Oxygenated Metabolites of n-3 Polyunsaturated Fatty Acids as Potential Oxidative Stress Biomarkers: Total Synthesis of 8-F3t-IsoP, 10-F4t-NeuroP and [D4]-10-F4t-NeuroP
Alexandre Guy, Camille Oger, Johannes Heppekausen, Cinzia Signorini, Claudio de Felice, Alois Fürstner, Thierry Durand, Jean-Marie Galano

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Abstract: A wide variety of metabolic products of polyunsaturated fatty acids is of paramount importance for improving our medical knowledge in the field of oxidized lipids. Two novel metabolites of n-3 polyunsaturated fatty acids, 8-F3t-IsoP and 10-F4t-NeuroP as well as a deuterated derivative thereof were synthesized based on an acetylenic intermediate. An original approach achieved lateral chain insertion of 8-F3t-IsoP by a ring-closing alkyne metathesis/semi-reduction strategy together with a temporary tether.

Omega-3 polyunsaturated fatty acids (n-3 PUFAs), especially docosahexaenoic acid (DHA, C22:6 n-3), are highly prone to peroxidation both in vitro and in vivo due to the presence of skipped diene units. The H-atom abstraction at the bisallylic position followed by oxygenation can either occur enzymatically or by a free-radical mechanism, leading to neuroprotec-tins[1] or neuroprostanes (NeuroPs), respectively.[2] Similar to the NeuroPs, the F2t-isoprostanes (F2t-IsoPs) are isomers of prostaglandin PGF2t. These arachidonic acid (AA) derivatives, which are formed by a non-enzymatic pathway, were confirmed as the most reliable markers for systemic oxidative stress,[3] and possess relevant biological activities in humans.[4, 5] For these reasons, the formation of NeuroPs deserves attention because it is the only pathway that can generate PG-like isomer of DHA. Specifically, DHA is not a substrate for mammalian cyclooxygenase (COX), and it actually inhibits cyclooxygenation of arachidonic acid.

Although NeuroPs are increasingly explored in clinical settings, only few applications yet exist. These compounds might have paramount importance if one considers that the DHA precursor is specifically distributed in the neuronal membrane. In several pathologies, the availability of biochemical markers would be advantageous to discriminate the damage of the grey (concentrated with DHA) from that of white brain matter (concentrated with adrenic acid). Peripheral biological fluids are not universally considered to represent the biochemical oxidative events occurring in the brain.[6] However, our group has demonstrated the relevance of changes of plasma levels of NeuroPs in patients with Rett syndrome, a rare genetic cause of autism in girls,[7] while other authors have confirmed the importance of monitoring the plasma levels of NeuroPs in patients with Parkinson’s disease.[8]

Presently, it is largely unknown which NeuroP isomer is the most abundant and/or most relevant in a given human or experimental condition or disease state. In this context, however, we could previously show that 7-F2t-dihomo-IsoP is the most abundant of the IsoP isomers in the early stage (stage 1) of Rett syndrome.[9, 10]

Since the identification of NeuroPs,[2] several synthetic approaches to such compounds were reported,[11] but no consensus has been reached as to which of these biomarkers is most significant. A priori, one might expect that such a reference molecule 1) would be the most abundant isomer, 2) must not interfere with the products of oxidation deriving from other PUFAs (such as F2t-dihomo-IsoPs)[12] and 3) can be quantified with sufficient sensitivity and reproducibility. To reach these goals and to ameliorate our knowledge about the role of NeuroP in human diseases, we describe herein the syntheses of 10-F4t-NeuroP 1a and its deuterated derivative 2a, as well as of 8-F3t-IsoP 3a (Scheme 1).
Results and Discussion

We have recently reported the total synthesis of [D₄]-4-F₄t-NeuroP to provide a deuterated internal standard for accurate quantification of NeuroPs in vivo. In pursuit of this work, we decided to focus our attention on another potentially interesting isomer, that is, 10-F₄t-NeuroP and its deuterated variant. Its relative 8-F₃t-IsoP derived from eicosapentaenoic acid (EPA, C20:5 n-3) possesses similar structural features. Since this compound could, a priori, also be a β-oxidized metabolite of 10-F₄t-NeuroP, reference samples are essential for tracking down the metabolisation of 10-F₄t-NeuroP.

