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Selective Oxidation of Primary-Secondary Diols with Methyl Hypochlorite in Acid Buffered Medium

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Abstract: A convenient, low cost method was developed for the selective oxidation of secondary alcohols, leaving primary alcohol functions intact. Methyl hypochlorite, generated from chlorine or trichloroisocyanuric acid in methanol, is used as a 'positive chlorine' reagent in the presence of an appropriate buffer which is acidic enough to warrant good transfer of 'positive chlorine'. 1,9(*R*)-octadecanediol was converted to 1-hydroxy-9-octadecanone with 98% selectivity.

INTRODUCTION

In previous work we expressed our interest in the oxidation of methyl 9(*R*)-hydroxyoctadecanoate (**1**) and derivatives from *Dimorphotheca pluvialis* seed oil[1,2]. Reduction of **1** affords 1,9(*R*)-octadecanediol (**2**) as a primary-secondary diol. A challenge is the cheap and selective oxidation of the secondary hydroxyl group of **2**. Such oxidation gives the 1-hydroxy-9-octadecanone (**3**) as a very interesting building block for further synthesis. For instance, with a Grignard reaction at the ketone, branched-chain molecules can be synthesized. Branched-chain fatty acids, in general, have found many applications in industry due to their unusual physical properties[3]. The same selective conversion can be performed with the commercially available 1,12-octadecanediol (**4**) derived from castor oil.

Oxidation of alcohols is often accomplished conveniently by or via hypochlorites, where in the case of primary-secondary diols a selectivity of 1:7-20 is reached for the secondary hydroxyl group. In general, sodium hypochlorite in acetic acid solution is used for this purpose[4].

We obtained very good results, based on chlorine or trichloroisocyanuric acid (TCIA) in methanol in acid buffered medium. The hydroxyketone (**3**) can reliably be formed with a selectivity of 1:50-65. The improved selectivity is based on the use of the lowest convenient temperature and on the promotion of exchange of 'positive chlorine' between primary and secondary alcohol positions (including from relatively stable methyl hypochlorite).

RESULTS AND DISCUSSION

Reduction of methyl 9(*R*)-hydroxyoctadecanoate (**1**)[2] with lithium aluminum hydride in tetrahydrofuran afforded the 1,9(*R*)-octadecanediol (**2**) (yield > 93%). An optimized Oppenauer oxidation[1,2] of **2** with benzoquinone (3 mol/mol **2**) and aluminum *t*-butoxide (0.2 mol/mol **2**) gave 1-hydroxy-9-octadecanone (**3**) with a selectivity of 7:1 for the secondary alcohol function (96-99% conversion after 6-16h at 55°C with 20% of **2** in tetrahydrofuran). Another method[5] based on TCIA (1.36 eq/mol **2**) and pyridine in acetone (4-5% of **2**) also gave a 7:1 proportion (99.6% conversion in 20 minutes at 20°C).

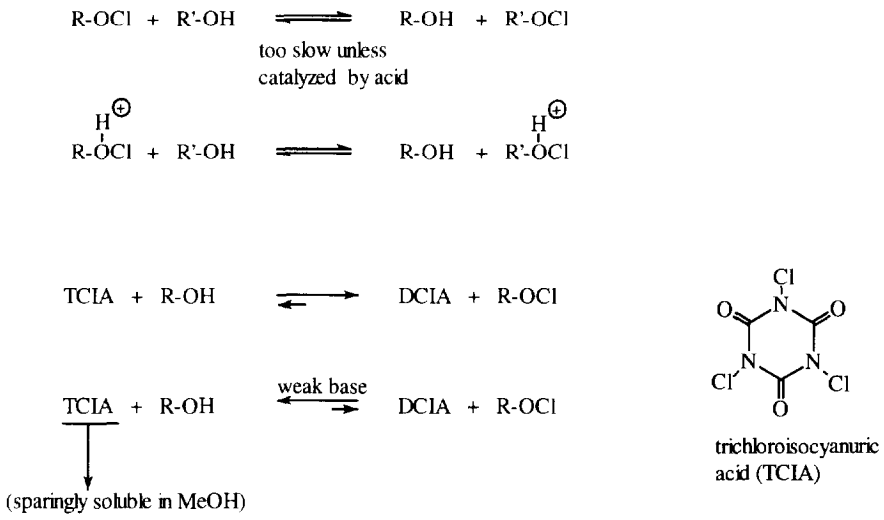
A 'positive chlorine' method, such as the method based on TCIA, appeared the most attractive as a starting point, because it is simple and allows further fine tuning of the selectivity, e.g. by lowering the reaction temperature. However, the most direct way to bring 'positive chlorine' in contact with alcohols is the introduction of chlorine gas in the solution. Methanol as the simplest alcohol can even be used as a solvent. In general, the principal reaction of scheme 1, can be proposed:

$$ROH + Cl_2 \rightleftharpoons RO(Cl)\text{-}H^{\oplus} + Cl^{\ominus} \rightleftharpoons ROCl + HCl$$

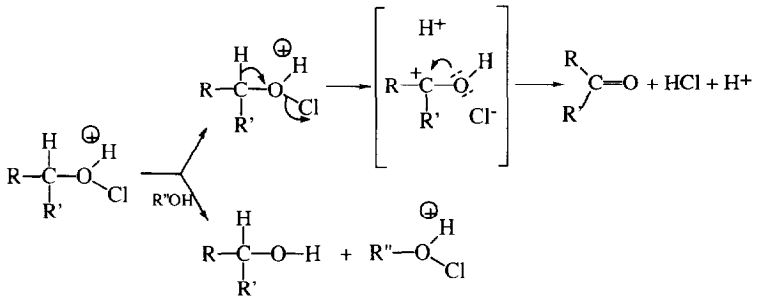
Scheme 1. Reversible Formation of Alkyl Hypochlorites

The alkyl hypochlorites are relatively unstable[6] towards decomposition to a carbonyl compound (oxidation) in the general sequence of stability: $CH_3OCl > RCH_2OCl >> R_2CHOCl$. The transfer of 'positive chlorine' from methyl hypochlorite, generated with chlorine in cold methanol in the presence of some excess of sodium bicarbonate, was studied first. Neutralization of hydrogen chloride will shift the equilibrium from the left to the right side. The presence of MeOCl can be detected and monitored by NMR spectroscopy: ^1H δ = 3.87 ppm, ^{13}C δ = 69.7 ppm. At room temperature, those signals disappear slowly and after several hours only the signals of methyl formate and methylal are left. When 2-octanol, as a model, was added to a fresh solution of methyl hypochlorite (at 5-15°C) a reaction was occasionally detectable by its exothermicity. With NMR spectroscopy, oxidation to 2-octanone was then measured. This oxidation started only when 2-octanol was added before essential decolorization of the yellow colour of chlorine. If the reaction does not start, apparently the chlorine is completely converted to the relatively stable methyl hypochlorite (see scheme 1). The reaction can be initiated by the addition of a few drops of conc. hydrogen chloride. So it is obvious, that for an effective transfer of 'positive chlorine' the methyl hypochlorite is not active enough by itself. A more active species is needed, such as a protonated form of the hypochlorite and/or chlorine itself (scheme 2).
The decomposition of an unstable alkyl hypochlorite (e.g. to a ketone) produces hydrogen chloride, promoting further reaction. However, an excess of hydrogen chloride is not permitted since the carbonyl derivatives will become enolized and further chlorinated, resulting in the formation of chloroketones. Therefore conditions

must be created where hydrogen chloride is suppressed, although a certain acidity is required to promote the protonated form of hypochlorite which is effective as a transmitter of 'positive chlorine'. In a mixture of alcohols an equilibration of hypochlorites can be expected. The least stable hypochlorite will decompose selectively to oxidized products without further chlorination (see scheme 3). Therefore, it is important to remove chloride ions while maintaining a sufficient acidity. This was accomplished with suitable buffer systems. The concomitant suppression of elemental chlorine also serves as a supplementary protection against chlorination of any enols, since the other chlorinating agents available in the medium are less reactive.



Scheme 2. Transfer of 'Positive Chlorine'



Scheme 3. Decomposition of Alkyl Hypochlorites

In practice two kinds of buffer systems were used: 1) in general, the most convenient way was to use a suspension of sodium bicarbonate that dissolved at a rate adjustable by its particle size and by the presence of some acetic acid; 2) in some cases, the acidity was better controlled with a dissolved buffer based on dichloro- or trichloroacetic acid and their salts.

