/or ninhydrin both in ethanol stain. All solvents were purified by standard techniques. Reactions requiring anhydrous conditions were performed under argon. Anhydrous magnesium sulfate was used for drying solutions.

*3.1. General procedure for the one-pot protection of free α-amino acids: dimethyl (*S*)-2-*tert*-butoxycarbonylamino-pentanodioate **7***

To a stirred suspension of commercially available L-glutamic acid (1.47 g, 10 mmol) in dry MeOH (33 ml, 0.3 M) was added slowly Me_3SiCl (5.6 ml, 44 mmol, 4.4 equiv.) in an ice-cold bath. After the addition was completed the ice-cold bath was removed and the reaction was stirred overnight until TLC showed complete conversion. Then, Et_3N (9 ml, 65 mmol, 6.5 equiv.) and $(Boc)_2O$ (2.4 g, 11 mmol, 1.1 equiv.) were sequentially added. The reaction mixture was stirred until TLC showed complete protection. The solvent was removed under reduced pressure and the residue triturated and washed with Et_2O (3×150 ml, 15 ml/mmol) using a pad of Celite. The combined organic layers were evaporated and the resulting crude was purified by silica gel column chromatography to afford **7** (2.60 g, 95% yield) as an oil: $[\alpha]_D^{25}$ +12.9 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.91 (m, 1H), 2.14 (m, 1H), 2.37 (m, 2H), 3.64 (s, 3H), 3.70 (s, 3H), 4.29 (br s, 1H), 5.14 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.7 (t), 28.2 (q), 30.0 (t), 51.7 (q), 52.3 (q), 52.8 (d), 79.9 (s), 155.3 (s), 172.6 (s), 173.1 (s); IR ($CHCl_3$) (cm^{-1}) 3436, 3025, 2981, 1737, 1714, 1503, 1369, 1167; MS *m/z* (relative intensity) 276 $(M+1)^+$ (1), 219 (22), 216 (48), 187 (25), 174 (31), 160 (63), 142 (41), 116 (99), 84 (86), 57 (100). Anal. calcd for $C_{12}H_{21}NO_6$: C, 52.35; H, 7.69; N, 5.09. Found: C, 52.26; H, 7.81; N, 5.05.

3.2. General procedure for the N,N-*di-Boc-protection of the* N-*Boc-methyl ester of α-amino acids: dimethyl (2*S*)-2-{(*tert*-butoxy)-*N*-[(*tert*-butyl)oxy- carbonyl]carbonylamino}-pentanedioate **8***

To a stirred solution of the *N*-Boc amino ester **7** (2.5 g, 9 mmol) and DMAP (220 mg, 1.8 mmol, 0.2 equiv.) in dry CH_3CN (30 ml, 0.3 M) was added $(Boc)_2O$ (2.2 g, 9.9 mmol, 1.1 equiv.) at rt. The reaction became slightly red with gas evolution. The mixture was stirred for 2 h, after which time TLC showed that some starting material still remained. More $(Boc)_2O$ (1.1 g, 4.9 mmol, 0.5 equiv.) was added and the mixture was additionally stirred overnight. The solvent was evaporated, and the crude purified by silica gel column chromatography, to afford **8** (3.32 g, 98% yield) as an oil: $[\alpha]_D^{25}$ −37.2 (*c* 2.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 18H), 2.17 (m, 1H), 2.40 (m, 2H), 2.46 (m, 1H), 3.67 (s, 3H), 3.71 (s, 3H), 4.93 (dd, *J*=9.2, 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.2 (t), 27.9 (q), 30.6 (t), 51.6 (q), 52.2 (q), 57.3 (d), 83.3 (s), 151.9 (s), 170.8 (s), 173.1 (s); IR ($CHCl_3$) (cm^{-1}) 3024, 2984, 1789, 1742, 1699, 1370, 1141; MS *m/z* (relative intensity) 376 $(M+1)^+$ (3), 320 (58), 264 (42), 220 (100), 176 (100), 116 (66), 84 (16). Anal. calcd for $C_{17}H_{29}NO_8$: C, 54.37; H, 7.79; N, 3.73. Found: C, 54.64; H, 7.92; N, 3.73.

