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Convenient and High-Yielding Preparations of Mono(5-carboxy-2-ethylpentyl) Phthalate and its Ring-Deuterated Isomer – The "Third" Major Metabolite of Bis(2-ethylhexyl) Phthalate

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Summary. The synthesis of an oxidative major metabolite of bis(2-ethylhexyl) phthalate is described. The target molecule and its ring-deuterated isomer were obtained via acylation of the appropriate ω-hydroxy benzyl ester or the corresponding carboxylate with phthalic anhydride or phthalic anhydride-d_4. All transformation steps proceed with high yields.

Keywords. Bis(2-ethylhexyl) phthalate; Oxidative metabolites; Carboxylic acids; Protecting groups; Ozonolysis.

Introduction

Due to their use as additives in many products of every day life phthalates can be found as ubiquitous contaminants in the environment [1]. Recently human exposure to phthalates has been proven unequivocally [2]. Several phthalates cause hepatic peroxisome proliferation [3] and testicular damage [4] in animal experiments. The relevance of these results with regard to human health is still debated controversially [5] so that further toxicological investigations must reveal potentially existing risks. The metabolism of bis(2-ethylhexyl) phthalate (*DEHP*) has been elucidated [6] and compounds **1**, **2**, and **3** have been identified as major metabolites (Scheme 1).

The major metabolites are formed by different ω- and (ω-1)-oxidation steps proceeding consecutively from mono(2-ethylhexyl) phthalate (*MEHP*) which is the

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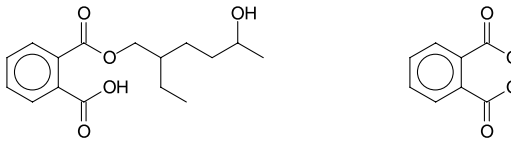

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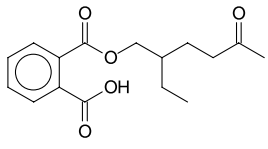

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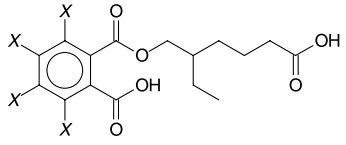


3 $X = H$
10 $X = D$

Scheme 1

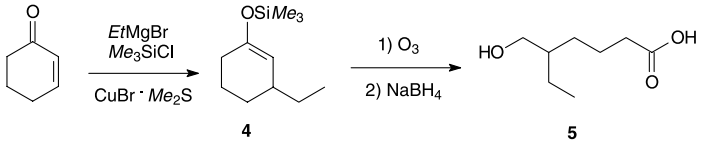
primary metabolite of *DEHP*. Compound **3** is metabolized further by degradation [7] with loss of a two-carbon fragment. The concentration of **3** detected in rats has been found to be time dependent and strongly related to the amount of *DEHP* or *MEHP* administered [8].

A new powerful method [9] of biological monitoring allows the measurement of exposure to *DEHP* by determination of its oxidative metabolites **1** and **2** in urine. This method needs the original compounds and their isotopically labelled analogues as reference materials. In the past it has been necessary to gain reference material from animal experiments until a synthetic access to **1** and **2** and their deuterated isomers has been developed [10]. We now report our efforts in the synthesis of **3** [11] and its deuterated isomer **10**, which may also serve as biomarkers.

Results and Discussion

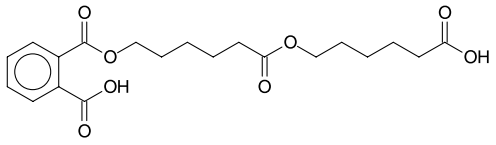
The retrosynthetic disconnection of the target molecule **3** leads to phthalic anhydride and **5** [12], which is a derivative of 6-hydroxycaproic acid. The introduction of the ethyl group was achieved by copper catalyzed conjugate addition [13] of the appropriate *Grignard* reagent to 2-cyclohexenone in the presence of chlorotrimethylsilane and ozonolytic cleavage [14] of the resulting silyl enol ether **4** [15]. These steps yielded **5** with very good overall yield (Scheme 2).

