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Synthesis of Aromatic Analogs of 8(*S*)-HETE and Their Biological Evaluation as Activators of the PPAR Nuclear Receptors

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A new family of 8-HETE analogs has been synthesized as dual PPAR α and γ agonists. A versatile strategy has been developed to allow modulations not only around the aromatic core but also on the side chains of these analogs. The affinity of these compounds towards the PPARα and PPARγ receptors is reported, together with their transactivation percentage. The derivatives having a propargylic type side chain gave the most promising results as dual agonists.

Introduction

The peroxisome proliferator activated receptors (PPARs) have been discovered in 1990 by I. Issemann and S. Green.[1] They are a subfamily of nuclear receptors also comprising steroid-, thyroid-, retinoic acid-, and vitamin D_3 receptors. These nuclear receptors have three subtypes: PPARα, PPARβ (or PPARδ), and PPARγ.[2] The first one, PPARα, regulates the expression of numerous genes involved in lipid uptake, catabolism, and homeostasis. The second, PPARβ, has an ubiquitous distribution and its role is not clearly defined yet. The last one, PPARγ, has been shown to regulate the expression of genes that mediate adipocyte differentiation, energy metabolism, and insulin action.[3]

Disorders of the lipid metabolism are a major threat to human health, leading to obesity, atherosclerosis, cardiovascular disease, insulin resistance, and type 2 diabetes. PPARγ is the predominant molecular target for the insulin-sensitizing thiazolidinedione drugs (TZDs) such as pioglitazone and rosiglitazone.[4] TZD derivatives activate PPARγ and improve insulin resistance by increasing the number of small adipocytes. PPARα is the molecular target for the fibrate class of lipid-modulating drugs.[5] Considering the potential benefits of fibrates in the treatment of coronary disease in diabetic patients,[6] the combined profile of dual PPARα/γ agonists would offer a very attractive option. Such compounds could add a hypolipidemic effect, by the activation of subtype α,[7] to an improvement of insulin sensitivity by activation of subtype γ.[8] Another interesting aspect of PPARα/γ coactivation is the limitation of side effects observed in the actual treatment of diabetes mellitus by TZDs, such as increase in weight and/or edema. Therefore, a new focus for medicinal chemistry is to discover dual PPAR α/γ agonists, and several examples of active molecules have been reported recently in the literature. They have good to excellent affinities for the PPAR receptors, but in most cases the activity is higher on PPARγ than on subtype α.[9] Several years ago, we started a program in this field, and our goal was to develop a new family of dual PPAR α/γ agonists with a better activity on PPARα than on PPARγ.[10]

Many fatty acids and their corresponding metabolites are known to activate the PPAR receptors.[11] Among them, the 8(*S*)-HETE appears to be a very attractive molecule, because it has an excellent activity on subtype α (EC_{50} = 100 nM), together with some activity on subtype γ.[12] Furthermore, the 8(*R*) enantiomer was found to be inactive.[13] On the basis of these data, we designed as our target molecules various carbo- and heterocyclic analogs of the 8(*S*)-HETE, as indicated in Figure 1.

The conjugated *E*,*Z* diene was first replaced by an aromatic or a heteroaromatic core, linking carbons 9 and 14. Simultaneously, the sp^2 carbon at position 15 was replaced by an oxygen atom. These modulations, classical in the area of fatty acid metabolites, lead to analogs which are more stable than the polyunsaturated natural products.[14] In this first structure–activity relationship (SAR) study, we have kept the three-carbon-atom chain between the acid and the unsaturation at position 5 and we have also maintained the

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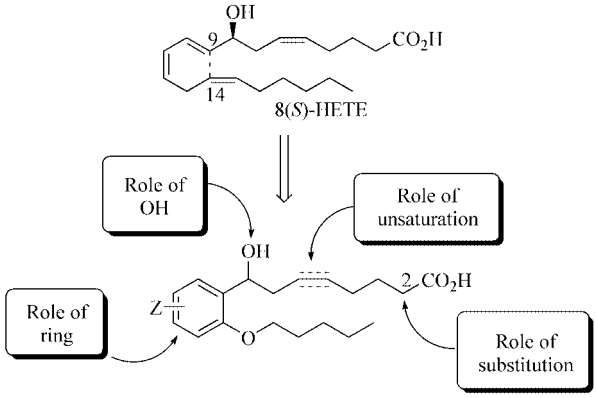


Figure 1. Design of target molecules.

five-carbon terminal chain (C_{16} to C_{20}) which exists in the 8-HETE. Therefore, the main variations that we have considered in this series of molecules dealt with four key aspects:

(1) What is the effect of the nature of the aromatic (benzene, naphthalene) or heteroaromatic ring (pyridine) on the activation of the PPAR nuclear receptors?

(2) What could be the role of the alcohol function at position 8? Does the absolute configuration at this stereocenter have any effect? Is it possible to replace the OH group by a methoxy group or a hydrogen atom?

(3) What is the influence of the degree of unsaturation (triple bond, double bond, or single bond) on carbons 5 and 6?

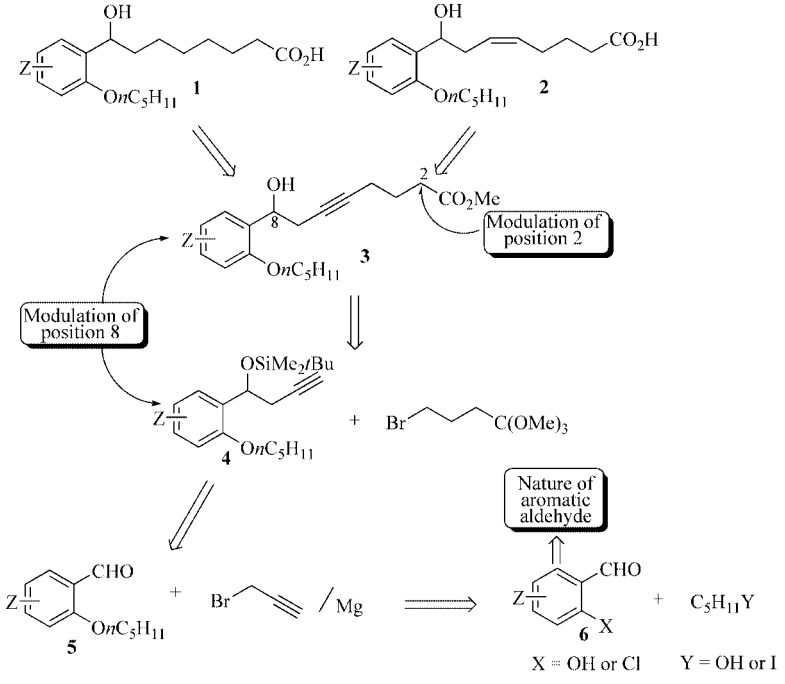
(4) Most of the synthetic compounds, which are presently developed as PPAR activators have substituents at position 2, close to the acid function (or some bioisostere of it). Therefore, the effect of methyl groups at position 2 has also been studied.

The purpose of this publication is to report our studies dealing with the synthesis and biological evaluation of all these 8-HETE analogs.

Results and Discussion

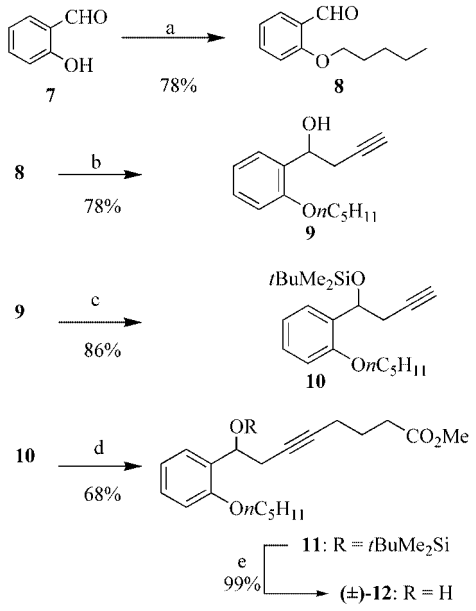
Our retrosynthesis is given in Scheme 1. The propargylic derivatives **3** were considered as the key intermediates since they should afford easily either the *Z* alkenes **2** or the saturated compounds **1**. Furthermore, the modulations at positions 2 and 8 could be performed starting from **3**. The latter derivatives should be obtained by alkylation, with trimethyl 4-bromoorthobutyrate, of the intermediates **4**. These homopropargylic derivatives could be prepared by Grignard additions on aldehydes **5**, which are easily obtained from compounds **6**. In our target molecules, the modulations of the aromatic system are obtained by changing the nature of the starting aldehyde **6**, and in this paper we will consider three basic skeletons: benzene, naphthalene, and pyridine.

For the benzene-derived 8-HETE analogs, the preparation of the key intermediate **(±)-12** is reported in Scheme 2. The first step was a reaction between salicylaldehyde (**7**) and 1-iodopentane, affording **8** in 78% yield. The reaction of this aldehyde with the Grignard reagent prepared from propargyl bromide afforded, in 78% yield, the homopropargylic alcohol **9** which was then protected as the silyl ether **10**. The alkylation of this derivative by trimethyl 4-bromoorthobutyrate was performed at –80 °C to 0 °C, affording **11** in 68% yield. This reaction required a good control of temperature, since, above 0 °C, an elimination prod-



Scheme 1. Retrosynthetic analysis of the target molecules.

uct was also obtained. After cleavage of the silyl group, the key intermediate **(±)-12** was obtained in 35% overall yield from salicylaldehyde.

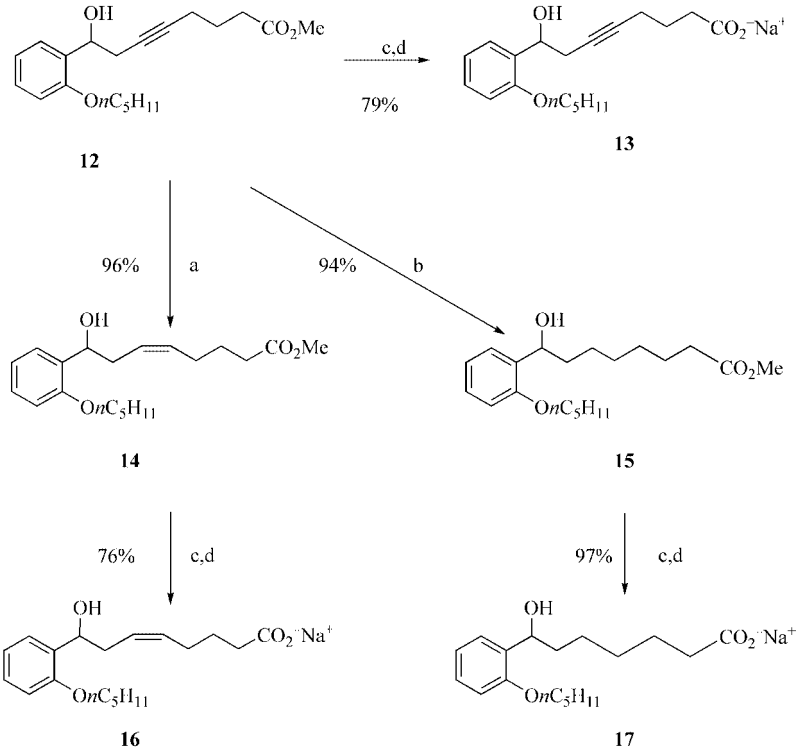


Scheme 2. Synthesis of the propargylic key intermediate **(±)-12**. (a) KOH, 1-iodopentane, EtOH/H_2O, 80 °C, 16 h; (b) propargyl bromide, Mg, Et_2O, –80 °C, 20 min; (c) *t*$BuMe_2SiCl$, imidazole, DMF, 0 °C to room temp., 24 h; (d) *n*BuLi/THF, –80 °C, $Br(CH_2)_3C(OMe)_3$/HMPA, –80 °C to 0 °C, aq. NH_4Cl (workup); (e) *n*Bu_4NF, THF, 45 °C, 3 h.

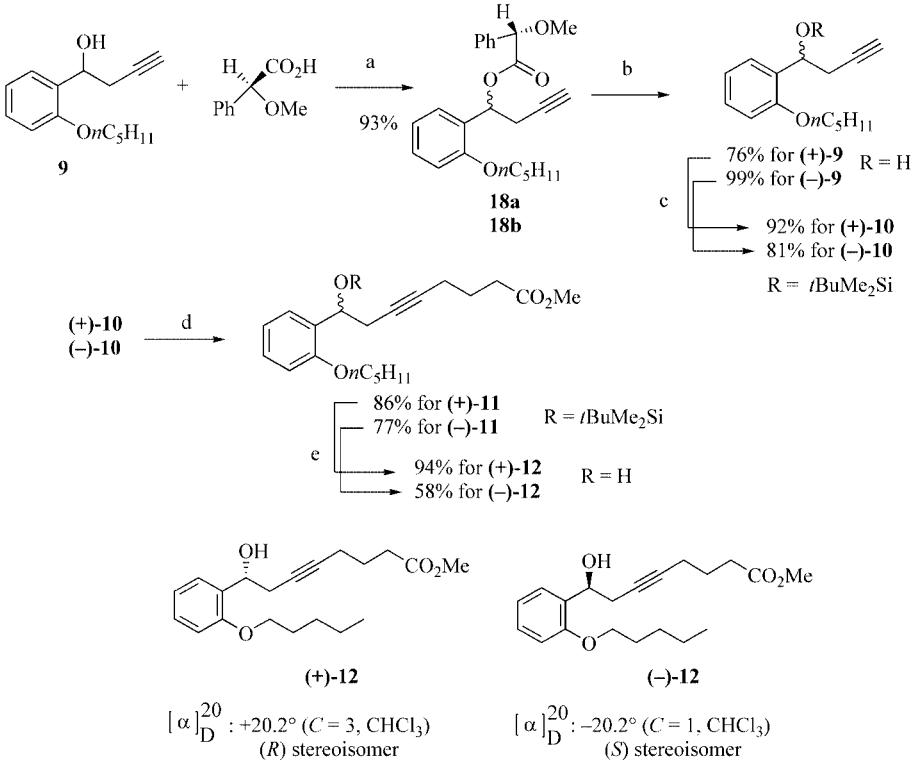
The first targeted 8-HETE analogs were obtained as indicated in Scheme 3. Starting from **12**, semihydrogenation with Ni/P_2 catalyst afforded the *Z* alkene **14**, while the saturated compound **15** was obtained by hydrogenation with palladium on activated charcoal. Saponification of the three methyl esters **12**, **14**, and **15** were performed under mild conditions by using lithium hydroxide. Then, acidification with oxalic acid gave the corresponding acids, which were easily purified by flash chromatography before transformation into the desired (hygroscopic) sodium salts **13**, **16**, and **17**.

The activity of these six compounds towards the PPAR receptors will be discussed in the last part of this paper. However, it is important to note that among the three series, the propargylic derivatives, such as **(±)-12**, gave the most promising preliminary results. For this reason, several modulations around the positions 2 and 8 were performed, starting from **(±)-12**.

It has been established that, in the case of the 8-HETEs, only the 8(*S*) enantiomer was efficient in the activation of the PPAR nuclear receptors. Therefore, it was of much interest to prepare both enantiomers of **12**. Towards this goal, a resolution strategy was followed, as indicated in Scheme 4. The reaction between homopropargylic alcohol **9** and *O*-methyl-L-mandelic acid afforded two diastereoisomers, **18a** and **18b**. which could be separated by chromatography on silica gel by gradient elution using a mixture of *tert*-butyl methyl ether and petroleum ether (from 1:99 to 5:95). The less polar compound **18a** was isolated in 39% yield while the more polar diastereoisomer **18b** was ob-



Scheme 3. Synthesis of the 8-HETE analogs **12**–**17** with a benzene core. (a) H_2, $Ni(OAc)_2$, $NaBH_4$, EtOH, 5 h; (b) Pd/C, H_2, MeOH; (c) LiOH, MeOH/H_2O; (d) $(CO_2H)_2$, then NaOH.

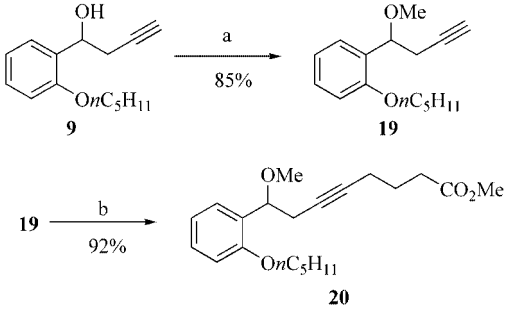


Scheme 4. Synthesis of the two enantiomers **(+)-12** and **(–)-12**. (a) DCC, DMAP, CH_2Cl_2, room temp., 30 min; then chromatographic separation; yields: 39% (less polar diastereoisomer **18a**) and 25% (more polar diastereoisomer **18b**); (b) KOH, MeOH, 0 °C, 2 h, then room temp., 1 h; (c) tBuMe$_2$SiCl, imidazole, DMF, 0 °C to room temp., 24 h; (d) nBuLi/THF, –80 °C, Br(CH$_2$)$_3$C(OMe)$_3$/HMPA, aq. NH_4Cl (workup); (e) nBu$_4$NF, THF, 45 °C, 3 h.

tained in 25% yield. After saponification of each pure diastereoisomeric ester, the two enantiomers **(+)-9** and **(–)-9** were obtained. Then, the same sequence of reactions as that for the racemic compound was performed on each enantiomer to obtain the two target enantiomers **(+)-12** and **(–)-12**. The absolute configuration at the carbinol center was assigned by ^{1}H NMR analysis of the esters **18a** and **18b**. It has been clearly established in the literature that, for this type of esters, the two hydrogen atoms vicinal to the carbinol center should be more shielded in the case of the (*R*,*S*) diastereoisomer, than in the case of the (*S*,*S*) derivative.[15] The chemical shifts were 2.72 ppm and 2.59 ppm in the case of **18a** and 2.81 ppm and 2.64 ppm for **18b**. Therefore, the (*R*) absolute configuration has been assigned to **18a** and consequently to the alcohol **(+)-12**.

