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Synthesis and spectroscopic characterization of double chained and sulfurated derivatives of L-ascorbic acid

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Dedicated to Prof. Jacek Młochowski on the occasion of his 80th anniversary

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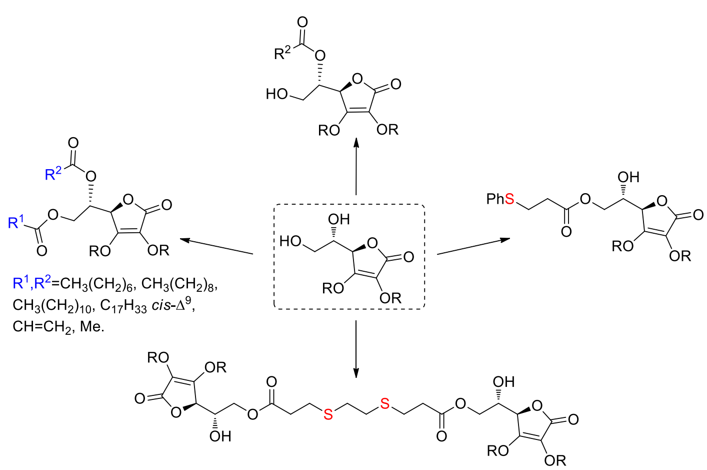
Abstract

Lipophilic saturated and unsaturated L-ascorbyl 5,6-*O*-diesters from fatty acids are prepared and fully characterized through NMR and MS spectra. Derivatives with different sulfurated moieties are obtained as well through thio-Michael addition of thiols on ascorbyl acrylates. The new amphiphilic structures exhibit very high antioxidant activity using the DPPH assay.



Keywords: L-Ascorbic acid, fatty acids, antioxidant, sulfurated ascorbyl esters, thio-Michael addition

Introduction

Antioxidants are widely used in different fields, for example the food, cosmetic and pharmaceutical industries. Our interest in the chemistry of sulfurated and selenated compounds led us to develop an access to organo-chalcogen derivatives, such as selenides, diselenides and heterocyclic compounds,[1-6] which evidenced interesting antioxidant activity. The chemistry of organosulfur, and more recently of organoselenium compounds has in fact experienced a strong development.[7,8] Such derivatives are used as reagents in organic synthesis and, due to their interest from the biological point of view, in the preparation of molecules with biological activity. Recently we were involved in the study of modifications of natural products, with the aim to introduce on the same molecular skeleton sulfurated or selelenated moieties, which could possess a synergistic effect together with the natural core. We found a convenient method for the synthesis of selenium-derivatives of resveratrol as antioxidants and free radical scavengers.[9] These structures evidenced antioxidant activity with Trolox-like capacity.

In this context considerable interest has also been devoted to the study of liposoluble ester derivatives of L-ascorbic acid (L-ASC), which is a well known, potent and versatile antioxidant. Their physico-chemical properties have been extensively investigated[10-17] in particular their phase behavior in the solid state and in aqueous dispersions. The amphiphilic derivatives of ascorbic acid fully retain the antioxidant power of the parent molecule, and produce nanostructured self-assembled systems both in aqueous and non aqueous media, and therefore they can act as carriers for important hydrophobic molecules such as drugs and nutraceutics.

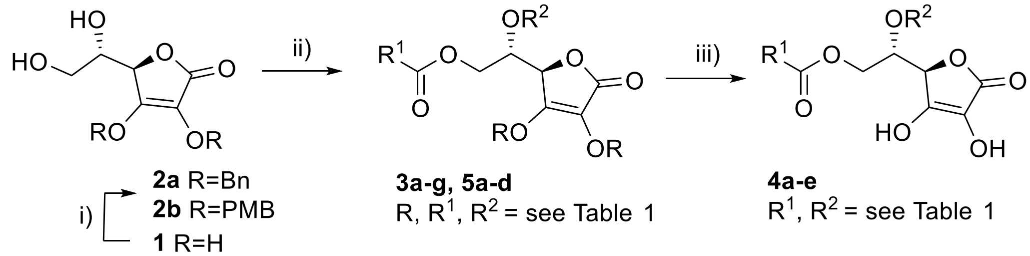
Certainly, a very large number of contributions have been reported on vitamin C, most of them dealing with the elaboration at positions 2, 3 or 6, depending on the application needs.[18-22] Generally 6-*O*-ascorbyl esters are obtained via different methods, by reacting vitamin C and fatty acids under catalysis of lipases[20] or in concentrated sulfuric acid.[23]

Here we report the preparation and full characterization of lipophilic saturated and unsaturated 5,6-*O*-diesters of L-ASC, as well as of sulphur-containing 6-*O*-ascorbyl alkanoates. Preliminary evaluation of their antioxidant properties will also be described.

Results and Discussion

To the best of our knowledge, few examples of synthesis of 5,6-diesters of L-ASC have been reported. Nevertheless, a very large number of examples of esterification at C-6 with palmitoyl chloride were described in a patent, bearing different substituents and protecting groups on selected hydroxyls.[24] Chemical modifications of vitamin C are often limited by its intrinsic instability. Typically, together with the methods cited above, the chemical synthesis of ascorbyl esters is carried out by selective protection and deprotection of functional groups. Several steps are required to obtain the target compounds. Usually the first step involves the protection of hydroxyl groups on C-6 and C-5 as an acetonide, followed by treatment of the enol hydroxyls with benzyl bromide.[21,25] Nevertheless, on the basis of results recently reported[26] and of our own results in separate experiments, we observed a high, selective reactivity of the ene-diol portion with benzyl bromide by comparison with the alcohols at the 5 and 6 positions. This allowed us to treat L-ASC **1** with BnBr and K_2CO_3 in

THF/DMSO (Scheme 1) directly, thus avoiding preliminary protection as 5,6-*O*-isopropylidene derivative and the following deprotection step.



Scheme 1. (i) RBr/K_2CO_3, THF/DMSO, 50 °C, 3 h; (ii) acyl chlorides, 4-DMAP/DCC or Et_3N (see experimental); (iii) H_2, Pd/C or $SnCl_4$/PhSH (see experimental).

The dibenzyl ether **2a** was then treated with saturated fatty acid derivatives. Thus acyl chlorides of octanoic (caprylic, C_8), decanoic (capric, C_{10}) and dodecanoic (lauric, C_{12}) acid were reacted in the presence of DMAP/DCC in acetonitrile (Scheme 1). L-Ascorbyl 5,6-*O*-dialkanoates **3a-c** were obtained in high yields (Table 1, entries 1-3). Cleavage with H_2, Pd/C led to the formation in quantitave yield of the previously unreported 2,3-$(OH)_2$-5,6-diesters **4a-c**, which were fully characterized by means of NMR and MS spectra.

Table 1. Synthesis of saturated and unsaturated L-ASC esters

Entry	R	R¹	R²	Products (Yield %)[a]	Products **4** (Yield %)[a]
1	Bn	$CH_3(CH_2)_6$	$CO(CH_2)_6CH_3$	**3a** (90)	**4a** (>98)
2	Bn	$CH_3(CH_2)_8$	$CO(CH_2)_8CH_3$	**3b** (88)	**4b** (>98)
3	Bn	$CH_3(CH_2)_{10}$	$CO(CH_2)_{10}CH_3$	**3c** (91)	**4c** (>98)
4	Bn	$CH_3(CH_2)_{10}$	$COCH_3$	**3d** (63)[b]	**4d** (>98)
5	Bn	$C_{17}H_{33}$ *cis*-Δ^9	$(CO)C_{17}H_{33}$ *cis*-Δ^9	**3e** (78)	-
6	PMB	$C_{17}H_{33}$ *cis*-Δ^9	$(CO)C_{17}H_{33}$ *cis*-Δ^9	**3f** (83)	**4e** (34)
7	Bn	$CH=CH_2$	$(CO)CHCH_2$	**3g** (75)	-
8	PMB	$C_{17}H_{33}$ *cis*-Δ^9	H	**5a** (48)	-
9	Bn	$CH=CH_2$	H	**5b** (53)[c]	-
10	PMB	$CH=CH_2$	H	**5c** (48)[c]	-
11	Bn	$CH_3(CH_2)_{10}$	H	**5d** (68)	-

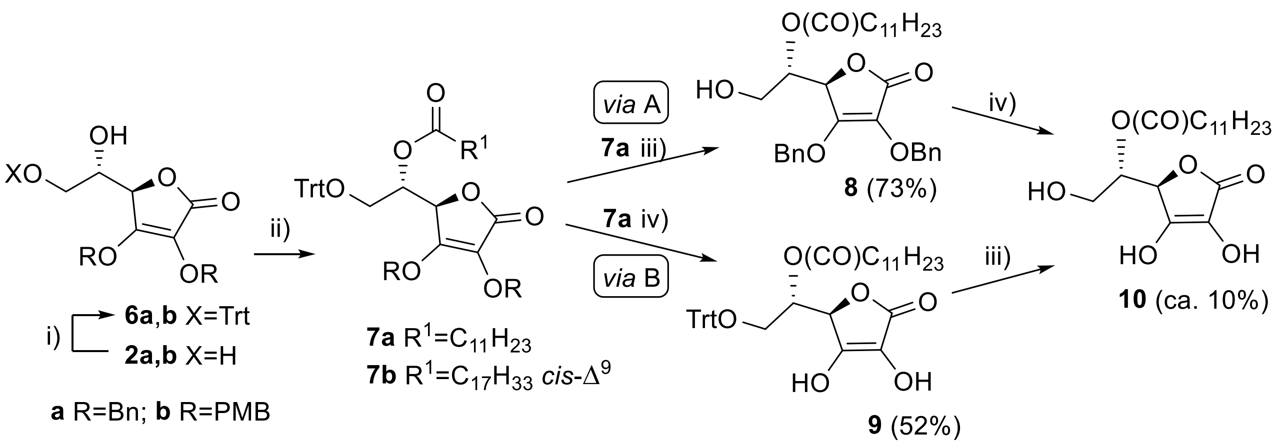
[a] Isolated yields. [b] Global yield over two steps. [c] 10% of diester was also formed.

