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Synthesis and Olfactory Properties of New Macrolides from Unsaturated Fatty Acids and 1,ω-Diols

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Abstract

A sequence to oxo lactones **1** via Barbier-type Gilman-Van-Ess reaction, sonochemical Lemieux oxidation, one-step ether cleavage iodination and phase transfer catalyzed cyclization is presented. Conversion of the oxo lactones **1** into methyl(en)ated macrolides **11** - **13** resulted in highly potent musk fragrances.

Keywords: Cyclization; Flavours and fragrances; Macrolides; Phase transfer; Sonochemistry; Wittig reactions

Introduction

Due to low production cost nitromusks and polycyclic musks became the dominating musk fragrances for perfumery. However, the use of nitromusks was subsequently reduced in recent years because of their health damaging properties. As for polycyclic musks problems became evident, too [1]. The accumulation of polycyclic musks in the aquatic food chain due to their persistence and hydrophobicity finally led to their detection in human adipose tissues and breast milk [2]. Hence, there is a need for the development of new nature-like, biodegradable non-toxic odorants with the aim to substitute problematic compounds and to stimulate new creations in perfumery [3,4]. In recent work [5,6] we have shown that the musk notes of macrolides depend strongly on the number of methyl groups, on their position in the ring and on the absolute configurations of stereogenic centres. In this context, we are interested in the relationship between odour and structure of saturated methylated macrolides and their unsaturated counterparts with a semicyclic or an endocyclic carbon-carbon double bond. Well-

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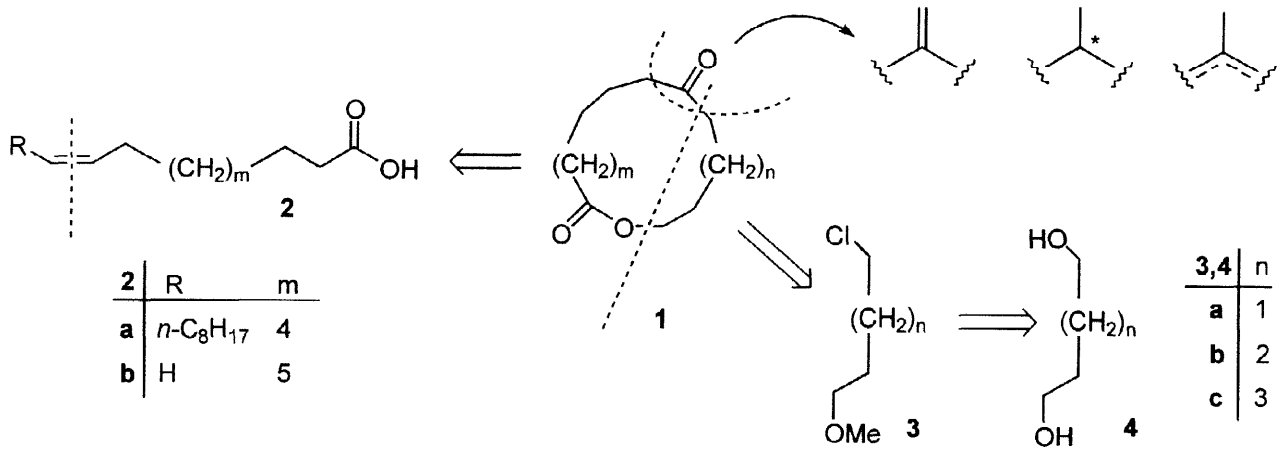


Scheme 1: Retrosynthetic analysis of the oxo lactone synthesis from **2** and **4**.

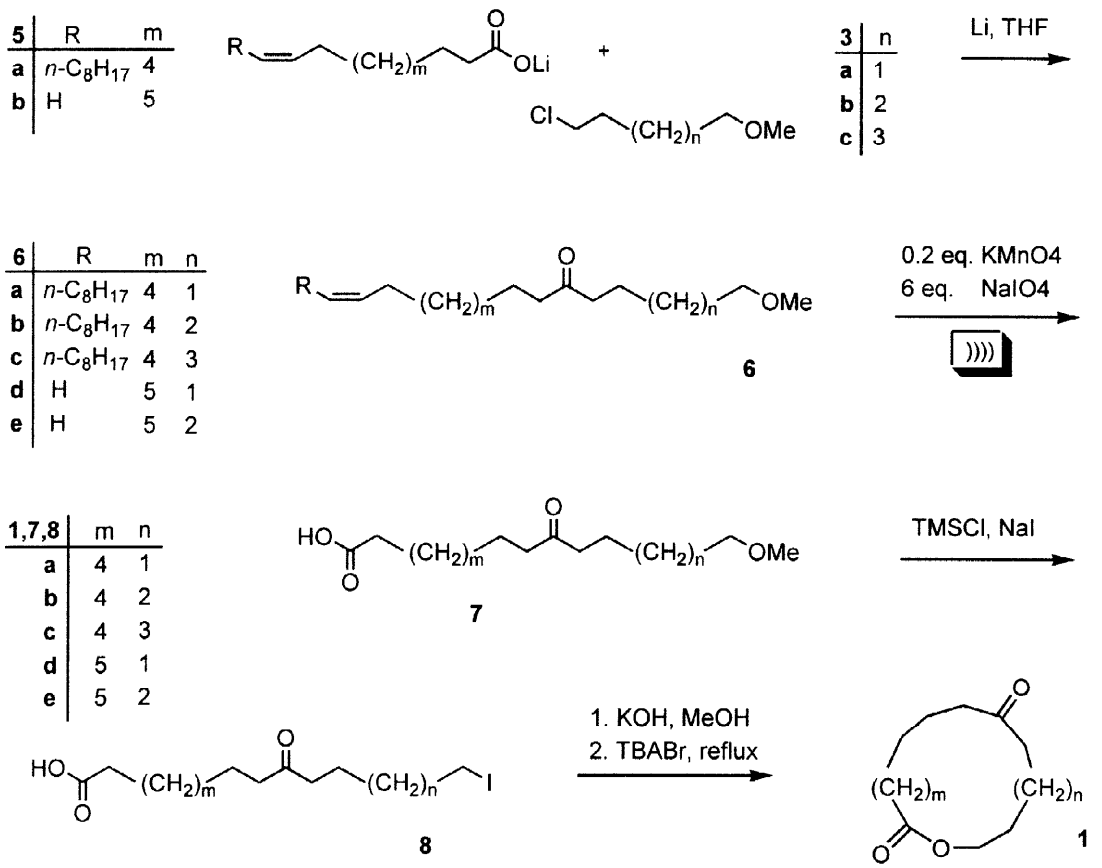
known examples of this class of musk fragrances are 15-pentadecanolide and related compounds [7,8]. Apart from the olfactory properties of new fragrances the choice of starting compounds from the pool of renewable resources and from cheap industrial chemicals is important for ecological and economical reasons.

Here we report on our approach to the target molecules **11** - **13** from unsaturated fatty acids **2** and 1,ω-diols **4** via oxo lactones **1**. Variation of the numbers of methylene groups in **2** and **4** (see Scheme 1) offers the advantage to place the oxo group of **1** and in consequence the methylene and methyl substituents in various positions of the macrocyclic ring. This principle is demonstrated here by the synthesis of methyl(en)ated tri-, tetra- and pentadecanolides **11** - **13** [9].

Results

The synthesis of oxo lactones **1** started with a Gilman-Van-Ess coupling [10] of lithium salts **5** and the chloroalkyl methyl ethers **3** (Scheme 2), that were prepared in two steps from the corresponding diols **4** [11]. In a one-pot reaction under Barbier reaction conditions metal-halogen exchange of **3** with lithium (in pieces from bars) and subsequent reaction with the lithium salts **5** led to the enones **6** [12]. Facile work-up, with purification by vacuum distillation, led to yields between 85% and 88% in a 150 mmol scale. Thereafter, the double bonds in **6** had to be cleaved oxidatively to the carboxylic acids **7**. As ozonolysis followed by oxidative work-up did not proceed successfully we tried Lemieux oxidation with $KMnO_4$ and $NaIO_4$ [13]. Lemieux cleavage often suffers from poor solubility of organic compounds in aqueous media or $KMnO_4$ and $NaIO_4$ in organic solvents. Compromises were reported that use

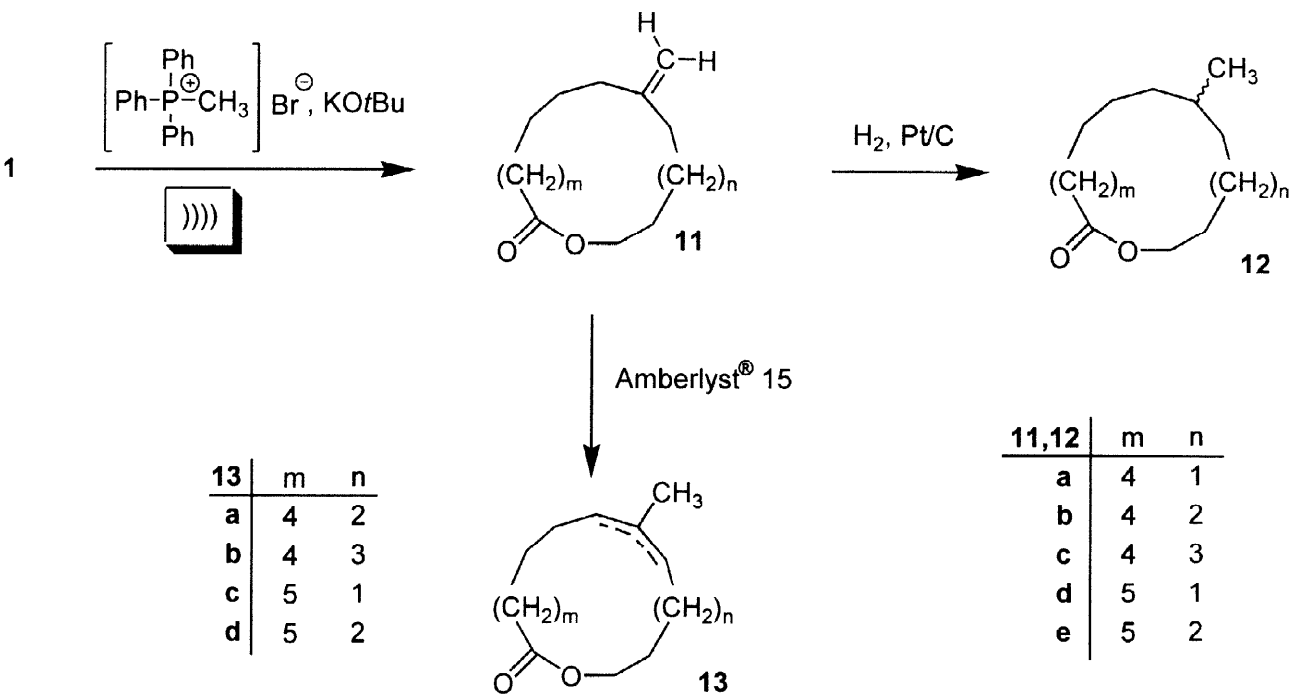
large amounts of alcohol/water-mixtures [14] or additional solvent mediators [15]. We applied a new sonochemical procedure of the Lemieux oxidation that allowed us to work in 6-times higher concentrations than usual and to make more efficient use of $NaIO_4$. $KMnO_4$ was only needed in catalytic amounts. Separation of **7a-c** from the by-product nonanoic acid or direct crystallization of **7d/e** furnished the carboxylic acids **7** in 61% - 83% yield. Without the use of ultrasound cleavage under these reaction conditions yielded only 7% of **7**. Olah's [16] mixture of trimethylsilyl chloride and sodium iodide, used for the in situ generation of trimethylsilyl iodide, cleaves alkyl ethers rapidly and under mild conditions leading to high yields of the corresponding alcohols. However, direct transformation of these ethers into the corresponding alkyl iodides was observed when the reaction mixture is heated for a prolonged time. Application of this method on the synthesis of **8** enabled us to perform a one step deprotection and activation of **7** to give the ω-iodo acids in 68% - 88% yield.