These targets possess the same short ω-chain (lower part) and share a common homoallylic unit on the α-chain, which only differs by the number of carbon atoms and unsaturations (Scheme 1). This led us envisage a convergent retrosynthetic analysis, such that variations of α-chain would only be a matter of late-stage modifications during the synthesis. Intermediate A would be obtained from the previously described pivotal lactol intermediate 4.

Lactol 4, when treated with commercially available propyl triphenyl phosphonium bromide and tBuOK in THF, afforded alcohol 5 in good yield (Scheme 2). A tactic that was never used in IsoP synthesis is the regioselective propargylation or alkylation by using an acylsilane as the electrophile. Compound 5 was oxidized with Dess–Martin reagent, followed by reaction with methyl 2-(triphenylphosphoranylidene)acetate, subsequent DIBAL-H reduction and Dess–Martin periodinane oxidation (Scheme 3). An epimeric mixture of homopropargyl alcohols 10 was easily obtained on treatment with freshly prepared propargyl magnesium bromide in THF, afforded alcohol 5 in good yield (Scheme 2). A tactic that was never used in IsoP synthesis is the regioselective propargylation or alkylation by using an acylsilane as the electrophile. Compound 5 was oxidized with Dess–Martin periodinane and the resulting aldehyde treated with [(trimethylsilyl)-acetyl]trimethylsilane and lithium diisopropylamine to give the E-configured α,β-unsaturated acylsilane 6 in 85% yield. Reaction with the zinc reagent derived from 7-bromo-hept-5-ynoic acid methyl ester in THF gave the desired tertiary silanol derivative 7 in 73% yield. Unfortunately, however, treatment with TBAF in THF did not provide the desired compound 8, but only cleaved the TBD ethers while not affecting the C-TMS group. Formylation of the tertiary alcohol, as described in the original paper, followed by TBAF deprotection was not satisfactory either, resulting only in the loss of material. Other fluorine sources or acidic conditions were tested in the attempt to deprotect the TMS moiety, but in all cases investigated only TBD cleavage was observed.

Therefore, we decided to explore another convergent strategy by using a more advanced acetylenic intermediate 13 that would then lead to NeuroP 1 and F₃-IsoP 3.

To this end, the unsaturated conjugated aldehyde 9 was prepared by oxidation of 5 with the Dess–Martin reagent, followed by reaction with methyl 2-(triphenylphosphoranylidene)acetate, subsequent DIBAL-H reduction and Dess–Martin periodinane oxidation (Scheme 3).
are needed to access the full spectrum of IsoP/NeuroP isomers, but also to establish the configuration of the stereocenter at the allylic position. Saponification with K₂CO₃ in MeOH and protection with TBSCI yielded the pivotal intermediates 13a and 13b in 79 and 81% yields, respectively.

Starting from intermediate 13a, both IsoP 3 and NeuroPs 1 and 2 should be easily obtained by coupling with 2-(4-bromo-butoxy)tetrahydropyran and the bromopropargyl partner 15, respectively.

In the case of the 8-F₃t-IsoP synthesis, we found that the propargyl alcohol subunit of 13a could not be coupled with 2-(4-bromo-butoxy)tetrahydropyran when using nBuLi in THF/hexamethylphosphoramide (HMPA) as the reagent, whereas a similar transformation was feasible in well reproducible yield in a model study (Scheme 3). Indeed, the desired adduct 14a could not be observed and the reaction mainly resulted in OTBS elimination and/or OTBS deprotection. In contrast, introduction of a skipped diyne unit following the Caruso conditions[18] with the bromo propargyl partner 15 provided diyne 16a in 56% yield. The resulting diyne 16a was contaminated with an approximately 5–10% of a mixture of allenic byproducts, and further purification was not successful at this stage (Scheme 4).