3.3. General procedure for the selective reduction of the ω-ester group of dimethyl N,N-*di-Boc-α-amino-diesters to semialdehydes: methyl (2*S*)-2-{(*tert*-butoxy)-*N*-[(*tert*-butyl)oxycarbonyl]-carbonylamino}-5-oxopentanoate **9***

To a stirred solution of the dimethyl ester **8** (1 g, 2.7 mmol) in dry Et_2O (27 ml, 0.1 M) was added dropwise DIBAL® (3 ml, 1.0 M in hexane, 3 mmol, 1.1 equiv.) at −78°C. The reaction was stirred for 5 min and then quenched with H_2O (0.4 ml, ≈7 equiv.). The mixture was stirred for 30 min, dried over $MgSO_4$, and filtered through a pad of Celite. The solvent was evaporated and the crude purified by silica gel column chromatography to afford **9** (2.5 g, 85% yield) as an oil: $[\alpha]_D^{25}$ −35.3 (*c* 2.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 18H), 2.17 (m, 1H), 2.50 (m, 2H), 2.59 (m, 1H), 3.71 (s, 3H), 4.87 (dd, *J*=9.6, 5.2 Hz, 1H), 9.76 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.5 (t), 27.9 (q), 40.5 (t), 52.2 (q), 57.3 (d), 83.4 (s), 151.9 (s), 170.7 (s), 200.9 (d); IR ($CHCl_3$) (cm^{-1}) 3028, 2984, 1789, 1743, 1699, 1370, 1144; MS *m/z*

(relative intensity) 234 $(M-111)^+$ (1), 206 (15), 189 (10), 174 (37), 162 (35), 144 (31), 128 (100), 102 (26), 86 (35). Anal. calcd for $C_{16}H_{27}NO_7$: C, 55.64; H, 7.88; N, 4.06. Found: C, 55.45; H, 8.10; N, 4.09.

3.4. General procedure for the synthesis of lipidic (Z)-unsaturated N,N-*di-Boc-α-amino esters: methyl (2S)(5Z)-2-{(*tert-*butoxy)*-N-*[(*tert-*butyl)oxycarbonyl]carbonylamino}icos-5-enoate* **10**

To a stirred suspension of *n*-pentadecyl-triphenylphosphonium bromide (3.85 g, 7 mmol, 1.2 equiv.) in dry toluene (0.15 M) under argon was added dropwise $KN(TMS)_2$ (12.8 ml, 0.5 M, 6.4 mmol, 1.1 equiv.) at 0°C. After 15 min the flask was cooled to −78°C and **9** (2 g, 5.8 mmol, 1 equiv.) dissolved in toluene (5 ml) was added dropwise. The reaction mixture was stirred for 2 h after which time TLC showed complete conversion. Then the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (50 ml) and extracted with ether (3×10 ml). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the solvent evaporated. The crude was purified by silica gel column chromatography to afford **10** (2.7 g, 87% yield) as an oil: $[\alpha]_D^{25}$ −26.2 (*c* 2.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J*=6.8 Hz, 3H), 1.25 (br s, 24H), 1.49 (s, 18H), 1.90 (m, 1H), 2.00 (dd, *J*=13.6, 6.8 Hz, 2H), 2.08 (dd, *J*=14.0, 7.2 Hz, 2H), 2.15 (m, 1H), 3.71 (s, 3H), 4.86 (dd, *J*=8.8, 4.8 Hz, 1H), 5.38 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 22.7 (t), 24.0 (t), 27.3 (t), 28.0 (q), 29.3 (t), 29.4 (t), 29.5 (t), 29.6 (t), 29.7 (t), 30.1 (t), 31.9 (t), 52.1 (q), 57.7 (d), 83.0 (s), 128.1 (d), 131.3 (d), 152.1 (s), 171.4 (s); IR ($CHCl_3$) (cm^{-1}) 2928, 2855, 1787, 1742, 1698, 1458, 1370, 1144; MS *m/z* (relative intensity) 382 $(M-157)^+$ (4), 366 (9), 339 (30), 280 (83), 156 (10), 143 (25), 133 (100), 106 (24). Anal. calcd for $C_{31}H_{57}NO_6$: C, 68.96; H, 10.65; N, 2.60. Found: C, 68.67; H, 10.88; N, 2.65.

3.5. General procedure for the synthesis of lipidic N-*Boc-α-amino acids: (2S)(5Z)-2-[(*tert-*butoxy)-carbonylamino]icos-5-enoic acid* **12**

A solution of **10** (540 mg, 1 mmol) in HCl/THF (4 M, 25 ml, 100 mmol) was stirred for 30 min at rt. The excess acid and the solvent were evaporated and the residue was treated twice with dry THF (2×5 ml) and evaporated. The solid mixture was dissolved in MeOH (2 ml) and treated with an aqueous solution of NaOH (1 M aqueous solution, 2.80 ml, 2.8 mmol) with vigorous stirring for 2 h at rt. The organic solvent was removed and the aqueous residue carefully neutralized with aqueous HCl (1 M) affording **11** as a white solid that was filtered and washed with H_2O.