Scheme 2: Route to oxo lactones **1**

For the synthesis of large ring macrolides from hydroxy acids, many efficient activation protocols were established [17]. In addition, cyclization of ω-halogen acids by bases like K_2CO_3 in 2-butanone [18] or DMSO [19] under conditions such as high dilution is another useful possibility for the synthesis of macrolides. High dilution can be avoided by the phase transfer catalyzed ring closure method introduced by Regen [20] for the cyclization of ω-bromo acids.

This cyclization method required first the synthesis of the potassium salts of acids **8** by titration with KOH in MeOH against phenolphthaleine. The potassium salts were dried and suspended in toluene (or toluene/dioxane) with catalytic amounts of tetrabutylammmonium bromide* and finally heated under reflux to give the oxo lactones **1** in 62% - 85% yield.† The reaction can be performed in concentrations up to 100 mmol/l without high dilution conditions. Stoll's statement [21] that an additional carbonyl group eliminates the musk odour of macrocycles is fulfilled in our cases with exception of oxo lactone **1c** which possesses a clearly musk note with animalic and erogenous accents of weak intensity.



13	m	n
a	4	2
b	4	3
c	5	1
d	5	2

11,12	m	n
a	4	1
b	4	2
c	4	3
d	5	1
e	5	2

Scheme 3: Synthesis of musks **11**, **12** and **13**

* The use of tetrabutylammonium bromide instead of the iodide was preferred due to the lower melting point of the bromide.

† The synthesis of **8a** and **1a** was already reported in ref. [18].

Now the stage was set for transformation of the oxo lactones **1** into the desired musk fragrances. First we converted **1** into the exo-methylene macrolides **11** by Wittig reaction with methyltriphenylphosphonium bromide and KO*t*Bu in toluene (Scheme 3). Sonication was applied according to ref. [22] and furnished **11** in 83% - 99% yield [23]. The efficiency of sonochemical conditions was checked in the case of **11c** where the yield without sonication decreased by 20%. Hydrogenation of alkenes **11** with platinum on a carbon catalyst furnished the methyl lactones **12** in 87% - 99% yield. We were pleased to notice different olfactory properties for **11** and their saturated counterparts **12**. This indicates a highly structure-sensitive receptor macrolide interaction, which one would not expect by modifications of parts of the ring distant from the osmophore group.

Table 1.
Olfactory properties of musk macrolides

Compound	Olfactory properties of **11 - 13***	Musk intensity
11a	musk but less intensive than **12a**; clearly woody, sweet and animalic, with nitro musk aspects	+
11b	strong musk with carbide-like by-note (less intensive than in **12b**), fresh and very strong woody with sweet accents	+++
11c	clearly and strong musk, sweeter than ambrettolide with animalic tonality	+++
11d	clearly musk, fresh, woody, resemblance to ambrettolide, erogenous, animalic and sweet character	+++
11e	neutral musk note, not fresh more animalic, erogenous and sweet with stearinic undertone	+++
12a	clearly musk with cedarwood-like and musty undertone, not fresh	++
12b	strong and aggressive musk note with carbide-like by-note, very fresh but not woody as **11b**	+++
12c	typical musk, animalic and erogenous, not fresh like pentadecanolide more towards cedarwood	+++
12d	clean and crystal-clear musk note, strong and sweet, woody-fresh, smells like skin	+++
12e	pure but subtle musk, not animalic nor sweet more fresh accents	++
13a	strong and clear musk with animalic character, stronger than the musk note appears a woody-powdery-cedarwood-like note	+++
13b	like **11c** less cedarwood-like but fresher	+++
13c	like **11e** but with woody and warm accents, sandelwood-like tonality	+++
13d	like **11e** but fresher, woody-metallic and camphoraceous aspects	+++

* Evaluated by the perfumers of Haarmann & Reimer GmbH, D-37601 Holzminden.

This result encouraged us to carry out also the isomerization of **11** to give **13** as mixtures of endocyclic isomers. Treatment of **11** with Amberlyst® 15 in dichloromethane quantitatively furnished the isomeric mixtures **13** that exude musk top notes clearly different from their precursors despite their structural similarity. All compounds described above possess musk top notes described in table 1. Finally, we also introduced ethyl and ethylidene groups into **1a-c** by analogous procedures. However, these compounds were more or less odourless or had only very weak musk notes [9a].

Discussion

Table 1 shows in agreement with our previous work [5,6] that slight structural changes as are the transformations of semicyclic methylene groups into methyl groups (**11** → **12** or **11** → **13**) can effect clear changes of olfactory properties. This emphasizes the statement that the interaction of musk macrolides with a musk receptor appears to be very sensitive to conformational changes. The influence of the variation of substituent positions and/or ring size on the olfactory properties do not seem to follow characteristic patterns, nevertheless in the range between 14 to 16 ring atoms musk top notes can be expected. In addition, a trend of increasing woody notes with decreasing ring size can also be noticed (e.g. **11a** and **11c**). We cannot deny the fact that olfactory properties and odour intensities of macrocyclic musks are still only predictable in respect to their common musk top note. However, the special character of a new musk will still be a secret until the detailed evaluation by the perfumer. Further work on this topic is in progress [24].

Conclusion

In summary, we presented a new versatile synthesis of unsaturated and substituted musk macrolides from unsaturated fatty acids and 1,ω-diols [25]. In this context, we worked out a new sonochemical variation of the Lemieux oxidation and applied the cyclization method of Regen [20] on ω-iodo carboxylic acids. Our procedure also nicely completes other recent successful approaches to unsaturated and oxo macrolides, for instance via ring-closing metathesis [26] or radical carbonylation [27].

Experimental

IR spectra were recorded on a Perkin-Elmer Paragon 1600 FTIR spectrometer. $^{1}H/^{13}C$ NMR spectra (reference: TMS int) were taken on Bruker AC 200 P, Bruker AM 300 or Bruker DRX 500 spectrometers, respectively. The assignment of related data marked with * or ** may be exchanged. EI (70 eV) and CI (*i*BuH) mass spectra were obtained on a Finnigan-MAT 8230 spectrometer. Gas chromatography (GC) was performed on a Varian 3400 gas chromatograph equipped with a capillary column, MN Permabond® SE 30, (25 m), using nitrogen as carrier gas; the detector and injector temperatures were 250 °C. Sonications were carried out in a Bandelin Sonorex Super RK 255 H cleaning bath (frequency 35 kHz, acoustic power 400 W, capacity 3 dm^3) thermostated by tap water, and a Bandelin Sonoplus HD 60, Sonotrode UW 60 horn, respectively. Column chromatography was performed on Baker Silicagel 30-60 μm and analytical TLC on Macherey-Nagel SIL G/UV_{254} plates. Melting points were determined using a Büchi 510 melting apparatus and are uncorrected. Elemental analyses were performed by the Mikroanalytisches Laboratorium Ilse Beetz, D-96301 Kronach.

Synthesis of Oxo Lactones ***1a-c***

General procedure: Lithium oleate was prepared by neutralization of oleic acid with LiOH in toluene under reflux and azeotropic removal of water. The solvent was evaporated and the resulting residue washed with ether. The remainig solvent traces were removed in vacuo. Lithium oleate (43.2 g, 150 mmol; **5a**) and pieces of lithium of 1 cm in diameter (3.00 g, 432 mmol) were added to THF/cyclohexane (7:1, 500 mL) under argon atmosphere. The suspension was stirred at room temp. 4-Chloro-1-methoxybutane (23.0 g, 188 mmol; **3a**) [11a] was added in 4 portions within 4 h. The remaining lithium was removed and the reaction mixture was poured into water (200 mL) and extracted with Et_2O (3 x 200 mL). The combined organic extracts were washed with water (2 x 200 mL) and brine (1 x 100 mL). The organic solvents were dried (Na_2SO_4) and then removed under reduced pressure. The residue was purified by distillation (0.005 mbar, 165 - 195 °C) to give **6a** (44.9 g, 85%) as a colourless oil.

*(13Z)-1-Methoxy-13-docosen-5-one (**6a**)*. IR (film, cm^{-1}) $\tilde{\nu}$ 1715 (s, C=O), 1121 (s, C-O); ^{1}H NMR ($CDCl_3$, ppm) δ 0.88 (t, J = 7.0 Hz, 3H, 22-H_3), 1.22 - 1.37 (m, 20H, 8-H_2 - 11-H_2, 16-H_2 - 21-H_2), 1.51 - 1.67 (m, 6H, 2-, 3-, 7-H_2), 1.95 - 2.05 (m, 4H, 12-, 15-H_2), 2.38 (t, J = 7.7 Hz, 2H, 4-H_2^*), 2.43 (t, J = 6.9 Hz, 2H, 6-H_2^*), 3.32 (s, 3H, OCH_3), 3.37 (t, J = 6.1 Hz, 2H, 1-H_2), 5.33 part A of an ABX_2Y_2 system (dtt, J = 10.7 Hz, 5.7 Hz, 1.4 Hz, 1H, 13 H^{**}), 5.36 part B of an ABX_2Y_2 system (dtt, J = 10.7 Hz, 5.7 Hz, 1.4 Hz, 1H, 14-H^{**}); ^{13}C NMR ($CDCl_3$, ppm) δ = 14.03 (q, C-22), 20.45 (t, C-3), 22.61 (t, C-21), 23.75 (t, C-7), 27.07 / 27.12

(t, C-12, -15), 29.03 / 29.05 / 29.15 / 29.25 / 29.45 / 29.61 / 29.69 (7 t for 9C, C-2, C-8 - C-11, C-16 - C-19), 31.70 (t, C-20), 42.32 / 42.69 (t, C-4, -7), 58.42 (q, OCH_3), 72.37 (t, C-1), 129.64 / 129.85 (d, C-13, -14), 210.97 (s, C-5); MS (CI, %): *m/z* 354 (25) [M^+ + 2H], 353 (100) [M^+ + H], 325 (41), 299 (77); Anal calcd for $C_{23}H_{44}O_2$ (352.6), C 78.35, H 12.58; found C 78.38, H 12.49.

*(14Z)-1-Methoxy-14-tricosen-6-one (**6b**).* Scale 100 mmol of lithium oleate (**5a**), 346 mmol of lithium and 130 mmol of 5-chloro-1-methoxypentane (**3b**) [11a], yield 88% (32.3 g), bp 165 - 183 °C/0.005 mbar; IR (film, cm^{-1}) $\tilde{\nu}$ 1715 (s, C=O), 1121 (s, C–O); ^1H NMR ($CDCl_3$, ppm) δ 0.88 (t, *J* = 7.1 Hz, 3H, 23-H_3), 1.22 - 1.37 (m, 22H, 3-, 9-H_2 - 12-H_2, 17-H_2 - 22-H_2), 1.51 - 1.62 (m, 6H, 2-, 4-, 8-H_2), 1.91 - 2.10 (m, 4H, 13-, 16-H_2), 2.38 (t, *J* = 7.5 Hz, 2H, 5-H_2^*), 2.40 (t, *J* = 7.4 Hz, 2H, 7-H_2^*), 3.33 (s, 3H, OCH_3), 3.36 (t, *J* = 6.6 Hz, 2H, 1-H_2), 5.33 part A of an ABX_2Y_2 system (dtt, *J* = 11.1 Hz, 5.7 Hz, 2.2 Hz, 1H, 14-H**), 5.36 part B of an ABX_2Y_2 system (dtt, *J* = 11.1 Hz, 5.7 Hz, 2.2 Hz, 1H, 15-H**); ^{13}C NMR ($CDCl_3$, ppm) δ 14.85 (q, C-23), 22.45 (t, C-22), 23.33 / 23.56 (t, C-4, -8), 26.90 / 26.94 (t, C-13, -16), 25.56 / 28.86 / 28.98 / 29.01 / 29.08 / 29.10 / 29.21 / 29.30 / 29.45 / 29.52 (t, C-2, C-3, C-9 - C-12, C-17 - C-20), 31.68 (t, C-21), 42.33 / 42.50 (t, C-5, -7), 58.20 (q, OCH_3), 72.26 (t, C-1), 129.42 / 129.94 (d, C-14, -15), 210.63 (s, C-6); MS (CI, %): *m/z* 368 (38) [M^+ + 2H], 367 (100) [M^+ + H], 339 (12); Anal calcd for $C_{24}H_{46}O_2$ (366.6), C 78.63, H 12.64; found C 78.69, H 12.63.

