Synthesis of Analogues of 2-iodohexadecanal, a Regulator of Iodine Metabolism in the Thyroid Gland

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Com o objetivo futuro de fazer um estudo da relação estrutura-atividade, foram sintetizados vários derivados do 2-iodo-hexadecanal [1], um regulador do metabolismo de iodo na glândula tireóide, que diferem no comprimento da cadeia, natureza do substituinte e grupo funcional terminal.

With the object of performing a structure-activity relationship study, we have synthesized several analogues of 2-iodohexadecanal [1], a regulator of iodine metabolism in the thyroid gland, differing by the chain length, the nature of the substituent, and/or the terminal functional group.

**Keywords:** α-halogenocarbonyl compounds, 2-iodohexadecanal

**Introduction**

As a part of a program dealing with the regulation of the thyroid gland metabolism by iodide, 2-iodohexadecanal [1] has been identified as a major iodolipid [1]. It is formed upon addition of iodine to the vinyl diethylether group of plasmalogens followed by hydrolysis [1,2]. The investigation of the biological activities of synthetic (±)-I revealed its ability to inhibit both H2O2 production in cultured dog thyroid cells [3] and the human thyroid adenylyl cyclase [4]. (2S)-1 and (2R)-1 exhibit identical biological activities, thus suggesting the lack of stereoselectivity in their interaction with the biological receptors [5].

Prompted by these interesting findings, we decided to investigate the structural parameters of 1 required for observation of biological activities. Thus, a series of analogues of 1 differing by the chain length (n), the nature of the substituent (X) and that of the terminal function (Y) have been synthesized. The syntheses of these analogues, all of them new compounds, are presented in this paper.

**Results and Discussion**

**Syntheses of 2-halogenoaldehydes 1-8, 2-iodohexadecanoic acid [18], methyl 2-iodohexadecanoate [19] and 2-iodohexadecanamide [22]**

2-Iodoaldehydes 1-5 were synthesized by direct iodination of the corresponding long chain aldehydes using the mixture HgCl2/I2 (yield: 50-60%) [6]. In our hands, this method was superior to the alternative one passing through substitution of the bromine of 2-bromoaldehydes by iodine (NaI/CH3CN; yield 86%), as bromination of the n-aldehydes was only achieved with rather low yields. For example, 2-bromohexadecanal [6] was synthesized by direct bromination of n-hexadecanal with t-BuBr/DMSO in a 41% yield [7].

n-Octanal and n-dodecanal are commercially available. n-Hexadecanal, n-octadecanal and n-eicosanal were synthesized by PCC oxidation of the corresponding alcohols in an 80-90% yield [8].

2-Chlorohexadecanal [7] was synthesized in two steps by chlorination of n-hexadecanal dimethylacetal [24], using the mixture MnCl2/MnO2/TMSCl [9] to afford 25 in 67% yield, followed by acid hydrolysis of 25 with CF3COOH/H2O/CH2Cl2 (yield 71%). We have found these α-chloroacetal hydrolysis conditions to be an efficient al-
ternative to those described by Boni et al. (AcOH/HCl\textsuperscript{10} or Ac\textsubscript{2}O/AcCl/AcONa.3H\textsubscript{2}O\textsuperscript{11}). Moreover, neither direct chlorination of n-hexadecanal \textsuperscript{9} with SO\textsubscript{2}Cl\textsubscript{2}\textsuperscript{12}, or n-hexadecanal trimethylsilylenolether with Cl\textsubscript{2}\textsuperscript{13} led to the formation of 2-chlorohexadecanal \textsuperscript{7}, probably because n-hexadecanal or 2-chlorohexadecanal polymerized under the reaction conditions.

Several methods have been described in the literature for the preparation of 2-fluoroaldehydes but they present significant drawbacks, such as poor yields or the need of fluorine gas\textsuperscript{14-18}. Our approach to the synthesis of 2-fluoroaldehydes avoids these drawbacks. Our synthesis of 2-fluorohezadecanal\textsuperscript{8} was based on a described synthesis of 2-fluoroacetadecanoic acid\textsuperscript{39}. Hexadecanoic acid\textsuperscript{26} was brominated using the mixture P/Br\textsubscript{2}, esterified with methanol (yield: 67%), and the bromine of the resulting bromoester\textsuperscript{[27]} exchanged by fluorine [AgF/ CH\textsubscript{3}CN/ H\textsubscript{2}O; yield: 50%]) to afford methyl 2-fluorohexadecanoate [29] (Scheme 2). Several attempts to reduce the ester function of 29 into an aldehyde using DIBAH under different reaction conditions (-78 °C; in hexane, diethylether, CH\textsubscript{2}Cl\textsubscript{2} or toluene) always led to a mixture of the reactant and 2-fluorohexadecimalno. Therefore, 29 was first reduced to 2-fluorohexadecanol in an 83% yield using LiAlH\textsubscript{4}, followed by Swern oxidation\textsuperscript{20} which cleanly afforded 2-fluorohexadecanal [8] in a 90% yield.

Methyl 2-iodohexadecanoate [19] was synthesized following two different procedures. 2-Iodohexadecanoic acid [18] was first prepared by direct iodination of hexadecanoic acid [26] using the mixture Cl\textsubscript{2}SO\textsubscript{2}H / I\textsubscript{2}\textsuperscript{21}. Addition of methanol to the reaction mixture afforded 19 in a 38% yield after purification by column chromatography on silica gel\textsuperscript{21}. Alternatively, compound 19 was prepared by substitution of the bromine of methyl 2-bromohexadecanoate [27] using NaI in CH\textsubscript{3}CN (yield: 93%).

2-Iodohexadecanamide [22] was prepared by aminolysis of 27 with gaseous NH\textsubscript{3} in MeOH-CHCl\textsubscript{3}\textsuperscript{22} (yield: 55%), followed by substitution of the bromine by iodine which gave 2-iodohexadecanamide [22] in a 92% yield.