In order to investigate if direct acylation of **5** is possible some screening experiments with commercial 6-hydroxycaproic acid were done. Whereas the acylation of this compound with acetic anhydride is known [16] the reaction with phthalic anhydride showed only low conversion. Using pyridine as solvent gave **6** as single



4 **5**

Scheme 2



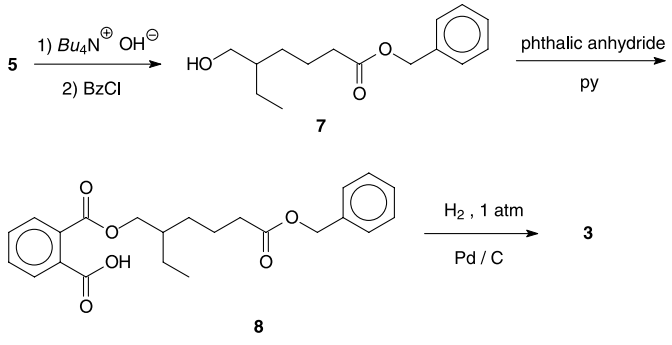
6

Scheme 3

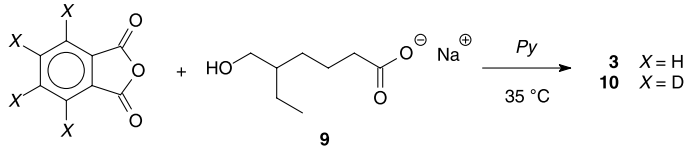
product, which is formed by intermolecular esterification and was identified by comparison of its NMR spectra with published data [17] of similar structures (Scheme 3). Attempted acylation in chloroform with 4-(dimethylamino)pyridine as catalyst [18] was not successful.

As a conclusion of these results the benzyl group was choosen for the protection [19] of the carboxylic group of **5** because it can be removed easily in the presence of another ester group. The benzylation of **5** *via* the tetrabutylammonium salt [20] gave the hydroxy benzyl ester **7**. The target molecule **3** was obtained in high overall yield by acylation of **7** using an excess of phthalic anhydride and subjecting the resulting monophthalate **8** to hydrogenolysis [21] with Pd/C as catalyst (Scheme 4).

This reaction sequence provides an easy access to the target structure. In the view of the expensive deuterated anhydride, however, it is desired to avoid isotopically labelled intermediates. Therefore we checked the acylation [22] of ω-hydroxycarboxylate **9**. Although it was necessary to increase the temperature slightly in order to dissolve the salt and the solution remained thick during the reaction acidic work-up gave **10** with 69% yield (Scheme 5).



Scheme 4



Scheme 5

Experimental

IR spectra were recorded on a Perkin-Elmer 1430 spectrophotometer using the film technique. NMR spectra were recorded on a Varian Mercury plus-BB/4-nuc spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. High resolution mass spectra were recorded on a VG 7070 double focusing mass spectrometer using the CI and the NCI mode. Elemental analyses were carried out using a CE Instruments CHNS-Elemental Analyzer EA 1110. All new compounds gave satisfactory data of elemental analysis or high resolution mass spectrometry. All reactions except the neutralization of **5** were carried out under an atmosphere of Ar. 6-Hydroxycaproic acid and phthalic anhydride-d_4 (99.4%) were purchased from Aldrich and used as received. Purifications by column chromatography were performed on silica gel (Merck 63-200 mesh).

3-(Ethylcyclohex-1-enyloxy)trimethylsilane (**4**)

To a solution of ethylmagnesium bromide, prepared from 1.70 g of Mg turnings (70.0 mmol) and 5.23 cm^3 of ethyl bromide (70.0 mmol) in 100 cm^3 of anhydrous *THF* was added 0.51 g of $CuBr \cdot Me_2S$ (2.5 mmol) at −78°C. A solution of 20.88 cm^3 of *HMPT* (120.0 mmol) in 100 cm^3 of *THF* was then added dropwise. The mixture was stirred for 15 min, a solution of 3.85 cm^3 of 2-cyclohexenone (39.8 mmol) and 12.68 cm^3 of chlorotrimethylsilane (100.0 mmol) in 20 cm^3 of *THF* was then added dropwise. The reaction mixture was stirred for 3 h at −78°C, and a solution of 14.05 cm^3 of triethylamine (100.0 mmol) in 20 cm^3 of *THF* was added. The mixture was stirred for additional 30 min, warmed up to room temperature, hydrolyzed with a saturated aqueous solution of $NaHCO_3$ and diluted with 100 cm^3 of diethyl ether:heptane = 1:1. The mixture was filtered and the filter cake was washed with 5×30 cm^3 of heptane. The filtrate was washed with 10×20 cm^3 of a saturated aqueous solution of $NaHCO_3$ and dried (Na_2SO_4). The drying agent was filtered off, the solvent was evaporated under reduced pressure, and the product was isolated from the residue by Kugelrohr distillation. Yield 6.57 g (83%); colourless liquid; the analytical data agreed with the published ones [15].

