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Graphical Abstract

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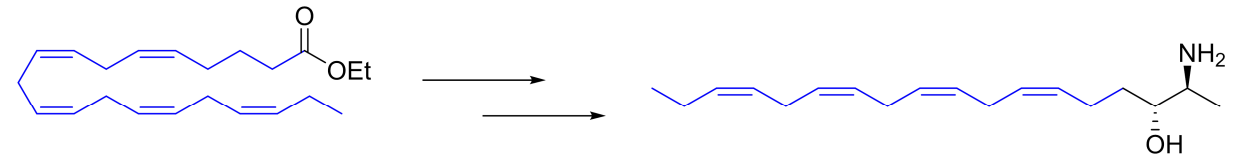

Ethyl ester of eicosapentaenoic acid → **Obscuraminol A**

Synthesis of Obscuraminol A using an organocatalyzed enantioselective Henry reaction

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Abstract: The first synthesis of the polyunsaturated amino alcohol natural product obscuraminol A is reported. This stereoselective synthesis was based on an *anti*- and enantioselective organocatalyzed Henry reaction followed by a chemoselective SmI_2-mediated reduction that affected only the nitro-group of the Henry product. These efforts yielded obscuraminol A where the configuration of the all-*Z* skipped double bonds was conserved from the starting material, *i.e*. the ethyl ester of (all-*Z*)-eicosa-5,8,11,14,17-pentaenoic acid. Our synthesis confirmed the reported structure of obscuraminol A.

Keywords: obscuraminol A; sphingolipids; *anti*-selective Henry reaction; organocatalysis; Wang catalyst; SmI_2 reduction

1. Introduction

Sphingosines are common biomembrane constituents as the backbone of sphingolipids. Sphingolipids are involved in many biological functions.[1] The sphingolipid class of natural products derived from long-chain vicinal amino alcohols with the 1-deoxygenated sphingosines base are widely distributed among marine invertebrates, especially in marine ascidian.[1] The wide spectrum of bioactivities reported for these substances, such as cytotoxicity, antimicrobial and antifungal effects, makes them interesting targets in marine bioprospecting efforts towards the development of novel pharmaceuticals.[2-7] For example, (2*S*,3*R*)-2-amino-3-octadecanol (**1**), isolated from the mollusk *Spisula polinima*, also known as spisulosine (Figure 1),[8] showed activity against several tumor cell lines. The structural simple saturated natural product **1** has been subjected to clinical trial development programs against solid tumors.[9] However, the related compounds with a polyunsaturated *Z*-skipped side chain have been less explored. Examples of this class of the sphingoids are obscuraminol A (**2**) and crucigasterin 277 (**3**) (Figure 1).

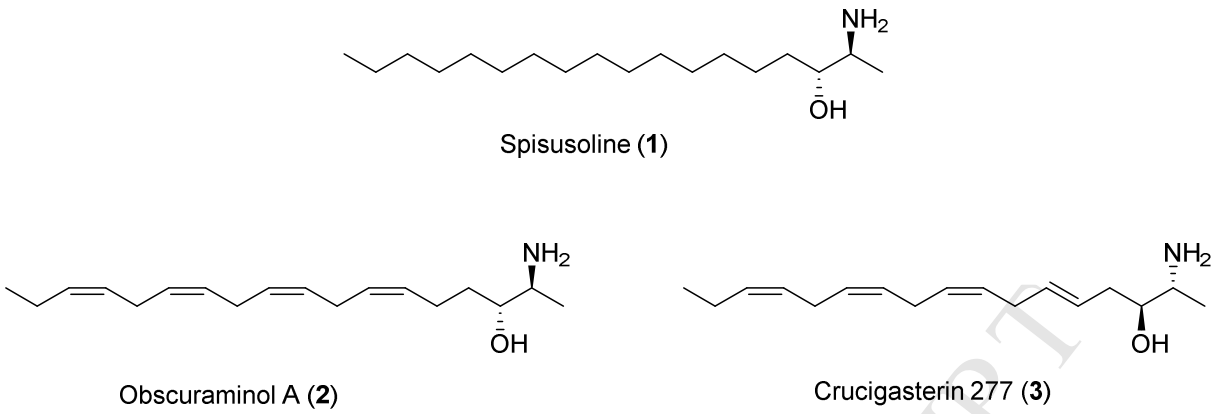
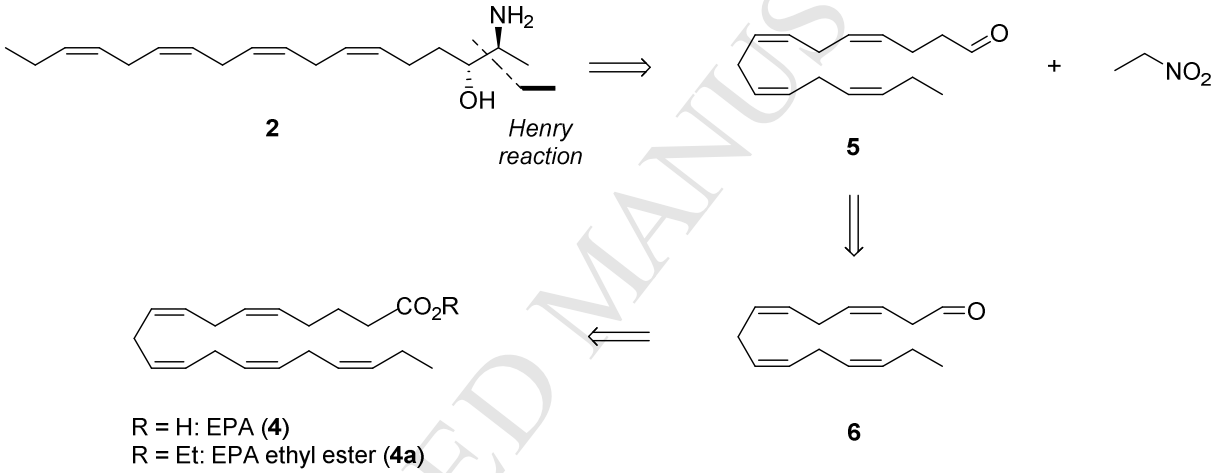


