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Oxygenated Metabolites of *n*-3 Polyunsaturated Fatty Acids as Potential Oxidative Stress Biomarkers: Total Synthesis of 8-F_{3t}-IsoP, 10-F_{4t}-NeuroP and [D₄]-10-F_{4t}-NeuroP

Alexandre Guy,^[a] Camille Oger,^[a] Johannes Heppekausen,^[b] Cinzia Signorini,^[c] Claudio De Felice,^[d] Alois Fürstner,^[b] Thierry Durand,^[a] and Jean-Marie Galano^{*[a]}

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-F_{3t}-IsoP and 10-F_{4t}-NeuroP as well as a deuterated derivative

thereof were synthesized based on an acetylenic intermediate. An original approach achieved lateral chain insertion of 8-F_{3t}-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 neuroprotectins^[1] or neuroprostanes (NeuroPs), respectively.^[2] Similar to the NeuroPs, the F₂-isoprostanes (F₂-IsoPs) are isomers of prostaglandin PGF₂α. 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-F_{2t}-dihomo-IsoP is the most abundant of the IsoP isomers in the early stage (stage 1) of Rett syndrome.^[9,10]

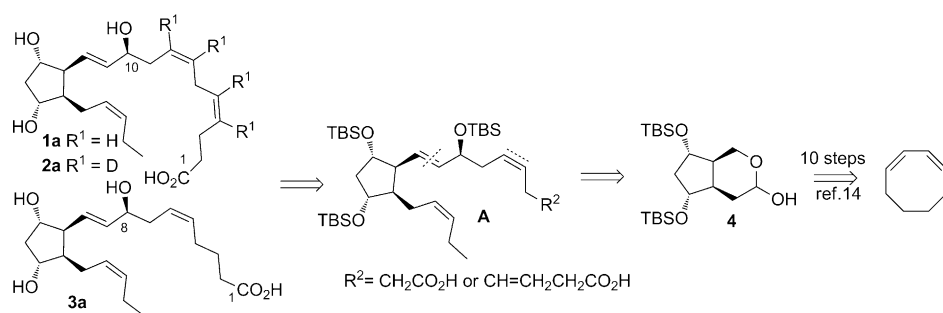
Since the identification of NeuroPs,^[2] several synthetic approaches to such compounds were reported,^[11] but no consensus has been reached as to which of these biomarkers is most significant. A priori, one might expect that such a reference molecule 1) would be the most abundant isomer, 2) must not interfere with the products of oxidation deriving from other PUFAs (such as F₂-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-F_{4t}-NeuroP **1 a** and its deuterated derivative **2 a**, as well as of 8-F_{3t}-IsoP **3 a** (Scheme 1).

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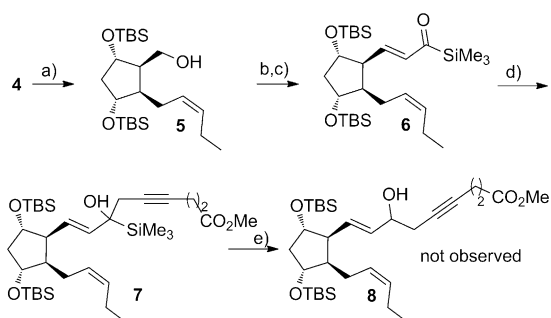
Scheme 1. Retrosynthetic analysis of 10- F_{4t} -NeuroP **1a** and [D_4]-10- F_{4t} -NeuroP **2a** and 8- F_{3t} -IsoP **3a**.

Results and Discussion

We have recently reported the total synthesis of [D_4]-4- F_{4t} -NeuroP to provide a deuterated internal standard for accurate quantification of NeuroPs *in vivo*.^[11f] In pursuit of this work, we decided to focus our attention on another potentially interesting isomer, that is, 10- F_{4t} -NeuroP **1** and its deuterated variant **2**. Its relative 8- F_{3t} -IsoP **3** 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- F_{4t} -NeuroP,^[13] reference samples are essential for tracking down the metabolisation of 10- F_{4t} -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**.^[14]

Lactol **4**, when treated with commercially available propyl triphenyl phosphonium bromide and *t*BuOK in THF, afforded alcohol **5** in good yield (Scheme 2). A tactic that was never



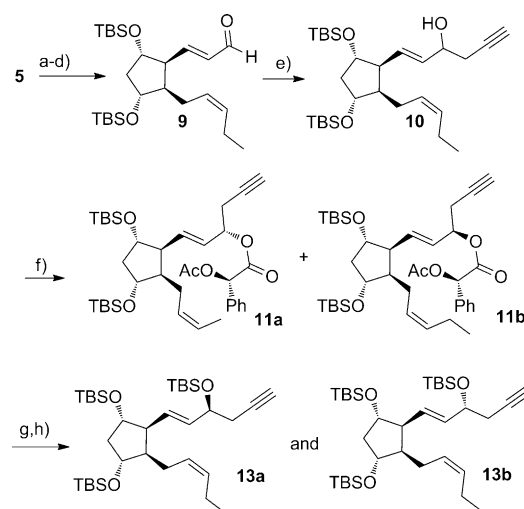
Scheme 2. a) $Br^+Ph_3P^+CH_2C_2H_5$, *t*BuOK, THF, 0 °C, 94%; b) Dess–Martin periodinane, CH_2Cl_2 , RT; c) $Me_3SiCH_2COSiMe_3$, LDA, –78 °C, 85% (over two steps); d) $BrCH_2CCC_2H_4CO_2Me$, Zn dust, THF, 30 °C, 73%; e) TBAF, THF. LDA = lithium diisopropylamide; TBAF = tetrabutylammonium fluoride.