*(15Z)-1-Methoxy-15-tetracosen-7-one (**6c**).* Scale 150 mmol of lithium oleate (**5a**), 450 mmol of lithium and 200 mmol of 6-chloro-1-methoxyhexane (**3c**) [11b], yield 85% (48.5 g), bp 180 - 200 °C/0.02 mbar; IR (KBr, cm^{-1}) $\tilde{\nu}$ 1714 (s, C=O), 1120 (s, C–O); ^1H NMR ($CDCl_3$, ppm) δ 0.88 (t, *J* = 6.9 Hz, 3H, 24-H_3), 1.22 - 1.40 (m, 24H, 3-, 4-, 10-H_2 - 13-H_2, 18-H_2 - 23-H_2), 1.51 - 1.62 (m, 6H, 2-, 5-, 9-H_2), 1.91 - 2.10 (m, 4H, 14-, 17-H_2), 2.38 (t, *J* = 7.7 Hz, 2H, 6-H_2^*), 2.39 (t, *J* = 7.3 Hz, 2H, 8-H_2^*), 3.33 (s, 3H, OCH_3), 3.36 (t, *J* = 6.5 Hz, 2H, 1-H_2), 5.33 part A of an ABX_2Y_2 system (dtt, *J* = 10.9 Hz, 5.5 Hz, 2.0 Hz, 1H, 15-H**), 5.35 part B of an ABX_2Y_2 system (dtt, *J* = 10.9 Hz, 5.5 Hz, 2.0 Hz, 1H, 16-H**); ^{13}C NMR ($CDCl_3$, ppm) δ 14.08 (q, C-24), 22.72 (t, C-23), 23.87 / 23.96 (t, C-5, -9), 26.03 (t, C-3), 27.24 / 27.28 (t, C-14, -17), 29.17 / 29.33 / 29.37 / 29.48 / 29.53 / 29.58 / 29.67 / 29.69 / 29.76 / 29.83 / 31.96 (t, C-2, C-4, C-10 - C-13, C-18 - C-21), 32.64 (t, C-22), 42.71 / 42.84 (t, C-6, -8), 58.47 (q, OCH_3), 72.81 (t, C-1), 129.75 / 129.98 (d, C-15, -16), 211.03 (s, C-7); MS (CI, %) *m/z* 382 (27) [M^+ + 2H], 381 (100) [M^+ + H], 353 (23); Anal calcd for $C_{25}H_{48}O_2$ (380.7), C 78.87, H 12.72; found C 78.87, H 12.68.

Sonochemical Lemieux Oxidations

General procedure: To a solution of **6a** (20.7 g, 59.0 mmol) in water/*tert*-butanol (2:1, 500 mL) were added K_2CO_3 (24.0 g, 174 mmol) and $NaIO_4$ (101 g, 470 mmol). The suspension

was sonicated with a horn and vigorously stirred with a stirring bar. After pre-sonication of 1 h a solution of $KMnO_4$ (1.86 g, 12 mmol) in water (100 mL) was added dropwise over a period of 7 h. The reaction mixture was sonicated for a further 3 h. The solution was carefully acidified with H_2SO_4 (10%) and the precipitate of MnO_2 was filtered off. The filtrate was extracted with Et_2O (5 x 100 mL). The combined organic extracts were washed with water (2 x 100 mL) and brine (1 x 100 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was separated from nonanoic acid by fractional crystallization (ethanol/water) at -18 °C. Further purification by recrystallization (Et_2O/*n*-pentane) gave **7a** (9.3 g, 61%) as colourless crystals, mp 47 - 49 °C.

*13-Methoxy-9-oxo-tridecanoic acid (**7a**)*; IR (KBr, cm^{-1}) $\tilde{\nu}$ 3100 (br., O–H), 1696 (br. s, C=O, OC=O), 1233 / 1135 (s, C–O); ^1H NMR ($CDCl_3$, ppm) δ 1.11 - 1.42 (m, 6H, 4-H_2 - 6-H_2), 1.40 - 1.70 (m, 8H, 3-, 7-, 11-, 12-H_2), 2.33 (t, J = 7.4 Hz, 2H, 2-H_2), 2.40 (t, J = 7.5 Hz, 2H, 8-H_2^*), 2.43 (t, J = 6.9 Hz, 2H, 10-H_2^*), 3.33 (s, 3H, OCH_3), 3.39 (t, J = 6.1 Hz, 2H, 13-H_2), 11.2 (br. s, exchangeable, 1H, COOH); ^{13}C NMR ($CDCl_3$, ppm) δ 20.43 (t, C-11), 23.64 (t, C-7), 24.54 (t, C-3), 28.76 / 28.91 (2 t for 4C, C-4 - C-6, C-12), 33.90 (t, C-2), 42.32 / 42.59 (t, C-8, -10), 58.33 (q, OCH_3), 72.37 (t, C-13), 179.16 (s, C-1), 211.23 (s, C-9); MS (CI, %) *m/z* 259 (91) [M^+ + H], 241 (25), 227 (100); Anal calcd for $C_{14}H_{26}O_4$ (258.4), C 65.09, H 10.14; found C 65.09, H 10.06.

*14-Methoxy-9-oxo-1-tetradecanoic acid (**7b**)*. Scale 84.5 mmol **6b**, 621 mmol of $NaIO_4$ and 17 mmol of $KMnO_4$ in water (100mL), yield 83% (19.0 g), mp 57.5 - 58.5 °C; IR (KBr, cm^{-1}) $\tilde{\nu}$ 3100 (br., O–H), 1702 (br. s, C=O, OC=O), 1236 / 1119 (s, C–O); ^1H NMR ($CDCl_3$, ppm) δ 1.20 - 1.42 (m, 8H, 4-H_2 - 6-H_2, 12-H_2), 1.48 - 1.75 (m, 8H, 3-, 7-, 11-, 13-H_2), 2.34 (t, J = 7.5 Hz, 2H, 2-H_2), 2.39 (t, J = 7.2 Hz, 2H, 8-H_2^*), 2.41 (t, J = 7.1 Hz, 2H, 10-H_2^*), 3.33 (s, 3H, OCH_3), 3.38 (t, J = 6.4 Hz, 2H, 14-H_2), 11.2 (br. s, exchangeable, 1H, COOH); ^{13}C NMR ($CDCl_3$, ppm) δ 23.45 / 23.57 (t, C-7, -11), 24.47 (t, C-3), 25.59 / 28.70 / 28.84 / 29.14 (4 t for 5C, C-4 - C-6, C-12, -13), 33.84 (t, C-2), 42.57 / 42.57 (t, C-8, -10), 58.26 (q, OCH_3), 72.42 (t, C-14), 179.05 (s, C-1), 211.37 (s, C-9); MS (CI, %) *m/z* 273 (100) [M^+ + H], 255 (76), 241 (21); Anal calcd for $C_{15}H_{28}O_4$ (272.4), C 66.14, H 10.36; found C 66.16, H 10.34.

*15-Methoxy-9-oxo-1-pentadecanoic acid (**7c**)*. Scale 53.0 mmol of **6c**, 318 mmol of $NaIO_4$ and 5.22 mmol of $KMnO_4$ in water (50mL), yield 66% (10.1 g) after fractional crystallization (ethanol/water) at room temp and recrystallization (Et_2O/*n*-pentane), mp 62 - 63 °C; IR (KBr, cm^{-1}) $\tilde{\nu}$ 2900 (br. O-H), 1738 / 1703 (s, C=O, OC=O), 1235 / 1121 (s, C–O); ^1H NMR ($CDCl_3$, ppm) δ 1.20 - 1.47 (m, 10H, 4-H_2 - 6-H_2, 12-, 14-H_2), 1.48 - 1.75 (m, 8H, 3-, 7-, 11-, 13-H_2), 2.34 (t, J = 7.3 Hz, 2H, 2-H_2), 2.38 (t, J = 7.3 Hz, 2H, 8-H_2^*), 2.39 (t, J = 7.3 Hz, 2H, 10-H_2^*), 3.33 (s, 3H, OCH_3), 3.37 (t, J = 6.6 Hz, 2H, 15-H_2), 9.30 (br. s, exchangeable, 1H, COOH); ^{13}C NMR ($CDCl_3$, ppm) δ 23.72 / 23.76 (t, C-7, -11), 24.59 (t, C-3), 25.87 (t, C-13), 28.81 / 28.94 / 28.97 / 29.03 / 29.33 (t, C-4 - C-6, C-12, C-14), 33.90 (t, C-2), 42.40 / 42.65 (t,

C-8, -10), 58.36 (q, OCH_3), 72.73 (t, C-15), 178.97 (s, C-1), 211.32 (s, C-9); MS (EI, %) *m/z* 286 (2) [M^+], 186 (39), 83 (100); Anal calcd for $C_{16}H_{30}O_4$ (286.4), C 67.10, H 10.56; found C 67.16, H 10.61.

Synthesis of Iodo Carboxylic Acids ***8a-c***

General procedure: To a mixture of **7a** (9.26 g, 36.0 mmol) and NaI (32.0 g, 213 mmol) in CH_3CN (250 mL) under argon atmosphere pyridine (4.40 mL, 54.0 mmol) was added. The suspension was heated to 60 °C for 10 min and cooled to room temp. Trimethylsilyl chloride (16.0 mL, 126 mmol) was introduced and the reaction mixture was stirred at 100 °C for 3 d. After cooling to room temp the suspension was quenched with Et_2O (500 mL) and the precipitate of NaI was filtered off. The solvents were removed under reduced pressure to leave a solid residue, which was dissolved in 2 N HCl (100 mL) and Et_2O (100 mL). The aqueous layer was extracted with Et_2O (2 x 100 mL). After washing with a solution of $NaHSO_3$ (10%) and brine the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by recrystallization (EtOAc/*n*-pentane) to provide **8a** (8.6 g, 68%) as a colourless solid, mp 77.5 - 78.5 °C.

*13-Iodo-9-oxo-1-tridecanoic acid (**8a**)*; IR (KBr, cm^{-1}) $\tilde{\nu}$ 3430 (br., O–H), 1704 (br. s, C=O, OC=O); ^1H NMR ($CDCl_3$, ppm) δ 1.20 - 1.43 (m, 6H, 4-H_2 - 6-H_2), 1.44 - 1.90 (m, 8H, 3-, 7-, 11-, 12-H_2), 2.35 (t, *J* = 7.7 Hz, 2H, 2-H_2), 2.40 (t, *J* = 7.7 Hz, 2H, 8-H_2^*), 2.44 (t, *J* = 6.9 Hz, 2H, 10-H_2^*), 3.19 (t, *J* = 6.9 Hz, 2H, 13-H_2), 11.0 (br. s, exchangeable, 1H, COOH); ^{13}C NMR ($CDCl_3$, ppm) δ 6.09 (t, C-13), 23.62 / 24.52 (t, C-7, -11*), 24.48 (t, C-3*), 28.73 / 28.88 (2 t for 3C, C-4 - C-6), 32.76 (t, C-12), 33.93 (t, C-2), 41.28 / 42.65 (t, C-8, -10), 179.93 (s, C-1), 210.61 (s, C-9); MS (EI, %) *m/z* 354 (1) [M^+], 336 (3), 227 (100), 209 (45); Anal calcd for $C_{13}H_{23}IO_3$ (354.2), C 44.08, H 6.54; found C 44.17, H 6.55.

