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Article

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 sintetisados 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 (±)-**1** revealed its ability to inhibit both H_2O_2 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**)

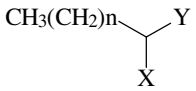


Figure 1. X = I and Y = CHO: 1 n = 13; 2 n = 5; 3 n = 9; 4 n = 15; 5 n = 17 . Y = CHO and n = 13: 6 X = Br; 7 X = Cl; 8 X = F; 9 X = H; 10 X = OMs. Y = $COCH_3$ and n = 5: 11 X = I; 12 X = Br; 13 X = Cl; 14 X = F; 15 X = H; 16 X = OTs. X = I and n = 13: 17 Y = $COCH_3$; 18 Y = COOH; 19 Y = $COOCH_3$; 20 Y = CH_2OH; 21 Y = $CH(OCH_3)_2$; 22 Y = $CONH_2$; 23 Y = CN

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 $HgCl_2/I_2$ (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/CH_3CN; 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 $MnCl_2$/ MnO_2 / TMSCl[9] to afford **25** in 67% yield, followed by acid hydrolysis of **25** with $CF_3COOH/H_2O/CH_2Cl_2$ (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[10] or Ac_2O/AcCl/AcONa.$3H_2O$[11]). Moreover, neither direct chlorination of *n*-hexadecanal **[9]** with SO_2Cl_2[12], or *n*-hexadecanal trimethylsilylenolether with Cl_2[13] led to the formation of 2-chlorohexadecanal **[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[14-18]. Our approach to the synthesis of 2-fluoroaldehydes avoids these drawbacks. Our synthesis of 2-fluorohexadecanal **[8]** was based on a described synthesis of 2-fluorooctadecanoic acid[19]. Hexadecanoic acid **[26]** was brominated using the mixture P/Br_2, esterified with methanol (yield: 67%), and the bromine of the resulting bromoester **[27]** exchanged by fluorine [AgF/ CH_3CN/ H_2O; 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_2Cl_2 or toluene) always led to a mixture of the reactant and 2-fluorohexadecanol. Therefore, **29** was first reduced to 2-fluorohexadecanol in an 83% yield using $LiAlH_4$, followed by Swern oxidation[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 $ClSO_3H$ /I_2[21]. Addition of methanol to the reaction mixture afforded **19** in a 38% yield after purification by column chromatography on silica gel[21]. Alternatively, compound **19** was prepared by substitution of the bromine of methyl 2-bromohexadecanoate **[27]** using NaI in CH_3CN (yield: 93%).

2-Iodohexadecanamide **[22]** was prepared by aminolysis of **27** with gaseous NH_3 in MeOH-$CHCl_3$[22] (yield: 55%), followed by substitution of the bromine by iodine which gave 2-iodohexadecanamide **[22]** in a 92% yield.

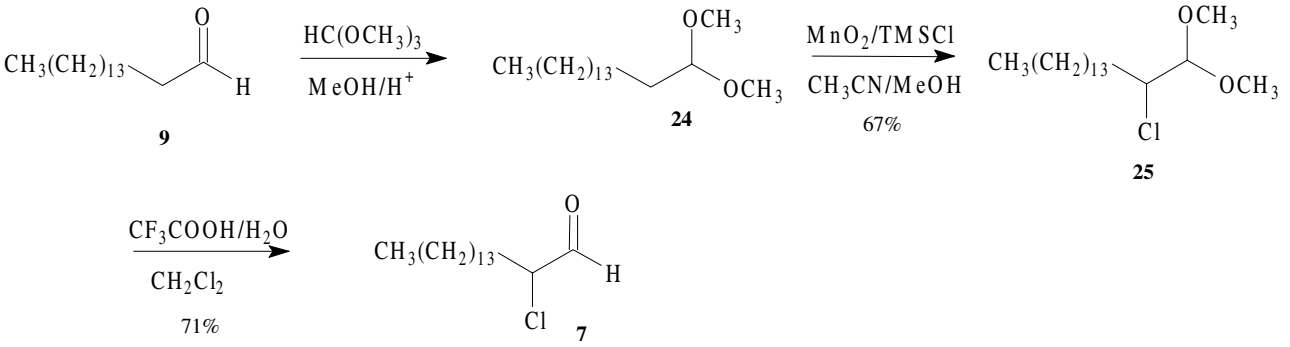
Synthesis of 2-mesyloxyhexadecanal **[10]**

The preparation of 2-mesyloxy-[23] and 2-tosyloxyketones[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[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 **[10]** by hydrolysis of the S,S-dioxydedithioketal[26] or the dimethylketal of 2-mesyloxyhexadecanal[27] probably due to the strong inductive effect of the mesyloxy group. Finally, **10** was synthesized starting from 1-hexadecene **[30]**. Dihydroxylation of **30** into **31** with OsO_4[28] followed by selective protection of the primary hydroxyl group of **31** with TBDMSCl[29], mesylation of the secondary hydroxyl group of **32** with MsCl[30] and deprotection of the primary hydroxyl group of **33** with TFA[31] led to 2-mesyloxyhexadecanol **[34]**. Swern oxidation[20] of **34** gave 2-mesyloxyhexadecanal **[10]** which proved to be a relatively unstable compound.

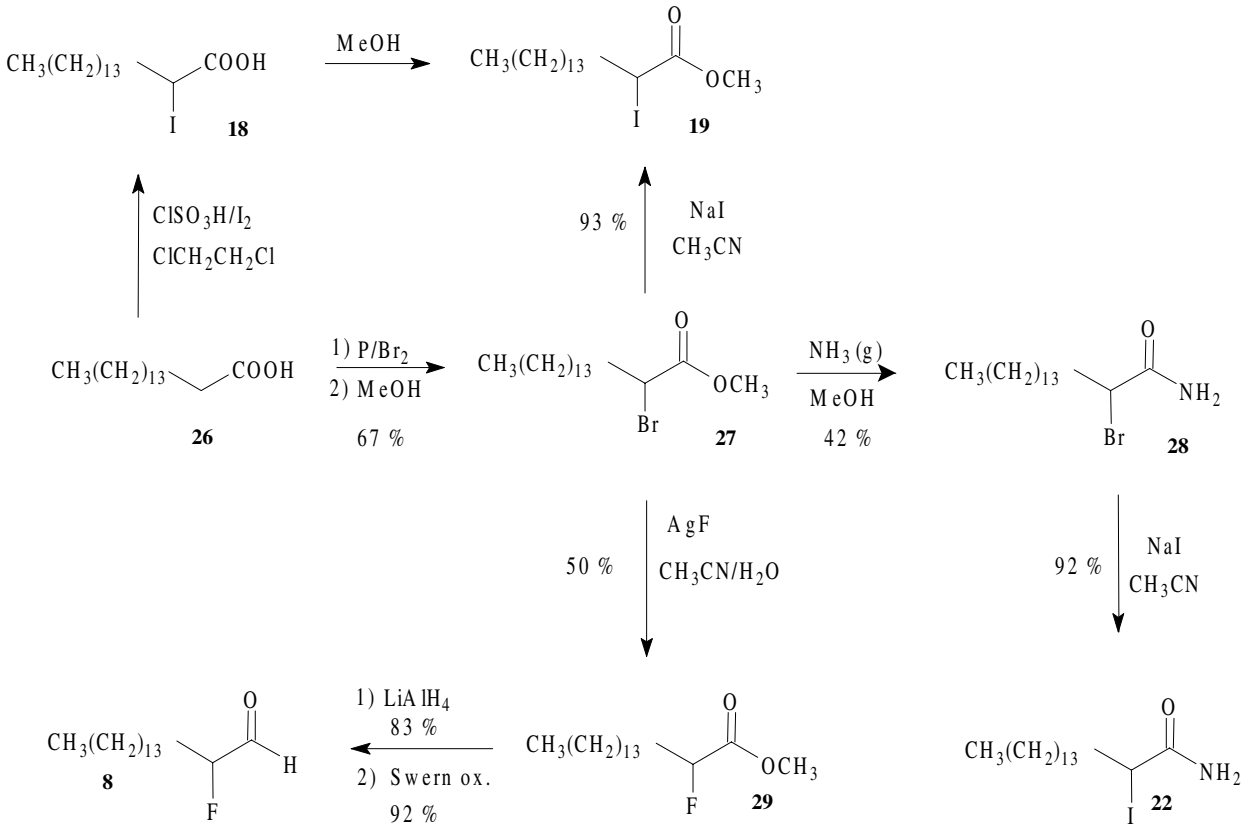
Synthesis of 3-halogeno-2-ketones **11-14**, *and* **17** *and of 3-tosyloxy-2-nonanone [***16***]*