Figure 1. Structures of spisulosine (**1**), obscuraminol A (**2**) and crucigasterin 277 (**3**).

The vicinal *anti*-amino alcohol **2** was assigned the same (2*S*,3*R*)-configuration as spisulosine (**1**) by application of Mosher's method.[10] However, this has not yet been established by matching data obtained from total synthesis efforts, which is very often necessary for determination of absolute configurations of vicinal amino alcohols. Obscuraminol A (**2**) was isolated by Garrido *et al.* in 2001 from the chloroform extracts of the marine ascidian *Pseudodistoma obscurum*.[4] Shortly after, Clark *et al.* reported the isolation of the *N*-acetyl derivative of **2** from the sponge *Haliclona* sp. 1031, and named it halaminol D.[3] Structurally, compound **2** is related to the cytotoxic and antimicrobial polyunsaturated amino alcohol crucigasterin 277 (**3**), the latter has been isolated from the Mediterranean tunicate *Pseudodistoma crucigaster*.[5] Recently we reported a total synthesis of **3** that proved its structure and afforded sufficient amount of material for biological studies.[11] This synthesis, as well as those of several other polyunsaturated natural products with a *Z*-skipped moiety, utilized the commercially available polyunsaturated fatty acid (all-*Z*)-eicosa-5,8,11,14,17-pentaenoic acid (EPA, **4**), Scheme 1, as a convenient starting material.[12,13] For most of these synthetic studies, four of the five *Z*-skipped double bonds in **4** were conserved in the final targets. Therefore, the formation of multiple skipped Z-double bonds from either repeated, steroselective reduction reaction of internal alkynes,[13,14] or using multiple *Z*-selective Wittig reactions,[13,15] is omitted. These advantages were also taken into consideration in our retrosynthetic analysis of obscuraminol A (**2**). To date, there are no reports on the synthesis of this highly unsaturated *anti*-amino alcohol. Herein, we report our efforts towards a stereoselective synthesis of obscuraminol A (**2**), employing **4a** as a convenient starting material.