In order to synthesize derivatives with different acyl chain lengths, for evaluating the influence on physico-chemical properties, compound **3d** (Table 1, entry 4) was prepared in two steps from lauroyl- and acetyl-chlorides (see experimental). The final deprotection afforded the mixed diester **4d** (Scheme 1) . All the diesters were obtained with high selectivity (>99%), no trace of monoesters being observed.

Our interest also focused in the preparation of ascorbyl oleates. These compounds bear, on the same molecular skeleton, both oleic and ascorbic acid residues, that each possess antioxidant properties. However, the synthesis was not straightforward, the products being rather sensitive compounds. This makes ascorbyl oleate difficult to produce with traditional chemical methods. To the best of our knowledge only one example has been described for ascorbyl 6-monooleate,[27] while enzymatic methodologies are generally reported.[28-34] The search for alternative methods is therefore a challenge to access these molecules.

Following a similar approach, oleoyl chloride was reacted with **2a** leading to the formation of 2,3-*O*-dibenzyl-5,6-*O*-ascorbyl dioleate **3e** in good yield (Scheme 1 and Table 1, entry 5). For the cleavage of benzylic ethers, the incompatibility of H_2, Pd/C system with the double bonds prompted us to seek alternative, mild methods. Unfortunately, treatment with CSI (chlorosulfonyl isocyanate)[35] did not afford the desired compound, but a complex mixture of products was formed. Thus, a different protecting group – *p*-methoxybenzyl (PMB) – was chosen. PMB can be more easily cleaved with numerous reagents, avoiding strong conditions.[36,37] PMB-protected ascorbic acid **2b** was prepared under the same conditions by direct treatment of L-ASC with PMBBr/K_2CO_3 (Scheme 1). Subsequent reaction with oleyl chloride afforded 2,3-*O*-*p*-methoxybenzyl-5,6-*O*-ascorbyl dioleate **3f** (Scheme 1 and Table 1, entry 6) or 2,3-*O*-*p*-methoxybenzyl-6-*O*-ascorbyl oleate **5a** (Table 1, entry 8), depending on the reaction conditions (treatment with DMAP/DCC for diester, with Et_3N for monoester). Efficient cleavage of **3f** with $SnCl_4$/thiophenol[37] at -78 °C led to the isolation of the 2,3-deprotected ascorbyl dioleate **4e**, while reaction on **5a** allowed cleavage of only one PMBO-group (most likely on C-2). Further experiments are under investigation to obtain complete deprotection at both positions. Nonetheless, the result obtained is rather interesting, providing new ascorbyl oleates through a convenient, alternative access.

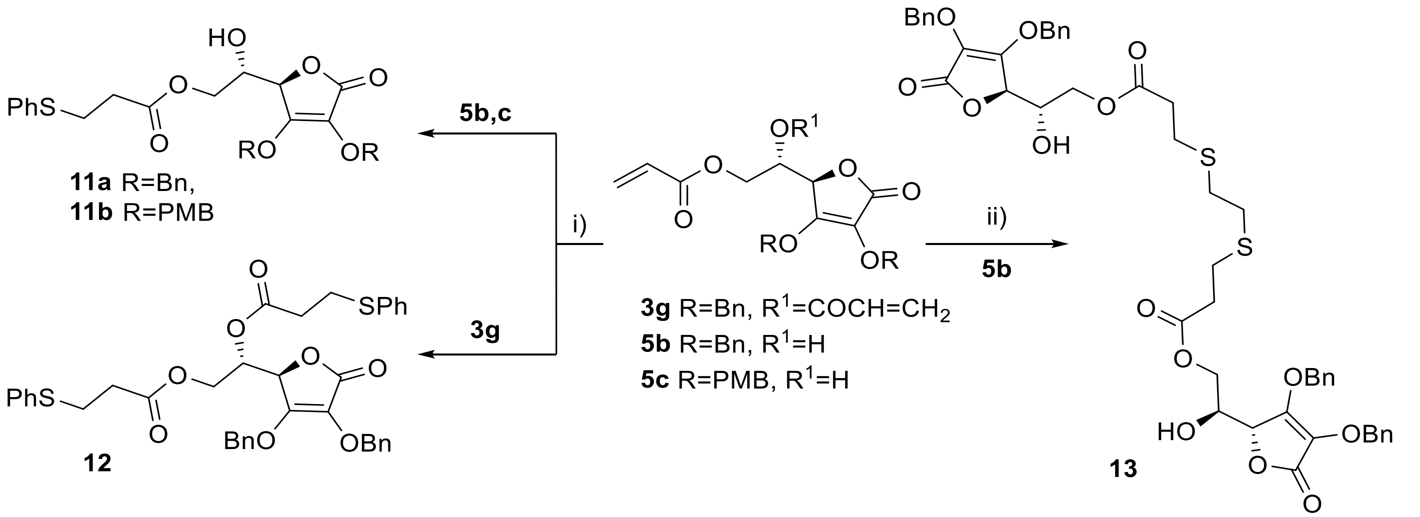
As a further step, we decided to evaluate the esterification on the secondary OH at position 5, retaining a free hydroxyl at C-6. To achieve this, a preliminary protection of 6-OH with trityl chloride was carried out on **2a** and **2b** following literature procedures (Scheme 2).[25]



Scheme 2. (i) Trityl chloride/Et_3N; (ii) R^1COCl/DMAP/DCC; (iii) $BF_3{\cdot}Et_2O$; iv) H_2, Pd/C.

After purification, the so obtained products **6a,b** were reacted respectively with lauroyl chloride and oleoyl chloride in the presence of DMAP/DCC, leading to **7a** and **7b** in good yields (Scheme 2). Deprotection of 6-OTrt under acidic conditions[38] was performed by treatment of **7a** with BF_3 etherate, leading to **8** (Scheme 2, *via A*). When reductive cleavage was carried out to obtain complete deprotection on C-2/C-3, a very complex mixture was observed, and the desired product **10** was present in only very low yield (<10%).

In order to seek better conditions, we firstly considered deprotection of benzyl groups in **7a** with H_2/Pd/C (Scheme 2, *via B*). Compound **9** was isolated, and then treated under acidic conditions (BF_3) to remove the trityl group. Unfortunately, through this sequence, compound **10** was also formed in comparable yields (ca. 10%), and optimization of this step is surely required.



Scheme 3. (i) PhSH, Neutral Al_2O_3; (ii) $HSCH_2CH_2SH$, neutral Al_2O_3 (see experimental).

Nevertheless, compound **9** is interesting, in so far as the enediol moiety, responsible of the antioxidant activity of vitamin C, is still present in this molecule.

Finally, to introduce a sulfurated or selenated group on the skeleton of vitamin C, we prepared ascorbyl 5,6-*O*-diacrylate **3g** and 6-*O*-acrylates **5b**,[24] **5c** (Scheme 1 and Table 1, entries 3, 9 and 10). Then **5b, 5c** and **3g** were reacted respectively with one or two equivalents of a sulfur nucleophile (PhSH) in the presence of Al_2O_3[39] (Scheme 3). Under these conditions compounds **11a, 11b** and **12** were isolated, arising from a thio-Michael addition to the enones.

Even more interesting was the reaction of **5b** with 1,2-ethanedithiol, providing the synthesis of the diascorbyl derivative **13**, containing a sulfurated linker between the two vitamin C moieties (Scheme 3). It will be of interest to investigate the characteristics of such derivatives, including chains of different length, to compare their properties with the behaviour of bolaform surfactants studied by some of us.[12] Search for conditions to deprotect 2,3-positions is currently under study in our laboratory.

Finally, in order to preliminary evaluate whether the antioxidant capacity was maintained for these new amphiphilic structures, they were tested through the DPPH assay,[40] which provides an easy and rapid way to assess antioxidant potency. Substances **4a-e** and **9** exhibited a very high ability to act as free radical scavengers, in fact they instantaneously reacted with DPPH.

Conclusions

Different saturated and unsaturated ascorbyl derivatives, including novel sulfurated compounds, were prepared from fatty acids, and characterized by mono- and bidimensional NMR experiments. Their antioxidant activity was determined with the DPPH assay.