used in IsoP synthesis is the regioselective propargylation or allylation by using an acylsilane as the electrophile.^[15] Compound **5** was oxidized with Dess–Martin periodinane^[16] and the resulting aldehyde treated with [(trimethylsilyl)-acetyl]trimethylsilane and lithium diisopropylamine to give the *E*-con-

figured 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 TBS ethers while not affecting the C-TMS group. Formylation of the tertiary alcohol, as described in the original paper,^[15] 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 TBS 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 F_3 -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). An epimeric mixture of ho-



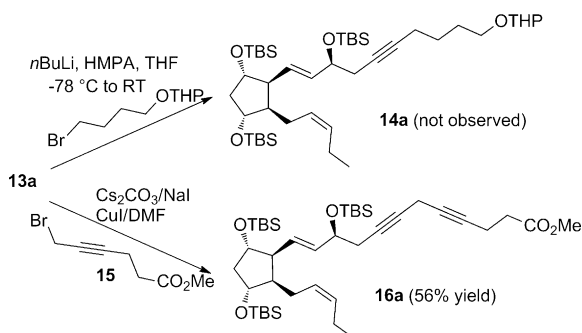
Scheme 3. a) Dess–Martin periodinane, RT; b) $Ph_3=CHCO_2Me$, THF, RT, 75% (over two steps); c) DIBAL-H, CH_2Cl_2 , –78 °C; d) Dess–Martin periodinane, RT; 92% (over two steps); e) $BrMgCH_2C_2H_5$, Et_2O , 0 °C, 80%; f) (*S*)-acetyl phenyl acetic acid, EDCI, DMAP, CH_2Cl_2 , 40% (**11a**) and 48% (**11b**); g) K_2CO_3 , MeOH, RT; h) TBSCl, imidazole, CH_2Cl_2 , 79% (over two steps); DIBAL-H = diisobutylaluminium hydride; DMAP = 4-dimethylaminopyridine; EDCI = *N'*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide.

mopropargyl alcohols **10** was easily obtained on treatment with freshly prepared propargyl magnesium bromide in THF (80%). Separation of the resulting epimers was accomplished by the corresponding diastereomeric mandelic ester derivatives **11a** and **11b** in 40 and 48% yields, respectively.^[17] This strategy not only allowed both epimers to be separated, which

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 K_2CO_3 in MeOH and protection with TBSCl 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.

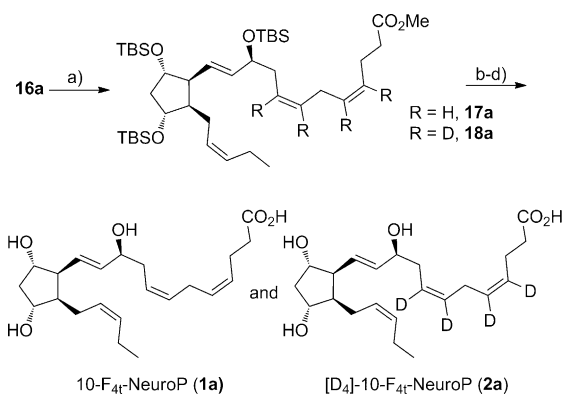
In the case of the 8- F_{3t} -IsoP synthesis, we found that the propargyl alcohol subunit of **13a** could not be coupled with 2-(4-bromo-butoxy)tetrahydropyran when using *n*BuLi in THF/hexamethylphosphoramide (HMPA) as the reagent, whereas a similar transformation was feasible in well reproducible 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).



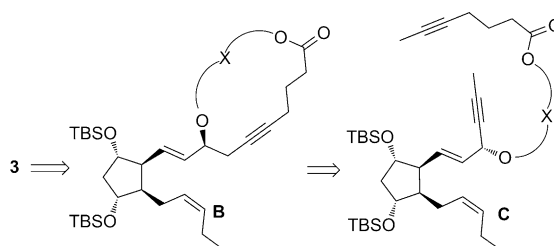
Scheme 4. Failure and success in accessing F_4 -NeuroP and F_3 -IsoP precursors from **13a**.

