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Monophthalates with Oxidized C5-Carbon in the Ester Chain: A Simple Synthetic Access to Two Major Metabolites of Bis-(2-ethylhexyl)-phthalate

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Summary. The synthesis of two oxidized metabolites of bis-(2-ethylhexyl)-phthalate is described. The target structures were obtained by esterification of the appropriate alcohol carrying a protected hydroxy group with phthalic anhydride, followed by deprotection and further oxidation.

Keywords. Mono-(2-ethylhexyl)-phthalate; Bis-(2-ethylhexyl)-phthalate; Metabolites; Alcohols; Protecting groups.

Introduction

Bis-(2-ethylhexyl)-phthalate (*DEHP*) is the worldwide most frequently used plasticizer for polymer resins [1] and can be found in a variety of consumer products. Because of its ubiquitous spreading it is important to gain knowledge of the toxicology of the parent compound and its metabolites. In the early 1970s it has been noticed that blood is able to leach *DEHP* to some extent out of polyvinylchloride plastics used for medical devices [2], leading to a significant exposure of patients undergoing hemodialysis and blood transfusions [3]. The metabolism of *DEHP* has been elucidated in animal experiments [4] wherein it was found that in the first step *DEHP* is hydrolyzed to mono-(2-ethylhexyl)-phthalate (*MEHP*) [5], which is further oxidized at different positions in the ester chain. The oxidized metabolites have been isolated from urine samples, separated by chromatographic methods, and identified by NMR and mass spectroscopy [6]. The major metabolites are compounds **1**, **2**, and **3** (Scheme 1) which result from oxidation at the ω- and the (ω-1)-position.

The same metabolism also occurs in humans [7]. The major oxidative metabolites were found in urine samples of workers who had had contact with *DEHP* [8]. Investigations concerning their toxicology [9] revealed **2** and mainly **3** as peroxisome

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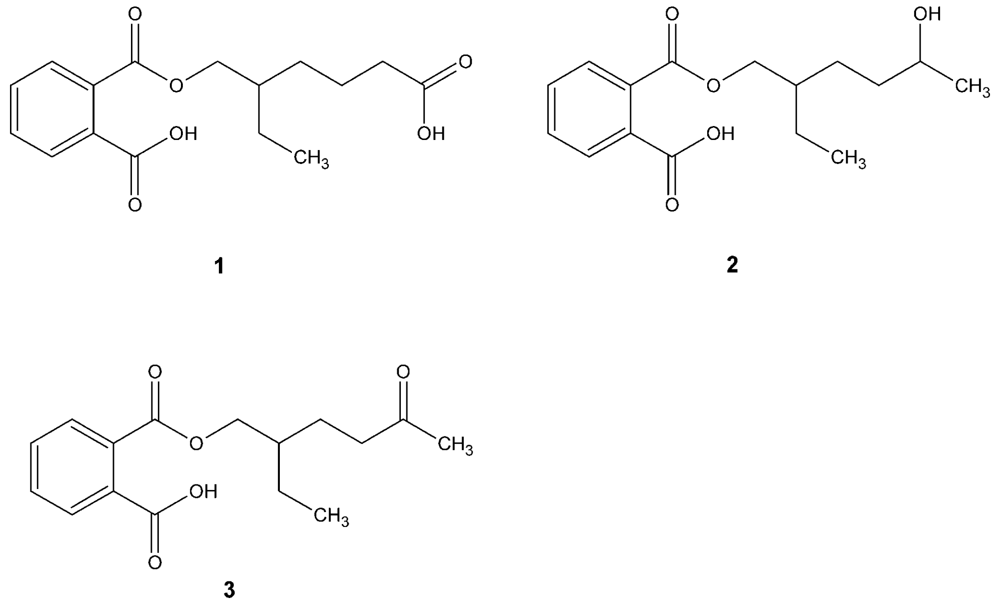