*14-Iodo-9-oxo-1-tetradecanoic acid (**8b**)*. Scale 35.0 mmol of **7b**, 210 mmol of NaI, 52.0 mmol of pyridine and 122 mmol of trimethylsilyl chloride, yield after recrystallization (EtOAc/cyclohexane) 79% (10.2 g), mp 69 - 70 °C; IR (KBr, cm^{-1}) $\tilde{\nu}$ 3100 (br., O–H), 1703 (br. s, C=O, OC=O); ^1H NMR ($CDCl_3$, ppm) δ 1.15 - 1.43 (m, 8H, 4-H_2 - 6-H_2, 12-H_2), 1.43 - 1.65 (m, 6H, 3-, 7-, 11-H_2), 1.77 (dtt, *J* = 6.9 Hz, 6.9 Hz, 1.0 Hz, 2H, 13-H_2), 2.28 (td, *J* = 7.6 Hz, 0.8 Hz, 2H, 2-H_2), 2.33 (t, *J* = 7.4 Hz, 2H, 8-H_2^*), 2.36 (t, *J* = 7.0 Hz, 2H, 10-H_2^*), 3.12 (td, *J* = 6.9 Hz, 1.0 Hz, 2H, 14-H_2), 11.4 (br. s, exchangeable, 1H, COOH); ^{13}C NMR ($CDCl_3$, ppm) δ 6.63 (t, C-14), 22.54 / 23.63 (t, C-7, -11), 24.48 (t, C-3), 28.74 / 28.90 / 29.96 (3 t for 4C, C-4 - C-6, C-12), 33.17 (t, C-13), 33.94 (t, C-2), 42.31 / 42.69 (t, C-8, -10), 179.94 (s, C-1), 211.05 (s, C-9); MS (EI, %) *m/z* 368 (1) [M^+], 241 (41), 223 (57), 171 (36), 186 (37), 69 (100); Anal calcd for $C_{14}H_{25}IO_3$ (368.3), C 45.66, H 6.84; found C 45.70, H 6.78.

*15-Iodo-9-oxo-1-pentadecanoic acid (**8c**).* Scale 31.9 mmol of **7c**, 190 mmol of NaI, 48.0 mmol of pyridine and 112 mmol of trimethylsilyl chloride, yield after recrystallization (Et_2O/*n*-pentane) 76% (9.23 g), mp 68 - 71 °C; IR (KBr, cm^{-1}) $\tilde{\nu}$ 2900 (br. O–H), 1703 (s, C=O, OC=O); ^1H NMR ($CDCl_3$, ppm) δ 1.22 - 1.46 (m, 10H, 4-H_2 - 6-H_2, 12-, 13-H_2), 1.47 - 1.70 (m, 6H, 3-, 7-, 11-H_2), 1.82 (tt, *J* = 7.5 Hz, 6.7Hz, 2H, 14-H_2), 2.35 (t, *J* = 7.7 Hz, 2H, 2-H_2), 2.39 (t, *J* = 7.1 Hz, 2H, 8-H_2^*), 2.40 (t, *J* = 7.2 Hz, 2H, 10-H_2^*), 3.18 (t, *J* = 6.9 Hz, 2H, 15-H_2), 8.80 (br. s, exchangeable, 1H, COOH); ^{13}C NMR ($CDCl_3$, ppm) δ 7.14 (t, C-15), 23.49 / 23.70 (t, C-7, -11), 24.56 (t, C-3), 28.04 / 28.81 / 28.97 / 30.20 (4 t für 5C, C-4 - C-6, C-12, -13), 33.19 (t, C-14), 34.01 (t, C-2), 42.53 / 42.74 (t, C-8, -10), 179.97 (s, C-1), 211.49 (s, C-9); MS (EI, %) *m/z* 382 (1) [M^+], 255 (25), 237 (36), 186 (52), 171 (30), 83 (100); Anal calcd for $C_{15}H_{27}IO_3$ (382.3), C 47.13, H 7.12; found C 47.20, H 7.20.

*Cyclization to **1a-c***

General procedure: A solution of **8a** (8.967 g, 25.32 mmol) in MeOH (100 mL) was titrated against phenolphthaleine in MeOH (0.02 mL, 10%) with a solution of KOH in MeOH (49.83 mL, 0.508 N). The solvent was evaporated in vacuo and the residue was dried at 100 °C/1 mbar for 2 h. Part of the resulting dry potassium 13-iodo-9-oxo-1-tridecanoate (2.20 g, 5.61 mmol) was added to dioxane/toluene (1:2, 30 mL) under nitrogen atmosphere and tetrabutylammonium bromide (10.0 mg, 0.03 mmol) was introduced. The suspension was heated to 100 °C for 24 h. After cooling to room temp the reaction mixture was filtered with CH_2Cl_2 (1 L) through silicagel (30 g, 0.06-0.2 mm). The filtrate was concentrated under reduced pressure and the residue was purified by silicagel column chromatography (Et_2O/*n*-pentane, 1:3) to provide **1a** (826 mg, 65%) as a colourless solid, mp 30 - 31 °C.

*9-Oxo-13-tridecanolide (**1a**)*; IR (KBr, cm^{-1}) $\tilde{\nu}$ 1724 (s, OC=O), 1702 (s, C=O), 1210 / 1169 (m, C–O); ^1H NMR ($CDCl_3$, ppm) δ 1.30 - 1.44 (m, 6H, 4-H_2 - 6-H_2), 1.60 - 1.74 (m, 6H, 3-, 7-, 11-H_2), 1.81 (tt, *J* = 7.6 Hz, 7.6 Hz, 2H, 12-H_2), 2.39 (dd, *J* = 6.3 Hz, 6.3 Hz, 2H, 2-H_2), 2.41 (dd, *J* = 7.3 Hz, 7.3 Hz, 2H, 8-H_2^*), 2.44 (dd, *J* = 7.4 Hz, 7.4 Hz, 2H, 10-H_2^*), 4.16 (dd, *J* = 5.4 Hz, 5.4 Hz, 2H, 13-H_2); ^{13}C NMR ($CDCl_3$, ppm) δ 21.51 (t, C-11), 22.32 (t, C-7), 24.12 (t, C-3), 25.45 / 26.32 / 26.44 / 27.50 (t, C-4 - C-6, C-12), 33.78 (t, C-2), 39.93 (t, C-10), 41.52 (t, C-8) 63.16 (t, C-13), 173.39 (s, C-1), 212.13 (s, C-9); MS (EI, %) *m/z* 226 (13) [M^+], 98 (100); Anal calcd for $C_{13}H_{22}O_3$ (226.3), C 68.99, H 9.80; found C 68.91, H 9.79.

*9-Oxo-14-tetradecanolide (**1b**).* Scale 16.7 mmol of potassium 14-iodo-9-oxo-1-tetradecanoate and 0.25 mmol tetrabutylammonium bromide in dioxane/toluene (1:1, 100 mL), yield 62 % (2.48 g), mp 32 - 33 °C; IR (KBr, cm^{-1}) $\tilde{\nu}$ 1731 (s, OC=O), 1707 (s, C=O), 1256 / 1162 (m, C–O); ^1H NMR ($CDCl_3$, ppm) δ 1.26 - 1.44 (m, 8H, 4-H_2 - 6-H_2, 12-H_2), 1.60 - 1.74 (m, 8H, 3-, 7-, 11-, 13-H_2), 2.32 - 2.34 (m in it dd, *J* = 6.3 Hz, 6.3 Hz, 2H, 2-H_2), 2.42 (dd, *J* =

6.6 Hz, 6.6 Hz, 2H, 8-H_2*), 2.42 (dd, J = 6.4 Hz, 6.4 Hz, 2H, 10-H_2*), 4.11 - 4.13 (m therein dd, J = 5.4 Hz, 5.4 Hz, 2H, 14-H_2); ^{13}C NMR ($CDCl_3$, ppm) δ 22.56 / 24.07 (t, C-7, -11), 24.37 (t, C-3), 25.83 / 26.83 / 27.39 / 27.69 (t, C-4 - C-6, C-12), 28.26 (t, C-13), 34.03 (t, C-2), 41.30 (t, C-10*), 42.13 (t, C-8*), 64.82 (t, C-14), 173.62 (s, C-1), 212.04 (s, C-9); MS (EI, %) *m/z* 240 (28) [M^+], 183 (12), 112 (100); Anal calcd for $C_{14}H_{24}O_3$ (240.3), C 69.97, H 10.06; found C 69.94, H 10.08.

*9-Oxo-15-pentadecanolide (**1c**).* Scale 20.0 mmol of potassium 15-iodo-9-oxo-1-pentadecanoate and 0.10 mmol tetrabutylammonium bromide in dioxane/toluene (1:1, 150 mL), yield 68 % (3.44 g), mp 31 - 33 °C; scale 0.5 mmol of potassium 15-iodo-9-oxo-1-pentadecanoate, yield 81 % (0.103 g); IR (KBr, cm^{-1}) $\tilde{\nu}$ 1729 (s, OC=O), 1706 (s, C=O), 1218 / 1162 (m, C–O); ^{1}H NMR ($CDCl_3$, ppm) δ 1.26 - 1.44 (m, 10H, 4-H_2 - 6-H_2, 12-, 13-H_2), 1.56 - 1.74 (m, 8H, 3-, 7-, 11-, 14-H_2), 2.32 (dd, J = 6.6 Hz, 6.9 Hz, 2H, 2-H_2), 2.40 (dd, J = 6.9 Hz, 6.9 Hz, 2H, 8-H_2*), 2.46 (dd, J = 6.3 Hz, 6.3 Hz, 2H, 10-H_2*), 4.11 (dd, J = 5.4 Hz, 4.4 Hz, 2H, 15-H_2); ^{13}C NMR ($CDCl_3$, ppm) δ 23.16 / 23.61 (t, C-7, -11), 24.71 (t, C-3), 26.03 (t, C-13), 27.14 / 27.50 / 27.68 / 27.96 (t, C-4 - C-6, C-12), 28.76 (t, C-14), 34.23 (t, C-2), 41.34 (t, C-8*), 41.54 (t, C-10*) 64.23 (t, C-15), 173.70 (s, C-1), 212.09 (s, C-9); MS (EI, %) *m/z* 254 (20) [M^+], 236 (13), 197 (35), 83 (100); Anal calcd for $C_{15}H_{26}O_3$ (254.4), C 70.83, H 10.30; found C 70.74, H 10.35.

*Synthesis of Oxo Lactones **1d/e***

General procedure: Lithium undec-10-enoate was prepared as Lithium oleate (see **1a**). Lithium undec-10-enoate (19.0 g, 100 mmol; **5b**) and pieces of lithium of 1 cm in diameter (2.1 g, 0.30 mmol) were added to THF (330mL) under argon atmosphere. The suspension was stirred at room temp. 4-Chloro-1-methoxybutane (19.4 g, 158 mmol; **3a**) [11a] was added in 2 portions within 4 h. The remaining lithium was removed and the reaction mixture was poured into water (200 mL) and extracted with Et_2O (3 x 200 mL). The combined organic extracts were washed with water (2 x 200 mL) and brine (1 x 100 mL). The organic extracts were dried (Na_2SO_4) and the solvents removed under reduced pressure. The residue was purified by distillation (0.05 mbar, 105 °C) to give **6d** (22.0g, 87%) as a colourless oil.

