A General Approach to the Asymmetric Synthesis of Unsaturated Lipidic α-Amino Acids. The First Synthesis of α-Aminoarachidonic Acid

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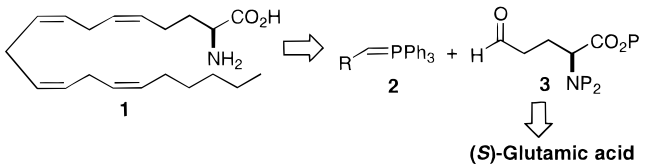
Introduction

Nonproteinogenic, nonnatural α-amino acids have increasingly attracted the attention of numerous disciplines in connection with the design and synthesis of potential constituents of pharmaceuticals, for example enzyme inhibitors, and of optically active starting materials for a variety of synthetic applications. In consequence, a large effort has been devoted to the preparation of amino acids in the enantiomerically pure form of either configuration, a subject already covered by general reviews.[1−3]

On the other hand, particular attention has been focused on lipidic acids and their involvement in signal transduction and medicine. Thus, arachidonic acid acts both as a modulator and messenger, particularly of signals triggered at the level of cell membranes.[4,5] The fatty acids in the cell membranes determine many of their physical properties, modulate the configuration of all the membrane-associated proteins, and are able to influence directly or indirectly almost every second messenger system which controls cell function. Unsuitable concentrations of 20- and 22-carbon essential fatty acids in cell membrane phospholipids and inappropriate ratios between the $n - 6$ and $n - 3$ essential fatty acids may be the ultimate causal factors in coronary heart disease and peripheral vascular disease.[6]

To combine structural features of amino acids with those of fatty acids, we have prepared chiral lipidic α-amino acids which are unnatural α-amino acids with saturated long aliphatic side chains.[7] The synthesis and the properties of lipidic amino acids and related lipid mimetics have been reviewed.[8]

Scheme 1



Approaches using regioselective functionalization of readily available chiral building blocks, e.g. derivatives of natural amino acids, are especially attractive for the synthesis of unnatural amino acids. L-Glutamic acid is an inexpensive starting material, which may be modified selectively at the γ-carboxylic acid function after suitable protection of the α-amino group.[9] Our strategy for the synthesis of chiral unsaturated lipidic amino acids is based on the regioselective functionalization of the suitably protected glutamic acid γ-aldehyde.

Here we report on a simple, efficient, and general method to prepare unsaturated α-amino fatty acids in their enantiomeric forms, which eventually can be transformed into the saturated products by simple hydrogenation. We have illustrated these procedures by the synthesis of α-amino arachidonic acid **1** (Scheme 1). The synthesis of such substances should provide us with a general methodology to gain access to analogues and, importantly, to permit the analysis of structure−activity relationships.

Results and Discussions

Our strategy was based on the possibility of building the chain using Wittig-type reactions from aldehydes such as **3** that could be obtained from acids such as glutamic acid. This approach permitted both convergence in the synthetic procedure and stereoselectivity in the formation of the double bond. Although the synthesis of aldehyde **3** from glutamic acid is known,[10] we explored a new and more direct method that permitted us to easily increase the scale of the reaction. Thus, (*S*)-glutamic acid was perbenzylated under known conditions[11] to yield the diester **4**. When this product was submitted to reduction with DIBAL under controlled conditions (1.1 equiv, −78 °C, 1 h), the aldehyde **3** (P = P′ = Bn) was obtained in 87% isolated yield (Scheme 2). Although the synthesis of this aldehyde is a promising result, its use for the synthesis of unsaturated amino acid would be drastically limited because of the cleavage of the *N*,*N*-dibenzyl protecting group.[12] In light of these results it was decided to further explore the method by changing the protecting groups in the starting unit. Thus, the dimethyl *N*-Boc-glutamate **5** was reduced under the above conditions