Simple oxidation of 2-octanol with a reagent based on methyl hypochlorite (freshly formed from 80-85% excess of chlorine, methanol, sodium bicarbonate and sodium acetate, 20-30 min 7->25°C) gave 99% conversion to the ketone. Oxidation at a lower temperature (bath -14°C, 40% excess of chlorine) of an equimolecular mixture of 2-octanol and 1-hexanol afforded overnight 2-octanone with 99% yield and a selectivity of 28:1 with respect to oxidation of 1-hexanol to methyl hexanoate (3.5%) and a trace of the dimethyl acetal.

These procedures need adaptation in cases of rather poorly soluble substrates, like the alcohols and diols derived from long chain fatty acids, which are the focus of our interest. In the standard experiments the production of hydrogen chloride and its delayed neutralization with undissolved sodium bicarbonate maintains a relatively high level of acidity. However, this acidity is not sufficient to promote unwanted chlorination of the ketone if some soluble sodium acetate and acetic acid are present. Sodium acetate instead of bicarbonate produced slow (overnight) oxidation. In the case of **2** and of methyl 12-hydroxyoctadecanoate (**5**) the low solubility of the substrates requires an acidity of the reaction medium that is more fixed in the correct range. Thus the use of acid buffers based on dichloro- or trichloroacetic acid was needed for the diol (**2**), while the oxidation of the hydroxy ester (**5**) proceeded very well with a combination of dichloromethane and acetic acid as promoters of solubility resp. acidity (see Tables 1 and 2). The solvent systems used have the advantage of being applicable at quite low temperature. In this way the highest selectivity can be reached. The differences in stability of alkyl hypochlorites are exploited, under (acidic) equilibrating conditions, to effect preponderant oxidation of the alcohol that produces the least stable hypochlorite. Excess of chlorinating agent can suffer autodestruction or is easily quenched (bisulphite, 2-propanol). For the selective oxidation of the secondary function in primary-secondary diols the competition with an added primary alcohol (e.g. ethanol) makes a very careful adjustment of the oxidant unnecessary.

TCIA can be a rather inexpensive alternative for chlorine. NMR analysis showed that in a fresh solution of TCIA in methanol about one third of the available chlorine atoms was converted to methyl hypochlorite. Addition of 2-octanol did not result in its oxidation. When pyridine or a mixture of sodium acetate and acetic acid was subsequently added the TCIA precipitated almost completely (anion of DCIA recovers 'positive chlorine' from hypochlorite). These results show a special mechanism for the mobility of 'positive chlorine' for TCIA (see scheme 2). The problem of precipitation can be avoided by using a relatively strong acid buffer (trichloroacetic acid) and a high proportion of cosolvents (acetone, dichloromethane) which dissolve better the TCIA.

Table 1. Oxidation of 1,9(*R*)-octadecanediol (**2**) with 'Positive Chlorine' in Methanol[a]

Exp.	MeOH (ml)	ETOH (ml)	t (h)	T (°C)	$NaHCO_3$ (eq)	Cl_3CCOOH (eq)	Cl^+ (eq)	**2** (%)	**3** (%)	**6** (%)	**7** (%)	**8** (%)	selectivity (sec.:prim.)
1	40	-	0	8-9	3	1.7	1.5	99.9	-	-	-	-	-
			1					18.7	78.2	0.8	0.8	-	36:1
			3					4.5	91.8	0.7	1.6	0.3	28:1
			10					2.5	92.9	0.5	2.2	0.9	22:1
2	40	-	0	8-9	3	1.7	1.5	99.9	-	-	-	-	-
			2			+0.9		5.7	92.0	0.3	1.4	0.5	42:1
			5					3.8	92.7	0.4	1.5	0.7	29:1
3	40	5	0	8-9	4.5	3.9	2.25	99.9	-	-	-	-	-
			night					2.5	94.8	0.4	1.1	0.6	41:1
4	20	5	0	8-9	4.5	3.9	2.25	99.9	-	-	-	-	-
			1		+0.9		+0.45	9.4	88.6	0.4	1.0	0.2	49:1
			3					4.1	92.9	0.3	1.6	0.4	39:1
5	20	5	0	8-9	4.5	3.9	2.25	99.9	-	-	-	-	-
			1	-5	+1.8		+0.9	9.1	89.3	0.4	0.9	-	64:1
			4					4.7	**93.0**	0.3	1.5	-	**49:1**
6[a]	20	5	0	8-10	2.25	3.9	2.25	99.9	-	-	-	-	-
			3	0	+1.5		+1.5	49.2	50.0	0.2	0.4	-	83:1
			10	-5				4.8	**93.0**	0.2	1.3	-	**55:1**