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

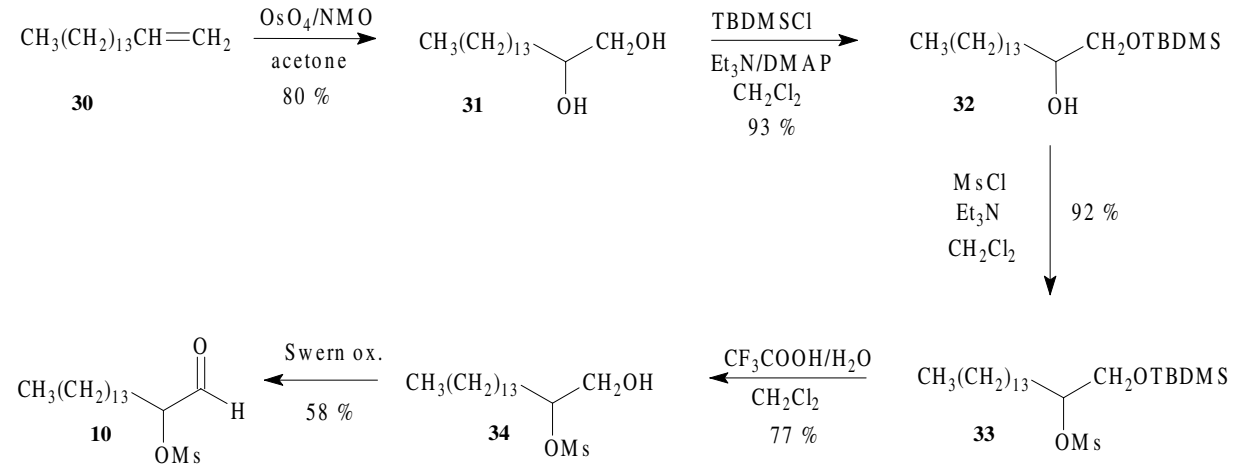
3-Iodo-2-nonanone **[11]** was cleanly synthesized in a 77% yield by substitution of the bromine of **12** by NaI in CH_3CN. In contrast with literature claims[6], direct iodination of 2-nonanone **[15]** with $HgCl_2$ and I_2 was not regioselective and gave a mixture of 3-iodo-2-nonanone **[11]** and 1-iodo-2-nonanone (82:18), which have the same R_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.



Scheme 1. Synthesis of 2-chlorohexadecanal **[7]**.



Scheme 2. Synthesis of 2-fluorohexadecanal **[8]**, methyl 2-iodohexadecanoate **[19]** and 2-iodohexadecanamide **[22]**.



Scheme 3. Synthesis of 2-mesyloxyhexadecanal **[10]**.

3-Chloro-2-nonanone **[13]** was prepared in a 92% yield by direct chlorination of 2-nonanone **[15]** with MnO_2/TMSCl in AcOH[33]. Another chlorinating system, 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 AgF[19].

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[8], followed by addition of methylmagnesiumbromide, hydrolysis and PCC oxidation of the resulting 2-heptadecanol **[35]** gave 2-heptadecanone **[36]**. Iodination of the latter with $HgCl_2/I_2$[6] 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.

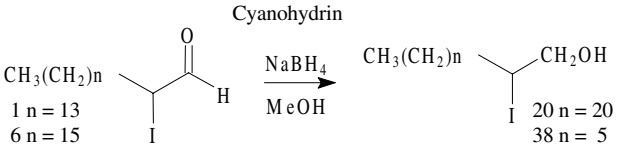
Synthesis of 2-iodohexadecanol **[20]** *and 2-iodooctanol* **[38]**

2-Iodohexadecanol **[20]** and 2-iodooctanol **[38]** were prepared respectively by reduction of 2-iodohexadecanal **[1]** and 2-iodooctanal **[2]** by $NaBH_4$ (Scheme 6)[5].

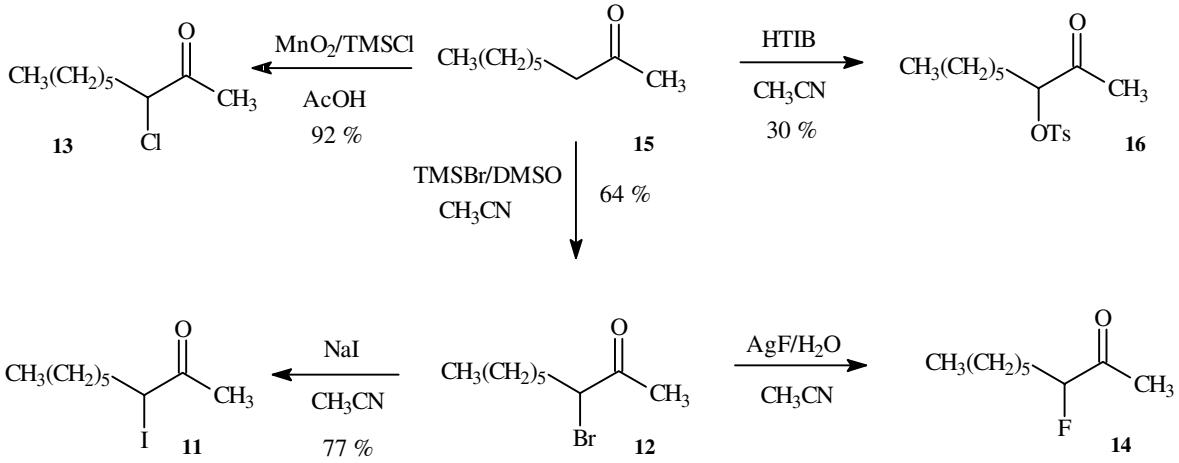
Synthesis of 2-iodohexadecanenitrile **[23]**

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 ZnI_2[35-38] 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 $ClSO_2CH_3$ afforded 2-mesyloxy-hexadecanenitrile **[43]** in a 100% yield[30]. Finally, 2-iodo-hexadecanenitrile was obtained in a 57% yield by substitution of the mesyloxy group of **43** by iodide.

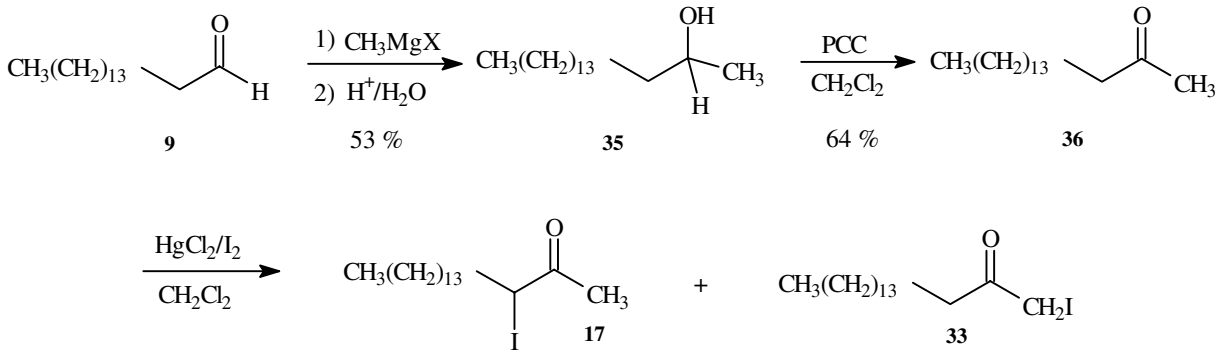
The testing of these analogues on the H_2O_2 production and on the thyroid gland adenylyl cyclase has been performed and the results have been published elsewhere[3,4].



