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α-Cycloalkyl-substituted ω-keto-dicarboxylic acids as lipid regulating agents

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Abstract—A series of cycloalkyl-substituted oxo-alkanedicarboxylic acids have been prepared by the TosMIC methodology departing from haloalkyl-substituted cycloalkylcarboxylic esters. cyclopropyl derivatives showed IC_{50} activity in the 0.3–1.0 μM range on the de novo incorporation of radiolabeled acetate into lipids in primary cultures of rat hepatocytes, and they showed lipid-regulating properties when tested in vivo in female obese Zucker fatty rats.

1. Introduction

We recently identified several functionalized long chain-hydrocarbon derivatives as possessing lipid-regulating activity in an animal model of diabetic dyslipidemia (i.e., obese female Zucker fatty rat).[1,2] This pharmacologic activity consisted of plasma triglyceride reduction, decreases in non-HDL-cholesterol (non-HDL-C), and increases in HDL-cholesterol (HDL-C). Unlike HMG-CoA reductase inhibitors (statins), these compounds inhibit both fatty acid and cholesterol syntheses in cultured liver cells at micromolar concentrations, and also increase fatty acid oxidation. In this way they reduce the availability of lipids for triglyceride synthesis and very low density lipoprotein (VLDL) assembly. Our earlier work was focused on the design of long hydrocarbon chain ether- and keto-diols and -diacids with *gem*-dialkyl and alkyl/aryl substitution to the terminal acid or methylenehydroxy functions.[1,2] The most active compounds reported displayed symmetrical structures with four to five methylene groups separating central ether and ketone functionalities and the *gem*-dimethyl or methyl/aryl substituents. Furthermore, biological activity was found to be greatest in both in vivo and in vitro assays for the tetramethyl substituted keto-diacids and -diols, and the least active were shown to be the bis-(aryl–methyl) derivatives.[2] In vitro activities in these series were found to be at the micromolar level. We now report the synthesis of a series of cycloalkyl-substituted oxo-alkanedicarboxylic acids, some of which possess submicromolar activity in vitro and exhibit more marked alterations in plasma lipids/lipoproteins.

2. Biological data

Compounds were tested for inhibition of lipid synthesis in primary cultures of rat hepatocytes using the radiolabeled precursor [1-^{14}C] acetate. Interestingly, the compounds with symmetrical terminating cyclopentyl substitutions varied by 50-fold in terms of in vitro activity, the only difference being chain length on either side of the central ketone (Table 1). Thus, **7g** (4,4-ketone) was a weak inhibitor of lipid synthesis (113 μM) compared to **7m** (2 μM, 5,5-ketone). The symmetrical 4,4-cyclobutyl derivative was also a weak inhibitor (**7f**). The symmetrical cyclopropyl compounds were potent regardless of chain length (**7d**, **7l**), but not the corresponding ester compounds (e.g., *t*-butyl ester **6d**). In fact, these two compounds (**7d**,**l**) were submicromolar inhibitors of lipid synthesis in liver cells. The unsymmetrical cyclopropyl compounds (**7c**,**k**) retained potent

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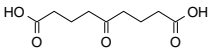
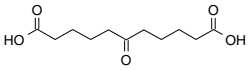
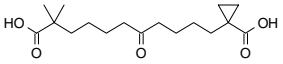
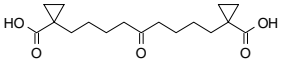
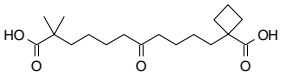
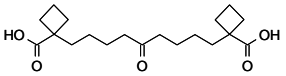
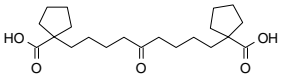
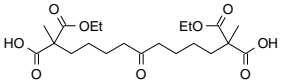
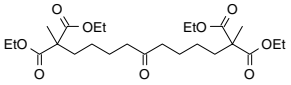
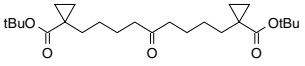
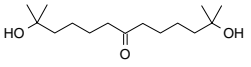
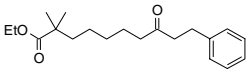
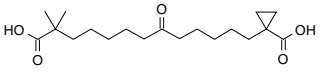
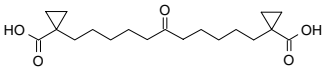
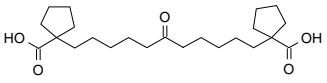
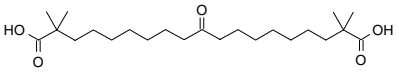
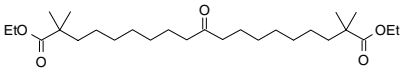
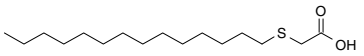
Table 1. Effect of cycloalkyl compounds on lipid synthesis in primary rat hepatocytes

Compound	IC_{50} (μM)	95% Confidence interval		r^{2a}	Structure
		Lower	Upper		
7a	NA[b]			0.39	
7b	NA[b]			0.00	
7c	0.6	0.3	0.9	0.98	
7d	0.3	0.1	5	0.98	
7e	6	5	8	0.95	
7f	121	11	1268	0.89	
7g	113	7	1794	0.95	
7h	NA[b]			0.32	
6h	NA[b]			0.00	
6d	35	26	48	0.99	
7i	NA[b]			0.32	
6j	40	17	92	0.98	
7k	1	0.7	1.4	0.94	
7l	0.5	0.4	0.7	0.99	
7m	2	2	2	0.99	
7n	10	4	21	0.97	
6n	13	4	46	0.93	
3-Thia fatty acid	43	28	64	0.99	

[a] r^2 is the goodness of fit of the data to the non-linear sigmoidal model.
[b] No IC_{50} is derived using the non-linear regression model. We have defined these compounds as 'not active'.

in vitro activity. Alkyl compounds with various bulky substituents other than cycloalkyl (**7i**, **6j**, **7n**, **6n**) and linear dicarboxylic acids **7a** and **7b** were all weak inhibitors (i.e., $\geqslant 10\,\mu M$).