3: 1-hydroxy-9-octadecanone. **6**: 9-oxo-octadecanal. **7**: methyl 9-oxo-octadecanoate. **8**: 1,1-dimethoxy-9-octadecanone.
[a] Experiments on 1g of **2**. Exp. 5: start 8-9°C (15 min) than cooling to -5°C. Exp. 6 start 8-10°C (15 min) than cooling to 0°C and after 3 hours further cooling to -5°C. Exp. 6 with TCIA other experiments with Cl_2.

Table 2. Oxidation of Methyl 12-Hydroxyoctadecanoate (**5**) with Chlorine in Methanol and Dichloromethane.

Exp.	t (h)	T (°C)	$NaHCO_3$ (mol/mol Cl_2)	NaOAc (mol/mol Cl_2)	HOAc (ml)	Cl_2 (eq)	**5** (%)	**9** (%)	**10** (%)
1[d]	0	4	1.1	1.1		1.5	99.9	-	-
	1.1						98.7	1.1	-
	2	10			+10		97.6	2.2	-
	4				+10		70.2	29.7	-
	8	15			+10		30.4	69.2	-
	restart[d]	10		+1.2	+10	+0.6			
	5						8.0	91.1	-
	night						3.7	95.9	-
2[b]	0	10	1.1	-	40	2.25	99.9	-	-
	0.3						**0.7**	**98.8**	-
3[c]	0	10	2.2	-	40	1.05	99.9	-	-
	0.45						10.4	87.5	1.8
	1.4						2.7	95.5	1.7
	2.35						**1.3**	**96.9**	**1.8**

9: methyl 12-oxo-octadecanoate. **10**: methyl 11 and 13-chloro-12-oxo-ocadecanoate.
[a] **5** was added as a fine powder to the methanolic suspension. [b] **5** was added as a 30% solution in CH_2Cl_2. [c] chlorine was added as a solution in CH_2Cl_2 to the reaction mixture in CH_2Cl_2. [d] after overnight period.

Exp. 6 of table 1 shows optimized results for a case where chlorine was replaced with TCIA, showing that their use can be interchanged when appropriate. On a 10g scale of the oxidation of **2** with chlorine

(selectivity 52:1), 1-hydroxy-9-octadecanone (**3**) was isolated in 74% yield in two crops of 99.5 resp. 98% purity (from ethanol). The oxidation of 1,12-octadecanediol (**4**) with TCIA on a 5-10 g scale was frequently incomplete, until acetone (20%) was used as a cosolvent to improve the solubilities.

In summary, it can be stated that 'positive chlorine' is not easily transferred from a neutral alkyl hypochlorite to a neutral alcohol oxygen. Either the alkyl hypochlorite must be activated by protonation before it can transfer 'positive chlorine' to an alcohol, or the electron density of the alcohol oxygen must be increased by (partial or complete) deprotonation by a base. The latter reaction path is suggested to proceed during the selective oxidation of an 1,2 diol by *t*BuOCl in the presence of pyridine[7] (unusual higher acidity of the 1,2-diol system). In principle transfer of 'positive chlorine' can also be achieved using the equilibrium between partially dechlorinated derivatives of TCIA and alkyl hypochlorites in the presence of weak bases. This unexploited possibility might be useful if the presence of acid is to be avoided.

