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The first synthesis of Crucigasterin 277—a polyunsaturated C-18 amino alcohol from the Mediterranean tunicate *Pseudomonas crucigaster*

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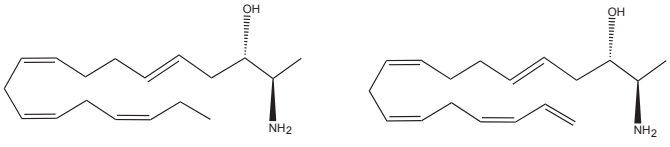
ABSTRACT

Starting from eicosapentaenoic acid (EPA) and D-alanine, the first synthesis of (2*R*, 3*S*)-crucigasterin 277, a polyunsaturated C-18 amino alcohol from the Mediterranean tunicate, *Pseudodistoma crucigaster*, is described.

1. Introduction

The α-amino alcohol structural moiety is present in a large number of naturally occurring compounds.[1] Amino alcohols related to sphingosines have been isolated from marine organisms,[2] and several of these compounds have in common a polyunsaturated carbon chain with methylene interrupted double bonds, terminated by either one or two α-amino alcohol residues.

Some years ago Rinehart and co-workers[3] isolated two polyunsaturated C-18 amino alcohols from the Mediterranean tunicate, *Pseudodistoma crucigaster*. The compounds named crucigasterin 277 (**1**) and 275 (**2**), shown in Fig. 1, exhibited moderate cytotoxic and antimicrobial activity. All but one of the double bonds of **1** have the *Z*-configuration, and at first glance it seems that the compound is derived biosynthetically from D-alanine and an ω-3 polyunsaturated fatty acid. The absolute configuration was assigned based on comparison of a degradation product with that of an authentic compound.[4] The compounds **1** and **2** have not yet been synthesized. The present paper describes the synthesis of crucigasterin 277 (**1**), starting from commercially available *N*-Boc-protected D-alanine (**3**) and (all-*Z*)-eicosa-5,8,11,14,17-pentaenoic acid (EPA, **4**) (see Scheme 2).



Crucigasterin 277 (1) Crucigasterin 275 (2)

Fig. 1. Structures of crucigasterins.[3]

2. Results and discussion

Retrosynthetic analysis suggested cleavage of the C3–C4 bond in the target molecule 1 introducing chirality utilizing an α-amino acid derivative as outlined in Scheme 1. In the synthesis it was contemplated that this bond would be formed by reaction of the *N*-Boc-protected aldehyde 5 derived from 3, with a carbanion equivalent corresponding to the polyunsaturated C-15 residue. We

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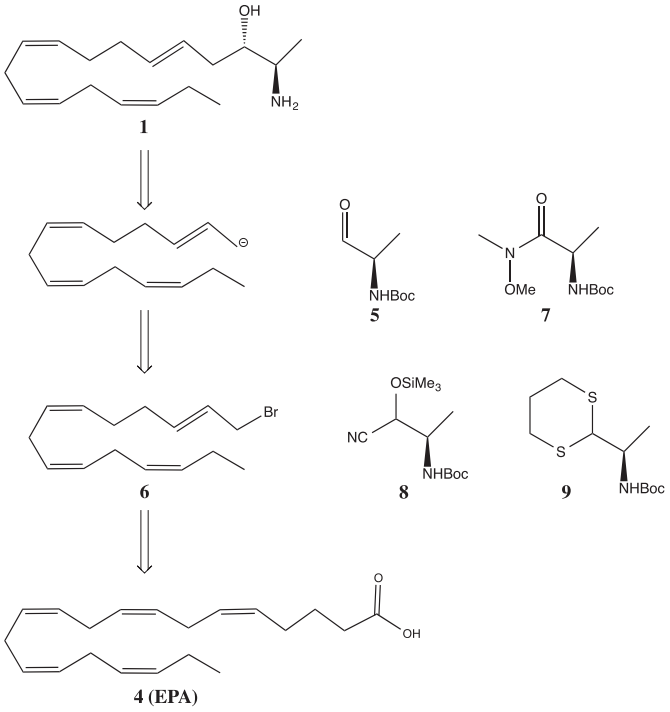
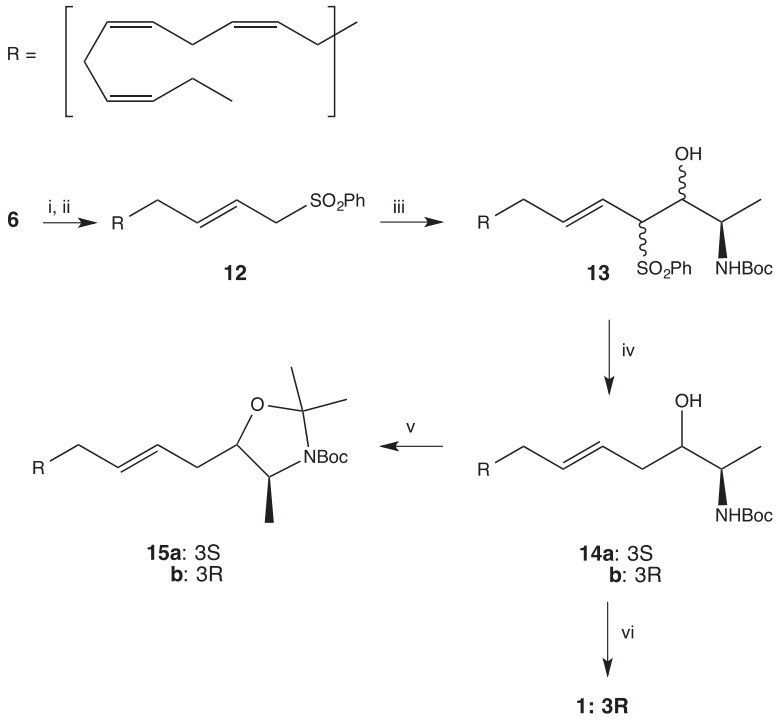