Experimental Section

General. NMR spectra were recorded in $CDCl_3$ with Varian Gemini 200, Mercury 400, Inova 400 and Bruker 400 spectrometers operating at 200 and 400 MHz (^{1}H), 50 and 100 MHz (^{13}C). NMR signals were referenced to non deuterated residual solvent signals of deuterochloroform (7.26 ppm for ^{1}H, 77.0 ppm for ^{13}C). Mass spectra (MS) were obtained by ESI. IR spectra were recorded on a Perkin Elmer Instrument (FT-IR). Only selected absorptions are reported, in wavenumbers (cm^{-1}). Solvents were dried using a solvent purification system (Pure-Solv^{TM}). Flash column chromatography was performed using silica gel (230-400 mesh). Where not specified, products were commercially available or obtained through reported procedures. 4-Methoxybenzyl bromide (PMBBr) was synthesised from (4-methoxyphenyl)methanol (PMBOH) upon treatment with phosphorus tribromide.[41] DPPH assay was performed according to the literature,[40] by measuring the adsorbance decreasing of a DPPH methanolic solution (10^{-4} M) treated with an equimolar amount of ascorbic acid derivatives (**4 a-e**, **9**).

General procedure for the protection of L-ascorbic acid as 2,3-dibenzyl- or 2,3-bis(*p*-methoxybenzyl)-ethers (GP1)[25]

Benzyl bromide or *p*-methoxybenzyl bromide (2.4 eq) was added to a suspension of L-ascorbic acid (1.0 eq) and K_2CO_3 (3.0 eq) in DMSO/THF (2:1 vol) and the reaction was stirred at 50 °C for 3 h. Afterwards, the mixture was filtered through a Celite pad and the organic phase was extracted with EtOAc and washed with brine and H_2O. The organic layer was dried on Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc).

(*R*)-5-((*S*)-1,2-Dihydroxyethyl)-3,4-bis((4-methoxybenzyl)oxy)furan-2(5H)-one (2b). Following the general procedure, 1.8 g of L-ascorbic acid and 4.94 g of *p*-methoxybenzyl bromide gave, after purification, **2b** (1.91 g, 45%) as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.80 (s, 3H), 3.81 (s, 3H), 3.71-3.81 (m, 2H), 3.85-3.90 (m, 1H), 4.64 (d, *J* 2.4 Hz, 1H, CHO), 5.06 (ap s, 2H), 5.07 (d, *J* 11.2 Hz, 1H), 5.12 (d, *J* 11.2 Hz, 1H), 6.86 (ap d, ls 8.6 Hz, 2H), 6.91 (ap d, ls 8.6 Hz, 2H), 7.15 (ap d, ls 8.6 Hz, 2H), 7.33 (ap d, ls 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 55.3, 63.3, 69.9, 73.4, 73.7, 76.1, 113.9, 114.0, 120.8, 127.3, 128.1, 129.9, 130.9, 157.6, 159.9, 160.0, 170.1. Elemental Analysis: $C_{22}H_{24}O_8$ C 63.45%, H 5.81%. Found: C 63.22%, H 5.83%.

General procedure for the synthesis of ascorbyl 5-*O*-,6-*O*-dialkanoates protected as 2,3-dibenzyl ethers or 2,3-bis((4-methoxybenzyl) ethers. (GP2). 4-DMAP (12 mmol, 3 eq.) and DCC (12 mmol, 3 eq.) were added to a stirred solution of **2a** or **2b** (4 mmol, 1 eq.) in MeCN (40 mL) under inert atmosphere at rt. Then the alkanoyl chloride (9.2 mmol, 2.3 eq.) was slowly added and the mixture was stirred for 12 h. Afterwards the solvent was removed under reduced pressure and the crude material purified by flash chromatography (petroleum ether/EtOAc 8:1).

(*S*)-1-((*R*)-3,4-Bis(benzyloxy)-5-oxo-2,5-dihydrofuran-2-yl)ethane-1,2-diyl dioctanoate (3a). Following the general procedure *GP2*, **2a** (1.0 g, 2.80 mmol) and octanoyl chloride (1.043 g, 6.44 mmol) gave, after flash chromatography, **3a** (1.53 g, 90%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 0.82-0.89 (m, 6H), 1.18-1.27 (m, 16H), 1.43-1.54 (m, 4H), 2.15-2.33 (m, 4H), 4.22 (dd, *J* 7.4, 11.6 Hz, 1H, $C\mathbf{H_a}H_bO$), 4.33 (dd, *J* 5.6, 11.6 Hz, 1H, $CH_a\mathbf{H_b}O$), 4.80 (d, *J* 2.2 Hz, 1H, CHO), 5.10 (ap. s, 2H, C**H**$_2$Ph), 5.15 (ap. s, 2H, C**H**$_2$Ph), 5.34-5.42 (m, 1H, C**H**CH$_2$), 7.19-7.25 (m, 4H), 7.27-7.42 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 13.9, 22.5, 24.6, 24.7, 24.8, 28.7, 28.8, 28.9, 31.5, 33.8, 61.8, 67.3, 73.5, 73.6, 121.2, 127.9, 128.0, 128.6, 128.7, 128.8, 128.9, 129.0, 135.0, 135.9, 154.9, 168.3, 172.1, 172.8. MS (ESI positive) *m/z* (%): 632 [M+Na]$^+$, (100). Elemental Analysis: $C_{36}H_{48}O_8$ C 71.03%, H 7.95%. Found: C 70.82%, H 7.98%.

(*S*)-1-((*R*)-3,4-Bis(benzyloxy)-5-oxo-2,5-dihydrofuran-2-yl)ethane-1,2-diyl didecanoate (3b). Following the general procedure *GP2*, **2a** (1.0 g, 2.80 mmol) and decanoyl chloride (1.22 g, 6.44 mmol) gave, after flash chromatography, **3b** (1.64 g, 88%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.84-0.90 (m, 6H), 1.25 (m, 24H), 1.52-1.66 (m, 4H), 2.19 (dt, *J* 2.2, 7.1 Hz, 2H), 2.22-2.33 (m, 2H), 4.22 (dd, *J* 7.0, 11.7 Hz, 1H, C$\mathbf{H_a}$$H_b$O), 4.32 (dd, *J* 5.9, 11.7 Hz, 1H, C$H_a$$\mathbf{H_b}$O), 4.80 (d, *J*2.0 Hz, 1H, CCHO), 5.10 (ap s, 2H, C$\mathbf{H}_2$Ph), 5.14 (ap s, 2H, C$\mathbf{H}_2$Ph), 5.35-5.39 (m, 1H, C**H**CH_2), 7.21-7.23 (m, 2H), 7.33-7.39 (m, 8H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 13.7, 22.3, 24.3, 24.5, 24.7, 25.2, 28.8, 28.9, 29.1, 31.6, 33.6, 34.6, 55.3, 61.6, 67.2, 73.3, 73.5, 121.2, 127.7, 128.3, 128.4, 134.9, 135.7, 154.7, 168.1, 171.7, 172.5. MS (ESI positive) *m/z* (%): 687 $[M+Na]^+$, (100). Elemental Analysis: $C_{40}H_{56}O_8$ C 72.26%, H 8.49%. Found: C 72.01%, H 8.52%.

(*S*)-1-((*R*)-3,4-Bis(benzyloxy)-5-oxo-2,5-dihydrofuran-2-yl)ethane-1,2-diyl didodecanoate (3c). Following the general procedure *GP2*, **2a** (1.41 g, 3.95 mmol) and dodecanoyl chloride (1.981 g, 9.1 mmol) gave, after flash chromatography, **3c** (2.59 g, 91%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 0.84-0.90 (m, 6H), 1.24 (m, 32H), 1.48-1.53 (m, 4H), 2.14-2.26 (m, 4H), 3.83 (ap d, ls 6.2 Hz, 2H, CH_2O), 4.90 (d, *J* 1.8 Hz, 1H, CCHO), 5.10 (ap s, 2H, C$\mathbf{H}_2$Ph), 5.17 (ap.s, 2H, C$\mathbf{H}_2$Ph), 5.18-5.23 (m, 1H, C**H**CH_2), 7.17-7.28 (m, 2H), 7.33-7.41 (m, 8H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 14.0, 22.7, 24.8, 25.0, 29.1, 29.3, 29.4, 29.6, 31.9, 34.0, 61.9, 67.5, 73.8, 121.6, 128.0, 128.7, 128.8, 128.9, 135.2, 136.0, 155.1, 168.5, 172.2, 173.0. MS (ESI positive) *m/z* (%): 744 $[M+Na]^+$, (100). Elemental Analysis: $C_{44}H_{64}O_8$ C 73.30%, H 8.95%. Found: C 73.46%, H 8.92%.

