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A synthetic approach towards novel alkyl 4,5-dibromo-2-methylbenzoate derivatives

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ABSTRACT

Alkyl 4,5-dibromo-2-methylbenzoate derivatives **16**–**18** were synthesized from 1,2-dibromo-4-alkoxymethyl-5-methylbenzene **2**–**4** in the presence of catalytic amounts of NBS as a radical initiator. Only primary ether derivatives rendered the corresponding esters.

1. Introduction

Benzyl ethers react with NBS in carbon tetrachloride under free radical conditions to give favorable yields of the corresponding benzaldehydes.[1,2] When benzylic trimethylsilyl ethers are allowed to react with NBS in the presence of a catalytic amount of 2,2′-azobisisobutyronitrile in boiling carbon tetrachloride, the corresponding aldehydes are obtained in good yields.[3] However, aliphatic primary trimethylsilyl ethers give esters directly formed from two molecular equivalents of the starting trimethylsilyl ethers rather than the expected aliphatic aldehydes.[4] In addition, alcohols were found to be oxidized to the corresponding carboxylic acid in the presence of catalytic NBS in an oxygen atmosphere at room temperature and irradiation with a 400 W high-pressure mercury lamp. Among the solvents examined, ethyl acetate and acetonitrile were found to be the most effective to afford the corresponding carboxylic acid. Additionally, 4-substituted electron-donating or electron-withdrawing benzyl alcohols afforded the corresponding benzoic acids in good yields.[5,6]

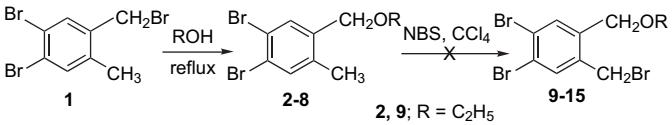
Methyl bromination of 1,2-dibromo-4-alkoxymethyl-5-methylbenzene (**2**–**8**) could be a possible route to prepare precursors for different degrees of liphophilic derivatives by replacing the bromine atom. However, the reaction of **2**–**8** (1 equiv) with NBS (1 equiv) to obtain desired compounds **9**–**15** gave unexpected results.

2. Results and discussion

2.1. Synthesis and characterization

Attempts to obtain compounds **9**–**15** by reaction of **2**–**8** (1 equiv) and NBS (1 equiv) under reflux in carbon tetrachloride failed. As shown in Scheme 1, the starting material was 1,2-dibromo-4-bromomethyl-5-methylbenzene (**1**) synthesized from 1,2-dibromo-4,5-dimethylbenzene (1 equiv) and NBS (1 equiv) in boiling carbon tetrachloride. This reaction was achieved without a radical initiator since there was no difference whatever with or without benzoyl peroxide, used as an initiator; results were practically the same.[7] The reaction of **1** with sodium alkoxide gave 1,2-dibromo-4-alkoxymethyl-5-methylbenzenes **2**–**8**.

When a mixture of **2**–**4** (1 equiv) and NBS (1 equiv) was heated overnight under reflux in carbon tetrachloride esters **16**–**18** were



1 **2-8** **9-15**

2, 9; R = C_2H_5
3, 10; R = $CH_2(CH_2)_3CH_3$
4, 11; R = $CH_2(CH_2)_6CH_3$
5, 12; R = $CH_2C_6H_5$
6, 13; R = C_6H_5
7, 14; R = $CH(CH_3)_2$
8, 15; R = $(CH_3)CH(CH_2)_5CH_3$

Scheme 1. Obtention of ethers **2**–**8** from compound **1**.

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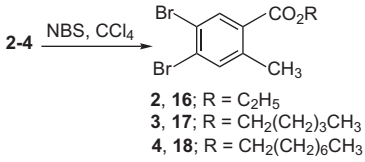
obtained in good yields (Scheme 2),[8] while benzylic (**5**) and phenol (**6**) ethers, as well as secondary alcohol ethers (**7**, **8**) yielded 4,5-dibromo-2-methylbenzoic acid (**19**), in fair to good yields.