Scheme 1. Retrosynthetic analysis for the synthesis of **1**.

carbanion derived either from the protected cyanohydrin **8** or the thioacetal **9**. Subsequent reduction should yield the target amino alcohol. It was also observed that preparation of the compounds with the stereogenic center α to a carbonyl group was problematic due to fast racemization. The first alternative seemed the most promising, particularly since it would lead directly to the *N*-Boc-protected amino alcohol. It was anticipated that the protecting group could be removed without problems.

The *N*-Boc-protected D-alaninal (**5**) is known in the literature,[3,4] and several methods for the preparation **5** are reported. Accordingly commercially available *N*-Boc-protected D-alanine was converted to the methyl ester by standard conditions.[3,4] Reduction of the ester with DIBAL-H in THF at −78 °C furnished the aldehyde **5** in moderate yield.[4] The main problem with this reaction was the lack of reproducibility with regard to optical purity because of racemization. A second approach involved the oxidation of commercially available *N*-Boc-protected D-alaninol. Use of the Dess-Martin reagent furnished the aldehyde **5** in 80% yield, but with considerable racemization, but switching to the Parikh-Doering oxidation method gave *N*-Boc D-alaninal in excellent optical purity and moderate to good yield.[7] The optical purity was determined by optical rotation and comparison with the literature value. The aldehyde was used immediately to avoid any racemization.

Having the precursors for the vicinal amino alcohol moiety in place, we turned to the problem of transforming the bromide **6** into a carbanion equivalent, corresponding to the C-15 polyunsaturated residue.



Scheme 2. Synthesis of crucigasterin 277.

envisioned that the latter could be obtained from 1-bromo-2*E*,6*Z*,9*Z*,12*Z*-pentadecatetraene (6), a compound that is readily available from EPA in better than 50% overall yield.[5,6]

A second approach to the target molecule would involve reaction of the carbanion with the commercially available *N*-Boc-protected reactive amide **7**. This should afford the amino ketone and subsequently the amino alcohol by reduction. A third way of forming the C3–C4 bond involves reversal of polarities; the amino ketone might be formed by reaction of the bromide **6** with the

We anticipated that the bromide **6** could be converted into the corresponding Grignard, zinc or lithium derivatives, which are all allylic carbanion equivalents. Reactions at both the α- and γ-carbon atoms were expected, the latter being actually the preferred reaction mode with aldehydes,[8] but examples of α preference have been reported.[9] Reaction of the bromide **6** with magnesium metal in THF proceeded smoothly with partial consumption of the metal, and was followed by addition of the aldehyde **5**. However, the product obtained consisted according to GLC analysis of essentially

two compounds which we have tentatively assigned the dimeric structures **10** and **11** (see Fig. 2). The same dimers were also the sole products from reactions of the bromide with either zinc metal or methyllithium. We were unable to separate the dimers by chromatography and the assignments are based on spectral data obtained on the mixture. It has been reported[1,11,12] that the use of Rieke magnesium in this kind of reactions caused less Wurtz coupling, but insignificant change was observed in the present case.