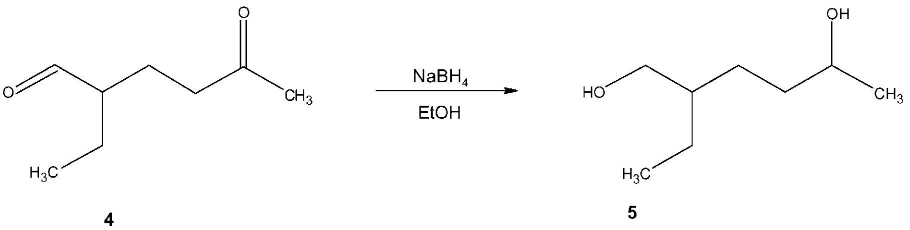
Scheme 1

proliferators in rats [10]. Like the phthalates in general, *DHEP* is also suspected to cause endocrine effects. In order to estimate the resulting health risk it is necessary to record the dose of the noxious substance taken up [11]. The quantities of noxious substances and their metabolites in body fluids are usually determined by methods of biological monitoring. In the case of biological monitoring of *DEHP* [12], the metabolites **2** and **3** must be accessible as reference materials. Although **2** and **3** have been fully characterized [13] and their synthesis has been claimed several years ago [14], to our knowledge no preparation procedure has been published until today. Therefore, we here report a simple synthetic access to these two compounds of toxicological interest.

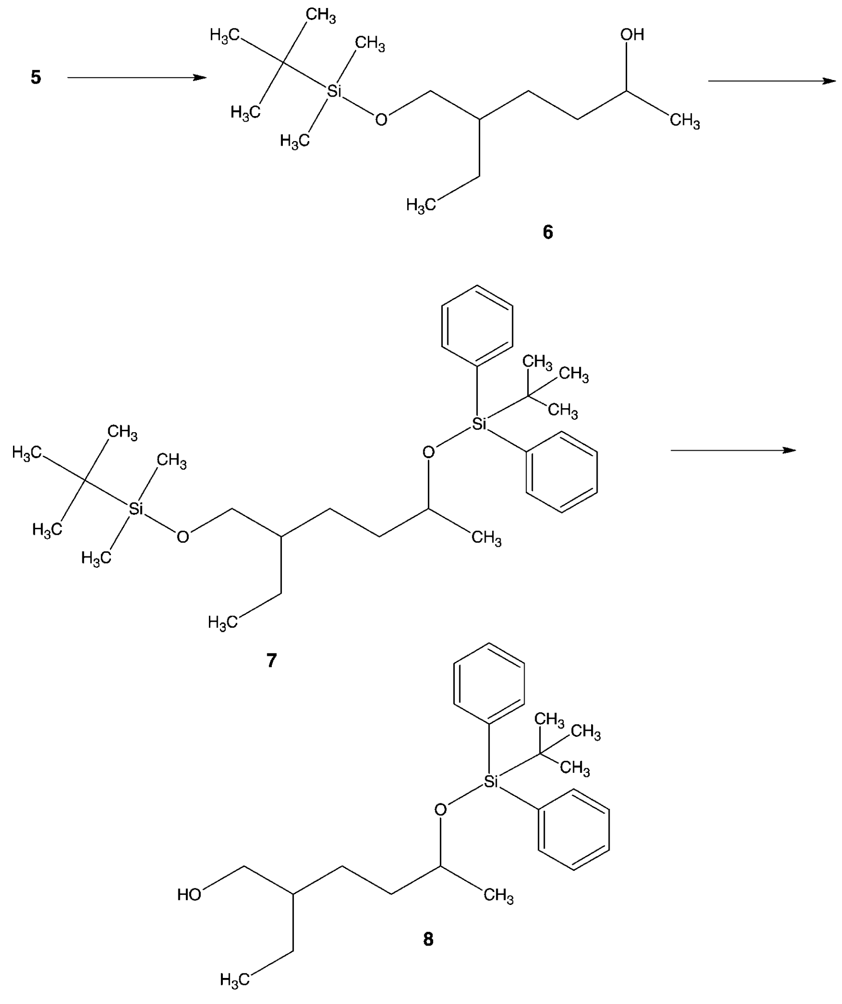
Results and Discussion

The retrosynthetic disconnection of the target molecules **2** and **3** leads to phthalic anhydride and the diol **5** or the hydroxyketone **10a**, respectively. The synthesis of **2** was started from the ketoaldehyde **4** [15], which was prepared following a known procedure [16] and purified by column chromatography. The diol **5** [17] was obtained in good yields as a diastereomeric mixture from **4** *via* reduction with sodium borohydride (Scheme 2).