(*S*)-2-Acetoxy-2-((*R*)-3,4-bis(benzyloxy)-5-oxo-2,5-dihydrofuran-2-yl)ethyl dodecanoate (3d). Acetyl chloride (154 mg, 1.95 mmol, 1.5 eq.) was slowly added, to a cooled solution (0 °C) of **5d** (*vide infra*) (700 mg, 1.30 mmol, 1.0 eq.) and Et_3N (400 mg, 3.9 mmol, 3.0 eq.) in CH_2Cl_2 (10 mL). The reaction was allowed to warm up to rt and the mixture was stirred overnight under inert atmosphere. The reaction was then diluted with H_2O (10 mL), the layers separated and the aqueous layer extracted into Et_2O (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by flash column chromatography (petroleum ether/EtOAc 4:1) to give **3d** (695 mg, 92%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 0.87 (ap t, *J* 7.0 Hz, 3H), 1.24 (m, 16H), 1.42-1.63 (m, 2H), 1.93 (s, 3H), 2.27 (t, *J* 8 Hz, 2H), 4.25 (dd, *J* 7.3, 12.0 Hz, 1H, C$\mathbf{H_a}$$H_b$O), 4.32 (dd, *J* 6.6, 12.0 Hz, 1H, C$H_a$$\mathbf{H_b}$O), 4.80 (d, *J* 2.2 Hz, 1H, CHO), 5.06-5.13 (m, 2H), 5.15 (ap. s, 2H, C$\mathbf{H}_2$Ph), 5.26-5.39 (m, 1H), 7.17-7.26 (m, 2H), 7.33-7.40 (m, 8H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 14.1, 20.4, 22.6, 24.7, 29.1, 29.2, 29.3, 29.4, 29.6, 31.9, 33.9, 61.8, 67.7, 73.7, 121.4, 128.0, 128.4, 128.8, 129.0, 135.1, 135.9, 155.1, 168.5, 169.4, 173.0. MS (ESI positive) *m/z* (%): 603 $[M+Na]^+$, (100). Elemental Analysis: $C_{34}H_{44}O_8$ C 70.32%, H 7.64%. Found: C 70.08%, H 7.67%.

(*S*)-1-((*R*)-3,4-Bis(benzyloxy)-5-oxo-2,5-dihydrofuran-2-yl)ethane-1,2-diyl dioleate (3e). Following the general procedure *GP2*, **2a** (500 mg, 1.40 mmol) and oleoyl chloride (969 mg, 3.22 mmol) gave, after flash chromatography, **3e** (966 mg, 78%) as a slightly yellowish oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 0.88 (ap t, *J* 6.4 Hz, 6H), 1.17-1.40 (m, 40H), 1.48-1.68 (m, 4H), 1.93-2.08 (m, 8H), 2.18-2.31 (m, 4H), 4.23 (dd, *J* 7.1, 11.5 Hz, 1H, C$\mathbf{H_a}$$H_b$O), 4.34 (dd, *J* 5.0, 11.5 Hz, 1H, C$H_a$$\mathbf{H_b}$O), 4.80 (d, *J* 2.1 Hz, 1H, CHO), 5.11 (s, 2H), 5.16 (s, 2H), 5.26-5.44 (m, 5H), 7.21-7.43 (m, 10H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 14.0, 22.6, 24.8, 25.0, 27.2, 29.1, 29.3, 29.5, 29.7, 29.8, 31.9, 34.0, 61.9, 67.6, 73.7, 121.7, 128.0, 128.2, 128.7, 128.8, 128.9, 129.7, 130.0, 135.2, 136.1, 155.0, 168.4, 172.1, 172.9. MS (ESI positive) *m/z* (%): 908 $[M+Na]^+$, (100). Elemental Analysis: $C_{56}H_{84}O_8$ C 75.98%, H 9.56%. Found: C 75.77%, H 9.58%.

(*S*)-1-((*R*)-3,4-Bis((4-methoxybenzyl)oxy)-5-oxo-2,5-dihydrofuran-2-yl)ethane-1,2-diyl dioleate (3f). Following the general procedure *GP2*, **2b** (200 mg, 0.48 mmol) and oleoyl chloride (301 mg, 1.0 mmol) gave, after flash chromatography, **3f** (376 mg, 83%) as a slightly yellowish oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 0.83-0.91 (m, 6H), 1.19-1.29 (m, 40H), 1.41-1.66 (m, 4H), 1.87-2.05 (m, 8H), 2.17-2.36 (m, 4H), 3.78 (s, 3H), 3.79 (s, 3H), 4.19

(dd, *J* 7.3, 11.7 Hz, 1H, C**H$_a$**H$_b$O), 4.31 (dd, *J* 5.5, 11.7 Hz, 1H, CH$_a$**H$_b$**O) 4.75 (d, *J* 2.2 Hz, 1H, CHO), 5.06 (ap. s, 4H, C**H**$_2$Ar), 5.27-5.38 (m, 5H), 6.83-6.91 (m, 4H), 7.17 (ap d, ls 8.8 Hz, 2H), 7.32 (ap d, ls 8.8 Hz, 2H). ^{13}C NMR (50 MHz, CDCl$_3$): δ (ppm) 14.0, 22.6, 24.7, 24.9, 27.1, 29.0, 29.1, 29.2, 29.5, 29.6, 29.7, 31.8, 33.9, 55.2, 61.8, 67.4, 73.3, 73.4, 73.7, 114.0, 121.2, 127.2, 128.1, 129.6, 129.9, 130.6, 155.2, 160.0, 168.6, 172.1, 172.9. MS (ESI positive) *m/z* (%): 968 [M+Na]$^+$, (100). Elemental Analysis: $C_{58}H_{88}O_{10}$ C 73.69%, H 9.38%. Found: C 73.91%, H 9.40%.

(*S*)-1-((*R*)-3,4-Bis(benzyloxy)-5-oxo-2,5-dihydrofuran-2-yl)ethane-1,2-diyl diacrylate (3g). Following the general procedure *GP2*, **2a** (200 mg, 0.56 mmol) and acryloyl chloride (117 mg, 1.29 mmol) gave, after flash chromatography, **3g** (195 mg, 75%) as a colourless oil. ^{1}H NMR (200 MHz, CDCl$_3$): δ (ppm) 4.36-4.45 (m, 2H, CH$_2$O), 4.87 (d, *J* 2.2 Hz, 1H, CHO), 5.06 (d, *J* 10.2, 1H, C**H**$_2$Ph), 5.08 (ap. s, 2H, C**H**$_2$Ph), 5.14 (d, *J* 10.2, 1H, C**H**$_2$Ph), 5.42-5.56 (m, 1H), 5.81-6.19 (m, 4H), 6.37-6.51 (m, 2H), 7.19-7.38 (m, 10H). ^{13}C NMR (50 MHz, CDCl$_3$): δ (ppm) 62.0, 67.6, 73.6, 73.7, 73.9, 121.7, 127.9, 127.2, 127.5, 128.0, 128.6, 128.7, 128.9, 131.8, 132.5, 134.9, 135.8, 155.2, 164.3, 165.2, 168.6. MS (ESI positive) *m/z* (%): 487 [M+Na]$^+$, (100). Elemental Analysis: $C_{26}H_{24}O_8$ C 67.23%, H 5.21%. Found: C 67.13%, H 5.22%.

Cleavage of benzyl ethers. General procedure (GP3). To a solution of ascorbyl 5-*O*-,6-*O*-dialkanoate-2,3-dibenzyl ethers **3a-d** (3.0 mmol) in EtOAc (30 mL), Pd/C (10%) was added. Then a balloon filled with H_2 was attached to the flask and the reaction was stirred for 2 h. The reaction progress was monitored by TLC. After the complete consumption of the starting product, the mixture was filtered through Celite and the solvent was removed under reduced pressure. Crystallization from Et_2O/petroleum ether gave ascorbyl 5-*O*-,6-*O*-dialkanoates **4a-d** in almost quantitative yield.

(*S*)-1-((*R*)-3,4-Dihydroxy-5-oxo-2,5-dihydrofuran-2-yl)ethane-1,2-diyl dioctanoate (4a). Prepared from **3a** according to the general procedure *GP3*. White solid. ^{1}H NMR (200 MHz, CDCl$_3$): δ (ppm) 0.84-0.90 (m, 6H), 1.22-1.29 (m, 16H), 1.51-1.67 (m, 4H), 2.28-2.36 (m, 4H), 4.29 (dd, *J* 6.6, 11.8 Hz, 1H, C**H$_a$**H$_b$O), 4.42 (dd, *J* 4.8, 11.8.0 Hz, 1H, CH$_a$**H$_b$**O), 4.91 (d, *J* 3.4 Hz, 1H, CHO), 5.38-5.46 (1H, m, CHO). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 13.9, 22.5, 24.7, 24.8, 28.8, 28.9, 29.0, 31.5, 34.0, 62.0, 68.2, 74.6, 119.5, 148.9, 170.1, 172.9, 173.7. Elemental Analysis: $C_{22}H_{36}O_8$ C 61.66%, H 8.47%. Found: C 61.59%, H 8.50%.