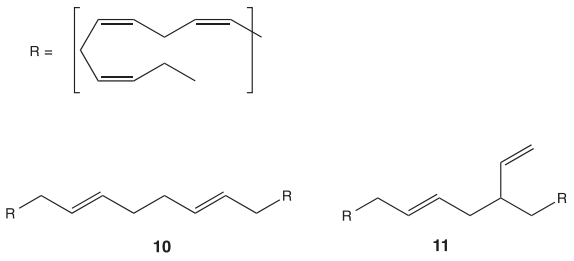


Fig. 2. Dimeric structures from Grignard reaction.

The Grignard type approach was abandoned and different ways of generating the carbanion analog were explored.

It is well known that allylic α-sulfonyl carbanions react with aldehydes at the α-carbon furnishing the straight chain compound,[13] usually as an *erythro-threo* product mixture. A reductive elimination of the sulfonyl group should then provide the desired alcohol **13** as outlined in Scheme 2.

The phenyl sulfone **12** was originally obtained in 58% overall yield from reaction of the bromide **6** with thiophenol, followed by oxidation of the intermediate sulfide with oxone, but subsequently we found that the sulfone was formed in one step and higher yield by reacting the same bromide with $NaSO_2Ph$ in DMF.[14]

The α-sulfonyl carbanion was generated in THF with *n*-butyllithium at −78 °C, and the reaction with aldehyde **5** furnished the *N*-Boc-protected amino alcohol **13** in 69% yield, as a mixture of four stereoisomers. Only the two major isomers were obtained pure by column chromatography, in 45% and 23% yield, respectively. Several methods are known to reductively remove the phenylsulfonyl group, but in the case of compound **13** the possibilities of elimination and double bond migration had to considered when choosing a reagent. The use of sodium amalgam was excluded (Julia elimination) and magnesium metal elimination as well. On the other hand, the palladium(II) catalyzed reduction with lithium borohydride as reported by Kotake and co-workers appeared successful.[14–16]

When the two pure isomers were reacted with this constellation of reagents, one single product was obtained in each case. According to spectral data the compounds were the *N*-Boc amino alcohols **14a** and **14b**, differing only in the configuration at C-3. Based on the NMR data, we were unable to establish their absolute configurations. However, according to the literature *cis*- and *trans*-substituted isomers of 1,3-oxazolidines exhibit significantly different values for the vicinal coupling constants of the protons at C-4 and C-5, the constant being smaller for the *trans* isomer.[17] Hence, the two diastereoisomers were converted with 2,2-dimethoxypropane in the presence of PTSA in 74% yield to the 1,3-oxazolidines **15a** and **15b**, respectively. The NMR measurements were hampered by the presence of rotamers at room temperature, which was particularly apparent for the isomer **15a**. This is apparently a common phenomenon for 1,3-oxazolidines,[18] and the spectra were therefore recorded at about 60 °C, above the coalescence temperature. The vicinal coupling constants for the protons at C-4 and C-5 of the ring were 5.0 Hz for isomer **15a** and 6.3 Hz for isomer **15b**. This result was certainly not conclusive, and the spectra were further analyzed by NOESY experiments. They showed for isomer **15a** a correlation of the methylene protons attached to C-4 and the methyl protons at C-5, while no correlation was observed for **15b**. This result was further confirmed by ROESY experiments.

Reagents and conditions: i) $PhSO_2Na$, DMF, 80 °C.; ii) oxone, MeOH, rt.; iii), n-BuLi, THF, 0 °C, **5**; iv) $LiBH_4$, $Pd(PPh_3)_2Cl_2$, −25 °C; v) 2,2-dimethoxypropane, PTSA, PhH, Δ; vi) 80% aq formic acid, 82% (only on **14b**).

It remained only to remove the protecting group of the (2*R*, 3*R*) isomer **14a** in order to complete the synthesis of crucigasterin 277 (**1**). This was expected to be a simple operation, but standard conditions for deprotection, including reactions with either trifluoroacetic acid or hydrochloric acid, caused partial isomerization of the double bonds. However, the removal of the *N*-Boc group of the isomer **14a** was successfully achieved using 80% formic acid giving crucigasterin 277 (**1**) in 82% yield. The diacetate was prepared according to the procedure reported previously.[3] The spectroscopic and physical data of both **1** and the corresponding diacetate was in agreement with data reported by Rinehart and co-workers[3] and thus confirmed the absolute configuration of the natural product.