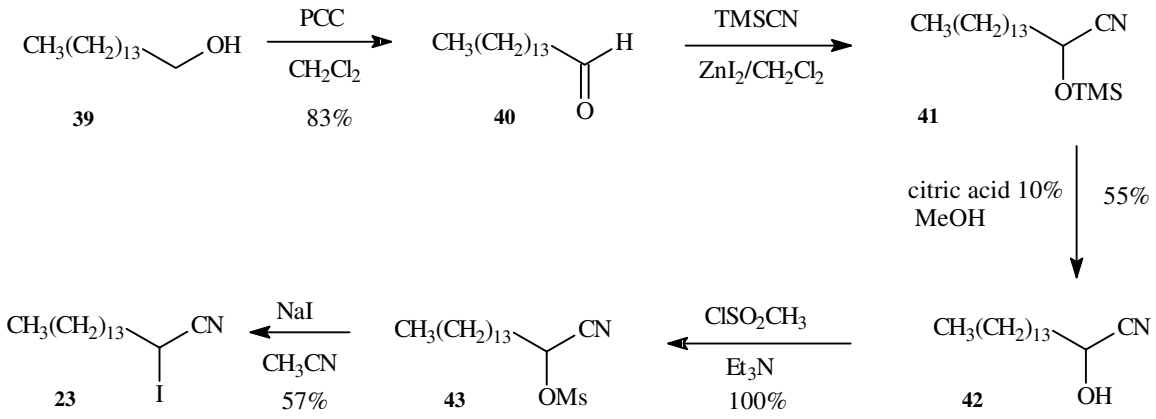
Scheme 6. Synthesis of 2-iodohexadecanol **[20]** and 2-iodooctanol **[38]**.



Scheme 4. Synthesis of 3-halogeno-2-ketones **11-14**, and of 3-tosyloxy-2-nonanone **[16]**.



Scheme 5. Synthesis of 3-iodo-2-heptadecanone **[17]**.



Scheme 7. Synthesis of 2-iodohexadecanamide **[23]**.

Experimental

^{1}H-NMR spectra were recorded on a BRUKER WM 250 spectrometer and are reported in ppm from internal TMS on the δ 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. Peak intensities are expressed as % relative to the base peak. Thin layer chromatography analyses were performed on 0.25 mm POLYGRAM silica gel SIL G/UV$_{254}$ precoated plates (MACHEREY-NAGEL). Column chromatographies were performed over silica gel (MERCK 60 0.04-0.063 mm), using the flash technique. All reactions were run under nitrogen atmosphere. During work-up, organic solutions were dried over $MgSO_4$.

n-Pentadecanal, *n*-hexadecanal [9], *n*-octadecanal and *n*-eicosanal were prepared by PCC oxidation of the corresponding alcohols. As an example, the procedure for the preparation of *n*-hexadecanal is given here.

n-Hexadecanal [9]. 5.33 g of PCC (24.7 mmol; 1.5 eq.) were suspended in 30 mL of dry CH_2Cl_2; 4.00 g of hexadecan-1-ol (16.4 mmol; 1.0 eq.) dissolved in 16 mL of dry CH_2Cl_2 were added at once and the reaction mixture was stirred at rt. for 1.5 h after which 30 mL of dry diethylether was added. The reaction mixture was filtered on a filter paper and the black precipitate washed with dry diethylether (3 x 10 mL). Evaporation of the combined extracts *in vacuo* and filtration of the residue on Florisil (elution with hexane/diethylether 8:2) afforded 3.21 g of *n*-hexadecanal (81%) as a white solid after evaporation of the solvent. M.p.: 30-31 °C. IR: 2954, 2923, 2853, 1712, 1728, 1465, 1456 cm^{-1}. EIMS: $C_{16}H_{32}O$ (M = 240); m/z: 240 ($M^{+\bullet}$, 0.8), 222 (0.8); 196 (1.6); 44 (23). ^{1}H-NMR: 9.76 (t, 1.9 Hz, 1 H); 2.41 (dt, 1.9 Hz, 7.3 Hz, 2 H); 1.63 (m, 2 H); 1.26 (m, 24 H); 0.88 (m, 3 H).

n-Pentadecanal. M.p.: 55-59 °C. IR: 2956, 2918, 2850, 1704, 1466 cm^{-1}. EIMS: $C_{15}H_{30}O$ (M = 226); m/z = 226 ($M^{+\bullet}$, > 0), 225 (50), 183 (58), 182 (83), 44 (100). ^{1}H-NMR: 9.76 (t, 1.9 Hz, 1 H); 2.41 (dd, 7.3 Hz, 1.9 Hz, 2 H); 1.57-1.72 (m, 2 H); 1.26 (m, 22 H), 0.88 (m, 3 H).

n-Octadecanal. M.p.: 41-42 °C. IR: 2953, 2914, 2849 , 2746, 1711, 1470 cm^{-1}. EIMS: $C_{18}H_{36}O$ (M = 268); m/z = 268 ($M^{+\bullet}$), 250 (21), 224 (10), 85 (48), 71 (84), 57 (99), 44 (50), 43 (100), 29 (67). ^{1}H-NMR: 9.76 (t, 1.9 Hz, 1 H); 2.41 (td, 7.3 Hz, 1.9 Hz, 2 H); 1.63 (m, 2 H); 1.26 (m, 28 H); 0.88 (m, 3 H).

n-Eicosanal. IR: 2915, 2848, 1711, 1471 cm^{-1}; in CCl_4: 2932, 2854; 2714; 1729; 1468 cm^{-1}. EIMS: $C_{20}H_{40}O$ (M = 296); m/z = 296 ($M^{+\bullet}$, 1); 278 (2); 252 (3); 44 (18). ^{1}H-NMR: 9.76 (t, 1.9 Hz, 1 H); 2.41 (dt, 7.3 Hz, 1.9 Hz, 2 H); 1.66-1.57 (m, 2 H); 1.26 (m, 32 H); 0.88 (m, 3 H).

2-Iodooctanal [2], 2-iodododecanal [3], 2-iodohexadecanal [1], 2-iodooctadecanal [4], 2-iodoeicosanal [5] were prepared by direct iodination of the corresponding aldehydes using $HgCl_2/I_2$. As an example, the procedure for the preparation of 2-iodohexadecanal is given here.

2-Iodohexadecanal [1]. To 250 mg (1.04 mmol) of *n*-hexadecanal in 2 mL of CH_2Cl_2 were added 0.141 g (0.520 mmol; 0.5 eq.) of $HgCl_2$ and 264 mg (1.04 mmol; 1 eq.) of iodine. The heterogeneous reaction mixture was stirred vigorously at rt. for 2 h after which the solution was filtered and the filtrate washed successively with an aqueous 0.1 N sodium thiosulfate solution (until discoloration) and an aqueous saturated KI solution. The organic phase was dried, evaporated *in vacuo* and the resulting residue submitted to flash chromatography on silica gel (hexane/diethylether 8:2) affording 212 mg of 2-iodohexadecanal (56%) as an oil. IR: 2953, 2923, 2852, 2710, 1719, 1466 cm^{-1}. EIMS: $C_{16}H_{31}OI$ (M = 366); m/z 366 ($M^{+\bullet}$, 0.4), 239 (19); 221 (12); 170 (14); 43 (100). ^{1}H-NMR: 9.26 (d, 3.2 Hz, 1 H); 4.45 (dt, 7.3 Hz, 3.2 Hz, 1 H), 1.96-1.91 (m, 2 H); 1.26 (m, 24 H); 0.88 (m, 3 H).

2-Iodooctanal [2]. Oil. IR: 2956, 2927, 2857, 2718, 1717, 1466 cm^{-1}. EIMS: $C_8H_{15}OI$ (M = 254); m/z = 254

($M^{+\bullet}$, 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); 1.56-1.23 (m, 8 H); 0.88 (m, 3 H).

2-Iodododecanal [3]. Oil. IR: 2954, 2924, 2854, 2722, 1721, 1465 cm^{-1}. EIMS: $C_{12}H_{23}OI$ (M = 310); m/z = 310 ($M^{+\bullet}$, 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); 1.49-1.26 (m, 16 H); 0.88(m, 3 H).