The next modulations involved the modifications of the hydroxy group at position 8. It was first replaced by a methoxy group, as indicated in Scheme 5. The homopropargylic alcohol **9** was alkylated by dimethyl sulfate to afford **19** in 85% yield. The same reactions as described previously gave the desired product **20** in racemic form.

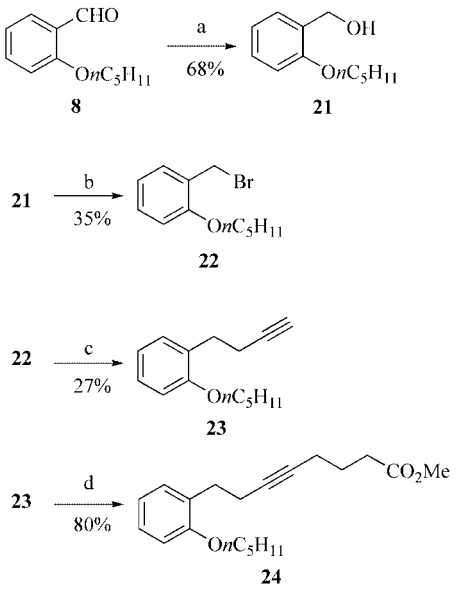
The next modification at this position involved the replacement of the OH by a hydrogen. The direct deoxygenation of **12** was an attractive strategy for that purpose. However, all our experiments in this direction failed, leading only to decomposition products. Therefore, an alternative route was designed, as indicated in Scheme 6. The benzyl bromide **22**, easily prepared in two steps from **8**, was



Scheme 5. Synthesis of the methoxy analog **20**. (a) NaH, Me_2SO_4, THF/DMF, 0 °C then room temp., 16 h; (b) nBuLi/THF, –80 °C to 0 °C, Br(CH$_2$)$_3$C(OMe)$_3$/HMPA, aq. NH_4Cl (workup).

coupled with propargyl bromide to give the deoxygenated intermediate **23**. The alkylation by trimethyl 4-bromoorthobutyrate afforded the target compound **24**. These reactions were not optimized and the yields were poor. However, enough material could be isolated to perform the desired biological tests.

Many of the drugs, already used or under development and involving an activation of the PPAR receptors, have one or two substituents vicinal to the acid group. Some representative examples are given in Scheme 7: They may have a *gem*-dimethyl group, such as in the widely used clofibrate and fenofibrate. Alternatively, new compounds have appeared more recently with alkoxy groups at position 2, such



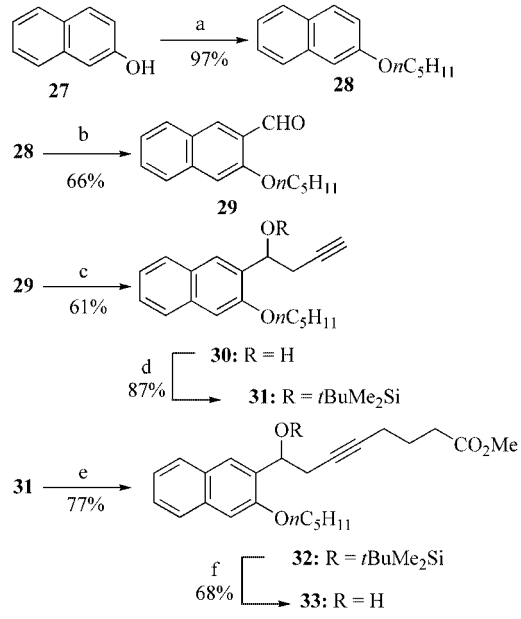
Scheme 6. Synthesis of the dehydroxylated analog **24**. (a) $NaBH_4$, EtOH/THF, room temp., 1 h; (b) PBr_3, pyridine, Et_2O, 0 °C, 1 h; (c) Propargyl bromide, Mg, CuI, Et_2O, –80 °C then room temp., 24 h; (d) *n*BuLi/THF, –80 °C to 0 °C, $Br(CH_2)_3C(OMe)_3$/HMPA, aq. NH_4Cl (workup).

as LY-510929 and Tesaglitazar. Such substituents have been shown to be important not only to improve the affinities towards the receptors but also to limit the degradation by β-oxidation. Therefore another model analog **26**, bearing two methyl groups at position 2, was prepared as indicated in Scheme 8.

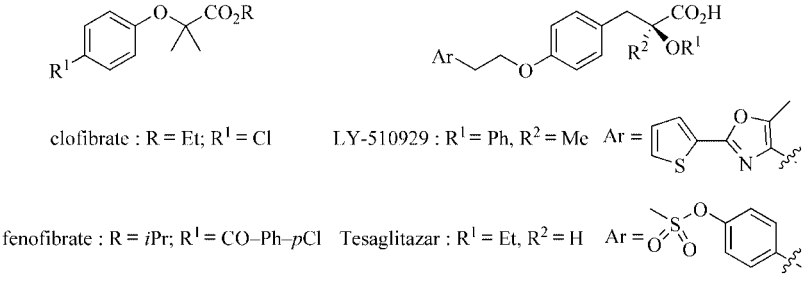
The alkylation of **11** with two equivalents of iodomethane gave **25** which, after deprotection, afforded the target molecule **26** in good yield.

After performing modulations on the "upper part" of our 8-HETE analogs, we have considered the modifications of the nature of the aromatic group. In these first SAR studies, we have considered naphthalene and pyridine derivatives. The quinoline derivatives are under active study and will be reported in a future publication.

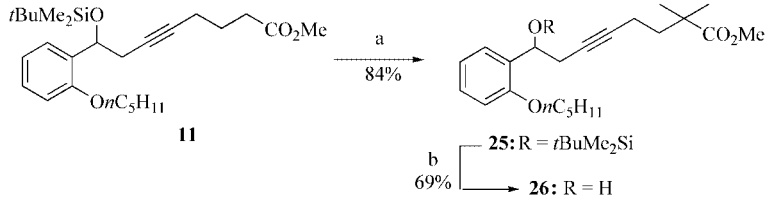
A similar strategy was followed for the preparation of the naphthalene-derived analogs. The synthesis of the key intermediate **33** is described in Scheme 9. The aldehyde **29** was obtained easily in two steps from 2-naphthol (**27**). The



Scheme 9. Synthesis of intermediates with a naphthalene core. (a) KOH, 1-iodopentane, EtOH/H_2O, 80 °C, 16 h; (b) *t*BuLi, THP, 0 °C then DMF room temp. 20 h; (c) propargyl bromide, Mg, Et_2O, –80 °C, 20 min; (d) $tBuMe_2SiCl$, imidazole, DMF, 0 °C to room temp., 24 h; (e) *n*BuLi/THF, –80 °C to 0 °C, $Br(CH_2)_3C(OMe)_3$/HMPA, aq. NH_4Cl (workup); (f) nBu_4NF, THF, 45 °C, 3 h.



Scheme 7. Examples of compounds with subsituents vicinal to the acid group.



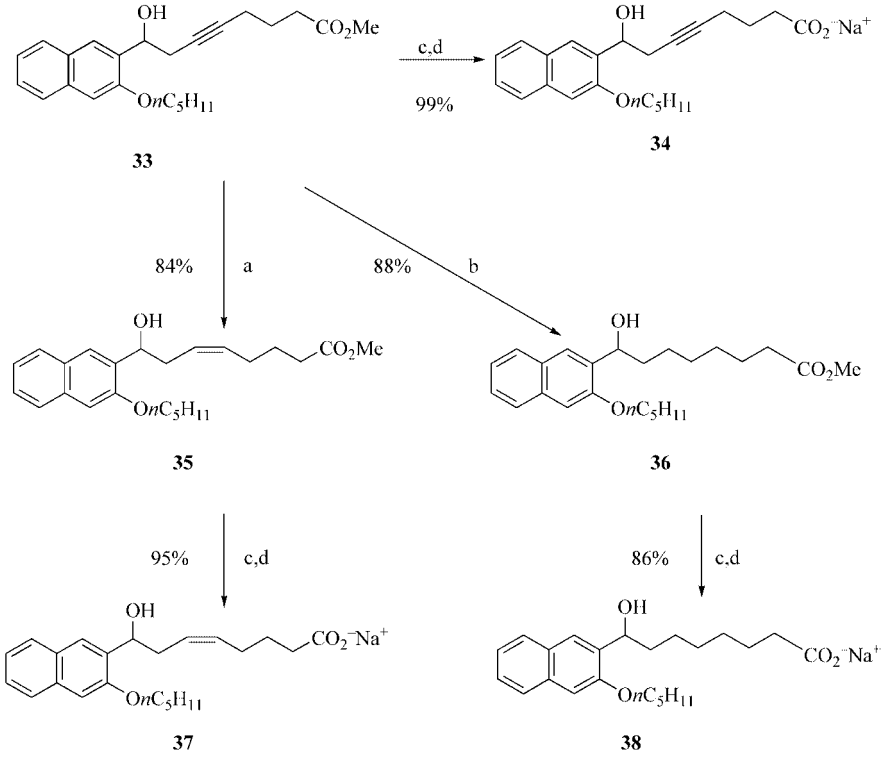
Scheme 8. Synthesis of the *gem*-dimethyl analog **26**. (a) MeI, LDA, THF, –80 °C then room temp., 3 h; (b) nBu_4NF, THF, 45 °C, 3 h.

O-alkylation by 1-iodopentane, followed by formylation with dimethylformamide, afforded **29** in 64% overall yield. The four next steps were identical to the reactions performed in the benzene series, and the intermediate **33** was obtained in 18% overall yield from **27**.

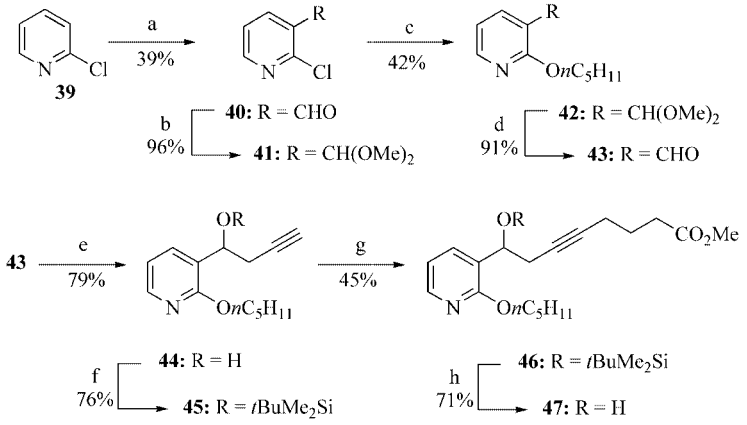
Starting from this propargylic intermediate, the target molecules with a naphthalene core (**34**–**38**) were prepared in good yields by the same sequence of reactions as before (Scheme 10).

The last series of analogs to be studied had a pyridine core and the synthesis of the key intermediate **47** is indicated in Scheme 11. The starting 2-chloro-3-pyridinecarboxaldehyde (**40**) was obtained by formylation of 2-chloropyridine (**39**).[16] After protection as the dimethyl acetal **41**, nucleophilic substitution by the pentyloxy group afforded **42**, and a final deprotection gave aldehyde **43**. The next four steps, allowing the introduction of the acid side chain, were identical to those of the benzene and naphthalene series.

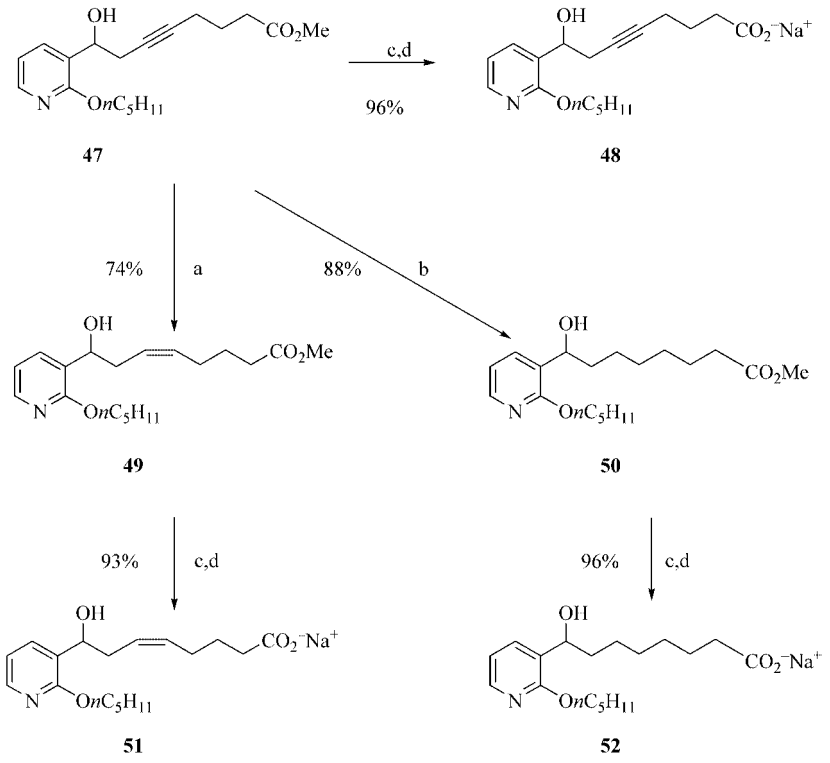
The six target molecules of the pyridine family were obtained from **47** by hydrogenation and saponification reactions in the same manner as previously described for the benzene series (Scheme 12). For these pyridine derivatives,



Scheme 10. Synthesis of 8-HETE analogs with a naphthalene core. (a) H_2, $Ni(OAc)_2$, $NaBH_4$, EtOH, 5 h; (b) Pd/C, H_2, MeOH; (c) LiOH, $MeOH/H_2O$; (d) $(CO_2H)_2$, then NaOH.



Scheme 11. Synthesis of the key intermediate with a pyridine core. (a) PhLi, iPr_2NH cat, –60 °C, then *N*-formylpiperidine, THF; (b) $HC(OMe)_3$ NH_4NO_3 cat, MeOH, reflux 2.5 h; (c) NaH, 1-pentyl alcohol, NMP, 0 °C to room temp. 16 h; (d) PTSA, THF/H_2O, reflux, 3 h; (e) propargyl bromide, Mg, Et_2O, –80 °C, 20 min; (f) $tBuMe_2SiCl$, imidazole, DMF, 0 °C to room temp., 24 h; (g) *n*BuLi/THF, –80 °C to 0 °C, $Br(CH_2)_3C(OMe)_3$/HMPA, aq. NH_4Cl (workup); (h) nBu_4NF, THF, 45 °C, 3 h.



Scheme 12. Synthesis of 8-HETE analogs with a pyridine core. (a) H_2, Lindlar Pd, MeOH; (b) Pd/C, H_2, MeOH; (c) LiOH, MeOH/H_2O; (d) $(CO_2H)_2$, then NaOH.

the semihydrogenation did not work with NiP_2 catalyst, and therefore we employed the classical conditions using Lindlar palladium.

Biological Studies on Human PPARγ and Human PPARα

The biological tests were performed on a chimera human PPAR/Gal_4 gene reporter luciferase system to determine the maximal transactivation response and the EC_{50} for each compound. The results are given in Table 1. Our goal was to obtain partial dual potent PPAR agonists with a better activity on PPARα than on PPARγ in order to reduce the PPARγ side effects. Therefore, our 8-HETE analogs were compared to the classical references, WY 14,643 for subtype α and rosiglitazone for PPARγ. We report here only the results for these two subtypes, but each product was also tested on PPARβ on which it showed no activity.

From the data given in Table 1, several interesting points emerged:

(1) The most important result is that the degree of unsaturation at the 5–6 position plays a key role: the propargylic derivatives [cf. **(±)-12**, **33**, and **47** for instance] always exhibited higher affinities than the corresponding *Z* alkenes, while the saturated compounds did not have any significant activity. More studies, including the preparation of other molecules, will be necessary in order to propose a tentative explanation for this point. However, this is a key result for the design of more potent derivatives.

(2) Except for **(±)-12**, there is no significant difference between the esters and the corresponding sodium salts.

(3) If we now consider the propargylic derivatives with a benzene core, several points can be noted. The alcohol function at C_8 is important: the transformation into a methoxy group (derivative **20**) or a hydrogen atom (compound **24**) induced a complete loss in activity. However, the control of the absolute configuration at this carbinol center afforded unexpected results. The racemic compound **(±)-12** had a good activity, mainly on PPARα. The (*R*) enantiomer **(+)-12** has maintained an important percentage of transactivation on hPPARα (99%), as compared with the (*S*) enantiomer **(–)-12** (28%). It also gave a low hPPARγ binding affinity (4.13 μM), as opposed to the lack of affinity in the case of **(–)-12**. The weak activity on PPARγ (14% transactivation) was similar for both enantiomers. At this stage, we have no clear explanation for these results. The addition of the two methyl groups at position 2 (compound **26**) also produced a derivative with a low activity.