*1-Methoxy-14-pentadecen-5-one (**6d**)*; IR (film, cm^{-1}) $\tilde{\nu}$ 1714 (s, C=O), 1121 (s, C–O); ^{1}H NMR ($CDCl_3$, ppm) δ 1.47 - 1.72 (m, 16H, 2-, 3-H_2, 7-H_2 - 12-H_2), 1.98 - 2.09 (m, 2H, 13-H_2), 2.39 (t, J = 7.7 Hz, 2H, 6-H_2*), 2.42 (t, J = 7.5 Hz, 2H, 4-H_2*), 3.32 (s, 3H, OCH_3), 3.37 (t, J = 6.1 Hz, 2H, 1-H_2), 4.93 (ddt, J = 10.3 Hz, 2.2 Hz and 1.2 Hz, 1H, 15-H_{cis}), 4.99 (ddt, J = 17.2 Hz, 2.2 Hz and 1.4 Hz, 1H, 15-H_{trans}), 5.81 (ddt, J = 17.1 Hz, 10.3 Hz and 6.8 Hz, 1H, 14-H); ^{13}C NMR ($CDCl_3$, ppm) δ 20.43 / 23.72 / 28.76 / 28.92 / 29.01 / 29.10 / 29.16 / 29.22 (t, C-2, -3, C-7 - C-12), 33.64 (t, C-13), 42.27 (t,C-4), 42.62 (t, C-6), 58.36 (q, OCH_3), 72.32 (t,

C-1), 114.00 (t, C-15), 138.95 (d, C-14), 210.86 (s, C-5); MS (CI, %) *m/z* 255 (100) [M^++ H], 237 (1), 223 (63); Anal calcd for $C_{16}H_{30}O_2$ (254.4), C 75.54, H 11.89; found C 75.42, H 11.86.

*1-Methoxy-15-hexadecen-6-one (**6e**).* Scale 80 mmol of lithium undec-10-enoate (**5b**), 241 mmol of lithium and 123 mmol of 5-chloro-1-methoxypentane (**3b**) [11a], yield 86% (18.4 g), bp 136 °C/0.05 - 0.01 mbar; IR (film, cm^{-1}) $\tilde{\nu}$ 1714 (s, ν C=O), 1640 (s, ν C=C), 1121 (s, C-O); ^{1}H NMR ($CDCl_3$, ppm) δ 1.23 - 1.67 (m, 18H, 2-, 3-, 4-H_2, 7-H_2 - 12-H_2), 1.97 - 2.09 (m, 2H, 14-H_2), 2.38 (t, *J* = 7.3 Hz, 2H, 7-H_2^*), 2.40 (t, *J* = 7.2 Hz, 2H, 5-H_2^*), 3.32 (s, 3H, OCH_3), 3.36 (t, *J* = 6.5 Hz, 2H, 1-H_2), 4.93 (ddt, *J* = 10.2 Hz, 2.2 Hz und 1.2 Hz, 1H, 16-H_{cis}), 4.99 (ddt, *J* = 17.1 Hz, 2.3 Hz and 1.4 Hz, 1H, 16-H_{trans}), 5.81 (ddt, *J* = 17.0 Hz, 10.3 Hz and 6.7 Hz, 1H, 15-H); ^{13}C NMR ($CDCl_3$, ppm) δ 23.37 / 23.58 / 25.57 / 28.64 / 28.81 / 28.98 / 29.05 / 29.11 / 29.20 (t, C-2 - C-4, C-8 - C-13), 33.52 (t, C-14), 42.36 (t, C-5), 42.51 (t, C-7), 58.20 (q, OCH_3), 72.29 (t, C-1), 113.88 (t, C-16), 138.76 (d, C-15), 210.68 (s, C-6); MS (CI, %) *m/z* 269 (100) [M^++ H], 237 (12); Anal calcd for $C_{17}H_{32}O_2$ (268.4), C 75.06, H 12.02; found C 76.14, H 11.98.

Sonochemical Lemieux Oxidations

General procedure: To a solution of **6d** (11.0 g, 43.0 mmol) in water/*tert*-butanol (2:1, 410 mL) K_2CO_3 (19.6 g, 142 mmol) and $NaIO_4$ (55.6 g, 260 mmol) were added. The suspension was sonicated with a horn and vigorously stirred with a stirring bar. After pre-sonication of 1 h a solution of $KMnO_4$ (1.35 g, 8.5 mmol) in water (80 mL) was added dropwise over a period of 14 h. The reaction mixture was sonicated for a further 3 h. The solution was carefully acidified with H_2SO_4 (10%) and the precipitate of the MnO_2 was filtered off. The filtrate was extracted with Et_2O (5 x 80 mL). The combined organic extracts were washed with water (2 x 100 mL) and brine (1 x 100 mL). The organics were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by recrystallization (Et_2O/*n*-pentane) to provide **7d** (8.75 g, 74%) as colourless crystals, mp 55.5 - 56.5 °C.

*14-Methoxy-10-oxo-tetradecanoic acid (**7d**).*; IR (KBr, cm^{-1}) $\tilde{\nu}$ 2650 - 3300 (br., O–H), 1697 (br. s, C=O, OC=O), 1134 (s, C–O); ^{1}H NMR ($CDCl_3$, ppm)* δ 1.17 - 1.34 (m, 8H, 4-H_2 - 7-H_2), 1.43 - 1.67 (m, 8H, 3-, 8-, 12-, 13-H_2), 2.29 (t, *J* = 7.5 Hz, 2H, 2-H_2), 2.34 (t, *J* = 7.5 Hz, 2H, 9-H_2^{**}), 2.37 (t, *J* = 7.5 Hz, 2H, 11-H_2^{**}), 3.27 (s, 3H, OCH_3), 3.33 (t, *J* = 6.2 Hz, 2H, 14-H_2), (*Acid proton was not detectable.); ^{13}C NMR ($CDCl_3$, ppm) δ 23.58 / 20.33 / 23.62 / 24.49 / 28.81 / 28.86 / 28.95 / 28.98 (t, C-3 - C-8, C-12, -13), 33.85 (t, C-2), 42.21 (t, C-9), 42.54 (t, C-11), 58.24 (q, OCH_3), 72.28 (t, C-14), 179.11 (s, C-1), 211.22 (s, C-10); MS (CI, %) *m/z* 273 (63) [M^++ H], 255 (36), 241 (100); Anal calcd for $C_{15}H_{28}O_4$ (272.4), C 66.14, H 10.36; found C 66.01, H 10.30.

15-Methoxy-10-oxo-1-pentadecanoic acid (7e). Scale 37.0 mmol of **6e**, 224 mmol of $NaIO_4$ and 5.51 mmol of $KMnO_4$ in water (55 mL), yield 82% (8.73 g), mp 60.5 - 61.0 °C; IR (KBr, cm^{-1}) $\tilde{\nu}$ 2600 - 3350 (br. O–H), 1696 (s, C=O, OC=O), 1135 (s, C–O); ^1H NMR ($CDCl_3$, ppm) δ 1.24 - 1.39 (m, 10H, 4-H_2 - 7-H_2, 13-H_2), 1.50 - 1.65 (m, 8H, 3-, 8-, 12-, 14-H_2), 2.34 (t, J = 7.5 Hz, 2H, 2-H_2), 2.38 (t, J = 7.4 Hz, 2H, 9-H_2^*), 2.40 (t, J = 7.4 Hz, 2H, 11-H_2^*), 3.33 (s, 3H, OCH_3), 3.38 (t, J = 6.7 Hz, 2H, 15-H_2), 10.8 (br., s, exchangeable, 1H, COOH); ^{13}C NMR ($CDCl_3$, ppm) δ 23.60 / 23.79 / 24.65 / 25.75 / 28.97 / 29.05 / 29.14 / 29.17 / 29.33 (t, C-3 - C-8, C-12 - C-14), 34.03 (t, C-2), 42.65 (t, C-9), 42.79 (t, C-11), 58.48 (q, OCH_3), 72.58 (t, C-15), 179.53 (s, C-1), 211.65 (s, C-10); MS (CI, %) *m/z* 286 (9) [M^+], 200 (39), 185 (23), 144 (92), 129 (40); Anal calcd for $C_{16}H_{30}O_4$ (286.4), C 67.10, H 10.56; found C 67.16, H 10.48.

Synthesis of Iodo Carboxylic Acids ***8d/e***

General procedure: To a mixture of **7d** (8.66 g, 31.8 mmol) and NaI (28.4 g, 189 mmol) in CH_3CN (250 mL) under argon atmosphere pyridine (3.90 mL, 47.9 mmol) was added. The suspension was heated to 80 °C for 10 min and cooled back to room temp. Trimethylsilyl chloride (14.2 mL, 112 mmol) was introduced and the reaction mixture was heated at 100 °C for 14 h. After cooling to room temp the suspension was quenched with Et_2O (500 mL) and the precipitate of NaI was filtered off. The solvents were removed under reduced pressure to leave a solid residue, which was dissolved in 2 N HCl (100 mL) and Et_2O (100 mL). The aqueous layer was extracted with Et_2O (2 x 100 mL). After washing with a solution of $NaHSO_3$ (10%) and brine the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by recrystallization (Et_2O/*n*-pentane) to provide **8d** (9.96 g, 85%) as colourless solid, mp 73 - 74 °C.

14-Iodo-10-oxo-1-tetradecanoic acid (8d).; IR (KBr, cm^{-1}) $\tilde{\nu}$ 2500 - 3250 (br. O-H), 1701 (s, C=O, OC=O); ^1H NMR ($CDCl_3$, ppm) δ 1.50 - 1.36 (m, 8H, 4-H_2 - 7-H_2), 1.49 - 1.82 (m, 8H, 3-, 8-, 12-, 13-H_2), 2.28 (t, J = 7.5 Hz, 2H, 2-H_2), 2.33 (t, J = 7.5 Hz, 2H, 9-H_2^*), 2.37 (t, J = 7.1 Hz, 2H, 11-H_2^*), 3.11 (t, J = 6.6 Hz, 2H, 14-H_2), 11.0 (br., s, exchangeable, 1H, COOH); ^{13}C NMR ($CDCl_3$, ppm) δ 6.10 (t, C-14), 23.71 / 24.55 / 28.88 / 28.94 / 29.05 / 29.07 / 29.09 / 32.81 (t, C-3 - 8, C-12, -13), 33.99 (t, C-2), 41.28 (t, C-11), 42.71 (t, C-9), 179.99 (s, C-1), 210.69 (s, C-10); MS (CI, %) *m/z* 369 (4) [M^++ H], 351 (100), 241 (41), 211 (29); Anal calcd for $C_{14}H_{25}IO_3$ (368.3), C 45.66, H 6.84; found C 45.64, H 6.76.