5-(Hydroxymethyl)heptanoic acid (**5**)

A solution of 5.25 g of **4** (26.5 mmol) in 20 cm^3 of anhydrous *Me*OH and 5 cm^3 of CH_2Cl_2 was treated with O_3 at −78°C until a blue colour persisted. 1.00 g of sodium borohydride (26.5 mmol) was added in portions and the mixture was stirred for 1 h. Additional portions of 1.00 g of sodium borohydride (26.5 mmol) were then added, the mixture was warmed up to room temperature, and poured into 200 cm^3 of a saturated aqueous solution of $NaHCO_3$. The organic layer was discarded and the aqueous layer was extracted with 3×20 cm^3 of diethyl ether. The aqueous phase was then acidified with 400 cm^3 of a 5% aqueous HCl, saturated with NaCl and extracted with 4×100 cm^3 of $CHCl_3$. The combined extracts were dried ($MgSO_4$). The drying agent was filtered off and the solvent was evaporated under reduced pressure. Yield 4.04 g (96%); colourless oil; ^{1}H NMR (400 MHz, *DMSO*-d_6): $\delta = 0.81–0.86$ (m, $CHCH_2CH_3$), 1.10–1.65 (m, $HOCH_2CH–(CH_2CH_3)CH_2CH_2CH_2CO_2H$), 2.11–2.22 (m, CH_2CO_2H), 3.17–3.42 (m, CH_2OH), 4.25 (s, br, OH), 11.94 (s, br, CO_2H) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 10.9$, 22.0, 22.9, 29.7, 34.1, 41.3, 62.9, 174.4 ppm; IR (film): $\bar{\nu} = 3500–2400$, 2932, 2876, 1704, 1461, 1410, 1235, 1171, 1027, 755 cm^{-1}; HRMS (NH_3–CI) $[M + H]^+$: calcd.: 161.1178, found: 161.1182.

Phthalic acid mono[5-(5-carboxy-pentyloxycarbonyl)-pentyl]ester (**6**, $C_{20}H_{26}O_8$)

A solution of 1.90 g of phthalic anhydride (12.8 mmol) and 0.95 g of 6-hydroxycaproic acid (7.2 mmol) in 100 cm^3 of anhydrous pyridin was refluxed for 11 h, cooled, and stirred at room temperature for additional 40 h. The solvent was evaporated under reduced pressure and the residue was diluted with 50 cm^3 of $CHCl_3$, washed with 2×20 cm^3 of a 1 *M* aqueous HCl and 2×20 cm^3 of H_2O and dried

($MgSO_4$). The drying agent was filtered off and the solvent was evaporated under reduced pressure. The product was isolated from the residue by column chromatography using ethylacetate:heptane = 1:1 as eluent. Yield 0.14 g (10%); pale yellow waxy solid; ^{1}H NMR (400 MHz, *DMSO*-d_6): $\delta =$ 1.23–1.68 (m, $OCH_2CH_2CH_2CH_2CH_2CO_2CH_2CH_2CH_2CH_2CH_2CO_2H$), 2.17–2.32 (m, 2 CH_2CO_2), 4.00–4.04 (m, OCH_2), 4.18–4.27 (m, OCH_2), 7.60–7.63 (m, 3H, Ar), 7.72–7.76 (m, 1H, Ar), 12.54 (s, br, 2 CO_2H) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 24.1$, 24.9, 27.5, 27.6, 27.7, 27.8, 33.3, 33.5, 63.4, 64.8, 127.9, 128.5, 130.7, 131.0, 131.9, 132.2, 167.2, 167.7, 172.5, 174.0 ppm; IR (film): $\bar{\nu} = 3500$–2500, 2940, 2868, 1721, 1699, 1600, 1579, 1284, 1259, 1125, 1072, 743 cm^{-1}.

5-(Hydroxymethyl)heptanoic acid benzyl ester (**7**, $C_{15}H_{22}O_3$)