The use of the P2–Ni catalyst[19] for the simultaneous reduction of both alkyne units of 16a by using either hydrogen or deuterium gas following our recent protocol[11f] gave compounds 17a and 18a (Scheme 5). Deprotection of the hydroxyl groups with HCl (0.5 m) in MeOH/THF, followed by saponification with LiOH (0.5 m), H₂O, RT, gave 10-F₄t-NeuroP 1a and [D₄]-10-F₄t-NeuroP 2a. Final purification was performed by semipreparative HPLC to obtain analytically pure compounds 1a and 2a free of allenic and over-reduced byproducts in 48 and 50% yields, respectively. The same procedure was applied for the syntheses of the epimers 1b and 2b (not shown).

After having explored conventional routes to implement the α-chain of 8-F₃t-IsoP (see above), we turned our attention to ring-closing metathesis reactions, in particular the powerful ring-closing alkyne metathesis (RCAM)/semi-reductions strategy.[20] RCAM has previously been used in the prostaglandin series, for example for the synthesis of PGE₂-lactone and hybridlactone[21, 22] As seen in Scheme 6, a suitable RCAM strategy for the preparation of compound B with a lactone of at least 11-ring atoms requires the use of compound C endowed with a temporary tether.[23]

For this purpose, the synthesis of the acetylenic compound 19 was desired, but attempted homopropargylation of aldehyde 9 with the Grignard reagent of 1-bromo-but-2-yne gave the allenic compound 20 as the main product (Scheme 7).
Scheme 8. a) LDA, Mel, DMFU, −78 °C, 97%; b) 1,4-butanol, p-TsOH, heptane, reflux, 91%; c) oxalyl chloride, DMSO, Et$_3$N, CH$_2$Cl$_2$, −78−0 °C, 98%; d) NaClO$_2$, 2-methyl butene, KHPO$_4$, 78%.

Scheme 9. a) EDCI, DMAP, CH$_2$Cl$_2$, 95%; b) P$_2$-Ni, EDA, EtOH, H$_2$, RT; c) 1,4-butan-diol, p$_3$,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) to access the corresponding hept-5-ynoic acid in 97% yield. Esterification with 1,4-butan diol and p-TsOH in refluxing heptane provided ynoate 23 in 91% yield. Swern oxidation of 23 proceeded smoothly, and the last oxidation step was performed with NaClO$_2$ by using the Pinnick protocol[24] to give the corresponding acid 22 in 77% overall yield.

Coupling of precursors 19a and 22 in the presence of EDCI/DMAP cleanly provided ester 24 ready for macrocyclization by RCAM (Scheme 9). Treatment with 10 mol % of catalyst 25[25] in the presence of MnCl$_2$ and 5 Å in toluene at 80 °C delivered the desired 14-membered ring bislactone 26a. The stereoselective Z reduction of 26a was performed by P$_2$-Ni in the presence of EDA with complete regio- and chemoselectivity. Further treatment with HCl (0.5 M) led to the complete deprotection of the silyl ether groups. The final saponification to remove the incremental tether was accomplished with LiOH (0.5 M) and provided 8-F$_3$-IsoP 3a in 76% yield (over two steps). The same sequence was applied to the synthesis of the 3b, which is epimeric to 3a at the C8-position (not shown).

### Conclusion

Two novel metabolites of the free-radical peroxidation of DHA and EPA were synthesized. Specifically, 10-F$_2$-NeuroP 1 and 8-F$_3$-IsoP 3 together with their epimers and the novel tetra-deuterated derivative [D$_2$]-10-F$_2$-NeuroP 2 have been obtained, (the latter will serve as internal standard for the accurate quantification of 10-F$_2$-NeuroP in vivo). While a classical Caruso-type reaction allowed for the synthesis of F$_2$-NeuroP 1, the powerful RCAM/semi-reduction strategy gave access to F$_3$-IsoP derivatives for the first time. Further research is underway in trying to explore the usefulness of these natural products as potential biomarkers of neuronal oxidative stress.