3. Experimental section

The NMR spectra were recorded in $CDCl_3$, with a Bruker Avance DPX 200 or DPX 300 instruments. The IR spectra were obtained with a Perkin–Elmer 1310 infrared spectrophotometer or a Nicolet Magna-IR 550 spectrometer. Mass spectra were recorded at 70 eV with a Fisons VG Pro spectrometer. Optical rotations were measured with a Perkin Elmer 241 Polarimeter. Optical purity was determined using a Chrompack GC column: 3% OV 17 ON CHROM WHP. All reactions were performed under a nitrogen or argon atmosphere. The synthesis of **6** has previously been described by our group.[5,19]

3.1. *N*-Boc-D-Alaninal (5)

3.1.1. Method A. The compound was prepared from *N*-Boc-D-alanine methyl ester, according to literature[3] to give the D-alaninal (39% total yield) as crystals. Mp 74–76 °C; $[\alpha]_D^{25}$ =+41 (*c*=0.10, MeOH) (lit.[4] mp 76–78 °C and $[\alpha]_D^{25}$ =+40.8 (*c*=1.10, MeOH)). ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (d, *J*=7.3 Hz, 3 H), 1.43 (s, 9 H), 4.21 (m, 1 H), 5.17 (br s, 1 H, NH), 9.54 (s,1 H).

3.1.2. Method B. The compound was prepared from D-alaniol, according to literature to give the D-alaninal in 63% yield as crystals.[7] Mp 75–77, $[\alpha]_D^{25}$ =+39 (*c*=0.10, MeOH).

3.2. C-30 Hydrocarbons 10 and 11

A solution of the bromide **6** (0.64 g, 2.3 mmol) in dry ether (4 mL) was added dropwise to a stirred mixture of magnesium turnings (0.082 g, 3.4 mmol) and dry ether (1 mL). Once the reaction had started, the remaining bromide solution was added dropwise over a period of 20 min. After 2 h of gentle reflux, the mixture was cooled to −50 °C. A solution of *N*-Boc D-alaninal (**5**) (0.078 g, 0.45 mmol) in anhydrous THF (5 mL) was added. The mixture was left stirring at ambient temperature for 1 h. The reaction mixture was poured into a solution of 1 M aq NaH_2PO_4 and extracted with ether. The extract was washed with 1 M aq NaH_2PO_4, water, brine and dried ($MgSO_4$). Evaporation of solvents followed by flash chromatography (silica gel, 95:5 hexane/EtOAc) gave a mixture of dimers **10** and **11** (0.60 g, 65%). *m*/*z* (EI): 406 (1.0), 108 (48), 93 (63), 79 (100), 67 (83), 41 (54); (HRMS: found: M^+406.3607, $C_{30}H_{46}$ requires 406.3600).

3.3. (2*E*,6*Z*,9*Z*,12*Z*)-1-Phenylsulfonyl-2,5,9,12-pentadecatetraene (12)

3.3.1. Method A. To a stirred solution of LiOH×H_2O(1.1 g, 26.2 mmol) and thiophenol (1.7 g, 15.5 mmol) in MeOH (130 mL) was added, at room temperature, a solution of the bromide **6** (4.0 g, 14.1 mmol) in MeOH (20 mL). After stirring for 3 h at rt, water (100 mL) was added and the mixture extracted with hexane. The extract was washed with brine and dried ($MgSO_4$). Evaporation of solvents under reduced pressure followed by filtration through a plug of silica (hexane as eluent) gave (2*E*, 6*Z*, 9*Z*, 12*Z*)-1-Phenylthio-2,5,9,12-pentadecatetraene (4.1 g, 93%) as an oil. R_f (20% EtOAc/hexane): 0.80; IR: 3011, 2962, 2931, 1652, 1585, 1480, 1452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, *J*=7.5 Hz, 3 H), 2.03–2.21 (m, 6 H), 2.75–2.93 (m, 4 H), 3.43–3.52 (m, 2 H), 5.20–5.44 (m, 7 H), 5.45–5.55 (1 H), 7.17–7.25 (m, 1 H), 7.27–7.40 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ14.2 (CH_3), 20.5, 25.5, 25.6, 26.8, 32.2, 36.4 (6×CH_2), 125.4, 126.0, 127.0, 128.0, 128.2, 128.3 (6×CH═), 128.6 (2×CH═), 129.1 (CH═), 129.8 (2×CH═), 131.9, 133.5 (2×CH═), 136.2 (C═); *m*/*z* (EI) 312 (M^+, 8%), 203 (22), 79 (100) (HRMS: found: M^+ 312,1919. $C_{21}H_{28}S$ requires 312, 1912).