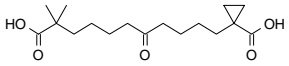
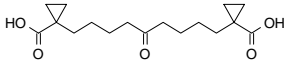
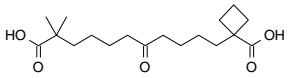
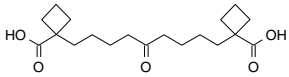
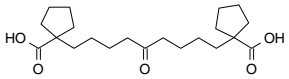
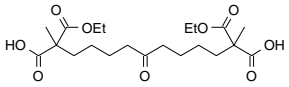
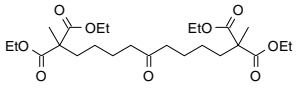
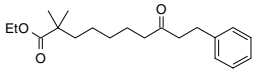
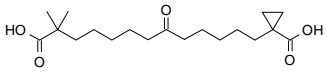
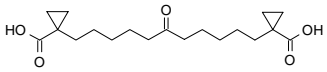
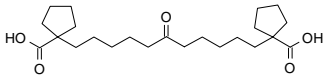
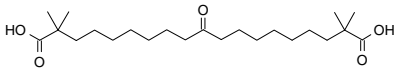
To prove that the decreased incorporation of acetate into lipids is not due to a general toxic effect, we used a standard method for assessing compound effects on plasma membrane integrity, which directly correlates

with cell viability in primary rat hepatocytes. Briefly, release of the cytosolic enzyme lactate dehydrogenase (LDH) into the media compartment due to plasma membrane damage is assessed by measuring LDH enzyme activity.[3] Compound-dependent increases in the activity in the media are compared to vehicle-treated cultures. We tested all the active compounds, and the test results indicate that toxicity does not correlate with inhibition of [1-^{14}C] acetate incorporation into lipids. The compounds that caused increased LDH leakage did so only at the 300 μM treatment concentration and the increases were minimal at 20–40% above control values (data not shown). A direct toxic agent tested in this assay will produce 400–500% increases in LDH activity in the media.

Compounds with the greatest in vitro activity, <1 μM (**7c**,**d**,**l**) also produced the greatest elevations in HDL-C in vivo (Table 2). Cyclopropyl substitutions, whether symmetrical (**7l**) or unsymmetrical (**7k**), provided potent and long-lasting reductions in non-HDL-C (>90%), but only for 5,5-carbon length hydrocarbons. Compounds that were poorly active in vitro provided weak lipid-regulating activity in vivo (**7h**, **6h**, **6j**). Not all compounds that lowered plasma triglycerides elevated HDL-C (**7d** vs **7f**). With the exception of compound **7d**, we generally see a good predictable relation between observations in vitro and in vivo for reduction of non-HDL-C. In regard to triglyceride lowering, we observed that all compounds were active. The symmetrical 5,5-cyclopropyl compound (**7l**) shows the best correlation of in vivo and in vitro activities, and the highest HDL-C elevation, which is in agreement with earlier findings in the *gem*-dimethyl series, and shows enhanced properties compared to its congeners in both the ether and ketone series.[2]

The mechanism of action is clearly a key component of drug discovery. As we performed our structure optimization in vivo, multiple MoAs may be responsible for the biological activity in such a complex biological system as the whole animal. This phenomenon is not unusual in compounds presenting HDL-elevating properties in various animal models.[4a] We have performed multiple experiments on this class of compounds (with terminal

Table 2. Effect of cycloalkyl compounds in female Obese Zucker rats

Compound	Serum variables (percent change from pre-treatment)[a]								Structure
	Dose (mg/kg)	No animals	Non-HDL-cholesterol		HDL-cholesterol		TG		
			1 wk	2 wk	1 wk	2 wk	1 wk	2 wk	
7c	100	3	−84	−20	104	248	−93	−64	
7d	100	3	22	63	180	260	−51	−28	
7e	100	4	4	28	30	60	−54	−51	
7f	100	4	−32	−40	−1	10	−58	−59	
7g	100	4	−68	−67	36	40	−67	−70	
7h	100	4	47	26	11	19	14	13	
6h	100	4	62	85	5	−1	48	40	
6j	30	4	−11	57	54	95	−5	44	
7k	100	4	−90	−99	43	84	−93	−98	
7l	100	4	−92	−83	136	171	−95	−94	
7m	100	4	−54	−32	12	27	−63	−48	
7n	100	3	−80	−45	44	86	−85	−64	

[a] 100% represents a 2-fold increase from pre-treatment value.

cycloalkyl and dimethyl substitution) and have determined that a major mode of action (within minutes of dosing) is inhibition of fatty acid synthesis (FAS) at the acetylCoA-carboxylase (ACC) step via an allosteric mechanism. The inhibition of fatty acid synthesis produced by such a MoA is consistent with the lowering of serum triglycerides. We have also shown that these compounds rapidly block de novo cholesterol synthesis at a step between acetoacetyl-CoA formation and HMG-CoA.[4b] Thus, they are dual inhibitors of lipid synthesis.

3. Biological methods

3.1. In vitro measurement of lipid synthesis in isolated hepatocytes

Compounds were tested for inhibition of lipid synthesis in primary cultures of rat hepatocytes. Male Sprague–Dawley rats were anesthetized with intraperitoneal injection of sodium pentobarbital (80 mg/kg). Rat hepatocytes were isolated essentially as described by the method of Seglen.[5] Hepatocytes were suspended in Dulbecco's Modified Eagles Medium containing 25 mM D-glucose, 14 mM HEPES, 5 mM L-glutamine, 5 mM leucine, 5 mM alanine, 10 mM lactate, 1 mM pyruvate, 0.2% bovine serum albumin, 17.4 mM non-essential amino acids, 20% fetal bovine serum, 100 nM insulin, and 20 μg/mL gentamycin and plated at a density of 1.5×10^5 cells/cm^2 on collagen-coated 96-well plates. Four hours after plating, media was replaced with the same media without serum. Cells were grown overnight to allow formation of monolayer cultures. Lipid synthesis incubation conditions were initially assessed to ensure the linearity of [1-^{14}C]-acetate incorporation into hepatocyte lipids for up to 4 h. Hepatocyte lipid synthesis inhibitory activity was assessed during incubations in the presence of 0.25 μCi [1-^{14}C]-acetate/well (final radiospecific activity in assay is 1 Ci/mol) and 0, 1, 3, 10, 30, 100, or 300 μM of compounds for 4 h. At the end of the 4 h incubation period, medium was discarded and cells were washed twice with ice-cold phosphate buffered saline and stored frozen prior to analysis. To determine total lipid synthesis, 170 μL of MicroScint-E® and 50 μL water was added to each well to extract and partition the lipid soluble products to the upper organic phase containing the scintillant. Lipid radioactivity was assessed by scintillation spectroscopy in a Packard TopCount NXT. Lipid synthesis rates were used to determine the IC_{50}s of the compounds.