### Experimental Section

**Methyl 6-bromohex-4-ynoate (15)**

2,4-Dihydropryan (12.35 mL, 243 mmol, 1.2 equiv) diluted in CH$_2$Cl$_2$ (20 mL) was added dropwise at room temperature to a solution of 4-pentynol (10 g, 119 mmol, 1 equiv) and p-toluene sulfonic acid (565 mg, 2.9 mmol, 0.025 equiv) in CH$_2$Cl$_2$ (120 mL). The mixture was stirred all the night and then a saturated solution of NaHCO$_3$ 150 mL was added. The mixture was stirred for 15 min and then the layers were separated. The azeotropic layer was extracted with 2×200 mL of Et$_2$O. The combined organic layers were washed with 100 mL of a saturated solution of NaHCO$_3$ and 2×100 mL of brine, dried over MgSO$_4$, filtered, and the solvents removed under reduced pressure. The crude of the reaction was purified under silica gel chromatography (95:5 pentane/EtOAc) and the protected alcohol (18.9 g, 95 %) was obtained. $R_t=0.5$ (8:2 cyclohexane/AcOEt); $^1$H NMR (300 MHz, CDCl$_3$): δ = 5.46 (t, $^3$(H,H) = 3.5 Hz, 1H); 3.84–3.73 (m, 2H); 3.48–3.38 (m, 2H); 2.24 (dd, $^3$(H,H) = 4.2, 11.2 Hz, 2H); 1.88 (m, $^3$(H,H) = 2.7 Hz, 1H); 1.78 (q, $^3$(H,H) = 5.1 Hz, 2H); 1.71–1.73 ppm (m, 6H); $^1$C NMR (75 MHz, CDCl$_3$): δ = 98.6 (CH(O-)$_2$); 83.8 (C=C); 68.3 (H=C); 65.4 (CH$_2$); 62.0 (CH$_2$O); 30.5 (CH$_3$); 28.6 (CH$_3$); 25.4 (CH$_3$); 19.4 (CH$_3$); 15.2 ppm (CH$_3$).