In order to avoid product mixtures during esterification, the secondary hydroxy group in **5** had to be protected. The monosilylated alcohol **8** was synthesized according to the method of *Black et al.* [18] in three steps from **5** *via* selective silylation and desilylation of the primary hydroxy group. The reaction of **5** with *tert*-butyldimethylsilyl chloride gave the monosilylated diol **6**, wherein the secondary hydroxy group was reacted with *tert*-butyldiphenylsilyl chloride. In the resulting disilyl ether **7** the primary hydroxy group was deprotected selectively using pyridinium *p*-toluenesulfonate (Scheme 3).

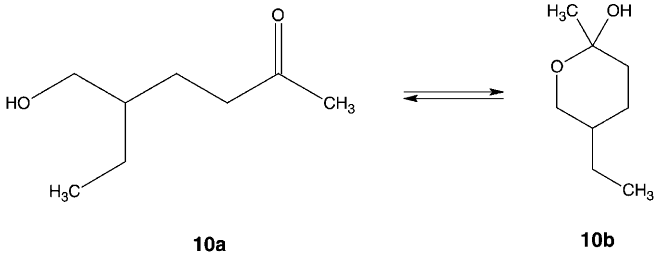


Scheme 2



Scheme 3

The selective reduction of the aldehyde group in **4** with zinc borohydride [19], which is a useful reagent for the reduction of aldehydes in the presence of ketones, gave only low yields of the expected product **10a**. Thin layer chromatography during the reaction showed several additional spots probably originating from side and consecutive products of **10a**. The reduction of **4** with K-Selectride® [20] under much



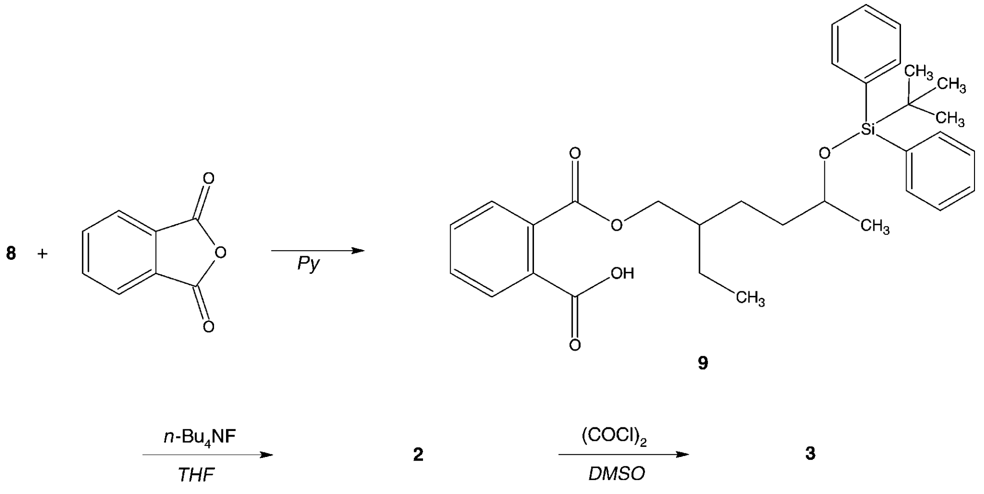
10a **10b**

Scheme 4

more smoother conditions did not result in better yields of **10a**. The selective oxidation of the secondary hydroxy group in diol **5** with sodium bromate [21] or sodium hypochlorite [22] also lead to complex product mixtures. From ^{1}H NMR data it is obvious that the product of the selective reduction of the aldehyde group in **4** consists of equal amounts of the hydroxyketone **10a** and the cyclic isomer **10b** (Scheme 4).

The existence of the hemiketal **10b** is indicated by a singlet ($\delta = 1.28$ ppm) belonging to the methyl group at the quarternary carbon and additional signals (triplet at 0.91 ppm and multiplet at 3.55 ppm) originating from the terminal methyl group and the ether protons, respectively. The additional signals are slightly shifted relative to the appropriate resonances of **10a**. The ring-chain tautomerism is typical for γ-hydroxyketones [23] and has also been observed for other derivatives [24] of 5-oxo-1-hexanol, even in more complex molecules [25].