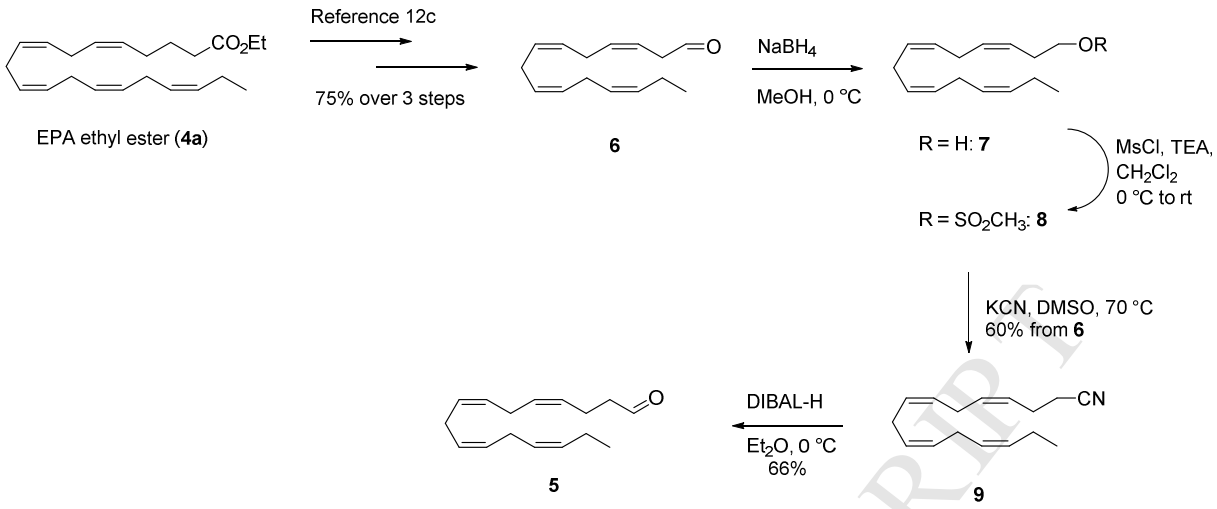
2. Results and discussion

As outlined in Scheme 1, the retrosynthetic analysis suggests cleavage of the C2-C3 bond in the target molecule. Towards the synthesis it was contemplated that the two stereogenic centers at C2 and C3 will be formed in an *anti*-selective Henry reaction between nitroethane and the C16 polyenoic aldehyde **5** followed by a selective reduction of the nitro group. The ethyl ester **4a** can be readily converted into aldehyde **6**, and then a one-carbon homologation should give the C16 unsaturated aldehyde **5**. The *anti*- and concomitant enantioselective Henry reaction between nitroethane and the chemical sensitive aldehyde **5** was considered to be the biggest challenge toward the preparation of **2**. As of today, very few protocols have been reported with linear aldehydes to give enantioselectively *anti*-nitro aldol products. This is particular true for γ,δ-unsaturated aldehydes, such as **5**.[16]



Scheme 1. Retrosynthetic analysis of obscuraminol A (**5**).

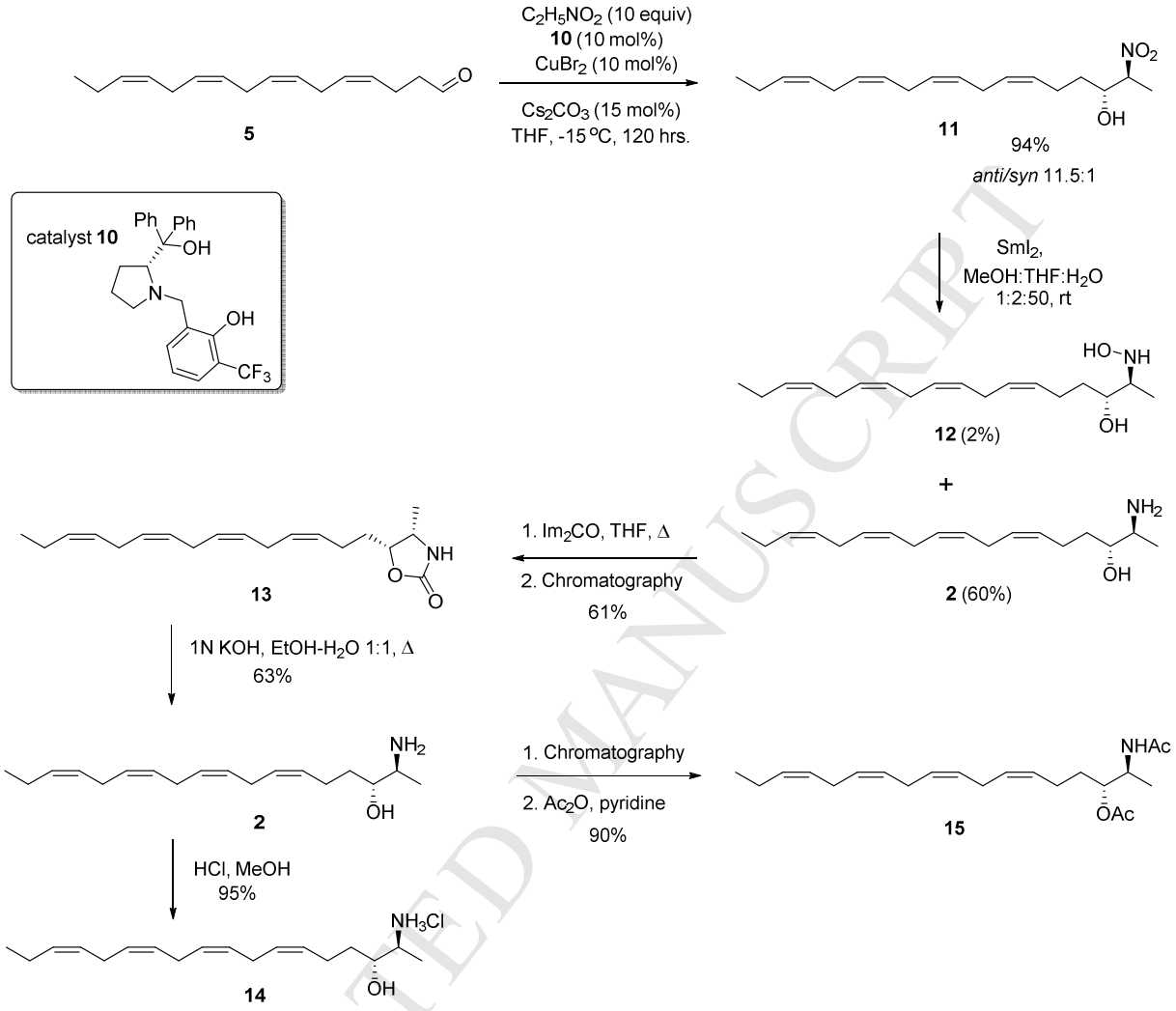
The synthesis of aldehyde **5** started from the aldehyde **6**, the latter was available in 75% overall yield using a degradation protocol of the ethyl ester **4a** (See Supporting Information). The aldehyde **6** was then reduced with sodium borohydride to yield the corresponding C15 alcohol **7** that was transformed into its mesylate **8**. This mesylate was immediately converted into the nitrile **9** that was subjected to a DIBAL-H reduction, see Scheme 2. Overall, aldehyde **5** was obtained in seven steps in an overall yield of 30% from the ethyl ester **4a**.