2-Iodooctadecanal [4]. M.p.: 42-44 °C. IR: 2923, 2853, 2719, 1722, 1464 cm^{-1}. EIMS: $C_{18}H_{35}OI$ (M = 394); m/z = 394 ($M^{+\bullet}$, 1.5), 267 (99), 249 (99), 224 (21), 170 (100), 141 (16), 127 (25), 113 (43), 99 (96), 85 (100), 71 (100), 57 (100), 43 (100), 29 (100). ^{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-Iodoeicosanal [5]. IR: 2953, 2918, 2850, 2725, 1716, 1471 cm^{-1}. EIMS: $C_{20}H_{39}OI$ (M = 422); m/z = 422 ($M^{+\bullet}$, 5); 421 (10); 295 (100); 277 (100); 252 (52); 170 (100). ^{1}H-NMR: 9.25 (d, 3.2 Hz, 1H); 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*-hexadecanal, 200 μL (218 mg, 240 mmol, 1.7 eq.) of DMSO and 630 μL *t*-butyl bromide (766 mg, 560 mmol, 4 eq.) was stirred at 60-65 °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 chromatographed on Florisil (toluene/hexane 5:5) to afford 175 mg (0.548 mmol) of 2-bromohexadecanal **[6]** (41%) as an oil. IR: 2923, 2853, 2714, 1732, 1467, 1456 cm^{-1}. EIMS: $C_{16}H_{31}OBr$ (M = 318); m/z = 318 ($M^{+\bullet}$, 4); 239 (9); 221 (19); 124 (41); 57 (100). ^{1}H-NMR: 9.42 (d, 3.2 Hz, 1 H); 4.21 (m, 1 H); 1.2-2.4 (m, 26 H); 1.26 (m, 3 H).

n-Hexadecanal methyl acetal [24]. To 100 mg (0.416 mmol; 1 eq.) of *n*-hexadecanal and 45.5 L (0.416 mmol; 1 eq.) of methylorthoformate dry methanol (13 mL) were added 8 mg (0.0416 mmol; 0.1 eq.) of *p*-toluenesulfonic acid. The reaction mixture was stirred at reflux for 2 h after which it was diluted with pentane (10 mL), washed with an aqueous NaOH solution (0.5%; 10 mL) and the aqueous phase extracted with pentane (3 x 10 mL). The combined organic phases were dried, evaporated *in vacuo* and the resulting residue was flash chromatographed on silica gel (hexane/AcOEt 95:5) to afford 95.9 mg (80%) *n*-hexadecanal methyl acetal **[24]** as an oil. IR: 2924, 2854, 1466, 1192, 1124, 1074, 1056 cm^{-1}. EIMS: $C_{18}H_{38}O_2$ (M = 286); m/z = 286 ($M^{+\bullet}$, 7), 285 (22), 255 (63), 75 (100). ^{1}H-NMR: 4.35 (t, 5.7 Hz, 1 H); 3.31 (s, 6 H); 1.57 (m, 2 H); 1.25 (m, 26 H); 0.88 (m; 3 H).

2-Chlorohexadecanal methylacetal [25]. 237 mg (0.829 mmol, 1 eq.) of *n*-hexadecanal methyl acetal and 52.1 mg (0.415 mmol, 0.5 eq.) of $MnCl_2$ were dissolved in an acetonitrile-methanol mixture (0.41mL: 0.41mL). After complete dissolution of $MnCl_2$, 86.4 mg (0.994 mmol; 1.2 eq.) of MnO_2 were added. The reaction mixture was stirred at 40 °C and 505 μL (3.98 mmol; 4.8 eq.) of TMSCl were added at once. The reaction mixture became black and was stirred at 40 °C for 19 h after which it was diluted with pentane (20 mL) and washed with an aqueous NaOH solution (1.5%; 2 x 20 mL). The aqueous phase was extracted with pentane (2 x 20 mL). The combined organic phases were dried, evaporated *in vacuo* and the resulting residue was flash chromatographed on silica gel (hexane/CH_2Cl_2 7:3) to afford 196 mg of a mixture of 2-chlorohexadecanal methyl acetal **[25]** (67%) and methyl palmitate (12%). IR: 2924, 2854, 1468, 1190, 1120, 1080, 722 cm^{-1}. EIMS: $C_{18}H_{37}O_2Cl$ (M = 320, 322); m/z = 322 ($M^{+\bullet}$ ^{37}Cl, 0.3), 320 ($M^{+\bullet}$ ^{35}Cl, 0.7), 321 (0.7), 319 (2.6), 75 (100). ^{1}H-NMR: 4.31 (d, 5.7 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 [7]. To 46.0 mg (0.143 mmol) of 2-chlorohexadecanal methyl acetal **[25]** in 0.5 mL of CH_2Cl_2 were added 125 μL of trifluoroacetic acid and 125 μL of water. The reaction mixture was stirred at reflux for 4 h after which it was diluted with CH_2Cl_2 (20 mL) and washed with an aqueous $NaHCO_3$ solution (5%; 3 x 20 mL). The aqueous phase was extracted with CH_2Cl_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_2Cl_2 7:3) to afford 28 mg (71%) of 2-chlorohexadecanal **[7]** as a solid. M.p.: 49-50 °C. IR: 2924, 2854, 2714, 1738, 1466, 722 cm^{-1}. EIMS: $C_{16}H_{31}OCl$ (M = 274, 276); m/z = 276 ($M^{+\bullet}$ ^{37}Cl, 3.6), 274 ($M^{+\bullet}$ ^{35}Cl, 7.9), 256 (2.1), 239 (1.4), 221 (8.6), 196 (14), 80 (14), 78 (41), 43 (100). ^{1}H-NMR: 9.48 (d, 2.5 Hz, 1 H); 4.15 (ddd, 8.1 Hz, 5.5 Hz, 2.5 Hz, 1 H); 1.88 (m; 2 H); 1.26 (m, 24 H); 0.88 (m, 3 H).

2-Bromopalmitic acid methyl ester [27]. A mixture of 1.00 g (3.90 mmol; 1eq.) of palmitic acid **[26]** and 121 mg (3.90 mmol; 1eq.) of red phosphorus was heated at 80 °C. After melting of the palmitic acid, 728 μL (14.2 mmol; 3.6 eq.) of bromine was added dropwise over 1 h. The reaction mixture was stirred at 80 °C for 24 h, after which it was cooled at 0 °C (ice bath) and 440 μL of methanol were added dropwise over 1 h. The reaction mixture was stirred at rt. for 30 min. and heated at 80 °C for 1 h. It was diluted under stirring with hexane (25 mL) and with an aqueous $NaHSO_3$ solution (50 mL, 1%). The aqueous phase was extracted with hexane (25 mL) and the combined organic phases were washed with water (4 x 25 mL) until neutral pH. The organic phase was dried, evaporated *in vacuo* and the resulting residue was flash chromatographed on silica gel (hexane/ CH_2Cl_2 7:3) to afford 906 mg (67%) of 2-bromopalmitic acid methyl ester as an oil. IR: 2924, 2854, 1748, 1464, 1436, 1272, 1152 cm^{-1}. EIMS: $C_{17}H_{33}O_2Br$ (M = 348, 350); m/z = 350 ($M^{+\bullet 81}$Br, 37), 348 ($M^{+\bullet 79}$Br, 36),

319 (2), 317 (1.5), 269 (100), 138 (100), 136 (100), 59 (83). ^{1}H-NMR: 4.22 (t, 7.4 Hz, 1 H); 3.78 (s, 3 H); 2.00 (m, 2 H); 1.26 (m, 24 H); 0.88 (m, 3 H).

2-Fluoropalmitic acid methyl ester [29]. To 107 mg of 2-bromopalmitic acid methyl ester **[27]** (0.306 mmol; 1 eq.) dissolved in 704 µL of acetonitrile were added 1.8 µL of water and 176 mg (1.38 mmol; 4.5 eq.) of AgF. The reaction mixture was stirred at 80 °C for 48 h after which it was filtered with CH_2Cl_2 (10 mL) on a short silica gel column. The organic phase was evaporated *in vacuo* and the resulting residue was flash chromatographed on silica gel (hexane/ CH_2Cl_2 7:3) to afford 44.3 mg (50%) of 2-fluoropalmitic acid methyl ester **[29]** as a white solid. M.p.: 34-35 °C. IR: 2954, 2925, 2854, 1770, 1747, 1467, 1440, 1287, 1212 cm^{-1}. EIMS: $C_{17}H_{33}O_2F$ (M = 288); m/z: 288 ($M^{+\bullet}$, 69), 269 (0.7), 227 (76), 161 (96), 147 (67), 105 (48), 92 (100), 59 (24). ^{1}H-NMR: 4.90 (dt, 48.9 Hz, 6.3 Hz, 1 H); 3.79 (s, 3 H); 1.88 (m, 2 H); 1.26 (m, 24 H); 0.88 (m, 3 H).