15-Iodo-10-oxo-1-pentadecanoic acid (8e). Scale 23.1 mmol of **7e**, 139 mmol of NaI, 34.7 mmol of pyridine and 81 mmol of trimethylsilyl chloride, yield 88% (7.75 g), mp 78.5 - 79.5 °C; IR (KBr, cm^{-1}) $\tilde{\nu}$ 2500 - 3250 (br., O–H), 1700 (br. s, C=O, OC=O); ^1H NMR ($CDCl_3$, ppm)* δ 1.30 - 1.47 (m, 10H, 4-H_2 - 7-H_2, 13-H_2), 1.52 - 1.66 (m, 6H, 3-, 8-, 12-H_2), 1.83 (tt, J = 7.2 Hz, 7.2 Hz, 2H, 14-H_2), 2.34 (t, J = 7.6 Hz, 2H, 2-H_2), 2.39 (t, J = 7.4 Hz, 2H,

9-H_2**), 2.42 (t, J = 7.2 Hz, 2H, 11-H_2**), 3.19 (t, J = 7.0 Hz, 2H, 15-H_2), (*Acid proton was not detectable.); ^{13}C NMR ($CDCl_3$, ppm) δ 6.78 (t, C-15), 22.61 / 23.77 / 24.61 / 28.95 / 29.03 / 29.13 / 29.15 / 30.03 / 33.25 (t, C-3 - C-8, C-12 - C-14), 34.04 (t, C-2), 42.39 (t,C-11), 42.82 (t, C-9), 180.06 (s, C-1), 211.25 (s, C-10); MS (CI, %) *m/z* 383 (31) [M^++ H], 365 (100), 255 (21), 239 (13); Anal calcd for $C_{15}H_{27}IO_3$ (382.3), C 47.13, H 7.12; found C 47.12, H 7.11.

Cyclization to ***1d/e***

General procedure: A solution of **8d** (3.00 g, 8.1 mmol) in MeOH (100 mL) was titrated with a solution of KOH in MeOH (16.04 mL, 0.508 N) against phenolphthaleine in MeOH (0.02 mL, 10%). The solvent was evaporated in vacuo and the residue dried under reduced pressure (1 mbar) for 15 h. The resulting potassium 14-iodo-10-oxo-1-tetradecanoic acid (3.23 g, 8.0 mmol) was added to toluene (60 mL) under nitrogen atmosphere and tetrabutylammonium bromide (38.4 mg, 0.12 mmol) was introduced. The suspension was heated to 100 °C and stirred at this temperature for 3 d. After 2 d further tetrabutylammonium bromide was added (12.8 mg, 0.04 mmol). The reaction mixture was cooled to room temp and filtered with CH_2Cl_2 (400 mL) through silicagel (12 g, 0.06 - 0.2 mm). The filtrate was concentrated under reduced pressure and the residue purified by silicagel column chromatography (Et_2O/*n*-pentane, 1:2) to provide **1d** (1.54 g, 81%) as colourless solid, mp 40.5 - 41.5 °C.

*10-Oxo-14-tetradecanolide (**1d**)*. IR (KBr, cm^{-1}) $\tilde{\nu}$ 1725 (s, OC=O), 1701 (s, C=O), 1257 / 1237 (s, C–O); ^{1}H NMR ($CDCl_3$, ppm) δ 1.24 - 1.38 (m, 8H, 4-H_2 - 7-H_2), 1.61 - 1.76 (m, 8H, 3-, 8-, 12-, 13-H_2), 2.36 (dd, J = 6.3 Hz, 6.3 Hz, 2H, 2-H_2), 2.41 (dd, J = 6.7 Hz, 6.7 Hz, 2H, 9-H_2*), 2.44 (t, J = 7.6 Hz, 2H, 11-H_2*), 4.15 (dd, J = 5.4 Hz, 5.4 Hz, 2H, 14-H_2); ^{13}C NMR ($CDCl_3$, ppm) δ 21.56 (t, C-12), 23.51 (t, C-8), 24.68 (t, C-3), 26.77 / 26.79 / 26.81 / 27.16 (t, C-4 - C-7), 27.76 (t, C-13), 34.20 (t, C-2), 41.49 (t, C-9), 42.28 (t, C-11), 63.49 (t, C-14), 173.78 (s, C-1), 212.37 (s, C-10); MS (EI, %) *m/z* 240 (7) [M^+], 98 (100); Anal calcd for $C_{14}H_{24}O_3$ (240.3), C 69.96, H 10.07; found C 69.92, H 10.05.

*10-Oxo-15-pentadecanolide (**1e**)*. Scale 9.8 mmol of potassium 15-iodo-10-oxo-1-pentadecanoic acid and 0.15 mmol of tetrabutylammonium bromide, yield 85% (2.12 g), mp 40.5 - 41.5 °C; IR (KBr, cm^{-1}) $\tilde{\nu}$ 1732 (s, OC=O), 1710 (s, C=O), 1256 (s, C–O); ^{1}H NMR ($CDCl_3$, ppm) δ 1.21 - 1.38 (m, 10H, 4-H_2 - 7-H_2, 13-H_2), 1.58 - 1.69 (m, 8H, 3-, 8-, 12-, 14-H_2), 2.31 (dd, J = 6.6 Hz, 6.6 Hz, 2H, 2-H_2), 2.41 (dd, J = 6.4 Hz, 6.4 Hz, 2H, 9-H_2*), 2.44 (dd, J = 6.2 Hz, 6.2 Hz, 2H, 11-H_2*), 4.10 (dd, J = 5.5 Hz, 5.5 Hz, 2H, 15-H_2); ^{13}C NMR ($CDCl_3$, ppm) δ 23.27 (t, C-8), 23.76 (t, C-12), 24.94 (t, C-3), 26.43 (t, C-13), 27.40 (t, C-7), 27.61 (2t, C-4, -6), 27.74 (t, C-5), 28.69 (t, C-14), 34.56 (t, C-2), 41.96 (t, C-9), 42.31 (t,C-11),

64.25 (t, C-15), 174.03 (s, C-1), 211.93 (s, C-10); MS (EI, %) *m/z* 254 (26) [M^+], 114 (25), 112 (100), 70 (22); Anal calcd for $C_{15}H_{26}O_3$ (254.4) C 70.83, H 10.30; found C 70.87, H 10.36.

Synthesis of Musk Macrolides ***11***

General procedure: To methyltriphenylphosphonium bromide (1.89 g, 5.30 mmol) and KO*t*Bu (593 mg, 5.30 mmol) toluene (50 mL) was added and the suspension was heated up under sonication to 50 °C for 15 min. The solution was cooled to room temp and slowly injected via a syringe to a solution of **1a** in toluene. The addition of the ylide was stopped when the reaction mixture was not destained anymore and water (100mL) was added. The reaction mixture was extracted with Et_2O (100 mL) followed by the extraction of the aqueous layer with Et_2O (3 x 50 mL). The combined organic extracts were washed with water (2 x) and brine (1 x). The organic extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure. Triphenylphosphine oxide was separated from the crude product by fractional crystallization (Et_2O/*n*-pentane) at -18 °C. Further purification by silicagel column chromatography (Et_2O/*n*-pentane, 1:30) provided **11a** (328 mg, 83%) as a colourless liquid.

*9-Methylene-13-tridecanolide (**11a**)*. IR (film, cm^{-1}) $\tilde{\nu}$ 3068 (w, C–H exo-methylene), 1734 (s, OC=O), 1643 (m, C=CH_2), 1245 / 1137 (s, C–O), 887 (s, C–H exo-methylene); ^{1}H NMR ($CDCl_3$, ppm) δ 1.30 - 1.35 / 1.37 - 1.43 (m, 8H, 4-H_2 - 7-H_2), 1.52 - 1.58 (m, 2H, 11-H_2), 1.60 - 1.70 (m, 4H, 3-, 12-H_2), 1.99 - 2.02 (m therein dd, *J* = 7.7 Hz, 7.7 Hz, 2H, 8-H_2^*), 2.08 - 2.11 (m therein dd, *J* = 7.7 Hz, 7.7 Hz, 2H, 10-H_2^*), 2.37 - 2.40 (m therein dd, *J* = 6.2 Hz, 6.2 Hz, 2H, 2-H_2), 4.15 - 4.18 (m therein dd, *J* = 5.2 Hz, 5.2 Hz, 2H, 13-H_2), 4.706 - 4.721 (m, 2H, 9=CH_2); ^{13}C NMR ($CDCl_3$, ppm) δ 23.47 (t, C-11), 24.62 (t, C-3), 24.37 (t, C-7), 25.53 / 25.69 / 26.15 / 27.59 (t, C-4 - C-6, -12), 34.20 (t, C-2), 33.09 / 34.72 (t, C-8, -10), 64.04 (t, C-13), 110.35 (t, 9=CH_2), 149.20 (s, C-9), 173.56 (s, C-1); MS (CI, %) *m/z* 225 (100) [M^+ + H], 207 (54) [M^+ - H_2O]; Anal calcd for $C_{14}H_{24}O_2$ (224.3) C 76.96, H 10.78; found C 74.96, H 10.81.

*9-Methylene-14-tetradecanolide (**11b**)*. Scale 5.00 mmol of methyltriphenylphosphonium bromide, 5.00 mmol of KO*t*Bu and 2.50 mmol of **1b**, yield 90% (539 mg); IR (film, cm^{-1}) $\tilde{\nu}$ 3070 (w, C–H exo-methylene), 1733 (s, OC=O), 1641 (m, C=CH_2), 1245 / 1178 (s, C-O), 887 (s, C–H exo-methylene); ^{1}H NMR ($CDCl_3$, ppm) δ 1.32 - 1.52 (m, 12H, 4-H_2 - 7-H_2, 11-, 12-H_2), 1.60 - 1.70 (m, 4H, 3-, 13-H_2), 2.00 (ddd, *J* = 7.0 Hz, 7.0 Hz, 1.3 Hz, 2H, 8-H_2^*), 2.09 (ddd, *J* = 6.4 Hz, 6.4 Hz, 1.2 Hz, 2H, 10-H_2^*), 2.33 - 2.35 (m in it dd, *J* = 6.3 Hz, 6.3 Hz, 2H, 2-H_2), 4.12 - 4.14 (m therein dd, *J* = 5.4 Hz, 5.4 Hz, 2H, 14-H_2), 4.706 - 4.716 (m, 1H, 9=CH_a), 4.735 - 4.743 (m, 1H, 9=CH_b); ^{13}C NMR ($CDCl_3$, ppm) δ 24.68 (t, C-3), 25.50 / 25.83 / 26.77 / 26.91 / 27.18 (5 t für 6C, C-4 - C-7, C-11, -12), 28.14 (t, C-13), 34.19 (t, C-2), 33.96 / 36.21 (t, C-8,-10), 64.02 (t, C-14), 109.98 (t, 9=CH_2), 148.83 (s, C-9), 173.78 (s, C-1); MS (CI,

%) *m/z* 239 (100) [M^+ + H], 221 (30) [M^+ - H_2O]; Anal calcd for $C_{15}H_{26}O_2$ (238.4) C 75.58, H 11.00; found C 75.47, H 10.94.

*9-Methylene-15-pentadecanolide (**11c**).* Scale 11.9 mmol of methyltriphenylphosphonium bromide, 11.9 mmol of KO*t*Bu and 5.94 mmol of **1c**, yield 83% (1.24 g); IR (KBr, cm^{-1}) $\tilde{\nu}$ 3070 (w, C–H exo-methylene), 1735 (s, OC=O), 1642 (m, C=CH_2), 1247 / 1180 (s, C-O), 887 (s, C–H exo-methylene); ^{1}H NMR ($CDCl_3$, ppm) δ 1.27 - 1.37 (m, 8H, 5-, 6-, 12-, 13-H_2), 1.39 - 1.44 (m, 4H, 7-, 11-H_2), 1.48 (tt, 2H, J = 7.1 Hz, 7.1 Hz, 4-H_2), 1.62 (tt, J = 6.6 Hz, 6.6 Hz, 2H, 14-H_2), 1.60 - 1.67 (m, 2H, 3-H_2), 2.03 (dd, J = 7.5 Hz, 7.5 Hz, 2H, 8-H_2^*), 2.04 (dd, J = 7.5 Hz, 7.5 Hz, 2H, 10-H_2^*), 2.3 - 2.35 (m therein dd, J = 6.5 Hz, 6.5 Hz, 2H, 2-H_2), 4.15 (dd, J = 5.5 Hz, 5.6 Hz, 2H, 15-H_2), 4.72 (s, 2H, 9=CH_2); ^{13}C NMR ($CDCl_3$, ppm) δ 25.31 (t, C-3), 25.68 / 26.06 / 26.45 / 27.31 / 27.36 / 27.77 / 27.82 (t, C-4 - C-7, C-11 - C-13), 28.52 (t, C-14), 34.27 (t, C-2), 34.77 (t, C-8*), 35.09 (t, C-10*) 63.97 (t, C-15), 109.82 (t, 9=CH_2), 149.23 (s, C-9), 173.93 (s, C-1); MS (CI, %) *m/z* 253 (100) [M^+ + H], 235 (12) [M^+ - H_2O]; Anal calcd for $C_{16}H_{28}O_2$ (252.4) C 76.14, H 11.18; found C 76.17, H 11.26.