(4) Finally, it appears that modulations of the nature of the aromatic core are possible: while the benzene derivative **(±)-12** had the highest activity towards PPARα (173 nM), together with a very partial activity towards PPARγ and a good affinity towards PPARγ (642 nM), the naphthalene derivative **33** and even more so the pyridine analog **47**, still retained affinities in the micromolar range together with significant activities on the two receptors in terms of the percentage of transactivation and EC_{50} values. These results

Table 1. In vitro activity of 8-HETE analogs in cell-based transactivation assay against human PPARα/Gal4 and PPARγ/Gal4 receptors and binding assay PPARγ ligand binding domain. (NA = not active).

Compounds	hPPARα/Gal_4		hPPARγ/ Gal_4		Binding Rosiglitazone hPPARγ
	EC_{50} [μM]	Transactivation [%][a]	EC_{50} [μM]	Transactivation [%][b]	K_i [nM]
Rosiglitazone	>10	15	4	100	8
WY 14,643	10	100	>10	15	NA
(±)-12	0.173	81	0.642	16	1050
13	>10	41	>10	32	>10 000
14	>10	20	0.028	24	3 760
15	>10	30	>10	42	515
16	>10	35	0.340	13	>10 000
17	>10	35	>10	29	6 690
(–)-12	>10	99	>10	14	4 130
(+)-12	>10	28	>10	14	>10 000
20	>10	0	>10	0	>10 000
24	>10	42	>10	15	>10 000
26	>10	60	>10	23	2 200
33	1.142	112	>10	58	695
34	0.723	75	>10	100	4 390
35	1.454	122	>10	26	718
36	1.531	100	1.356	34	579
37	1.194	80	1.503	85	1 030
38	1.485	138	>10	51	969
47	1.632	148	0.549	45	>10 000
48	1.543	183	>10	25	>10 000
49	>10	121	>10	19	>10 000
50	>10	187	>10	13	>10 000
51	>10	155	>10	31	>10 000
52	>10	204	>10	27	>10 000

[a] Maximal signal obtained in comparison to WY 14,643: 10^{-5} M. [b] Maximal signal obtained at 10^{-5} M, in comparison to rosiglitazone: 10^{-6} M.

open the field to new types of analogs with more potent activities.[10]

Conclusion

In conclusion, we have reported an efficient and flexible strategy towards new 8-HETE analogs with an aromatic core. Such synthesis should allow for many modulations around this basic skeleton. Several products exhibited already interesting properties as dual PPARα/γ agonists. These first structure–activity relationships obtained in this study open the route to new and more potent derivatives to be developed in various pathologies, such as type 2 diabetes and dislipidemia.

Experimental Section

General: All reagents were obtained from Aldrich and used without further purification. All reactions were carried out under a nitrogen atmosphere and dry conditions. The solvents used were freshly distilled under anhydrous conditions, unless otherwise specified. The reaction mixtures were magnetically stirred with Teflon stirring bars, and the temperatures were measured externally. Reactions that require anhydrous conditions were carried out by using oven-dried (120 °C, 24 h) or flame-dried (vacuum <0.5 Torr) glassware. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, and the reactions were monitored by thin layer chromatography (TLC), carried out on 0.25 mm Merck silica gel plates (60 F_{254}). The eluents used were mixtures of low-boiling (<50 °C) petroleum ether (PE) and ethyl acetate (EtOAc), with detection by UV light, or a *p*-anisaldehyde staining solution. Merck silica gel (60, particle size 0.040–0.063 mm) was used for column chromatography. Nuclear magnetic resonance (NMR) spectra were recorded with a Bruker ARX 400 spectrometer. ^{1}H NMR spectra: (400 MHz); δ (H) are given in ppm relative to tetramethylsilane (TMS) [TMS, δ (H) = 0.00 ppm] as internal reference. ^{13}C NMR spectra: (100.6 MHz); δ (C) are given in ppm relative to TMS [$CDCl_3$, δ (C) = 0.00 ppm] as internal reference. Multiplicities were designated as singlet (s), doublet (d), triplet (t), or multiplet (m).

Pharmacological in vitro assays: These assays are described in ref.[10]

2-Pentyloxybenzaldehyde (8): 1-Iodopentane (10.5 mL, 80 mmol) was added to a solution of salicylaldehyde (5.3 mL, 50 mmol) and KOH (3.6 g, 55 mmol) in DMSO (25 mL). The reaction mixture was heated to 80 °C for 16 h. The product was extracted with EtOAc, and the organic phase was washed with water (3×). The aldehyde **8** was purified by Kugelrohr distillation (105 °C/2 Torr): yield 78% (7.45 g, 38.75 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.52 (s, 1 H, C*H*O), 7.83 (dd, *J* = 7.7, 1.8 Hz,1 H, 6-H), 7.52 (ddd, *J* = 8.1, 7.3, 1.8 Hz, 1 H, 4-H), 6.98 (m, 2 H, 5-H, 3-H), 4.07 (t, *J* = 6.5 Hz, 2 H, O$CH_2$$CH_2$), 1.90–1.80 (m, 2 H, OCH$_2$$CH_2$), 1.53–1.35 (m, 4 H, C$H_2$$CH_2$$CH_3$), 0.94 (t, *J* = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.96 (*C*HO) 161.59 (C-2), 135.94 (C-4), 128.16 (C-6), 124.86 (C-1), 120.43 (C-5), 112.48 (C-3), 68.50 (O*C*H$_2$CH$_2$) 28.78 (OCH$_2$*C*H$_2$), 28.23 (*C*H$_2$CH$_2$CH$_3$), 22.41 (CH$_2$*C*H$_2$CH$_3$), 14.02 (*C*H$_3$) ppm.

1-(2-Pentyloxyphenyl)-but-3-yn-1-ol (9): In a double-necked round-bottom flask, magnesium metal turnings (175 mg, 7.2 mmol) were flame-dried under nitrogen. After cooling to room temperature, anhydrous ether (9.5 mL) along with (20 mg, 0.072 mmol) mercury(II)

chloride were added, and then propargyl bromide (840 μL, 7.8 mmol) was added slowly dropwise until the ether started boiling. If not, the solution was warmed gently with a heat gun. When the magnesium turnings were consumed (20 to 30 min) the reaction was cooled to –80 °C. At this temperature, a solution of aldehyde **8** (1.15 g, 6 mmol) in diethyl ether (1 mL) was added. The reaction mixture was stirred for 20 min at this temperature, and then the mixture was warmed to –5 °C and hydrolyzed with a NH_4Cl solution (10%) followed by extraction with EtOAc. The combined organic layers were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. After purification by column chromatography (R_f: 0.11, PE/EtOAc, 95:5) alcohol **9** was obtained as a colorless oil. Yield 78% (1.083 g, 4.66 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (dd, J = 7.5, 1.4 Hz, 1 H, 6-H), 7.25 (ddd, J = 8.2, 7.5, 1.4 Hz, 1 H, 4-H), 6.96 (ddd, J = 7.5, 7.5, 0.9 Hz, 1 H, 5-H), 6.86 (d, J = 8.2 Hz,1 H, 3-H), 5.07 (ddd, J = 7.5, 6.3, 5.1 Hz, 1 H, C*H*OH), 4.05–3.96 (m, 2 H, OCH_2CH$_2$), 2.99 (d, J = 6.3 Hz, 1 H, O*H*), 2.78 (ddd, J = 16.5, 5.1, 2.6 Hz, 1 H, CHCH_2), 2.66 (ddd, J = 16.5, 7.5, 2.6 Hz, 1 H, CHCH_2), 2.05 (t, J = 2.6 Hz, 1 H, C≡C*H*), 1.82–1.78 (m, 2 H, OCH$_2$CH_2), 1.51–1.34 (m, 4 H, CH_2CH_2CH$_3$), 0.94 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.69 (C-2), 130.27 (C-4), 128.65 (C-6), 126.87 (C-1), 120.45 (C-5), 111.05 (C-3), 81.36 and 70.36 (*C*≡*C*H), 69.15 (O*C*H$_2$), 67.87 (*C*HOH), 28.93 (OCH$_2$*C*H$_2$), 28.34 (*C*H$_2$CH$_2$CH$_3$), 27.41 (CH*C*H$_2$), 22.41 (*C*H$_2$CH$_3$), 14.02 (*C*H$_3$) ppm.

(1*R*)-1-(2-Pentyloxyphenyl)-but-3-yn-1-ol [(+)-9] and (1*S*)-1-(2-Methylphenyl)-but-3-yn-1-ol [(–)-9]: To a solution of **18a** (329 mg, 0.86 mmol) in MeOH (1 mL) was added KOH (241 mg, 5 equiv., 4.3 mmol) under nitrogen at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and then for 1 h at room temperature. After addition of water, the product was extracted with EtOAc. The alcohol **(+)-9** was purified by filtration through silica gel with PE/EtOAc (95:5) as eluent and obtained as a yellow oil in 76% yield (212 mg, 0.66 mmol). Using the same procedure, **(–)-9** was obtained from **18b** in 99% yield (126 mg, 0.54 mmol). Their NMR spectroscopic data were similar to those of **9**. **(+)-9:** $[\alpha]_D^{20}$: +21.5 (c = 4, $CHCl_3$); **(–)-9:** $[\alpha]_D^{20}$: –23.0 (c = 2, $CHCl_3$).

***tert*-Butyldimethyl[1-(2-pentyloxyphenyl)-but-3-ynyloxy]silane (10):** To a solution of **9** (1.083 g, 4.66 mmol) in DMF (4.7 mL) were added *tert*-butyldimethylsilyl chloride (843 mg, 5.59 mmol) and imidazole (793 mg, 11.65 mmol) at 0 °C under nitrogen. The reaction mixture was stirred for 24 h at room temperature. The hydrolysis was performed with a saturated NH_4Cl solution, and the product was extracted with PE. The combined organic layers were washed with water, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by column chromatography (PE), R_f: 0.42 (PE/EtOAc, 95:5) to afford **10** in 86% yield (1.388 g, 4.81 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (dd, J = 7.6, 1.7 Hz, 1 H, 6-H), 7.19 (ddd, J = 8.2, 7.5, 1.7 Hz, 1 H, 4-H), 6.96 (dd, J = 7.6, 7.5 Hz, 1 H, 5-H), 6.86 (d, J = 8.2 Hz,1 H, 3-H), 5.26 (dd, J = 7.7, 3.7 Hz, 1 H, C*H*OSi), 4.01–3.91 (m, 2 H, OCH_2CH$_2$), 2.58 (ddd, J = 16.6, 3.7, 2.7 Hz, 1 H, CHCH_2), 2.66 (ddd, J = 16.6, 7.7, 2.7 Hz, 1 H, CHCH_2), 1.93 (t, J = 2.7 Hz, 1 H, C≡C*H*), 1.80–1.75 (m, 2 H, OCH$_2$CH_2), 1.51–1.34 (m, 4 H, CH_2CH_2CH$_3$), 0.94 (t, J = 7.2 Hz, 3 H, CH$_3$), 0.91 (s, 9 H, *tBu*Si), 0.10 (s, 3 H, CH_3Si), –0.05 (s, 3 H, CH_3Si) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.75 (C-2), 132.37 (C-4), 127.99 (C-6), 126.76 (C-1), 120.13 (C-5), 110.56 (C-3), 82.52 (*C*≡CH), 69.12 (C≡*C*H), 67.69 (O*C*H$_2$), 67.41 (*C*HOSi), 29.05 (OCH$_2$*C*H$_2$), 28.94 (*C*H$_2$CH$_2$CH$_3$), 28.39 (CH*C*H$_2$), 25.86 [3C, (*C*H$_3$)$_3$CSi], 22.42 (*C*H$_2$CH$_3$), 18.35 [(CH$_3$)$_3$-*C*Si], 14.08 (*C*H$_3$), –4.81 and –4.93 [2C, (*C*H$_3$)$_2$Si] ppm.

(1*R*)-*tert*-Butyldimethyl[1-(2-pentyloxyphenyl)-but-3-ynyloxy]silane [(+)-10] and (1*S*)-*tert*-Butyldimethyl[1-(2-pentyloxyphenyl)-but-3-ynyloxy]silane [(–)-10]: The procedures for the preparation of **(+)-10** (yield 92%, 210 mg; 0.61 mmol) and **(–)-10** (yield 81%, 151 mg; 0.44 mmol) were the same as those described for the synthesis of **10**. Their NMR spectroscopic data were similar to **10**. **(+)-10:** $[\alpha]_D^{20}$: +34.2 (c = 4, $CHCl_3$); **(–)-10:** $[\alpha]_D^{20}$: –36.4 (c = 2.8, $CHCl_3$).

Methyl 8-(*tert*-Butyldimethylsilanyloxy)-8-(2-pentyloxyphenyl)-oct-5-ynoate (11): To a solution of **10** (1.276 g, 3.67 mmol) in THF (3.7 mL), was added slowly *n*BuLi (4.5 mL, 4.4 mmol), and the reaction mixture was stirred under nitrogen at –80 °C for 20 min. Then HMPA (3.7 mL) and trimethyl 4-bromoorthobutyrate (764 μL, 4.4 mmol) were added. The temperature of the reaction mixture was slowly raised to 0 °C, and the mixture was kept overnight at 0 °C. Then it was poured into a NH_4Cl solution (10%) and extracted with PE. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography, using PE as eluent, R_f: 0.23 (PE/EtOAc, 95:5), to afford **11** as a colorless oil in 68% yield (1.115 g, 2.50 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (dd, J = 7.5, 1.7 Hz, 1 H, 6-H), 7.18 (ddd, J = 8.2, 7.8, 1.7 Hz, 1 H, 4-H), 6.92 (dd, J = 7.8, 7.5 Hz, 1 H, 5-H), 6.79 (d, J = 8.2 Hz, 1 H, 3-H), 5.15 (dd, J = 7.6, 3.8 Hz, 1 H, C*H*OSi), 3.94–3.84 (m, 2 H, OCH_2), 3.61 (s, 3 H, CO$_2$*Me*), 2.46 (ddt, J = 16.4, 3.8, 2.4 Hz, 1 H, CHCH_2), 2.40 (ddt, J = 16.4, 7.6, 2.3 Hz, 1 H, CHCH_2), 2.40 (t, J = 7.55 Hz, 2 H, CH_2CO$_2$Me), 2.20 (tdd, J = 6.9, 2.4, 2.3 Hz, 2 H, C≡CCH_2), 1.85–1.72 (m, 4 H, OCH$_2$CH_2 and CH_2CH$_2$CO$_2$Me), 1.55–1.34 (m, 4 H, CH_2CH_2CH$_3$), 0.94 (t, J = 7.2 Hz, 3 H, CH_3), 0.90 (s, 9 H, *tBu*Si), 0.07 (s, 3 H, CH_3Si), –0.05 (s, 3 H, CH_3Si) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.87 (*C*O$_2$Me), 154.76 (C-2), 132.77 (C-1), 127.80 (C-4), 126.80 (C-6), 120.12 (C-5), 110.56 (C-3), 79.65 and 79.06 (*C*≡*C*), 67.79 (O*C*H$_2$), 67.68 (*C*HOSi), 51.48 (CO$_2$*Me*), 32.83 (*C*H$_2$CO$_2$Me), 29.32 (CH*C*H$_2$), 28.95 (C≡C*C*H$_2$), 28.39 (OCH$_2$*C*H$_2$), 25.82 [3C, (*C*H$_3$)$_3$CSi], 24.08 (*C*H$_2$CH$_2$CH$_3$), 22.42 (*C*H$_2$CH$_3$), 18.35 [(CH$_3$)$_3$*C*Si], 18.33 (*C*H$_2$CH$_2$CO$_2$Me), 14.07 (*C*H$_3$), –4.83 and –4.99 [(*C*H$_3$)$_2$Si] ppm.

(8*R*)-Methyl 8-(*tert*-Butyldimethylsilanyloxy)-8-(2-pentyloxyphenyl)-oct-5-ynoate [(+)-11] and (8*S*)-Methyl 8-(*tert*-Butyldimethylsilanyloxy)-8-(2-pentyloxyphenyl)-oct-5-ynoate [(–)-11]: The procedures for the preparation of **(+)-11** (yield 86%, 233 mg; 0.52 mmol) and **(–)-11** (yield 77%, 151 mg; 0.34 mmol) were the same as those described for the synthesis of **11**. Their NMR spectroscopic data were similar to **11**. **(+)-11:** $[\alpha]_D^{20}$: +35.3 (c = 4, $CHCl_3$); **(–)-11:** $[\alpha]_D^{20}$: –36.2 (c = 3, $CHCl_3$).