The synthesis of **2** was performed in high yields by reaction of silyl alcohol **8** and phthalic anhydride in the presence of pyridine [26] and subsequent deprotection of **9** with tetrabutyl ammonium fluoride [27]. **3** was obtained from **2** by *Swern* oxidation [28] with dimethyl sulfoxide and oxalic dichloride. An excess of the oxidizing agent was necessary in order to complete the conversion of **2** to **3** and to suppress the formation of side products (Scheme 5).



Scheme 5

Experimental

IR spectra were recorded on a Perkin-Elmer 1430 spectrophotometer using the film technique. NMR spectra were recorded on a Varian Gemini 300 spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C. High resolution mass spectra were recorded on a VG 7070 double focusing mass spectrometer equipped with a FAB ion source or on a Finnigan MAT 95 mass spectrometer. All new compounds gave satisfactory data of elemental analysis or high resolution mass spectrometry. Purifications by column chromatography were performed on silica gel (Merck 63–200 mesh). Compound **4** was prepared according to the method described in Ref. [16] and purified by column chromatography (elution first with ethylacetate:heptane = 1:20 and then with ethylacetate:heptane = 1:1). The analytical data of **4** agreed with the published ones.

2-Ethyl-hexane-1,5-diol (**5**; $C_8H_{18}O_2$)

$NaBH_4$ (6.4 g, 169 mmol) was added in portions to a solution of compound **4** (23.8 g, 167 mmol) in 240 cm^3 anhydrous EtOH at 0°C. The mixture was stirred at room temperature for 2 h. After dropwise addition of MeOH:H_2O = 1:1 until the evolution of H_2 had ceased the solution was poured in 600 cm^3 saturated aqueous NaCl. Diol **5** was extracted with diethyl ether and dried. After removal of the solvent, the crude product was purified by column chromatography (elution with ethylacetate:heptane = 1:1).

Colourless oil; 18.8 g (77%); ^{1}H NMR (300 MHz, δ, $CDCl_3$): 0.91 (t, 3H, $J = 7.2$ Hz, $\mathrm{C}\mathit{H}_3\mathrm{CH_2CH}$), 1.21 (d, 3H, $J = 6.3$ Hz, $\mathrm{C}\mathit{H}_3\mathrm{CHOH}$), 1.32–1.48 (m, 7H, $\mathrm{C}\mathit{H}_2\mathrm{C}\mathit{H}_2\mathrm{C}\mathit{H}\mathrm{C}\mathit{H}_2\mathrm{CH_3}$), 3.00 (br s, 2H, 2 × OH), 3.49–3.62 (m, 2H, $\mathrm{C}\mathit{H}_2\mathrm{OH}$), 3.81 (m, 1H, $\mathrm{C}\mathit{H}\mathrm{OH}$) ppm; ^{13}C NMR (75 MHz, δ, $CDCl_3$): 11.29, 11.30, 23.42, 23.46, 23.57, 23.71, 26.02, 26.50, 35.58, 36.29, 41.57, 42.07, 64.50, 64.82, 67.96, 68.49 ppm; IR (film): $\nu = 3361$, 2963, 2932, 2875, 1461, 1376, 1054 cm^{-1}.

1-(tert-Butyldimethylsilyloxy)-2-ethyl-hexane-5-ol (**6**; $C_{14}H_{32}O_2Si$)

Imidazole (23.0 g, 338 mmol) and *t*-butyldimethylchlorosilane (25.5 g, 169 mmol) were added to a solution of compound **5** (24.7 g, 169 mmol) in 400 cm^3 anhydrous *DMF* at 0°C. The mixture was stirred at room temperature for 3 h and then diluted with 1500 cm^3 H_2O. Silyl alcohol **6** was extracted with diethyl ether and dried. After removal of the solvent the crude product was purified by column chromatography (elution with ethylacetate:heptane = 3:7).