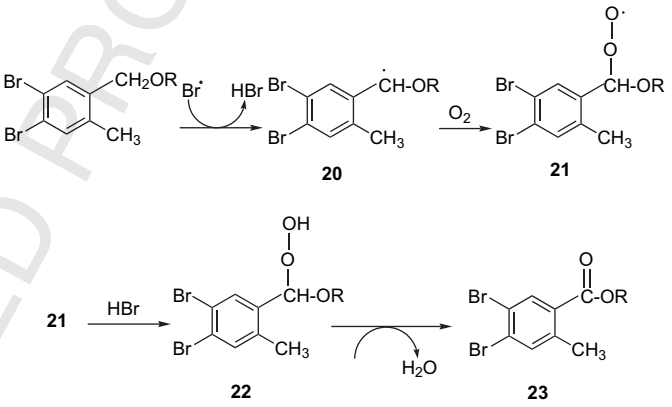
Scheme 2. Conversion of ethers **2**–**4** to esters **16**–**18**.

Based on these results, further studies have been initiated to investigate the reaction of **2**–**8** with catalytic amounts of NBS. Therefore, **2**–**4** (1 equiv) and NBS (0.02 equiv) were reacted in boiling carbon tetrachloride. Different reaction times were analyzed, showing 40% yield during the first 2 h of the reaction and reaching 71, 63 and 87% yield after 4 h reaction for compounds **16**, **17** and **18**, respectively. The reaction of **5**–**8** with NBS (0.02 equiv) carried out in boiling carbon tetrachloride afforded **19** after a 2 h reaction, Figure 1. The reaction of **2**–**8** with NBS (0.02 equiv) in the presence of benzoyl peroxide (0.02 equiv) as initiator in carbon tetrachloride at reflux temperature, under the above conditions, rendered the same products and yields obtained without any radical initiator. These results are consistent with those obtained by our group some years ago.[7]

The formation of acid **19** can be understood taking into account that secondary alcohol derivatives, as well as benzylic alcohol and phenol esters, are capable of giving a stable carbonium ion in the acidic medium after protonation and S_N1 hydrolysis thus allowing us to obtain 4,5-dibromo-2-methylbenzoic acid (**19**). On account of the instability of the corresponding carbocation, ester derivatives of the primary alcohols are unable to follow the proposed mechanism, hence esters **16**–**18** are obtained as the main product.

On the other hand, an attempt to purify 1,2-dibromo-4-*tert*-butoxymethyl-5-methylbenzene by filtering through a silica gel column failed to afford it. 1,2-Dibromo-4-hydroxymethyl-5-methylbenzene was obtained in good yields due to hydrolysis.

Formation of the esters can be rationalized as outlined in Scheme 3. A radical species **20** is generated by the abstraction of a hydrogen radical with a bromo radical. The radical species traps molecular oxygen to afford peroxy radical **21**, which subsequently turns into ester **23** via hydroperoxide **22**. This mechanism is similar to that reported by Kuwabara and Itoh[5] who described the oxidation of benzyl alcohols to acids by means of *N*-bromosuccinimide, oxygen and light at room temperature. Traces of 4,5-dibromo-2-methylbenzoic acid (**19**) were obtained as an additional evidence of the proposed mechanism. Besides, the obtention of esters **16**–**18** in the presence of catalytic amount of NBS is a further evidence of the proposed path.



Scheme 3. Mechanism of ether oxidation.