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) gave 10- F_{4t} -NeuroP **1a** and [D_4]-10- F_{4t} -NeuroP **2a**. Final purification was performed by semi-preparative 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- F_{3t} -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 hybridalactone.^[21,22] As seen in Scheme 6, a suitable RCAM strat-



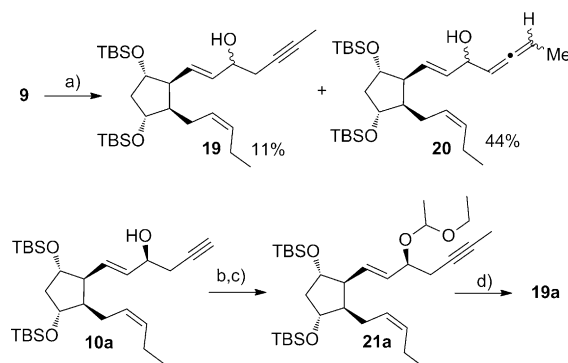
Scheme 5. a) P2-Ni, EDA, EtOH, H₂ or D₂, RT; b) HCl (0.5 M), MeOH/THF; c) LiOH (0.5 M), H₂O, RT; d) semipreparative HPLC, 48% (**1a**) and 50% (**2a**); P2-Ni = Ni(OAc)₂·4 H₂O/NaBH₄; EDA = ethylenediamine.



Scheme 6. Retrosynthetic analysis of **3** by using a RCAM/semi-reduction strategy.

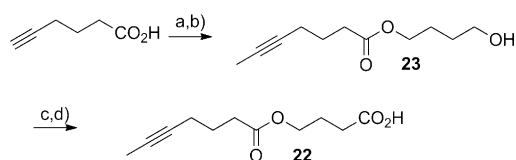
egy for the preparation of compound **B** with a lactone of at least 11-ring atoms requires the use of compound **C** endowed with a temporary tether.^[23]

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 7. a) $MgBrCH_2C\equiv CCH_3$, Et₂O, 0 °C; b) ethylvinyl ether, PPTS, CH₂Cl₂, RT; c) LDA, MeI, DMPU, -78 °C, 71%; d) PPTS, propanol/CH₂Cl₂, 71%. PPTS = pyridinium *p*-toluenesulfonate.

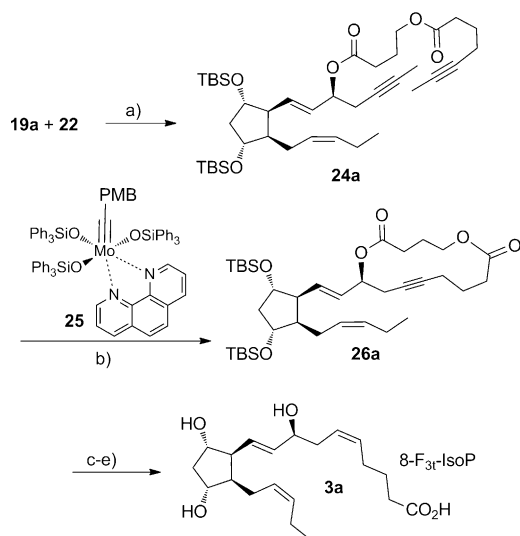
Therefore, ethylether protection of **10a** was necessary and accomplished under standard conditions in 77% yield, followed by treatment with LDA and MeI in THF/1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) to access compound **21a** in 71% yield. Deprotection under mild acidic conditions afforded **19a**



Scheme 8. a) LDA, MeI, DMPU, -78°C , 97%; b) 1,4-butan-diol, *p*-TsOH, heptane, reflux, 91%; c) oxalyl chloride, DMSO, Et₃N, CH₂Cl₂, $-78\rightarrow 0^{\circ}\text{C}$, 98%; d) NaClO₂, 2-methyl butene, KHPO₄, 78%.

in good yield (71%). This compound was ready for coupling with the appropriate appendage **22**, which was prepared by a four-step sequence (Scheme 8). Specifically, hexynoic acid was treated with LDA followed by MeI in THF/1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) to access the corresponding hept-5-ynoic acid in 97% yield. Esterification with 1,4-butane 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 NaClO₂ 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



Scheme 9. a) EDCI, DMAP, CH₂Cl₂, 95% b) **25** (10 mol%), MS 5 Å, toluene, $80^{\circ}\text{C}\rightarrow\text{RT}$; 69% c) P2-Ni, EDA, EtOH, H₂, RT; d) HCl (0.5 M), MeOH/THF; RT; e) LiOH (0.5 M), H₂O, RT, 75% (over two steps).