The preparation of 2-mesyloxy\textsuperscript{23} and 2-tosyloxyketones\textsuperscript{24} is already described but up to now, no method was available for the preparation of 2-mesyloxy- and 2-tosyloxyaldehydes. Attempts to prepare 2-tosyloxyhexadecanal by direct reaction of n-hexadecanal with HTIB\textsuperscript{25} only led to complex reaction mixtures. In contrast, the attempted reduction of 2-mesyloxyhexadecanenitrile with DIBAH led to the recovery of the starting material. We also failed to obtain 2-mesyloxyhexadecanal \textsuperscript{10} by hydrolysis of the S,S-dioxoydithioketal\textsuperscript{26} or the dimethylketal of 2-mesyloxyhexadecanal\textsuperscript{27} probably due to the strong inductive effect of the mesyloxy group. Finally, 10 was synthesized starting from 1-hexadecene \textsuperscript{30}. Dihydroxylation of 30 into 31 with OsO\textsubscript{4}\textsuperscript{28} followed by selective protection of the primary hydroxyl group of 31 with TBDMSCl\textsuperscript{29}, mesylation of the secondary hydroxyl group of 32 with MsCl\textsuperscript{30} and deprotection of the primary hydroxyl group of 33 with TFA\textsuperscript{31} led to 2-mesyloxyhexadecanal [34]. Swern oxidation\textsuperscript{30} of 34 gave 2-mesyloxyhexadecanal [10] which proved to be a relatively unstable compound.

3-Bromo-2-nonanone [12] was synthesized regiospecifically by direct bromination of 2-nonanone [15] with the system TMSBr/DMSO\textsuperscript{32}.

3-Iodo-2-nonanone [11] was cleanly synthesized in a 77% yield by substitution of the bromine of 12 by NaI in CH\textsubscript{3}CN. In contrast with literature claims\textsuperscript{6}, direct iodination of 2-nonanone [15] with HgCl\textsubscript{2} and I\textsubscript{2} was not regioselective and gave a mixture of 3-iodo-2-nonanone [11] and 1-iodo-2-nonanone (82:18), which have the same R\textsubscript{f} on TLC in different eluent systems, together with small amounts of 1,3-diiodo-2-nonanone. The same problem of regioselectivity was encountered in the direct iodination of 2-heptadecanone (see below). Thus, the first method is superior to the second one because the bromination reaction is regiospecific.

\[ \text{CH}_3(\text{CH}_2)_{13} \text{O} + \text{HC(OCH}_3)_3 \rightarrow \text{CH}_3(\text{CH}_2)_{13} \text{OCH}_3 \]

\[ \text{CF}_3\text{COOH/H}_2\text{O} \rightarrow \text{CH}_3(\text{CH}_2)_{13} \text{Cl} \]

\[ \text{OCH}_3 \rightarrow \text{CH}_3(\text{CH}_2)_{13} \text{OCH}_3 \]

\[ \text{CH}_3(\text{CH}_2)_{13} \text{O} \rightarrow \text{CH}_3(\text{CH}_2)_{13} \text{Cl} \]

\[ \text{OCH}_3 \rightarrow \text{CH}_3(\text{CH}_2)_{13} \text{OCH}_3 \]

\[ \text{MeOH/H}^+ \rightarrow \text{CH}_3(\text{CH}_2)_{13} \text{OCH}_3 \]

\[ \text{MnO}_2/\text{TMSCl} \rightarrow 67\% \]

\[ \text{CH}_3(\text{CH}_2)_{13} \text{OCH}_3 \rightarrow \text{CH}_3(\text{CH}_2)_{13} \text{Cl} \]

\[ \text{Scheme 1. Synthesis of 2-chlorohexadecanal [7].} \]
3-Chloro-2-nonanone [13] was prepared in a 92% yield by direct chlorination of 2-nonanone [15] with \( \text{MnO}_2/\text{TMSCl} \) in AcOH 33. Another chlorinating system, \( \text{TMSCl/DMSO} \) in acetonitrile, is described for the introduction of a chlorine atom into the more substituted position of a ketone 34. In our hands, the use of these conditions only led to 3-methylthio-2-nonanone in a 66% yield.

3-Fluoro-2-nonanone [14] was obtained by substitution of the bromine atom of 3-bromo-2-nonanone [12] with \( \text{AgF} \). 3-Tosyloxy-2-nonanone [16] was synthesized by direct oxidation of 2-nonanone [15] by HTIB 25 which gave a mixture of 3-tosyloxy-2-nonanone [16] (yield: 30%) and 1-tosyloxy-2-nonanone (yield: 15%). The two compounds could be easily separated by flash chromatography.
3-Iodo-2-heptadecanone [17] was synthesized starting from hexadecan-1-ol. Oxidation of hexadecan-1-ol by PCC, followed by addition of methylmagnesiumbromide, hydrolysis and PCC oxidation of the resulting 2-heptadecanol [35] gave 2-heptadecanone [36]. Iodination of the latter with HgCl₂/I₂ at rt. gave a 77:23 mixture of 3-iodo-2-heptadecanone [17] and 1-iodo-2-heptadecanone [33] (yield: 53%). A higher regioselectivity could be obtained at reflux (95:5; 48%). The two regioisomers could be separated by reversed phase HPLC.

**Synthesis of 2-iodohexadecanol [20] and 2-iodooctanol [38]**

2-Iodohexadecanol [20] and 2-iodooctanol [38] were prepared respectively by reduction of 2-iodohexadecanal [1] and 2-iodooctanal [2] by NaBH₄ (Scheme 6).