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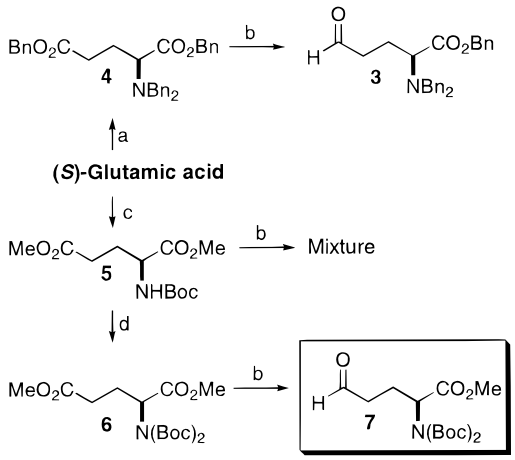
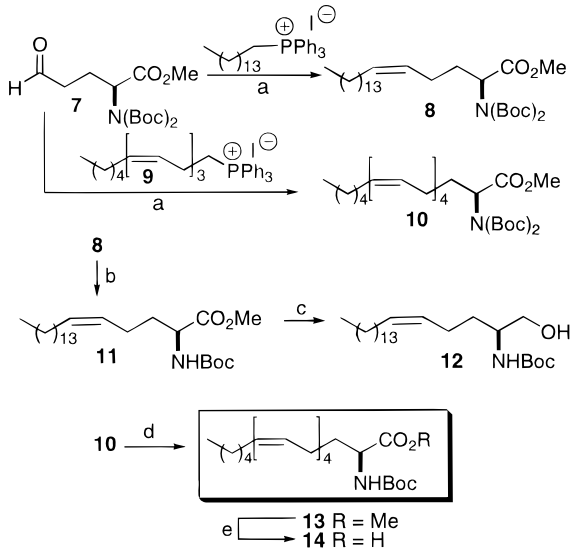
Scheme 2[a]



[a] BnBr, K_2CO_3, H_2O, Δ; (b) (i) DIBAL, ether, −78 °C, (ii) H_2O; (c) (i) TMSCl, MeOH, (ii) Boc_2O, Et_3N, MeOH; (d) Boc_2O, DMAP, CH_3CN.

Scheme 3[a]



[a] $KN(TMS)_2$, toluene, −78 °C; (b) (i) HCl, THF, (ii) $(Boc)_2O$, Et_3N, MeOH, (iii) NaOH, dioxane, (iv) CH_2N_2, ether; (c) DIBAL, benzene, 0 °C; (d) (i) HCl, THF, (ii) $(Boc)_2O$, Et_3N, MeOH; (e) NaOH, dioxane.

(Scheme 2). Disappointingly, we were unable, in this case, to obtain satisfactory results, presumably due to some participation of the nitrogen. This result led us to try to minimize the nucleophilic power of the nitrogen by the introduction of a second Boc group.[13] In this case, when the dimethyl *N*,*N*-di-Boc-glutamate **6** was reduced with DIBAL under our conditions, the aldehyde **7** was obtained in 85% yield (Scheme 2).

To obtain the desired unsaturated lipidic α-amino acids, the aldehyde **7** was submitted to usual Wittig conditions (*n*-BuLi, THF, −78 °C). However, satisfactory results were not obtained. This disappointment induced us to change the Wittig reaction conditions. Encouragingly, using $NaN(TMS)_2$ as base, in THF, the unsaturated ester was obtained in 10% yield, but even better, 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 **8** was obtained in 92% isolated yield.[14] This result prompted us to achieve the synthesis of methyl *N*,*N*-di-Boc-(S)-α-amino arachidonate in a straightforward manner. Thus, when the phosphonium salt **9**[15] was submitted to the ylide formation under the later conditions and reacted with the aldehyde **7**, the protected (*S*)-α-amino arachidonic acid **10** was obtained in 88% isolated yield.

Although it is known that the cleavage of the protecting groups in methyl *N*-Boc-α-amino esters to afford the corresponding α-amino acids occurs without any epimerization,[16] in our case, we were worried about such a possibility because of the presence of the additional *N*-Boc group. To investigate this we submitted **8** to standard basic conditions to cleave the methyl ester. We found that even after 48 h, at room temperature, under alkaline treatment (NaOH, dioxane), the removal of the ester was incomplete. Furthermore, the optical rotation of the obtained free acid changed with time, showing clearly that racemization had occurred. In light of this result, we decided to try a different strategy and remove the protecting groups of the nitrogen in the first stage. Thus, we treated **8** under acidic conditions to remove the two *N*-Boc groups, and the resulting compound was *N*-Boc protected. This compound was smoothly hydrolyzed under alkaline conditions,[17] in an almost quantitative manner, with uniform optical activity (Scheme 3). To ensure the enantiomeric purity of such a product we again protected the free acid as the methyl *N*-Boc-α-amino ester **11**, which was then reduced to the primary alcohol **12**. The ^1H NMR and HPLC analysis of the corresponding (*R*)- and (*S*)-Mosher esters showed no detectable racemization.[18]

Finally, considering the possibility of using these compounds in the synthesis of lipidic peptides,[7] we prepared the *N*-Boc-α-amino arachidonic acid (**14**) using the above-described methodology, yielding **14** in 88% overall yield.[19]

In summary, we have described a new methodology which can be used for the synthesis of a wide range of unsaturated and saturated α-amino acids, with almost unlimited possibilities, the only potential limitations of which are the synthesis of the suitable ylide and the corresponding Wittig reaction. The new compound named (*S*)-α-aminoarachidonic acid has been reported for the first time. Although the methodology presented here has been described for one enantiomeric series only, the choice of the proper stereoisomer of glutamic acid permits the control of the absolute configuration in the final products.