CONCLUSIONS

The transfer of 'positive chlorine' of alkyl hypochlorites is promoted by acid. Methods are described that allow excellent oxidation of secondary alcohols like 2-octanol and methyl 12-hydroxyoctadecanoate (**5**) and very selective oxidation of 1,9- and 1,12-octadecanediol with methyl hypochlorite in the presence of a suitable buffer. It is shown that TCIA can replace chlorine as a source of 'positive chlorine'.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectrometry, GC and GC-MS analysis and the measurement of the onset temperature of melting and specific rotation $[\alpha]_D$ (of **2**) were performed as previously described [1,2]. The compounds **2**, **3**, **4** and 1-hydroxy-12-octadecanone were also silylated for GC-MS analysis. FT-IR spectroscopy - DRIFT spectra were recorded on a BioRad FTS-60A spectrometer. Samples were prepared by mixing 5-10% (w/w) material with KBr. The Kubelka Munk-transformed spectra were recorded with a resolution of 4 cm^{-1} against a KBr background. Microanalyses were carried out on a Carlo Erba CHN-elemental analyzer 1106.

Oxidation of 2-octanol.

To a cold solution (ice-water bath) of 8.8 g of chlorine (124 mmol) in 100 ml of MeOH, 11.4 g of sodium bicarbonate (135.8 mmol) and 11.1 g of sodium acetate (135.8 mmol) was added as a fine powder. A solution of 8.7 g of 2-octanol (66.7 mmol) in 9 ml of MeOH was added dropwise in a few minutes. After addition of 4 drops of conc. HCl, the reaction temperature increased from 7 to 26°C in 20 minutes with formation of carbon dioxide and then fell to 10°C after 15 minutes. The suspension was transferrred to a separatory funnel, containing 8.6 g of sodium disulfite (45 mmol) and 7.6 g of sodium bicarbonate (90 mmol) in 500 ml of ice-water. The aqueous fraction was extracted with CH_2Cl_2 (50 + 20 ml) and the combined

organic layers were concentrated to about 1/4 for NMR analysis (99% conversion).

To a suspension of 15.3 g of chlorine (215 mmol), 19.9 g of sodium bicarbonate (237 mmol) and 19.4 g of sodium acetate (237 mmol) in 130 ml of MeOH an equimolar mixture (150.8 mmol) of 19.6 g of 2-octanol and 15.4 g of 1-hexanol in 35 ml of MeOH was added over 40 minutes at a bath temperature of -14°C. After stirring over night the suspension was worked up and analyzed by NMR (99% conversion of 2-octanol, 3.5% of 1-hexanol).

1,9(R)-octadecanediol (2)

Methyl 9(*R*)-hydroxyoctadecanoate (**1**) was isolated from *Dimorphotheca pluvialis* seed oil[2]. Reduction with $LiAlH_4$ in THF afforded the 1,9(*R*) octadecanediol (**2**) (yield > 93%). $[\alpha]_D^{20}$ -0.10° (c5, methanol), $[\alpha]_D^{20}$ +0.13° (c5, ethanol). Onset temperature of melting: 78.5±0.2°C (purity 99.9% GC), m.p. lit.[8] (rac.) 76.1-76.9°C. ^{1}H NMR: δ = 0.882 (H-18, t, $J_{18,17}$ = 6.8 Hz), 1.3 (H-3, 4, 5, 6, 7, 11, 12, 13, 14, 15, 16, 17, m), 1.43 (H-8, 10, m), 1.490 (1-OH, 9-OH), 1.567 (H-2, m, $J_{2,1}$ = 6.6 Hz, $J_{2,3}$ = 7 Hz), 3.58 (H-9, m), 3.640 (H-1, t, $J_{1,2}$ = 6.6 Hz). ^{13}C NMR: δ = 14.13 (C-18), 22.71 (C-17), 25.65 (C-7)[a], 25.69 (C-11)[a], 25.73 (C-3), 29.6 (C-4, 5, 6, 12, 13, 14, 15)[b], 31.93 (C-16), 32.80 (C-2), 37.48 (C-8)[c], 37.54 (C-10)[c], 63.05 (C-1), 72.04 (C-9). [a,c] values may have to be interchanged, [b] these signals could not be assigned unambiguously. M/e (%): 81 (100), 83 (97), 123 (86), 55 (72), 69 (63), 67 (56), 97 (44), 57 (37), 82 (34), 159 (32), 43 (31), 51 (30). FT-IR (cm^{-1}): 3346, 3259, 1133, 1114, 1074, 1040, 1021, 859, 728, 719. See also ref. 9 for a mixture of 1,9- and 1,10-octadecanediol.