At room temperature, a commercial solution of methyl magnesium bromide (3 M in Et$_2$O, 42 mL, 127 mmol, 2.0 equiv) was added dropwise in a solution of allyne (10.7 g, 63.6 mmol, 1 equiv) in anhydrous THF (60 mL). The solution was refluxed for 1.5 h. The solution was cooled (0 °C) and p-formaldehyde (2.86 g, 95 mmol, 1.5 equiv) was added. The reaction was refluxed for 2 h and more p-formaldehyde (2.4 g, 80 mmol, 1.5 equiv) was added. After refluxing overnight, the solution was cooled at 0 °C, and Et$_2$O (200 mL) and a saturated solution of NaHCO$_3$ (100 mL) were added dropwise. Celite (50 mL) was added and the mixture was filtered. The solid was washed with Et$_2$O (4×100 mL). The layers were separated. The azeotropic layer was extracted with 2×100 mL of EtO. The combined organic layers were washed with 2×100 mL of brine and a saturated solution of NaHCO$_3$ (50 mL) and over MgSO$_4$ filtered and the solvents removed under reduced pressure. The crude of the reaction was purified under silica gel chromatography (8:2 to 1:1 pentane/EtO) and the alcohol (9.69 g, 79 %) was obtained. $R_t=0.5$ (5:5 cyclohexane/AcOEt); $^1$H NMR (300 MHz, CDCl$_3$): δ = 4.55 (t, $^3$(H,H) = 3.4 Hz, 1H); 4.17 (dt, $^3$(H,H) = 2.1, 5.9 Hz, 2H); 3.82–3.73 (m, 2H); 3.48–3.39 (m, 2H); 2.46 (t, $^3$(H,H) = 5.8 Hz, 1H); 2.8 (t, $^3$(H,H) = 5.8, 7.2 Hz, 2H); 1.74 (q, $^3$(H,H) = 6.8 Hz, 2H); 1.67–1.45 ppm (m, 6H); $^1$C NMR (75 MHz, CDCl$_3$): δ = 98.7 (CH(O-)$_2$); 85.4 (C=C); 78.8 (C=C); 65.8 (CH$_2$); 62.1 (CH$_2$O); 51.0 (CH$_2$); 30.5 (CH$_3$); 28.6 (CH$_3$); 25.3 (CH$_3$); 19.4 (CH$_3$); 15.6 ppm (CH$_3$).
A solution of CBr₄ (19.4 g, 58.5 mmol, 1.5 equiv) in CH₂Br₂ (35 mL) was added to a solution of the propargyl alcohol (7.5 g, 39 mmol, 1 equiv), triphenylphosphine (17.2 g, 58.5 mmol, 1.5 equiv) and triethylamine (0.54 mL, 3.9 mmol, 0.1 equiv) in CH₂Br₂ (35 mL) at −10 °C. The mixture was stirred for 3 h at room temperature. The mixture was then quenched with a 10% solution of Na₂S₂O₃ (100 mL) and a saturated solution of NaHCO₃ (100 mL). The layers separated. The aqueous layer was then extracted with CH₂Cl₂ (3 × 250 mL) and the combined organic layers were extracted with Na₂SO₄ (20 mL) and brine (20 mL), and finally dried over MgSO₄ filtered and the solvents removed in vacuo. The crude was diluted in a mixture of pentane/Et₂O 4:1 (250 mL) and filtered. After evaporation, the crude of the reaction was purified under silica gel chromatography (100:0 to 80:20 pentane/Et₂O) and protected alcohol (4.2 g, 41%) was obtained. Rᵣ = 0.7 (5.5 cyclohexane/ACOEt); 1H NMR (300 MHz, CDCl₃): δ = 4.56 (t, J = 2.2 Hz, 1 H); 1.53 (s, 3 H); 0.98 (t, J = 3.9 Hz, 1 H); 2.52–2.42 (m, 4 H); 2.30–2.13 (m, 2 H); 1.68–1.46 ppm (m, 2 H). The mixture was added to a solution of the propargyl alcohol (7.5 g, 39 mmol, 1 equiv) in Et₂O (320 mL). The solution was stirred 3 h at 0 °C and 2 h at room temperature. Isopropanol (45 mL) was slowly added. The mixture was filtered over Celite and rinsed with pentane/Et₂O 1:1 (3 mL). The organic layer was washed with 4 × 250 mL of acidified brine, dried over MgSO₄, filtered and the solvents removed under reduced pressure. The crude was diluted in anhydrous MeOH (65 mL) and BF₃·Et₂O (510 μL, 4.0 mmol, 0.25 equiv) was added. The solution was refluxed for 1 h and then a saturated solution of NaHCO₃ (250 mL) was added. The mixture was extracted with 3 × 250 mL of pentane/Et₂O 1:1. The organic layers were washed with 3 × 100 mL of brine, dried over MgSO₄ filtered and the solvents removed. The crude of the reaction was purified under silica gel chromatography (95:5 pentane/Et₂O) and 1H NMR (300 MHz, CDCl₃): δ = 2.56–2.49 ppm (m, 4 H); 15C NMR (75 MHz, CDCl₃): δ = 172.0 (C quat); 85.7 (C quat); 76.0 (C quat); 51.7 (CH₄); 32.9 (CH₂); 15.0 (CH₃); 14.8 ppm (CH₂); HRMS (ESI⁺): m/z: calcld for C₆H₇O₂Br: 204.9864 [M+H⁺]⁺; found: 204.9866.
MnCl₂ was dried under vacuum at 150 °C overnight and 5 Å molecular sieves powder was dried under vacuum at 400 °C for 30 min. 24a was dried by azotropic evaporation with toluene. Compound 25 (50 mg, 0.04 mmol, 15% mol), MnCl₂ (10.3 mg, 0.08 mmol, 30% mol) and the molecular sieves powder (5 Å, 1 g) in toluene (5 mL) were heated at 80 °C over 30 min. 24a (191 mg, 0.17 mmol, 1 equiv) in toluene (10 mL) was added and the resulting reaction mixture heated for 6 h at 80 °C and stirred overnight at room temperature. For workup, the molecular sieves were filtered off through a short pad of silica, the filtrate was evaporated and the residue purified by flash chromatography (97.9 to 90.10, pentane/EtOAc). Compound 26a was obtained as a colourless syrup (126 mg, 69% with traces of silanol impurities). Rₚ = 0.21 (9:1 cyclohexane/AcOEt); ¹H NMR (400 MHz, CDCl₃); δ = 5.64 (dd, ¹J(H,H) = 9.5, 14.8 Hz, 1H); 5.49–5.28 (m, 4H); 4.19–4.07 (m, 2H); 3.91–3.87 (m, 1H); 3.83–3.78 (m, 1H); 2.68–2.57 (m, 2H); 2.47–2.24 (m, 9H); 2.06–1.81 (m, 1H); 1.74–1.65 (m, 1H); 1.53 (dt, ¹J(H,H) = 5.3, 7.5 Hz, 1H); 0.96 (t, ¹J(H,H) = 7.5 Hz, 3H); 0.88 (s, 9H); 0.86 (s, 9H); 0.03 (s, 6H); 0.01 (s, 3H); 0.00 ppm (s, 3H); ¹³C NMR (100 MHz, CDCl₃); δ = 173.3 (C–O); 172.2 (C–O); 134.3 (CH); 129.2 (CH); 127.7 (CH); 79.8 (C≡N); 78.0 (C≡O); 75.8 (HCO–); 75.5 (HCO–); 73.3 (HCO–); 63.9 (HCO–); 52.2 (CH₃); 50.6 (CH₂); 44.2 (CH₂); 31.9 (CH₃); 31.6 (CH₂); 26.0 (CH₃); 25.8 (CH₂); 25.1 (CH₃); 23.3 (CH₂); 22.1 (CH); 20.6 (CH₂); 18.0 (CH₂); 17.9 (C quaternary); 17.6 (C quaternary); 14.2 (CH₂); −4.4 (CH₃); −4.5 (CH₂); −4.6 (CH₃); −4.7 ppm (CH₃); HRMS (ESI⁺): m/z: calcd for C₁₉H₂₆O₅Si: 467.4163 [M+H⁺]; found: 467.4154.