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(19) Compound **1** was actually prepared as the intermediate to **14**. However, such a compound was insoluble in most NMR solvents, being found to be soluble only in CF_3CO_2D, in which decomposition was extremely fast.

Experimental Section

Materials and Methods. See ref 20 for details.

Preparation of Dimethyl (*S*)-2-*tert*-Butoxycarbonylaminopentanedioate (5). To a stirred solution of (*S*)-glutamic acid (1.47 g, 10 mmol) in dry MeOH (26 mL) was added Me_3SiCl (5.6 mL, 44 mmol) at 0 °C. The temperature was allowed to reach rt and the mixture was stirred overnight. Then, Et_3N (9 mL, 65 mmol) and Boc_2O (2.4 g, 11 mmol) were added and the resulting mixture stirred until the evolution of gas was completed. The solvent was evaporated under reduced pressure, and the residue was triturated and washed with ether (3 × 100 mL). The combined filtrates were concentrated, to provide a crude that was purified by silica gel chromatography to yield **5** (2.6 g, 95% yield) as an oil: $[\alpha]^{25}_D = +12.9$ (*c* 2.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9 H), 1.91 (m, 1H), 2.14 (m, 1H), 2.37 (m, 2 H), 3.64 (s, 3 H), 3.70 (s, 3 H), 4.29 (bs, 1 H), 5.14 (bs, 1 H); ^{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, 1737, 1503, 1369, 1167; MS *m*/*z* (relative intensity) 276 $(M + 1)^+$ (1), 219 (22), 187 (25), 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.

Preparation of Dimethyl (*S*)-2-Di-*tert*-butoxycarbonylaminopentanedioate (6). To a stirred solution of **5** (2.5 g, 9 mmol) and DMAP (220 mg, 1.8 mmol) in dry CH_3CN (30 mL) was added Boc_2O (2.2 g, 9.9 mmol) at room temperature. 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. Then, more Boc_2O (1.1 g, 4.9 mmol) was added and the mixture was additionally stirred overnight. The solvent was evaporated, and the crude purified by silica gel chromatography, yielding **6** (3.32 g, 98% yield) as an oil: $[\alpha]^{25}_D = -37.2$ (*c* 2.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 18 H), 2.17 (m, 1 H), 2.40 (m, 2 H), 2.46 (m, 1 H), 3.67 (s, 3 H), 3.71 (s, 3 H), 4.93 (dd, $J = 9.2$, 4.4 Hz, 1 H); ^{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, 1789, 1742, 1699, 1370; MS *m*/*z* (relative intensity) 376 $(M + 1)^+$ (3), 320 (58), 264 (42), 220 (100), 176 (100). 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.

Preparation of Methyl (*S*)-2-Di-*tert*-butoxycarbonylamino-5-oxopentanoate (7). To a stirred solution of **6** (1 g, 2.7 mmol) in dry ether (27 mL) was added dropwise DIBAL (3 mL, 1.0 M in hexane, 3 mmol) to −78 °C. The reaction mixture was stirred for 5 min. It was then quenched with H_2O (0.4 mL) and allowed to warm to room temperature. The mixture was stirred for 30 min, dried over $MgSO_4$ and filtered through a pad of Celite. The solvent was evaporated and the residue was purified by silica gel column chromatography, to yield **7** (790 mg, 85% yield) as an oil: $[\alpha]^{25}_D = -35.3$ (*c* 2.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 18 H), 2.16 (m, 1 H), 2.52 (m, 2 H), 2.59 (m, 1 H), 3.71 (s, 3 H), 4.87 (dd, $J = 9.6$, 5.2 Hz, 1 H), 9.76 (s, 1 H);^{13}C NMR ($CDCl_3$) δ 22.5 (t), 27.9 (q), 40.5 (t), 52.2 (q), 57.3 (d), 83.4 (s), 152.0 (s), 170.7 (s), 200.9 (d); IR ($CHCl_3$) (cm^{-1}) 3028, 2984, 1789, 1370, 1231, 1144; MS *m*/*z* (relative intensity) 302 (M − 43) (1), 206 (15), 174 (37), 162 (35), 128 (100). 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.