Colourless oil; 29.9 g (68%); ^{1}H NMR (300 MHz, δ, $CDCl_3$): 0.01 (s, 6H, $SiMe_2$), 0.87 (m, 12H, C_4H_9, $\mathrm{CH_2C}\mathit{H}_3$), 1.16 (d, $J = 6.0$ Hz, 3H, $\mathrm{C}\mathit{H}_3\mathrm{CHOH}$), 1.22–1.48 (m, 7H, $\mathrm{C}\mathit{H}_2\mathrm{C}\mathit{H}_2\mathrm{C}\mathit{H}\mathrm{C}\mathit{H}_2$), 1.65 (br s, 1H, OH), 3.48 (m, 2H, $\mathrm{C}\mathit{H}_2\mathrm{OSi}$), 3.55 (m, 1H, $\mathrm{C}\mathit{H}\mathrm{OH}$) ppm; ^{13}C NMR (75 MHz, δ, $CDCl_3$): -5.45, 11.17, 11.20, 18.27, 23.33, 23.38, 23.49, 23.61, 25.90, 26.47, 26.62, 36.45, 36.56, 41.83, 41.93, 65.18, 65.20, 68.35, 68.51 ppm; IR (film): $\nu = 3344$, 2958, 2930, 2858, 1095, 836, 774 cm^{-1}; HRMS (ESI+) [M–Na]$^+$: calcd.: 283.20693, found: 283.20702.

1-(tert-Butyldimethylsilyloxy)-2-ethyl-5-(tert-butyldiphenylsilyloxy)-hexane (**7**; $C_{30}H_{50}O_2Si_2$)

Imidazole (11.7 g, 172 mmol), *t*-butyldiphenylchlorosilane (31.8 g, 116 mmol), and 4-dimethylaminopyridine (0.1 g) were added to a solution of compound **6** (29.9 g, 115 mmol) in 400 cm^3 anhydrous CH_2Cl_2. The mixture was stirred at room temperature for 17 h and then filtrated. After removal of the solvent, silyl ether **7** was isolated from the residue by column chromatography (elution with ethylacetate:heptane = 2:98).

Colourless oil; 50.2 g (88%); ^{1}H NMR (300 MHz, δ, $CDCl_3$): 0.01 (s, 6H, $SiMe_2$), 0.88 (m, 12H, C_4H_9, $\mathrm{CH_2C}\mathit{H}_3$), 1.06 (m, 12H, C_4H_9, $\mathrm{C}\mathit{H}_3\mathrm{CHOSi}$), 1.19–1.58 (m, 7H, $\mathrm{C}\mathit{H}_2\mathrm{C}\mathit{H}_2\mathrm{C}\mathit{H}\mathrm{C}\mathit{H}_2\mathrm{OSi}$), 3.41 (d, $J = 6.0$ Hz, 2H, $\mathrm{C}\mathit{H}_2\mathrm{OSi}$), 3.80 (m, 1H, $\mathrm{C}\mathit{H}\mathrm{OSi}$), 7.36–7.68 (m, 10H, ArH) ppm; ^{13}C NMR (75 MHz, δ,

$CDCl_3$): −5.40, 11.11, 18.29, 19.26, 23.08, 23.27, 25.80, 25.94, 27.05, 36.53, 41.96, 65.21, 69.95, 127.37, 127.44, 129.34, 129.41, 134.65, 135.00, 135.88 ppm; HRMS (ESI+) $[M–Na]^+$: calcd.: 521.32471, found: 521.32474.

5-(tert-Butyldiphenylsilyloxy)-2-ethyl-hexane-1-ol (**8**; $C_{24}H_{36}O_2Si$)

Pyridinium *p*-toluenesulfonate (8.1 g, 33 mmol) was added to a solution of 50.2 g (10.1 mmol) of **7** in 430 cm^3 anhydrous EtOH. The mixture was stirred at room temperature for 66 h, and the solvent was evaporated. Silyl alcohol **8** was isolated from the residue by column chromatography (elution with ethylacetate:heptane = 1:5).

Colourless oil; 29.5 g (76%); ^1H NMR (300 MHz, δ, *DMSO*-d_6): 0.75 (m, 3H, CH_2CH_3), 0.99 (m, 12H, C_4H_9, CH_3CHOSi), 1.10–1.46 (m, 7H, $CH_2CH_2CHCH_2$), 3.20 (m, 2H, CH_2OH), 3.80 (m, 1H, CHOSi), 4.22 (m, 1H, OH), 7.37–7.63 (m, 10H, ArH) ppm; ^{13}C NMR (75 MHz, δ, $CDCl_3$): 10.99, 19.22, 23.17, 25.62, 25.74, 27.02, 36.50, 41.89, 65.08, 69.82, 127.37, 127.44, 129.38, 129.44, 134.58, 134.80, 135.85 ppm; IR (film): $\nu = 3333, 2930, 2857, 1105, 700\ cm^{-1}$; HRMS (ESI+) $[M–Na]^+$: calcd.: 407.23823, found: 407.23860.