Scheme 2. Synthesis of aldehyde **5**.

The organocatalyzed Henry reaction was then to be investigated. Recently, several examples of enantioselective versions of the Henry reaction have appeared using metal-based catalysts,[17] enzymatic protocols[18] or organocatalysts.[19] Organoatalysts for both *syn*- and *anti*-diastereoselective variations of the Henry reaction have been developed as well.[20] However, most of the *anti*-diastereoselective catalysts reported give high selectivity only towards aromatic aldehydes.[20] Recently, we reported an asymmetric Henry reaction using a pinane-derived ligand copper (II) complex that worked reasonably well for aliphatic aldehydes.[21] Unfortunately, when this system was applied for the reaction between **5** and nitroethane, the expected nitroaldol product was obtained in very low yields and with poor selectivity towards the undesired *syn*-diastereomer. So we turned our attention to literature protocols for the generation of aliphatic *anti*-nitro alcohols. The phenol-proline derived ligand **10** reported by Wang and co-workers[20e] seemed the most promising one, and was prepared as previously described (See Supporting Information).[20e] Applying **10** to the nitroaldol reaction using the original conditions (THF, −15 °C) resulted in a sluggish reaction. However, after a prolonged reaction time, the (2*S*,3*R*)-nitroaldol adduct **11** was isolated in 94% yield and in good diastereoselectivity (*anti/syn* 11.5:1) as determined by ^{1}H NMR analysis (Scheme 3). The enantiomeric excess was determined to be *ee* = 83% by HPLC analyses (See Supporting Information). The absolute configuration of the isolated major product of the nitro-alcohol **11** was not determined at this stage. However, based on NMR data and by comparison with analogs reported by Wang and co-workers, the relative configuration was tentatively assigned as *anti*.[20e] Raising the reaction temperature to −8 °C significantly reduced the reaction time,

but resulted in a diminished diastereoselectivity (*anti/syn* 5.7:1). Lowering the temperature to −20 °C did not improve the selectivity.



Scheme 3. Synthesis of obscuraminol A (**2**) and derivatives.