2-Fluorohexadecanol. To a suspension of 11.8 mg (0.312 mmol; 3 eq.) of $LiAlH_4$ in 2 mL of dry diethylether under stirring, were added dropwise 30.0 mg (0.104 mmol; 1eq.) of 2-fluoropalmitic acid methyl ester **[29]** dissolved in 2 mL of dry diethylether. The reaction mixture was refluxed for 4 h, after which it was quenched by addition of ethyl acetate (1 mL) and water (1 mL). The resulting mixture was stirred at rt. for 4 h. Filtration on a short silica gel column (elution with 10 mL of diethylether) and evaporation of the solvent *in vacuo* afforded 22.6 mg (83%) of 2-fluorohexadecanol as a white solid. M.p.: 58-60 °C. IR: 3269 , 2955, 2916, 2849, 1470, 1072 cm^{-1}. EIMS: $C_{16}H_{33}OF$ (M = 260); m/z = 260 ($M^{+\bullet}$, > 0), 196 (24), 113 (26), 99 (44), 85 (100), 71 (100), 57 (100), 43 (100), 31 (85), 29 (100). ^{1}H-NMR: 4.50 (dm, 48.3 Hz, 1 H); 3.77 (dm, 23 Hz, 2 H); 1.87 (t, 6.4 Hz, 1 H); 1.64 (m, 2 H); 1.26 (m, 24 H), 0.88 (m, 3 H).

2-Fluorohexadecanal [8]. 23.0 l (0.251 mmol; 3.3 eq.) of oxalyl chloride were dissolved in 200 µL of dry CH_2Cl_2 and stirred at –40 °C (dry ice-acetonitrile bath); 39 µL (0.502 mmol; 6.6 eq.) of DMSO were added over 2 min; then, 19.8 mg (0.0760 mmol; 1 eq.) of 2-fluorohexadecanol dissolved in 1 mL of CH_2Cl_2 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 CH_2Cl_2 (10 mL) and washed with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic phases were dried, evaporated *in vacuo* to afford 18.0 mg (92%) of 2-fluorohexadecanal as a white solid. M.p.: 58-59 °C. IR: 2916, 2848, 1736, 1468 cm^{-1}. EIMS: $C_{16}H_{31}OF$ (M: 258); m/z = 258 ($M^{+\bullet}$, 3), 239 (3), 238 (7), 98 (100), 84 (59), 71 (21), 62 (5), 57 (44), 43 (49), 29 (14). ^{1}H-NMR: 9.76 (dd, 6.2 Hz, 0.73 Hz, 1 H); 4.81 (dm, 48.8 Hz, 1 H); 1.82 (m, 2 H); 1.46 (m, 2 H), 1.26 (m, 22 H), 0.88 (m, 3 H).

1,2-Hexadecanediol [31]. To a solution of 1.00 g (4.46 mmol; 1 eq.) 1-hexadecene **[30]** in 100 mL of acetone, were added 15.0 mg (0.0579 mmol; 0.013 eq.) of osmium tertroxide and 90.0 mg (6.68 mmol; 1.5 eq.) of N-methylmorpholine monohydrate. The reaction mixture was stirred for 24 h at rt. It was then diluted with an aqueous sodium bisulfite solution (10%, 100 mL) and stirred for 45 min. after which it was washed with 50 mL of brine and the aqueous phase was extracted with CH_2Cl_2 (4 x 50 mL). The organic extracts were dried and evaporated *in vacuo* and the resulting residue was flash chromatographed on silica gel (hexane/diethylether 7:3) affording 913 mg of **[31]** (80%) as a white solid. IR (solution, $CHCl_3$, 0.01 M)**:** 3684, 3626, 3594, 3574, 3038, 3006, 2928, 2856, 1464, 1240, 1194, 1054, 928 cm^{-1}. EIMS: $C_{16}H_{34}O_2$ (M = 258); m/z = 227 (61), 83 (100), 69, 61 (35), 55, 43. ^{1}H-NMR: 3.72 (m, 1 H); 3.66 (dd, 10.8 Hz, 3.0 Hz, 1H); 3.43 (dd, 10.8 Hz, 7.5 Hz, 1H); 1.84 (bs, 2 H); 1.26 (m, 26 H); 0.88 (m, 3H).

1-*Tert*-butyldimethylsilyloxy-2-hydroxyhexadecane [32]. To a solution of 700 mg (2.71 mmol; 1 eq.) of 1,2-hexadecanediol **[31]** in 13 mL of CH_2Cl_2 were added 13.2 mg (0.108 mmol; 0.04 eq.) of DMAP, 450 mg (2.99 mmol; 1.1 eq.) of *tert*-butyldimethylsilyl chloride and 414 µL (2.99 mmol; 1.1 eq.) of triethylamine. The reaction mixture was stirred for 22 h after which it was diluted with CH_2Cl_2 (20 mL), washed with water (20 mL) and with a saturated aqueous NH_4Cl solution (20 mL). The combined organic phases were dried, concentrated *in vacuo* and the residue flash chromatographed on silica gel (hexane/diethylether 6:4) to afford 940 mg of 1-*tert*-butyldimethylsilyloxy-2-hydroxyhexadecane **[32]** as an oil (93%). IR: 3466, 2954, 2926, 2854, 1464, 1362, 1254, 1112, 1096, 1006, 838, 778 cm^{-1}. EIMS: $C_{22}H_{48}O_2Si$ (M = 372); m/z = 341 ($M^{+\bullet}$- CH_3 - CH_3 - H, 5), 315 ($M^{+\bullet}$- C_4H_9, 33), 297 (21), 175 ($M^{+\bullet}$- $C_{14}H_{29}$, 6), 147 (11), 131 (29), 115 (16), 105 (80), 75 (100). ^{1}H-NMR: 3.61 (m, 1H); 3.61 (dd, 10.5 Hz, 3.2 Hz, 1H); 3.38 (dd, 10.5 Hz, 8.3 Hz, 1H); 2.38 (bs, 1H); 1.25 (m, 28 H); 0.90 (s, 9 H); 0.87 (m, 3H); 0.065 (s, 6 H).

1-*Tert*-butyldimethylsilyloxy-2-mesyloxyhexadecane [33]. To a solution of 940 mg (2.52 mmol; 1 eq.) of 1-*tert*-butyldimethylsilyloxy-2-hydroxyhexadecane **[32]** and 526 µL (3.78 mmol; 1.5 eq.) of triethylamine in 13 mL of dry CH_2Cl_2 at 0 °C, were added dropwise over 3 min 215 µL (2.78 mmol; 1.1 eq.) of mesylchloride. The reaction mixture was stirred for 10 min at 0 °C, 80 min. at rt. and then, diluted with brine (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were dried, concentrated *in vacuo* to afford pure 1-*tert*-butyldimethylsilyloxy-2-mesyloxyhexadecane **[33]**

as an oil (1.02 g, 92%). IR: 2954, 2926, 2856, 1464, 1360, 1254, 1178, 1118, 920, 838, 780 cm^{-1}. EIMS: $C_{23}H_{50}O_4SiS$ (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). ^{1}H-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 (m, 3 H), 0.082 (s, 3 H); 0.075 (s, 3 H).

2-Mesyloxyhexadecanol [34]. To a solution of 77.3 mg (0.190 mmol; 1 eq.) of 1-*tert*-butyldimethylsilyloxy-2-mesyloxyhexadecane **[33]** in 2 mL of CH_2Cl_2 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 CH_2Cl_2 (10 mL) and neutralized with an aqueous $NaHCO_3$ solution (10%). The aqueous phase was extracted with CH_2Cl_2 (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-mesyloxyhexadecanol **[34]** as a white solid (49.3 mg, 77%). M.p.: 50-51 °C. IR**:** 3532, 3034, 2956, 2918, 2852, 1470, 1328, 1164, 1072, 976, 920, 804, 720 cm^{-1}. EIMS: $C_{17}H_{36}O_4S$ (M = 336); m/z = 269 (0.7), 240 (2), 241 (4), 227 (37), 194 (12), 180 (6), 43 (100). ^{1}H-NMR: 4.76 (m, 1H); 3.81 (dd, 12.5 Hz, 3.0 Hz, 1 H); 3.71 (dd, 12.5 Hz, 6.8 Hz, 1 H); 3.09 (s, 3H); 1.50-1.74 (m, 2 H); 1.26 (m, 24 H); 0.88 (m, 3 H).