A mixture of 1.64 cm^3 of an 40% aqueous solution of tetrabutylammonium hydroxide (2.5 mmol) and 0.40 g of **5** (2.5 mmol) was stirred at 65°C until a clear solution appeared. The solvent was removed under reduced pressure and the residual oil was dried under high vacuum. 1.00 g of oil (2.5 mmol) was dissolved in 15 cm^3 of anhydrous *DMF* and 0.32 cm^3 of benzylchloride (2.8 mmol) were added and the mixture was stirred at room temperature for 24 h. The reaction mixture was poured into 150 cm^3 of H_2O and was extracted with 3×50 cm^3 of diethyl ether. The combined extracts were dried (Na_2SO_4). The drying agent was filtered off and the solvent was evaporated under reduced pressure. The product was isolated from the residue by column chromatography using ethylacetate:heptane = 2:3 as eluent. Yield 0.50 g (81%); colourless oil; ^{1}H NMR (400 MHz, *DMSO*-d_6): $\delta = 0.81$ (t, $J = 7.3$ Hz, $CHCH_2CH_3$), 1.19–1.31 (m, $HOCH_2CH(CH_2CH_3)CH_2$), 1.54 (t, $J = 7.3$ Hz, $CH_2CH_2CO_2CH_2Ar$), 2.33 (t, $J = 7.3$ Hz, $CH_2CO_2CH_2Ar$), 3.26–3.30 (m, CH_2OH), 4.28 (t, $J = 5.3$ Hz, OH), 5.08 (s, OCH_2Ar), 7.31–7.37 (m, 5H, Ar) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 10.9$, 21.9, 22.9, 29.5, 33.9, 41.2, 62.9, 65.2, 127.8, 127.9, 128.4, 136.3, 172.7 ppm; IR (film): $\bar{\nu} = 3450$, 2959, 2931, 2875, 1733, 1456, 1158, 1029, 736, 696 cm^{-1}; HRMS (NH_3–NCI) $[M-H]^-$: calcd.: 249.1491, found: 249.1495.

Phthalic acid mono(5-benzyloxycarbonyl-2-ethylpentyl)ester (**8**, $C_{23}H_{26}O_6$)

A solution of 1.07 g of phthalic anhydride (7.2 mmol) and 0.72 g of **7** (2.9 mmol) in 50 cm^3 of anhydrous pyridine was stirred at room temperature for 72 h. The mixture was evaporated under reduced pressure and the residue was diluted with 100 cm^3 of diethyl ether. The solution was washed with 3×20 cm^3 of a 10% aqueous HCl, dried (Na_2SO_4), and evaporated. The product was isolated from the residue by column chromatography using ethylacetate:heptane = 5:1 as eluent. Yield 0.94 g (82%); colourless oil; ^{1}H NMR (400 MHz, *DMSO*-d_6): $\delta = 0.86$ (t, $J = 7.3$ Hz, $CHCH_2CH_3$), 1.24–1.39 (m, $OCH_2CH(CH_2CH_3)CH_2CH_2CH_2CO_2CH_2Ar$), 1.55–1.67 (m, $OCH_2CH(CH_2CH_3)CH_2CH_2CH_2$–$CO_2CH_2Ar$), 2.33–2.38 (m, $CH_2CO_2CH_2Ar$), 4.09–4.16 (m, OCH_2CH), 5.08 (s, OCH_2Ar), 7.29–7.38 (m, 5H, Ar), 7.60–7.65 (m, 3H, Ar), 7.71–7.76 (m, 1H, Ar), 13.18 (s, br, CO_2H) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 10.7$, 21.7, 23.1, 29.5, 33.6, 37.8, 65.2, 67.0, 127.9, 128.1, 128.3, 128.7, 130.9, 131.1, 132.3, 136.2, 167.5, 168.0, 172.6 ppm; IR (film): $\bar{\nu} = 3400$–2500, 3034, 2961, 2877, 1725, 1698, 1600, 1580, 1456, 1383, 1285, 1259, 1123, 1072, 742, 697, 639 cm^{-1}; HRMS (NH_3–NCI) $[M]^-$: calcd.: 398.1729, found: 398.1743.

Phthalic acid mono(5-carboxy-2-ethylpentyl)ester (**3**, $C_{16}H_{20}O_6$)

To a solution of 0.30 g of **8** (0.8 mmol) in 25 cm^3 of anhydrous *Me*OH was added 0.03 g of Pd/C (10% Pd). Hydrogen was passed through at room temperature for 8 h and the reaction mixture was stirred under 1 atm of hydrogen for additional 16 h. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was diluted with 100 cm^3 of diethyl ether and the solution was washed with 2×100 cm^3 of a saturated aqueous solution of $NaHCO_3$. The organic layer was discarded