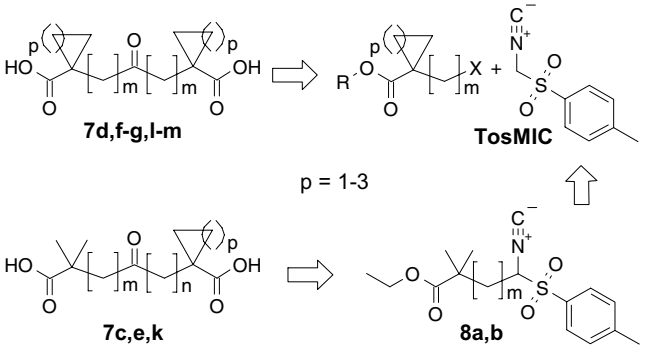
3.2. In vivo effects on lipid variables in female obese Zucker fatty rats

Ten- to twelve-week old (400–500 g) female Zucker fatty rats Crl: (Zuc)-faBR were obtained from Charles River Laboratories. Animals were acclimated to the laboratory environment for 7 days. During the acclimation and study period, animals were housed by group in shoebox polycarbonate cages on Cellu-Dri bedding. The temperature and humidity in the animals' quarters (68–78 °F; 30–75% RH) were monitored and the airflow in the room was sufficient to provide several exchanges per hour with 100% fresh filtered air. An automatic timing device provided an alternating 12 h cycle of light and dark. Rats received pelleted Purina Laboratory Rodent Chow® (5001) prior to and during the drug intervention period except for a 6 h phase prior to blood sampling. Fresh water was supplied ad libitum via an automatic watering system. Compounds were dissolved, suspended by mixing in a dosing vehicle consisting of 20% ethanol and 80% polyethylene glycol-200 [v/v]. Dose volume of vehicle or vehicle plus each compound was set at 0.25% of body weight in order to deliver the appropriate dose. Doses were administered daily by oral gavage, approximately between 8 and 10 AM. Regarding blood sampling, animals were fasted for 6 h prior to all blood collections. Prior to and after 7 days of dosing, a 1.0–2.0 mL sample of blood was collected by administering O_2/CO_2 anesthesia and bleeding from the orbital venous plexus. Following 14 days of dosing, blood was collected by cardiac puncture after euthanasia with CO_2. All blood samples were processed for separation of serum and stored at −80 °C until analysis. Commercially available kits were used to determine serum triglycerides (Roche Diagnostic Corporation, Kit no 148899 or Boehringer Mannheim, Kit no 1488872), total cholesterol (Roche Diagnostic Corporation, Kit no 450061), non-esterified fatty acids (Wako Chemicals, Kit no 994-75409), and β-hydroxybutyrate (Wako Chemicals, Kit no 417-73501 or Sigma Kit no 310-0) on a Hitachi 912 Automatic Analyzer (Roche Diagnostic Corporation). In some instances, an in-house cholesterol reagent was used to determine total serum cholesterol levels. Serum lipoprotein cholesterol levels were determined by lipoprotein profile analysis. Lipoprotein profiles were analyzed using gel-filtration chromatography on a Superose 6HR (1 × 30 cm) column equipped with on-line detection of total cholesterol as described by Kieft et al.[6] The total cholesterol content of each lipoprotein was calculated by multiplying the independent values determined for serum total cholesterol by the percent area of each lipoprotein in the profile.

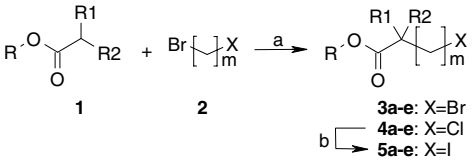
4. Chemistry

A series of long hydrocarbon chain keto-diacids (**7a**–**h**, **7k**–**n**)[7] was prepared. Characteristic for all of these molecules is the central ketone moiety connected via two linear carbon spacers to the terminating acids, which differ in their pattern of α-substitution. The key step in the syntheses of most of these ketones is the alkylation of the formaldehyde synthon: tosylmethyl isocyanide (TosMIC)[8] with a properly functionalized halo-ester (Scheme 1). Keto-diol **7i** was included in this study as well.

The halo-esters were prepared via alkylation of commercially available or known esters (**1**) with a dihaloalkane (**2**) of proper length (Scheme 2, Table 3). It was planned to use the ethyl ester analogues of **1** as starting material, but since it is known that ethyl cyclopropylcarboxylate is prone to self-condensate on treatment with various



Scheme 1.



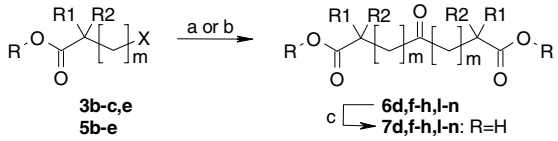
Scheme 2. Reagents and condition: (a) LDA, THF, −60 °C to rt; (b) NaI, 2-butanone, Δ.