1,9-bis(trimethylsiloxy)octadecane: 229 (100), 73 (79), 303 (54), 75 (43), 83 (27), 230 (23), 103 (20), 129 (20), 147 (20), 149 (19), 81 (19), 69 (18).

1-hydroxy-9-octadecanone (3)

To 10 g of **2** (34.97 mmol, 99.9% purity GC) dissolved in a mixture of 200 ml of MeOH and 50 ml of EtOH, 13.2 g of $NaHCO_3$ (157.1 mmol) and 22.5 g of trichloroacetic acid (137.7 mmol) was added. This suspension was cooled to 11°C and 41 ml of a cold solution of chlorine (5.6 g, 79 mmol) in MeOH was added in 5 minutes. The yellow suspension was stirred for 15 minutes (-> 8°C) and then cooled to -5°C. After 1 hour, an extra 16 ml (31.5 mmol) of cold chlorine solution and 5.3 g of $NaHCO_3$ (62.8 mmol) was added. The reaction mixture was stirred for another 3 hours, quenched with 10.7 g (56.5 mmol) of sodium disulfite and transferred to a separatory funnel containing 2.2% aq. $NaHCO_3$ (1l). The aqueous fraction was extracted with CH_2Cl_2 (100 ml and 2 x 50 ml) and the combined organic layers were dried ($MgSO_4$). The solvent was evaporated yielding 9.8 g of residue (GC analysis: 94.2 % of **3**, 3.8% of **2**, 0.3% of **6**, 1.3% of **7**, 0.1% of **8** and 0.1% of ethyl 9-oxo-octadecanoate, selectivity 52:1). The crude product was recrystallized from 20 ml of EtOH to give 6.88 g of crystals (98.4% of **3**) at rt. Recrystallization from EtOH (16 ml) yielded 5.6 g of crystals with a purity of 99.5%. The combined mother liquors gave on further processing a second crop of

97.9% pure crystals (1.82 g) leaving a mother liquor (2.13 g) with 71.9 % of **3**, 16.4 % of **2** and 7.9 % of **7**. Combined yield of crop 1 and 2: 74%.

1-hydroxy-9-octadecanone (**3**): onset temperature of melting: 70.4±0.1°C (purity 99.5% GC). ^{1}H NMR: δ = 0.877 (H-18, t, $J_{18,17}$ = 6.8 Hz), 1.3 (H-3, 4, 5, 6, 7, 11, 12, 13, 14, 15 ,16, 17, m), 1.555 (H-2, m, $J_{2,1}$ = 6.6 Hz, $J_{2,3}$ = 7 Hz), 2.004 (1-OH), 2.381 (H-8, 10, t, $J_{8,7}$ =7.4 Hz, $J_{10,11}$ = 7.4 Hz), 3.618 (H-1, t, $J_{1,2}$ = 6.6 Hz). ^{13}C NMR: δ = 14.11 (C-18), 22.69 (C-17), 23.86 (C-7)[a], 23.93 (C-11)[a], 25.73 (C-3), 29.3 (C-4, 5, 6, 12, 13, 14, 15)[b], 31.90 (C-16), 32.77 (C-2), 42.79 (C-8)[c], 42.86 (C-10)[c], 62.86 (C-1), 211.82 (C-9). [a,c] values may have to be interchanged, [b] these signals could not be assigned unambiguously. M/e (%): 71 (100), 55 (73), 69 (72), 43 (69), 58 (62), 41 (47), 96 (44), 57 (40), 85 (36), 155 (34), 170 (34), 81 (30). FT-IR (cm^{-1}): 3291, 1703, 1419, 1069. Anal. Calc. for $C_{18}H_{36}O_2$: C, 75.99; H, 12.76. Found C, 75.73; H, 13.23.

1-trimethylsiloxy-9-octadecanone: M/e (%): 341 (100), 75 (91), 73 (87), 97 (83), 55 (63), 69 (57), 43 (54), 71 (51), 95 (50), 81 (45), 111 (43), 130 (36).