To a stirred suspension of the crude free amino acid in MeOH (10 ml), was added Et_3N (1 ml, 7.14 mmol) and Boc_2O (327 mg, 1.5 mmol) at rt. The mixture was vigorously stirred for 15 min at 50–60°C and for 30 min at rt. The solvent was evaporated and the residue cooled, acidified with 0.5 M aqueous HCl and extracted immediately with AcOEt (3×10 ml). The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated. The crude was purified by silica gel column chromatography using $CHCl_3$:MeOH (9:1) as eluent, to yield **12** (383 mg, 90%): $[\alpha]_D^{25}$ +13.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J*=7.0 Hz, 3H), 1.25 (br s, 24H), 1.45 (s, 9H), 1.72 (m, 1H), 1.92 (m, 1H), 2.01 (m, 2H), 2.14 (m, 2H), 4.30 (br s, 1H), 5.00 (br s, 1H), 5.32 (m, 1H), 5.43 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 22.6 (t), 23.2 (t), 27.2 (t), 28.0 (q), 29.2 (t), 29.3 (t), 29.4 (t), 29.5 (t), 29.6 (t), 29.7 (t), 31.9 (t), 32.2 (t), 53.1 (d), 80.2 (s), 127.4 (d), 131.8 (d), 155.6 (s), 177.6 (s); IR ($CHCl_3$) (cm^{-1}) 3441, 2928, 2855, 1712, 1504, 1369, 1165; MS (FAB) *m/z* (relative intensity) 464 (M+K) (10), 448 (M+Na) (85), 404 (7), 392 (28), 380 (4), 370 (28), 364 (56), 348 (15), 326 (100). Anal. calcd for $C_{25}H_{47}NO_4$: C, 70.53; H, 11.14; N, 3.29. Found: C, 70.52; H, 10.61; N, 3.39.

3.6. *General procedure for the synthesis of saturated lipidic* N,N-*di-Boc-α-amino esters: methyl (2*S*)-2-{(*tert-*butoxy)*-N-*[(*tert-*butyl)oxycarbonyl]carbonylamino}icosanoate* ***17***

To a stirred solution of **10** (202 mg, 0.37 mmol) in dry EtOAc (0.1 M) was added Pd/C (20 mg). The reaction was stirred under hydrogen atmosphere until TLC showed complete conversion. The mixture was filtered through a pad of Celite, the solvent was evaporated and the crude purified by silica gel column chromatography to afford **15** (196 mg, 98% yield) as an oil: $[\alpha]_D^{25}$ −26.0 (*c* 2.07, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, *J*=6.5 Hz, 3H), 1.25 (br s, 32H), 1.49 (s, 18H), 1.88 (m, 1H), 2.06 (m, 1H), 3.70 (s, 3H), 4.83 (dd, *J*=9.6, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 22.6 (t), 26.1 (t), 28.0 (q), 29.2 (t), 29.3 (t), 29.4 (t), 29.5 (t), 29.6 (t), 29.7 (t), 29.8 (t), 31.9 (t), 52.0 (q), 58.1 (d), 82.9 (s), 152.1 (s), 171.5 (s); IR ($CHCl_3$) (cm^{-1}) 3044, 2925, 2856, 1725, 1700, 1540, 1369, 1238, 1125; MS *m/z* (relative intensity) 385 $(M-157)^+$ (2), 326 (48), 282 (26), 133 (5), 57 (100). Anal. calcd for $C_{31}H_{59}NO_6$: C, 68.72; H, 10.98; N, 2.59. Found: C, 68.66; H, 10.92; N, 2.74.

3.7. *Methyl (2*S*)(5*Z*,8*Z*)-2-{(*tert-*butoxy)*-N-*[(*tert-*butyl)oxycarbonyl]carbonylamino}icosa-5,8-dienoate* ***18***