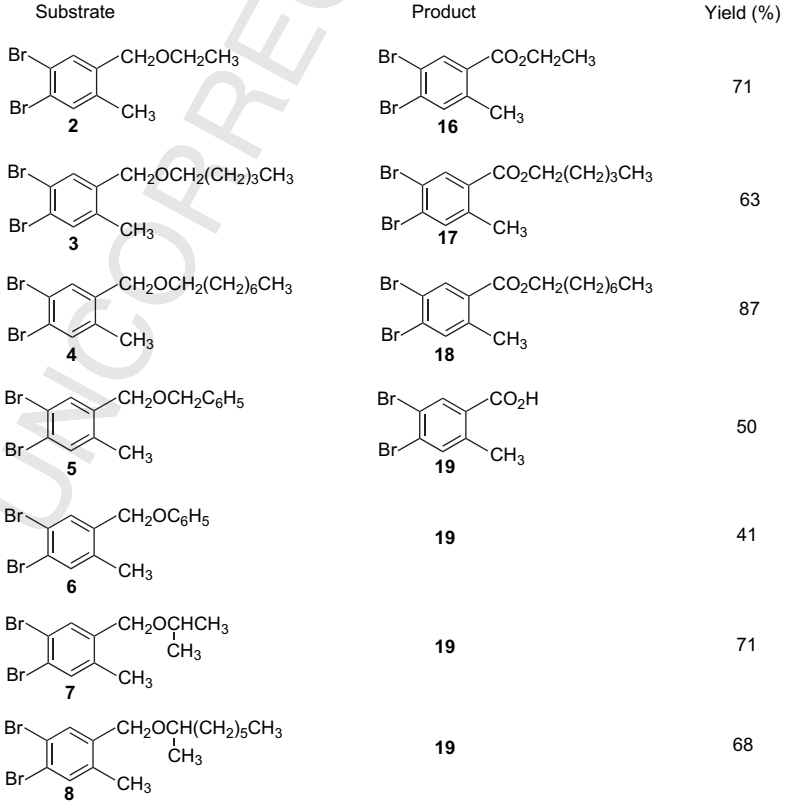


Figure 1. Reaction products of 1,2-dibromo-4-alkoxymethyl-5-methylbenzene with catalytic amounts of NBS.

All compounds were characterized by ^{1}H NMR, IR and mass spectrometry. Traditionally, electron and chemical ionization were the principal methods to produce ions for mass spectrometry. The advent of atmospheric pressure ionization (API) provided a method of ionizing labile and non-volatile substances so that they could be examined by mass spectrometry. API has become strongly linked to HPLC as a basis for ionizing the eluent on its way into the mass spectrometry. As a consequence, compounds **4**, **18** and 1,2-dibromo-4-hydroxymethyl-5-methylbenzene, which cannot be vaporized without thermal decomposition were effectively performed by APCI(+) TOF/TOF mass spectrometry in order to achieve a better molecular cluster ion abundance leading to [M$^+$] (100).

3. Conclusions

Taking into account that 1,2-dibromo-4-alkoxycarbonyl-methylbenzene derivatives cannot be successfully obtained by using 1-alkoxycarbonyl-2-methylbenzene,[9] NBS oxidation of the primary alcohol derivatives of 1,2-dibromo-4-alkoxymethyl-5-methylbenzene is a useful method to prepare the corresponding esters in good yields. This reaction was achieved with catalytic amounts of NBS as radical initiator.

4. Experimental

4.1. General

Melting points were determined on an Electrothermal 9100 capillary melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker MSL 300 spectrometer. Mass spectra were obtained with a TRIO 2 (electronic ionization 70 eV) spectrometer and a Perkin Elmer Claruss 500 mass spectrometer (electronic ionization 20 eV). Infrared spectra were performed with a Perkin Elmer Spectrum One FT-IR spectrometer. Microanalyses were carried out with a Carlo Erba EA 1108 elemental analyzer. Chromatography columns were prepared with TLC Kieselgel (Merck). Reagents were purchased from Sigma–Aldrich.

4.2. 1,2-Dibromo-4-ethoxymethyl-5-methylbenzene (2)