**Synthesis of 2-iodohexadecanenitrile [23]**

2-Iodohexadecanenitrile [23] was prepared in several steps from pentadecan-1-ol [39]. The latter was first oxidized into n-pentadecanal [40] by PCC (yield 83%)8. Treatment of 40 with TMSCN and ZnI₂ afforded trimethylsilylcyanohydrin 41, which was deprotected with citric acid into 42 (yield for the two steps: 55%). This compound was also obtained in approximately the same yield by column chromatography of crude 41 on silica gel. These moderate yields can be explained by partial polymerisation of n-pentadecanal [40] under the reaction conditions used for the cyanohydrin formation. Mesylation of cyanohydrin 42 with ClSO₂CH₃ afforded 2-mesyloxyhexadecanenitrile [43] in a 100% yield30. Finally, 2-iodohexadecanenitrile was obtained in a 57% yield by substitution of the mesyloxy group of 43 by iodide.

The testing of these analogues on the H₂O₂ production and on the thyroid gland adenyl cyclase has been performed and the results have been published elsewhere3,4.
Experimental

$^1$H-NMR spectra were recorded on a BRUKER WM 250 spectrometer and are reported in ppm from internal TMS on the $\delta$ scale (CDCl$_3$). Data are reported as follows: chemical shift [multiplicity (s: singlet; bs: broad singlet; d: doublet; bd: broad doublet; t: triplet; m: multiplet; dm: double multiplet), coupling constant in Hertz, integration].

Infrared spectra were taken with Bruker IFS 25 instrument as a film on a NaCl disk unless otherwise stated. EIMS were recorded on a VG Micromass 7070 or Autospec spectrometer and are reported in ppm from internal TMS on the $\delta$ scale (CDCl$_3$). Data are reported as follows:

$\delta$ (integration, coupling constants)

For example:

- 1H-NMR: 9.76 (t, 1.9 Hz, 1 H); 2.41 (dt, 7.3 Hz, 1.9 Hz, 2 H); 1.63 (m, 2 H); 1.26 (m, 28 H); 0.88 (m, 3 H).

- EIMS: C$_{16}$H$_{32}$O (M = 240); m/z 240 (M$^+$).

- EIMS: C$_{15}$H$_{30}$O (M = 226); m/z 226 (M$^+$).

- EIMS: C$_{16}$H$_{31}$OI (M = 366); m/z 366 (M$^+$).

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- EIMS: C$_{15}$H$_{30}$O (M = 226); m/z 226 (M$^+$).

- EIMS: C$_{16}$H$_{31}$OI (M = 366); m/z 366 (M$^+$).
(M\(^{+}\), 2); 170 (85); 127 (100); 109 (100); 84 (21). \(^{1}\)H-NMR: 9.26 (d, 3.2 Hz, 1 H); 4.45 (td, 7.3 Hz, 3.2 Hz, 1 H); 2.04-1.84 (m, 2 H); 1.56-2.13 (m, 8 H); 0.88 (m, 3 H).

2-Iodododecanal [3]. Oil. IR: 2954, 2924, 2854, 2722, 1721; 1465 cm\(^{-1}\). EIMS: C\(_{12}\)H\(_{22}\)O\(_2\) (M = 210); m/z = 210 (M\(^{+}\), 0.8); 183 (100); 170 (100); 165 (69); 140 (32). \(^{1}\)H-NMR: 9.26 (d, 3.2 Hz, 1 H); 4.45 (dt, 7.3 Hz, 3.2 Hz, 1 H); 2.00-1.90 (m, 2 H); 1.56-1.26 (m, 32 H); 0.88 (m, 3 H).

2-Iodoctadecanal [4]. M.p.: 42-44 \(^{\circ}\)C. IR: 2923, 2819, 1722, 1464 cm\(^{-1}\). EIMS: C\(_{18}\)H\(_{36}\)O\(_2\) (M = 334); m/z = 334 (M\(^{+}\), 25); 188 (100); 156 (141); 141 (141); 127 (141). \(^{1}\)H-NMR: 9.25 (d, 3.2 Hz, 1 H); 4.45 (t, 7.3 Hz, 3.2 Hz, 1 H); 1.94 (m, 2 H); 1.26 (m, 28 H); 0.88 (m, 3 H).

2-Iodoicosanal [5]. IR: 2923, 2918, 2850, 2725, 1716, 1471 cm\(^{-1}\). EIMS: C\(_{20}\)H\(_{40}\)O\(_2\) (M = 422); m/z = 422 (M\(^{+}\), 5); 242 (10); 295 (100); 277 (100); 252 (52); 170 (100). \(^{1}\)H-NMR: 9.25 (d, 3.2 Hz, 1 H); 4.45 (dt, 7.3 Hz, 3.2 Hz, 1 H); 2.00-1.89 (m, 2 H); 1.49-1.26 (m, 32 H); 0.88 (m, 3 H).

2-Bromohexadecanal [6]. A mixture of 336 mg (140 mmol, 1 eq.) of \(n\)-hexadecan-1-ol, 200 \(\mu\)L of methanol, 240 mmol, 1.7 eq.) of DMSO and 630 \(\mu\)L of \(\beta\)-butyl bromide (766 mg, \(4\) mmol, 4 eq.) was stirred at 60-65 \(^{\circ}\)C for 6 h. The reaction mixture was poured into water and extracted with diethylether. The organic phase was dried, evaporated in vacuo and the resulting residue was flash chromatographed on Florisil (toluene/hexane 5:5) to afford 95.9 mg (80%) as an oil. IR: 2924, 2854, 2719, 2673, 1720, 1467, 1456 cm\(^{-1}\). EIMS: C\(_{16}\)H\(_{31}\)OBr (M = 318); m/z = 318 (M\(^{+}\), 76); 292 (100); 239 (99); 221 (8.6); 196 (19); 92 (44); 78 (80). \(^{1}\)H-NMR: 9.42 (d, 3.2 Hz, 1 H); 4.45 (td, 7.3 Hz, 3.2 Hz, 1 H); 1.88 (m, 2 H); 1.25 (m, 16 H); 0.88 (m, 3 H).