The general procedure for the synthesis of (*Z*)-unsaturated lipidic α-amino esters was applied to **9** on a 1 g (2.9 mmol) scale using the ylide of (3*Z*)-3-pentadecenyl-triphenylphosphonium iodide, yielding **16** (1.32 g, 85% yield) as an oil: $[\alpha]_D^{25}$ −29.2 (*c* 3.37, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, *J*=7.0 Hz, 3H), 1.26 (br s, 18H), 1.49 (s, 18H), 1.93 (m, 1H), 2.02 (m, 2H), 2.15 (m, 3H), 2.76 (dd, *J*=5.7, 5.7 Hz, 2H), 3.71 (s, 3H), 4.87 (dd, *J*=8.8, 4.5 Hz, 1H), 5.35 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 22.7 (t), 24.0 (t), 25.6 (t), 27.2 (t), 28.0 (q), 29.3 (t), 29.5 (t), 29.6 (t), 29.7 (t), 30.0 (t), 31.9 (t), 52.1 (q), 57.7 (d), 83.0 (s), 127.6 (d), 128.4 (d), 129.4 (d), 130.5 (d), 152.1 (s), 171.3 (s); IR ($CHCl_3$) (cm^{-1}) 3021, 2928, 2855, 1790, 1742, 1698, 1457, 1369, 1143; MS *m/z* (relative intensity) 362 $(M-175)^+$ (12), 337 (28), 278 (90), 222 (37), 194 (38), 157 (46), 142 (67), 128 (100), 114 (30). Anal. calcd for $C_{31}H_{55}NO_6$: C, 69.22; H, 10.31; N, 2.61. Found: C, 69.14; H, 10.55; N, 2.57.

3.8. *Methyl (2*S*)(5*Z*,11*Z*)-2-{(*tert-*butoxy)*-N-*[(*tert-*butyl)oxycarbonyl]carbonylamino}icosa-5,11-dienoate* ***19***

The general procedure for the synthesis of (*Z*)-unsaturated lipidic α-amino esters was applied to **9** on a 1.42 g (4.11 mmol) scale using the ylide of (6*Z*)-6-pentadecenyl-triphenylphosphonium iodide, yielding **17** (1.8 g, 84% yield) as an oil: $[\alpha]_D^{25}$ −29.9 (*c* 2.76, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J*=7.2 Hz, 3H), 1.30 (br s, 16H), 1.49 (s, 18H), 1.92 (m, 1H), 2.02 (m, 6H), 2.15 (m, 3H), 3.71 (s, 3H), 4.87 (dd, *J*=8.8, 4.4 Hz, 1H), 5.36 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 22.7 (t), 24.0 (t), 27.1 (t), 27.2 (t), 28.0 (q), 29.3 (t), 29.4 (t), 29.5 (t), 29.8 (t), 30.1 (t), 31.9 (t), 52.1 (q), 57.7 (d), 83.0 (s), 128.2 (d), 129.6 (d), 130.0 (d), 131.1 (d), 152.1 (s), 171.4 (s); IR ($CHCl_3$) (cm^{-1}) 3021, 2928, 2856, 1790, 1742, 1698, 1457, 1370, 1142; MS *m/z* (relative intensity) 364 $(M-173)^+$ (11), 337 (21), 278 (68), 196 (10), 143 (24), 133 (100), 115 (22). Anal. calcd for $C_{31}H_{55}NO_6$: C, 69.22; H, 10.31; N, 2.61. Found: C, 69.15; H, 10.47; N, 2.60.

3.9. *Methyl (2*S*)(5*Z*,14*Z*)-2-{(*tert-*butoxy)*-N-*[(*tert-*butyl)oxycarbonyl]carbonylamino}icosa-5,14-dienoate* ***20***

The general procedure for the synthesis of (*Z*)-unsaturated lipidic α-amino esters was applied to **9** on a 536 mg (1.55 mmol) scale using the ylide of (9*Z*)-9-pentadecenyl-triphenylphosphonium iodide, yielding **19** (716 mg, 86% yield) as an oil: $[\alpha]_D^{25}$ −27.5 (*c* 2.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, *J*=6.9 Hz, 3H), 1.30 (br s, 16H), 1.48 (s, 18H), 1.90 (m, 1H), 1.99 (m, 6H), 2.07 (m, 3H), 3.69 (s, 3H), 4.85 (dd, *J*=8.8, 4.4 Hz, 1H), 5.33 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 22.5 (t), 24.0 (t), 27.1 (t), 27.2 (t), 28.0 (q), 29.2 (t), 29.4 (t), 29.6 (t), 29.7 (t), 30.1 (t), 31.4 (t), 52.0 (q), 57.7 (d), 82.9 (s), 128.0 (d), 129.8 (d), 129.8 (d), 131.2 (d), 152.0 (s), 171.3 (s); IR ($CHCl_3$) (cm^{-1}) 3030, 2929, 2856, 1787, 1742, 1698, 1457, 1370, 1143; MS *m/z* (relative intensity) 381 $(M-156)^+$ (5), 337 (15), 278 (32), 142 (10), 133 (83), 101 (17), 57 (100). Anal. calcd for $C_{31}H_{55}NO_6$: C, 69.22; H, 10.31; N, 2.61. Found: C, 69.14; H, 10.74; N, 2.64.