the presence of MnCl₂ and MS 5 Å in toluene at 80°C delivered the desired 14-membered ring bislactone **26a**. The stereoselective *Z* reduction of **26a** was performed by P2-Ni in the presence of EDA with complete regio- and chemoselectivity. Further treatment with HCl (0.5 M) led to the clean 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_{3t}-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_{4t}-NeuroP **1** and 8-F_{3t}-IsoP **3** together with their epimers and the novel tetra-deuterated derivative [D₄]-10-F_{4t}-NeuroP **2** have been obtained, (the latter will serve as internal standard for the accurate quantification of 10-F_{4t}-NeuroP in vivo). While a classical Carosuto-type reaction allowed for the synthesis of F₄-NeuroP **1**, the powerful RCAM/semi-reduction strategy gave access to F₃-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-Dihydropyran (12.35 mL, 243 mmol, 1.2 equiv) diluted in CH₂Cl₂ (20 mL) was added dropwise at room temperature to a solution of the 4-pentynol (10 g, 119 mmol, 1 equiv) and *p*-toluene sulfonic acid (565 mg, 2.9 mmol, 0.025 equiv) in CH₂Cl₂ (120 mL). The mixture was stirred all the night and then a saturated solution of NaHCO₃ 150 mL was added. The mixture was stirred for 15 min and then the layers were separated. The aqueous layer was extracted with 2×200 mL of Et₂O. The combined organic layers were washed with 100 mL of a saturated solution of NaHCO₃ and 2×100 mL of brine, dried over MgSO₄, filtered and the solvents removed under reduced pressure. The crude of the reaction was purified under silica gel chromatography (95:5 pentane/Et₂O) and the protected alcohol (18.9 g, 95%) was obtained. *R*_f=0.5 (8:2 cyclohexane/AcOEt); ¹H NMR (300 MHz, CDCl₃): δ=4.54 (lt, ³J(H,H)=3.5 Hz, 1H); 3.84–3.73 (m, 2H); 3.48–3.38 (m, 2H); 2.24 (dt, ³J(H,H)=4.2, 11.2 Hz, 2H); 1.88 (t, ³J(H,H)=2.7 Hz, 1H); 1.78 (quint, ³J(H,H)=5.1 Hz, 2H); 1.71–1.73 ppm (m, 6H); ¹³C NMR (75 MHz, CDCl₃): δ=98.6 (CH(O-)₂); 83.8 (C≡); 68.3 (HC≡); 65.4 (CH₂O); 62.0 (CH₂O); 30.5 (CH₂); 28.6 (CH₂); 25.4 (CH₂); 19.4 (CH₂); 15.2 ppm (CH₂).

At room temperature, a commercial solution of methyl magnesium bromide (3 M in Et₂O, 42 mL, 127 mmol, 2.0 equiv) was added dropwise in a solution of alkyne (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 Et₂O (200 mL) and a saturated solution of NaHCO₃ (100 mL) were added dropwise. Celite (50 mL) was added and the mixture was filtered. The solid was washed with Et₂O (4×100 mL). The layers were separated. The aqueous one was extracted with 2×100 mL of Et₂O. The combined organic layers were washed with 2×100 mL of brine and a saturated solution of NaHCO₃ (50 mL), dried over MgSO₄, 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/Et₂O) and the alcohol (9.65 g, 79%) was obtained. *R*_f=0.5 (5:5 cyclohexane/AcOEt); ¹H NMR (300 MHz, CDCl₃): δ=4.55 (t, ³J(H,H)=3.4 Hz, 1H); 4.17 (dt, ³J(H,H)=2.1, 5.9 Hz, 2H); 3.82–3.73 (m, 2H); 3.48–3.39 (m, 2H); 2.46 (t, ³J(H,H)=5.8 Hz, 1H); 2.8 (tt, ³J(H,H)=5.8, 7.2 Hz, 2H); 1.74 (quint, ³J(H,H)=6.8 Hz, 2H); 1.67–1.45 ppm (m, 6H); ¹³C NMR (75 MHz, CDCl₃): δ=98.7 (CH(O-)₂); 85.4 (C≡); 78.8 (C≡); 65.8 (CH₂O); 62.1 (CH₂O); 51.0 (CH₂O); 30.5 (CH₂); 28.6 (CH₂); 25.3 (CH₂); 19.4 (CH₂); 15.6 ppm (CH₂).

A solution of CBr_4 (19.4 g, 58.5 mmol, 1.5 equiv) in CH_2Br_2 (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 CH_2Br_2 (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 $\text{Na}_2\text{S}_2\text{O}_3$ (100 mL) and a saturated solution of NaHCO_3 (100 mL). The layers separated. The aqueous layer was then extracted with CH_2Cl_2 (3×250 mL) and the combined organic layers were extracted with $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL) and brine (20 mL), and finally dried over MgSO_4 , filtered and the solvents removed in vacuo. The crude was diluted in a mixture of pentane/ Et_2O 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/ Et_2O) and protected alcohol (4.2 g, 41%) was obtained. $R_f=0.7$ (5:5 cyclohexane/ AcOEt); $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta=4.56$ (t, $^3J(\text{H,H})=2.8$ Hz, 1 H); 3.88 (t, $^3J(\text{H,H})=2.3$ Hz, 2 H); 3.82–3.75 (m, 2 H); 3.49–3.41 (m, 2 H); 2.36–2.30 (m, 2 H); 1.76 (quint, $^3J(\text{H,H})=6.5$ Hz, 2 H); 1.68–1.46 ppm (m, 6 H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta=98.7$ ($\text{CH}(\text{O}-)$); 87.4 ($\text{C}\equiv$); 75.5 ($\text{C}\equiv$); 65.7 (CH_2O); 62.1 (CH_2O); 30.6 (CH_2); 28.5 (CH_2); 25.4 (CH_2); 19.4 (CH_2); 15.8 (CH_2); 15.5 ppm (CH_2O).