1,1-dimethoxy-9-octadecanone (**8**): M/e (%): 75 (100), 71 (76), 94 (26), 95 (25), 155 (17), 43 (16), 55 (15), 41 (14), 57 (12), 84 (12), 85 (12), 67 (11).

9-oxo-octadecanal (**6**): M/e (%): 71 (100), 155 (74), 57 (69), 43 (69), 109 (69), 110 (65), 58 (61), 55 (61), 94 (47), 67 (46), 127 (45), 85 (44).

Methyl 12-hydroxyoctadecanoate (**5**) (98.6%, GC) was prepared by esterification of 12-hydroxystearic acid (Fluka, 70-80%), followed by crystallization from hexane.

*Methyl 12-oxo-octadecanoate (**9**)*

Method A:. At 10°C, $NaHCO_3$ (2.6 g, 31.3 mmol) and acetic acid (20 ml) were added to a solution of chlorine (2.02 g, 28.45 mmol) in MeOH (25 ml). A concentrated solution of **5** (3.97 g, 12.64 mmol, 98.6%) in CH_2Cl_2 (8 ml) was added dropwise over a period of 10 minutes. The suspension was stirred further for 50 minutes and then transferred to a separatory funnel, containing a solution of aqueous sodium disulfite. The aqueous layer was extracted with CH_2Cl_2 (60+20 ml). The CH_2Cl_2 layers were washed with aq. $NaHCO_3$ solution and dried ($MgSO_4$). The solvent was evaporated to give crude **9** of 97.8% purity.

Method B: At 10°C and in the dark, a solution of chlorine (2.77 g, 39 mmol) in CH_2Cl_2 (25 ml) was added dropwise to a suspension of **5** (11.67 g, 37.15 mmol, 98.6%) and $NaHCO_3$ (7.21 g, 85.8 mmol) in CH_2Cl_2 (23 ml) and acetic acid (20 ml). The addition was done over a period of 25 minutes by monitoring the temperature (max 11.1°C). The suspension was further stirred for 4.5 hours and worked up. The crude product contained 96.5% of **9**, 0.3% of **5** and 1.7% of **10**.

The crude products were crystallised to give pure **9**. A crude product (25.9 g) with 95.9% of **9**, 1.8% of **5** and 0.8% of **10**, gave by crystallisation from hexane (50 ml, 65°C to r.t.) a first crop of 18.8 g, with 98.2% of **9** and 1.5% of **5**, and a second crop of 4.1 g, with 96.0% of **9** and 2.2% of **5**. Recrystallisation of

the combined crops from a MeOH (20 ml) - hexane (40 ml) mixture (60°C to 3°C) yielded 17.45 g of 99.6% pure **9**.

*1,12-octadecanediol (**4**)*

This compound **4** is available in 80% purity from Henkel KGaA (loxanol®) and can be purified by selective extraction[10] with petrolcum ether. It was also prepared from methyl 12-hydroxyoctadecanoate (**5**) with $LiAlH_4$ or less conveniently with $NaBH_4$ in *t*BuOH and MeOH[11]. Onset temperature of melting: 78.1±0.1°C (purity 99.9% GC), m.p. lit.[8] (rac) 75.7-76.4°C. ^{1}H NMR: δ = 0.885 (H-18, t, $J_{18,17}$ = 6.8 Hz), 1.28 (H-3, 4, 5, 6, 7, 8, 9, 10, 14, 15, 16, 17, m), 1.43 (H-11, 13, m), 1.57 (H-2, 1-OH, 9-OH, m, $J_{2,1}$ = 6.6 Hz), 3.58 (H-12, m), 3.629 (H-1, t, $J_{1,2}$ = 6.6 Hz). ^{13}C NMR: δ = 14.10 (C-18), 22.66 (C-17), 25.66 (C-10)[a], 25.68 (C-14)[a], 25.78 (C-3), 29.6 (C-4, 5, 6, 7, 8, 9, 15)[b], 31.89 (C-16), 32.84 (C-2), 37.53 (C-11)[c], 37.54 (C-13)[c], 63.05 (C-1), 72.06 (C-12).[a,c] values may have to be interchanged, [b] these signals could not be assigned unambiguously. M/e (%): 55 (100), 97 (94), 95 (60), 69 (53), 83 (52), 109 (46), 81 (40), 96 (33), 57 (29), 43 (27), 67 (27), 82 (25). FT-IR (cm^{-1}): 3301, 3202, 1131, 1077 (sh), 1067, 1041, 1005, 852, 720.