The most common way for the reduction of vicinal nitroaldols into their corresponding amino alcohols with retention of configuration is by hydrogenation using Pd/C.[20b,c,e,h] Obviously, this method is not applicable towards substrates with a high degree of unsaturation, such as **11**. Transfer hydrogenation protocols have also been reported,[22] but in our hands only complex reaction mixtures were returned. The conventional reduction of the nitro-group using zinc powder in acidic media (HCl/AcOH)[20a,23] afforded the reduced product, but in addition to a low yield of the reaction, these attempts were accompanied by partial elimination of the hydroxyl group. Attempts to protect the hydroxyl functionality as its TBDPS-ether[24] gave a complex mixture of products. Reduction protocols employing nickel boride, which has previously been utilized in nitroaldol reduction reactions,[25] affected the double bonds. When

using the $NaBH_4$-$ZnCl_2$ reductive system, the retro-nitroaldol reaction was observed to take place.[26] Finally, we tried a previously reported SmI_2-mediated reduction protocol[27] on the nitroaldol product **11**. Gratifyingly, this resulted in the isolation of the desired amino-alcohol **2** in 60% yield. In addition, the hydroxylamine **12** was detected as a by-product (Scheme 3). The structure of **12** was assigned based on NMR- and MS-analyses of mixed fractions with unreacted **11**, **2** and **12**. Full conversion to the target molecule **2** was not achieved even when increasing the molar equivalents of SmI_2 to 10 equivalents or using prolonged reaction times. After purification by column chromatography, this reduction protocol afforded the target aminoalcohol **2** with a lower diastereoselectivity than expected from the starting material. The diastereomeric ratio was determined to be 5.2:1 in favor of the desired *anti*-isomer (See Supporting Information). The origin of the lowered diastereomeric ratio is currently under investigation. Unfortunately, the resulting mixture of the two diastereomers of the target the amino-alcohol **2** was inseparable at this stage. In order to enhance the separation of these isomers, as well as to remove compound **12**, the diasteromeric mixture of **2** and with minor amounts of **12** present, was treated with 1,1'-carbonyldiimidazole to afford two cyclic oxazolidinones where the major product was the *cis*-isomer **13**, that was isolated after chromatography in 61% yield. The configuration of **13** was confirmed by NOESY and ROESY experiments (See Supporting Information), which showed a clear correlation for the protons of C3 and C4. Similar observations have been reported by Garrido *et al*..[4] Moreover, these experiments provided evidence for the initial assignment of the relative configuration of **11** also as *anti*.

The isolated oxazolidinone **13** was hydrolyzed[28] under alkaline conditions that provided access to the target amino alcohol **2** (dr > 20:1 determined by ^{1}H NMR). Unfortunately, there was a discrepancy in the specific optical rotation values and the NMR data of the synthetic product with data reported for naturally occurring obscuraminol A (**2**) (See Supporting Information).[4] Examination of the literature data revealed that **2** was isolated as its hydrochloride salt. So, the amino-alcohol was converted to its hydrochloride salt **14** after treatment with excess hydrogen chloride in MeOH. The spectral data for **14** were in agreement with those reported earlier.[4] Moreover, the specific optical rotation data of synthetic **14** ($[\alpha]_D^{20}$ = +2.0, c = 0.14, MeOH) was dextrorotary, as previously reported ($[\alpha]_D^{20}$ = +4.8, c = 0.14, MeOH).[4] These data supported that the absolute configuration of **2** is 2*S*,3*R*, but a significant difference in the rather low figures for the specific optical rotation data was observed. In order to build more confidence in establishing the absolute configuration at C2 and C3, the diacetate

15 was also prepared (See Supporting Information).[4] To our delight, the specific optical rotation data of the synthetic diacetate of **2** showed similar values as reported in the literature,[4] $[\alpha]_D^{20}$ = −23.8 (c = 0.65, $CHCl_3$) and $[\alpha]_D^{20}$ = −23.3 (c = 0.65, $CHCl_3$), respectively.[29] Hence, the absolute configuration of the stereogenic centers in **2** is indeed 2*S*,3*R* as originally assigned by Garrido *et al.* The enantiomeric excess of **15** was determined by GLC-analyses to be *ee* = 88% (see Supporting Information).

3. Conclusions

To summarize, the first synthesis of obscuraminol A (**2**) has been presented using an organocatalyzed *anti*- and enantioselective Henry reaction using the Wang catalyst **10**. Several synthetic strategies have been used for the stereoselective synthesis of vicinal amino-alcohols,[31] but organocatalysis offers many advantages.[32] An important part for advancing this important field of environmentally benign asymmetric synthesis is to apply such methodology in the total synthesis of natural products, now extended to polyunsaturated sphingolipids. Of note, the challenging chemoselective reduction of the nitro group in **11** was achieved by employing a mild and rather underutilized SmI_2-mediated reduction protocol.[27] These efforts yielded the naturally occurring obscuraminol A (**2**) in 6% overall yield over 11 steps from the ethyl ester of eicosapentaenoic acid (**4**). Noteworthy, the stereochemistry of the four *Z*-skipped double bonds has been conserved from the starting material **4a**. The synthetic work presented confirmed the assigned structure of the natural product **2** and provided sufficient material for biological testing. However, a highly stereoselective preparation of obscuraminol A (**2**) is still elusive. Such efforts are ongoing and will be reported in due time.