(R,E)-10-(15,2R,3R,5S)-3,5-Bis[(tert-butyldimethylsilyl)oxy]-2-(Z)-pent-2-enyl)cyclopentyl)-8-(4-hydroxybutanoyloxy)dec-9-en-5-ynoate (26b)

Prepared in an analogous procedure to 26a from 24b (174 mg). Product 26b was obtained as a colourless syrup (110 mg; 66%); Rₚ = 0.30 (9:1 cyclohexane/AcOEt); ¹H NMR (400 MHz, CDCl₃); δ = 5.61 (dd, ¹J(H,H) = 9.6, 14.5 Hz, 1H); 5.47–5.25 (m, 4H); 4.19–4.06 (m, 2H); 3.92–3.87 (m, 3H); 3.80–3.76 (m, 1H); 2.62–2.55 (m, 2H); 2.44–2.18 (m, 9H); 2.05–1.80 (m, 7H); 1.74–1.65 (m, 1H); 1.52 (dt, ¹J(H,H) = 5.5, 13.6 Hz, 1H); 0.95 (t, ¹J(H,H) = 7.5 Hz, 3H); 0.87 (s, 9H); 0.85 (s, 9H); 0.02 (s, 6H); 0.00 (s, 3H); −0.01 ppm (s, 3H); ¹³C NMR (100 MHz, CDCl₃); δ = 173.3 (C–O); 172.2 (C–O); 134.0 (CH); 132.3 (CH); 129.3 (CH); 127.6 (CH₂); 79.8 (C≡N); 78.0 (C≡O); 75.7 (HCO–); 75.5 (HCO–); 73.2 (HCO–); 63.8 (HCO–); 52.3 (CH₃); 50.5 (CH₂); 44.2 (CH₂); 32.0 (CH₃); 31.7 (CH₂); 26.1 (CH₃); 25.8 (CH₂); 25.2 (CH₂); 23.3 (CH₂); 22.2 (CH); 20.7 (CH₂); 18.0 (CH₂); 17.9 (C quaternary); 15.6 (C quaternary); 14.2 (CH₂); −4.4 (CH₃); −4.5 (CH₂); −4.6 (CH₃); −4.7 ppm (CH₃); HRMS (ESI⁺): m/z: calcd for C₂₀H₂₆O₅Si: 421.2590 [M+H⁺]; found: 421.2588.