2-Mesyloxyhexadecanal [10]. It was synthesized following the same procedure as that described for the synthesis of 2-fluorohexadecanal (see above). Oil (yield: 58%). IR: 3030, 2920, 2852, 1742, 1468, 1348, 1174, 1072, 1046, 972, 942, 920, 722 cm^{-1}. EIMS: $C_{17}H_{34}O_4S$ (M = 334); m/z = 334 ($M^{+\bullet}$, 0.24), 305 (0.86), 291 (0.12), 278 (0.18), 209 (7), 138 (14), 55 (100). ^{1}H-NMR: 9.54 (d, 0.7 Hz, 1 H); 4.86 (ddd, 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*-hexadecanal 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 H_2SO_4 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: $C_{17}H_{36}O$ (M = 256); m/z = 256 ($M^{+\bullet}$, 2.2), 255 (14), 241 (27), 238 (73), 210 (37), 99 (30), 85 (100), 71 (100), 57 (100), 43 (100), 29 (64). ^{1}H-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-Heptadecanone [36]. 53.0 mg (0.246 mmol; 1.5 eq.) of PCC (freshly recrystallised from water) were suspended in 600 µL of dry CH_2Cl_2; 42.0 mg (0.164 mmol; 1 eq.) of 2-heptadecanol **[35]** dissolved in 250 µL of dry CH_2Cl_2 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-heptadecanone 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: $C_{17}H_{34}O$ (M = 254); m/z = 254 ($M^{+\bullet}$, 99), 239 (25), 196 (50), 99 (13), 85 (100), 71 (100), 58 (100), 57 (100), 43 (100), 29 (63). ^{1}H-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-heptadecanone [17]. To 42.0 mg (0.165 mmol; 1 eq.) of 2-heptadecanone **[36]** in solution in 330 µL of CH_2Cl_2 were added 22.4 mg (0.0826 mmol; 0.5 eq.) of $HgCl_2$ 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 CH_2Cl_2 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/ CH_2Cl_2 8:2) affording 33.2 mg of a mixture of 3-iodo-2-heptadecanone **[17]** (46%) and 1-iodo-2-heptadecanone (7%). The two regioisomers were separated by HPLC (reversed phase LichroCart C_{18} 100µm; elution with CH_3CN).M.p.: 33-34 °C. IR: 2953, 2923, 2853, 1713, 1464 cm^{-1}. EIMS: $C_{17}H_{34}OI$ (M = 380); m/z = 380 ($M^{+\bullet}$, > 0), 253 (56), 184 (42), 99 (22), 85 (37), 71 (100), 69 (63), 57 (98), 43 (100), 29 (39); ^{1}H-NMR: 4.44 (t, 7.5 Hz, 1 H); 2.41 (s, 3 H); 1.92 (m, 2 H); 1.26 (m, 24 H); 0.88 (m, 3 H).

2-Iodopalmitic acid [18]. 400 mg (1.56 mmol; 1 eq.) of palmitic acid **[26]**, 99.0 mg (0.390 mmol; 0.25 eq.) of iodine and 104 µL (1.56 mmol; 1 eq.) of chlorosulfonic acid were dissolved in 1.60 mL of dry 1,2-dichloroethane. The 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 $Na_2S_2O_3$ 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% CF_3COOH) affording 366 mg of a 75:25 mixture of 2-iodopalmitic acid **[18]** and palmitic acid **[26].** The two products were separated by HPLC [LicroCart, C_{18} (100 µm), λ = 200 nm, CH_3CN/water 9:1 + 0.1%

CF_3COOH, 10 mL/min: t_{R1} = 8.35 min (palmitic acid), t_{R2} = 9.29 min (2-iodopalmitic acid)]; 2-iodopalmitic acid **[18]** was isolated as an oil. IR: 2920, 2850, 1696, 1464, 1416 cm^{-1}. EIMS: $C_{16}H_{31}O_2I$ (M = 382); m/z = 382 ($M^{+\bullet}$, 1.5), 381 (3), 255 (83), 237(46), 57 (100). ^{1}H-NMR: 4.32 (dd, 7.6 Hz, 7.6 Hz, 1 H); 1.97 (m, 2 H); 1.26 (m, 28 H); 0.88 (m, 3 H).

2-Iodooctanoic 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 afforded after purification of the crude product by flash chromatography (AcOEt to AcOEt/EtOH 5:5 + 0.1% CF_3COOH) 248 mg of a 86:14 mixture of 2-iodooctanoic acid and octanoic acid. The two products were separated by HPLC [Licro-Cart, C_{18} (100 µm), λ = 200 nm, CH_3CN/water 7:3 + 0.1% CF_3COOH, 10 mL/min: t_{R1} = 2.40 min (octanoic acid), t_{R2} = 3.54 min (2-iodooctanoic acid)]; 2-iodooctanoic acid was isolated as an oil. IR: 2956, 2927, 2857, 1713, 1704, 1435, 1417 cm^{-1}. EIMS: $C_8H_{15}O_2I$ (M = 270); m/z = 270 ($M^{+\bullet}$, 9), 143 (27), 125 (56), 28 (100). ^{1}H-NMR: 4.43 (dd, 7.6 Hz, 7.6 Hz, 1 H); 1.97 (m, 2 H); 1.29 (m, 8 H); 0.89 (m, 3 H).

2-Iodopalmitate methyl ester [19]

By iodination of palmitic acid and esterification with methanol. 200 mg (0.780 mmol; 1 eq.) of palmitic acid and 49.0 mg (0.195 mmol; 0.25 eq.) of iodine were dissolved in 780 µL of 1,2-dichloroethane. The reaction mixture was heated at 80 °C and after 2 h 30, 1 mL of methanol (24.7 mmol, 32 eq.) was added. After 3 h, the reaction mixture was cooled, diluted with CH_2Cl_2 (3 mL) and washed successively with water (2 x 5 mL) and an aqueous $Na_2S_2O_3$ solution (0.1 N) until the color changed from pink to colorless. The organic phase was dried, evaporated *in vacuo* and the resulting residue flash chromatographed on silica gel (hexane/ CH_2Cl_2 7:3) affording 58.3 mg of 2-iodopalmitate methyl ester **[19]** and 6.8 mg of palmitate methyl ester.

By substitution of the bromine of 2-bromopalmitate methyl ester by iodine. 102 mg (0.291 mmol; 1 eq.) of 2-bromopalmitate methyl ester **[27]** and 305 mg (2.03 mmol; 7 eq.) of anhydrous NaI were dissolved in 1 mL of acetonitrile at 50 °C. After 20 h, the reaction mixture was diluted with water (10 mL) and CH_2Cl_2 (10 mL). An aqueous sodium thiosulfate solution (0.1N) was added until discoloration of the aqueous phase. The latter was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were dried, evaporated *in vacuo* affording 108 mg (93%) of 2-iodopalmitate methyl ester **[19]** as an oil. IR: 2951, 2924, 2853, 1740, 1464, 1435, 1261, 1134 cm^{-1}. EIMS: $C_{17}H_{33}O_2I$ (M = 396); m/z = 396 ($M^{+\bullet}$, 2), 365 (2), 269 (74), 237 (26), 219 (20), 200 (4.4), 87 (67), 85 (19), 71 (36), 59 (20), 57 (77), 43 (100), 29 (33). ^{1}H-NMR: 4.30 (t, 7.6 Hz, 1 H); 3.75 (s, 3 H); 1.97 (m, 2 H); 1.26 (m, 24 H); 0.88 (m, 3 H).

2-Iodooctanoate 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/ CH_2Cl_2 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: $C_9H_{17}O_2I$ (M = 284); m/z = 284 ($M^{+\bullet}$, 4), 253 (4), 200 (5), 157 (78), 125 (99), 97 (99), 83 (99), 57 (11), 55 (100), 43 (46), 29 (30). ^{1}H-NMR: 4.30 (t, 7.6 Hz, 1 H); 3.75 (s, 3 H); 1.97 (m, 2 H); 1.29 (m, 8 H); 0.88 (m, 3 H).