(*S*)-1-((*R*)-3,4-Dihydroxy-5-oxo-2,5-dihydrofuran-2-yl)ethane-1,2-diyl didecanoate (4b). Prepared from **3b** according to the general procedure *GP3*. White solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 0.87 (ap t, ls 6.6 Hz, 6H), 1.26 (m, 24H), 1.51-1.68 (m, 4H), 2.29-2.38 (m, 4H), 4.30 (dd, *J* 6.8, 11.6 Hz, 1H, C**H$_a$**H$_b$O), 4.42 (dd, *J* 4.8, 11.6 Hz, 1H, CH$_a$**H$_b$**O), 4.92 (d, *J* 3.6 Hz, 1H, CHO), 5.41-5.45 (m, 1H, C**H**CH$_2$). ^{13}C NMR (50 MHz, CDCl$_3$): δ (ppm) 13.9, 22.5, 24.6, 24.7, 28.9, 29.0, 29.1, 29.3, 31.7, 33.9, 34.0, 62.1, 68.1, 74.8, 119.1, 150.9, 171.5, 173.1, 173.9 ppm. MS (ESI negative) *m/z* (%): 483 [M-H]$^-$, (100). IR [CDCl$_3$] ν (cm^{-1}): 3350-3400, 3100-3200, 2800-2950, 1550, 1690, 1620, 1100-1200. Elemental Analysis: $C_{26}H_{44}O_8$ C 64.44%, H 9.15%. Found: C 64.09%, H 9.25%.

(*S*)-1-((*R*)-3,4-Dihydroxy-5-oxo-2,5-dihydrofuran-2-yl)ethane-1,2-diyl didodecanoate (4c). Prepared from **3c** according to the general procedure *GP3*. White solid ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 0.88 (m, 6H), 1.26 (m, 32H), 1.54-1.65 (m, 4H), 2.29-2.34 (m, 4H), 4.31 (dd, *J* 6.6, 11.7 Hz, 1H, C**H$_a$**H$_b$O), 4.41 (dd, *J* 4.8, 11.7 Hz, 1H, CH$_a$**H$_b$**O), 4.90 (d, *J* 3.1 Hz, 1H, CHO), 5.38-5.43 (m, 1H, C**H**CH$_2$). ^{13}C NMR (100 MHz, CDCl$_3$): δ (ppm) 13.9, 22.5, 24.6, 24.7, 28.9, 29.0, 29.2, 29.4, 29.5, 31.8, 33.8, 33.9, 62.1, 68.1, 74.7, 118.8, 151.4, 171.5, 173.0, 173.8. MS (ESI negative) *m/z* (%): 539 [M-H]$^-$, (100). IR [CDCl$_3$] ν (cm^{-1}): 3300-3500, 2800-2950, 1770, 1690, 1100-1190. Elemental Analysis: $C_{30}H_{52}O_8$ C 64.64%, H 9.69%. Found C 64.32%, H 9.59%.

(*S*)-2-Acetoxy-2-((*R*)-3,4-dihydroxy-5-oxo-2,5-dihydrofuran-2-yl)ethyl dodecanoate (4d). Prepared from **3d** according to the general procedure *GP3*. White solid ^{1}H NMR (400 MHz, CDCl$_3$): δ (ppm) 0.87 (t, *J* 6.8 Hz, 3H), 1.19-1.38 (m, 16H), 1.54-1.69 (m, 2H), 2.09 (s, 3H), 2.34 (t, *J* 7.6Hz, 2H), 4.31 (dd, *J* 6.6, 11.8 Hz, 1H, C**H$_a$**H$_b$O), 4.42 (dd, *J* 4.8, 11.8 Hz, 1H, CH_a**H_b**O), 4.95 (d, *J* 3.5 Hz, 1H, CHO), 5.38-5.46 (1H, m, CHO). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 14.1, 20.6, 22.7, 24.8, 29.1, 29.2, 29.3, 29.4, 29.6, 31.9, 34.0, 61.9, 68.5, 74.7, 119.2, 150.4, 170.4, 171.3, 173.9. MS (ESI negative) *m/z* (%): 399 [M-H]$^-$, (100). Elemental Analysis: $C_{20}H_{32}O_8$ C 59.98%, H 8.05%. Found C 59.63%, H 8.19%.

(*S*)-1-((*R*)-3,4-Dihydroxy-5-oxo-2,5-dihydrofuran-2-yl)ethane-1,2-diyl dioleate (4e). To a solution of **3f** (155 mg, 0.16 mmol, 1 eq.) and benzenethiol (43 mg, 0.38 mmol, 2.4 eq.) in dry CH_2Cl_2 (3 mL) cooled at -78 °C, $SnCl_4$ (39.4 mL, 0.336 mmol, 2.1 eq.) was dropwise added and the reaction was stirred for 30 min. Then the mixture was quenched with saturated aqueous $NaHCO_3$, allowed to warm up at rt and extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether/EtOAc 1:1) to give **4e** (38 mg, 34%) as a slightly yellow sticky solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 0.83-0.95 (m, 6H), 1.21-1.32 (m, 40H), 1.46-1.63 (m, 4H), 1.93-2.04 (m, 8H), 2.24-2.36 (m, 4H), 4.27 (dd, *J* 6.6, 11.9 Hz, 1H, C**H_a**H_bO), 4.41 (dd, *J* 5.0, 11.9 Hz, 1H, CH_a**H_b**O), 4.89 (d, *J* 2.6 Hz, 1H, CHO), 5.31-5.36 (m, 4H), 5.37-5.47 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 13.8, 22.6, 24.8, 24.8, 27.0, 29.0, 29.1, 29.3, 29.4, 29.6, 29.7, 31.9, 34.2, 61.8, 67.4, 73.5, 129.7, 130.0, 155.3, 168.9, 172.6, 173.8. MS (ESI negative) *m/z* (%): 704 [M-H]$^-$, (100). Elemental Analysis: $C_{42}H_{72}O_8$ C 71.55%, H 10.29%. Found: C 71.38%, H 10.31%.

(*S*)-2-((*R*)-3,4-Bis((4-methoxybenzyl)oxy)-5-oxo-2,5-dihydrofuran-2-yl)-2-hydroxyethyl oleate (5a). Oleoyl chloride (331 mg, 1.1 mmol) was slowly added to a solution of **2b** (416 mg, 1.0 mmol) and Et_3N (507 mg, 5.0 mmol) in CH_2Cl_2 (10 mL). The reaction was stirred overnight under inert atmosphere at ambient temperature. Afterwards, the mixture was diluted with H_2O (10 mL) and the aqueous layer extracted into Et_2O (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by flash column chromatography (petroleum ether/EtOAc 4:1) to give the product **5a** (327 mg, 48%). Colourless oil ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 0.83-0.91 (m, 3H), 1.19-1.29 (m, 20H), 1.47-1.61 (m, 2H), 1.87-2.11 (m, 4H), 2.17-2.35 (m, 2H), 3.79 (s, 3H), 3.81 (s, 3H), 4.02-4.36 (m, 3H), 4.62 (d, *J* 2.2 Hz, 1H, CHO), 5.07 (ap. s, 4H), 5.29-5.36 (m, 2H), 6.84-6.91 (m, 4H), 7.17 (ap d, Is 8.8 Hz, 2H), 7.32 (ap d, Is 8.8 Hz, 2H). MS (ESI positive) *m/z* (%): 704 [M+Na]$^+$, (100). Elemental Analysis: $C_{40}H_{56}O_9$ C 70.56 %, H 8.29%. Found: C 70.69%, H 8.30%.

(*S*)-2-((*R*)-3,4-Bis(benzyloxy)-5-oxo-2,5-dihydrofuran-2-yl)-2-hydroxyethyl acrylate (5b). Acryloyl chloride (99.6 mg, 1.1 mmol) was slowly added to a solution of **2a** (356 mg, 1.0 mmol) and Et_3N (152 mg, 1.5 mmol) in CH_2Cl_2 (10 mL). The reaction was stirred overnight under inert atmosphere at ambient temperature. Afterwards, the mixture was diluted with H_2O (10 mL), the layers separated and the aqueous layer extracted into Et_2O (2 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by flash column chromatography (petroleum ether/EtOAc 3:1) to give the product **5b** (218 mg, 53%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 2.10 (bs, 1H), 3.70-4.18 (m, 1H, C**H**CH_2), 4.30 (dd, *J* 5.1, 11.7 Hz, 1H, C**H_a**H_bO), 4.40 (dd, *J* 6.6, 11.7 Hz, 1H, CH_a**H_b**O), 4.69 (d, *J* 2.2 Hz, 1H, CHO), 5.10 (ap. s, 2H, C**H_2**Ph), 5.13 (d, *J* 10.6, 1H, C**H_2**Ph), 5.22 (d, *J* 10.6, 1H, C**H_2**Ph), 5.87 (dd, 1H, *J* 1.5, 10.3 Hz), 6.13 (dd, 1H, *J* 10.3, 17.2 Hz), 6.45 (dd, 1H, *J* 1.8, 17.2 Hz), 7.19-7.26 (m, 4H), 7.33-7.41 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 64.9, 67.9, 73.6, 73.9, 75.4, 121.7, 127.9, 128.7, 128.8, 129.1, 131.8, 135.2, 135.9, 156.5, 165.9, 169.3. MS (ESI positive) *m/z* (%): 433 [M+Na]$^+$, (100). Elemental Analysis: $C_{23}H_{22}O_7$ C 67.31%, H 5.40%. Found: C 67.21%, H 5.41%.