Table 3. Synthesis of halo-esters **3a**–**e**, **4a**–**e**, and **5a**–**e**

Compound	*m*	R	R1	R2	X	Yield (%)
3a	4	Et	Me	Me	Br	[a]
3b	4	*t*Bu	cyclopropyl		Br	34[b]
3c	4	Et	CO_2Et	Me	Br	[c]
3d	5	Et	Me	Me	Br	[d]
3e	7	Et	Me	Me	Br	45
4a	4	*t*Bu	cyclopropyl		Cl	52
4b	4	Et	cyclobutyl		Cl	86
4c	4	Et	cyclopentyl		Cl	86
4d	5	*t*Bu	cyclopropyl		Cl	73
4e	5	Et	cyclopentyl		Cl	90
5a	4	*t*Bu	cyclopropyl		I	94[b]
5b	4	Et	cyclobutyl		I	99
5c	4	Et	cyclopentyl		I	94[b]
5d	5	*t*Bu	cyclopropyl		I	99
5e	5	Et	cyclopentyl		I	93[b]

[a] See: Ref. 18.
[b] Purity >90%.
[c] See: Ref. 20.
[d] See: Ref. 1.

bases,[9] the corresponding *t*-butyl analogue, of which a couple of successful alkylations are reported,[10] was prepared. At first, the bromo-esters **3a**–**e** were prepared via treatment of **1** with LDA and a large excess of a dibromoalkane (**2**, X = Br). However, due to substantial amount of dialkylation products, a more selective alkylating agent: bromo-chloroalkane (**2**, X = Cl) was used. As another advantage, it turned out that the crude product (**4**) was easier to separate from excess of **2** (X = Cl) via fractional distillation, when compared to crude **3** and **2** (X = Br). Compound **3d** was prepared as described earlier.[1] Where the chloro-ester derivatives (**4a**–**e**) were converted to the corresponding iodides (**5a**–**e**) prior to their reaction with TosMIC, bromo-esters



Scheme 3. Symmetrical ketones. Reagents and conditions: (a) **6d**,**g**,**h**,**m**,**n**: Method A:[11] (1) NaH, TosMIC, Bu_4NI, DMSO, rt, (2) HCl (concd), CH_2Cl_2, rt; (b) **6f**,**l**: Method B:[11] (1) KO*t*Bu, TosMIC, DMAc, 0 °C–rt, (2) HCl (concd), CH_2Cl_2, rt; (c) **6d**,**l**: Method E:[11] HCO_2H, rt, **6f**,**g**,**m**,**n**: Method D:[11] LiOH, EtOH/H_2O, Δ, **6h**: KOH, EtOH/H_2O, rt.

(**3a**–**e**) were treated with a catalytic amount of Bu_4NI to form the corresponding iodo compounds in situ.

Initially, for the alkylation of TosMIC, Method A[11] (TosMIC, NaH, **3**, Bu_4NI in DMSO) was applied (Scheme 3). The intermediate dialkylated TosMIC derivatives were treated with concd HCl in CH_2Cl_2 to provide keto-diesters **6d**,**h**,**n** in moderate to good yield (Table 4). For the preparation of symmetrical keto-diacids **6f**,**g**,**l**,**m** a modified procedure (Method B:[11] KO*t*Bu, **5** in *N*,*N*-dimethylacetamide (DMAc)) was used (Table 4). On applying this method, side product formation was significantly suppressed.

A set of mono-alkylated TosMIC derivatives (**8a**,**b**) was desired for the preparation of unsymmetrical ketones **6c**,**e**,**j**,**k** (Scheme 4). As such intermediates could only be produced in low yield via Method A, more selective conditions (K_2CO_3, DMAc) were applied, providing **8a**,**b** in good yield. Subsequent treatment of **8a**,**b** as reported for Method C[11] (KO*t*Bu, **5**, DMAc) afforded the unsymmetrical ketones **6c**,**e**,**k** (Scheme 4, Table 4). Unsymmetrical ketone **6j** was prepared, starting from **8b** and 2-bromoethylbenzene, via method A (Scheme 4, Table 4).

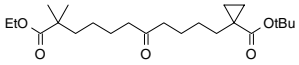
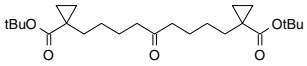
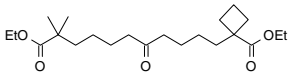
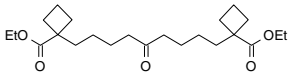
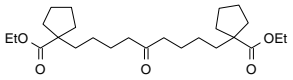
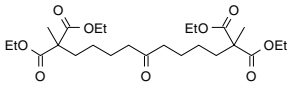
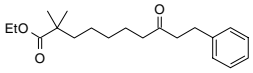
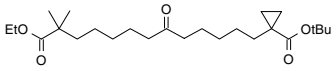
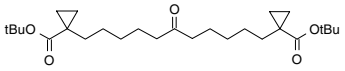
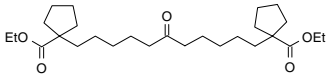
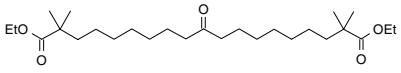
The target keto-diacids (**7**) were prepared from the corresponding ester analogues (**6**) by saponification of the appropriate ethyl esters, treatment of *t*-butyl esters with HCO_2H, or a combination of the two (Schemes 3 and 4 Table 4).

Further, the known compounds **7a**[12] and **7b**[13] were prepared as depicted in Scheme 5 and 6, respectively. Subsequent treatment of **7b** with trimethyl orthoformate under acidic conditions provided the symmetrical acetal-diester **15**, which on treatment with MeMgCl and acidic workup afforded keto-diol **7i** in good yield (Scheme 6).[14]

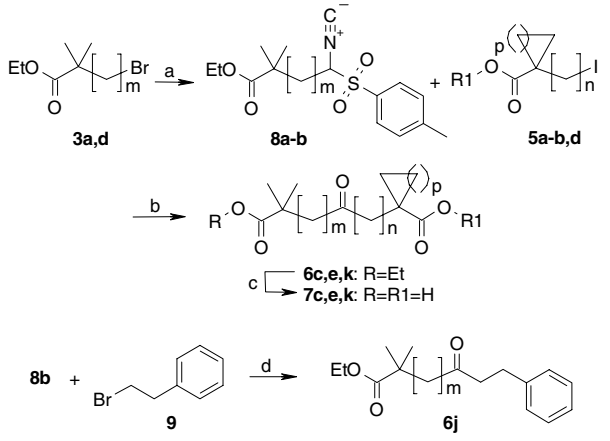
5. Conclusion

In summary, we have identified micromolar inhibitors in vitro of both fatty acid and cholesterol biosynthesis among a group of cyclopropyl derivatives. The most potent compounds **7c**,**d**,**l** markedly elevate HDL-cholesterol, and also significantly reduce plasma triglycerides and non-HDL-cholesterol levels (**7c**,**l**) in a rodent model of dyslipidemia. Amongst them, compound **7l** is the most promising lipid regulating agent, producing the