To an ice-cooled solution of the sulfide (4.0 g, 12.8 mmol) in MeOH (30 mL) and dioxane (20 mL) was added dropwise an aqueous solution of oxone (23.7 g, 38.4 mmol). The mixture was left stirring at rt overnight. Water (50 mL) was added and the mixture extracted with $CHCl_3$. The extract was washed with brine and dried ($MgSO_4$). Evaporation of solvents under reduced pressure followed by flash chromatography (silica gel, 8:2 hexane/EtOAc) gave the sulfone **12** (2.7 g, 62%) as an oil. R_f (30% EtOAc/hexane): 0.45; IR: 3000, 2965, 2923, 1445, 1318, 1306, 1152 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, *J*=7.5 Hz, 3 H), 1.91–2.08 (m, 6 H), 2.62–2.81 (m, 4 H), 3.71 (d, *J*=7.2 Hz, 2 H), 5.12–5.51 (m, 8 H), 7.49–7.57 (m, 2 H), 7.58–7.62 (m, 1 H), 7.78–7.86 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ14.2 (CH_3), 20.4 (CH_2), 25.4 (CH_2), 25.5 (CH_2), 26.2 (CH_2), 32.4 (CH_2), 59.9 (CH_2), 116.3, 126.8, 127.7 (3×CH═), 128.4 (2×CH═), 128.5 (2×CH═), 128.5 (CH═), 128.9 (2×CH═), 131.9, 133.5 (2×CH═), 138.2 (C═), 140.8 (CH═); *m*/*z* (EI) 344 (M^+, 3%), 203 (82), 79 (100) (HRMS: found: M^+344,1802. $C_{21}H_{28}O_2S$ requires 344, 1810).

3.3.2. Method B. A solution of bromide **6** (4.0 g, 17.0 mmol) and $PhSO_2Na$ (5.55 g, 34.0 mmol) in DMF (100 mL) was heated at 80 °C for 15 h. Mixture was cooled to rt followed by addition of water (100 mL) and DCM (100 mL). Phases were separated, and the organic phase was washed with water (3×100 mL). Purification by chromatography (silica gel, 8:2 hexane/EtOAc) gave the sulfone **12** (4.1 g, 85%) as an oil.

3.4. (2*R*,5*E*,9*Z*,12*Z*,15*Z*)-*N*-Boc-2-Amino-3-hydroxy-4-phenysulfonyl-5,9,12,15-octadecatetraene (13)

n-BuLi (1.3 M in hexane, 5.50 mL, 7.15 mmol) was added to a solution of the sulfone **12** (2.67 g, 7.76 mmol) in THF (25 mL) at −78 °C. The mixture was stirred for 30 min before a solution of *N*-Boc-D-alaninal (**5**, 0.80 g, 4.62 mmol) in THF (5 mL) was added dropwise (0.5 mL/min using a syringe pump). The reaction mixture was stirred at −78 °C for 1.5 h before the reaction was quenched by addition of water and the mixture extracted with ether. The extract was washed with water (3×), brine and dried ($MgSO_4$). Evaporation of solvents under reduced pressure gave a residue that contained a mixture of unreacted **12** and four diastereomers. Purification by flash chromatography (silica gel, 8:2 hexane/EtOAc) gave the sulfone **12** (1.05 g), diastereomer **13a** (0.33 g), diastereomer **13b** (0.62 g), and an inseparable mixture of diastereomers **13c** and **13d** (0.61 g, 54:46 according to NMR). The combined yield of **13** was 69% based on alaninal.