A Jones' solution (2.17 M, 37 mL, 80 mmol, 5.0 equiv) was added dropwise at 0°C to a solution of protected alcohol (4.2 g, 16 mmol, 1.0 equiv) in acetone (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/ Et_2O 1:1 (3×500 mL). The organic layer was washed with 4×250 mL of acidified brine, dried over MgSO_4 , filtered and the solvents removed under reduced pressure. The crude was diluted in anhydrous MeOH (65 mL) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (510 μL , 4 mmol, 0.25 equiv) was added. The solution was refluxed for 1 h and then a saturated solution of NaHCO_3 (250 mL) was added. The mixture was extracted with 3×250 mL of pentane/ Et_2O 1:1. The organic layers were washed with 3×100 mL of brine, dried over MgSO_4 , filtered and the solvents removed. The crude of the reaction was purified under silica gel chromatography (95:5 pentane/ Et_2O) and **15** (2.65 g, 80%) was obtained. $R_f=0.5$ (8:2 cyclohexane/ AcOEt); IR (neat): $\tilde{\nu}=1733$ cm^{-1} ($\text{C}=\text{O}$); $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta=3.85$ (t, $^3J(\text{H,H})=2.1$ Hz, 2 H); 3.65 (s, 3 H); 2.56–2.49 ppm (m, 4 H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta=172.0$ (C quat); 85.7 (C quat); 76.0 (C quat); 51.7 (CH_3); 32.9 (CH_2); 15.0 (CH_2); 14.8 ppm (CH_2); HRMS (ESI $^+$): m/z : calcd for $\text{C}_7\text{H}_{10}\text{O}_{2\text{Br}}$: 204.9864 [$M+\text{H}$] $^+$; found: 204.9866.

(*S,E*)-Methyl 12-((1*S*,2*R*,3*R*,5*S*)-3,5-bis(*tert*-butyldimethylsilyloxy)-2-[(*Z*)-pent-2-enyl]cyclopentyl)-10-(*tert*-butyldimethylsilyloxy)dodeca-11-en-4,7-diyne (16a)

CsCO_3 (120 mg, 0.28 mmol, 3 equiv), NaI (55 mg, 0.38 mmol, 3 equiv) and CuI (58 mg, 0.31 mmol, 2.5 equiv) were added successively at room temperature to a solution of **13a** (75 mg, 0.12 mmol, 1.0 equiv) and **15** (44 mg, 0.21 mmol, 1.75 equiv) in DMF (4 mL). The reaction was stirred for 2 days. A solution of NH_4Cl 10% (25 mL) and NH_4OH (0.5 mL) were then added. The mixture was extracted with 3×25 mL of Et_2O . The organic layers were washed with 2×25 mL of brine, dried over MgSO_4 , filtered and the solvents removed. The crude of the reaction was purified under silica gel (30 nm, spherical) with pentane/ Et_2O (98:3 in presence of butylated hydroxytoluene (BHT)) and **13a** was obtained (46 mg, 56%) in the presence of allene. $R_f=0.4$ (8:2 cyclohexane/ AcOEt); $^1\text{H NMR}$ (300 MHz, CDCl_3): $\delta=5.55$ – 5.45 (m, 2 H); 5.36– 5.27 (m, 2 H); 4.18 (q, $^3J(\text{H,H})=5.9$ Hz, 1 H); 3.88 (dt, $^3J(\text{H,H})=4.3$, 6.9 Hz, 1 H); 3.79 (q, $^3J(\text{H,H})=6.9$ Hz, 1 H); 3.67 (s, 3 H); 3.06 (t, $^3J(\text{H,H})=2$ Hz, 2 H); 2.64– 2.53 (m, 1 H); 2.52– 2.42 (m, 4 H); 2.38– 2.21 (m, 3 H);

2.10– 1.86 (m, 5 H); 1.50 (dt, $^3J(\text{H,H})=5.0$, $^2J(\text{H,H})=13.7$ Hz, 1 H), 0.93 (t, $^3J(\text{H,H})=7.5$ Hz, 3 H); 0.88 (s, 9 H); 0.86 (s, 9 H); 0.84 (s, 9 H); 0.07 (s, 3 H); 0.03 (s, 3 H); 0.01– -0.01 ppm (12 H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3): $\delta=173.0$ (C quat); 133.0 (CH); 132.0 (CH); 129.1 (CH); 127.8 (CH); 78.3 (C quat); 77.7 (C quat); 76.0 (CHO-); 75.9 (CHO-); 75.6 (C quat); 75.5 (C quat); 72.1 (CHO-); 52.1 (CH); 51.6 (OCH $_3$); 50.0 (CH); 44.2 (CH $_2$); 33.3 (CH $_2$); 30.3 (CH $_2$); 28.9 (CH $_2$); 26.0 (CH $_2$); 25.8 (CH $_3$); 20.6 (CH $_2$); 18.1 (C quat); 17.9 (C quat); 14.6 (CH $_3$); 9.7 (CH $_2$); -4.5 (CH $_3$); -4.6 (CH $_3$); -4.8 ppm (CH $_2$).