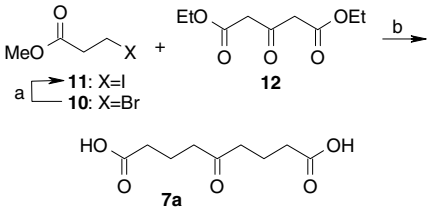
Table 4. Syntheses of keto-esters (**6**) and corresponding keto-acids (**7**) using TosMIC chemistry

Compound **6**				Compound **7**				
6	Structure	Method[a]	Yield (%)	**6**→**7**		Elemental analysis found (calculated)		
				Method[a]	Yield (%)	C	H	Mp (°C)
c		C	43[b]	F	80[b]	65.06 (65.36)	9.02 (9.03)	49–52
d		A	49	E	99	65.40 (65.78)	8.37 (8.44)	132–134
e		C	75[b]	D	76	66.26 (66.23)	9.37 (9.26)	53–55
f		B	82	D	56	67.19 (67.43)	8.97 (8.93)	69–70
g		B	83[b]	D	99[b]	68.78 (68.82)	9.47 (9.35)	104–106
h		A	71	[c]	81	—	—	—
j		A	68	—	—	—	—	—
k		C	57[b]	F	84	66.86 (67.03)	9.50 (9.47)	65–66
l		B	46[b]	E	99	67.20 (67.43)	9.05 (8.93)	122–123
m		B	87[b]	D	91	70.37 (70.02)	9.72 (9.71)	78–85
n		A	57	D	74	69.41 (69.31)	10.73 (10.62)	74–77

[a] See Ref. 11.
[b] Purity >90%.
[c] KOH, EtOH, rt.



Scheme 4. Asymmetrical ketones. Reagents and conditions: (a) K_2CO_3, Bu_4NI, DMF, rt, **8a** ($m = 4$) 67%, **8b** ($m = 5$) 61%; (b) Method C:[11] (1) KO*t*Bu, TosMIC, DMAc, 0 °C–rt, (2) HCl (concd), CH_2Cl_2, rt; (c) **6c**,**k**: Method F:[11] (1) HCO_2H, rt, (2) NaOH, EtOH/H_2O, Δ, **6e**: Method D:[11] LiOH, EtOH/H_2O, Δ; (d) Method A:[11] (1) NaH, TosMIC, Bu_4NI, DMSO, rt, (2) HCl (concd), CH_2Cl_2, rt, 68%.



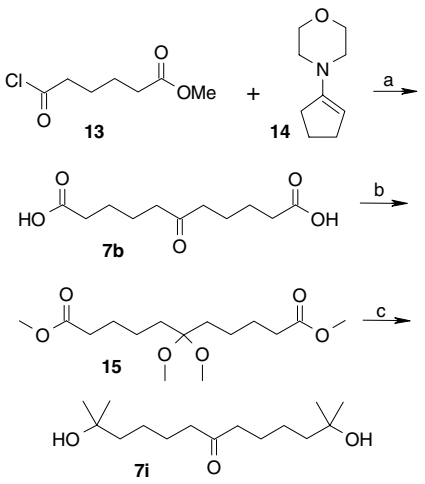
Scheme 5. Reagents and conditions: (a) NaI, acetone, rt, 95%; (b) (1) NaOEt, 90 °C, (2) HCl (concd), H_2O, Δ, 44%.

most favorable lipoprotein profile of the compounds tested in this report.

6. Experimental section

6.1. General

All reagents and solvents were purchased from commercial suppliers and used without prior treatment unless



Scheme 6. Reagents and conditions: (a) (1) Et_3N, Δ, (2) 1 M HCl, Δ, (3) 17 M KOH, 100 °C, 69%; (b) $CH(OMe)_3$, TsOH, MeOH, Δ, 85%; (c) (1) MeMgCl, Et_2O/THF, 0 °C–rt, (2) 1 M HCl, rt, 93%.

stated otherwise. All product solutions were dried over Na_2SO_4 prior to evaporation of the solvent under reduced pressure by using a rotary evaporator. Column chromatography was performed with silica gel (Fluka: silica gel 60 with particle size 70–230 mesh or Acros: silica gel with particle size 0.060–0.200 mm). Reactions were monitored by GC or TLC on Macherey-Nagel Polygram® SIL G/UV_{254} plastic sheets. Compounds on TLC were visualized by UV detection and/or dipping in *p*-anisaldehyde/H_2SO_4/EtOH = 1:1:19 or basic $KMnO_4$ and subsequent heating. GC analysis was performed on a Hewlett Packard 5890A gas chromatograph with a flame ionization detector and an Alltech EC1 fused silica capillary column, 30 m × 0.32 mm internal diameter, film thickness 0.25 μm and N_2 as carried gas. GC peak areas were integrated electronically with a Hewlett Packard HP3396 seriesII integrator. LC/MS analysis was performed on a Shimadzu QP8000α with DAD (210–370 ηm)/MSD (100–600 D) detection and an Alltech Prefail C18, 50 × 4.6 mm internal diameter, film thickness 3 μm column with 10 mM HCO_2H in CH_3CN/10 mM HCO_2H in H_2O as elutes or a Agilent 1100-SL with ELSD/DAD (220–320 ηm)/MSD (100–800 D) detection and a Zorbax® SB-C18, 150 mm × 4.6 mm internal diameter, film thickness 3.5 μm column with CH_3CN/10 mM HCO_2H in H_2O as elutes or a Zorbax® Extend-C18, 150 mm × 4.6 mm internal diameter, film thickness 3.5 μm column with CH_3CN/10 mM NH_3 in H_2O as elutes, flow = 1 mL/min and column temperature = 35 °C. All ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer in $CDCl_3$ unless otherwise stated. Chemical shifts are reported in parts per million (δ) relative to Me_4Si. HRMS data were obtained with a VG Micromass VG7070E, Finnigan MAT95Q or Finnigan MAT900S spectrometer. Elemental analysis were carried out on a Carlo Erba Instruments CHNSO EA 1108 element analyzer. Melting points were measured on a Büchi Melting Point B-540 and are uncorrected. All prepared compounds were >95% pure unless otherwise stated.