*10-Methylene-14-tetradecanolide (**11d**).* Scale 4.80 mmol of methyltriphenylphosphonium bromide, 4.80 mmol of KO*t*Bu and 2.10 mmol of **1d**, yield 99% (0.49 g); IR (KBr, cm^{-1}) $\tilde{\nu}$ 3066 (s, C–H exo-methylene), 1734 (s, OC=O), 1642 (m, C=CH_2), 1238 / 1171 (s, C-O), 887 (s, C–H exo-methylene); ^{1}H NMR ($CDCl_3$, ppm) δ 1.26 - 1.46 (m, 10H, 4-H_2 - 8-H_2), 1.51 - 1.59 (m, 2H, 12-H_2), 1.63 - 1.72 (m, 4H, 3-, 13-H_2), 2.05 (2t, J = 6.8 Hz or 8.0 Hz, 4H, 9-, 11-H_2), 2.35 (dd, J = 6.2 Hz, 6.2 Hz, 2H, 2-H_2), 4.16 (dd, J = 5.3 Hz, 5.3 Hz, 2H, 14-H_2), 4.70 - 4.73 (m, 2H, 10=CH_2); ^{13}C NMR ($CDCl_3$, ppm) δ 24.87 (t, C-12), 25.42 (t, C-8), 25.67 (t, C-3), 26.47 / 26.60 / 26.87 / 27.49 (t, C-4 - C-7), 28.41 (t, C-13), 34.02 (t, C-2), 35.14 (t, C-9), 36.17 (t, C-11), 63.67 (t, C-14), 110.53 (t, 10=CH_2), 149.34 (s, C-10), 174.06 (s, C-1); MS (EI, %) *m/z* 238 (29) [M^+], 96 (100); Anal calcd for $C_{15}H_{26}O_2$ (238.4) C 75.58, H 10.99; found C 75.47, H 10.88.

*10-Methylene-15-pentadecanolide (**11e**).* Scale 6.00 mmol of methyltriphenylphosphonium bromide, 6.00 mmol of KO*t*Bu and 2.55 mmol of **1e**, yield 93% (597 mg); IR (film, cm^{-1}) $\tilde{\nu}$ 3074 (s, C–H exo-methylene), 1735 (s, OC=O), 1643 (m, C=CH_2), 1239 / 1174 (s, C-O), 887 (s, C–H exo-methylene); ^{1}H NMR ($CDCl_3$, ppm) δ 1.30 - 1.53 (m, 14H, 4-H_2 - 8-H_2, 12-, 13-H_2), 1.61 - 1.69 (m, 4H, 3-, 14-H_2), 2.01 (t, J = 7.0 Hz, 2H, 9-H_2^*), 2.06 (t, J = 6.4 Hz, 2H, 11-H_2^*), 2.33 (dd, J = 6.5 Hz, 6.5 Hz, 2H, 2-H_2), 4.12 (dd, J = 5.6 Hz, 5.6 Hz, 2H, 15-H_2), 4.73 / 4.74 (2t, J = 1.1 Hz or 1.0 Hz, 2H, 10=CH_2); ^{13}C NMR ($CDCl_3$, ppm) δ 25.08 (t, C-12), 25.68 (t, C-8), 25.85 (t, C-3), 26.58 / 26.70 / 27.09 / 27.48 / 27.70 (t, C-4 - C-7, C-13), 28.54 (t, C-14), 34.25 (t, C-2), 34.48 (t, C-9), 35.76 (t, C-11), 64.00 (t, C-15), 109.43 (t, 10=CH_2), 148.87 (s, C-10), 174.16 (s, C-1); MS (EI, %) *m/z* 252 (27) [M^+], 96 (90), 95 (100); Anal calcd for $C_{16}H_{28}O_2$ (252.4) C 76.14, H 11.10; found C 76.18, H 11.16.

Hydrogenation of Macrolides ***11***

General procedure: Platinum on carbon (10%) (179 mg) was suspended under argon in ethyl acetate and the suspension hydrogenated for 0.5 h. **11a** (206 mg, 0.92 mmol) was added and the hydrogenation continued for a further 24 h. The catalyst was filtered off by filtration through Na_2SO_4 and washed with Et_2O. The solvents were removed under reduced pressure and the crude product was purified by silicagel column chromatography (Et_2O/*n*-pentane, 1:30) to obtain **12a** (201 mg, 97%) as a colourless liquid.

*(±)-9-Methyl-13-tridecanolide (**12a**)*. IR (film, cm^{-1}) $\tilde{\nu}$ 1735 (s, OC=O), 1247 / 1144 (s, C–O); ^1H NMR ($CDCl_3$, ppm) δ 0.88 (d, J = 6.9 Hz, 3H, 9-CH_3), 1.18 - 1.45 (m, 15H, 4-H_2 - 8-H_2, 10-, 11-H_2, 9-H), 1.55 - 1.65 (m, 2H, 3-H_2), 1.66 - 1.74 (m, 2H, 12-H_2), 2.34 part A of an ABXX′-system (ddd, J = 14.5 Hz, 4.7 Hz, 1.0 Hz, 1H, 2-H_A), 2.40 part B of an ABXX′-system (ddd, J = 14.5 Hz, 5.0 Hz, 0.7 Hz, 1H, 2-H_B), 4.06 (ddd, J = 11.0 Hz, 8.8 Hz, 3.0 Hz, 1H, 13-H_a), 4.24 (ddd, J = 11.0 Hz, 6.4 Hz, 3.4 Hz, 1H, 13-H_b); ^{13}C NMR ($CDCl_3$, ppm) δ 20.99 (q, 9-Me), 20.90 / 21.23 (t, C-7, -11), 24.51 (t, C-3), 25.78 / 25.91 / 26.39 (t, C-4 - C-6), 28.19 (t, C-12), 30.73 (d, C-9), 31.68 / 32.65 (t, C-8, -10), 34.55 (t, C-2), 63.16 (t, C-13), 173.69 (s, C-1); MS (CI, %) *m/z* 227 (100) [M^+ + H], 209 (5) [M^+ - H_2O]; Anal calcd for $C_{14}H_{26}O_2$ (226.4) C 74.29, H 11.58; found C 74.36, H 11.62.

*(±)-9-Methyl-14-tetradecanolide (**12b**)*. Scale 0.84 mmol of **11b** and 162 mg of platinum on carbon, purification by silica-gel column chromatography (Et_2O/*n*-pentane, 1:50), yield 87% (176 mg); IR (film, cm^{-1}) $\tilde{\nu}$ 1735 (s, OC=O), 1246 / 1160 (s, C–O); ^1H NMR ($CDCl_3$, ppm) δ 0.85 (d, J = 6.7 Hz, 3H, 9-CH_3), 0.92 - 1.00 / 1.20 - 1.52 (m, 17H, 4-H_2 - 8-H_2, 10-H_2 - 12-H_2, 9-H), 1.55 - 1.74 (m, 4H, 3-, 13-H_2), 2.33 part A of an ABXX′-system (ddd, J = 14.8 Hz, 8.5 Hz, 4.1 Hz, 1H, 2-H_A), 2.37 part B of an ABXX′-system (ddd, J = 14.8 Hz, 8.2 Hz, 4.2 Hz, 1H, 2-H_B), 4.09 (ddd, J = 11.1 Hz, 8.0 Hz, 3.0 Hz, 1H, 14-H_a), 4.18 (ddd, J = 11.1 Hz, 7.2 Hz, 3.2 Hz, 1H, 14-H_b); ^{13}C NMR ($CDCl_3$, ppm) δ 21.03 (q, 9-Me), 23.95 (t, C-3), 24.94 / 25.20 / 25.80 / 26.63 / 27.06 / 27.67 (t, C-4 - C-7, C-11, -12), 28.38 (t, C-13), 29.99 (d, C-9), 32.31 / 35.42 (t, C-8, -10), 34.17 (t, C-2), 64.07 (t, C-14), 174.14 (s, C-1); MS (CI, %) *m/z* 241 (100) [M^+ + H], 223 (7) [M^+ - H_2O]; Anal calcd for $C_{15}H_{28}O_2$ (240.4) C 74.95, H 11.74; found C 74.98, H 11.71.

*(±)-9-Methyl-15-pentadecanolide (**11c**)*. Scale 0.86 mmol of **12c** and 168 mg of platinum on carbon, purification by silicagel column chromatography (Et_2O/*n*-pentane, 1:50), yield 95% (208 mg); IR (film, cm^{-1}) $\tilde{\nu}$ 1737 (s, OC=O), 1249 / 1160 (s, C–O); ^1H NMR ($CDCl_3$, ppm) δ 0.84 (d, J = 6.6 Hz, 3H, 9-CH_3), 1.03 - 1.41 (m, 17H, 5-, 6-, 7-, 8-, 10-, 11-, 12-, 13-H_2, 9-H), 1.42 - 1.55 (m, 2H, 4-H_2), 1.55 - 1.74 (m, 4H, 3-, 14-H_2), 2.31 part A of an ABXX′-system (ddd, J = 13.3 Hz, 7.3 Hz, 5.6 Hz, 1H, 2-H_A), 2.31 part B of an ABXX′-system (ddd, J = 13.3 Hz, 7.7 Hz, 5.8 Hz, 1H, 2-H_B), 4.04 (ddd, J = 11.0 Hz, 7.0 Hz, 4.4 Hz, 1H, 15-H_a), 4.23 (ddd, J

= 11.0 Hz, 6.7 Hz, 4.4 Hz, 1H, 15-H_b); ^{13}C NMR ($CDCl_3$, ppm) δ 20.62 (q, 9-Me), 24.52 (t, C-3), 25.01 / 25.19 / 25.54 / 27.32 / 27.52 / 27.58 / 27.90 (t, C-4 - C-7, C-11 - C-13), 28.51 (t, C-14), 29.72 (d, C-9) 33.23 / 34.63 (t, C-8, -10), 34.53 (t, C-2), 63.99 (t, C-15), 174.04 (s, C-1); MS (CI, %) *m/z* 255 (100) [M^+ + H], 254 (1) [M^+]; Anal calcd for $C_{16}H_{30}O_2$ (254.4) C 75.54, H 11.88; found C 75.52, H 11.83.

*(±)-10-Methyl-14-tetradecanolide (**11d**)*. Scale 1.30 mmol of **12d** and 0.25 g of platinum on carbon, purification by silicagel column chromatography (Et_2O/*n*-pentane, 1:30), yield 96% (0.29 g); IR (film, cm^{-1}) $\tilde{\nu}$ 1735 (s, OC=O), 1241 / 1162, (s, C–O); ^1H NMR ($CDCl_3$, ppm) δ 0.88 (d, J = 6.8 Hz, 3H, 10-CH_3), 1.18 - 1.44 (m, 16H, 4-H_2 - 9-H_2, 11-, 12-H_2), 1.52 - 1.72 (m, 5H, 3-, 13-H_2, 10-H), 2.28 - 2.43 (m, 2H, 2-H_2), 4.05 (ddd, J = 11.0 Hz, 7.6 Hz and 3.4 Hz, 1H, 14-H_a), 4.18 (ddd, J = 11.0 Hz, 6.9 Hz and 3.4 Hz, 1H, 14-H_b); ^{13}C NMR ($CDCl_3$, ppm) δ 21.50 (q, 10-CH_3), 22.37 / 22.83 / 24.97 / 26.51 / 26.71 / 27.09 / 27.81 / 28.73 / 31.34 (t, C-3 - C-9, C-11, -12), 33.78 (t, C-13), 34.00 (d, C-10), 34.07 (t,C-2), 63.81 (t, C-14), 174.25 (s, C-1); MS (EI, %) *m/z* 240 (9) [M^+], 83 (100); Anal calcd for $C_{15}H_{28}O_2$ (240.4) C 74.95, H 11.74; found C 74.97, H 11.80.