(*S*,4*Z*,7*Z*,11*E*)-Methyl 12-((1*S*,2*R*,3*R*,5*S*)-3,5-bis(*tert*-butyldimethylsilyloxy)-2-[(*Z*)-pent-2-enyl]cyclopentyl)-10-(*tert*-butyldimethylsilyloxy)dodeca-4,7,11-trienoate (17a)

NaBH_4 in ethanol (0.5 M, 139 μL , 0.07 mmol, 0.6 equiv) was added to a suspension of $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (9.6 mg, 0.04 mmol, 0.33 equiv), in ethanol with 0.01% BHT (3 mL) under a H_2 atmosphere. The ethylenediamine in solution in ethanol, (0.5 M, 348 μL , 0.17 mmol, 1.5 equiv) was added after 10 min under the black suspension. After a further 10 min, skipped diyne **16a** (85 mg, 0.13 mmol, 1.0 equiv) in ethanol with 0.01% BHT (4 mL) was added. Before and after each addition, three cycles of vacuum/ H_2 were realized. The reaction was then stirred for 4 h under a H_2 atmosphere (GC control). The mixture was then quenched with 20 mL of a saturated solution of NH_4Cl and stirred for 30 min. The layers were extracted with pentane/ Et_2O 1:1 (3×25 mL). The combined organic layers were washed with water (10 mL), brine (2×10 mL) and dried over MgSO_4 . The resulting mixture was then filtered and the solvents were removed in vacuo. Compound **17a** with allene, over-reduction byproducts and some solvents traces (98 mg) was obtained and used directly. $R_f=0.4$ (9:1 cyclohexane/ AcOEt).

10-F $_4$ -NeuroP (1a)

At room temperature, a solution of HCl (0.5 M in MeOH, 2.32 mL, 1.16 mmol, 10 equiv) was added to the crude of **17a** (0.12 mmol, 1.0 equiv) in MeOH/THF (10:16 mL). The mixture was stirred for 2 h and NaHCO_3 solid was added. After 15 min, Celite was added and the crude was filtered on Silica gel pad with AcOEt . The deprotected crude was directly used. The solution of crude (0.12 mmol) in THF (5.8 mL) was stirred for 2 h with LiOH (0.5 M in H_2O , 5.8 mL, 2.4 mmol, 25 equiv). The base was neutralized with a solution of NaHSO_4 (1 M in H_2O , 2.4 mL, 2.4 mmol, 25 equiv) and NaCl solid was added. The mixture was stirred for a further 2 h. The crude was extracted with AcOEt (3×20 mL). The organic layers were washed with 2×10 mL of brine, dried over MgSO_4 , filtered and the solvents removed. The crude was purified by flash chromatography (98:2 $\text{AcOEt}/\text{HCO}_2\text{H}$). To eliminate over-reduction products and allene, the mixture was purified by semi-preparative HPLC (250×8 mm C18 column, 2.5 mL min^{-1} (ACN/MeOH 95:5 with 0.1% HCO_2H)/ H_2O with 0.1% HCO_2H 35:65, $\lambda=205$ nm): a total of 21.4 mg, 48% of 10-F $_4$ -NeuroP (**1a**) was collected. $t_r=27.5$ min (250×4 mm C18 Nucleodur, 0.4 mL min^{-1} , (ACN/MeOH 95:5 with 0.1% HCO_2H)/ H_2O with 0.1% HCO_2H 35:65, $\lambda=205$ nm); $[\alpha]_D^{20}=-6$ ($c=1$ in MeOH); $^1\text{H NMR}$ (300 MHz, MeOD): $\delta=5.60$ – 5.57 (m, 2 H); 5.47– 5.41 (m, 6 H); 4.1 (q, $^3J(\text{H,H})=5$ Hz, 1 H); 4.0 (dt, $^3J(\text{H,H})=2.3$, 7.0 Hz, 1 H); 3.91– 3.87 (m, 1 H); 2.87 (t, $^3J(\text{H,H})=4.5$ Hz, 2 H); 2.76– 2.69 (m, 1 H); 2.50 (dt, $^3J(\text{H,H})=7.1$, $^2J(\text{H,H})=14.2$ Hz, 1 H); 2.44– 2.29 (m, 6 H); 2.16– 2.04 (m, 5 H); 1.56 (dt, $^3J(\text{H,H})=4.9$, $^2J(\text{H,H})=14.2$ Hz, 1 H); 0.99 ppm (t, $^3J(\text{H,H})=7.4$ Hz, 3 H); $^{13}\text{C NMR}$ (75 MHz, MeOD): $\delta=177.2$ (C quat.); 133.0 (CH); 130.3 (CH); 127.7 (CH); 127.2 (CH); 127.1 (CH); 126.3 (CH); 125.8 (CH); 123.9 (CH); 73.2 ($2 \times \text{HCOH}$); 70.2 (HCOH); 50.5 (CH); 48.5 (CH); 40.7 (CH $_2$); 33.4 (CH $_2$); 24.2 ($2 \times$

CH₂); 23.8 (CH₂); 21.1 (CH₂); 18.7 (CH₂); 11.7 ppm (CH₃); HRMS (ESI⁺): *m/z*: calcd for C₂₂H₃₄O₅Na: 401.2304 [*M*+Na]⁺; found: 401.2308.