3.5. Diastereomer 13a

R_f (20% EtOAc/hexane): 0.32; $[\alpha]_D^{25}$ =+4.6 (*c*=0.32, CH_3OH); IR: 3506 (broad), 3443, 3388, 3008, 2973, 2933, 1710, 1501, 1447, 1299, 1167, 1144 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, *J*=7.5 Hz, 3 H), 1.17 (d, *J*=6.0 Hz, 3 H), 1.39 (s, 9 H), 1.86–2.10 (m, 6 H), 2.63–2.81 (m, 4 H), 3.46 (t, *J*=9.8 Hz, 1 H, H-4), 3.58–3.74 (m, 1 H, H-2), 4.17 (s, 1 H, OH), (4.26 m, 1 H, H-3), 4.26 (d, *J*=9.8 Hz, 1 H, H-3), 5,01–5.46 (m, 9 H), 7.44–7.54 (m, 2 H), 7.57–7.65 (m, 1 H), 7.73–7.86 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ12.3, 14.2 (2×CH_3), 20.6, 25.4, 25.5, 26.1 (4×CH_2), 28.3 (3×CH_3), 32.5 (CH_2), 47.6 (CHNH), 70.1 (CHOH), 72.8 ($CHSO_2Ph$), 79.3 (CO), 118.4, 126.7, 127.7, 128.3, 128.5 (5×CH═), 128.8 (3×CH═), 129.3 (2×CH═), 132.0 (CH═), 134.1 (CH═), 136.5 (C), 141.2 (CH═), 155.0 (C═O). *m*/*z* (CI): 518 (M^++1, 0.9), 57 (100); (HRMS (Electrospray): found: M^+ +1, 518.2938. $C_{29}H_{44}NO_5S$ requires 518.2935).

3.6. Diastereomer 13b

R_f (20% EtOAc/hexane): 0.20; $[\alpha]_D^{25}$ =−2.45 (*c*=0.41, CH_3OH); IR: 3501(broad), 3447, 2970, 2932, 1716, 1499, 1441, 1297, 1158, 1136 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ0.92 (t, *J*=7.5 Hz, 3 H), 1.17 (d, *J*=6.7 Hz, 3 H), 1.34 (s, 9 H), 1.83–2.08 (m, 6 H), 2.60–2.78 (m, 4 H), 3.56–3.77 (m, 2 H, H-2 and H-4), 4.09 (d, *J*=9.5 Hz, 1 H, H-3), 4.33 (s, 1 H, OH), 4.72–4.93 (m, 1 H, NH), 4,95–5.43 (m, 8 H), 7.41–7.52 (m, 2 H), 7.53–7.64 (m, 1 H), 7.77–7.84 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ14.2, 18.7 (2×CH_3), 20.5, 25.4, 25.5, 25.9 (4×CH_2), 28.2 (3×CH_3), 32.5 (CH_2), 47.7 (CHNH), 71.4 (CHOH), 72.9 ($CHSO_2Ph$), 78.9 (CO), 117.9, 126.9, 127.8, 128.4, 128.7 (5×CH═), 128.8 (3×CH═), 129.1 (2×CH═), 132.0, 133.9 (2×CH═), 137,0 (C), 141.6 (CH═), 154.8 (C═O). *m*/*z* (CI): 518 (M^++1, 0.6), 57 (100). *m*/*z* (EI): 461 (1.4), 44 (100); (HRMS (Electrospray): found: M^+ +1, 518.2934. $C_{29}H_{44}NO_5S$ requires 518.2935).

3.7. Mixture of diastereomers 13c and 13d

R_f (20% EtOAc/hexane): 0.12; ^1H NMR (300 MHz, $CDCl_3$) δ0.92 (t, *J*=7.5 Hz, 2×3 H), 1.12 (d, *J*=6.7 Hz, 3 H), 1.34 (d, *J*=6.5 Hz, 3 H), 1.37 (s, 9 H), 1.39 (s, 9 H), 1.29–2.15 (m, 2×6 H), 2.58–2.28 (m, 2×4 H), 3.38–3.77 (m, 2×2 H), 4.26–4.45 (m, 2×1 H), 4.58 (d, *J*=8.6 Hz, 1 H), 4.82 (d, *J*=9.4 Hz, 1 H), 5.05–5.48 (m, 2×8 H), 5.49–5.64 (m, 2×1 H), 7.38–7.62 (m, 2×3 H), 7.72–7.81 (m, 2×2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ14.1, 18.3, 20.4, 25.4 (2×CH_2), 26.1, 32.5, 32.6, 49.1, 50.3, 70.4, 70.5, 71,2, 72.0, 77.2, 79.4, 117.4, 117.6, 126.8, 127.7, 128.4, 128.5, 128.6 (2×CH), 128.7, 128.8, 129.0, 129.2, 131.8, 131.9, 133.5, 133.6, 137.2, 137.3, 140.8, 142.1, 155.2, 155.7.