6.1.1. *t*-Butyl 1-(4-bromobutyl)-cyclopropanecarboxylate (3b). Under a N_2 atmosphere at −60 °C, a solution of *t*-butyl cyclopropanecarboxylate[15] (80.05 g, 0.507 mol) and 1,4-dibromobutane (219.3 g, 1.01 mol) in dry THF (800 mL) was added drop wise to a solution of LDA (2 M in THF/heptane/ethylbenzene, 380 mL, 0.76 mol) in 1.5 h. Stirring was continued for 5 h, during which the reaction mixture was allowed to slowly reach rt. After that, the reaction mixture was poured into saturated aqueous NH_4Cl (1 L). The organic layer was separated and concentrated in vacuo to a smaller volume. The aqueous layer was extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with saturated aqueous NH_4Cl (2 × 400 mL) and brine (400 mL) and dried. The remaining residue was purified by fractional distillation under reduced pressure to give **3b** (51.4 g, 94% pure by GC, 34%) as a slightly yellow oil. Bp: T = 93–96 °C (p = 0.075–0.087 Torr). ^1H NMR: δ 3.40 (t, J = 6.8 Hz, 2H), 1.85 (quintet, J = 7.1 Hz, 2H), 1.65–1.46 (m, 4H), 1.43 (s, 9H), 1.12 (q, J = 3.5 Hz, 2H), 0.60 (q, J = 3.5 Hz, 2H). ^{13}C NMR: δ 174.0, 79.8, 33.6, 33.2, 32.8, 27.9 (3×), 26.3, 23.9, 15.1 (2×). HRMS calcd for $C_{12}H_{21}BrO_2$ (MH^+): 277.0803, found: 277.0807.

6.1.2. Ethyl 2,2-dimethyl-9-bromononanoate (3e). Under a N_2 atmosphere at 0 °C, LDA (2 M in THF/heptane/ethylbenzene, 13.0 mL, 26.0 mmol) was added drop wise to a mixture of ethyl *iso*-butyrate (3.5 mL, 25.9 mmol) and 1,7-dibromoheptane (9.84 g, 38.2 mmol) in dry THF (50 mL) in 1.5 h, while keeping the temperature below 5 °C. After 3 h, the mixture was poured into ice-cold saturated aqueous NH_4Cl (150 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with aqueous HCl (1 M, 100 mL), saturated aqueous $NaHCO_3$ (100 mL), and brine (100 mL) and dried. The remaining residue was purified by column chromatography (heptane/EtOAc = 40:1) twice to give **3e** (3.42 g, 45%) as a colorless liquid. ^1H NMR: δ 4.11 (q, J = 7.2 Hz, 2H), 3.40 (t, J = 6.9 Hz, 2H), 1.85 (quintet, J = 6.9 Hz, 2H), 1.52–1.47 (m, 2H), 1.45–1.36 (m, 2H), 1.35–1.20 (m, 6H), 1.24 (t, J = 7.2 Hz, 3H), 1.15 (s, 6H). ^{13}C NMR: δ 177.8, 60.0, 42.0, 40.5, 33.7, 32.7, 29.7, 28.5, 28.0, 25.0 (2×), 24.7, 14.1. HRMS calcd for $C_{13}H_{25}BrO_2$ (M^+): 292.1038, found: 292.1034.

6.1.3. *t*-Butyl 1-(4-chlorobutyl)-1-cyclopropanecarboxylate (4a). Compound **4a** was prepared, likewise the procedure described for **3b**, starting from *t*-butyl cyclopropanecarboxylate[15] (12.5 g, 88 mmol), 1-bromo-4-chlorobutane (13.7 mL, 117 mmol), and LDA (prepared from BuLi (2.5 M in hexanes, 37 mL, 92.5 mmol) and iPr_2NH (12.3 mL, 88 mmol, distilled from NaOH)) to give, after purification by fractional distillation under reduced pressure, **4a** (10.73 g 52%) as a colorless oil. Bp: T = 57–61 °C (p = 0.001 mbar). ^1H NMR: δ 3.52 (t, J = 6.6 Hz, 2H), 1.76 (quintet, J = 6.8 Hz, 2H), 1.64–1.54 (m, 2H), 1.51–1.46 (m, 2H), 1.42 (s, 9H), 1.12 (dd, J = 6.6, 3.9 Hz, 2H), 0.60 (dd, J = 6.6, 3.9 Hz, 2H). ^{13}C NMR: δ 173.9, 80.0, 45.1, 33.6, 32.9, 28.2 (3×), 25.3, 24.2, 15.4 (2×). HRMS calcd for $C_{12}H_{22}ClO_2$ (MH^+): 233.1308, found: 233.1308.

6.1.4. Ethyl 1-(4-chlorobutyl)-1-cyclobutanecarboxylate (4b). Compound **4b** was prepared, likewise the procedure described for **4d**, starting from LDA (prepared from BuLi (2.5 M in hexanes, 52.8 mL, 132 mmol) and iPr$_2$NH (18.52 mL, 132 mmol, distilled from NaOH)), ethyl 1-cyclobutanecarboxylate[16] (14.05 g, 110 mmol, the resultant mixture was allowed to warm to 0 °C and cooled again to −60 °C) and 1-bromo-4-chlorobutane (19.1 mL, 165 mmol) to give, after purification by fractional distillation under reduced pressure, **4b** (20.53 g, 86%) as a thin, colorless oil. Bp: T = 64–71 °C (p = 0.001 Torr). ^{1}H NMR: δ 4.13 (q, J = 7.1 Hz, 2H), 3.51 (t, J = 6.8 Hz, 2H), 2.50–2.32 (m, 2H), 1.96–1.70 (m, 8H), 1.40–1.20 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H). ^{13}C NMR: δ 176.6, 60.3, 47.6, 44.8, 37.3, 32.8, 30.1 (2×), 22.4, 15.8, 14.4. HRMS calcd for $C_{11}H_{20}(^{37}Cl)O_2$ (MH^+): 221.1122, found: 221.1116.