(*S,E*)-10-((1*S*,2*R*,3*R*,5*S*)-3,5-Bis(*tert*-butyldimethylsilyl)-2-[(*Z*)-pent-2-enyl]cyclopentyl)-8-(4-hydroxybutanoyloxy)dec-9-en-5-ynoate (26a)

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 azeotropic evaporation with toluene. Catalyst **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, 0.27 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 (97:3 to 90:10, pentane/Et₂O). Compound **26a** was obtained as a colourless syrup (126 mg, 69% with traces of silanol impurities). *R*_f=0.21 (9:1 cyclohexane/AcOEt); ¹H NMR (400 MHz, CDCl₃): δ=5.64 (dd, ³*J*(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, 7H); 1.74–1.65 (m, 1H); 1.53 (dt, ³*J*(H,H)=5.5, ²*J*(H,H)=13.6 Hz, 1H); 0.96 (t, ³*J*(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); 132.2 (CH); 129.2 (CH); 127.7 (CH); 79.8 (C≡); 78.0 (C≡); 75.8 (HCO–); 75.5 (HCO–); 73.3 (HCO–); 63.9 (H₂CO–); 52.2 (CH); 50.6 (CH); 44.2 (CH₂); 31.9 (CH₂); 31.6 (CH₂); 26.0 (CH₂); 25.8 (CH₃); 25.1 (CH₂); 23.3 (CH₂); 22.1 (CH₂); 20.6 (CH₂); 18.0 (CH₂); 17.9 (C quat); 17.6 (C quat); 14.2 (CH₃); –4.4 (CH₃); –4.5 (CH₃); –4.6 (CH₃); –4.7 ppm (CH₃); HRMS (ESI⁺): *m/z*: calcd for C₃₆H₆₃O₆Si₂: 647.4163 [*M*+H]⁺; found: 647.4154.

(*R,E*)-10-((1*S*,2*R*,3*R*,5*S*)-3,5-Bis(*tert*-butyldimethylsilyl)-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%). *R*_f=0.21 (9/1: cyclohexane/AcOEt); ¹H NMR (400 MHz, CDCl₃): δ=5.61 (dd, ³*J*(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, 1H); 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, ³*J*(H,H)=5.5, ²*J*(H,H)=13.6 Hz, 1H); 0.95 (t, ³*J*(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 (CH); 79.8 (C≡); 78.0 (C≡); 75.7 (HCO–); 75.5 (HCO–); 73.2 (HCO–); 63.8 (H₂CO–); 52.3 (CH); 50.5 (CH); 44.2 (CH₂); 32.0 (CH₂); 31.7 (CH₂); 26.1 (CH₂); 25.8 (CH₃); 25.2 (CH₂); 23.3 (CH₂); 22.2 (CH₂); 20.7 (CH₂); 18.0 (CH₂); 17.9 (2×C quat); 14.2 (CH₃); –4.4 (CH₃); –4.6 (2×CH₃); –4.7 ppm (CH₃); HRMS (ESI⁺): calcd for C₃₆H₆₃O₆Si₂: 647.4163 [*M*+H]⁺; found: 647.4146.

8-F_{3c}-IsoP (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 reaction 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/Et₂O) to obtain the ethylenic compound (88.3 mg, 70%). *R*_f=0.29 (9:1 cyclohexane/AcOEt); [*α*]_D²⁰=–50.5 (*c*=10 in CHCl₃); *ν*=1737 cm^{–1} (C=O); ¹H NMR (400 MHz, CDCl₃): δ=5.58–5.56 (m, 2H); 5.45–5.27 (m, 5H); 4.20 (dt, ³*J*(H,H)=4.4; ²*J*(H,H)=11 Hz, 1H); 4.03 (dt, ³*J*(H,H)=3.6; ²*J*(H,H)=11 Hz, 1H); 3.93–3.89 (m, 1H); 3.81 (q, ³*J*(H,H)=5.6 Hz, 1H); 2.69–2.65 (m, 1H); 2.54 (ddd, ³*J*(H,H)=4.4, 11.3, 15.6 Hz, 1H); 2.48–2.25 (m, 6H); 2.12–1.88 (m, 9H); 1.79 (quint., ³*J*(H,H)=5.6 Hz, 1H); 1.54 (dt, ³*J*(H,H)=5.5, ²*J*(H,H)=13.7 Hz, 1H); 0.96 (t, ³*J*(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=173.7 (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 (H₂CO–); 52.4 (CH); 50.5 (CH); 44.2 (CH₂); 33.7 (CH₂); 32.8 (CH₂); 30.3 (CH₂); 26.4 (CH₂); 26.1 (CH₂); 25.8 (CH₃); 24.9 (CH₂); 23.3 (CH₂); 20.6 (CH₂); 18.0 (C quat); 17.9 (C quat); 14.2 (CH₃); –4.4 (CH₃); –4.5 (CH₃); –4.6 (CH₃); –4.7 ppm (CH₃); HRMS (ESI⁺): *m/z*: calcd for C₃₆H₆₅O₆Si₂: 649.4320 [*M*+H]⁺; found: 649.4333.