General Procedure for the Synthesis of *Z*-Unsaturated α-Amino Acids by a Wittig Reaction over Methyl (*S*)-2-Di-*tert*-butoxycarbonylamino-5-oxo-pentanoate (7). Preparation of Methyl (5*Z*,2*S*)-2-Di-*tert*-butoxycarbonylaminoeicos-5-enoate (8). To a stirred suspension of pentadecyltriphenylphosphonium bromide (3.85 g, 7 mmol) in dry toluene (40 mL) under argon was added dropwise $KN(TMS)_2$ (12.8 mL, 0.5 M solution in toluene, 6.4 mmol) at 0 °C. After 15 min the flask was cooled to −78 °C and **7** (2 g, 5.8 mmol) 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 (50 mL), dried over $MgSO_4$, and filtered and the solvent evaporated. The crude was purified by silica gel column chromatography to afford **8** (2.7 g, 87% yield) as an oil: $[\alpha]^{25}_D = -26.2$ (*c* 2.18, $CHCl_3$); ^{1}H NMR ($CHCl_3$) δ 0.88 (t, $J = 6.8$ Hz, 3 H), 1.25 (bs, 24 H), 1.49 (s, 18 H), 1.90 (m, 1 H), 2.00 (dd, $J = 13.6$, 6.8 Hz, 2 H), 2.08 (dd, $J = 14$, 7.2 Hz, 2 H), 2.15 (m, 1H), 3.71 (s, 3 H), 4.86 (dd, $J = 8.8$, 4.8 Hz, 1 H), 5.38 (m, 2H); ^{13}C NMR ($CHCl_3$) 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, 1698, 1458, 1144; MS *m*/*z* (relative intensity) 382 $(M - 157)^+$ (4), 339 (30), 280 (83), 156 (10), 133 (100). 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.

Preparation of Methyl (5*Z*,8*Z*,11*Z*,14*Z*,2*S*)-2-Di-*tert*-butoxycarbonylaminoeicosa-5,8,11,14-tetraenoate (10). The general conditions used above to obtain **8** were applied by using **9**[15] on a 594 mg (1 mmol) scale, yielding **10** (390 mg, 88% yield) as an oil: $[\alpha]^{25}_D = -27.7$ (*c* 2.00, $CHCl_3$); 0.88 (t, $J = 6.2$ Hz, 3 H), 1.30 (m, 6 H), 1.93 (m, 1 H), 2.03 (m, 2 H), 2.15 (m, 3 H), 2.81 (m, 6 H), 3.70 (s, 3 H), 4.87 (dd, $J = 8.5$, 4.4 Hz, 1 H), 5.36 (m, 8 H); ^{13}C NMR ($CHCl_3$) δ 14.0 (q), 22.5 (t), 24.0 (t), 25.6 (t), 27.2 (t), 27.9 (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}) 3011, 2932, 2860, 1787, 1457; MS *m*/*z* (relative intensity) 378 $(M - 155)^+$ (1), 276 (3), 184 (7), 156 (11), 142 (55), 128 (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.