2-Chlorohexadecanal [7]. A mixture of 46.0 mg (0.143 mmol) of 2-chlorohexadecanal methyl acetal [25] in 0.5 mL of CH\(_{2}\)Cl\(_{2}\) were added 125 \(\mu\)L of trifluoroacetic acid and 125 \(\mu\)L of water. The reaction mixture was stirred at reflux for 4 h after which it was diluted with CH\(_{2}\)Cl\(_{2}\) (20 mL) and washed with an aqueous NaHCO\(_{3}\) solution (5\%; 3 x 20 mL). The aqueous phase was extracted with CH\(_{2}\)Cl\(_{2}\) (3 x 20 mL) and the combined organic phases were dried, evaporated in vacuo and the resulting residue was flash chromatographed on silica gel (hexane(CH\(_{2}\)Cl\(_{2}\); 7:3) to afford 28 mg (71%) of 2-chlorohexadecanal methyl acetal [25] as an oil. IR: 2924, 2854, 1748, 1466, 1190, 1120, 1080, 722 cm\(^{-1}\). EIMS: C\(_{17}\)H\(_{33}\)O\(_2\)Cl (M = 320, 322); m/z = 322 (M\(^{+}\)\(^{37}\)Cl, 0.3), 320 (M\(^{+}\)\(^{35}\)Cl, 0.7), 321 (0.7), 319 (2.6), 75 (100). \(^{1}\)H-NMR: 9.48 (d, 3.2 Hz, 1 H); 3.87 (m, 1 H); 3.44 (s, 6 H); 1.65 (m, 4 H); 1.26 (m, 22 H); 0.88 (m, 3 H).

2-Chlorohexadecanal methyl acetal [27]. A mixture of 1.00 g (3.90 mmol) of palmitic acid [26] and 121 mg (3.90 mmol, 1 eq.) of red phosphorus was heated at 80 \(^{\circ}\)C. After melting of the palmitic acid, 728 \(\mu\)L of water. The reaction mixture was stirred at reflux for 4 h after which it was diluted with CH\(_{2}\)Cl\(_{2}\) (20 mL) and washed with an aqueous NaHSO\(_{3}\) solution (5\%; 3 x 20 mL). The aqueous phase was extracted with CH\(_{2}\)Cl\(_{2}\) (3 x 20 mL) and the combined organic phases were dried, evaporated in vacuo and the resulting residue was flash chromatographed on silica gel (hexane(CH\(_{2}\)Cl\(_{2}\); 7:3) to afford 28 mg (71%) of 2-chlorohexadecanal methyl acetal [25] as a solid. M.p.: 49-50 \(^{\circ}\)C. IR: 2924, 2854, 2714, 1738, 1466, 722 cm\(^{-1}\). EIMS: C\(_{18}\)H\(_{35}\)OCl (M = 348, 350); m/z = 350 (M\(^{+}\), 8); 183 (100); 165 (69); 140 (32). \(^{1}\)H-NMR: 9.48 (d, 3.2 Hz, 1 H); 4.45 (t, 7.3 Hz, 3.2 Hz, 1 H); 2.00-1.90 (m, 2 H); 1.56-1.26 (m, 32 H); 0.88 (m, 3 H).
2-Fluorohexadecanal. To a suspension of 11.8 mg (0.312 mmol; 3 eq.) of LiAlH4 in 2 mL of dry diethyl ether under stirring, were added dropwise 30.0 mg (0.104 mmol; 1 eq.) of 2-fluoropalmitic acid methyl ester [29] as a white solid. M.p.: 34-35 °C. IR: 2916, 2848, 1736, 1468 cm⁻¹. EIMS: C16H33OF (M = 260); m/z = 260 (M⁺, min. The reaction mixture was stirred at –40 °C (dry ice-acetonitrile bath); 39 min and the reaction mixture was stirred at 80 °C for 48 h after which it was diluted with CH2Cl2 (10 mL) and washed with water (10 mL). The aqueous phase was extracted with CH2Cl2 (2 x 10 mL). The combined organic phases were dried, concentrated in vacuo and the residue was flash chromatographed on silica gel (hexane/CH2Cl2 7:3) to afford 44.3 mg (50%) of 2-fluorohexadecanal as a white solid. M.p.: 58-60 °C. IR: 2916, 2849, 1470, 1072 cm⁻¹. EIMS: C16H31OF (M⁺; 258); m/z = 258 (M⁺, 85), 238 (7), 98 (100), 84 (100), 71 (82), 69, 61 (35), 55, 43. 1H-NMR: 3.72 (m, 1H); 3.61 (dd, 10.5 Hz, 8.3 Hz, 1H); 2.38 (bs, 2H, 23 Hz, 2H); 1.87 (t, 6.4 Hz, 1H); 1.64 (m, 2H); 1.26 (m, 24 H); 0.88 (m, 3H). 2-Fluorohexadecanal [8], 23.0 l (0.251 mmol; 3.3 eq.) of oxalyl chloride were dissolved in 200 µL of dry CH2Cl2 and stirred at –40 °C (dry ice-acetonitrile bath); 39 µL (0.502 mmol; 6 eq.) of DMSO were added over 2 min; then, 19.8 mg (0.0760 mmol; 1 eq.) of 2-fluorohexadecanal dissolved in 1 mL of CH2Cl2 were added dropwise over 5 min and the reaction mixture was stirred at –40 °C for 15 min. The reaction mixture was quenched by addition of 159 µL (1.14 mmol; 15 eq.) of triethylamine, stirred 5 min at –40 °C and allowed to warm at rt. It was diluted with CH2Cl2 (10 mL) and washed with water (10 mL). The aqueous phase was extracted with CH2Cl2 (2 x 10 mL). The combined organic phases were dried, evaporated in vacuo to afford 22.6 mg (83%) of 2-fluorohexadecanal as a white solid. M.p.: 58-59 °C. IR: 2916, 2848, 1736, 1468 cm⁻¹. EIMS: C16H33OF (M⁺; 258); m/z = 258 (M⁺, 85), 238 (100), 228 (7), 216 (31), 196 (24), 184, (19), 172 (10), 161 (56), 149 (36), 138 (22), 136 (21), 128 (100), 117 (100), 105 (80), 93 (100). 1H-NMR: 4.50 (dm, 48.3 Hz, 1 H); 3.77 (dm, 48.3 Hz, 1 H); 3.79 (s, 3 H); 1.88 (m, 2 H); 1.26 (m, 26 H); 0.88 (m, 3H).
as an oil (1.02 g, 92%). IR: 2954, 2926, 2856, 1464, 1360, 1254, 1178, 1118, 920, 838, 780 cm⁻¹. EIMS: C₇₋H₆₅O₆SiS (M = 450); m/z = 429 (1.8), 355 (3.4), 341 (1.7), 298 (7), 297 (23), 195 (7), 171 (17), 153 (100), 75 (41), 73 (36).