*(±)-10-Methyl-15-pentadecanolide (**11e**)*. Scale 1.30 mmol of **12e** and 0.26 g of platinum on carbon, purification by silicagel column chromatography (Et_2O/*n*-pentane, 1:30), yield 99% (0.33 g); IR (film, cm^{-1}) $\tilde{\nu}$ 1736 (s, OC=O), 1238 / 1163 (s, C–O); ^1H NMR ($CDCl_3$, ppm) δ 0.85 (d, J = 6.7 Hz, 3H, 10-CH_3), 1.05 - 1.13 / 1.23 - 1.38 (m, 16H, 4-H_2 - 9-H_2, 11-, 12-H_2), 1.39 - 1.55 (m, 2H, 13-H_2), 1.58 - 1.72 (m, 5H, 3-, 14-H_2, 10-H), 2.34 (t, J = 6.6 Hz, 2H, 2-H_2), 4.06 (ddd, J = 11.2 Hz, 6.9 Hz and 4.5 Hz, 1H, 15-H_a), 4.20 (ddd, J = 10.9 Hz, 6.3 Hz and 4.6 Hz, 1H, 15-H_b); ^{13}C NMR ($CDCl_3$, ppm) δ 20.75 (q, 10-Me), 24.22 / 25.08 / 25.11 / 25.87 / 26.52 / 27.17 / 27.20 / 27.74 / 28.54 / 29.49 (t, C-3 - C-9, C-11 - C-13), 33.54 (t, C-14), 34.39 (d, C-10), 35.13 (t, C-2), 63.98 (t, C-15), 174.11 (s, C-1); MS (EI, %) *m/z* 254 (22) [M^+], 97 (100); Anal calcd for $C_{16}H_{30}O_2$ (254.4) C 75.54, H 11.89; found C 75.46, H 11.98.

*Isomerization of Methylene Macrolides **11***

General procedure: Amberlyst® 15 (0.20 g) was added to a solution of **11 b** (60.0 mg, 0.25 mmol) in dichloromethane (20 mL), and the mixture was stirred at room temp for 5 d. The resin was filtered off and the solvent was removed under reduced pressure. The mixture of isomers **13a** was obtained quantitatively. **13a** is a colourless oil containing 4 isomers (50 : 10 : 17 : 23) which can be separated by gas chromatography (t_{ret} = 13.06, 13.4, 13.66, 13.85). Temperature-program: 140(1)-1-150(10)-2-180(1).

*(8E/Z)-9-Methyl-14-tetradec-8-enolide/(9E/Z)-9-Methyl-14-tetradec-9-enolide (**13a**)*. ^1H NMR ($CDCl_3$, ppm) δ 1.09 - 1.45 (m, 10H, CH_2), 1.54 - 1.70 (m, 4H, 3-, 13-H_2), 1.56 / 1.57 / 1.66 / 1.67 (d, J = 1.4 Hz, 3H, 9-Me, 8-(*E/Z*) and 9-(*E/Z*)), 1.93 - 2.05 (m, 4H, CH_2-C=), 2.29

- 2.37 (4t, J = 8.8 Hz, 2H, 2-H_2), 4.11 / 4.12 / 4.13 / 4.16 (dd, J = 5.5 Hz, 5.5 Hz, 2H, 14-H_2), 5.03 / 5.06 / 5.20 / 5.22 (tq, J = 7.8 Hz, 1.4 Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$, ppm) δ 15.30 / 15.49 (q, 9-Me), 24.64 / 24.97 / 24.08 (t, C-3), 23.29 - 31.51 (28t, CH_2), 28.52 / 28.55 / 28.62 / 28.66 (t, C-13) 33.64 / 34.45 / 34.52 / 34.56 (t, C-2), 38.76 / 39.01 / 39.04 (t, allyl-CH_2), 63.74 / 63.99 / 64.07 / 64.66 (t, C-14), 124.65 / 125.40 / 126.20 / 126.39 (d, C-8 oder C-10, =CH), 134.08 / 134.83 / 134.98 / 136.16 (s, C-9), 173.94 / 174.07 / 174.08 (s, C-1); $C_{15}H_{26}O_2$ (238.4).

*(8E/Z)-9-Methyl-15-pentadec-8-enolide/(9E/Z)-9-Methyl-15-pentadec-9-enolide (**13b**).* Scale Amberlyst® 15 (0.20 g) and 0.40 mmol of **11c** in CH_2Cl_2 (10 mL), 3 d, yield 100%; two components were obtained by gas chromatography (150(1)-2-190(2)-5-240(15)): 12% (13.49) : 88% (13.85); ^{1}H NMR ($CDCl_3$, ppm) δ 1.09 - 1.53 (m, 12H, CH_2), 1.54 - 1.80 (m, 4H, 3-, 14-H_2), 1.55 / 1.66 (s, 3H, 9-Me, 8-(*E/Z*) und 9-(*E/Z*)), 1.83 - 2.19 (m, 4H, CH_2-C=), 2.25 - 2.41 (m, 2H, 2-H_2), 4.02 - 4.23 (m, 2H, 15-H_2), 5.04 - 5.23 (m, 1H, =CH); ^{13}C NMR ($CDCl_3$, ppm) δ 15.08 / 15.42 / 23.08 (q, 9-Me), 24.40 / 24.68 (t, C-3), 23.24 - 30.75 (30t, CH_2), 33.05 / 35.37 / 38.21 (t, allyl CH_2), 34.71 (t, C-2), 64.05 / 64.22 / 64.33 (t, C-15), 125.06 / 125.30 / 125.59 / 125.89 (d, C-8 or C-10, =CH), 134.23 / 135.23 / 135.60 (s, C-9), 173.68 / 173.80 / 173.94 / 174.02 (s, C-1); $C_{16}H_{28}O_2$ (252.4).

*(9E/Z)-10-Methyl-14-tetradec-9-enolide/(10E/Z)-10-Methyl-14-tetradec-10-enolide (**13c**).* Scale Amberlyst® 15 (0.20 g) and 0.46 mmol of **11d** in CH_2Cl_2 (5 mL), 3 d, yield 99%; three components were obtained by gas chromatography (130(0)-4-190(0)-1-220-10-270(30)): 1.55% (21.29) : 92.59% (21.47) : 5.86% (21.73); **11c** consists of 4 isomers: 5 : 11 : 54 : 30 (^{1}H NMR); ^{1}H NMR ($CDCl_3$, ppm) δ 1.25 - 1.53 / 1.57 - 1.60 (m, 10H, CH_2), 1.62 - 1.71 (m, 3H, 10-CH_3), 1.77 - 1.82 (m, 4H, 3-, 13-H_2), 1.92 - 2.07 (m, 2H, 8-H_2, *10*-(*E/Z*), 12-H_2, 9-(*E/Z*)), 2.10-2.15 (m, 2H, 9-H_2, *10*-(*E/Z*), 11-H_2, *9*-(*E/Z*)), 2.29 / 2.32 / 2.36 / 2.36 (4dd, J = 6.37 Hz, 6.65 Hz, 6.14 Hz or 6.23 Hz, 2H, 2-H_2), 4.10 / 4.13 (2t, J = 6.46 Hz or 6.72 Hz, 2H, 14-H_2), 4.12 / 4.15 (2dd, J = 5.19 Hz or 5.45 Hz, 2H, 14-H_2), 5.04 / 5.10 / 5.16 / 5.23 (4qt, J = 1.53 Hz and 6.83 Hz, 1.56 Hz and 7.66 Hz, 1.31 Hz and 7.46 Hz or 1.31 Hz and 5.23 Hz, 1H, 9-H, *9*-(*E/Z*), 11-H, *10*-(*E/Z*)); ^{13}C NMR ($CDCl_3$, ppm) δ 23.58 / 24.18 (q, 10-Me), 24.18 - 29.10 (t, C-3 - C-8, C-12. C-13), 31.00 / 31.80 / 37.99 / 38.06 (t, C-9, *10*-(*E/Z*) bzw. C-11, *9*-(*E/Z*)), 34.03 / 34.33 / 34.57 / 34.78 (t, C-2), 63.60 / 63.67 / 64.68 (t, C-14), 123.80 / 124.36 / 125.54 / 126.08 (d, C-9, *9*-(*E/Z*) bzw. C-11, *10*-(*E/Z*)), 134.37 / 135.03 / 135.30 / 136.98 (s, C-10), 173.98 / 174.04 / 174.21 (s, C-1), $C_{15}H_{26}O_2$ (238.37).

*(9E/Z)-10-Methyl-15-pentadec-9-enolide/(10E/Z)-10-Methyl-15-pentadec-10-enolide (**13d**).* Scale Amberlyst® 15 (0.20 g) and 0.39 mmol of **11e** in CH_2Cl_2 (5 mL), 4 d, yield 100%; two components were obtained by gas chromatography (130(0)-4-190(0)-1-220-10-270(30)): 21.00% (25.10) : 79.00% (25.35); ^{1}H NMR ($CDCl_3$, ppm) δ 1.08 - 1.17 / 1.23 - 1.46 (m, 12H, 4-H_2 - 7-H_2, 8-H_2, *9*-(*E/Z*), 12-H_2, *10*-(*E/Z*), 13-H_2), 1.55 - 1.66 (m, 3H, 10-CH_3), 1.96 - 2.11 (m, 8H, 3-, 14-H_2, 8-, 9-H_2, *10*-(*E/Z*), 11-, 12-H_2, *9*-(*E/Z*)), 2.30 / 2.31 / 2.34 / 2.35 (4dd,

J = 7.0 Hz, 7.1 Hz, 6.3 Hz or 6.2 Hz, 2H, 2-H_2), 4.07 / 4.08 / 4.13 / 4.15 (4dd, J = 5.7 Hz, 5.4 Hz, 6.8 Hz or 6.0 Hz, 2H, 15-H_2), 5.08 / 5.10 / 5.15 / 5.17 (4qt, J = 1.3 Hz and 7.4 Hz, 1.3 Hz and 7.4 Hz, 1.2 Hz and 7.6 Hz or 1.1 Hz and 8.8 Hz, 1H, 9-H, *9*-(*E/Z*), 11-H *10*-(*E/Z*)); ^{13}C NMR ($CDCl_3$, ppm) δ 15.15 / 15.88 (q, 10-Me), 22.79 - 29.33 (t, C-3 - C-8, C-12 - C-14), 31.03 / 31.37 / 38.96 / 39.48 (t, C-9, *10*-(*E/Z*) or C-11, *9*-(*E/Z*)), 33.92 / 34.48 / 34.61 / 35.26 (t, C-2), 64.08 / 64.19 / 64.25 / 64.78 (t, C-15), 125.20 / 125.32 / 125.68 / 125.96 (d, C-9, *9*-(*E/Z*) bzw. C-11, *10*-(*E/Z*)), 134.46 / 134.67 / 134.74 / 135.29 (s, C-10), 173.97 / 174.10 (s, C-1); $C_{16}H_{28}O_2$ (252.40).

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