2-Iodooctanol [38]. To a stirred solution of 40.2 mg (0.158 mmol; 1 eq.) of 2-iodooctanal **[3]** in 3 mL of methanol kept at rt., were added at once 4.50 mg (0.119 mmol; 0.75 eq.) of $NaBH_4$. After 75 min, the reaction mixture was quenched with water (10 mL), diluted with CH_2Cl_2 (10 mL) and the organic phase washed with water (3 x 10 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried, evaporated *in vacuo* and the resulting residue flash chromatographed on silica gel (hexane/ CH_2Cl_2 5:5) affording 19.9 mg (49%) of 2-iodooctanol **[38]** as an oil. IR: 3354, 2956, 2927, 2870, 2856, 1463 cm^{-1}. EIMS: $C_8H_{17}OI$ (M = 256); m/z = 256 ($M^{+\bullet}$, 9), 255 (18), 239 (15), 225 (96), 129 (21), 85 (57), 84 (44), 71 (79), 57 (100), 43 (100), 29 (79). ^{1}H-NMR: 4.23 (m, 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.

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/ CH_2Cl_2 7:3) to afford 258 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: $C_{16}H_{32}ONBr$ (M = 333, 335); m/z = 335 ($M^{+\bullet\ 81}Br$, 6), 333 ($M^{+\bullet\ 79}Br$, 6), 254 (100), 139 (90), 137 (90), 98 (28), 83 (20), 72 (80), 69 (30), 59 (41), 55 (42), 43 (54). ^{1}H-NMR: 6.27 (bs, 1 H); 5.59 (bs, 1 H); 4.29 (dd, 8.1 Hz, 5.3 Hz, 1 H); 1.94-2.18 (m, 2 H); 1.26-1.53 (m, 24 H); 0.88 (m, 3 H).

2-Iodohexadecanamide [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 NaI. The reaction mixture was stirred for 19 h at 80 °C, and then, diluted with water (10 mL) and CH_2Cl_2 (10 mL). An aqueous sodium thiosulfate solution (0.1 N) was added until discoloration of the aqueous phase, which was extracted with CH_2Cl_2 (3 x 10 mL) and the combined

organic phases were dried, concentrated *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: $C_{16}H_{32}ONI$ (M = 381); m/z = 381 ($M^{+\bullet}$, 2), 254 (100), 185 (11), 83 (18), 72 (70), 69 (26), 59 (74), 55 (38), 43 (56). ^{1}H-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 *n*-pentadecanal **[40]** in 17 mL of CH_2Cl_2 were added 618 µL (4.64 mmol; 1.5 eq.) of trimethylsilyl cyanide and 3.0 mg (0.00940 mmol; 0.003 eq.) of ZnI. After stirring for 5 h at rt., the 2-trimethylsilyloxyhexadecanenitrile **[41]** was hydrolyzed by addition of a citric acid solution in methanol (10%; 20 mL) at rt. After 18 h, the reaction mixture was diluted with water (20 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were washed with brine, dried, concentrated *in vacuo* and the residue flash chromatographed on silica gel (hexane/ CH_2Cl_2 9:1 to CH_2Cl_2, then diethylether) to afford 23.0 mg of starting *n*-pentadecanal (3%) and 431 mg (55%) of cyanohydrin **42** as a solid. M.p.: 39-40 °C. IR: 3400, 2956, 2920, 2850, 2248, 1468, 1078 cm^{-1}. EIMS: $C_{16}H_{31}NO$ (M = 253); m/z = 253 ($M^{+\bullet}$, 5), 208 (15), 182 (16) (100). ^{1}H-NMR: 4.46 (m, 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-Mesyloxyhexadecanitrile [43]. To a solution of 431 mg (2.55 mmol; 1 eq.) of cyanohydrin **[42]** and 355 µL (2.55 mmol; 1.5 eq.) of triethylamine in 8.5 mL of dry CH_2Cl_2 at 0 °C, were added dropwise over 3 min. 145 µL (1.87 mmol; 1.1 eq.) of mesylchloride. The reaction mixture was stirred for 10 min. at 0 °C, 20 min at rt. after which it was diluted with brine (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were dried and concentrated *in vacuo* to afford 566 mg (100%) of 2-mesyloxyhexadecanitrile **[43]** as a solid. M.p.: 59-61 °C. IR: 2958, 2916, 2848, 1470, 1368, 1182, 964-818 cm^{-1}. EIMS: $C_{17}H_{33}NO_3S$ (M = 253); m/z = 331 ($M^{+\bullet}$, > 0), 252 (97), 43 (100). ^{1}H-NMR: 5.17 (dd, 6.7 Hz, 6.7 Hz, 1 H); 3.18 (s, 3 H); 2.00 (m, 2 H); 1.26 (m, 24 H); 0.88 (m, 3 H).

2-Iodohexadecanenitrile [23]. 85.0 mg (0.256 mmol; 1 eq.) of 2-mesyloxyhexadecanenitrile **[43]** and 270 mg (1.79 mmol; 7 eq.) of anhydrous NaI were dissolved in 2 mL of acetonitrile at 80 °C. After 4 h, the reaction mixture was diluted with water (10 mL) and CH_2Cl_2 (10 mL). An aqueous sodium thiosulfate solution (0.1 N) was added until discoloration of the aqueous phase which was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phases were dried, concentrated *in vacuo* and the residue flash chromatographed on silica gel (hexane/ CH_2Cl_2 9:1) to afford 43.0 mg (57%) of 2-iodohexadecanenitrile **[23]** as an oil. IR: 2924, 2854, 2236, 1466 cm^{-1}. EIMS: $C_{16}H_{30}NI$ (M = 363); m/z = 363 ($M^{+\bullet}$, 2), 236 (100), 192 (55), 128 (47), 124 (39), 110 (51), 97 (83), 43 (81). ^{1}H-NMR: 4.20 (dd, 7.1 Hz, 7.1 Hz, 1 H); 1.96-2.05 (m, 2 H); 1.26 (m, 24 H); 0.88 (m, 3 H).

2-Bromo-2-nonanone [12]. To a solution of 855 µL (5.00 mmol; 1 eq.) of 2-nonanone **[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/ CH_2Cl_2 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:$C_9H_{17}OBr$ (M = 220, 222; ^{79}Br, ^{81}Br); m/z = 222 ($^{81}M^{+\bullet}$, 0.04), 220 ($^{79}M^{+\bullet}$, 0.05), 193 (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). ^{1}H-NMR: 4.22 (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-Iodo-2-nonanone [11]. 50.5 mg (0.228 mmol; 1eq.) of 3-bromo-2-nonanone **[12]** 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 CH_2Cl_2 (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-iodo-2-nonanone **[11]** as an oil. IR: 2956, 2926, 2856, 1712, 1462, 1432, 1358, 1126, 1200, 1166, 1130, 954, 722 cm^{-1}. EIMS:$C_9H_{17}OI$ (M = 268); m/z = 184 (0.2), 141 (0.4), 58 (47), 57 (29), 49 (93), 43 (100). ^{1}H-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]. 956 mg (11.0 mmol; 1.1 eq.) of MnO_2 were suspended in 20 mL of acetic acid in the presence of 1.71 mL (10.0 mmol; 1 eq.) of 2-nonanone **[15]**; 5.33 mL (42.0 mmol; 4.2 eq.) of TMSCl were added at once. The reaction mixture was stirred at rt. for 16 h after which it was poured into water (160 mL) and extracted with diethylether (3 x 20 mL). The combined organic extracts were neutralized with an aqueous NaOH solution (0.025 M; 2 x 80 mL), dried, concentrated *in vacuo* and the residue flash chromatographed on silica gel (hexane/ CH_2Cl_2 9: 1) to afford 162 mg (92%) of 3-chloro-2-nonanone **[13]** as an oil. IR**:** 2958, 2930, 2860, 1724, 1464, 1430, 1358, 1232, 1162, 1116 cm^{-1}. EIMS: $C_9H_{17}OCl$ (M = 176, 178; ^{35}Cl, ^{37}Cl); m/z = 178 ($^{37}M^{+\bullet}$, 0.15), 176 ($^{35}M^{+\bullet}$, 0.5), 147 (0.4), 141 (0.1), 94 (9), 92 (24), 86 (31), 84 (42), 58 (20), 51 (25), 49 (50), 43 (100). ^{1}H-NMR: 4.17 (dd, 8.3 Hz, 5.8 Hz, 1 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 µL 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 CH_2Cl_2). The filtrate was concentrated *in vacuo* and the residue flash chromatographed on silica gel (hexane/ CH_2Cl_2 9:1). Evaporation of the solvent under nitrogen afforded 3-fluoro-2-nonanone **[14]** as an oil. IR: 2956, 2930, 2860, 1728, 1464, 1424, 1358, 1170, 1122, 1078 cm^{-1}. EIMS: $C_9H_{17}OF$ (M = 160); m/z = 160 ($M^{+\bullet}$, 0.06), 72 (25), 76 (0.5), 43 (100). ^{1}H-NMR: 4.71 (dm, 50.6 Hz, 1 H); 2.24 (d, 4.7 Hz, 3 H); 1.69-1.89 (m, 2 H); 1.29 (m, 8 H); 0.88 (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 18 mL of dry acetonitrile was added 1.44 g (3.52 mmol; 1 eq.) of HTIB. The reaction mixture was refluxed for 10 min after which the solvent was evaporated *in vacuo*. The crude 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 **[16]** (30%) and 162 mg of 1-tosyloxy-2-nonanone (15%) (67:33) as oils.