1H-NMR: 4.64 (m, 1 H); 3.74 (d, 2.5 Hz, 1 H); 3.72 (d, 0.9 Hz, 1 H); 3.04 (s, 3 H); 1.65 (m, 2 H); 1.26 (m, 24 H); 0.90 (s, 9 H); 0.88 (s, 3 H), 0.075 (s, 3 H).

2-Mesyloxhexadecanol [34]. To a solution of 77.3 mg (0.190 mmol; 1 eq.) of 1-tert-butylidemethylsilislyloxy-2-mesyloxhexadecane [33] in 2 mL of CH₂Cl₂ were added 0.9 mL trifluoroacetic acid and 0.1 mL of water. The reaction mixture was stirred vigorously for 67 h at rt., and then, diluted with CH₂Cl₂ (10 mL) and neutralized with an aqueous NaHCO₃ solution (10%). The aqueous phase was extracted with CH₂Cl₂ (3 x 20 mL) and the combined organic phases were dried, concentrated in vacuo and the residue flash chromatographed on silica gel (hexane/diethylether 8:2) to afford 2-mesyloxhexadecanol [34] as a white solid (49.3 mg, 77%). M.p.: 50-51 °C. IR: 3345, 2956, 2916, 2849, 1467 cm⁻¹. EIMS: C₁₇H₃₆O₃ (M = 332); m/z = 332 (M⁺, 24), 305 (0.86), 291 (0.12), 278 (0.18), 209 (7), 138 (14), 55 (100).

1H-NMR: 9.54 (d, 0.7 Hz, 1 H); 4.86 (dd, 8.0 Hz, 4.7 Hz, 0.7 Hz, 1 H); 3.08 (s, 3 H); 1.66-1.89 (m, 2 H); 1.18 (m, 24 H); 0.80 (m, 3 H).

2-Heptadecanol [35]. To 152 mg (6.24 mmol; 3 eq.) of magnesium (Aldrich) suspended in 7 mL of dry diethylether at rt., were added dropwise 388 µL (6.24 mmol; 3 eq.) of methyl iodide dissolved in 7 mL of dry diethylether over 35 min. To this mixture under stirring, were added dropwise over 15 min 500 mg (2.08 mmol; 1 eq.) of n-hexadecanol dissolved in 7 mL of dry diethylether. After 45 min, the reaction mixture was quenched by addition of water (20 mL) and of an aqueous H₂SO₄ solution (15%; 4 mL) and diluted with diethylether (10 mL). After washing of the organic phase with water (3 x 15 mL), drying and evaporation in vacuo, the residue was flash chromatographed on silica gel (hexane/diethylether 7:3) to afford 2-heptadecanol [35] as a solid (298 mg, 53%). M.p.: 35-36 °C. IR: 3345, 2956, 2916, 2849, 1467 cm⁻¹. EIMS: C₁₇H₃₆O₃ (M = 256); m/z = 256 (M⁺, 2.2), 255 (14), 241 (27), 238 (73), 210 (37), 99 (30), 85 (70), 71 (100), 57 (100), 43 (100), 29 (64).

1H-NMR: 3.77 (m, 1 H); 1.42 (m, 2 H); 1.26 (m, 26 H); 1.18 (d, 6.1 Hz, 3 H); 0.88 (m, 3 H).

2-Heptadecanal [36]. 53.0 mg (0.246 mmol; 1.5 eq.) of PCC (freshly recrystallised from water) were suspended in 600 µL of dry CH₂Cl₂; 42.0 mg (0.164 mmol; 1 eq.) of 2-heptadecanol [35] dissolved in 250 µL of dry CH₂Cl₂ were added at once and the reaction mixture was stirred under reflux for 4 h. The reaction mixture was diluted with 3 mL of dry diethylether, filtered and the black precipitate washed with diethylether. Evaporation of the filtrate in vacuo and filtration of the residue on Florisil (elution with 50 mL diethylether) afforded 38.8 mg of crude 2-heptadecanal which was further flash chromatographed on silica gel (hexane/diethylether 95:5) to afford 26.6 mg (64%) of 2-heptadecanone [36] as a solid and 2.0 mg of the starting alcohol [35] (5%). M.p.: 42-43 °C. IR: 2955, 2916, 2849, 1712, 1472, 1463 cm⁻¹. EIMS: C₁₇H₃₆O₃ (M = 254); m/z = 254 (M⁺, 99), 239 (25), 196 (50), 99 (13), 85 (100), 71 (100), 58 (100), 57 (100), 43 (100), 29 (63).

1H-NMR: 2.41 (t, 7.4 Hz, 2 H); 2.13 (s, 3 H); 1.58 (m, 2 H); 1.26 (m, 24 H); 0.88 (m, 3 H).