Experiment To Prove that the Whole Sequence of the Protecting Group Cleavage Over the Di-Boc-α-Amino Esters Does Not Cause Racemization. Preparation of Methyl (5*Z*,2*S*)-2-*tert*-Butoxycarbonylaminoeicos-5-enoate (11) and *tert*-Butyl (*S*)-[(4*Z*)-(1-Hydroxymethylnonadec-4-enyl]carbamate (12). To a stirred solution of **8** (300 mg, 0.56 mmol) in THF (5 mL) was added HCl (5.2 N solution in dry THF, 5.3 mL, 27.8 mmol) at room temperature. The stirred mixture was monitored by TLC until complete conversion. The solvent was evaporated and the residue was treated with THF (2 × 5 mL) and evaporated. The solid residue was triturated, washed with ether (5 mL), and dried. Then, it was dissolved in a 10:1 mixture of MeOH:Et_3N (6 mL) and treated with Boc_2O (134 mg, 0.6 mmol) at room temperature. The mixture was stirred until no gas evolution was observed (≈3 h). The solvent was evaporated and the crude was purified by silica gel chromatography to obtain **11** (244 mg, 99% yield) as an oil: $[\alpha]^{25}_D = +16.3$ (*c* 1.23, $CHCl_3$); ^{1}H NMR ($CHCl_3$) δ 0.87 (t, $J = 7.0$ Hz, 3 H), 1.25 (bs, 24 H), 1.43 (s, 9 H), 1.68 (m, 1 H), 1.84 (m, 1 H), 2.00 (m, 2 H), 2.08 (m, 2 H), 3.72 (s, 3 H), 4.29 (bs, 1 H), 5.01 (bs, 1 H), 5.30 (m, 1 H), 5.39 (m, 1 H); ^{13}C NMR ($CHCl_3$) δ 14.0 (q), 22.6 (t), 23.1 (t), 27.2 (t), 27.3 (t), 28.2 (q), 29.3 (t), 29.5 (t), 29.6 (t), 29.8 (t), 31.8 (t), 31.9 (t), 32.6 (t), 52.1 (q), 53.1 (d), 79.7 (s), 127.5 (d), 131.5 (d), 155.3 (s), 173.3 (s); IR ($CHCl_3$) (cm^{-1}) 3442, 2928, 1740, 1712, 1501, 1368; MS *m*/*z* (relative intensity) 383 $(M - 57)^+$ (7), 366 (8), 339 (34), 156 (13), 142 (18), 133 (100). Anal. Calcd For $C_{26}H_{49}NO_4$: C, 71.01; H, 11.24; N, 3.11. Found: C, 70.98; H, 11.51; N, 3.09.

To prove that the hydrolysis of the methyl ester does not cause any racemization, **11** (100 mg, 0.23 mmol) was dissolved in dioxane (1 mL) and treated with NaOH (1 M aqueous solution, 6.2 mL, 6.2 mmol) at room temperature. The reaction mixture was stirred overnight. Then, HCl (3 M) was added at 0 °C until pH ≈ 2 was reached, and the mixture was extracted with EtOAc (4 × 5 mL). The combined organic phases were washed with 10 mL of a saturated solution of brine, dried, and evaporated in vacuo. The residue was dissolved in ether (10 mL) and treated with an ether solution of diazomethane until a yellow color persisted. Then a few drops of acetic acid were added to destroy the excess of diazomethane. The reaction mixture was washed with a saturated solution of $NaHCO_3$ (5 mL) and brine (5 mL), dried, and evaporated. The residue was purified by column chromatography to give **11** (90 mg, 90% overall yield) with a specific rotation almost similar to that previously obtained. This batch of **11** was used to obtain **12** in accordance with the following procedure.

To a slurry of **11** (42 mg, 0.1 mmol) in dry benzene (5 mL) was added dropwise DIBAL (200 μL, 1.0 M in hexane, 0.2 mmol) at 0 °C. The reaction mixture was stirred for 5 min. It was

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then quenched with H_2O (0.4 mL) and allowed to warm to room temperature. The mixture was stirred for 30 min, dried over $MgSO_4$, and filtered through a pad of Celite. The solvent was evaporated and the residue was purified by silica gel column chromatography, to yield **12** (34 mg, 85% yield) as an oil: $[\alpha]^{25}_D = -11.3$ (*c* 2.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, $J = 7.0$ Hz, 3 H), 1.25 (bs, 24 H), 1.43 (s, 9 H), 1.57 (m, 2 H), 2.00 (m, 2 H), 2.09 (m, 2 H), 2.67 (bs, 1 H), 3.53 (m, 1 H), 3.65 (m, 2 H), 4.68 (d, $J = 7.28$ Hz, 1 H), 5.31 (m, 1 H), 5.39 (m, 1 H); ^{13}C NMR ($CHCl_3$) δ 14.1 (q), 22.6 (t), 23.1 (t), 27.2 (t), 27.3 (t), 28.2 (q), 29.3 (t), 29.5 (t), 29.6 (t), 29.8 (t), 31.8 (t), 31.9 (t), 32.6 (t), 52.9 (d), 66.0 (t), 79.7 (s), 128.3 (d), 131.5 (d), 156.6 (s); IR ($CHCl_3$) (cm^{-1}) 3691, 3442, 2855, 1712, 1504, 1368; MS *m*/*z* (relative intensity) 354 $(M - 57)^+$ (3), 300 (26), 268 (18), 57 (100). Anal. Calcd For $C_{25}H_{49}NO_3$: C, 72.94; H, 12.00; N, 3.40. Found: C, 72.88; H, 12.03; N, 3.36.