3.10. *Methyl (5*Z*,8*Z*,11*Z*,14*Z*)-(2*S*)-2-di-*tert-*butoxycarbonylamino-5,8,11,14-eicosa-tetraenoate* ***21***

The general procedure for the synthesis of (*Z*)-unsaturated lipidic α-amino esters was applied to **9** on a 993 mg (2.87 mmol) scale using the ylide of (3*Z*,6*Z*,9*Z*)-3,6,9-pentadecatrienyl-triphenylphosphonium iodide, yielding **20** (1.34 g, 88% yield) as an oil: $[\alpha]_D^{25}$ −27.7 (*c* 2.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J*=6.2 Hz, 3H), 1.30 (m, 6H), 1.49 (s, 18H), 1.93 (m, 1H), 2.03 (m, 2H), 2.15 (m, 3H), 2.81 (m, 6H), 3.70 (s, 3H), 4.87 (dd, *J*=8.5, 4.4 Hz, 1H), 5.36 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 14.1 (q), 22.5 (t), 24.0 (t), 25.6 (t), 27.2 (t), 28.0 (q), 29.3 (t), 30.0 (t), 31.5 (t), 52.1 (q), 57.6 (d), 83.0 (s), 127.5 (d), 127.8 (d), 128.1 (d), 128.2 (d), 128.6 (d), 128.7 (d), 129.0 (d), 130.4 (d), 152.1 (s), 171.3 (s); IR ($CHCl_3$) (cm^{-1}) 3525, 3010, 2932, 2860, 1787, 1742, 1698, 1457, 1370, 1143; MS *m/z* (relative intensity) 377 $(M-157)^+$ (1), 274 (4), 174 (11), 142 (55), 133 (33), 128 (100), 95 (28), 81 (55), 57 (100). Anal. calcd for $C_{31}H_{51}NO_6$: C, 69.76; H, 9.63; N, 2.62. Found: C, 69.70; H, 9.90; N, 2.76.

3.11. *General procedure for the synthesis of unsaturated (*E*)-*N,N*-di-Boc-α-amino diesters: dimethyl (2*E*)(6*S*)-6-{(*tert-*butoxy)*-N-*[(*tert-*butyl)oxycarbonyl]carbonylamino}hept-2-ene-dioate* ***22***

To a stirred solution of **9** (345 mg, 1 mmol) in benzene (10 ml) was added commercially available methyl (triphenylphosphoranylidene)acetate (400 mg, 1.2 mmol) at 0°C. The mixture was stirred until TLC showed the end of the reaction. The reaction mixture was evaporated and the crude purified by silica gel chromatography to yield **21** (356 mg, 89% yield) as an oil: $[\alpha]_D^{25}$ −33.0 (*c* 2.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 18H), 2.00 (m, 1H), 2.23 (m, 3H), 3.67 (s, 6H), 4.92 (dd, *J*=9.5, 4.6 Hz, 1H), 5.80 (d, *J*=15.6 Hz, 1H), 6.90 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 27.9 (q), 28.3 (t), 28.8 (t), 51.3 (q), 52.1 (q), 57.4 (d), 83.2 (s), 121.6 (d), 147.8 (d), 151.9 (s), 166.7 (s), 170.8 (s); IR ($CHCl_3$) (cm^{-1}) 2987, 1781, 1735, 1645, 1361, 1142; MS *m/z* (relative intensity) 402 $(M+1)^+$ (1), 346 (4), 245 (15), 201 (60), 142 (100), 128 (27), 110 (49), 57 (100). Anal. calcd for $C_{19}H_{31}NO_8$: C, 56.83; H, 7.79; N, 3.49. Found: C, 56.54; H, 7.87; N, 3.49.

3.12. *Dimethyl (2*Z*)(6*S*)-6-{(*tert-*butoxy)*-N-*[(*tert-*butyl)oxycarbonyl]carbonylamino}hept-2-ene-dioate* ***23***