At room temperature, a HCl solution (0.5 M in MeOH, 2.46 mL, 1.23 mmol, 10 equiv) was added to a solution of protected compound (83 mg, 0.12 mmol, 1.0 equiv) in THF/MeOH (17:9 mL). The reaction was stirred for 2 h and NaHCO₃ powder was added. After 5 min of agitation, Celite was added and the solvent was evaporated. The crude of the reaction was purified by flash chromatography (95:5 to 90:10 pentane/Et₂O) to give free hydroxyl compound (44 mg, 84%). *R*_f=0.3 (AcOEt); [*α*]_D²⁰=–51.9 (*c*=10 in CHCl₃); IR *ν*=3389 (OH); 1732 cm^{–1} (C=O); ¹H NMR (400 MHz, CDCl₃): δ=5.61 (dd, ³*J*(H,H)=6.4, ²*J*(H,H)=16 Hz, 1H); 5.53 (dd, ³*J*(H,H)=8.8, ²*J*(H,H)=16 Hz, 1H); 5.45–5.31 (m, 5H); 4.19 (dt, ³*J*(H,H)=3.6; ²*J*(H,H)=11.2 Hz, 1H); 4.07–3.95 (m, 3H); 2.81–2.76 (m, 1H); 2.54 (ddd, ³*J*(H,H)=4.5, 11.1, 15.5 Hz, 1H); 2.46–2.37 (m, 4H); 3.31–2.24 (m, 2H); 2.21–2.16 (m, 1H); 2.12–1.90 (m, 8H); 1.78 (quint, ³*J*(H,H)=6.7 Hz, 2H); 1.66 (dt, ³*J*(H,H)=3.6, ²*J*(H,H)=14.4 Hz, 1H); 0.96 ppm (t, ³*J*(H,H)=7.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ=173.7 (C=O); 172.2 (C=O); 133.1 (CH); 132.0 (CH); 131.2 (CH); 130.5 (CH); 127.2 (CH); 124.6 (CH); 76.4 (HCOH); 76.2 (HCOH); 73.6 (HCO–); 62.2 (H₂CO–); 53.6 (CH); 50.9 (CH); 42.3 (CH₂); 33.6 (CH₂); 32.8 (CH₂); 30.4 (CH₂); 26.9 (CH₂); 26.4 (CH₂); 24.7 (CH₃); 23.4 (CH₂); 20.7 (CH₂); 14.2 ppm (CH₃); HRMS (ESI⁺): *m/z*: calcd for C₂₄H₃₇O₆: 421.2590 [*M*+H]⁺; found: 421.2588.

At room temperature, a solution of LiOH (0.5 M, 5 mL, 2.5 mmol, 2.5 equiv) was added to a solution of lactone (44 mg, 0.1 mmol, 1.0 equiv) in THF (5 mL). The reaction was stirred 4 h and was acidified with a solution of NaHSO₄ (1 M) until pH 2 was reached. The mixture was extracted with 3×20 mL of AcOEt. The combined organic layers were washed with brine (2×10 mL) and dried over MgSO₄, filtered and the solvents were removed. The crude of the reaction was purified by flash chromatography (100:0 to 98:2 AcOEt/HCO₂H) to obtain **3a** (34.8 mg, 94%). *R*_f=0.27 (AcOEt/HCO₂H 95:5); [*α*]_D²⁰=–8.0 (*c*=5 in MeOH); ¹H NMR (300 MHz, MeOD): δ=5.59–5.57 (m, 2H); 5.51–5.45 (m, 2H); 5.43–5.40 (m, 2H); 4.09 (q, ³*J*(H,H)=6.4 Hz, 1H); 4.03–3.97 (m, 1H); 3.91–3.87 (m, 1H); 2.74–2.69 (m, 1H); 2.50 (dt, ³*J*(H,H)=7.4, ²*J*(H,H)=14.2 Hz, 1H); 2.35–2.29 (m, 4H); 2.17–2.06 (m, 7H); 1.69 (quint., ³*J*(H,H)=7.3 Hz, 1H); 1.56 (dt, ³*J*(H,H)=4.9, ²*J*(H,H)=14.2 Hz, 1H); 0.99 ppm

(t , $^3\text{J}(\text{H,H}) = 7.5 \text{ Hz}$, 3H); ^{13}C NMR (75 MHz, MeOD): $\delta = 175.0$ (C=O); 133.0 (CH); 130.3 (CH); 128.7 (CH); 127.2 (CH); 125.8 (CH); 124.5 (CH); 73.2 (2 x HCOH); 70.3 (HCOH); 50.5 (CH); 48.5 (CH); 40.6 (CH₂); 33.4 (CH₂); 31.7 (CH₂); 24.7 (CH₃); 24.2 (CH₂); 23.1 (CH₂); 18.7 (CH₂); 11.7 ppm (CH₃); HRMS (ESI⁺): m/z : calcd for C₂₀H₃₂O₅: 375.2147 [M+Na]⁺; found: 375.2150.

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