Mono-(2-ethyl-5-(tert-butyldiphenylsilyloxy)-hexyl)-phthalate (**9**; $C_{32}H_{40}O_5Si$)

Phthalic acid anhydride (2.6 g, 18 mmol) was added to a solution of 4.0 g (10.4 mmol) of **8** in 200 cm^3 anhydrous pyridine. The mixture was stirred at room temperature for 72 h, and the solvent was evaporated. The residual oil was diluted with diethyl ether, washed with aqueous HCl and H_2O, and dried. After removal of the solvent the residue was diluted with heptane and filtrated in order to remove phthalic acid. The solvent was evaporated, and **9** was isolated from the residue by column chromatography (elution with ethylacetate:heptane = 5:1).

Colourless viscous oil; 4.7 g (86%); ^1H NMR (300 MHz, δ, *DMSO*-d_6): 0.81 (m, 3H, CH_2CH_3), 0.96 (s, 9H, C_4H_9), 1.01 (d, *J* = 6.0 Hz, 3H, CH_3CHOSi), 1.24–1.58 (m, 7H, $CH_2CH_2CHCH_2$), 3.80 (m, 1H, CHOSi), 4.04 (d, *J* = 3.6 Hz, 2H, OCH_2CH), 7.41–7.78 (m, 14H, ArH), 13.20 (br s, 1H, CO_2H) ppm; ^{13}C NMR (75 MHz, δ, $CDCl_3$): 10.83, 19.20, 23.15, 23.51, 26.05, 27.00, 36.30, 38.69, 65.85, 69.75, 127.37, 127.47, 128.81, 129.39, 129.49, 129.84, 130.36, 130.83, 131.94, 133.20, 134.39, 134.78, 135.84, 168.15, 171.81 ppm; IR (film): $\nu = 3072, 2961, 2857, 2667, 1728, 1704, 1600, 1581, 1288, 1112, 1076, 740, 703\ cm^{-1}$; HRMS (ESI-) $[M–H]^-$: calcd.: 531.256678, found: 531.255373.

Mono-(2-ethyl-5-hydroxy-hexyl)-phthalate (**2**; $C_{16}H_{22}O_5$)

Tetrabutylammonium fluoride (44.5 cm^3 of an 1 *M* solution in *THF*, 44.5 mmol) was added to a solution of 4.7 g (8.9 mmol) of **9** in 200 cm^3 *THF*. The mixture was stirred at room temperature for 72 h and then diluted with 800 cm^3 H_2O containing concentrated aqueous HCl (0.8 cm^3, 9.6 mmol). **2** was extracted with diethyl ether and dried over $MgSO_4$. The solvent was evaporated, and the crude product was purified by column chromatography (elution with ethylacetate:acetic acid = 100:1).

Colourless viscous oil; 2.5 g (96%); ^1H NMR (300 MHz, δ, *DMSO*-d_6): 0.87 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.03 (d, *J* = 6.0 Hz, 3H, CH_3CHOH), 1.20–1.48 (m, 6H, $CH_2CH_2CHCH_2$), 1.62 (m, 1H, $CH_2CH_2CHCH_2$), 3.58 (m, 1H, CHOH), 4.14 (m, 3H, CO_2CH_2, OH), 7.61–7.75 (m, 4H, ArH), 13.20 (br s, 1H, CO_2H) ppm; ^{13}C NMR (75 MHz, δ, *DMSO*-d_6): 10.77, 23.24, 23.62, 26.31, 35.99, 38.18, 66.03, 67.24, 128.18, 128.78, 131.01, 131.23, 132.25, 132.41, 167.61, 168.07 ppm; IR (film): $\nu = 3444, 2964, 2640, 1718, 1600, 1580, 1292, 1127, 1074, 746\ cm^{-1}$; HRMS (FAB) $[M–H]^-$: calcd.: 293.1345, found: 293.1389.