Methyl 8-Hydroxy-8-(2-pentyloxyphenyl)-oct-5-ynoate (12): To a solution of **11** (1.827 g, 4.06 mmol) in THF (16 mL) was added TBAF (5.7 mL, 5.69 mmol) at room temperature. Then the reaction mixture was stirred under nitrogen for 3 h at 45 °C. The product was extracted with EtOAc. The organic phase was washed with water, dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the residue by column chromatography with PE/Et_3N/toluene (99:0.5:0.5) and then PE/Et_3N/toluene/EtOAc (95:0.5:0.5:4) as eluents, R_f: 0.25 (PE/EtOAc, 80:20), afforded the ester **12** as a colorless oil in 99% yield (1.337 g, 4.02 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (dd, J = 7.5, 1.4 Hz, 1 H, 6-H), 7.23 (ddd, J = 8.2, 7.8, 1.4 Hz, 1 H, 4-H), 6.94 (ddd, J = 7.8, 7.5 Hz, 1 H, 5-H), 6.85 (d, J = 8.2 Hz,1 H, 3-H), 5.02 (ddd, J = 7.3, 6.1, 5.8 Hz, 1 H, C*H*OH), 4.04–3.95 (m, 2 H, OCH_2), 3.68 (s, 3 H, CO$_2$*Me*), 3.00 (d, J = 6.1 Hz, 1 H, O*H*), 2.74 (ddt, J = 16.5, 5.8, 2.3 Hz, 1 H, CHCH_2), 2.58 (ddt, J = 16.5, 7.3, 2.4 Hz, 1 H, CHCH_2), 2.39 (t, J = 7.4 Hz, 2 H, CH_2CO$_2$Me), 2.23 (tdd, J = 6.9, 2.4, 2.3 Hz, 2 H, C≡CCH_2), 1.85–1.74 (m, 4 H, OCH$_2$CH_2 and

$CH_2CH_2CO_2Me$), 1.50–1.33 (m, 4 H, $CH_2CH_2CH_3$), 0.94 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.81 (CO_2Me), 155.71 (C-2), 130.63 (C-1), 128.45 (C-4), 126.88 (C-6), 120.39 (C-5), 111.03 (C-3), 81.35 and 76.72 ($C\equiv C$), 69.40 ($CHOH$), 67.87 (OCH_2), 51.57 (CO_2Me), 32.83 (CH_2CO_2Me), 28.94 (OCH_2CH_2), 28.34 ($CH_2CH_2CH_3$), 27.87 ($CHCH_2$), 24.01 ($CH_2CH_2CO_2Me$), 22.41 (CH_2CH_3), 18.27 ($C\equiv CCH_2$), 14.07 (CH_3) ppm. $C_{20}H_{28}O_4$ (332.43): calcd. C 72.26, H 8.49; found C 72.30, H 8.56.

(8*R*)-Methyl 8-Hydroxy-8-(2-pentyloxyphenyl)-oct-5-ynoate [(+)-12] and (8*S*)-Methyl 8-Hydroxy-8-(2-pentyloxyphenyl)-oct-5-ynoate [(–)-12]: The procedures for the preparation of **(+)-12** (yield 94%, 163 mg; 0.49 mmol) and **(–)-12** (yield 58%, 66 mg; 0.20 mmol) were the same as those described for the synthesis of racemic **12**. Their NMR spectroscopic data were similar to those of **12**. **(+)-12:** $[\alpha]_D^{20}$: +20.2 (c = 3, $CHCl_3$); **(–)-12:** $[\alpha]_D^{20}$: –20.2 (c = 1, $CHCl_3$).

Sodium 8-Hydroxy-8-(2-pentyloxyphenyl)-oct-5-ynoate (13): The ester **12** (332 mg, 1 mmol) was added to a solution of MeOH/H_2O (9:1) (22.5 mL) and LiOH monohydrate (147 mg, 3.5 mmol). The reaction mixture was stirred for 36 h at room temperature, and then oxalic acid (463 mg, 5.14 mmol) was added. Water and methanol were removed under reduced pressure, and the residue was dissolved in EtOAc (10 mL), washed with water (1 mL), dried (Na_2SO_4), and concentrated under reduced pressure. After purification by column chromatography on SiO_2 with hexane/EtOAc (80:20) as the eluent, the acid was obtained in 83% yield (263 mg, 0.83 mmol). ^1H NMR (400 MHz, DMSO): δ = 7.44 (dd, J = 7.6, 1.5 Hz, 1 H, 6-H), 7.20 (ddd, J = 8.1, 7.6, 1.2 Hz, 1 H, 4-H), 6.95–6.90 (m, 2 H, 5-H and 3-H), 5.00 (dd, J = 7.1, 4.6 Hz, 1 H, $CHOH$), 3.98 (t, J = 6.6 Hz, 2 H, OCH_2), 2.55–2.47 (m, 3 H, $CHCH_2$ and CH_2CO_2H), 2.22 (ddt, J = 16.3, 7.1, 2.0 Hz, 1 H, $CHCH_2$), 2.18 (t, J = 7.6 Hz, 2 H, $C\equiv CCH_2$), 1.79–1.70 (m, 2 H, OCH_2CH_2), 1.63–1.53 (m, 2 H, $CH_2CH_2CO_2H$), 1.50–1.33 (m, 4 H, $CH_2CH_2CH_3$), 0.93 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 176.36 (CO_2H), 156.33 (C-2), 134.42 (C-1), 129.32 (C-4), 127.89 (C-6), 121.43 (C-5), 112.55 (C-3), 82.00 and 79.96 ($C\equiv C$), 68.84 ($CHOH$), 67.09 (OCH_2), 30.03 (CH_2CO_2H), 29.56 (OCH_2CH_2), 29.43 ($CH_2CH_2CH_3$), 26.14 ($CHCH_2$), 23.46 ($CH_2CH_2CO_2H$), 22.35 (CH_2CH_3), 19.41 ($C\equiv CCH_2$), 15.54 (CH_3) ppm. To this acid in methanol (1 mL) was added NaOH (32 mg, 1 equiv.), and the suspension was homogenized in an ultrasonic bath. After evaporation under reduced pressure, the (hygroscopic) salt **13** was obtained in 79% yield (278 mg), after drying for two days under vacuum (10^{-2} Torr). HRMS: calcd. for $C_{19}H_{25}NaO_4$ 341.17288; found 341.1730 (δ = 0 ppm).

Methyl 8-Hydroxy-8-(2-pentyloxyphenyl)-oct-5-enoate (14): To a solution of nickel acetate tetrahydrate (100 mg, 0.4 mmol) in EtOH (5 mL) was added a solution of sodium borohydride (15 mg, 0.4 equiv., 0.4 mmol) in EtOH (0.5 mL) under hydrogen. The reaction mixture was stirred for 15 min at room temperature, and then ethylenediamine (68 μL, 1 mmol) and **12** (332 mg, 1 mmol) were added. The reaction mixture was stirred for 5 h at room temperature. After addition of diethyl ether (2 mL), the suspension was filtered through silica gel and washed with diethyl ether. After concentration *in vacuo*, **14** was obtained as a viscous oil in 96% yield (322 mg, 0.96 mmol). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.31 (dd, J = 7.5, 1.7 Hz, 1 H, 6-H), 7.21 (ddd, J = 8.2, 7.8, 1.7 Hz, 1 H, 4-H), 6.94 (ddd, J = 7.8, 7.5, 0.9 Hz, 1 H, 5-H), 6.85 (d, J = 8.2 Hz,1 H, 3-H), 5.48–5.43 (m, 2 H, HC=CH), 4.90 (dd, J = 7.2, 5.9 Hz, 1 H, CHOH), 4.05–3.96 (m, 2 H, OCH_2), 3.65 (s, 3 H, CO_2Me), 2.81 (s, 1 H, OH), 2.62–2.48 (m, 2 H, $CHCH_2$), 2.27 (t, J = 7.6 Hz, 2 H, CH_2CO_2Me), 2.11–2.00 (m, 2 H, $HC{=}CCH_2$), 1.85–1.74 (m, 2 H, OCH_2CH_2), 1.68–1.58 (m, 2 H, $CH_2CH_2CO_2Me$), 1.53–1.31 (m, 4 H, $CH_2CH_2CH_3$), 0.94 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.14 (CO_2Me), 155.90 (C-2), 131.78 and 126.96 ($HC{=}CH$), 131.12 (C-1), 128.22 (C-4), 126.82 (C-6), 120.45 (C-5), 111.10 (C-3), 70.84 ($CHOH$), 67.85 (OCH_2), 51.50 (CO_2Me), 35.33 ($HC{=}CCH_2$), 33.43 (CH_2CO_2Me), 29.01 (OCH_2CH_2), 28.36 ($CH_2CH_2CH_3$), 26.66 ($CHCH_2$), 24.72 ($CH_2CH_2CO_2Me$), 22.41 (CH_2CH_3), 14.03 (CH_3) ppm. HRMS: calcd. for $C_{20}H_{30}O_4$ 303.19602; found 303.1966 (δ = 1 ppm).

Methyl 8-Hydroxy-8-(2-pentyloxyphenyl)-octanoate (15): To a suspension of palladium on charcoal (36 mg, 10 wt.-%) in methanol (4.4 mL) was added **12** (364 mg, 1.1 mmol) under hydrogen. The reaction mixture was stirred at room temperature overnight. Then it was filtered through silica gel with hexane/EtOAc (80:20) as eluent. After concentration under reduced pressure, the ester **15** was obtained as a yellow oil in 94% yield (348 mg, 1.03 mmol). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.41 (dd, J = 7.5, 1.8 Hz, 1 H, 6-H), 7.17 (ddd, J = 7.8, 7.6, 1.8 Hz, 1 H, 4-H), 6.92 (dd, J = 7.6, 7.5 Hz, 1 H, 5-H), 6.91 (d, J = 7.8 Hz, 1 H, 3-H), 4.88 (dd, J = 8.0, 4.3 Hz, 1 H, CHOH), 4.00–3.92 (m, 2 H, OCH_2), 3.59 (s, 3 H, CO_2Me), 2.29 (t, J = 7.5 Hz, 2 H, CH_2CO_2Me), 1.78–1.70 (m, 2 H, OCH_2CH_2), 1.64–1.23 (m, 15 H, $CH_2CH_2CH_2CH_2CH_2CH_2CO_2Me$ and $CH_2CH_2CH_3$ and OH), 0.94 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.90 (CO_2Me), 156.26 (C-2), 136.40 (C-1), 128.80 (C-4), 127.42 (C-6), 121.53 (C-5), 112.48 (C-3), 68.71 ($CHOH$), 67.43 (OCH_2), 52.73 (CO_2Me), 34.80, 30.14, 30.12, 30.08, 29.54, 26.93, 26.24, 25.99, 23.46 (9 C, $CH_2CH_2CH_2CH_2CH_2CH_2CO_2Me$ and $CH_2CH_2CH_2CH_3$), 15.53 (CH_3) ppm. $C_{20}H_{32}O_4$ (336.47): calcd. C 75.36, H 7.91; found C 75.47, H 8.42.

Sodium 8-Hydroxy-8-(2-pentyloxyphenyl)-oct-5-enoate (16): The procedure for the preparation of **16** was the same as that described for the synthesis of **13** (yield 76%, 176 mg, 0.46 mmol). Acid: ^1H NMR (400 MHz, DMSO): δ = 7.43 (dd, J = 7.6, 1.5 Hz, 1 H, 6-H), 7.18 (ddd, J = 7.6, 7.6, 1.5 Hz, 1 H, 4-H), 6.95–6.90 (m, 2 H, 5-H and 3-H), 5.54–5.30 (m, 2 H, HC=CH), 4.91 (dd, J = 7.6, 4 Hz, 1 H, CHOH), 4.09–3.91 (m, 2 H, OCH_2), 2.81 (s, 1 H, OH), 2.53 (t, J = 1.5 Hz, 2 H, $CHCH_2$), 2.45–2.15 (m, 2 H, CH_2CO_2H), 2.10 (t, J = 7.1 Hz, 2 H, $HC{=}CCH_2$), 1.98–1.90 (m, 2 H, OCH_2CH_2), 1.79–1.70 (m, 2 H, $CH_2CH_2CO_2H$), 1.53–1.31 (m, 4 H, $CH_2CH_2CH_3$), 0.91 (t, J = 7.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 175.16 (CO_2H), 155.04 (C-2), 134.35 and 130.26 ($HC{=}CH$), 127.73 (C-1), 127.63 (C-4), 126.48 (C-6), 120.25 (C-5), 111.24 (C-3), 67.55 ($CHOH$), 66.74 (OCH_2), 36.00 ($HC{=}CCH_2$), 34.25 (CH_2CO_2H), 28.85 (OCH_2CH_2), 28.22 ($CH_2CH_2CH_3$), 26.73 ($CHCH_2$), 25.13 ($CH_2CH_2CO_2H$), 22.21 (CH_2CH_3), 14.30 (CH_3) ppm. Salt **16**: HRMS: calcd. for $C_{19}H_{27}NaO_4$ 343.18853; found 343.1893 (δ = 2 ppm).

Sodium 8-Hydroxy-8-(2-pentyloxyphenyl)-octanoate (17): The procedure for the preparation of **17** was the same as that described for the synthesis of **13** (yield 97%, 247 mg, 0.60 mmol). Acid: ^1H NMR (400 MHz, DMSO): δ = 7.41 (dd, J = 7.1, 1.5 Hz, 1 H, H-6), 7.16 (ddd, J = 8.1, 7.6, 2.0 Hz, 1 H, 4-H), 6.93–6.89 (m, 2 H, 5-H and 3-H), 4.88 (dd, J = 7.6, 3.6 Hz, 1 H, CHOH), 4.00–3.90 (m, 2 H, OCH_2), 2.53 (t, J = 1.5 Hz, 2 H, CH_2CO_2H), 2.04 (t, J = 7.6 Hz, 2 H, OCH_2CH_2), 1.79–1.69 (m, 2 H, $CH_2CH_2CO_2H$), 1.64–1.18 (m, 12 H, $CH_2CH_2CH_2CH_2CH_2CH_2CO_2H$ and $CH_2CH_2CH_3$), 0.92 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 177.38 (CO_2H), 156.28 (C-2), 136.49 (C-1), 128.76 (C-4), 127.44 (C-6), 121.52 (C-5), 112.45 (C-3), 68.70 ($CHOH$), 67.48 (OCH_2), 39.78, 37.48, 30.70, 30.48, 30.12, 29.54, 27.12, 27.07, 23.47 (9 C, $CH_2CH_2CH_2CH_2CH_2CH_2CH_2CO_2H$ and $CH_2CH_2CH_2CH_3$), 15.55

(CH_3) ppm. Salt **17** was obtained as a white solid (m.p. = 54–59 °C). Salt: HRMS: calcd. for $C_{18}H_{27}NaO_4$ 345.20418; found 345.2040 (δ = 0 ppm).

1-(2-Pentyloxyphenyl)-but-3-ynyl Methoxyphenylacetate (18a and 18b): To a solution of DCC, (1.39 g, 2.8 equiv., 6.75 mmol), (*S*)-*O*-methyl-L-mandelic acid (800 mg, 2 equiv., 4.82 mmol) and DMAP (147 mg, 0.5 equiv., 1.2 mmol) in CH_2Cl_2 (5 mL) was added a solution of **9** (560 mg, 2.41 mmol) in CH_2Cl_2 (6 mL). The reaction mixture was stirred at room temperature for 30 min. The crude mixture was filtered first on Celite, which was washed further with EtOAc. After evaporation of the solvents under vacuum, the residue was filtered through silica gel with PE as eluent to afford a mixture of the two diastereoisomers **18a** and **18b** in 93% yield (852 mg). These derivatives were separated by several successive column chromatography steps on silica gel, using as eluents PE and then PE/*tert*-butylmethyl ether (TBME) mixtures 99:1, 98:2, 97:3, 96:4, and 95:5. The separation was monitored by TLC with PE/TBME (95:5 with 2 elutions) as eluent. The ester **18a** (the less polar product) was isolated in 39% yield (329 mg, 0.86 mmol), while the isomer **18b** (the more polar product) was obtained in 25% yield (210 mg, 0.60 mmol).

First Diastereoisomer (Less Polar) 18a: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.49 (m, 2 H, H-arom.), 7.38–7.31 (m, 3 H, 2 H-arom. and 6-H), 7.29–7.21 (m, 2 H, H-arom. and 4-H), 6.89 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1 H, 5-H), 6.83 (dd, *J* = 8.2, 1.0 Hz, 1 H, 3-H), 6.31 (dd, *J* = 7.0, 4.7 Hz, 1 H, C*H*OCO), 4.87 (s, 1 H, C*H*OMe), 3.95 (t, *J* = 6.5 Hz, 2 H, OCH_2), 3.46 (s, 3 H, OMe), 2.72 (ddd, *J* = 17.0, 4.7, 2.7 Hz, 1 H, CHCH_2), 2.59 (ddd, *J* = 17.0, 7.0, 2.7 Hz, 1 H, CHCH_2), 1.81–1.73 (m, 2 H, OCH$_2$CH_2), 1.70 (t, *J* = 2.7 Hz, 1 H, C≡C*H*), 1.48–1.32 (m, 4 H, CH_2CH_2CH$_3$), 0.92 (t, *J* = 7.1 Hz, 3 H, *CH*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.73 (CO), 155.50 (C-2), 136.29, 129.15, 128.56, 128.48, 127.24, 126.85, 126.44 (5 C-arom., C-4, C-6 and C-1), 120.13 (C-5), 111.16 (C-3), 82.69 (*C*≡CH), 79.45 (*C*HOMe), 76.72 (C≡*C*H), 69.37 (*C*HOCO), 68.05 (O*C*H$_2$), 57.57 (OMe), 28.85 (CH*C*H$_2$), 28.23 (OCH$_2$*C*H$_2$), 24.63 (*C*H$_2$CH$_2$CH$_3$), 22.39 (*C*H$_2$CH$_3$), 14.02 (*C*H$_3$). $[a]_D^{20}$: +27.2 (*c* = 3, $CHCl_3$) ppm.