8-F₂₃H₅IsoP (3a)

NaBH₄ in ethanol (0.5 m, 339 μL, 0.17 mmol, 0.9 equiv) was added under a H₂ atmosphere to a suspension of Ni(OAc)₂·4H₂O (23.5 mg, 0.09 mmol, 0.5 equiv) in ethanol with 0.01% BHT (5 mL). After 10 min, the ethylenediamine in solution in ethanol (0.5 m, 1.7 mL, 0.85 mmol, 4.5 equiv) was added under the black suspension. After 10 min, 26a (126 mg, 0.19 mmol, 1.0 equiv) in ethanol with 0.01% BHT (10 mL) was added. Before and after each addition, three cycles vacuum/H₂ were realized. The mixture was then stirred for 48 h under a H₂ atmosphere (GC control). The mixture was then quenched with 20 mL of a saturated solution of NH₄Cl and stirred for 30 min. The layers were extracted with Et₂O (3×20 mL). The combined organic layers were washed with brine (3×10 mL) and dried over MgSO₄, filtered and the solvents were removed. The crude of the reaction was purified by flash chromatography (97.3 pentane/EtOAc) to obtain the ethylenic compound (88.3 mg, 70%); Rₚ = 0.29 (9:1 cyclohexane/AcOEt); ¹H NMR (400 MHz, CDCl₃); δ = 5.58–5.56 (m, 2H); 5.45–5.27 (m, 5H); 4.20 (dt, ¹J(H,H) = 4.4, ¹J(H,H) = 11 Hz, 1H); 4.03 (dt, ¹J(H,H) = 3.6, ¹J(H,H) = 11 Hz, 1H); 3.93–3.89 (m, 1H); 3.81 (q, ¹J(H,H) = 5.6 Hz, 1H); 2.69–2.65 (m, 1H); 2.54 (ddd, ¹J(H,H) = 4.4, 11.3, 15.6 Hz, 1H); 2.48–2.25 (m, 6H); 2.12–2.18 (m, 9H); 1.79 (quint., ¹J(H,H) = 5.6 Hz, 1H); 1.54 (dt, ¹J(H,H) = 5.5, ¹J(H,H) = 13.7 Hz, 1H); 0.96 (t, ¹J(H,H) = 7.6 Hz, 3H); 0.88 (s, 9H); 0.86 (s, 9H); 0.03 (s, 6H); 0.02 (s, 3H); 0.01 ppm (s, 3H); ¹³C NMR (100 MHz, CDCl₃); δ = 173.3 (C–O); 172.0 (C–O); 132.8 (CH); 132.2 (CH); 131.8 (CH); 129.6 (CH); 127.7 (CH); 124.8 (CH); 75.9 (HCO–); 75.5 (HCO–); 73.7 (HCO–); 62.1 (H₂O-C); 52.4 (CH); 50.5 (CH₂); 44.2 (CH₂); 33.7 (CH₂); 32.8 (CH₂); 30.3 (CH₂); 26.4 (CH₂); 26.1 (CH₂); 25.8 (CH₂); 24.9 (CH₂); 23.3 (CH₂); 20.6 (CH₂); 18.0 (C quaternary); 17.9 (C quaternary); 14.2 (CH₂); −4.4 (CH₃); −4.5 (CH₂); −4.6 (CH₃); −4.7 ppm (CH₃); HRMS (ESI⁺): m/z: calcd for C₁₉H₂₆O₅Si: 469.4320 [M+H⁺]; found: 469.4333.
Keywords: fatty acids • NeuroPs • oxygenated metabolites • ring-closing metathesis • total synthesis

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