1,12-bis(trimethylsiloxy)octadecane: M/e (%): 187 (100), 73 (68), 75 (41), 97 (25), 83 (24), 95 (23), 103 (22), 69 (21), 55 (20), 149 (17), 109 (17), 147 (16). See also ref 12.

1-hydroxy-12-octadecanone (use of TCIA)

5 g of **4** (17.43 mmol, 99.7 % purity GC), 3.3 g of $NaHCO_3$ (39.3 mmol) and 11.25 g of trichloroacetic acid (68.8 mmol) were dissolved in a mixture of 75 ml of MeOH, 25 ml of EtOH and 25 ml of acetone. At 10°C, 3.4 g of TCIA (circa 13 mmol for 90% act.[13]) was added and the solution was first stirred for 15 minutes and further cooled to 0°C. After stirring for 1 hour the suspension was quenched with sodium disulfite and filtered. The residue was washed with CH_2Cl_2 and the combined filtrate transferred to a separatory funnel containing aq. $NaHCO_3$. GC-analysis of the CH_2Cl_2 layer showed: 2.9% of **4**, 93.3% of 1-hydroxy-12-octadecanone, 2.4% of **9**, 0.4% of 12-oxo-octadecanal, 0.4% of ethyl 12-oxo-octadecanoate, 0.3% of 1,1-dimethoxy-12-octadecanone and 0.2% of 13 and 11 chloro-1-hydroxy-12-octadecanone (selectivity 27:1). This mixture was further purified by crystallisation as described for 1-hydroxy-9-octadecanone (**3**).

1-hydroxy-12-octadecanone. Onset temperature of melting: 70.4±0.1°C (purity 99.3% GC). ^{1}H NMR: δ = 0.879 (H-18, t, $J_{18,17}$ = 6.6 Hz), 1.27 (H-3, 4, 5, 6, 7, 8, 9, 10, 14, 15, 16, 17, m), 1.558 (H-2, m, $J_{2,1}$ = 6.6 Hz, $J_{2,3}$ = 7 Hz), 1.752 (1-OH), 2.380 (H-11, 13, t, $J_{11,10}$ =7.4 Hz, $J_{13,14}$ = 7.4 Hz). 3.627 (H-1, t, $J_{1,2}$ = 6.6 Hz). ^{13}C NMR: δ = 14.00 (C-18), 22.48 (C-17), 23.86 (C-10)[a], 23.88 (C-14)[a], 25.74 (C-3), 29.4 (C-4, 5, 6, 7, 8, 9, 15)[b], 31.60 (C-16), 32.79 (C-2), 42.80 (C-11, 13), 62.96 (C-1), 211.78 (C-12). [a] values may have to be interchanged, [b] these signals could not be assigned unambiguously. M/e (%): 58 (100), 55 (98), 71 (89), 113 (87), 43 (78), 85 (66), 59 (63), 69 (59), 129 (54), 128 (50), 83 (38), 97 (35). FT-IR (cm^{-1}): 3296, 1700, 1419, 1068. Anal. Calc. for $C_{18}H_{36}O_2$: C, 75.99; H, 12.76. Found C, 75.71; H, 13.18.

1-trimethylsiloxy-12-octadecanone: M/e (%): 75 (100), 73 (83), 83 (57), 130 (53), 69 (52), 55 (50), 341 (47), 91 (43), 43 (42), 97 (40), 113 (32), 103 (31).

1,1-dimethoxy-12-octadecanone: M/e (%): 75 (100), 71 (51), 43 (21), 95 (16), 113 (14), 81 (13), 55 (13), 85 (11), 58 (10), 41 (9), 69 (9), 67 (9).

12-oxo-octadecanal: M/e (%): 58 (100), 43 (97), 113 (85), 55 (81), 71 (78), 85 (66), 59 (62), 95 (60), 69 (48), 57 (44), 81 (40), 86 (29).

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