3-Tosyloxy-2-nonanone [16]. IR: 2956, 2930, 2860, 1724, 1598, 1462, 1368, 1178, 1096, 952, 888, 832, 816, 772, 668, 556 cm^{-1}. EIMS: $C_{16}H_{24}O_4$ S (M = 312); m/z = 313 ($M^{+\bullet}$+ H, 0.5), 281 (1), 269 (21), 155 (100), 97 (25), 91 (100), 65 (22), 57 (14), 43 (42). ^{1}H-NMR: 7.80 (AA'XX' system, 2 H); 7.36 (AA'XX' system, 2 H); 4.59 (dd, 7.9 Hz, 4.9 Hz, 1 H); 2.46 (s, 3 H); 2.20 (s, 3 H); 1.61-1.70 (m, 2 H); 1.15 (m, 8 H); 0.84 (m, 3 H).

1-Tosyloxy-2-nonanone. IR: 2954, 2928, 2858, 1740, 1598, 1460, 1368, 1178, 1096, 1004, 818, 774, 668, 556 cm^{-1}. EIMS: $C_{16}H_{24}O_4S$ (M = 312); m/z = 312 ($M^{+\bullet}$, 0.4), 282 (4), 228 (5), 127 (100), 91 (50), 65 (20), 57 (75), 43 (35). ^{1}H-NMR: 7.82 (AA'XX' system, 2 H); 7.36 (AA'XX' system, 2 H); 4.49 (s, 2 H); 2.48 (t; 7.3 Hz, 2 H); 2.46 (s, 3 H); 1.52 (m, 2 H); 1.25 (m, 8 H); 0.88 (m, 3 H).

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References

1. Pereira, A.; Braekman, J.Cl.; Dumont, J.E.; Boeynaems, J.M. *J.Biol.Chem.* **1990**, *265*, 17018.
2. Panneels, V.; Macours, P.; Van den Bergen, H.; Braekman, J.C.; Van Sande, J.; Boeynaems, J.M. *J.Biol.Chem.* **1996**, *271*, 23006.
3. Panneels, V.; Van den Bergen, H.; Jacoby, C.; Braekman, J.C.; Van Sande, J.; Dumont, J.E.; Boeynaems, J.M. *Mol.Cell. Endocrinol.* **1994**, *102*,167.
4. Panneels, V.; Van den Bergen, H.; Jacoby, C.; Braekman, J.C.; Van Sande, J.; Dumont, J.E.; Boeynaems, J.M. *Mol.Cell. Endocrinol.* **1994**, *106*, 41.
5. Jacoby, C.; Braekman, J.C.; Daloze, D. *Tetrahedron* **1996**, *52*, 10473.
6. Barluenga, J.; Martinez-Gallo, J.M.; Najera, C.;Yus M. *Synthesis* **1986**, 678.
7. Armani, E.; Dossena, A.; Marchelli, R.; Castani, G. *Tetrahedron*, **1984**, *40*, 2035.
8. Corey , E.J.; Suggs, J.W. *Tetrahedron Lett*. **1975**, *31*, 2647.
9. Bellesia, F.; Boni, M.; Ghelfi, F.; Grandi, R.; Pagnoni, U.M.; Pinetti, A. *Tetrahedron Lett.*, **1992**, *48*, 4579.
10. Boni, M.; Ghelfi, F.; Pagnoni, U.M.; Pinetti, A. *Synth. Commun.* **1993**, *23*, 1915.
11. Benincasa, M.; Boni, M.; Ghelfi, F.; Pagnoni, U.M. *Synth. Commun.* **1995**, *25*, 1843.
12. Stevens, C.L.; Farbas, E.; Gillis, B. *J. Am. Chem. Soc.* **1954**, *76*, 2695.
13. Reuss, R.H.; Hassner, A. *J.Org.Chem.* **1974**, *39*, 1785.
14. Fry, A.J.; Migron, Y. *Tetrahedron Lett*. **1979**, *36*, 3357.
15. Purrington, S.; Lazaridis, N.; Bumgardner C. *Tetrahedron Lett.* **1986**, *27*, 2715.
16. Timothy, B.P.; Hosseini, S.; Bains, S. *Tetrahedron Lett*. **1990**, *31*, 179.
17. Suga, H.; Schlosser, M. *Tetrahedron* **1990**, *46*, 4261.
18. De Kimpe, N.; Verhé, R. In *The Chemistry of α-haloketones, α-haloaldehydes and α-haloimines*, Patai, S.; Rappoport, Z., eds., John Wiley Sons, Chichester, 1988.
19. Pogany, S.A.; Zentner, G.M.; Ringeisen, C.D. *Synthesis* **1987**, 718.
20. Mancuso, A.J.; Huang, S-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
21. Ogata, Y.; Watanabe, S. *J.Org.Chem.* **1980**, *45*, 2831.
22. Granet, R.; Pierkarski, S.; *C. R. Acad. Sc. Paris* **1974**, t279, serie C, 205.
23. Lodaya, J.S.; Koser, G.F. *J.Org.Chem.* **1988**, *53*, 210.
24. Koser, G.F.; Reelenyi, A.G.; Kalos, A.N.; Rebrovic, L.; Wettach, R.H. *J.Org.Chem.* **1982**, *47*, 2487.
25. Koser, G.F.; Reelenyi, A.G.; Kalos, A.N.; Rebrovic, L.; Wettach, R.H. *J.Org.Chem.* **1982**, *47*, 2487.

26. Ogura, K.; Tsurada, T.; Takahashi, K.; Iiida, H. *Tetrahedron Lett.* **1986**, *27*, 3665.
27. a) Kirrmann, A.; Druesne, F. *C. R. Acad. Sc. Paris* **1964**, *259*, 3285; b) Huet, F.; Lechevalier, A.; Pellet, M.; Conia, J.M. *Synthesi*s, **1978**, 63; d) Yung, M.E.; Andrus, W.A.; Ornstein, P.L.; *Tetrahedron Lett.* **1977**, *48*, 4175.
28. Jacobsen, E.N.; Mark, I.; France, M.B.; Svendsen, J.S.; Sharpless, K.B. *J. Am. Chem. Soc.* **1989**, *111*, 737.
29. Chaudhary, S.K.; Hernandez, O. *Tetrahedron Lett.* **1979**, *2*, 99.
30. Crossland, R.K.; Servis, K.L. *J.Org.Chem*. **1970**, *35*, 3195.
31. Baker, R.; Cummings, W.J.; Hayes, J.F.; Kumar, A. *J. Chem. Soc., Chem. Commun.* **1986**, 1237.
32. Bellesia, F.; Ghelfi, F.; Grandi, R.; Pagnoni, U.M. *J. Chem. Res. (S)* **1986**, 428.
33. Bellesia, F.; Ghelfi, F.; Pagnoni, U.M.; Pinetti, A. *J. Chem. Res. (S)* **1990**, 188.
34. Bellesia, F.; Ghelfi, F.; Grandi, R.; Pagnoni, U.M. *J. Chem. Res. (S)* **1986**, 426.
35. Evans, D.A.; Truesdale, L.K.; Carroll, G.L. *J. Chem. Soc., Chem. Commun*. **1973**, 55.
36. Gassman, G.; Talley, J.J. *Tetrahedron Lett*. **1978**, *40*, 3773.
37. Reetz, M.T.; Drews, M.W.; Harms, K.; Reif, W. *Tetrahedron Lett*. **1988**, *29*, 3295.
38. Golinski, M.; Brock, C.P.; Watt, D.S. *J.Org.Chem*. **1993**, *58*, 159.

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