2-Ethyl-5-oxo-hexane-1-ol/2-Methyl-5-ethyl-tetrahydropyran-2-ol (**10a**,**b**; $C_8H_{16}O_2$)

Zinc chloride (15.4 cm^3 of a 0.5 *M* solution in *THF*, 7.7 mmol) was added dropwise to $NaBH_4$ (0.69 g, 18.2 mmol) suspended in 35 cm^3 *THF*. The mixture was stirred overnight at room temperature under an atmosphere of Ar and then filtrated under Ar. The obtained solution of $Zn(BH_4)_2$ was added dropwise at -10°C to a solution of compound **4** (1.10 g, 7.7 mmol) in 50 cm^3 *THF*. After additional stirring for 15 min the cooling bath was removed, and the mixture was quenched and diluted with H_2O. The aqueous phase was saturated with NaCl, and the product was extracted with diethyl ether and dried over $MgSO_4$. The solvent was evaporated, and the isomeric mixture of **10a** and **10b** was isolated from the residue by column chromatography (elution with ethylacetate:heptane = 1:5).

Colourless oil; 0.28 g (25%), ^1H NMR (500 MHz, δ, $CDCl_3$): 0.88 (t, $J = 7.5$ Hz, 3H, CH_2CH_3), 0.91 (t, $J = 7.5$ Hz, 3H, CH_2CH_3), 1.20–1.82 (m, 12H, CH_2CHCH_2, $CH_2CH_2CHCH_2$), 1.28 (s, 3H, $OCOHCH_3$), 2.14 (br s, 2H, 2 × OH), 2.15 (s, 3H, $COCH_3$), 2.49 (t, $J = 9.0$ Hz, 2H, CH_2CO), 3.19–3.33 (m, 2H, CH_2O), 3.55 (m, 2H, CH_2O) ppm; ^{13}C NMR (75 MHz, δ, $CDCl_3$): 11.15, 11.20, 24.05, 24.31, 25.18, 25.23, 25.32, 29.83, 30.32, 36.62, 41.51, 41.56, 66.16, 66.31, 97.07, 209.41 ppm; IR (film): $\nu = 3428$, 2938, 2865, 1720, 1463, 1134, 1052 cm^{-1}; HRMS (FAB) $[M–H]^+$: calcd.: 145.1229, found: 145.1225.

Mono-(2-ethyl-5-oxo-hexyl)-phthalate (**3**; $C_{16}H_{20}O_5$)

A solution of oxalyl chloride (0.64 cm^3, 7.4 mmol) in 25 cm^3 CH_2Cl_2 was added dropwise to a solution of *DMSO* (1.21 cm^3, 17.0 mmol) in 15 cm^3 CH_2Cl_2 at -65°C under an atmosphere of Ar. After 5 min of stirring, a solution of compound **2** (0.50 g, 1.7 mmol) in 15 cm^3 CH_2Cl_2 was added dropwise at the same temperature. After additional 30 min of stirring, a solution of Et_3N (2.82 cm^3, 20.4 mmol) in 10 cm^3 CH_2Cl_2 was added dropwise at -65°C. After additional 5 min of stirring the cooling bath was removed, and the mixture was allowed to achieve room temperature. The mixture was poured into 400 cm^3 H_2O, and **3** was extracted with diethyl ether and dried over $MgSO_4$. The solvent was evaporated, and the crude product was purified by column chromatography (elution with ethylacetate).

Colourless viscous oil; 0.28 g (56%); ^1H NMR (300 MHz, δ, *DMSO*-d_6): 0.87 (t, $J = 7.8$ Hz, 3H, CH_2CH_3); 1.20–1.68 (m, 5H, CH_2CHCH_2), 2.07 (s, 3H, $COCH_3$), 2.45 (t, $J = 6.6$ Hz, 2H, CH_2CO), 4.12 (d, $J = 5.4$ Hz, 2H, CO_2CH_2), 7.61–7.75 (m, 4H, ArH), 13.20 (br s, 1H, CO_2H) ppm; ^{13}C NMR (75 MHz, δ, *DMSO*-d_6): 10.74, 23.08, 24.00, 29.61, 37.57, 39.71, 66.84, 128.10, 128.71, 130.95, 131.20, 132.05, 132.30, 167.52, 167.94, 208.24 ppm; IR (film): $\nu = 2963$, 2638, 2532, 1717, 1600, 1580, 1291, 1128, 1074, 791, 745 cm^{-1}; HRMS (ESI+) $[M–Na]^+$: calcd.: 315.12084, found: 315.12037.

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