3-Iodo-2-heptadecane [17]. To 42.0 mg (0.165 mmol; 1 eq.) of 2-heptadecanone [36] in solution in 330 µL of CH₂Cl₂ were added 22.4 mg (0.0826 mmol; 0.5 eq.) of HgCl₂ and 41.9 mg (0.165 mmol; 1 eq.) of iodine. The heterogeneous reaction mixture was stirred vigorously at rt. for 2 h after which it was filtered, the solid was washed with 10 mL of CH₂Cl₂ and the organic extracts washed successively with an aqueous sodium thiosulfate solution (0.1 N; 10 mL) and an aqueous saturated KI solution (10 mL). The organic phase was dried, evaporated in vacuo and the resulting residue flash chromatographed on silica gel (hexane/CH₂Cl₂ 8:2) affording 33.2 mg of a mixture of 3-iodo-2-heptadecane [17] (46%) and 1-iodo-2-heptadecanone (4%). The two regioisomers were separated by HPLC (reversed phase LiChroCart C₁₈ 100µm; elution with CH₃CN). M.p.: 33-34 °C. IR: 2953, 2923, 2853, 1713, 1464 cm⁻¹. EIMS: C₁₇H₃₄O (M = 336); m/z = 336 (M⁺, > 0), 295 (58), 184 (42), 99 (22), 85 (37), 71 (100), 69 (63), 57 (98), 43 (100), 29 (39).

1H-NMR: 4.76 (m, 1 H); 3.81 (dd, 12.5 Hz, 3.0 Hz, 1 H); 2.13 (s, 3 H); 1.58 (m, 2 H); 1.26 (m, 24 H); 0.88 (m, 3 H).

2-Iodopalmitic acid [26]. 400 mg (1.56 mmol; 1 eq.) of palmitic acid [26] in solution in 330 µL of CH₂Cl₂ were added 22.4 mg (0.0826 mmol; 0.5 eq.) of HgCl₂ and 41.9 mg (0.165 mmol; 1 eq.) of iodine. The heterogeneous reaction mixture was heated at 80 °C for 2 h, after which it was diluted with 1,2-dichloroethane (3 mL) and washed successively with water (2 x 5 mL) and an aqueous saturated KI solution (0.1 N) until the color changed from pink to white. The organic phase was dried, evaporated in vacuo and the resulting residue flash chromatographed on silica gel (AcOEt + 0.1% CF₃COOH) affording 366 mg of a 75:25 mixture of 2-iodopalmitic acid [18] and palmitic acid [26]. The two products were separated by HPLC (LichroCart, C₁₈ (100 µm), λ = 200 nm, CH₃CN/water 9:1 + 0.1%
2-Iodoheptanoic acid. The same procedure as the one described for the preparation of 2-iodopalmitic acid was used. Thus, 440 μL (2.77 mmol) of octanoic acid was afforded after purification of the crude product by flash chromatography (AcOEt to AcOEt/EtOH 7:3, 0.1% CF₃COOH). The combined organic phases were dried, evaporated in vacuo and the resulting residue flash chromatographed on silica gel (hexane/CH₂Cl₂ 7:3) affording 258 mg (45%) of 2-iodooctanoic acid. The same procedure as the one described for the preparation of 2-iodopalmitate methyl ester was used. Thus, 400 μL (2.77 mmol) of octanoic acid afforded, after purification by flash chromatography (hexane/CH₂Cl₂ 7:3) 210 mg of 2-iodooctanoate methyl ester and 51.6 mg of octanoate methyl ester as oils. IR: 2954, 2927, 2871, 2857, 1738, 1456, 1435, 1260, 1209, 1170, 1134 cm⁻¹. EIMS: C₈H₁₇OI (M = 256); m/z = 256 (M⁺, 9), 255 (18), 254 (100), 249 (85), 79 (99), 43 (94), 39 (93), 37 (89), 35 (86), 29 (84), 27 (82). ¹H-NMR: 4.14 (dd, 7.6 Hz, 1.5 Hz, 1 H); 3.73 (s, 3 H); 1.92 (t, 6.6 Hz, 1 H); 1.80 (m, 2 H); 1.08 (m, 3 H).

2-Iodoheptanoate methyl ester. The same procedure as the one described for the preparation of 2-iodopalmitate methyl ester was used. Thus, 400 μL (2.77 mmol) of octanoic acid afforded, after purification by flash chromatography (hexane/CH₂Cl₂ 7:3) 210 mg of 2-iodooctanoate methyl ester and 51.6 mg of octanoate methyl ester as oils. IR: 2954, 2927, 2871, 2857, 1738, 1456, 1435, 1260, 1209, 1170, 1134 cm⁻¹. EIMS: C₈H₁₇OI (M = 256); m/z = 256 (M⁺, 9), 255 (18), 254 (100), 249 (85), 79 (99), 43 (94), 39 (93), 37 (89), 35 (86), 29 (84), 27 (82). ¹H-NMR: 4.14 (dd, 7.6 Hz, 1.5 Hz, 1 H); 3.73 (s, 3 H); 1.92 (t, 6.6 Hz, 1 H); 1.80 (m, 2 H); 1.08 (m, 3 H).

2-iodohexadecanol [20]. The procedure was identical to the one described for the preparation of 2-iodooctanol.

2-Bromohexadecanamide [28]. A solution of 573 mg (1.64 mmol) of 2-bromopalmitate methyl ester [27] in a mixture of methanol/chloroform (17 mL/2 mL) was saturated with ammonia at 0 °C in a sealed tube. After 7 h, solvent and ammonia were evaporated and the residue flash chromatographed on silica gel (hexane/CH₂Cl₂ 7:3) to afford 285 mg (45%) of 2-bromopalmitate methyl ester [27] and 233 mg (42%) of 2-bromohexadecanamide [28] as a solid. M.p: 84-85 °C. IR: 3365, 3185, 2918, 2846, 1662, 1652, 1463 cm⁻¹. EIMS: C₁₆H₃₂O₂NBr (M = 333, 335); m/z = 335 (M⁺ + 1Br), 333 (M⁺ + 2Br), 324 (100), 139 (90), 137 (90), 98 (28), 83 (20), 32 (14), 43 (34). ¹H-NMR: 6.27 (bs, 1 H); 5.59 (bs, 1 H); 3.70 (s, 3 H); 1.94-2.18 (m, 2 H); 1.26-1.53 (m, 24 H); 0.88 (m, 3 H).