4. Experimental section

4.1 General methods.

All reactions were performed under a nitrogen atmosphere protected from light exposure. All reagents and solvents were commercial grade and used without further purification. Thin layer chromatography (TLC) was performed using aluminium backed silica gel 60 F_{254} plates and flash chromatography utilized silica gel 60 (40-63 μm) from Merck. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded in $CDCl_3$ on a Bruker Ascend^{TM} 400 spectrometer. Chemical shifts are measured in ppm relative to residual solvent peak as internal standard set to δ 7.26 and 77.0. HRMS was performed using EI method of ionization. IR spectra (4000-600 cm^{-1}) were recorded on Perkin-Elmer Specrtum BX series FT-IR spectrophotometer using a reflectance cell (HATR). Optical rotations were measured using a 1 mL cell with 1.0 dm path

length on Perkin Elmer 341 polarimeter in dedicated solvent. HPLC analyses were performed on Agilent 1200 Series instrument using an AD-H column with a chiral stationary phase. The GC analyses were performed on an Agilent GC system using Agilent J1W HP-5 GC column (20 m, i.d. = 0.18 mm) with FID detector or a CP Chirasil 7502 column with FID detector. Diastereomeric ratios or yields reported in this paper have not been validated by calibration, please see reference Hudlicky and Wernerova for discussions and guidelines.[33]

4.2 (4*Z*,7*Z*,10*Z*,13*Z*)-hexadeca-4,7,10,13-tetraenal (5)

The aldehyde **5** was prepared from **4a** as previously reported.[12l] The overall yield of **5** is 30%. All spectroscopic data were in full agreement with the literature.[12f,l] ^{1}H NMR (400 MHz, $CHCl_3$): δ 9.76 (t, *J* = 1.5 Hz, 1H), 5.47-5.23 (m, 8H), 2.89-2.75 (m, 6H), 2.56-2.44 (m, 2H), 2.44 -2.33 (m, 2H), 2.12-1.99 (m, 2H), 0.95 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.9, 132.0, 129.4, 128.6, 128.4, 127.8, 127.8, 127.6, 127.0, 43.7, 25.6, 25.6, 25.5, 20.6, 20.0, 14.3.

4.3 (*R*)-2-((2-(hydroxydiphenylmethyl)pyrrolidin-1-yl)methyl)-6-(trifluoromethyl)phenol

Catalyst **10** was prepared according to the procedure by Wang *et al.*[20e] A white solid resulted (64%), mp: 125-127 °C, with spectroscopic data in agreement with the literature.[20a] ^{1}H NMR (400 MHz, $CHCl_3$) δ 7.59-7.46 (m, 4H), 7.34-7.18 (m, 6H), 7.12-7.08 (m, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.68 (t, *J* = 7.7 Hz, 1H), 5.20 (s, 1H), 3.91 (dd, *J* = 9.5, 4.7 Hz, 1H), 3.47 (d, *J* = 13.6 Hz, 1H), 3.30 (d, *J* = 13.6 Hz, 1H), 2.96 (ddd, *J* = 10.0, 6.3, 3.4 Hz, 1H), 2.34 (td, *J* = 9.8, 6.5 Hz, 1H), 2.17-2.00 (m, 1H), 1.88 (ddt, *J* = 12.6, 8.2, 4.3 Hz, 1H), 1.74-1.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.7, 144.9, 144.3, 130.6, 127.4, 127.3, 126.0, 125.9, 125.0, 124.8, 123.1, 116.8, 78.8, 71.2, 59.4, 54.5, 28.3, 23.1.

4.4 (2*S*,3*R*,6*Z*,9*Z*,12*Z*,15*Z*)-2-Nitrooctadeca-6,9,12,15-tetraen-3-ol (11)