(*S*)-2-((*R*)-3,4-Bis((4-methoxybenzyl)oxy)-5-oxo-2,5-dihydrofuran-2-yl)-2-hydroxyethyl acrylate (5c). Following the same procedure as described above for **5b**, acryloyl chloride (72 mg, 0.79 mmol) and **2b** (300 mg, 0.72 mmol) gave, after purification by column chromatography (petroleum ether/EtOAc 2:1), **5c** (162 mg, 48%). Colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 2.20 (bs, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 4.03-4.12 (m, 1H, C**H**CH_2), 4.22 (dd, *J* 5.4, 11.4 Hz, 1H, C**H_a**H_bO), 4.37 (dd, *J* 6.8, 11.4 Hz, 1H, CH_a**H_b**O), 4.65 (d, *J* 2.2 Hz, 1H, CHO), 5.02 (d, *J* 12.2, 1H), 5.05 (ap. s, 2H), 5.12 (d, *J* 12.2, 1H), 5.85 (dd, 1H, *J* 1.8, 10.6 Hz), 6.11 (dd, 1H, *J* 10.4, 17.2 Hz), 6.42 (dd, 1H, *J* 1.8, 17.2 Hz), 6.82-6.91 (m, 4H), 7.14 (ap d, ls 7.14 Hz, 2H), 7.32 (ap d, ls 7.14 Hz, 2H). Elemental Analysis: $C_{25}H_{26}O_9$ C 63.82%, H 5.57%. Found: C 63.73%, H 5.58%.

(*S*)-2-((*R*)-3,4-Bis(benzyloxy)-5-oxo-2,5-dihydrofuran-2-yl)-2-hydroxyethyl dodecanoate (5d). Following the same procedure as described for **5a**, dodecanoyl chloride (0.90 g, 4.14 mmol), **2a** (1.34 g, 3.76 mmol) and Et_3N (1.90 g, 18.8 mmol) gave, after purification by column chromatography (petroleum ether/EtOAc 3:1), **5d** (1.38 g, 68%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 0.88 (ap t, *J* 7.2 Hz, 3H), 1.25 (m, 16H), 1.48-1.61 (m, 2H), 2.33 (t, *J* 8 Hz, 2H), 4.01-4.11 (m, 1H), 4.21 (dd, *J* 5.0, 11.9 Hz, 1H, C**H$_a$**H$_b$O), 4.36 (dd, *J* 6.2, 11.9 Hz, 1H, CH$_a$**H$_b$**O), 4.67 (d, *J* 1.8 Hz, 1H, CHO), 5.11 (ap. s, 2H, C**H**$_2$Ph), 5.11 (d, *J* 11.9, 1H, C**H**$_2$Ph), 5.22 (d, *J* 11.9, 1H, C**H**$_2$Ph), 7.18-7.26 (m, 2H), 7.33-7.41 (m, 8H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 14.0, 22.5, 24.8, 29.0, 29.1, 29.3, 29.4, 29.5, 31.6, 34.0, 64.1, 67.6, 73.1, 73.8, 75.7, 121.3, 127.8, 128.2, 128.4, 128.7, 135.1, 135.6, 156.8, 169.7, 173.5. Elemental Analysis: $C_{32}H_{42}O_7$ C 71.35%, H 7.86%. Found: C 71.13%, H 7.93%.

(*S*)-1-((*R*)-3,4-Bis(benzyloxy)-5-oxo-2,5-dihydrofuran-2-yl)-2-(trityloxy)-ethyl-dodecanoate (7a). Dodecanoyl chloride (279 mg, 1.28 mmol) was slowly added to a solution of (*R*)-3,4-bis(benzyloxy)-5-((*S*)-1-hydroxy-2-(trityloxy)ethyl)furan-2(5H)-one **6a**[24] (700 mg, 1.16 mmol), 4-DMAP (212 mg, 1.74 mmol) and DCC (358 mg, 1.74 mmol) in MeCN (13 mL). The reaction mixture was stirred for 18 h at rt under an inert atmosphere. The solvent was removed under reduced pressure and the crude material was purified by column chromatography (petroleum ether/EtOAc 8:1) to give **7a** (842 mg, 93%). Colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.88 (ap t, ls 6.5 Hz, 3H), 1.20-1.25 (m, 16H), 1.43-1.66 (m, 2H), 2.16-2.23 (m, 2H), 3.31 (dd, *J* 7.0, 9.5 Hz, 1H), 3.44 (dd, *J* 7.0, 9.5 Hz, 1H), 4.90 (d, *J* 1.8 Hz, 1H), 5.07 (s, 2H), 5.14 (s, 2H), 5.23-5.31 (m, 1H), 7.19-7.43 (m, 25H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 14.0, 22.6, 24.9, 29.1, 29.2, 29.3, 29.5, 31.8, 34.0, 61.9, 68.6, 73.7, 73.9, 87.3, 121.5, 127.1, 127.8, 128.0, 128.6, 128.7, 135.3, 136.1, 143.6, 155.5, 168.7, 172.1. MS (ESI positive) *m/z* (%): 433 $[M+Na]^+$, (100). Elemental Analysis: $C_{51}H_{56}O_7$ C 78.43%, H 7.23%. Found: C 78.68%, H 7.20%.

(*S*)-1-((*R*)-3,4-bis((4-methoxybenzyl)oxy)-5-oxo-2,5-dihydrofuran-2-yl)-2-(trityloxy)ethyl oleate (7b). Following the same procedure for the synthesis of **7a**, oleoyl chloride (166 mg, 0.55 mmol) and **6b** (329 mg, 0.50) gave, after purification by column chromatography (petroleum ether/EtOAc 8:1), product **7b** (402 mg, 87%). Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.82 (t, *J* 6.8 Hz, 3H), 1.15-1.25 (m, 20H), 1.41-1.56 (m, 2H), 1.84-1.95 (m, 4H), 2.10-2.18 (m, 2H), 3.25 (dd, *J* 6.8, 10.0 Hz, 1H), 3.38 (dd, *J* 6.4, 10.0 Hz, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 4.84 (d, *J* 2.0 Hz, 1H), 5.02 (s, 2H), 5.06-5.10 (m, 2H), 5.18-5.22 (m, 1H), 5.23-5.31 (m, 2H), 6.87 (ap d, ls 8.8 Hz, 2H), 6.89 (ap d, ls 8.8 Hz, 2H), 7.20-7.44 (m, 19H). ^{13}C NMR (50 MHz, $CDCl_3$) 14.0, 22.6, 25.0, 27.2, 29.1, 29.3, 29.5, 29.7, 29.8, 30.8, 31.9, 34.0, 34.1, 55.6, 61.4, 68.7, 70.6, 73.7, 73.8, 87.3, 113.8, 114.0, 121.6, 127.1, 127.4, 127.8, 128.2, 128.7, 130.0, 130.9, 160.0, 143.7, 129.7, 130.0, 155.6, 172.2, 172.8. Elemental Analysis: $C_{59}H_{70}O_9$ C 76.76%, H 7.64%. Found: C 76.59%, H 7.67%.

(*S*)-1-((*R*)-3,4-bis(benzyloxy)-5-oxo-2,5-dihydrofuran-2-yl)-2-hydroxyethyl dodecanoate (8). A solution of **7a** (156 mg, 0.2 mmol, 1 eq.) in dry CH_2Cl_2 (2 mL) was cooled at 0 °C, then $BF_3{\cdot}Et_2O$ (115 mL, 1.0 mmol, 5.0 eq.) was slowly added and the solution was stirred under an inert atmosphere for 1 h. Afterwards, a saturated aqueous solution of $NaHCO_3$ (3 mL) was added and the mixture was extracted with $CHCl_3$ (3 x 5 mL). The organic layers were dried on Na_2SO_4, filtered and the solvent was eliminated under reduced pressure. The crude material was purified by column chromatography (petroleum ether/EtOAc 8:1) affording **8** (79 mg, 73%) as a colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.89 (ap t, *J* 6.3 Hz, 3H), 1.20-1.29 (m, 16H), 1.45-1.65 (m, 2H), 2.15-2.28 (m, 2H), 2.95 (bs, 1H, OH), 3.80 (ap d, ls 6.5 Hz, 2H, CH_2O), 4.91 (d, *J* 1.8 Hz, 1H), 5.09 (s, 2H), 5.18 (s, 2H), 5.14-5.24 (m, 1H), 7.21-7.29 (m, 2H), 7.31-7.41 (m, 8H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 13.9, 22.5, 24.8, 29.0, 29.1, 29.2, 29.3, 29.4, 31.8, 33.9, 60.7, 70.1, 73.5, 73.7, 121.3, 127.1, 127.8, 128.5, 128.7, 135.2, 136.0, 155.8, 168.9, 172.7. Elemental Analysis: $C_{32}H_{42}O_7$ C 71.35%, H 7.86%. Found: C 71.13%, H 7.89%.