Compound **1** (0.200 g, 0.58 mmol) was added to a solution of Na (0.034 g, 1.48 mmol) in anhydrous EtOH (20 mL). The mixture was stirred and heated at 80 °C for 20 h. CH_2Cl_2 (30 mL) was added to the reaction mixture and then washed with H_2O (3×30 mL). The organic phase was dried with Na_2SO_4 and evaporated to dryness in vacuo and the solid residue was recrystallized from MeOH–H_2O. Yield: 0.166 g (93%); mp 32–34 °C. IR (KBr): 2973, 2852, 1469, 1454, 1408, 1375, 1356, 1344, 1273, 1249, 1225, 1158, 1123, 1107, 1033, 891, 878, 864, 654 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.26 (t, 3H, J=6.9 Hz, CH_3), 2.24 (s, 3H, CH_3), 3.54 (q, 2H, J=7.1 Hz, CH_2), 4.39 (s, 2H, CH_2), 7.41 (s, 1H, Ar), 7.58 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=15.70 (CH_3), 20.61 ($ArCH_3$), 65.70 (OCH_2CH_3), 71.63 ($ArCH_2O$), 125.51 (CBr), 125.82 (CBr), 131.43 (CH), 133.59 (CH), 136.36 (CCH_3), 141.18 (CCH_2O). MS (EI, 70 eV): m/z (%)=310 [M$^{\bullet+}$, 2 81Br, 7], 308 [M$^{\bullet+}$, 81Br and 79Br, 14], 306 [M$^{\bullet+}$, 2 79Br, 7], 265 [2 81Br, 18], 263 [81Br and 79Br, 34], 261 [2 79Br, 17]. Anal. Calcd for $C_{10}H_{12}Br_2O$: C, 38.99; H, 3.93. Found: C, 38.97; H, 3.97.

4.3. 1,2-Dibromo-4-methyl-5-pentoxymethylbenzene (3)

Compound **1** (0.320 g, 0.93 mmol) was added to a solution of Na (0.033 g, 1.43 mmol) in anhydrous pentanol (5 mL). The mixture was stirred and heated at 140 °C for 20 h. CH_2Cl_2 (30 mL) was added to the reaction mixture and then washed with H_2O (3×30 mL). The organic phase was dried with Na_2SO_4 and evaporated to dryness in vacuo. The oily residue was dissolved in a small volume of CH_2Cl_2–hexane (3:7) and filtered through a silica gel column packed and pre-washed with the same solvent. After evaporation of the solvent, an oil was obtained. Yield: 0.240 g (74%). IR (KBr): 2931, 2858, 1588, 1471, 1363, 1250, 1222, 1157, 1101, 1037, 881, 729, 655, 626 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.90 (t, 3H, CH_3), 1.34 (m, 4H, CH_2CH_2), 1.61 (m, 2H, CH_2), 2.24 (s, 3H, CH_3), 3.48 (t, 2H, J=7.0 Hz, CH_2), 4.38 (s, 2H, CH_2), 7.41 (s, 1H, Ar), 7.57 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.11 (CH_3), 20.61 ($ArCH_3$), 22.78 ($CH_2CH_2CH_3$), 28.51 (OCH_2CH_2), 29.26 ($CH_2CH_2CH_2CH_3$), 71.67 (OCH_2CH_2), 72.83 ($ArCH_2O$), 125.25 (CBr), 126.31 (CBr), 131.79 (CH), 133.32 (CH), 136.72 (CCH_3), 141.44 (CCH_2O). MS (EI, 70 eV): m/z (%)=352 [M$^{\bullet+}$, 2 81Br, 5], 350 [M$^{\bullet+}$, 81Br and 79Br, 10], 348 [M$^{\bullet+}$, 2 79Br, 5], 265 [2 81Br, 24], 263 [81Br and 79Br, 48], 261 [2 79Br, 23]. Anal. Calcd for $C_{13}H_{18}Br_2O$: C, 44.60; H, 5.18. Found: C, 44.62; H, 5.20.

4.4. 1,2-Dibromo-4-methyl-5-octyloxymethylbenzene (4)