6.1.5. Ethyl 1-(4-chlorobutyl)-1-cyclopentanecarboxylate (4c). Compound **4c** was prepared, likewise the procedure described for **4d**, starting from LDA (prepared from BuLi (2.5 M in hexanes, 46.0 mL, 115 mmol) and iPr$_2$NH (16.0 mL, 114 mmol, distilled from NaOH)), ethyl 1-cyclopentanecarboxylate[17] (13.05 g, 95% pure by ^{1}H NMR, 87.2 mmol), and 1-bromo-4-chlorobutane (20.0 mL, 173 mmol, after 1 h, the resultant mixture was allowed to warm to rt and stirred for 21 h) to give, after purification by fractional distillation under reduced pressure, **4c** (17.44 g, 86%) as a slightly yellow thin oil. Bp: T = 85–87 °C (p = 0.008 Torr). ^{1}H NMR: δ 4.11 (q, J = 7.0 Hz, 2H), 3.50 (t, J = 6.8 Hz, 2H), 2.15–2.07 (m, 2H), 1.74 (quintet, J = 7.1 Hz, 2H), 1.64–1.59 (m, 6H), 1.49–1.32 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 177.1, 60.2, 53.9, 44.7, 38.4, 36.1 (2×), 33.0, 25.0 (2×), 23.4, 14.4. HRMS calcd for $C_{12}H_{22}(^{35}Cl)O_2$ (MH^+): 233.1308, found: 233.1310.

6.1.6. t-Butyl 1-(5-chloropentyl)-1-cyclopropanecarboxylate (4d). Under an Ar atmosphere at 0 °C, BuLi (2.5 M in hexanes, 80 mL, 0.20 mol) was added drop wise to a solution of iPr$_2$NH (27.2 mL, 194 mmol, distilled from NaOH) in dry THF (200 mL) in 30 min. The reaction mixture was stirred for 30 min, cooled to −70 °C and then, t-butyl cyclopropanecarboxylate[15] (25.0 g, 176 mmol) was added drop wise in 30 min. The resultant mixture was allowed to warm up to −35 °C, cooled again to −70 °C, and then 1-bromo-5-chloropentane (36 mL, 50.7 g, 273 mmol) was added drop wise in 15 min. The reaction mixture was allowed to reach −5 °C, stirred for 3 h, poured into a mixture of ice (100 mL), H_2O (100 mL), brine (200 mL), and aqueous HCl (2 M, 200 mL) and extracted with Et_2O (2 × 300 mL). The combined organic layers were washed with a mixture of brine and saturated aqueous $NaHCO_3$ (10:1, 300 mL) and dried. The remaining oil was purified by fractional distillation under reduced pressure to give **4d** (31.5 g, 73%) as a colorless liquid. Bp: T = 67–74 °C (p = 0.001 mbar). ^{1}H NMR: 3.52 (t, J = 6.6 Hz, 2H), 1.77 (quintet, J = 6.8 Hz, 2H), 1.48–1.38 (m, 6H), 1.42 (s, 9H), 1.10 (dd, J = 6.5 Hz, 3.8 Hz, 2H), 0.59 (dd, J = 6.6, 3.9 Hz, 2H). ^{13}C NMR: δ 174.1, 79.9, 45.2, 34.2, 32.7, 28.2 (3×), 27.20, 27.17, 24.3, 15.4 (2×). HRMS calcd for $C_{13}H_{24}ClO_2$ (MH^+): 247.1465, found: 247.1465.

6.1.7. Ethyl 1-(5-chloropentyl)-1-cyclopentanecarboxylate (4e). Compound **4e** was prepared, likewise the procedure described for **4d**, starting from LDA (prepared from BuLi (2.5 M in hexanes, 48.0 mL, 120 mmol) and iPr$_2$NH (17.0 mL, 121 mmol, distilled from NaOH)), ethyl 1-cyclopentanecarboxylate[17] (15.12 g, 95% pure by ^{1}H NMR, 101 mmol, the resultant mixture was kept below −50 °C) and 1-bromo-5-chloropentane (25.53 g, 135 mmol, the resultant mixture was allowed to warm to rt and stirred for 18 h) to give, after purification by fractional distillation under reduced pressure, **4e** (22.34 g, 90%) as a thin, slightly yellow oil. Bp: T = 78–82 °C (p = 0.001 Torr). ^{1}H NMR: δ 4.11 (q, J = 7.1 Hz, 2H), 3.50 (t, J = 6.8 Hz, 2H), 2.14–2.06 (m, 2H), 1.75 (quintet, J = 7.1 Hz, 2H), 1.66–1.57 (m, 6H), 1.48–1.35 (m, 4H), 1.28–1.19 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 177.3, 60.2, 54.0, 45.1, 39.1, 36.2 (2×), 32.5, 27.4, 25.4, 25.1 (2×), 14.5. HRMS calcd for $C_{13}H_{24}(^{35}Cl)O_2$ (MH^+): 247.1465, found: 247.1465.

6.1.8. t-Butyl 1-(4-iodobutyl)-1-cyclopropanecarboxylate (5a). To a solution of **4a** (10.6 g, 45.7 mmol) in 2-butanone (50 mL) was added NaI (8.23 g, 54.5 mmol). The reaction mixture was stirred under reflux overnight, diluted with Et_2O (100 mL), washed with a mixture of H_2O (100 mL) and aqueous $Na_2S_2O_4$ (0.5 M, 10 mL) and brine (50 mL), and dried to give **5a** (14.8 g, 94% pure by GC, 94%) as a slightly yellow liquid. ^{1}H NMR: δ 3.18 (t, J = 6.9 Hz, 2H), 1.76 (quintet, J = 7.1 Hz, 2H), 1.62–1.45 (m, 4H), 1.43 (s, 9H), 1.12 (dd, J = 6.7 Hz, 3.8 Hz, 2H), 0.60 (dd, J = 6.6 Hz, 3.9 Hz, 2H). ^{13}C NMR: δ 173.9, 80.0, 33.8, 33.3, 28.9, 28.2 (3×), 24.2, 15.5 (2×), 7.2. HRMS calcd for $C_{12}H_{21}IO_2$ (M^+): 324.0587, found: 324.0587.