The general procedure for the synthesis of lipidic (*Z*)-unsaturated *N*,*N*-di-Boc-α-amino esters was applied to **9** on a 536 mg (1.55 mmol) scale, using methyl (diphenoxyphosphoryl)acetate (1.11 g, 1.86

mmol), yielding **23** (716 mg, 86% yield) as an oil: $[\alpha]_D^{25}$ −52.0 (*c* 1.56, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.41 (s, 18H), 1.96 (m, 1H), 2.19 (m, 1H), 2.26 (m, 2H), 3.60 (s, 3H), 3.62 (s, 3H), 4.81 (dd, *J*=9.6, 5.2 Hz, 1H), 5.70 (d, *J*=11.6 Hz, 1H), 6.90 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.7 (t), 27.9 (q), 29.2 (t), 50.8 (q), 52.0 (q), 57.5 (d), 83.0 (s), 120.1 (d), 148.6 (d), 151.9 (s), 166.3 (s), 170.9 (s); IR ($CHCl_3$) (cm^{-1}) 2984, 1788, 1742, 1646, 1439, 1370, 1143; MS *m/z* (relative intensity) 346 $(M-69)^+$ (20), 290 (16), 202 (50), 142 (36), 124 (10), 57 (100). Anal. calcd for $C_{19}H_{31}NO_8$: C, 56.83; H, 7.79; N, 3.49. Found: C, 56.52; H, 7.99; N, 3.47.

*3.13. Dimethyl (*S*)-2-*tert*-butoxycarbonylamino-butanodioate **25***

The general one-pot protection of free α-amino acids was applied to commercially available L-aspartic acid on a 1.33 g (10 mmol) scale yielding **25** (2.43 g, 93% yield) as a white solid: mp=60°C; $[\alpha]_D^{25}$ +30.8 (*c* 2.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.42 (s, 9H), 2.79 (dd, *J*=16.9, 4.7 Hz, 1H), 2.97 (d, *J*=16.9 Hz, 1H), 3.67 (s, 3H), 3.73 (s, 3H), 4.55 (br s, 1H), 5.48 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.2 (q), 36.6 (t), 49.9 (d), 51.9 (q), 52.6 (q), 80.1 (s), 155.3 (s), 171.3 (s), 171.5 (s); IR ($CHCl_3$) (cm^{-1}) 3440, 3029, 2982, 1733, 1711, 1501, 1369, 1227, 1166; MS *m/z* (relative intensity) 262 $(M+1)^+$ (20), 205 (79), 162 (58), 145 (73), 127 (20), 102 (100), 59 (85), 57 (100). Anal. calcd for $C_{11}H_{19}NO_6$: C, 50.55; H, 7.33; N, 5.36. Found: C, 50.66; H, 7.32; N, 5.28.

*3.14. Dimethyl (2*S*)-2-{(*tert*-butoxy)-*N*-[(*tert*-butyl)oxycarbonyl]carbonylamino}butane-1,4-dioate **26***

The general procedure for the di-*N*-Boc-protection was applied to **25** on a 2.1 g (8 mmol) scale, yielding **26** (2.83 g, 98% yield) as a white solid: mp=57°C; $[\alpha]_D^{25}$ −61.0 (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.49 (s, 18H), 2.72 (dd, *J*=16.4, 6.6 Hz, 1H), 3.23 (dd, *J*=16.4, 7.0 Hz, 1H), 3.69 (s, 3H), 3.72 (s, 3H), 5.43 (dd, *J*=6.8, 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 7.9 (q), 35.7 (t), 51.9 (q), 52.5 (q), 54.9 (d), 83.5 (s), 151.5 (s), 170.2 (s), 171.0 (s); IR ($CHCl_3$) (cm^{-1}) 3031, 2984, 1791, 1743, 1698, 1370, 1271, 1142; MS *m/z* (relative intensity) 362 $(M+1)^+$ (1), 302 (16), 217 (36), 205 (47), 188 (25), 162 (100), 146 (100), 128 (34), 102 (100), 86 (50), 57 (100). Anal. calcd for $C_{16}H_{27}NO_8$: C, 53.18; H, 7.53; N, 3.88. Found: C, 53.13; H, 7.51; N, 3.84.

*3.15. Methyl (2*S*)-2-{(*tert*-butoxy)-*N*-[(*tert*-butyl)oxycarbonyl]carbonylamino}-4-oxobutanoate **27***

The general reduction of the ω-ester to the corresponding aldehyde was applied to **26** on a 2.89 g (8.0 mmol) scale yielding **27** (2.33 g, 88% yield) as an oil: $[\alpha]_D^{25}$ −54.9 (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.48 (s, 18H), 2.82 (dd, *J*=17.0, 6.6 Hz, 1H), 3.38 (dd, *J*=17.0, 7.0 Hz, 1H), 3.71 (s, 3H), 5.50 (dd, *J*=6.6, 6.6 Hz, 1H), 9.76 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.9 (q), 44.9 (t), 52.5 (q), 52.9 (d), 83.6 (s), 151.6 (s), 170.2 (s), 198.3 (d); IR ($CHCl_3$) (cm^{-1}) 3026, 2984, 1792, 1744, 1698, 1370, 1146; MS *m/z* (relative intensity) 288 $(M-43)^+$ (4), 247 (12), 191 (51), 147 (70), 132 (100), 116 (100), 103 (59), 88 (100), 72 (83), 57 (100). Anal. calcd for $C_{15}H_{25}NO_7$: C, 54.35; H, 7.61; N, 4.23. Found: C, 54.29; H, 7.75; N, 4.19.