Preparation of Methyl (5*Z*,8*Z*,11*Z*,14*Z*,2*S*)-2-*tert*-Butoxycarbonylaminoeicosa-5,8,11,14-tetraenoate (13). To a stirred solution of **10** (120 mg, 0.22 mmol) in THF (5 mL) was added HCl (5.2 N solution in dry THF, 1 mL, 5.2 mmol) at room temperature. The stirred mixture was monitored by TLC until complete conversion. The solvent was evaporated and the residue was treated with THF (2 × 5 mL) and evaporated. The solid residue was triturated, washed with ether (5 mL), and dried. Then, it was dissolved in a 10:1 mixture of MeOH:Et_3N (6 mL) and treated with Boc_2O (53 mg, 0.24 mmol) at room temperature. The mixture was stirred until no gas evolution was observed (≈3 h). The solvent was evaporated and the crude was purified by silica gel chromatography to obtain **13** (94 mg, 97% yield) as an oil: $[\alpha]^{25}_D = +16.0$ (*c* 2.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, $J = 6.9$ Hz, 3 H), 1.30 (m, 6 H), 1.44 (s, 9 H), 1.70 (m, 1 H), 1.86 (m, 1 H), 2.05 (m, 2 H), 2.12 (m, 2 H), 2.81 (m, 6 H), 3.72 (s, 3 H), 4.31 (bs, 1 H), 5.00 (bs, 1 H), 5.37 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 22.5 (t), 23.1 (t), 25.5 (t), 25.6 (t), 27.2 (t), 28.3 (q), 29.3 (t), 29.6 (t), 31.5 (t), 32.5 (t), 52.2 (q), 53.1 (d), 79.8 (s), 127.5 (d), 127.8 (d), 128.0 (d), 128.3 (d), 128.6 (d), 129.2 (d), 129.6 (d), 130.5 (d), 155.3 (s), 173.2 (s); IR ($CHCl_3$) (cm^{-1}) 3525, 3010, 2932, 2860, 1742, 1698, 1368; MS *m*/*z* (relative intensity) 377 $(M - 57)^+$ (1), 274 (7), 150 (10), 128 (57), 57 (100). Anal. Calcd for $C_{26}H_{43}NO_4$: C, 72.00; H, 10.00; N, 3.23. Found: C, 71.57; H, 10.64; N, 3.09.

Preparation of (5*Z*,8*Z*,11*Z*,14*Z*,2*S*)-2-*tert*-Butoxycarbonylaminoeicosa-5,8,11,14-tetraenoic Acid (14). To a stirred solution of **13** (26.3 mg, 0.061 mmol) in dioxane (1 mL) was added NaOH (1 M aqueous solution, 6.2 mL, 6.2 mmol) at room temperature. The reaction mixture was stirred overnight. Then, HCl (3 M) was added at 0 °C until pH ≈ 2 was reached, and the mixture was extracted with EtOAc (4 × 5 mL). The combined organic phases were washed with 10 mL of a saturated solution of brine, dried, and evaporated in vacuo, and the residue was purified by column chromatography to give **14** (23.1 mg, 90% yield) as an oil: $[\alpha]^{25}_D = +9.7$ (*c* 0.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, $J = 6.8$ Hz, 3 H), 1.33 (m, 6 H), 1.44 (s, 9 H), 1.72 (m, 1 H), 1.92 (m, 1 H), 2.05 (m, 2 H), 2.16 (m, 2 H), 2.82 (m, 6 H), 4.28 (bs, 1 H), 5.06 (bs, 1 H), 5.38 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 14.0 (q), 22.5 (t), 23.2 (t), 25.6 (t), 26.8 (t), 27.2 (t), 28.3 (q), 29.3 (t), 30.3 (t), 31.5 (t), 32.1 (t), 53.2 (d), 80.2 (s), 127.5 (d), 127.8 (d), 128.0 (d), 128.3 (d), 128.6 (d), 129.4 (d), 130.0 (d), 130.5 (d), 155.7 (s), 177.0 (s); IR ($CHCl_3$) (cm^{-1}) 3525, 2928, 2855, 1735, 1501, 1369; MS *m*/z (relative intensity) 363 $(M - 57)^+$ (2), 114 (38), 79 (23), 57 (100). Anal. Calcd for $C_{25}H_{41}NO_4$: C, 71.55; H, 9.85; N, 3.34. Found: C, 71.25; H, 9.86; N, 3.02.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for the compounds **3**−**8** and **10**−**14** and the ^{1}H NMR spectra for the (*R*)- and (*S*)-Mosher esters of **12** (24 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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