(*S*)-1-((*R*)-3,4-dihydroxy-5-oxo-2,5-dihydrofuran-2-yl)-2-(trityloxy)ethyl dodecanoate (9). Prepared according to the general procedure *GP3* starting from **7a** (250 mg, 0.32 mmol). Purification by column chromatography (CH_2Cl_2/MeOH 10:1) gave the product **9** (168 mg, 52%). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.88 (ap t, *J* 6.2 Hz, 3H), 1.17-1.34 (m, 16H), 1.50-1.66 (m, 2H), 2.21-2.28 (m, 2H), 3.34 (dd, *J* 5.9, 9.4 Hz), 3.46 (dd, *J* 6.6, 9.4 Hz), 4.91 (d, *J* 2.7 Hz, 1H), 5.39-5.45 (m, 1H), 7.20-7.44 (m, 15H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 14.0, 22.5, 24.5, 24.9, 25.4, 29.1, 29.3, 29.4, 31.7, 33.9, 34.8, 61.8, 68.5, 73.5, 87.2, 121.3, 127.0, 127.8, 127.9, 128.5, 128.7, 135.2, 136.0, 143.4, 155.4, 168.2, 172.0. MS (ESI negative) *m/z* (%): 599 $[M-H]^-$, (100). Elemental Analysis: $C_{37}H_{44}O_7$ C 73.98%, H 7.38%. Found: C 73.72%, H 7.41%.

General procedure for the thiol-Michael addition on ascorbyl acrylates (GP4). Neutral alumina was added to a solution of thiol (benzenethiol or 1,2-ethanedithiol) and ascorbyl acrylate **3b, 5b** or **5c** in dry toluene.[39] The reaction was stirred under inert atmosphere at rt for 4 h. Afterwards the mixture was diluted with EtOAc, washed with H_2O, dried over Na_2SO_4, filtered and concentrated under reduced pressure.

(*S*)-2-((*R*)-3,4-bis(benzyloxy)-5-oxo-2,5-dihydrofuran-2-yl)-2-hydroxyethyl 3-(phenyl-thio)propanoate (11a). Following the general procedure *GP4*, **5b** (205 mg, 0.50 mmol, 1 eq.), neutral alumina (100 mg) and benzenethiol (66 mg, 0.60 mmol, 1 eq.) in dry toluene (5.0 mL), gave after flash chromatography (petroleum ether/EtOAc 3:1), **11a** (239 mg, 92%). Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.23 (bs, 1H), 2.65 (ap t, *J* 7.4 Hz, 2H), 3.16 (ap t, *J* 7.4 Hz, 2H), 4.02-4.11 (m, 1H, C**H**CH$_2$), 4.22 (dd, *J* 5.1, 11.4 Hz, 1H, C**H$_a$**H$_b$O), 4.34 (dd, *J* 6.6, 11.4 Hz, 1H, CH$_a$**H$_b$**O), 4.67 (d, *J* 2.2 Hz, 1H, CHO), 5.10 (ap. s, 2H, C**H**$_2$Ph), 5.12 (d, *J* 11.2, 1H, C**H**$_2$Ph), 5.21 (d, *J* 11.2 Hz, 1H, C**H**$_2$Ph), 7.20-7.38 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 28.9, 34.1, 64.9, 67.6, 73.6, 73.8, 75.4, 121.1, 126.6, 127.8, 128.5, 128.6, 128.7, 129.0, 130.1, 134.8, 135.1, 135.8, 156.7, 169.4, 171.2. Elemental Analysis: $C_{29}H_{28}O_7S$ C 66.91%, H 5.42%. Found: C 66.69%, H 5.43%.

(*S*)-2-((*R*)-3,4-bis((4-methoxybenzyl)oxy)-5-oxo-2,5-dihydrofuran-2-yl)-2-hydroxyethyl 3-(phenylthio)-propanoate (11b). Following the general procedure *GP4*, **5c** (118 mg, 0.25 mmol, 1 eq.), neutral alumina (50 mg) and benzenethiol (33 mg, 0.30 mmol, 1 eq.) in dry toluene (2.5 mL), gave after flash chromatography (petroleum ether/EtOAc 3:1), **11b** (131 mg, 91%) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.10 (bs, 1H), 2.64 (ap t, *J* 7.3 Hz, 2H), 3.14 (ap t, *J* 7.3 Hz, 2H), 3.79 (s, 3H), 3.80 (s, 3H), 3.97-4.14 (m, 1H, C**H**CH$_2$), 4.19 (dd, *J* 5.1, 11.4 Hz, 1H, C**H$_a$**H$_b$O), 4.31 (dd, *J* 6.7, 11.4 Hz, 1H, CH$_a$**H$_b$**O), 4.62 (d, *J* 2.2 Hz, 1H, CHO), 5.02 (d, *J* 11.2 Hz, 1H), 5.06 (ap. s, 2H), 5.12 (d, *J* 11.2 Hz, 1H), 6.83-6.92 (m, 4H), 7.12-7.38 (m, 9H). Elemental Analysis: $C_{31}H_{32}O_9S$ C 64.13%, H 5.56%. Found C 64.26%, H 5.21%.

(*S*)-1-((*R*)-3,4-bis(benzyloxy)-5-oxo-2,5-dihydrofuran-2-yl)ethane-1,2-diyl bis(3-(phenyl-thio)propanoate) (12). Following the general procedure *GP4*, **3g** (116 mg, 0.25 mmol, 1 eq.), neutral alumina (50 mg) and benzenethiol (66 mg, 0.60 mmol, 2.4 eq.) in dry toluene (2.5 mL), gave after flash chromatography (petroleum ether/EtOAc 5:1), **12** (152 mg, 88%) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.44-2.57 (m, 2H), 2.62 (ap t, *J* 7.3 Hz, 2H), 3.06 (ap t, *J* 7.4 Hz, 2H), 3.14 (ap t, *J* 7.4 Hz, 2H), 4.27 (dd, *J* 7.2, 11.6 Hz, 1H, C**H$_a$**H$_b$O), 4.36 (dd, *J* 5.3, 11.6 Hz, 1H, CH$_a$**H$_b$**O), 4.80 (d, *J* 2.2 Hz, 1H, CHO), 5.12 (AB system, ls 10.8 Hz, 2H, CH$_2$Ph), 5.20 (AB system, ls 11.3 Hz, 2H, CH$_2$Ph) 5.41 (ddd, *J* 2.2, 5.3, 7.2 Hz, 1H, C**H**CH$_2$), 7.17-7.37 (m, 20H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 28.8, 29.1, 33.8, 34.1, 62.2, 67.7, 73.6, 73.5, 73.6, 73.7, 121.3, 126.6, 126.7, 127.4, 128.1, 128.6, 128.7, 128.8, 128.9, 129.0, 129.1, 130.1, 130.3, 134.9, 135.0, 135.8, 154.8, 168.4, 170.2, 170.9. MS (ESI positive) *m/z* (%): 708 $[M+Na]^+$, (100). Elemental Analysis: $C_{38}H_{36}O_8S_2$ C 66.65%, H 5.30%. Found: C 66.78%, H 5.27%.

Bis((*S*)-2-((*R*)-3,4-bis(benzyloxy)-5-oxo-2,5-dihydrofuran-2-yl)-2-hydroxyethyl) 3,3'-(ethane-1,2-diylbis-(sulfanediyl))dipropionate (13). Following the general procedure *GP4*, **5b** (103 mg, 0.25 mmol, 1 eq.), neutral alumina (25 mg) and 1,2-ethanedithiol (10.6 mg, 0.11 mmol, 0.45 eq.) in dry toluene (2 mL), gave after flash chromatography (petroleum ether/EtOAc 3:2), **13** (95 mg, 94%). Slightly yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 2.61-2.93 (m, 12H), 3.38 (bd, *J* 7.9 Hz, 2H, OH), 4.05-4.20 (m, 2H), 4.27 (dd, *J* 5.6, 11.3 Hz, 2H, C$\mathbf{H_a}$H$_b$O), 4.36 (dd, *J* 7.0, 11.3 Hz, 2H, CH$_a\mathbf{H_b}$O), 4.74 (d, *J* 1.9 Hz, 2H, CHO), 5.06 (ap s, 4H, C$\mathbf{H}_2$Ph), 5.07 (d, *J* 11.6 Hz, 2H, C$\mathbf{H}_2$Ph), 5.22 (d, *J* 11.6 Hz, 4H, C$\mathbf{H}_2$Ph), 7.17-7.26 (m, 4H), 7.32-7.43 (m, 16H). ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 26.6, 31.9, 35.0, 65.1, 67.7, 73.7, 74.0, 75.7, 121.3, 127.9, 128.6, 128.7, 129.1, 135.3, 135.9, 156.9, 169.9, 171.8. Elemental Analysis: $C_{48}H_{50}O_{14}S_2$ C 63.01%, H 5.51%. Found C 62.86%, H 5.39%.