Second Diastereoisomer (More Polar) 18b: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.43 (m, 2 H, H-arom.), 7.38–7.31 (m, 3 H, 2 H-arom. and 6-H), 7.15 (ddd, *J* = 7.5, 7.5, 1.6 Hz, 1 H, 4-H), 6.80–6.74 (m, 2 H, H-arom. and 5-H), 6.67 (dd, *J* = 8.2, 1.0 Hz,1 H, 3-H), 6.31 (dd, *J* = 7.4, 4.2 Hz, 1 H, C*H*OCO), 4.90 (s, 1 H, C*H*OMe), 3.94–3.85 (m, 2 H, OCH_2), 3.46 (s, 3 H, O*Me*), 2.81 (ddd, *J* = 17.0, 4.2, 2.7 Hz, 1 H, CHCH_2), 2.64 (ddd, *J* = 17.0, 7.4, 2.7 Hz, 1 H, CHCH_2), 1.92 (t, *J* = 2.7 Hz, 1 H, C≡C*H*), 1.81–1.69 (m, 2 H, OCH$_2$CH_2), 1.48–1.32 (m, 4 H, CH_2CH_2CH$_3$), 0.93 (t, *J* = 7.0 Hz, 3 H, C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.42 (CO), 155.29 (C-2), 136.17, 128.89, 128.70, 128.55, 127.54, 126.79, 125.92 (5 C-arom., C-4, C-6 and C-1), 119.99 (C-5), 110.95 (C-3), 82.53 (*C*≡CH), 79.95 (*C*HOMe), 76.72 (C≡*C*H), 69.36 (*C*HOCO), 67.98 (O*C*H$_2$), 57.41 (O*Me*), 28.82 (CH*C*H$_2$), 28.23 (OCH$_2$*C*H$_2$), 24.90 (*C*H$_2$CH$_2$CH$_3$), 22.40 (*C*H$_2$CH$_3$), 14.03 (*C*H$_3$) ppm. $[a]_D^{20}$: +23.7 (*c* = 3, $CHCl_3$).

1-(1-Methoxybut-3-ynyl)-2-pentyloxybenzene (19): To a suspension of NaH (55 mg, 1.6 equiv., 1.38 mmol) in THF/DMF (5:1, 3.8 mL) was added a solution of **9** (200 mg, 0.86 mmol) in THF (1.7 mL). The reaction mixture was stirred for 20 min at room temperature, cooled to 0 °C before adding Me_2SO_4 (115 μL, 1.4 equiv., 1.2 mmol), and then stirred at room temperature overnight. After addition of water, the product was extracted with EtOAc, and the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. After flash chromatography with PE as eluent, the methoxy derivative **19** was obtained as a colorless oil in 85% yield (180 mg, 0.73 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (dd, *J* = 7.6, 1.8 Hz, 1 H, 6-H), 7.24 (ddd, *J* = 8.2, 7.5, 1.8 Hz, 1 H, 4-H), 6.97 (ddd, *J* = 7.6, 7.5, 1.0 Hz, 1 H, 5-H), 6.86 (d, *J* = 8.2 Hz,1 H, 3-H), 4.81 (dd, *J* = 7.3, 4.3 Hz, 1 H, C*H*OMe), 3.97 (t, *J* = 6.4 Hz, 2 H, OCH_2), 3.34 (s, 3 H, O*Me*), 2.68 (ddd, *J* = 16.9, 4.3, 2.6 Hz, 1 H, CHCH_2), 2.54 (ddd, *J* = 16.9, 7.3, 2.6 Hz, 1 H, CHCH_2), 1.98 (t, *J* = 2.6 Hz, 1 H, C≡C*H*), 1.86–1.76 (m, 2 H, OCH$_2$CH_2), 1.51–1.34 (m, 4 H, CH_2CH_2CH$_3$), 0.94 (t, *J* = 7.2 Hz, 3 H, C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.29 (C-2), 128.57 (C-4), 128.53 (C-6), 126.51 (C-1), 120.34 (C-5), 111.01 (C-3), 81.52 (*C*≡CH), 75.53 (C≡*C*H), 69.24 (O*C*H$_2$), 67.83 (*C*HOH), 57.37 (O*Me*), 28.95 (CH*C*H$_2$), 28.34 (OCH$_2$*C*H$_2$), 26.26 (*C*H$_2$CH$_2$CH$_3$), 22.42 (*C*H$_2$CH$_3$), 14.06 (*C*H$_3$) ppm.

Methyl 8-Methoxy-8-(2-pentyloxyphenyl)-oct-5-ynoate (20): The procedure for the preparation of **20** was the same as that described for the synthesis of **11** in 92% yield (210 mg, 0.61 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (dd, *J* = 7.6, 1.8 Hz, 1 H, 6-H), 7.23 (ddd, *J* = 8.2, 7.5, 1.8 Hz 1 H, 4-H), 6.94 (ddd, *J* = 7.6, 7.5, 1.0 Hz, 1 H, 5-H), 6.85 (dd, *J* = 8.2, 1.0 Hz,1 H, 3-H), 4.76 (dd, *J* = 7.0, 4.6 Hz, 1 H, C*H*OMe), 3.97 (t, *J* = 6.5 Hz, 2 H, OCH_2), 3.67 (s, 3 H, CO$_2$*Me*), 3.32 (s, 3 H, O*Me*), 2.63 (ddt, *J* = 16.7, 4.6, 2.3 Hz, 1 H, CHCH_2), 2.50 (ddt, *J* = 16.7, 7, 2.4 Hz, 1 H, CHCH_2), 2.37 (t, *J* = 7.6 Hz, 2 H, CH_2CO$_2$Me), 2.21 (tdd, *J* = 6.9, 2.4, 2.3 Hz, 2 H, C≡CCH_2), 1.85–1.74 (m, 4 H, OCH$_2$CH_2 and CH_2CH$_2$-CO$_2$Me), 1.50–1.33 (m, 4 H, CH_2CH_2CH$_3$), 0.94 (t, *J* = 7.2 Hz, 3 H, CH$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.88 (*C*O$_2$Me), 156.34 (C-2), 128.96 (C-1), 128.34 (C-4), 126.62 (C-6), 120.28 (C-5), 111.98 (C-3), 80.03 and 75.94 (*C*≡*C*), 67.83 (O*C*H$_2$), 57.27 (*C*HOH), 51.49 (CO$_2$*Me*), 32.76 (*C*H$_2$CO$_2$Me), 28.96 (CH*C*H$_2$), 28.34 (OCH$_2$*C*H$_2$), 26.49 (*C*H$_2$CH$_2$CH$_3$), 24.08 (*C*H$_2$CH$_2$CO$_2$Me), 22.42 (*C*H$_2$CH$_3$), 18.33 (CH*C*H$_2$), 14.07 (*C*H$_3$) ppm. $C_{21}H_{30}O_4$ (346.46): calcd. C 72.8, H 8.73; found C 73.14, H 8.70.

2-Pentyloxyphenyl-methanol (21): To a solution of **8** (1.748 g, 9.1 mmol) in EtOH/THF (7:3, 11 mL) was added $NaBH_4$ (344 mg, 1 equiv., 9.1 mmol). The reaction mixture was stirred at room temperature for 1 h. After addition of brine, the product was extracted with EtOAc to afford **21** as a colorless oil in 68% yield (1.016 g, 6.18 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.23 (m, 2 H, 6-H and 4-H), 6.92 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1 H, 5-H), 6.87 (d, *J* = 8.6 Hz,1 H, 3-H), 4.69 (d, *J* = 6.5 Hz, 2 H, CH_2OH), 4.01 (t, *J* = 6.5 Hz, 2 H, OCH_2), 2.47 (t, *J* = 6.5 Hz, 1 H, O*H*), 1.86–1.78 (m, 2 H, OCH$_2$CH_2), 1.50–1.34 (m, 4 H, CH_2CH_2CH$_3$), 0.94 (t, *J* = 7.2 Hz, 3 H, C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.98 (C-2), 129.12 (C-4), 128.88 (C-6), 128.65 (C-1), 120.48 (C-5), 111.01 (C-3), 67.93 (O*C*H$_2$), 62.44 (*C*H$_2$OH), 28.98 (OCH$_2$*C*H$_2$), 28.33 (*C*H$_2$CH$_2$CH$_3$), 22.44 (*C*H$_2$CH$_3$), 14.03 (*C*H$_3$) ppm.

1-Bromomethyl-2-pentyloxybenzene (22): To a solution of pyridine (600 μL, 2 equiv., 7.38 mmol) in Et_2O (15 mL) was added **21** (717 mg, 3.69 mmol) under nitrogen. Then, PBr_3 (210 μL, 0.6 equiv., 2.21 mmol) was added slowly at 0 °C. The reaction mixture was stirred for 1 h at 0 °C before addition of HCl (0.5 M solution). The product was extracted with EtOAc. It was purified by filtration through silica gel using PE as eluent to afford **22** as a colorless oil in 35% yield (334 mg, 1.3 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (dd, *J* = 7.5, 1.8 Hz, 1 H, 6-H), 7.27 (ddd, *J* = 8.3, 7.5, 1.8 Hz, 1 H, 4-H), 6.90 (ddd, *J* = 7.5, 7.4, 1.1 Hz, 1 H, 5-H), 6.87 (d, *J* = 8.3 Hz, 1 H, 3-H), 4.56 (s, 2 H, CH_2Br), 4.03 (t, *J* = 6.4 Hz, 2 H, OCH_2), 1.89–1.81 (m, 2 H, OCH$_2$CH_2), 1.55–1.46 (m, 2 H, CH_2CH$_2$CH$_3$), 1.46–1.35 (m, 2 H, CH_2CH$_3$), 0.94 (t, *J* = 7.2 Hz, 3 H, C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.90

(C-2), 130.8 (C-4), 130.13 (C-6), 126.15 (C-1), 120.38 (C-5), 111.68 (C-3), 68.14 (OCH_2), 29.22 (CH_2Br), 28.92 (OCH_2CH_2), 28.26 ($CH_2CH_2CH_3$), 22.42 (CH_2CH_3), 14.06 (CH_3) ppm.

1-But-3-ynyl-2-pentyloxybenzene (23): In a double-necked round-bottom flask, magnesium metal turnings (67 mg, 1.3 equiv., 2.74 mmol) were flame-dried under nitrogen. After cooling to room temperature, anhydrous ether (2.1 mL) and mercury(II) chloride (8 mg, 0.013 equiv., 0.027 mmol) were added. Propargyl bromide (340 μL, 1.5 equiv., 3.16 mmol) was added slowly, and the formation of the Grignard reagent induced a slight boiling of ether; if not, the reaction mixture was warmed with a heat gun. When the magnesium turnings were consumed (20 to 30 min), the reaction mixture was cooled to –80 °C and, at this temperature, CuI (27 mg, 5 wt.-%) and **22** (542 mg, 2.11 mmol) were added. The reaction mixture was stirred for 24 h at room temperature. After addition of water, the product was extracted with PE. The product was purified by filtration through silica gel using PE as eluent to afford **23** as an oil in 27% yield. (123 mg, 0.57 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.15 (m, 2 H, 6-H and 4-H), 6.87 (ddd J = 7.4, 7.4, 1.1 Hz, 1 H, 5-H), 6.82 (d, J = 8.5 Hz, 1 H, 3-H), 3.96 (t, J = 6.4 Hz, 2 H, OCH_2), 2.86 (t, J = 7.6 Hz, 2 H, $ArCH_2$), 2.48 (td, J = 7.6, 2.6 Hz, 2 H, $CH_2C{\equiv}C$), 1.95 (t, J = 2.6 Hz, 1 H, $C{\equiv}CH$), 1.84–1.77 (m, 2 H, OCH_2CH_2), 1.50–1.34 (m, 4 H, $CH_2CH_2CH_3$), 0.94 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.90 (C-2), 130.11 (C-4), 128.78 (C-6), 127.61 (C-1), 120.04 (C-5), 110.94 (C-3), 84.56 ($C{\equiv}CH$), 68.36 ($C{\equiv}CH$), 67.70 (OCH_2), 30.00 ($CHOH$), 29.02 (OCH_2CH_2), 28.36 ($CH_2CH_2CH_3$), 22.44 (CH_2CH_3), 18.76 ($CH_2C{\equiv}C$), 14.06 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3306, 3026, 2954, 2932, 2868, 2858, 2119, 1600, 1586, 1493, 1453, 1242, 1110, 1050, 748, 628 cm^{-1}.

Methyl 8-(2-Pentyloxyphenyl)-oct-5-ynoate (24): The procedure for the preparation of **24** was the same as that described for the synthesis of **11** (yield 80%, 195 mg, 0.62 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.14 (m, 2 H, 6-H and 4-H), 6.86 (ddd, J = 7.4, 7.4, 1.1 Hz, 1 H, 5-H), 6.81 (dd, J = 8.7, 1.1 Hz, 1 H, 3-H), 3.95 (t, J = 6.5 Hz, 2 H, OCH_2), 3.68 (s, 3 H, CO_2Me), 2.80 (t, J = 7.6 Hz, 2 H, $ArCH_2$), 2.42 (tt, J = 7.6, 2.4 Hz, 2 H, $CH_2C{\equiv}C$), 2.40 (t, J = 7.6 Hz, 2 H, CH_2CO_2Me), 2.21 (tt, J = 6.9, 2.4 Hz, 2 H, $C{\equiv}CCH_2$), 1.84–1.73 (m, 4 H, OCH_2CH_2 and $CH_2CH_2CO_2Me$), 1.50–1.34 (m, 4 H, $CH_2CH_2CH_3$), 0.94 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.86 (CO_2Me), 156.9 (C-2), 130.15 (C-4), 129.25 (C-6), 127.39 (C-1), 119.99 (C-5), 110.92 (C-3), 81.11 and 79.11 ($C{\equiv}CCH_2$), 67.70 (C-7), 51.52 (CO_2Me), 32.83 (CH_2CO_2Me), 30.48 ($ArCH_2$), 29.02 (OCH_2CH_2), 28.35 ($CH_2CH_2CH_3$), 24.37 ($CH_2CH_2CO_2Me$), 22.45 (CH_2CH_3), 19.10 ($CH_2C{\equiv}C$), 18.25 ($C{\equiv}CCH_2$), 14.06 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3023, 2953, 2934, 2871, 2860, 1739, 1601, 1494, 1455, 1436, 1243, 1192, 1162, 1110, 1050, 752 cm^{-1}. HRMS: calcd. for $C_{20}H_{28}O_3$ 316.20385; found 316.2031 (δ = 2 ppm).

Methyl 8-(*tert*-Butyldimethylsilanyloxy)-2,2-dimethyl-8-(2-pentyloxyphenyl)-oct-5-ynoate (25): To a solution of **11** (356 mg, 0.8 mmol) in THF (1.6 mL) was added LDA (2 M *in* THF, 1.4 mL, 3.5 equiv., 2.8 mmol) at –90 °C under nitrogen. The reaction mixture was stirred for 30 min at this temperature, and then raised to –80 °C before addition of iodomethane (400 μL, 8 equiv., 6.4 mmol). The solution was stirred for 30 min at this temperature, before being slowly warmed to room temperature in 3 h. After addition of water, the product was extracted with EtOAc. The organic phase was dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by flash chromatography with PE as eluent to afford **25** as a colorless oil in 84% yield (317 mg, 0.67 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (dd, J = 7.6, 1.7 Hz, 1 H, 6-H), 7.11 (ddd, J = 8.2, 7.8, 1.7 Hz, 1 H, 4-H), 6.85 (ddd, J = 7.6, 7.5, 0.9 Hz, 1 H, 5-H), 6.79 (dd, J = 8.2, 0.9 Hz, 1 H, 3-H), 5.14 (dd, J = 8.2, 3.5 Hz, 1 H, $CHOSi$), 3.92–3.84 (m, 2 H, OCH_2), 3.59 (s, 3 H, CO_2Me), 2.43 (ddt, J = 16.5, 3.5, 2.4 Hz, 1 H, $CHCH_2$), 2.29 (ddt, J = 16.5, 8.2, 2.2 Hz, 1 H, $CHCH_2$), 2.01 (tdd, J = 8.2, 2.4, 2.2 Hz, 2 H, $C{\equiv}CCH_2$), 1.77–1.66 (m, 4 H, OCH_2CH_2 and CH_2CMe_2), 1.45–1.27 (m, 4 H, $CH_2CH_2CH_3$), 1.10 (s, 6 H, CMe_2), 0.88 (t, J = 7.2 Hz, 3 H, CH_3), 0.84 (s, 9 H, *t*BuSi), 0.07 (s, 3 H, CH_3Si), –0.04 (s, 3 H, CH_3Si) ppm. ^{13}C NMR (100 M Hz, $CDCl_3$): δ = 177.86 (CO_2Me), 154.76 (C-2), 132.94 (C-1), 127.80 (C-4), 126.70 (C-6), 120.14 (C-5), 110.57 (C-3), 80.36 and 78.42 ($C{\equiv}C$), 67.94 (OCH_2), 67.71 ($CHOSi$), 51.75 (CO_2Me), 41.95 (CMe_2), 39.92 (CH_2CMe_2), 29.48 ($CHCH_2$), 28.97 ($C{\equiv}CCH_2$), 28.4 (OCH_2CH_2), 25.85 [3C, $(CH_3)_3CSi$], 24.93 ($CH_2CH_2CH_3$), 22.45 (CH_2CH_3), 18.40 [$(CH_3)_3CSi$], 14.89 (2C, CMe_2), 14.09 (CH_3), –4.78 and –4.99 [$(CH_3)_2Si$] ppm.