*3.16. Methyl (2*S*)(4*Z*)-2-{(*tert*-butoxy)-*N*-[(*tert*-butyl)oxycarbonyl]carbonylamino}nonadec-4-enoate **28***

The general procedure for the synthesis of (*Z*)-unsaturated lipidic α-amino esters was applied to **27** on a 2 g (6 mmol) scale using n-pentadecyl-triphenylphosphonium bromide (3.85 g, 7 mmol), yielding **28** (2.8 g, 89% yield) as an oil: $[\alpha]_D^{25}$ −54.9 (*c* 2.02, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, *J*=6.4 Hz, 3H),

1.25 (br s, 22H), 1.49 (s, 18H), 2.02 (m, 2H), 2.74 (m, 1H), 2.81 (m, 1H), 3.71 (s, 3H), 4.92 (dd, *J*=10.0, 4.9 Hz, 1H), 5.33 (m, 1H), 5.48 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 22.6 (t), 27.3 (t), 28.0 (q), 29.3 (t), 29.5 (t), 29.6 (t), 31.9 (t), 52.1 (q), 58.1 (d), 82.8 (s), 124.4 (d), 133.4 (d), 152.0 (s), 171.0 (s); IR ($CHCl_3$) (cm^{-1}) 3029, 2927, 2854, 1787, 1738, 1696, 1370, 1278, 1145; MS *m/z* (relative intensity) 526 $(M+1)^+$ (1), 414 (8), 308 (32), 133 (15), 111 (16), 88 (20), 57 (100). Anal. calcd for $C_{30}H_{55}NO_6$: C, 68.52; H, 10.55; N, 2.71. Found: C, 67.99; H, 10.94; N, 2.71.

*3.17. Dimethyl (2*E*)(5*S*)-5-{(*tert*-butoxy)*-N-*[(*tert*-butyl)oxycarbonyl]carbonylamino}hex-2-ene-1,6-dioate* ***29***

The general procedure for the synthesis of unsaturated (*E*)-*N*,*N*-di-Boc-α-amino diesters was applied to **27** on a 2 g (6 mmol) scale, yielding **28** (2.1 g, 90% yield): $[\alpha]_D^{25}$ −55.5 (*c* 2.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 18H), 2.81 (m, 1H), 2.96 (m, 1H), 3.67 (s, 3H), 3.70 (s, 3H), 4.99 (dd, *J*=9.6, 5.1 Hz, 1H), 5.84 (d, *J*=15.6 Hz, 1H), 6.87 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 27.8 (q), 33.0 (t), 51.3 (q), 52.3 (q), 56.9 (d), 83.4 (s), 123.7 (d), 144.2 (d), 151.7 (s), 166.3 (s), 170.1 (s); IR ($CHCl_3$) (cm^{-1}) 2987, 1780, 1735, 1645, 1360, 1142; MS *m/z* (relative intensity) 316 $(M-71)^+$ (1), 302 (1), 228 (1), 100 (6), 57 (100). Anal. calcd for $C_{18}H_{29}NO_8$: C, 55.80; H, 7.54; N, 3.62. Found: C, 55.81; H, 7.74; N, 3.69.

*3.18. Dimethyl (2*S*)-2-{(*tert*-butoxy)*-N-*[(*tert*-butyl)oxycarbonyl]carbonylamino}heptanedioate* ***30***

The general procedure for the synthesis of saturated lipidic *N*,*N*-di-Boc-α-amino esters was applied to **22** on a 1.2 g (4 mmol) scale, yielding **30 (**1.14 g, 93% yield) as an oil: $[\alpha]_D^{25}$ −31.0 (*c* 2.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.38 (m, 2H), 1.49 (s, 18H), 1.65 (m, 2H), 1.87 (m, 1H), 2.10 (m, 1H), 2.31 (dd, *J*=7.5, 7.5 Hz, 2H), 3.66 (s, 3H), 3.70 (s, 3H), 4.84 (dd, *J*=9.4, 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.6 (t), 25.8 (t), 27.9 (q), 29.6 (t), 33.9 (t), 51.4 (q), 52.1 (q), 57.9 (d), 83.0 (s), 152.1 (s), 171.3 (s), 173.8 (s); IR ($CHCl_3$) (cm^{-1}) 3024, 2984, 1789, 1742, 1699, 1370, 1140; MS *m/z* (relative intensity) 344 $(M-59)^+$ (1), 288 (2), 244 (2), 188 (6), 57 (100). Anal. calcd for $C_{19}H_{33}NO_8$: C, 56.56; H, 8.24; N, 3.47. Found: C, 56.54; H, 8.29; N, 3.54.