Compound **1** (0.200 g, 0.58 mmol) was added to a solution of Na (0.034 g, 1.48 mmol) in anhydrous octanol (15 mL). The mixture was stirred and heated at 195 °C for 20 h. CH_2Cl_2 (50 mL) was added to the reaction mixture and then washed with H_2O (3×50 mL). The organic phase was dried with Na_2SO_4 and evaporated to dryness in vacuo. The oily residue was dissolved in a small volume of CH_2Cl_2–hexane (3:7) and filtered through a silica gel column packed and pre-washed with the same solvent. After evaporation of the solvent, an oil was obtained. Yield: 0.198 g (86%). IR (KBr): 2926, 2855, 1728, 1635, 1468, 1378, 1261, 1101, 880, 799, 655 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88 (t, 3H, J=7.0 Hz, CH_3), 1.27 (br s, 10H, $(CH_2)_5CH_3$), 1.59 (m, 2H, J=7.0 Hz, OCH_2CH_2), 2.26 (s, 3H, CH_3), 3.48 (t, 2H, J=7.0 Hz, OCH_2CH_2), 4.41 (s, 2H, $ArCH_2O$), 7.45 (s, 1H, Ar), 7.57 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.05 (CH_3), 20.61 ($ArCH_3$), 22.68 ($CH_2CH_2CH_3$), 27.06 ($OCH_2CH_2CH_2CH_2$), 29.24 ($OCH_2CH_2CH_2$), 29.33 ($OCH_2CH_2CH_2CH_2$), 29.37 ($CH_2CH_2CH_2CH_3$), 71.36 (OCH_2CH_2), 71.77 ($ArCH_2O$), 125.25 (CBr), 126.31 (CBr), 131.09 (CH), 133.32 (CH), 136.02 (CCH_3), 140.71 (CCH_2O). MS (EI, 20 eV): m/z (%)=394 [M$^{\bullet+}$, 2 81Br, 2], 392 [M$^{\bullet+}$, 81Br and 79Br, 4], 390 [M$^{\bullet+}$, 2 79Br, 2], 265 [2 81Br, 15], 263 [81Br and 79Br, 29], 261 [2 79Br, 15]. Anal. Calcd for $C_{16}H_{24}Br_2O$: C, 49.00; H, 6.17. Found: C, 49.05; H, 6.19.

4.5. 1,2-Dibromo-4-benzyloxymethyl-5-methylbenzene (5)

The reaction of **1** with anhydrous benzyl alcohol at 140 °C using the procedure described for **4** afforded **5** after purification by filtering through a column, packed and pre-washed with CH_2Cl_2. Yield: 0.121 g (96%). IR (KBr): 2926, 2855, 1718, 1691, 1583, 1544, 1496, 1467, 1452, 1380, 1363, 1264, 1092, 1028, 904, 880, 801, 738, 698, 640 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.23 (s, 3H, CH_3), 4.44 (s, 2H, CH_2), 4.58 (s, 2H, CH_2), 7.35 (br s, 5H, Ar), 7.42 (s, 1H, Ar), 7.62 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.61 ($ArCH_3$), 71.78 ($ArCH_2O$), 72.50 (OCH_2Ar), 125.46 (CBr), 126.31 (CBr), 128×3, 129×2 (Ar), 131.91 (CH), 133.53 (CH), 136.85 (CCH_3), 139.26 (OCH_2C), 141.39 (CCH_2O). MS (EI, 20 eV): m/z (%)=372 [M$^{\bullet+}$, 2 81Br, 3], 370 [M$^{\bullet+}$, 81Br and 79Br, 5], 368 [M$^{\bullet+}$, 2 79Br, 3], 265 [2 81Br, 21], 263 [81Br and 79Br, 38], 261 [2 79Br, 18]. Anal. Calcd for $C_{15}H_{14}Br_2O$: C, 48.68; H, 3.81. Found: C, 48.70; H, 3.79.

4.6. 1,2-Dibromo-4-methyl-5-phenoxymethylbenzene (6)

Compound **1** (0.100 g, 0.29 mmol) was added to a solution of phenol (0.027 g, 0.29 mmol) dissolved in anhydrous THF (6 mL) containing Na (0.007 g, 0.29 mmol). The mixture was stirred and heated at 65 °C for 20 h. CH_2Cl_2 (30 mL) was added to the reaction mixture and then washed with H_2O (3×30 mL). The organic phase was dried with Na_2SO_4 and evaporated to dryness in vacuo. The oily residue was dissolved in a small volume of CH_2Cl_2–hexane (1:9)