Methyl 8-Hydroxy-2,2-dimethyl-8-(2-pentyloxyphenyl)-oct-5-ynoate (26): The procedure for the preparation of **26** was the same as that described for the synthesis of **12** (yield 69%, 166 mg, 0.46 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (dd, J = 7.5, 1.7 Hz, 1 H, 6-H), 7.23 (ddd, J = 7.8, 7.8, 1.7 Hz, 1 H, 4-H), 6.95 (ddd, J = 7.8, 7.5, 1.0 Hz, 1 H, 5-H), 6.85 (dd, J = 7.8, 1.0 Hz, 1 H, 3-H), 5.02 (ddd, J = 7.7, 5.9, 4.8 Hz, 1 H, $CHOH$), 4.03–3.94 (m, 2 H, OCH_2), 3.67 (s, 3 H, CO_2Me), 3.02 (d, J = 5.9 Hz, 1 H, OH), 2.71 (ddt, J = 16.5, 4.8, 2.4 Hz, 1 H, $CHCH_2$), 2.54 (ddt, J = 16.5, 7.7, 2.4 Hz, 1 H, $CHCH_2$), 2.13 (tt, J = 8.0, 2.4 Hz, 2 H, $C{\equiv}CCH_2$), 1.85–1.75 (m, 4 H, OCH_2CH_2 and CH_2CMe_2), 1.50–1.33 (m, 4 H, $CH_2CH_2CH_3$), 1.20 (s, 6 H, CMe_2), 0.94 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.05 (CO_2Me), 155.72 (C-2), 130.80 (C-1), 128.48 (C-4), 126.84 (C-6), 120.46 (C-5), 111.05 (C-3), 82.11 and 80.21 ($C{\equiv}C$), 69.22 ($CHOH$), 67.93 (OCH_2), 51.57 (CO_2Me), 41.95 (CMe_2), 39.68 (CH_2CMe_2), 29.02 ($CHCH_2$), 28.40 ($C{\equiv}CCH_2$), 28.09 (OCH_2CH_2), 25.03 ($CH_2CH_2CH_3$), 22.49 (CH_2CH_3), 14.95 (2C, CMe_2), 14.10 (CH_3) ppm. $C_{22}H_{32}O_4$ (360.49): calcd. C 73.30, H 8.95; found C 73.44, H 9.10.

2-Pentyloxy-naphthalene (28): The procedure for the preparation of **28** was the same as that described for the synthesis of **8**. After purification by flash column chromatography (5% EtOAc in PE, R_f: 0.55), **28** was obtained in 97% yield (5.2 g, 24.27 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77–7.69 (m, 3 H, 8-H, 5-H and 4-H), 7.41 (ddd, J = 6.9, 6.9, 1.2 Hz, 1 H, 6-H) 7.31 (ddd, J = 6.9, 6.9, 1.2 Hz, 1 H, 7-H), 7.17–7.10 (m, 2 H, 4-H, 1-H), 4.05 (t, J = 6.6 Hz, OCH_2), 1.89–1.79 (m, CH_2CH_3), 1.52–1.38 (m, 4 H, OCH_2CH_2 and $CH_2CH_2CH_3$), 0.95 (t, J = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.09 (C-2), 134.60 (C-8$_a$), 129.28 (C-4), 128.84 (C-4$_a$), 127.62 (C-5), 126.67 (C-8), 126.26 (C-7), 123.43 (C-6), 119.03 (C-3), 106.47 (C-1), 67.96 (OCH_2), 28.95 (OCH_2CH_2), 28.27 ($CH_2CH_2CH_3$), 22.50 (CH_2CH_3), 14.06 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3058, 2955, 2931, 2871, 2860, 1629, 1601, 1512, 1465, 1390, 1268, 1258, 1217, 1182, 1119, 835, 809, 745, 624, 472 cm^{-1}.

3-Pentyloxy-2-carbaldehydenaphthalene (29): To *t*BuLi (1.7 M in pentane, 7.7 mL, 1.12 equiv., 13.08 mmol) was added a solution of **28** (2.5 g, 11.67 mmol) in tetrahydropyran (THP, 7 mL) at 0 °C under argon, and the reaction mixture was stirred at this temperature for 10 min. Then, the ice bath was removed, and the solution was stirred for 4 h at room temperature. After cooling down to 0 °C, a solution of DMF (2.7 mL, 3 equiv., 35 mmol) in THP (6 mL) was added. The solution became clear, and the reaction mixture was stirred overnight. The product was extracted with EtOAc, washed with water, and dried (Na_2SO_4). After evaporation of the solvent, the crystalline product was washed with PE. The naphthalene **29**

was obtained as a yellow powder (m.p. = 63–68 °C) in 66% yield (1.862 g, 7.68 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.62 (s, 1 H, C*H*O), 8.35 (s, 1 H, 4-H), 7.85 (d, *J* = 8.1 Hz, 1 H, 5-H), 7.7 (d, *J* = 8.2 Hz, 1 H, 8-H), 7.51 (ddd, *J* = 8.2, 6.9, 1.0 Hz, 1 H, 7-H), 7.36 (ddd, *J* = 8.1, 6.9, 0.9 Hz, 1 H, 6-H), 7.16 (s, 1 H, 1-H), 4.14 (t, *J* = 6.5 Hz, 2 H, OCH_2), 1.95–1.87 (m, 2 H, OCH$_2$CH_2), 1.56–1.38 (m, 4 H, CH_2CH_2CH$_3$), 0.96 (t, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.44 (*C*HO), 157.21 (C-2), 137.62 (C-8$_a$), 130.30 (C-4), 129.95 (C-4$_a$), 129.10 (C-5), 127.60 (C-8), 126.56 (C-7), 125.60 (C-6), 124.50 (C-3), 106.97 (C-1), 68.43 (OCH_2), 28.75 (OCH$_2$CH_2), 28.31 (CH_2CH$_2$CH$_3$), 22.45 (CH_2CH$_3$), 14.05 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3447, 3047, 2948, 2867, 1734, 1683, 1623, 1596, 1503, 1454, 1391, 1340, 1255, 1183, 1149, 1104, 1017, 836, 750, 700, 478 cm^{-1}.

1-(3-Pentyloxy-naphthalen-2-yl)-but-3-yn-1-ol (30): The procedure for the preparation of **30** was the same as that described for the synthesis of **9** (yield 61%, 1.497 g, 5.34 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (s, 1 H, 4-H), 7.78 (d, *J* = 8.0 Hz, 1 H, 5-H), 7.70 (d, *J* = 8.2 Hz, 1 H, 8-H), 7.43 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1 H, 7-H), 7.35 (ddd, *J* = 8.0, 6.8, 1.3 Hz, 1 H, 6-H), 7.11 (s, 1 H, 1-H), 5.2 (ddd, *J* = 7.4, 6.2, 5.0 Hz, 1 H, C*H*OH), 4.11 (m, 2 H, OCH_2), 3.03 (d, *J* = 6.2 Hz, 1 H, OH), 2.89 (ddd, *J* = 16.8, 5.0, 2.6 Hz, 1 H, CHCH_2), 2.72 (ddd, *J* = 16.8, 7.4, 2.6 Hz, 1 H, CHCH_2), 2.06 (t, *J* = 2.6 Hz, 1 H, C≡C*H*), 1.93–1.86 (m, 2 H, OCH$_2$CH_2), 1.55–1.38 (m, 4 H, CH_2CH_2CH$_3$), 0.96 (t, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.70 (C-2), 134.29 (C-8$_a$), 132 (C-4), 128.81 (C-4$_a$), 128.28 (C-5), 126.76 (C-8), 126.71 (C-7), 126.56 (C-6), 124.29 (C-3), 106.41 (C-1), 81.56 (*C*≡CH), 71.04 (C≡*C*H), 69.92 (*C*HOH), 68.41 (OCH_2), 29.25 (OCH$_2$CH_2), 28.80 (CH_2CH$_2$CH$_3$), 27.97 (CHCH_2), 22.83 (CH_2CH$_3$), 14.44 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3329, 3305, 3297, 3056, 2951, 2932, 2861, 2121, 1632, 1601, 1503, 1465, 1394, 1322, 1251, 1219, 1183, 1149, 1103, 1071, 1015, 872, 840, 747, 643, 621, 480 cm^{-1}.

***tert*-Butyldimethyl[1-(3-pentyloxy-naphthalen-2-yl)-but-3-ynyloxy]-silane (31):** The procedure for the preparation of **31** was the same as that described for the synthesis of **10** (yield 87%, 1.819 g, 4.6 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (s, 1 H, 4-H), 7.78 (d, *J* = 8.0 Hz, 1 H, 5-H), 7.70 (d, *J* = 8.2 Hz, 1 H, 8-H), 7.43 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1 H, 7-H), 7.35 (ddd, *J* = 8.0, 6.8, 1.3 Hz, 1 H, 6-H), 7.11 (s, 1 H, 1-H), 5.20 (ddd, *J* = 7.4, 6.2, 5.0 Hz, 1 H, C*H*OSi), 4.11–4.06 (m, 2 H, OCH_2), 2.89 (ddd, *J* = 16.8, 5.0, 2.6 Hz 1 H, CHCH_2), 2.72 (ddd, *J* = 16.8, 7.4, 2.6 Hz, 1 H, CHCH_2), 2.06 (t, *J* = 2.6 Hz, 1 H, C≡C*H*), 1.93–1.86 (m, 2 H, OCH$_2$CH_2), 1.55–1.38 (m, 4 H, CH_2CH_2CH$_3$), 0.96 (t, *J* = 7.2 Hz, 3 H, CH_3), 0.91 (s, 9 H, *tBu*Si), 0.10 (s, 3 H, CH_3Si), –0.05 (s, 3 H, CH_3Si) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.70 (C-2), 134.29 (C-8$_a$), 132.00 (C-4), 128.81 (C-4$_a$), 128.28 (C-5), 126.76 (C-8), 126.71 (C-7), 126.56 (C-6), 124.29 (C-3), 106.41 (C-1), 81.56 (*C*≡CH), 71.04 (C≡*C*H), 69.92 (*C*HOH), 68.41 (OCH_2), 29.25 (OCH$_2$CH_2), 28.80 (CH_2CH$_2$CH$_3$), 27.97 (CHCH_2), 25.86 [3C, (CH_3)$_3$CSi], 22.83 (CH_2CH$_3$), 18.35 [(CH$_3$)$_3$*C*Si], 14.44 (CH_3), 4.81 and –4.93 (CH_3Si) ppm. IR: $\tilde{\nu}$ = 3302, 3056, 2953, 2929, 2857, 2359, 1633, 1601, 1502, 1465, 1398, 1329, 1250, 1215, 1184, 1117, 1095, 1014, 934, 836, 776, 746, 645, 482 cm^{-1}.

Methyl 8-(*tert*-Butyldimethylsilanyloxy)-8-(3-pentyloxy-naphthalen-2-yl)-oct-5-ynoate (32): The procedure for the preparation of **32** was the same as that described for the synthesis of **11** (yield 77%, 1.759 g, 3.54 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (s, 1 H, 4-H), 7.77 (d, *J* = 7.9 Hz, 1 H, 5-H), 7.70 (d, *J* = 8.1 Hz, 1 H, 8-H), 7.39 (ddd, *J* = 8.1, 6.7, 1.2 Hz, 1 H, 7-H), 7.35 (ddd, *J* = 7.9, 6.7, 1.2 Hz, 1 H, 6-H), 7.05 (s, 1 H, 1-H), 5.30 (dd, *J* = 7.3, 3.4 Hz, 1 H, C*H*OH), 4.08 (t, *J* = 6.4 Hz, OCH_2), 3.66 (s, 3 H, CO$_2$*Me*), 2.65 (ddt, *J* = 16.5, 3.4, 2.5 Hz, 1 H, CHCH_2), 2.47 (ddt, *J* = 16.5, 7.3, 2.3 Hz, 1 H, CHCH_2), 2.40 (t, *J* = 7.5 Hz, 2 H, CH_2CO$_2$Me), 2.24–2.18 (m, 2 H, C≡CCH_2), 1.93–1.85 (m, 2 H, OCH$_2$CH_2), 1.82–1.73 (m, 2 H, CH_2CH$_2$CO$_2$Me), 1.55–1.38 (m, 4 H, CH_2CH_2CH$_3$), 0.96 (t, *J* = 7.2 Hz, 3 H, CH_3), 0.95 (s, 9 H, Sit*Bu*), 0.12 (s, 3 H, *Me*Si), –0.08 (s, 3 H, *Me*Si) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.84 (*C*O$_2$Me), 153.86 (C-2), 134.4 (C-8$_a$), 133.71 (C-4$_a$), 128.48 (C-3), 127.81 (C-5), 126.20 (C-8), 126.09 (C-4), 125.84 (C-7), 123.41 (C-6), 105.22 (C-1), 79.88 and 78.93 (*C*≡*C*H), 68.34 (*C*HOH), 67.73 (OCH_2), 51.48 (CO$_2$*Me*), 32.81 (*C*H$_2$CO$_2$Me), 29.47 (CH*C*H$_2$), 28.80 (OCH$_2$*C*H$_2$), 28.44 (*C*H$_2$CH$_2$CH$_3$), 25.86 [3C, (*C*H$_3$)$_3$CSi], 24.08 (*C*H$_2$CH$_2$CO$_2$Me), 22.42 (*C*H$_2$CH$_3$), 18.33 [2C, C≡C*C*H$_2$ and (CH$_3$)$_3$*C*Si], 14.10 (*C*H$_3$), –4.78 and –4.95 (*Me*$_2$Si) ppm. IR (KBr): $\tilde{\nu}$ = 3055, 2953, 2929, 2856, 2357, 1738, 1634, 1504, 1463, 1330, 1248, 1209, 1179, 1109, 1084, 938, 834, 777, 745 cm^{-1}.

Methyl 8-Hydroxy-8-(3-pentyloxy-naphthalen-2-yl)-oct-5-ynoate (33): The procedure for the preparation of **33** was the same as that described for the synthesis of **12** (yield 68%, 892 mg, 2.33 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (s, 1 H, 4-H), 7.78 (d, *J* = 8.0 Hz, 1 H, 5-H), 7.70 (d, *J* = 8.1 Hz, 1 H, 8-H), 7.42 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1 H, 7-H), 7.35 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 1 H, 6-H), 7.26 (s, 1 H, 1-H), 5.15 (s, 1 H, C*H*OH), 4.11–4.05 (m, 2 H, OCH_2), 3.65 (s, 3 H, CO$_2$*Me*), 3.06 (s, 1 H, O*H*), 2.85 (ddt, *J* = 16.5, 5.0, 2.4 Hz, 1 H, CHCH_2), 2.47 (ddt, *J* = 16.5, 7.1, 2.4 Hz, 1 H, CHCH_2), 2.36 (t, *J* = 7.4 Hz, 2 H, CH_2CO$_2$Me), 2.22 (tt, *J* = 6.8, 2.4 Hz, 2 H, C≡CCH_2), 1.92–1.84 (m, 2 H, OCH$_2$CH_2), 1.77 (tt, *J* = 7.4, 6.8 Hz, 2 H, CH_2CH$_2$CO$_2$Me), 1.55–1.38 (m, 4 H, CH_2CH_2CH$_3$), 0.96 (t, *J* = 7.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.76 (*C*O$_2$Me), 154.35 (C-2), 133.81 (C-8$_a$), 132.05 (C-4$_a$), 128.44 (C-3), 127.82 (C-5), 126.26 (C-8), 126.19 (C-4), 126.05 (C-7), 123.77 (C-6), 105.87 (C-1), 81.67 and 77.56 (*C*≡*C*), 69.54 (*C*HOH), 67.94 (OCH_2), 51.56 (CO$_2$*Me*), 32.78 (*C*H$_2$CO$_2$Me), 28.85 (CH*C*H$_2$), 28.40 (OCH$_2$*C*H$_2$), 28.01 (*C*H$_2$CH$_2$CH$_3$), 23.98 (*C*H$_2$CH$_2$CO$_2$Me), 22.43 (*C*H$_2$CH$_3$), 18.26 (C≡C*C*H$_2$), 14.05 (*C*H$_3$) ppm. $C_{24}H_{30}O_4$ (382.49): calcd. C 75.36, H 7.91; found C 75.47, H 8.42.

Sodium 8-Hydroxy-8-(3-pentyloxy-naphthalen-2-yl)-oct-5-ynoate (34): The procedure for the preparation of **34** was the same as that described for the synthesis of **13** (yield 99%, 164 mg, 0.42 mmol). Acid: ^{1}H NMR (400 MHz, DMSO): δ = 7.84 (s, 1 H, 4-H), 7.77 (d, *J* = 8.0 Hz, 1 H, 5-H), 7.69 (d, *J* = 8.1 Hz, 1 H, 8-H), 7.41 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1 H, 7-H), 7.35 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 1 H, 6-H), 7.26 (s, 1 H, 1-H), 5.15 (dd, *J* = 6.6, 5.3 Hz, 1 H, C*H*OH), 4.14–4.04 (m, 2 H, OCH_2), 2.85 (ddt, *J* = 16.5, 4.8, 2.3 Hz, 1 H, CHCH_2), 2.66 (ddt, *J* = 16.5, 7.0, 2.3 Hz, 1 H, CHCH_2), 2.36 (t, *J* = 7.4 Hz, 2 H, CH_2CO$_2$H), 2.23 (tt, *J* = 6.7, 2.3 Hz, 2 H, C≡CCH_2), 1.92–1.82 (m, 2 H, OCH$_2$CH_2), 1.77 (tt, *J* = 7.4, 6.7 Hz, 2 H, CH_2CH$_2$CO$_2$H), 1.54–1.34 (m, 4 H, CH_2CH_2CH$_3$), 0.96 (t, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 179.01 (*C*O$_2$H), 154.31 (C-2), 133.81 (C-8$_a$), 131.90 (C-4$_a$), 128.41 (C-3), 128.41 (C-5), 126.25 (C-8), 126.22 (C-4), 126.10 (C-7), 123.81 (C-6), 105.89 (C-1), 81.49 and 77.72 (*C*≡*C*), 69.69 (*C*HOH), 67.95 (OCH_2), 32.66 (*C*H$_2$CO$_2$H), 28.83 (CH*C*H$_2$), 28.38 (OCH$_2$*C*H$_2$), 27.93 (*C*H$_2$CH$_2$CH$_3$), 23.68 (*C*H$_2$CH$_2$CO$_2$Me), 22.42 (*C*H$_2$CH$_3$), 18.17 (C≡C*C*H$_2$), 14.04 (*C*H$_3$) ppm. Salt: $C_{23}H_{27}NaO_4$ (390.45) calcd. C 70.75, H 7.97; found C 70.89, H 8.02.