To a solution of **10** (25 mg, 0.058 mmol), $CuBr_2$ (13 mg, 0.058 mmol) and Cs_2CO_3 (28 mg, 0.087 mmol) in 1.2 mL of THF, nitroethane (5.9 mmol, 440 μL) was added. The mixture was left stirring for the next four hours at room temperature until a white precipitate appeared. The tube was centrifuged for 5 min (6000 rpm), and the supernatant was transferred to the test tube containing pre-cooled to −15 °C aldehyde **5** (137 mg, 0.59 mmol). The mixture was reacted at −15 °C until completion as monitored by TLC (120 h). Then the volatiles were removed under reduced pressure and the residue was then directly subjected to silica gel column eluting with hexane:EtOAc (10:1) to afford 170 mg (94%) of the nitroaldol **11** as a colorless oil; $[\alpha]_D^{20}$ = -11.5 (c = 0.3, $CHCl_3$, *anti/syn* 11.5:1); ν_{max} (liquid film) 3665-3250 (br), 3011, 2963, 2933, 2874, 1547, 1453, 1392, 1020, 797, 705 cm^{-1}; *ee* = 83% (HPLC,

Chiracel AD-H column, hexane:isopropanol 98:2, 1.0 mL/min, 25 °C, 215 nm): t_R (*anti* minor) = 10.98 min, t_R (*anti* major) = 12.05 min, t_R (*syn* major) = 13.93 min, t_R (*syn* minor) = 14.47 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.49-5.23 (m, 8H), 4.47 (qd, *J* = 6.9, 3.0 Hz, 1H), 4.16 (dq, *J* = 7.5, 3.6 Hz, 1H anti), 2.86-2.75 (m, 6H), 2.32-2.12 (m, 3H), 2.05 (td, *J* = 7.4, 1.3 Hz, 2H), 1.61-1.37 (m, 3H), 1.53 (d, *J* = 7.5 Hz 3H), 0.95 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.1, 129.6, 128.7, 128.4, 128.3, 127.9, 127.8, 127.0, 86.4, 71.4, 32.7, 25.6, 25.6, 23.4, 20.6, 14.3, 12.6.

4.5 Obscuraminol A (2) obtained by SmI_2-mediated reduction

To a stirred 0.1 M solution of SmI_2 in THF (1.5 mmol, 15 mL) a solution of nitro-alcohol **11** as mixture of *syn*- and *anti*-isomer (62 mg, 0.2 mmol) in THF:MeOH 2:1 was added. The mixture was left stirring at ambient temperature until full conversion of **11** (TLC). After six h the reaction was quenched with 10% aqueous solution of $Na_2S_2O_3$ and extracted with EtOAc (3 × 10 mL). The combined organic phase was dried (Na_2SO_4) and evaporated. The residue was subjected to silica gel column chromatography eluting with $CHCl_3$:MeOH (9:1) to afford 33 mg (60%) of the amino-alcohol **2** as a colorless oil; R_f = 0.13; dr (determined by ^{1}H NMR) 5.2:1 of*anti/syn*-isomers . The crude reaction product consisting of **2** and **12** was transformed into the corresponding oxazolidinone in the subsequent step.

4.6 *Cis*-(4*S*,5*S*)-4-methyl-5-((3*Z*,6*Z*,9*Z*,12*Z*)-pentadeca-3,6,9,12-tetraene-1-yl)oxazolidin-2-one (13)

To a solution of the amino-alcohol **2** (16 mg, 0.058 mmol) in dry THF (2 mL) was 1,1´-carbonyldiimidazole (14 mg, 0.087 mmol) added. The solution was refluxed for 12 h. The solvent was evaporated and the crude product was purified by silica gel chromatography eluting with hexane:EtOAc 7:3 to 1: 1 to obtain 10.3 mg (61%) of **13** as a colourless oil; R_f = 0.48 (hexane:EtOAc 1:1, $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57-5.53 (br s, 1H), 5.49-5.24 (m, 8H), 4.56 (ddd, *J* = 10.1, 7.4, 3.8 Hz, 1H), 3.89 (pentet, *J* = 6.6 Hz, 1H), 2.89-2.73 (m, 6H), 2.34-2.14 (m, 2H), 2.10-2.01 (m, 2H), 1.82 (m, 1H), 1.53 (m, 1H), 1.15 (d, *J* = 6.5 Hz, 3H), 0.95 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 132.0, 129.5, 128.6, 128.4, 128.1, 127.9, 127.8, 127.0, 79.4, 51.0, 29.2, 25.6, 25.58, 25.5, 23.5, 20.5, 16.0, 14.3.