and the aqueous layer was acidified, saturated with NaCl, and extracted with $3 \times 100\,cm^3$ of $CHCl_3$. The combined extracts were dried (Na_2SO_4) and evaporated to give the pure product. Yield 0.18 g (78%); colourless oil; ^1H NMR (400 MHz, *DMSO*-d_6): $\delta = 0.88$ (t, $J = 7.3$ Hz, $CHCH_2CH_3$), 1.23–1.40 (m, $OCH_2CH(CH_2CH_3)CH_2CH_2CH_2CO_2H$), 1.41–1.58 (m, $OCH_2CH(CH_2CH_3)CH_2CH_2CH_2CO_2H$), 1.60–1.69 (m, $OCH_2CH(CH_2CH_3)$), 2.15–2.23 (m, CH_2CO_2H), 4.09–4.17 (m, OCH_2CH), 7.60–7.66 (m, 3H, Ar), 7.72–7.76 (m, 1H, Ar), 12.56 (s, br, 2 CO_2H) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 10.7$, 21.7, 23.1, 29.6, 33.8, 37.9, 67.0, 128.1, 128.7, 130.9, 131.1, 132.2, 132.3, 167.5, 168.0, 174.3 ppm; IR (film): $\bar{\nu} = 3400$–2500, 2961, 2877, 2665, 1721, 1698, 1600, 1580, 1412, 1383, 1284, 1259, 1124, 1073, 742, 705, 675, 640 cm^{-1}; HRMS (NH_3–NCI) $[M-H]^-$: calcd.: 307.1182, found: 307.1168.

Sodium 5-(hydroxymethyl)heptanoate (**9**, $C_8H_{15}NaO_3$)

To a solution of 0.13 g of NaOH (3.1 mmol) in 15 cm^3 of distilled H_2O was added 0.50 g of **5** (3.1 mmol) and the mixture was stirred at 65°C until a homogenous phase appeared. The solvent was evaporated and the residue solidified upon drying under high vacuum. Yield 0.57 g (100%); colourless solid; mp 93–94°C; IR (film): $\bar{\nu} = 3170$, 2959, 2935, 2874, 1571, 1459, 1379, 1062, 883, 739 cm^{-1}.

*Preparation of **3** via Acylation of **9***

To a solution of 0.46 g of phthalic anhydride (3.1 mmol) in 25 cm^3 of anhydrous pyridine was added 0.57 g of **9** (3.1 mmol), the mixture was stirred at 35°C for 1 h to give a thick solution which was stirred at room temperature for additional 72 h. The solution was poured into 250 cm^3 of a 10% aqueous HCl. The aqueous solution was saturated with NaCl and extracted with $3 \times 100\,cm^3$ of $CHCl_3$. The combined extracts were dried (Na_2SO_4). The drying agent was filtered off and the solvent was evaporated under reduced pressure. The residue was partitionated between 200 cm^3 of a saturated aqueous solution of $NaHCO_3$ and 100 cm^3 of diethyl ether and the organic layer was discarded. The aqueous layer was acidified, saturated with NaCl, and extracted with $3 \times 100\,cm^3$ of $CHCl_3$. The combined extracts were dried and evaporated to give the pure product. Yield 0.63 g (66%).

Phthalic acid (3,4,5,6-$^2H_4$) mono(5-carboxy-2-ethylpentyl)ester (**10**, $C_{16}H_{16}D_4O_6$)

To a solution of 0.42 g of phthalic anhydride-d_4 (2.7 mmol) in 35 cm^3 of anhydrous pyridine was added 0.50 g of **9** (2.7 mmol), the mixture was stirred at 35°C for 1 h to give a thick solution which was stirred at room temperature for additional 72 h. After work-up as described above the pure product was obtained. Yield 0.59 g (69%); colorless oil; ^1H NMR (400 MHz, *DMSO*-d_6): $\delta = 0.88$ (t, $J = 7.3$ Hz, $CHCH_2CH_3$), 1.24–1.42 (m, $OCH_2CH(CH_2CH_3)CH_2CH_2CH_2$–$CO_2H$), 1.50–1.58 (m, $OCH_2CH(CH_2CH_3)CH_2CH_2CH_2CO_2H$), 1.60–1.68 (m, $OCH_2CH(CH_2CH_3)$), 2.19–2.23 (m, CH_2CO_2H), 4.11–4.13 (m, OCH_2CH), 12.61 (s, br, 2 CO_2H) ppm; ^{13}C NMR (100 MHz, *DMSO*-d_6): $\delta = 10.7$, 21.7, 23.1, 29.6, 33.9, 37.9, 67.0, 132.2, 132.3, 167.6, 168.0, 174.4 ppm; IR (film): $\bar{\nu} = 3400$–2500, 2962, 2936, 1697, 1557, 1432, 1235, 1077, 941, 751, 666 cm^{-1}; HRMS (NH_3–NCI) $[M-H]^-$: calcd.: 311.1433, found: 311.1436.

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