References

1. Tanini, D.; Degl'Innocenti, A.; Capperucci**,** A. *Eur. J. Org. Chem.* **2015**, 357 and references cited therein. http://dx.doi.org/10.1002/ejoc.201403015
2. Capperucci, A.; Tanini, D.; Borgogni, C.; Degl'Innocenti, A. *Heteroat. Chem*. **2014**, *25*, 678. http://dx.doi.org/10.1002/hc.21157
3. Tanini, D.; Barchielli, G.; Benelli, F.; Degl'Innocenti, A.; Capperucci, A. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2015**, *190*, 1265.
http://dx.doi.org/10.1080/10426507.2014.1002615
4. García Ruano, J. L.; Torrente, E.; Alonso, I.; Rodriguez, M.; Martín-Castro, A. M.; Degl'Innocenti, A.; Frateschi, L.; Capperucci, A. *J. Org. Chem.* **2012**, *77*, 1974.
http://dx.doi.org/10.1021/jo202611v
5. Capperucci, A.; Degl'Innocenti, A.; Tiberi, C. *Synlett* **2011**, 2248.
http://dx.doi.org/10.1055/s-0030-1261195
6. Menichetti, S.; Capperucci, A.; Tanini, D.; Braga, A. L.; Botteselle, G. V.; Viglianisi, C. *Eur. J. Org. Chem.* **2016**, 3097.
http://dx.doi.org/10.1002/ejoc.201600351
7. Vazquez-Prieto, M. A.; Miatello, R. M. *Mol. Aspects Med*. **2010**, *31*, 540 and references cited therein. http://dx.doi.org/10.1016/j.mam.2010.09.009
8. Wirth, T. *Organoselenium Chemistry. Synthesis and Reactions*; Wiley-VCH Verlag & Co, Weinheim, Germany, 2012 and references cited therein.
9. Tanini, D.; Panzella, L.; Amorati, R.; Capperucci, A.; Napolitano, A.; Menichetti, S.; d'Ischia, M. *Org. Biomol. Chem*. **2015**, 5757.
http://dx.doi.org/10.1039/C5OB00193E
10. Carretti, E.; Mazzini, V.; Fratini, E.; Ambrosi, M.; Dei, L.; Baglioni, P.; Lo Nostro, P. *Phys. Chem. Chem. Phys.* **2016**, *18*, 8865 and references cited therein.
http://dx.doi.org/10.1039/C5CP07792C
11. Venturini, C.; Pomposi, C.; Carretti, E.; Fratini, E.; Lo Nostro, P.; Baglioni, P. *J. Phys. Chem. B* **2014**, *118*, 3053.
http://dx.doi.org/10.1021/jp412127y
12. Dolle, C.; Marangone, P.; Riva, S.; Ambrosi, M., Fratini, E.; Peruzzi, N.; Lo Nostro, P. *J. Phys. Chem. B* **2011**, *115*, 11638.

http://dx.doi.org/10.1021/jp204920y
13. Lo Nostro, P.; Capuzzi, G.; Romani, A.; Mulinacci, N. *Langmuir* **2000**, 16, 1744. http://dx.doi.org/10.1021/la990796j
14. Palma, S.; Lo Nostro, P.; Manzo, R.; Allemandi, D. *Eur. J. Pharm. Sci.* **2002**, *16*, 37. http://dx.doi.org/10.1016/S0928-0987(02)00054-4
15. Lo Nostro, P.; Ninham, B.W.; Fratoni, L.; Palma, S.; Manzo, R.H.; Allemandi, D.; Baglioni, P. *Langmuir* **2003**, *19*, 3222. http://dx.doi.org/10.1021/la026807h
16. Ambrosi, M.; Lo Nostro, P.; Fratoni, L.; Dei, L.; Ninham, B.W.; Palma, S.; Manzo, R.H.; Allemandi, D.; Baglioni, P. *Phys. Chem. Chem. Phys.* **2004**, *6*, 1401. http://dx.doi.org/10.1039/B314061J
17. Ambrosi, M.; Lo Nostro, P.; Fratini, E.; Giustini, L.; Ninham, B. W.; Baglioni, P. *J. Phys. Chem. B* **2009,** *113*, 1404–1412. http://dx.doi.org/10.1021/jp8092644
18. Mottola, M.; Vico, R. V.; Villanueva, M. E.; Fanani, M. L. *J. Colloid Interface Sci.* **2015**, *45*, 232 and references cited therein. http://dx.doi.org/10.1016/j.jcis.2015.07.014
19. Thopate, S.R.; Rohit A. Dengale, R.A.; Kulkarni, M.G. *Synlett* **2013**, 1555. http://dx.doi.org/10.1055/s-0033-1338858
20. Karmee, S. K. *Lipid Technol*. **2011**, *23*, 227. http://dx.doi.org/10.1002/lite.201100146
21. Tripathi, R. P.; Singh, B.; Singh Bisht, S.; Pandey, J. *Curr. Org. Chem*. **2009**, *13*, 99 and references cited therein. http://dx.doi.org/10.2174/138527209787193792
22. Karmee, S. K. *Appl. Microbiol. Biotechnol.* **2009**, *81*, 1013. http://dx.doi.org/10.1007/s00253-008-1781-y
23. Capuzzi, G.; Lo Nostro, P.; Kulkarni, K.; Fernandez, J. E. *Langmuir* **1996**, *12*, 3957 and references cited.
24. Yoichi Ihori, Y.; Inoue, S.; Fujii, T.; Osawa, Y.; Tanaka, T.; Ikeuchi, H. PCT Int. Appl. WO 2014050894, 2014; *SciFinder Scholar* 2014:528792.
25. Choi, H.-I.; Kim, H.-J.; Park, J.-I.; Shin, E.-H.; Kim, D.-W.; Kim, S.-S. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 2079. http://dx.doi.org/10.1016/j.bmcl.2008.10.112
26. Zhuang, D.; Nie, J.; Yang, J *J. Polym. Sci., Part A: Polym. Chem.* **2011**, *49*, 1999. http://dx.doi.org/10.1002/pola.24627
27. Alam, M., Khan, M. H. *J. Pharm. (Lahore)* **1979**, *1*, 67.
28. Balen, M.; Silveira, C.; Kratz, J. M.; Simões, C.M.O.; Valério, A.; Ninow, J.L.; Nandi, L. G.; Di Luccio, M.; de Oliveira, D. *Biocatal. Agric. Biotechnol.* **2015**, *4*, 514 and references cited therein.
29. Yan, R.; Jiang, C.; Li, Z.; Liu, L.; Jiang, X., Pat. Appl. CN 104480156 A, 2015; *SciFinder Scholar* 2015:567544.
30. Stojanović, M.; Velićković, D.; Dimitrijević, A.; Milosavić, N.; Knežević-Jugović, Z.; Bezbradica, D. *J. Oleo Sci.* **2013**, *62*, 591. http://dx.doi.org/10.5650/jos.62.591
31. Moreno-Perez, S.; Filice, M.; Guisan, J.M.; Fernandez-Lorente, G. *Chem. Phys. Lipids* **2013**, *174*, 48. http://dx.doi.org/10.1016/j.chemphyslip.2013.06.003

32. Reyes-Duarte, D.; Lopez-Cortes, N.; Torres, P.; Comelles, F.; Parra, J. L.; Peña, S.; Ugidos, A. V.; Ballesteros, A.; Plou, F. J. *J. Am. Oil Chem. Soc.* **2011**, *88*, 57. http://dx.doi.org/10.1007/s11746-010-1643-5
33. Kaiyal, M. U.S. Pat. Appl. US 20110151525 A1, 2011; *SciFinder Scholar* 2011:787884.
34. Adamczak, M.; Bornscheuer, U. T. *Process Biochem.* **2009**, *44*, 257. http://dx.doi.org/10.1016/j.procbio.2008.10.014
35. Kim, J. D.; Han, G.; Zee, O. P.; Jung, Y. H. *Tetrahedron Lett.* **2003**, *44*, 733. http://dx.doi.org/10.1016/S0040-4039(02)02648-5
36. Jung, M. E.; Koch, P. *Tetrahedron Lett.* **2011**, *52*, 6051. http://dx.doi.org/10.1016/j.tetlet.2011.08.102
37. Yu, W.; Su, M.; Gao, X.; Yang, Z.; Jin, Z. *Tetrahedron Lett.* **2000**, *41*, 4015. http://dx.doi.org/10.1016/S0040-4039(00)00574-8
38. Máté Kicsák, M.; Bege, M.; Bereczki, I.; Csávás, M.; Herczeg, M.; Kupihár, Z.; Kovács, L.; Borbás, A.; Herczegh, P. *Org. Biomol. Chem.* **2016**, *14*, 3190 and references cited therein. http://dx.doi.org/10.1039/C6OB00067C
39. Suzuki, Y.; Saitoh, G.; Nawa, S.; Kodomari, M. *Nippon Kagaku Kaishi* **1998**, *12*, 824. http://dx.doi.org/10.1246/nikkashi.1998.824
40. Goupy, P.; Dufour, C.; Loonis, M.; Dangles, O. *J. Agric. Food Chem.,* **2003**, *51,* 615. http://dx.doi.org/10.1021/jf025938l
41. Ravindar, K., Caron, P-I., Deslongchamps, P. *J. Org. Chem.*, **2014**, *79*, 17, 7979.