2-Iodoheptadecanamide [22]. To a solution of 140 mg (0.420 mmol; 1 eq.) of 2-bromohexadecanamide [28] in 1 mL of acetonitrile were added 441 mg (2.94 mmol; 7 eq.) of anhydrous NaBH₄. After 75 min, the reaction mixture was quenched with water (10 mL), diluted with CH₂Cl₂ (10 mL) and the organic phase washed with water (3 x 10 mL). The aqueous phase was extracted with CH₂Cl₂ (2 x 20 mL). The combined organic phases were dried, evaporated in vacuo and the resulting residue flash chromatographed on silica gel (hexane/CH₂Cl₂ 5:5) affording 19.9 mg (49%) of 2-iodooctanol [38] as an oil. IR: 3354, 2956, 2927, 2870, 2856, 1463 cm⁻¹. EIMS: C₁₀H₁₇OBr (M = 270); m/z = 270 (M⁺, 9), 269 (18), 268 (25), 267 (21), 266 (20), 265 (20), 202 (100), 79 (99), 43 (94), 39 (93). ¹H-NMR: 4.26 (d, 7.6 Hz, 1 H); 3.73 (m, 2 H); 1.92 (t, 6.6 Hz, 1 H); 1.80 (m, 2 H); 1.29 (m, 8 H); 0.89 (m, 3 H).

2-iodohexadecanol [20]. The procedure was identical to the one described for the preparation of 2-iodooctanol.
organic phases were dried in vacuo to afford 147 mg (92%) of 2-iodohexadecanamide [22]. M.p.: 105-107 °C. IR: 3366, 3176, 2916, 2870, 1650, 1464, 1426 cm⁻¹. EIMS: C₁₆H₃₂O⁻NI (M = 381); m/z = 381 (M⁺, 2), 254 (100), 185 (11), 83 (18), 72 (10), 69 (16), 59 (17), 55 (38), 43 (56). ¹H-NMR: 6.77 (bs, 1 H); 5.40 (bs, 1 H); 4.26 (t, 7.4 Hz, 1 H); 1.94-2.03 (m, 2 H); 1.26-1.53 (m, 24 H); 0.88 (m, 3 H).

2-Hydroxyhexadecanenitrile [42]. To a solution of 700 mg (3.09 mmol; 1 eq.) of 2-iodohexadecanamide [40] in 17 mL of CH₂Cl₂, then diethylether to afford 23.0 mg of starting material as an oil. IR: 2924, 2854, 2236, 1466 cm⁻¹. EIMS: C₁₆H₃₀NI (M = 363); m/z = 363 (M⁺, 2), 236 (100), 192 (55), 128 (47), 124 (39), 110 (51), 97 (83), 43 (81). ¹H-NMR: 4.46 (t, 7.5 Hz, 1 H); 4.20 (t, 7.9 Hz, 6.7 Hz, 1 H); 2.35 (s, 3 H); 1.96 (m, 2 H); 1.29 (m, 24 H); 0.89 (m, 3 H).

2-Mesyloxyhexadecanenitrile [43]. To a solution of 431 mg (55%) of 2-mesyloxyhexadecanenitrile [43] in 17 mL of CH₂Cl₂ at 80 °C. After 4 h, the reaction mixture was diluted with water (20 mL) and CH₂Cl₂, then diethylether) to afford 566 mg (100%) of 2-mesyloxyhexadecanitrile [43]. EIMS: C₁₇H₃₃NO₃S (M = 253); m/z = 331 (M⁺, 5), 208 (15), 182 (16) (100). ¹H-NMR: 4.43 (t, 7.5 Hz, 1 H); 4.20 (t, 7.9 Hz, 6.7 Hz, 1 H); 2.96 (bd; 5.6 Hz, 1 H); 1.84 (m, 2 H); 1.26 (m, 24 H); 0.88 (m, 3 H).

2-Chlorohexadecanenitrile [13]. 956 mg (11.0 mmol; 1 eq.) of MnO₂ were suspended in 20 mL of acetic acid in the presence of 1.71 mL (5.50 mmol; 1 eq.) of 2-chloro-2-nonanone [13] in 10 mL of acetonitrile. The reaction mixture was stirred at rt. for 16 h after which it was poured into water (50 mL). The aqueous phase was extracted with diethylether (3 x 20 mL) and the combined organic phases were dried, concentrated in vacuo and the residue flash chromatographed on silica gel (hexane/ CH₂Cl₂ 9:1) to afford 712 mg (64%) of 3-bromo-2-nonanone [12] as an oil. IR: 2958, 2928, 2858, 1720, 1462, 1428, 1358, 1228, 1172, 1148, 724 cm⁻¹. EIMS: C₉H₁₇OBr (M = 220, 222; 79Br, 81Br); m/z = 222 (83M⁺, 0.04), 220 (83M⁺, 0.05), 191 (0.02), 191 (0.03), 180 (0.04), 178 (0.04), 151 (0.05), 141 (1), 138 (8), 136 (9), 71 (5), 55 (9), 43 (100), 41 (20), 39 (10). ¹H-NMR: 4.42 (dd, 7.9 Hz, 6.7 Hz, 1 H); 2.35 (s, 3 H); 1.96 (m, 2 H); 1.29 (m, 8 H); 0.89 (m, 3 H).

3-Chloro-2-nonanone [13]. 5.50 mg (0.228 mmol; 1 eq.) of 3-chloro-2-nonanone [13] and 205 mg (1.37 mmol; 6 eq.) of anhydrous NaI were dissolved in 2 mL of acetonitrile at rt. After 3 h, the reaction mixture was diluted with water (10 mL) and CH₂Cl₂ (10 mL). The organic phase was washed with water (3 x 10 mL), dried and concentrated in vacuo to afford 47.2 mg (77%) of pure 3-chloro-2-nonanone [13] as an oil. IR: 2958, 2926, 2856, 1712, 1462, 1432, 1358, 1126, 1200, 1166, 954, 722 cm⁻¹. EIMS: C₉H₁₇OCl (M = 268); m/z = 184 (0.2), 141 (0.4), 58 (47), 57 (29), 49 (93), 43 (100). ¹H-NMR: 4.43 (t, 7.5 Hz, 1 H); 2.41 (s, 3 H); 1.92 (m, 2 H); 1.28 (m, 8 H); 0.88 (m, 3 H).