*3.19. Dimethyl (2*S*)-2-{(*tert*-butoxy)*-N-*[(*tert*-butyl)oxycarbonyl]carbonylamino}hexanedioate* ***31***

The general procedure for the synthesis of saturated lipidic *N*,*N*-di-Boc-α-amino esters was applied to **29** on a 0.6 g (2.1 mmol) scale, yielding **31 (**570 g, 93% yield) as an oil: $[\alpha]_D^{25}$ −35.9 (*c* 2.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 18H), 1.67 (m, 2H), 1.91 (m, 1H), 2.09 (m, 1H), 2.33 (m, 2H), 3.64 (s, 3H), 3.71 (s, 3H), 4.85 (dd, *J*=9.6, 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.7 (t), 28.0 (q), 29.4 (t), 33.6 (t), 51.5 (q), 52.1 (q), 57.8 (d), 83.2 (s), 152.1 (s), 171.1 (s), 173.6 (s); IR ($CHCl_3$) (cm^{-1}) 3020, 2982, 1786, 1740, 1699, 1370, 1140; MS *m/z* (relative intensity) 330 $(M-59)^+$ (1), 274 (1), 230 (4), 174 (17), 57 (100). Anal. calcd for $C_{18}H_{31}NO_8$: C, 55.51; H, 8.02; N, 3.60. Found: C, 55.51; H, 8.07; N, 3.69.

*3.20. Methyl (2*S*)-2-{(*tert*-butoxy)*-N-*[(*tert*-butyl)oxycarbonyl]carbonylamino}-7-oxoheptanoate* ***32***

The general reduction of the ω-ester to the corresponding aldehyde was applied to **29** on a 2 g (5.1 mmol) scale, yielding **31** (1.6 g, 87% yield) as an oil: $[\alpha]_D^{25}$ −32.4 (*c* 4.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.38 (m, 2H), 1.49 (s, 18H), 1.65 (m, 2H), 1.87 (m, 1H), 2.10 (m, 1H), 2.43 (dd, *J*=9.7, 1.93 Hz, 2H), 3.71 (s, 3H), 4.84 (dd, *J*=12.5, 7.0 Hz, 1H), 9.75 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.8 (t), 27.1 (t), 28.0 (q), 29.6 (t), 43.6 (t), 52.1 (q), 57.8 (d), 83.1 (s), 152.1 (s), 171.2 (s), 202.2 (s); IR ($CHCl_3$) (cm^{-1}) 3028,

2984, 1789, 1742, 1370, 1144; MS *m/z* (relative intensity) 330 $(M-43)^+$ (2), 300 (1), 230 (6), 57 (100). Anal. calcd for $C_{18}H_{31}NO_7$: C, 57.89; H, 8.37; N, 3.75. Found: C, 57.86; H, 8.48; N, 3.59.

*3.21. Methyl (2*S*)-2-{(*tert*-butoxy)*-N*-[(*tert*-butyl)oxycarbonyl]carbonylamino}-7-oxohexanoate **33***

The general reduction of the ω-ester to the corresponding aldehyde was applied to **30** on a 1.2 g (3.2 mmol) scale, yielding **31** (905 mg, 82% yield) as an oil: $[\alpha]_D^{25}$ −30.2 (*c* 3.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 18H), 1.67 (m, 2H), 1.92 (m, 1H), 2.12 (m, 1H), 2.41 (m, 1H), 2.48 (m, 1H), 3.70 (s, 3H), 4.85 (dd, *J*=9.4, 5.1 Hz, 1H), 9.75 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.7 (t), 21.3 (t), 28.0 (q), 29.3 (t), 52.2 (q), 57.6 (d), 83.3 (s), 152.0 (s), 171.1 (s), 201.9 (s); IR ($CHCl_3$) (cm^{-1}) 3024, 2980, 1789, 1742, 1699, 1370, 1142; MS *m/z* (relative intensity) 330 $(M-29)^+$ (1), 258 (1), 230 (1), 57 (100). Anal. calcd for $C_{17}H_{29}NO_7$: C, 56.81; H, 8.13; N, 3.90. Found: C, 56.88; H, 8.38; N, 3.50.

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