3.8. (2*R*,5*E*,9*Z*,12*Z*,15*Z*)-*N*-Boc-2-Amino-3-hydroxy-5,9,12,15-octadecatetraene (14a)

To a solution of compound **13a** (0.150 g, 0.29 mmol) and $LiBH_4$ (0.032 g, 1.45 mmol) in dry THF (10 mL), cooled to −25 °C, was added a suspension of $Pd(PPh_3)_2Cl_2$ in THF (5 mL).[10] The mixture was left stirring at −25 °C overnight. 0.1 M aq NaOH (3 mL) was added and the mixture extracted with ether/hexane 1:1. The extract was washed with water until neutral, then with brine and dried ($MgSO_4$). Evaporation of solvents followed by flash chromatography (silica gel, 8:2 hexane/EtOAc) gave the compound **14a** (0.09 g, 82%) as an oil; *Rf* (40% EtOAc/hexane): 0.60; $[\alpha]_D^{25}$ =+11.6 (*c*=0.17, $CHCl_3$) IR:3439 (broad), 3010, 2974, 2932, 1690 (broad), 1505, 1366, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ0.94 (t, *J*=7.5 Hz, 3 H), 1.06 (d, *J*=6.7 Hz, 3 H), 1,42 (s, 9 H), 1.90–2.28 (m, 9 H), 2.62–2.81 (m, 4 H), 3.51–3.72 (m, 2 H, H-2 and H-3), 4.68–4.82 (m, 1 H, NH), 5.21–5.60 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 14.5 (2×CH_3), 20.5, 25.5, 25.6, 27.0 (4×CH_2), 28.4 (3×CH_3), 32.5, 37.2 (2×CH_2), 50.1 (CHNH), 73.4 (CHOH), 79.3 (CO), 126.3, 127.0, 128.0,

128.3, 128.4, 129.3, 132.0, 133.7 (8×CH=), 155.7 (C=O); *m/z* (CI): 378 (M^++1, 2.6), 278 (100); (HRMS (Electrospray): found: M^+ +1, 378.3000. $C_{23}H_{40}NO_3$ requires 378.3003).

3.9. (*2R,5E,9Z,12Z,15Z*)-*N*-Boc-2-Amino-3-hydroxy-5,9,12,15-octadecatetraene (14b)

Reduction of compound **13b** (0.35 g, 0.67 mmol), as described above for **13a,** gave compound **14b** (0.19 g, 75%) as an oil; *Rf* (40% EtOAc/hexane): 0.60; $[\alpha]_D^{25}$ =+9.3 (*c*=0.37, CH_3OH); *IR:* 3390 (broad), 2988, 2935, 2900, 1670 (broad), 1485, 1350, 1155 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ0.94 (t, *J*=7.5 Hz, 3 H), 1.14 (d, *J*=6.8 Hz, 3 H), 1,41 (s, 9 H), 1.90–2.32 (m, 9 H), 2.66–2.83 (m, 4 H), 3.38–3.52 (m, 1 H, H-3), 3.53–3.69 (m, 1 H, H-2), 4.66–4.82 (m, 1 H, NH), 5.20–5.58 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2 (CH_3), 18.5 (CH_3), 20.5, 25.5, 25.6, 27.0 (4×CH_2), 28.3 (3×CH_3), 32.5, 37.7 (2×CH_2), 49.7 (CHNH), 73.8 (CHOH), 79.2 (CO), 126.1, 127.0, 128.0, 128.1, 128.2, 128.3, 128.4, 129.2, 129.3, 131.9, 133.9 (11×CH=), 156.0 (C=O); *m/z* (EI): 321 (3.4), 44(100); *m/z* (CI): 378 (M^++1, 11.6), 278 (100). HRMS (Electrospray): found: M^++1, 378.3005, $C_{23}H_{40}NO_3$ requires 378.3003.