3-Chloro-2-nonanone [13]. 50.5 mg (0.228 mmol; 1 eq.) of 3-chloro-2-nonanone [13] and 205 mg (1.37 mmol; 6 eq.) of anhydrous NaI were dissolved in 2 mL of acetonitrile at rt. After 3 h, the reaction mixture was diluted with water (10 mL) and CH₂Cl₂ (10 mL). The organic phase was washed with water (3 x 10 mL), dried and concentrated in vacuo to afford 162 mg (92%) of 3-chloro-2-nonanone [13] as an oil. IR: 2958, 2926, 2856, 1712, 1462, 1432, 1358, 1126, 1200, 1166, 954, 722 cm⁻¹. EIMS: C₉H₁₇Cl (M = 201); m/z = 178 (37M⁺, 0.2), 151 (0.4), 141 (0.5), 139 (1), 138 (2), 136 (3), 124 (40), 116 (79), 114 (81), 108 (95), 106 (100). ¹H-NMR: 2.35 (s, 3 H); 1.92 (m, 2 H); 1.28 (m, 8 H); 0.88 (m, 3 H).

2-Bromo-2-nonanone [12]. To a solution of 855 µL (5.00 mmol; 1 eq.) of 2-bromonitrile [15] in 10 mL of acetonitrile, were added dropwise and successively 726 µL (5.50 mmol; 1.1 eq.) of TMSBr and 390 µL (5.50 mmol; 1 eq.) of DMSO. The reaction mixture was stirred for 40 min. at rt. after which it was poured into water (50 mL). The aqueous phase was extracted with diethylether (3 x 20 mL) and the combined organic phases were dried, concentrated in vacuo and the residue flash chromatographed on silica gel (hexane/ CH₂Cl₂ 9:1) to afford 712 mg (64%) of 3-bromo-2-nonanone [12] as an oil. IR: 2958, 2928, 2858, 1720, 1462, 1428, 1358, 1228, 1172, 1148, 724 cm⁻¹. EIMS: C₉H₁₇OBr (M = 220, 222; 79Br, 81Br); m/z = 222 (83M⁺, 0.04), 220 (83M⁺, 0.05), 191 (0.02), 191 (0.03), 180 (0.04), 178 (0.04), 151 (0.05), 141 (1), 138 (8), 136 (9), 71 (5), 55 (9), 43 (100), 41 (20), 39 (10). ¹H-NMR: 4.42 (dd, 7.9 Hz, 6.7 Hz, 1 H); 2.35 (s, 3 H); 1.96 (m, 2 H); 1.29 (m, 8 H); 0.89 (m, 3 H).
2.31 (s, 3 H); 1.75-2.00 (m, 2 H); 1.29 (m, 8 H), 0.89 (m, 3 H).

3-Fluoro-2-nonanone [14]. To a solution of 122 mg (0.550 mmol; 1 eq.) of 3-bromo-2-nonanone [12] in 2.75 mL of acetonitrile were added 1.4 mL of water (0.1% in weight of AgF) and 140 mg (1.10 mmol; 2 eq.) of AgF. The reaction mixture was stirred at 80 °C for 24 h after which it was filtered on a short column of silica gel (elution with 20 mL CH2Cl2). The filtrate was concentrated in vacuo and the residue was dissolved in pentane (20 mL) and the solution washed with water (2 x 10 mL), dried and evaporated in vacuo. The residue afforded 3-fluoro-2-nonanone [14] as oils. IR: 2954, 2928, 2858, 1740, 1682, 1598, 1591, 1460, 1368, 1178, 1096, 1004, 832, 816, 772, 668, 556 cm⁻¹. EIMS: C₉H₁₇OF (M = 160); m/z = 160 (M⁺, 0.55), 159 (0.5), 146 (0.55), 136 (14), 124 (42), 119 (100), 107 (42), 88 (42), 77 (91), 65 (22), 57 (14), 43 (42), 31 (91), 29 (25), 17 (25), 15 (100), 13 (25). ¹H-NMR: 2.31 (s, 3 H); 1.75-2.00 (m, 2 H); 1.29 (m, 8 H), 0.89 (m, 3 H).

3-Tosyloxy-2-nonanone [16] and 1-tosyloxy-2-nonanone. To 600 µL (3.52 mmol; 1 eq.) of 2-nonanone in 2.75 mL of water (0.1% in AgF) and 140 mg (1.10 mmol; 2 eq.) of AgF. The reaction mixture was stirred at 80 °C for 24 h after which it was filtered on a short column of silica gel (elution with 20 mL CH2Cl2). The filtrate was concentrated in vacuo and the residue was dissolved in pentane (20 mL) and the solution washed with water (2 x 10 mL), dried and evaporated in vacuo. The residue was flash chromatographed on silica gel (hexane/diethylether 8:2) to afford 333 mg of 3-tosyloxy-2-nonanone (15%) (67:33) as oils. IR: 2956, 2928, 2858, 1740, 1682, 1598, 1591, 1460, 1368, 1178, 1096, 1004, 832, 816, 772, 668, 556 cm⁻¹. EIMS: C₁₆H₂₄O₄S (M = 312); m/z = 312 (M⁺, 100), 300 (91), 191 (57), 172 (42), 159 (15), 148 (71), 137 (91), 126 (71), 115 (100), 101 (42), 89 (42), 77 (91), 65 (22), 57 (14), 43 (42). ¹H-NMR: 2.31 (s, 3 H); 1.75-2.00 (m, 2 H); 1.29 (m, 8 H), 0.89 (m, 3 H).

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References


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