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and filtered through a silica gel column packed and pre-washed with the same solvent. After evaporation of the solvent, an oil was obtained. Yield: 0.069 g (66%). IR (KBr): 3062, 3040, 2925, 2854, 1736, 1599, 1587, 1496, 1474, 1457, 1383, 1347, 1301, 1239, 1172, 1152, 1121, 1078, 1933, 1014, 913, 883, 835, 788, 751, 690, 656, 630, 613, 509 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.30 (s, 3H, CH_3), 4.94 (s, 2H, CH_2), 6.96 (m, 3H, Ar), 7.32 (m, 2H, Ar), 7.48 (s, 1H, Ar), 7.69 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.61 ($ArCH_3$), 71.09 ($ArCH_2O$), 115.2×2 (CH), 120.84 (CH), 126.07 (CBr), 126.52 (CBr), 129.89×2 (CH), 131.77 (CH), 134.14 (CH), 136.71 (CCH_3), 140.88 (CCH_2O), 157.61 ($COCH_2$). MS (EI, 70 eV): *m*/*z* (%)=358 [$M^{\bullet+}$, 2 81Br, 4], 356 [$M^{\bullet+}$, 81Br and 79Br, 7], 354 [$M^{\bullet+}$, 2 79Br, 4], 265 [2 81Br, 45], 263 [81Br and 79Br, 100], 261 [2 79Br, 49]. Anal. Calcd for $C_{14}H_{12}Br_2O$: C, 47.23; H, 3.40. Found: C, 47.20; H, 3.37.

4.7. 1,2-Dibromo-4-isopropyloxymethyl-5-methylbenzene (7)

Compound **1** (0.200 g, 0.58 mmol) was added to a solution of Na (0.034 g, 1.48 mmol) in anhydrous isopropyl alcohol (15 mL). The mixture was stirred and heated at 90 °C for 20 h. The work-up and purification were performed using the procedure described for **3**. An oil was obtained that decomposed by standing at room temperature. Yield: 0.0915 g (49%). IR (KBr): 2965, 1689, 1579, 1455, 1382, 1261, 1211, 1086, 892, 802 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.22 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.68 (m, 1H, CH), 4.38 (s, 2H, CH_2), 7.41 (s, 1H, Ar), 7.59 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.61 ($ArCH_3$), 22.24×2 (CH_3), 69.82 ($ArCH_2O$), 70.73 (OCH), 125.61 (CBr), 125.77 (CBr), 130.57 (CH), 133.68 (CH), 135.50 (CCH_3), 141.40 (CCH_2O). MS (EI, 20 eV): *m*/*z* (%)=324 [$M^{\bullet+}$, 2 81Br, 6], 322 [$M^{\bullet+}$, 81Br and 79Br, 10], 320 [$M^{\bullet+}$, 2 79Br, 6], 265 [2 81Br, 25], 263 [81Br and 79Br, 48], 261 [2 79Br, 25]. Anal. Calcd for $C_{11}H_{14}Br_2O$: C, 41.03; H, 4.38. Found: C, 41.05; H, 4.39.

4.8. 1,2-Dibromo-4(1-methylheptyloxy)methyl-5-methylbenzene (8)

Compound **1** (0.200 g, 0.58 mmol) was added to a solution of Na (0.034 g, 1.48 mmol) in anhydrous 2-octanol (15 mL). The mixture was stirred and heated at 180 °C for 20 h. The work-up and purification were performed using the procedure described for **3**. After filtering through a silica gel column, packed and pre-washed with CH_2Cl_2–hexane (4:6) an oil was obtained. Yield: 0.177 g (77%). IR (KBr): 2927, 2856, 1627, 1465, 1378, 1263, 1121, 1088, 882, 745, 593 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.89 (t, 3H, *J*=7.0 Hz, CH_3), 1.20 (d, 3H, $CHCH_3$), 1.31 (m, 8H, $(CH_2)_4CH_3$), 1.42 (m, 2H, *J*=7.0 Hz, $OCHCH_2$), 2.25 (s, 3H, CH_3), 3.39 (m, 1H, CH), 4.46 (s, 2H, $ArCH_2O$), 7.39 (s, 1H, Ar), 7.60 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.00 (CH_3), 20.61 ($ArCH_3$), 21.60 ($CHCH_3$), 22.80 (CH_2CH_3), 25.30 ($CHCH_2CH_2$), 30.40 ($CHCH_2CH_2CH_2$), 32.20 ($CH_2CH_2CH_3$), 34.88 ($CHCH_2CH_2$), 69.96 ($ArCH_2O$), 72.39 ($OCHCH_2$), 125.15 (CBr), 126.31 (CBr), 130.57 (CH), 133.23 (CH), 135.50 (CCH_3), 141.06 (CCH_2O). MS (EI, 20 eV): *m*/*z* (%)=394 [$M^{\bullet+}$, 2 81Br, 2], 392 [$M^{\bullet+}$, 81Br and 79Br, 3], 390 [$M^{\bullet+}$, 2 79Br, 2], 265 [2 81Br, 51], 263 [81Br and 79Br, 100], 261 [2 79Br, 52]. Anal. Calcd for $C_{16}H_{24}Br_2O$: C, 49.00; H, 6.17. Found: C, 49.03; H, 6.19.