3.10. 2,2-Dimethyl-1,3-oxazolidine (15a)

A solution of the amino alcohol **14a** (52 mg, 0.14 mmol), 2,2-dimethoxypropane (0.035 mL, 0.028 mmol) and *p*-toluenesulfonic acid (cat. amount) in benzene (5 mL) was heated under reflux for 1 h. Ether (10 mL) was added and the mixture neutralized with satd aq $NaHCO_3$, washed with brine and dried ($MgSO_4$). Evaporation of solvents followed by flash chromatography (silica gel, 95:5 hexane/EtOAc) gave the oxazolidine **15a** (45 mg, 78%) as an oil; R_f (40% EtOAc/hexane): 0.60; $[\alpha]_D^{25}$ =+0.50 (*c*=0.77, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6, 79 °C) δ 0.91 (t, *J*=7.5 Hz, 3 H), 1.13 (bd, *J*=5.3 Hz, 3 H), 1.43 (s, 9 H), 1.56 (br s, 3 H), 1.68 (br s, 3 H), 1.93–2.14 (m, 7 H), 2.07–2.15 (m, 1 H), 2.66–2.86 (m, 4 H), 3.78–4.01 (m, 1 H), 3.92 (m, 1 H), 5.31–5.52 (m, 8 H); ^{13}C NMR (75 MHz, C_6D_6, 79 °C) δ 13.9, 14.2 (2×CH_3), 20.9, 26.0, 26.1, 27.5 (4×CH_2), 28.6 (5×CH_3), 32.9 (CH_2), 55.7 (CH–N), 76.7 (CH–O), 79.0, (N–C–O), 92.8 (CO), 126.4, 127.6, 128.5, 128.6, 128.8, 129.7, 132.2, 132.6 (8×CH=), 151.8 (C=O).

3.11. 2,2-Dimethyl-1,3-oxazolidine (15b)

The amino alcohol **14b** (0.13 g, 0.34 mmol) was treated with 2,2-dimethoxypropane (0.085 mL, 0.069 mmol) and *p*-toluenesulfonic acid (cat. amount) as described for **15a** to give the oxazolidine **15b** (0.11 g, 76%) as an oil. $[\alpha]_D^{25}$ =−10.5 (*c*=0.57, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, 35 °C) δ 0.94 (t, *J*=7.5 Hz, 3 H), 1.25 (d, *J*=5.9 Hz, 3 H), 1,45 (s, 12 H), 1,55 (s, 3 H), 1.88–2.13 (m, 6 H), 2.21–2.36 (m, 2 H), 2.68–2.82 (m, 4 H), 3.52 (br s, 1 H), 3.67 (q, *J*=6.2 Hz, 1 H), 5.23–5.54 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$, 35 °C) δ 14.2,18.5 (2×CH_3), 20.5, 24.5, 25.6, 26.1 (4×CH_2), 28.4 (5×CH_3), 32.6, 36.8 (2×CH_2), 57.2, (CH–N), 79.3 (N–C–O), 81.2 (CH–O), 93.8 (CO), 125.5, 127.0, 128.1, 128.2, 128.3, 129.3, 131.8, 132.9 (8×CH=), 152.1 (CH=O); HRMS (Electrospray): found: M^+ +1, 418.3315, $C_{26}H_{44}NO_3$ requires 418.3316.

(2*R*,3*R*,5*E*,9*Z*,12*Z*,15*Z*)-2-aminooctadeca-5,9,12,15-tetraen-3-ol (Crucigasterin 277, **1**). The amino alcohol **14b** (0.18 g, 0.48 mmol) was dissolved in 80% formic acid (20 mL). The reaction mixture was left stirring at room temperature overnight. Water (20 mL) was added and most of the formic acid was removed by evaporation. Saturated $NaHCO_3$ was added to neutral pH and then the reaction mixture was extracted with EtOAc (3×20 mL). The extract was washed with water (20 mL) and brine (20 mL) and dried ($MgSO_4$). Evaporation of solvents under reduced pressure gave the amino alcohol **1** (0.11 g, 82%) as an oil. $[\alpha]_D^{25}$ =+4.7 (*c*=0.60, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, *J*=6, 3 H), 1.13–1.42 (m, 6H), 1.90–2.24 (m, 9H), 2.39–2.24 (m, 2 H), 2.69–2.84 (m, 4 H), 3.14 (br s, 1H), 3.55 (s, 2H), 4.74 (br s, 3H), 5.21–5.57 (m, 8 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.47, 18.74, 20.75, 25.73, 25.86, 27.29, 32.89, 38.21, 52.11, 73.27, 125.35, 127.25, 128.24, 128.48, 128.64, 129.51, 132.19, 134.07.

The diacetyl derivative was made according to literature[3] giving $[\alpha]_D^{25}$ =+41 (*c*=0.62, CH_3OH); that is in accord with the published one. All spectral data were consistent with the published ones.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.06.009.

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