Methyl 8-Hydroxy-8-(3-pentyloxy-naphthalen-2-yl)-oct-5-enoate (35): The procedure for the preparation of **35** was the same as that described for the synthesis of **14** (yield 84%, 251 mg, 0.65 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (s, 1 H, 4-H), 7.76 (d, *J* =

8.0 Hz, 1 H, 5-H), 7.69 (d, *J* = 8.0 Hz, 1 H, 8-H), 7.40 (ddd, *J* = 8.0, 7.0, 1.2 Hz, 1 H, 7-H), 7.32 (ddd, *J* = 8.0, 7.0, 1.2 Hz, 1 H, 6-H), 7.10 (s, 1 H, 1-H), 5.60–5.40 (m, 2 H, *H*C=C*H*), 5.04 (dd, *J* = 7.5, 5.3 Hz, 1 H, C*H*OH), 4.15–4.06 (m, 2 H, OCH_2), 3.63 (s, 3 H, CO_2*Me*), 2.72–2.64 (m, 1 H, CHCH_2), 2.63–2.54 (m, 1 H, CHCH_2), 2.25 (t, *J* = 7.5 Hz, 2 H, CH_2CO_2Me), 2.11–2.02 (m, 2 H, C=CCH_2), 1.92–1.83 (m, 2 H, OCH_2CH_2), 1.68–1.59 (m, 2 H, C$H_2CH_2CO_2$Me), 1.55–1.37 (m, 4 H, C$H_2CH_2CH_3$), 0.96 (t, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.19 (*C*O_2Me), 154.60 (C-2), 133.70 (C-8_a), 133.29 (C-4_a), 131.29 and 126.73 (*C*H=*C*H), 128.50 (C-3), 127.71 (C-5), 126.27 (C-8), 126.08 (C-4), 125.95 (C-7), 123.76 (C-6), 105.90 (C-1), 70.94 (*C*HOH), 67.92 (O*C*H_2), 51.52 (CO_2*Me*), 35.35 (C=C*C*H_2), 33.40 (*C*H_2CO_2Me), 28.91 (CH*C*H_2), 28.42 (OCH_2*C*H_2), 26.69 (*C*$H_2CH_2CH_3$), 24.71 (*C*$H_2CH_2CO_2$Me), 22.43 (*C*H_2CH_3), 14.05 (*C*H_3) ppm. $C_{24}H_{32}O_4$ (384.51): calcd. C 74.97, H 8.39; found C 75.38, H 8.58.

Methyl 8-Hydroxy-8-(3-pentyloxy-naphthalen-2-yl)-octanoate (36): The procedure for the preparation of **36** was the same as that described for the synthesis of **15** (yield 88%, 165 mg, 0.43 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.0 Hz, 1 H, 5-H), 7.72 (s, 1 H, 4-H), 7.70 (d, *J* = 8.1 Hz, 1 H, 8-H), 7.40 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1 H, 7-H), 7.32 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 1 H, 6-H), 7.11 (s, 1 H, 1-H), 4.97 (dd, *J* = 12.5, 6.2 Hz, 1 H, C*H*OH), 4.11 (t, *J* = 6.4 Hz, 2 H, OCH_2), 3.65 (s, 3 H, CO_2*Me*), 2.72 (d, *J* = 6.2 Hz, 1 H, O*H*), 2.25 (t, *J* = 7.5 Hz, 2 H, CH_2CO_2Me), 1.92–1.83 (m, 4 H, C$H_2CH_2CH_2CO_2$Me and OCH_2CH_2), 1.66–1.56 (m, 2 H, C$H_2CH_2CO_2$Me), 1.55–1.27 (m, 10 H, CHC$H_2CH_2CH_2$ and C$H_2CH_2CH_3$), 0.96 (t, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.29 (*C*O_2Me), 154.79 (C-2), 134.00 (C-8_a), 133.65 (C-4_a), 128.54 (C-3), 127.66 (C-5), 126.27 (C-8), 126.08 (C-4), 125.89 (C-7), 123.78 (C-6), 105.99 (C-1), 71.70 (*C*HOH), 67.88 (O*C*H_2), 51.46 (CO_2*Me*), 37.35, 34.07, 29.19, 29.11, 28.90, 28.44, 26.02, 24.90, 22.42 (9 C, *C*$H_2CH_2CH_2CH_2CH_2CH_2CO_2$Me and *C*$H_2CH_2CH_2CH_3$), 14.06 (*C*$H_3$) ppm. $C_{24}H_{34}O_4$ (386.52): calcd. C 74.58, H 8.87; found C 74.83, H 8.97.

Sodium 8-Hydroxy-8-(3-pentyloxy-naphthalen-2-yl)-oct-5-enoate (37): The procedure for the preparation of **37** was the same as that described for the synthesis of **13** (yield 95%, 165 mg, 0.42 mmol). Acid: ^{1}H NMR (400 MHz, DMSO): δ = 7.93 (s, 1 H, 4-H), 7.74 (d, *J* = 7.9 Hz, 1 H, 5-H), 7.79 (d, *J* = 8.1 Hz, 1 H, 8-H), 7.42 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1 H, 7-H), 7.33 (ddd, *J* = 7.9, 6.9, 1.1 Hz, 1 H, 6-H), 7.28 (s, 1 H, 1-H), 5.62–5.33 (m, 2 H, *H*C=C*H*), 5.03 (m, 1 H, C*H*OH), 4.18–4.07 (m, 2 H, OCH_2), 2.59–2.50 (m, 1 H, CHCH_2), 2.32–2.21 (m, 1 H, CHCH_2), 2.15 (t, *J* = 7.5 Hz, 2 H, CH_2CO_2H), 2.01–1.94 (m, 2 H, C=CCH_2), 1.87–1.79 (m, 2 H, OCH_2CH_2), 1.54–1.35 (m, 6 H, C$H_2CH_2CO_2$H and C$H_2CH_2CH_3$), 0.94 (t, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 175.91 (*C*O_2H), 155.45 (C-2), 137.40 (C-8_a), 134.81 (C-4_a), 131.37 and 126.54 (*C*H=*C*H), 129.98 (C-3), 129.64 (C-5), 129.01 (C-8), 127.82 (C-4), 127.19 (C-7), 124.97 (C-6), 106.96 (C-1), 68.93 (*C*HOH), 68.54 (O*C*H_2), 37.13 (C=C*C*H_2), 34.67 (*C*H_2CO_2H), 29.98 (CH*C*H_2), 29.51 (OCH_2*C*H_2), 27.87 (*C*$H_2CH_2CH_3$), 23.47 (*C*$H_2CH_2CO_2$H), 22.35 (*C*H_2CH_3), 15.57 (*C*H_3) ppm. Salt: HRMS: calcd. for $C_{23}H_{29}NaO_4$ 393.20418; found 393.2060 (δ = 5 ppm).

Sodium 8-Hydroxy-8-(3-pentyloxy-naphthalen-2-yl)-octanoate (38): The procedure for the preparation of **38** was the same as that described for the synthesis of **13** (yield 86%, 146 mg, 0.41 mmol). Acid: ^{1}H NMR (400 MHz, DMSO): δ = 7.82 (d, *J* = 7.9 Hz, 1 H, 5-H), 7.90 (s, 1 H, 4-H), 7.78 (d, *J* = 8.0 Hz, 1 H, 8-H), 7.41 (dd, *J* = 8.0, 7.0 Hz, 1 H, 7-H), 7.33 (ddd, *J* = 7.9, 7.0, 1.2 Hz, 1 H, 6-H), 7.27 (s, 1 H, 1-H), 4.98 (dd, *J* = 8.1, 3.6 Hz, 1 H, C*H*OH), 4.14–4.06 (m, 2 H, OCH_2), 2.20 (t, *J* = 7.3 Hz, 2 H, CH_2CO_2H), 1.87–1.77 (m, 2 H, C$H_2CH_2CH_2CO_2$H), 1.77–1.68 (m, 2 H, OCH_2CH_2), 1.55–1.21 (m, 2 H, C$H_2CH_2CO_2$H), 1.55–1.27 (m, 10 H, CHC$H_2CH_2CH_2$ and C$H_2CH_2CH_3$), 0.96 (t, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 176.05 (*C*O_2H), 155.51 (C-2), 138.37 (C-8_a), 134.71 (C-4_a), 129.69 (C-3), 128.91 (C-5), 127.80 (C-8), 127.10 (C-4), 126.13 (C-7), 124.93 (C-6), 106.89 (C-1), 68.82 (*C*HOH), 68.09 (O*C*H_2), 39.66, 35.22, 30.25, 30.20, 30.03, 29.61, 27.11, 26.09, 23.49 (9 C, *C*$H_2CH_2CH_2CH_2$-*C*$H_2CH_2CO_2$H and *C*$H_2CH_2CH_2CH_3$), 15.57 (*C*H_3) ppm. Salt: HRMS: calcd. for $C_{23}H_{31}NaO_4$ 395.21983; found 395.2192 (δ = 2 ppm).

2-Chloro-3-carbaldehydepyridine (40): To a solution of phenyllithium (9.35 mL, 2 M in pentane/THF, 1.1 equiv., 18.7 mmol) in THF (34 mL) were added, at –60 °C under argon, 2-chloropyridine (1.61 mL, 17 mmol) and diisopropylamine (50 μL, 0.02 equiv., 0.34 mmol). The temperature was raised to –40 °C and the reaction mixture was stirred for 1 h at this temperature. Then, after cooling the reaction mixture to –60 °C, *N*-formylpiperidine (4.80 mg, 2.5 equiv., 42.5 mmol) was added. The temperature was warmed to –40 °C, and the reaction mixture was stirred for 1 h at this temperature. The hydrolysis was performed by addition of HCl (0.5 M). The aqueous phase was neutralized by a saturated $NaHCO_3$ solution, and the product was extracted with Et_2O. The organic phase was dried (Na_2SO_4) and concentrated under vacuum. The pyridine was purified by column chromatography, with PE as eluent, R_f: 0.07 eluent PE/EtOAc (95:5), to afford **40** as a colorless powder (m.p.: 33–37 °C) in 39% yield (942 mg, 6.65 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.46 (d, *J* = 0.8 Hz, 1 H, CHO), 8.62 (dd, *J* = 4.8, 2.1 Hz, 1 H, 6-H), 8.25 (dd, *J* = 7.7, 2.1 Hz, 1 H, 4-H), 7.44 (ddd, *J* = 7.7, 4.8, 0.8 Hz, 1 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.22 (*C*HO), 154.20 (C-6), 153.64 (C-2), 138.07 (C-4), 128.88 (C-3), 123.25 (C-5) ppm. IR (KBr): $\tilde{\nu}$ = 3353, 3040, 2887, 1698, 1579, 1416, 1378, 1263, 1068, 834, 808, 730, 417 cm^{-1}.

2-Chloro-3-dimethoxy-methylpyridine (41): To a solution of **40** (1.838 g, 13 mmol) and ammonium nitrate (52 mg, 0.05 equiv., 0.65 mmol) in methanol (13 mL) was added trimethyl orthoformate (1.7 mL, 1.2 equiv., 15.6 mmol, 1.653 g). The reaction mixture was heated to reflux for 2.5 h. After addition of a saturated Na_2CO_3 solution, the product was extracted with Et_2O (2×). The organic phase was dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by filtration through silica gel with PE as eluent to afford **41** as a colorless oil in 96% yield (2.189 g, 12.47 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (dd, *J* = 4.8, 2.0 Hz, 1 H, 6-H), 7.97 (dd, *J* = 7.6, 2.0 Hz, 1 H, 4-H), 7.29 (dd, *J* = 7.6, 4.8 Hz, 1 H, 5-H), 5.59 [s, 1 H, C*H*$(OMe)_2$], 3.40 [s, 6 H, $(OMe)_2$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.16 (C-6), 149.58 (C-2), 137.23 (C-4), 132.18 (C-3), 122.38 (C-5), 100.44 (*C*H), 54.05 [2C, $(OMe)_2$] ppm.

2-Pentyloxy-3-dimethoxy-methylpyridine (42): To a suspension of NaH (1.995 g, 60% dispersion in oil which was washed three times with petroleum ether, 4 equiv., 49.88 mmol) in NMP (10 mL) was added *n*-pentyl alcohol (5.42 mL, 4 equiv., 49.88 mmol) very slowly at 0 °C. The reaction mixture was stirred for 10 min at this temperature, and a solution of **41** (2.189 g, 12.47 mmol) in NMP (2.5 mL) was added. After stirring overnight at room temperature, the reaction mixture was poured on ice and the product was extracted with PE. After filtration through silica gel, using PE as eluent, the pyridine **42** was isolated as a colorless oil in 42% yield (1.247 g, 5.2 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (dd, *J*

= 5.0, 2.0 Hz, 1 H, 6-H), 7.79 (dd, *J* = 7.3, 2.0 Hz, 1 H, 4-H), 6.88 (dd, *J* = 7.3, 5.0 Hz, 1 H, 5-H), 5.55 [s, 1 H, C*H*(OMe)$_2$], 4.34 (t, *J* = 6.7 Hz, 2 H, OC*H*$_2$), 3.39 [s, 6 H, (O*Me*)$_2$], 1.84–1.75 (m, 2 H, OCH$_2$C*H*$_2$), 1.48–1.33 (m, 4 H, C*H*$_2$C*H*$_2$CH$_3$), 0.93 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.22 (C-2), 146.89 (C-6), 135.99 (C-4), 120.54 (C-3), 116.24 (C-5), 99.13 [*C*H(O*Me*)$_2$], 66.09 (O*C*H$_2$), 53.99 [2C, (O*Me*)$_2$], 28.71 (OCH$_2$*C*H$_2$), 28.24 (*C*H$_2$CH$_2$CH$_3$), 22.45 (*C*H$_2$CH$_3$), 14.07 (*C*H$_3$) ppm.

2-Pentyloxy-3-carbaldehydepyridine (43): To a solution of **42** (1.247 g, 5.2 mmol) in THF/H_2O (9:1, 52 mL) was added *p*-toluenesulfonic acid (149 mg, 0.15 equiv., 0.78 mmol). The reaction mixture was heated to reflux for 3 h. The product was extracted with PE (3×). After filtration through silica gel, **43** was obtained as a yellow oil in 91% yield (910 mg, 4.71 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.45 (d, *J* = 0.9 Hz, 1 H, CHO), 8.36 (dd, *J* = 4.9, 2.1 Hz, 1 H, 6-H), 8.11 (dd, *J* = 7.5, 2.1 Hz, 1 H, 4-H), 6.99 (ddd, *J* = 7.5, 4.9, 0.9 Hz, 1 H, 5-H), 4.44 (t, *J* = 6.7 Hz, 2 H, OC*H*$_2$), 1.88–1.80 (m, 2 H, OCH$_2$C*H*$_2$), 1.5–1.37 (m, 4 H, C*H*$_2$C*H*$_2$CH$_3$), 0.94 (t, *J* = 7.1 Hz, 3 H, CH$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.38 (*C*HO), 164.59 (C-2), 152.95 (C-6), 137.40 (C-4), 118.76 (C-3), 117.03 (C-5), 66.77 (O*C*H$_2$), 28.58 (OCH$_2$*C*H$_2$), 28.24 (*C*H$_2$CH$_2$CH$_3$), 22.44 (*C*H$_2$CH$_3$), 14.03 (*C*H$_3$) ppm.

1-(2-Pentyloxypyridin-3-yl)-but-3-yn-1-ol (44): The procedure for the preparation of **44** was the same as that described for the synthesis of **9** (yield 79%, 856 mg, 3.66 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 5.0, 1.9 Hz, 1 H, 6-H), 8.11 (dd, *J* = 7.3, 1.9 Hz, 1 H, 4-H), 6.99 (dd, *J* = 7.3, 5.0 Hz, 1 H, 5-H), 4.99 (ddd, *J* = 7.1, 6.0, 5.2 Hz, 1 H, C*H*OH), 4.39–4.30 (m, 2 H, OC*H*$_2$), 3.00 (d, *J* = 6.0 Hz, 1 H, OH), 2.81 (ddd, *J* = 16.7, 5.2, 2.6 Hz, 1 H, CHC*H*$_2$), 2.62 (ddd, *J* = 16.7, 7.1, 2.6 Hz, 1 H, CHC*H*$_2$), 2.05 (t, *J* = 2.6 Hz, 1 H, C≡C*H*), 1.84–1.73 (m, 2 H, OCH$_2$C*H*$_2$), 1.47–1.39 (m, 4 H, C*H*$_2$C*H*$_2$CH$_3$), 0.93 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.30 (C-2), 145.82 (C-6), 135.44 (C-4), 124.50 (C-3), 116.69 (C-5), 80.60 (*C*≡CH), 70.98 (C≡*C*H) 68.12 (*C*HOH), 66.09 (O*C*H$_2$), 29.44 (OCH$_2$*C*H$_2$), 28.71 (*C*H$_2$CH$_2$CH$_3$), 26.97 (CH*C*H$_2$), 22.51 (*C*H$_2$CH$_3$), 14.05 (*C*H$_3$) ppm.