4.9. Ethyl 4,5-dibromo-2-methylbenzoate (16)

NBS (0.0012 g, 0.007 mmol) was added to a solution of **2** (0.107 g, 0.35 mmol) in CCl_4 (20 mL). The mixture was stirred under reflux for 4 h. After cooling, the precipitate was filtered, washed with CCl_4 and the filtrate evaporated in vacuo to eliminate the solvent. The residue was then dissolved in a small volume of CH_2Cl_2–hexane (4:6) and filtered through a silica gel column packed and pre-washed with the same solvent. After evaporation of the solvent, the solid residue was recrystallized from MeOH–H_2O. Yield: 0.080 g (71%); mp 46–48 °C. IR (KBr): 2987, 2924, 2853, 1721 (CO_2R), 1580, 1540, 1460, 1446, 1387, 1365, 1333, 1284, 1246, 1119, 1089, 1018, 904, 867, 823, 779, 642 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.41 (t, 3H, *J*=7.0 Hz, CH_3), 2.52 (s, 3H, CH_3), 4.36 (q, 2H, *J*=7.3 Hz, CH_2), 7.52 (s, 1H, Ar), 8.13 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.65 (CH_3), 23.60 ($ArCH_3$), 61.53 (OCH_2), 125.18 (CBr), 128.50 (CBr), 132.38 (CCO_2), 133.05 (CH), 133.19 (CH), 137.56 (CCH_3), 167.57 (CO). MS (EI, 70 eV): *m*/*z* (%)=324 [$M^{\bullet+}$, 2 81Br, 10], 322 [$M^{\bullet+}$, 81Br and 79Br, 21], 320 [$M^{\bullet+}$, 2 79Br, 11], 295 [2 81Br, 42], 293 [81Br and 79Br, 100], 291 [2 79Br, 52]. Anal. Calcd for $C_{10}H_{10}Br_2O_2$: C, 37.30; H, 3.13. Found: C, 37.32; H, 3.15.

4.10. Pentyl 4,5-dibromo-2-methylbenzoate (17)

Compound **3** (0.110 g, 0.31 mmol) in CCl_4 (5 mL) and NBS (0.0011 g, 0.006 mmol) were reacted applying the procedure described for **16**. An oil was obtained. Yield: 0.072 g (63%) after purification by filtering through a silica gel column, packed and pre-washed with CH_2Cl_2–hexane (4:6). IR (KBr): 2957, 1725 (CO_2R), 1465, 1383, 1280, 1243, 1088, 780 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.92 (t, 3H, CH_3), 1.39 (m, 4H, $(CH_2)_2CH_3$), 1.75 (m, 2H, OCH_2CH_2), 2.52 (s, 3H, CH_3), 4.28 (t, 2H, OCH_2CH_2), 7.52 (s, 1H, Ar), 8.12 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.20 (CH_3), 23.10 ($CH_2CH_2CH_3$), 23.60 ($ArCH_3$), 29.33 (OCH_2CH_2), 30.68 ($CH_2CH_2CH_2CH_3$), 65.70 (OCH_2CH_2), 125.18 (CBr), 128.50 (CBr), 132.50 (CCO_2), 133.05 (CH), 133.60 (CH), 138.18 (CCH_3), 169.56 (CO). MS (EI, 70 eV): *m*/*z* (%)=366 [$M^{\bullet+}$, 2 81Br, 2], 364 [$M^{\bullet+}$, 81Br and 79Br, 5], 362 [$M^{\bullet+}$, 2 79Br, 2], 296 [2 81Br, 15], 294 [81Br and 79Br, 29], 292 [2 79Br, 16]. Anal. Calcd for $C_{13}H_{16}Br_2O_2$: C, 42.89; H, 4.43. Found: C, 42.87; H, 4.40.