4.7 Obscuraminol A (2) obtained by hydrolysis of 13

A solution of the *cis*-carbamate **13** (6.9 mg, 0.023 mmol) in a 1N aqueous solution of KOH in EtOH-H_2O 1:1 (1 mL) was refluxed for four hours. After cooling to room temperature, the mixture was diluted with water (1 mL) and was extracted with EtOAc (3 x 2.5 mL). The combined organic phase was dried ($MgSO_4$) and evaporated to afford 4 mg (63%) of **2** as a yellow oil; ν_{max} (liquid film) 3680-3200 (br), 3011, 1621, 1435, 1024, 801, 704 cm^{-1}; ^{1}H

NMR (400 MHz, $CDCl_3$): δ 5.45-5.28 (m, 8H), 3.61-3.58 (m, 1H), 3.08-3.00 (m, 1H), 2.85-2.76 (m, 6H), 2.75 (br s, 4H), 2.28-2.24 (m, 1H), 2.19-2.16 (m, 1H), 2.07 (m, 2H), 1.51-1.40 (m, 2H), 1.09 (d, *J* = 6.6 Hz, 2H), 0.97 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.0, 129.5, 128.6 (2 x), 128.2 (2 x), 127.9, 127.0, 73.1, 50.8, 32.3, 25.6, 25.5, 23.9, 20.6, 15.7, 14.3.

4.8 (2*R*,3*S*,6*Z*,9*Z*,12*Z*,15*Z*)-2-aminooctadeca-6,9,12,15-tetraene-3-ol hydrochloride (14)

The amino-alcohol **2**, obtained by hydrolysis of **13**, (5 mg, 0.017 mmol) in 0.5 mL of dry MeOH at 5 °C was immediately treated with a five-fold excess of HCl-gas in MeOH for 30 min. The solvent was removed by evaporation flushing with nitrogen to afford 5 mg (95%) its hydrochloride salt **14** as a pale yellow oil; $[\alpha]_D^{20}$ = +2.0 (c = 0.14, CH_3OH), lit.[4] $[\alpha]_D^{20}$ = +4.8 (c = 0.14, CH_3OH);[4] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (br s, 3H), 5.40-5.26 (m, 8H), 4.00 (m, 1H), 3.43 (m, 1H), 2.81-2.76 (m, 6H), 2.27-2.20 (m, 1H), 2.15-2.00 (m, 3H), 1.59-1.53 (m, 1H), 1.42-1.40 (m, 1H), 1.30 (d, *J* = 6.7 Hz, 3H), 0.95 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.0, 129.0, 128.6, 128.4, 128.1, 127.8, 127.0, 70.1, 52.0, 32.8, 25.6, 25.5, 23.6, 20.6, 14.3, 12.0; HRMS (EI^+): Exact mass calculated for $C_{18}H_{32}NO$ $(M\text{-}Cl)^+$: 278.2474, found 278.2484.

4.9 (2*S*,3*R*,6*Z*,9*Z*,12*Z*,15*Z*)-2-acetamidooctadeca-6,9,12,15-tetraen-3-yl acetate (15, diacetate of obscuraminol A)

The amino-alcohol **2** (13 mg, 0.047 mmol) was dissolved in pyridine (0.2 mL) and Ac_2O (510 mg, 0.47 mmol was added at ambient temperature. The mixture was left stirring for two hours, then the solvents were removed by evaporation flushing with nitrogen and the residue was purified using column chromatography eluting with hexane:EtOAc 1:1 to obtain 15 mg (90%) of **15** as a yellow oil in a 14:1 diasteromeric ratio; $[\alpha]_D^{20}$ = −23.8 (c = 0.65, $CHCl_3$), lit.[4] $[\alpha]_D^{20}$ = −23.3 (c = 0.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84 (d, *J* = 8.6 Hz, 1H), 5.43-5.22 (m, 8H), 4.83 (ddd, *J* = 9.3, 4.3, 3.2 Hz, 1H), 4.14 (dqd, *J* = 10.1, 8.4, 6.9, 3.2 Hz, 1H), 2.88-2.69 (m, 5H), 2.14-1.98 (m, 8H), 1.93 (s, 3 H), 1.71-1.48 (m, 2H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.95 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 169.3, 132.0, 129.0, 128.6, 128.4, 128.3, 128.0, 127.8, 127.0, 76.4, 47.7, 31.2, 25.6, 25.6, 25.5, 23.5, 23.4, 21.1, 20.6, 14.9, 14.3; HRMS (EI^+): Exact mass calculated for $C_{22}H_{35}NO_3$: 361.2617, found 361.2637; *ee* = 88% (GLC, CP Chirasil 7502, 25m, film 0.25 mm, i.d. 0.25 mm, 80 °C (45 min.), then 2 °C/min, 150 °C (10 min.)).

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Supplementary data

Supplementary data include experimental procedures and characterization data of starting materials for making catalyst **10**, copies of IR-spectra, ^{1}H- and ^{13}C-NMR spectra, as well as copies of chromatograms of GLC and HPLC analyses.

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