3-[1-(*tert*-Butyldimethylsilanyloxy)-but-3-ynyl]-2-pentyloxypyridine (45): The procedure for the preparation of **45** was the same as that described for the synthesis of **10** (yield 76%, 963 mg, 2.77 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (dd, *J* = 5.0, 1.9 Hz, 1 H, 6-H), 8.11 (dd, *J* = 7.3, 1.9 Hz, 1 H, 4-H), 6.99 (dd, *J* = 7.3, 5.0 Hz, 1 H, 5-H), 5.12 (dd, *J* = 6.9, 3.8 Hz, 1 H, C*H*OSi), 4.32 (t, *J* = 6.6 Hz, 2 H, OC*H*$_2$), 2.62 (ddd, *J* = 16.7, 3.9, 2.7 Hz, 1 H, CHC*H*$_2$), 2.47 (ddd, *J* = 16.7, 6.9, 2.6 Hz, 1 H, CHC*H*$_2$), 1.93 (dd, *J* = 2.7, 2.6 Hz, 1 H, C≡C*H*), 1.83–1.74 (m, 2 H, OCH$_2$C*H*$_2$), 1.49–1.33 (m, 4 H, C*H*$_2$C*H*$_2$CH$_3$), 0.93 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$), 0.91 (s, 9 H, *tBu*Si), 0.12 (s, 3 H, C*H*$_3$Si), –0.03 (s, 3 H, C*H*$_3$Si) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.75 (C-2), 145.42 (C-6), 135.53 (C-4), 126.34 (C-3), 116.57 (C-5), 81.64 (*C*≡CH), 69.70 (C≡*C*H), 67.10 (*C*HOSi), 65.84 (O*C*H$_2$), 28.74 (OCH$_2$*C*H$_2$), 28.39 (*C*H$_2$CH$_2$CH$_3$), 25.84 (CH*C*H$_2$), 25.71 [3C, (*C*H$_3$)$_3$CSi], 22.46 (*C*H$_2$CH$_3$), 18.29 [(CH$_3$)$_3$*C*Si], 14.09 (*C*H$_3$), –4.82 and –4.90 [(*C*H$_3$)$_2$Si] ppm.

Methyl 8-(*tert*-Butyldimethylsilanyloxy)-8-(2-pentyloxypyridin-3-yl)-oct-5-ynoate (46): The procedure for the preparation of **46** was the same as that described for the synthesis of **11** (yield 45%, 558 mg, 1.25 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (dd, *J* = 5.0, 1.9 Hz, 1 H, 6-H), 7.75 (dd, *J* = 7.3, 1.9 Hz, 1 H, 4-H), 6.87 (dd, *J* = 7.3, 5.0 Hz, 1 H, 5-H), 5.07 (dd, *J* = 6.8, 4.0 Hz, 1 H, C*H*OSi), 4.31 (t, *J* = 6.1 Hz, 2 H, OC*H*$_2$), 3.68 (s, 3 H, CO$_2$*Me*), 2.57 (ddt, *J* = 16.6, 4.0, 2.2 Hz, 1 H, CHC*H*$_2$), 2.43 (ddt, *J* = 16.6, 6.8, 2.2 Hz, 1 H, CHC*H*$_2$), 2.39 (t, *J* = 7.4 Hz, 2 H, C*H*$_2$CO$_2$Me), 1.83–1.72 (m, 4 H, OCH$_2$C*H*$_2$ and C*H*$_2$CH$_2$CO$_2$Me), 1.48–1.24 (m, 6 H, C*H*$_2$C*H*$_2$CH$_3$ and C≡CC*H*$_2$), 0.93 (t, *J* = 6.8 Hz, 3 H, C*H*$_3$), 0.91 (s, 9 H, *tBu*Si), 0.09 (s, 3 H, C*H*$_3$Si), –0.04 (s, 3 H, C*H*$_3$Si) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.80 (*C*O$_2$Me), 159.76 (C-2), 145.22 (C-6), 135.50 (C-4), 126.72 (C-3), 116.52 (C-5), 80.29 and 78.19 (*C*≡*C*), 67.48 (O*C*H$_2$), 65.77 (*C*HOSi), 51.51 (CO$_2$*Me*), 32.81 (*C*H$_2$CO$_2$Me), 28.73 (C≡C*C*H$_2$), 28.64 (CH*C*H$_2$), 28.37 (OCH$_2$*C*H$_2$), 24.07 (*C*H$_2$CH$_2$CH$_3$), 25.78 [3C, (*C*H$_3$)$_3$CSi], 22.45 (*C*H$_2$CH$_3$), 18.27 [2C, *C*H$_2$CH$_2$CO$_2$Me and (CH$_3$)$_3$*C*Si], 14.07 (*C*H$_3$), –4.86 and –4.96 [(*C*H$_3$)$_2$Si] ppm.

Methyl 8-Hydroxy-8-(2-pentyloxypyridin-3-yl)-oct-5-ynoate (47): The procedure for the preparation of **47** was the same as that described for the synthesis of **12** (yield 71%, 566 mg, 1.69 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (dd, *J* = 5.0, 1.9 Hz, 1 H, 6-H), 7.69 (dd, *J* = 7.3, 1.9 Hz, 1 H, 4-H), 6.89 (dd, *J* = 7.3, 5.0 Hz, 1 H, 5-H), 4.94 (ddd, *J* = 7.0, 5.9, 5.0 Hz, 1 H, C*H*OH), 4.34 (t, *J* = 6.7 Hz, 2 H, OC*H*$_2$), 3.69 (s, 3 H, CO$_2$*Me*), 2.96 (d, *J* = 5.9 Hz, 1 H, O*H*), 2.77 (ddt, *J* = 16.5, 5.0, 2.5 Hz, 1 H, CHC*H*$_2$), 2.56 (ddt, *J* = 16.5, 7.0, 2.4 Hz, 1 H, CHC*H*$_2$), 2.38 (t, *J* = 7.4 Hz, 2 H, C*H*$_2$CO$_2$Me), 2.23 (tdd, *J* = 6.9, 2.5, 2.4 Hz, 2 H, C≡CC*H*$_2$), 1.83–1.75 (m, 4 H, OCH$_2$C*H*$_2$ and C*H*$_2$CH$_2$CO$_2$Me), 1.48–1.34 (m, 4 H, C*H*$_2$C*H*$_2$CH$_3$), 0.93 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.76 (*C*O$_2$Me), 160.33 (C-2), 145.59 (C-6), 135.36 (C-4), 124.89 (C-3), 116.62 (C-5), 82.02 and 76.71 (*C*≡*C*), 68.28 (O*C*H$_2$), 66.03 (*C*HOH), 51.62 (CO$_2$*Me*), 32.84 (*C*H$_2$CO$_2$Me), 28.72 (C≡C*C*H$_2$), 28.34 (CH*C*H$_2$), 27.39 (OCH$_2$*C*H$_2$), 23.95 (*C*H$_2$CH$_2$CH$_3$), 22.44 (*C*H$_2$CH$_3$), 18.22 (*C*H$_2$CH$_2$CO$_2$Me), 14.05 (*C*H$_3$) ppm.

Sodium 8-Hydroxy-8-(2-pentyloxypyridin-3-yl)-oct-5-ynoate (48): The procedure for the preparation of **48** was the same as that described for the synthesis of **13** (yield 96%, 92 mg, 0.27 mmol). Acid: ^{1}H NMR (400 MHz, DMSO): δ = 8.07 (dd, *J* = 5.1, 2.0 Hz, 1 H, 6-H), 7.69 (dd, *J* = 7.6, 1.5 Hz, 1 H, 4-H), 6.89 (dd, *J* = 7.1, 5.1 Hz, 1 H, 5-H), 4.95 (dd, *J* = 5.6, 5.0 Hz, 1 H, C*H*OH), 4.34 (t, *J* = 6.6 Hz, 2 H, OC*H*$_2$), 2.77 (ddt, *J* = 16.3, 5.0, 2.0 Hz, 1 H, CHC*H*$_2$), 2.58 (ddt, *J* = 16.3, 5.6, 2.5 Hz, 1 H, CHC*H*$_2$), 2.43 (t, *J* = 7.1 Hz, 2 H, C*H*$_2$CO$_2$H), 2.25 (tdd, *J* = 6.6, 2.0, 2.4 Hz, 2 H, C≡CC*H*$_2$), 1.84–1.74 (m, 4 H, OCH$_2$C*H*$_2$ and C*H*$_2$CH$_2$CO$_2$H), 1.48–1.34 (m, 4 H, C*H*$_2$C*H*$_2$CH$_3$), 0.93 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 178.33 (*C*O$_2$H), 160.30 (C-2), 145.59 (C-6), 135.43 (C-4), 124.89 (C-3), 116.66 (C-5), 81.87 and 77.18 (*C*≡*C*), 68.33 (O*C*H$_2$), 66.12 (*C*HOH), 32.69 (*C*H$_2$CO$_2$H), 28.70 (C≡C*C*H$_2$), 28.34 (CH*C*H$_2$), 27.33 (OCH$_2$*C*H$_2$), 23.67 (*C*H$_2$CH$_2$CH$_3$), 22.44 (*C*H$_2$CH$_3$), 18.16 (*C*H$_2$CH$_2$CO$_2$H), 14.04 (*C*H$_3$) ppm.

Methyl 8-Hydroxy-8-(2-pentyloxypyridin-3-yl)-oct-5-enoate (49): To a suspension of Lindlar catalyst (26 mg, 10 wt.-% Pd) in toluene (3.12 mL) was added **47** (261 mg, 0.78 mmol). The reaction mixture was stirred under hydrogen for 36 h at room temperature. After filtration through Celite, the alkene **49** was obtained as a yellow oil in 74% yield (193 mg, 0.58 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (dd, *J* = 5.0, 1.9 Hz, 1 H, 6-H), 7.61 (dd, *J* = 7.3, 1.9 Hz, 1 H, 4-H), 6.87 (dd, *J* = 7.3, 5.0 Hz, 1 H, 5-H), 5.54–5.43 (m, 2 H, *H*C=C*H*), 4.84 (dd, *J* = 7.3, 5.5 Hz, 1 H, CHC*H*$_2$), 4.38–4.30 (m, 2 H, OC*H*$_2$), 3.66 (s, 3 H, CO$_2$*Me*), 2.72 (broad s, 1 H, OH), 2.64–2.44 (m, 2 H, CHC*H*$_2$), 2.28 (t, *J* = 7.5 Hz, 2 H, C*H*$_2$CO$_2$Me), 2.09–1.99 (m, 2 H, C=CC*H*$_2$), 1.84–1.75 (m, 2 H, OCH$_2$C*H*$_2$), 1.70–1.61 (m, 2 H, C*H*$_2$CH$_2$CO$_2$Me), 1.48–1.34 (m, 4 H, C*H*$_2$C*H*$_2$CH$_3$), 0.93 (t, *J* = 7.0 Hz, 3 H, C*H*$_3$) ppm. ^{13}C NMR

(100 MHz, $CDCl_3$): δ = 174.10 (CO_2Me), 160.48 (C-2), 145.32 (C-6), 135.27 (C-4), 131.80 and 126.14 (H*C*=*C*H), 125.29 (C-3), 116.68 (C-5), 69.71 (C-7), 65.97 (CH*C*H_2), 51.52 (CO_2*Me*), 33.38 (*C*H_2CO_2Me), 28.77 (C=C*C*H_2), 28.38 (*C*$H_2CH_2CO_2$Me), 26.63 (OCH_2*C*H_2), 24.68 (*C*$H_2CH_2CH_3$), 22.45 (*C*H_2CH_3), 14.05 (*C*H_3) ppm. $C_{19}H_{29}NO_4$ (335.44): calcd. C 68.03, H 8.71, N 4.18; found C 68.08, H 8.85, N 4.21.

Methyl 8-Hydroxy-8-(2-pentyloxypyridin-3-yl)-octanoate (50): The procedure for the preparation of **50** was the same as that described for the synthesis of **15** (yield 88%, 169 mg, 0.50 mmol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (dd, *J* = 5.0, 1.9 Hz, 1 H, 6-H), 7.6 (dd, *J* = 7.3, 1.9 Hz, 1 H, 4-H), 6.88 (dd, *J* = 7.3, 5.0 Hz, 1 H, 5-H), 4.8 (t, *J* = 6.5 Hz, 1 H, C*H*OH), 4.38–4.29 (m, 2 H, OCH_2), 3.65 (s, 3 H, CO_2*Me*), 2.34 (t, *J* = 7.5 Hz, 2 H, CH_2CO_2Me), 1.84–1.72 (m, 4 H, OCH_2CH_2 and $CH_2CH_2CH_2CO_2$Me), 1.67–1.57 (m, 2 H, $CH_2CH_2CO_2$Me), 1.50–1.30 (m, 10 H, $CHCH_2CH_2CH_2$ and $CH_2CH_2CH_3$), 0.93 (t, *J* = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.10 (CO_2Me), 160.52 (C-2), 145.00 (C-6), 135.48 (C-4), 126.96 (C-3), 116.80 (C-5), 70.16 (OCH_2), 66.21 (*C*HOH), 51.85 (CO_2*Me*), 36.74, 33.96, 29.07, 28.72, 28.38, 25.66, 24.61, 22.42, 21.07 (9 *C*H_2, *C*$H_2CH_2CH_2CH_2CH_2CH_2CO_2$Me and *C*$H_2CH_2CH_2CH_3$), 14.05 (*C*$H_3$) ppm. $C_{19}H_{31}NO_4$ (337.45): calcd. C 67.63, H 9.26, N 4.15; found C 67.47, H 9.48, N 4.36.

Sodium 8-Hydroxy-8-(2-pentyloxypyridin-3-yl)-oct-5-enoate (51): The procedure for the preparation of **51** was the same as that described for the synthesis of **13** (yield 93%, 93 mg, 0.27 mmol). Acid: ^{1}H NMR (400 MHz, DMSO): δ = 8.07 (dd, *J* = 5.2, 1.9 Hz, 1 H, 6-H), 7.66 (dd, *J* = 7.3, 1.9 Hz, 1 H, 4-H), 6.91 (dd, *J* = 7.3, 5.2 Hz, 1 H, 5-H), 5.56–5.44 (m, 2 H, *H*C=C*H*), 4.87 (dd, *J* = 7.3, 5.5 Hz, 1 H, $CHCH_2$), 4.42–4.32 (m, 2 H, OCH_2), 2.64–2.44 (m, 2 H, $CHCH_2$), 2.31 (t, *J* = 7.4 Hz, 2 H, CH_2CO_2H), 2.10–2.00 (m, 2 H, C=CCH_2), 1.86–1.76 (m, 2 H, OCH_2CH_2), 1.70–1.60 (m, 2 H, $CH_2CH_2CO_2$H), 1.49–1.34 (m, 4 H, $CH_2CH_2CH_3$), 0.93 (t, *J* = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 176.92 (CO_2H), 160.16 (C-2), 144.61 (C-6), 135.97 (C-4), 135.97 and 131.83 (H*C*=*C*H), 126.02 (C-3), 116.77 (C-5), 69.57 (C-7), 66.62 (CH*C*H_2), 33.06 (*C*H_2CO_2H), 28.72 (C=C*C*H_2), 28.33 (*C*$H_2CH_2CO_2$H), 26.49 (OCH_2CH_2), 24.38 (*C*$H_2CH_2CH_3$), 22.41 (*C*H_2CH_3), 14.03 (*C*H_3) ppm. Salt: HRMS: calcd. for $C_{18}H_{26}NNaO_4$ 344.18378; found 344.1835 (δ = 1 ppm).

Sodium 8-Hydroxy-8-(2-pentyloxypyridin-3-yl)-octanoate (52): The procedure for the preparation of **52** was the same as that described for the synthesis of **13** (yield 96%, 83 mg, 0.24 mmol). Acid: ^{1}H NMR (400 MHz, DMSO): δ = 8.06 (dd, *J* = 5.1, 1.2 Hz, 1 H, 6-H), 7.60 (dd, *J* = 7.1, 2.0 Hz, 1 H, 4-H), 6.88 (dd, *J* = 7.1, 5.0 Hz, 1 H, 5-H), 4.8 (t, *J* = 6.6 Hz, 1 H, C*H*OH), 4.39–4.29 (m, 2 H, OCH_2), 2.33 (t, *J* = 7.6 Hz, 2 H, CH_2CO_2H), 1.84–1.70 (m, 4 H, OCH_2CH_2 and $CH_2CH_2CH_2CO_2$H), 1.68–1.56 (m, 2 H, $CH_2CH_2CO_2$H), 1.50–1.30 (m, 10 H, $CHCH_2CH_2CH_2$ and $CH_2CH_2CH_3$), 0.93 (t, *J* = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 179.26 (CO_2H), 160.52 (C-2), 145.00 (C-6), 135.48 (C-4), 126.96 (C-3), 116.78 (C-5), 70.16 (OCH_2), 66.20 (*C*HOH), 36.74, 33.96, 29.07, 28.73, 28.38, 25.65, 24.61, 22.42, 21.07 (9 *C*H_2, *C*$H_2CH_2CH_2CH_2CH_2CH_2CO_2$H and *C*$H_2CH_2CH_2CH_3$), 14.05 (*C*$H_3$) ppm.

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