4.11. Octyl 4,5-dibromo-2-methylbenzoate (18)

Compound **4** (0.137 g, 0.30 mmol) in CCl_4 (25 mL) and NBS (0.0012 g, 0.007 mmol) were reacted applying the procedure described for **16**. An oil was obtained. Yield: 0.123 g (87%) after purification by filtering through a silica gel column, packed and pre-washed with CH_2Cl_2–hexane (4:6). IR (KBr): 2956, 2927, 2855, 1728 (CO_2R), 1634, 1466, 1378, 1279, 1243, 1112, 871, 801, 722, 639 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.88 (t, 3H, CH_3), 1.30 (br s, 10H, $(CH_2)_5CH_3$), 1.56 (m, 2H, *J*=7.1 Hz, OCH_2CH_2), 2.53 (s, 3H, CH_3), 4.30 (t, 2H, *J*=6.8 Hz, OCH_2CH_2), 7.53 (s, 1H, Ar), 8.13 (s, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.05 (CH_3), 22.68 ($CH_2CH_2CH_3$), 23.60 ($ArCH_3$), 27.52 ($OCH_2CH_2CH_2CH_2CH_2$), 29.33 ($OCH_2CH_2CH_2CH_2$), 29.37 ($CH_2CH_2CH_2CH_3$), 29.58 ($OCH_2CH_2CH_2$), 31.90 ($CH_2CH_2CH_3$), 65.39 (OCH_2CH_2), 125.18 (CBr), 128.50 (CBr), 131.77 (CCO_2), 133.05 (CH), 133.10 (CH), 137.47 (CCH_3), 167.76 (CO). MS (EI, 20 eV): *m*/*z* (%)=408 [$M^{\bullet+}$, 2 81Br, 3], 406 [$M^{\bullet+}$, 81Br and 79Br, 6], 404 [$M^{\bullet+}$, 2 79Br, 3], 296 [2 81Br, 50], 294 [81Br and 79Br, 100], 292 [2 79Br, 51]. Anal. Calcd for $C_{16}H_{22}Br_2O_2$: C, 47.32; H, 5.46. Found: C, 47.30; H, 5.44.

4.12. 4,5-Dibromo-2-methylbenzoic acid (19)

Ethers **5**–**8** (1 equiv) and 0.02 equiv of NBS in carbon tetrachloride were refluxed for 2 h. The mixture was cooled, the succinimide formed was removed by filtration and the solution checked by TLC (R_f=0.5; CH_2Cl_2–hexane, 4:6). Evaporation of the solvent afforded a solid in good yields, which was recrystallized from EtOH; mp 98–99 °C, TLC (R_f=0.5; CH_2Cl_2–hexane, 4:6). IR (KBr): 2958, 1702 (CO_2H), 1582, 1542, 1465, 1413, 1385, 1345, 1282, 1244, 1125, 1090, 888, 781, 691, 641, 578 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.60 (s, 3H, CH_3), 7.57 (s, 1H, Ar), 7.99 (s, 1H, Ar), 10.16 (s, 1H, CO_2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=22.75 ($ArCH_3$), 126.33 (CBr), 129.53 (CBr), 131.55 (CCO_2), 133.75 (CH), 134.19 (CH), 138.32 (CCH_3),

169.58 (CO). MS (EI, 70 eV): m/z (%)=296 [$M^{\bullet+}$, 2 81Br, 38], 294 [$M^{\bullet+}$, 81Br and 79Br, 87], 292 [$M^{\bullet+}$, 2 79Br, 44]. Anal. Calcd for $C_8H_6Br_2O_2$: C, 32.69; H, 2.06. Found: C, 32.72; H, 2.04.

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