6.1.9. Ethyl 1-(4-iodobutyl)-1-cyclobutanecarboxylate (5b). Compound **5b** was prepared, likewise the procedure described for **5a**, starting from **4b** (21.21 g, 97.0 mmol) and NaI (19.07 g, 127 mmol) to give **5b** (29.91 g, 99%) as a slightly yellow oil. ^{1}H NMR: δ 4.14 (q, J = 7.1 Hz, 2H), 3.17 (t, J = 6.9 Hz, 2H), 2.49–2.32 (m, 2H), 1.98–1.69 (m, 8H), 1.37–1.19 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 176.5, 60.3, 47.5, 36.9, 33.7, 30.1 (2×), 26.0, 15.7, 14.5, 6.8. HRMS calcd for $C_{11}H_{20}IO_2$ (MH^+): 311.0508, found: 311.0511.

6.1.10. Ethyl 1-(5-iodopentyl)-1-cyclopentanecarboxylate (5c). Compound **4c** (15.11 g, 64.9 mmol) was treated, likewise the procedure described for **5a**, with NaI (12.53 g, 83.6 mmol and 2.12 g, 14.1 mmol after 17 h). The crude product was concentrated to ~35 mL, diluted with heptane and filtered through silica. The residue was eluted with a mixture of heptane/EtOAc = 3:1 (500 mL). The combined filtrate and washings were evaporated in vacuo to give **5c** (20.84 g, 95% pure by ^{1}H NMR, 94%) as a thin yellow oil. ^{1}H NMR: δ 4.12 (q, J = 7.0 Hz, 2H), 3.16 (t, J = 6.8 Hz, 2H), 2.15–2.05 (m, 2H), 1.79 (quintet, J = 7.1 Hz, 2H), 1.68–1.58 (m, 6H), 1.49–1.40 (m, 2H), 1.37–1.22 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H).

^{13}C NMR: δ 177.1, 60.3, 53.8, 38.0, 36.1 (2×), 33.9, 27.0, 25.0 (2×), 14.5, 6.8. HRMS calcd for $C_{12}H_{22}IO_2$ (MH^+): 325.0665, found: 325.0666.

6.1.11. *t*-Butyl 1-(5-iodopentyl)-1-cyclopropanecarboxylate (5d). Compound **5d** was prepared, likewise the procedure described for **5c**, starting from **4d** (31.5 g, 128 mmol) and added NaI (24.9 g, 166 mmol) to give **5d** (42.3 g, 99%) as a slightly yellow liquid. ^{1}H NMR: δ 3.18 (t, J = 7.1 Hz, 2H), 1.82 (quintet, J = 7.1 Hz, 2H), 1.48–1.33 (m, 6H), 1.42 (s, 9H), 1.10 (dd, J = 6.8 Hz, Hz, 2H), 0.58 (dd, J = 6.6, 3.9 Hz, 2H). ^{13}C NMR: δ 174.0, 79.9, 34.1, 33.6, 30.8, 28.2 (3×), 26.8, 24.3, 15.4 (2×), 7.4. HRMS calcd for $C_{13}H_{23}IO_2$ (M^+): 338.0743, found: 338.0743.

6.1.12. Ethyl 1-(5-iodopentyl)-1-cyclopentanecarboxylate (5e). Compound **5e** was prepared, likewise the procedure described for **5a**, starting from **4e** (21.26 g, 86.1 mmol), NaI (20.87 g, 139 mmol) and $NaHCO_3$ (0.10 g, 1.2 mmol) to give **5e** (28.74 g, 94% pure by GC, 93%) as a thin yellow oil. ^{1}H NMR: δ 4.11 (q, J = 7.1 Hz, 2H), 3.16 (t, J = 7.1 Hz, 2H), 2.14–2.06 (m, 2H), 1.80 (quintet, J = 7.1 Hz, 2H), 1.68–1.59 (m, 6H), 1.48–1.32 (m, 4H), 1.27–1.17 (m, 2H), 1.24 (t, J = 7.2 Hz, 3H). ^{13}C NMR: δ 177.3, 60.2, 54.0, 39.1, 36.1 (2×), 33.4, 31.0, 25.1 (2×), 25.0, 14.5, 7.2. HRMS calcd for $C_{14}H_{26}IO_2$ (MH^+): 339.0821, found: 339.0823.

6.1.13. {7-Ethoxy-6,6-dimethyl-1-[(4-methylphenyl)sulfonyl]-7-oxoheptyl}(methylidyne)ammonium (8a). To a mixture of K_2CO_3 (13.18 g, 95.6 mmol) and Bu_4NI (2.35 g, 6.36 mmol) in dry DMF (50 mL) was added a solution of **3a**[18] (24.00 g, 95.6 mmol) and TosMIC (12.41 g, 63.7 mmol) in dry DMF (50 mL) in 20 min under a N_2 atmosphere while stirring vigorously. After 4 d, H_2O (100 mL) was added drop wise while keeping the temperature below 25 °C by cooling with an ice-bath. The resultant mixture was extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 200 mL) and dried. The remaining residue was purified by column chromatography (silica, heptane/EtOAc = 6:1; a layer of $NaHCO_3$ was put on the base of the column) to give **8a** (15.68 g, 42.8 mmol, 67%) as a slightly yellow oil, which slowly solidified on standing. An analytical sample was obtained after recrystallization (0.43 g) from iPr$_2$O/heptane at ~4 °C to give **8a** (0.30 g) as a white solid. Mp: 38–39 °C. ^{1}H NMR: δ 7.84 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 7.8 Hz, 2H), 4.43 (dd, J = 3.3, 10.8 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 2.48 (s, 3H), 2.23–2.12 (m, 1H), 1.90–1.77 (m, 1H), 1.66–40 (m, 4H), 1.38–1.22 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 1.15 (s, 6H). ^{13}C NMR: δ 177.3, 164.6, 146.3, 131.0, 129.93 (2×), 129.87 (2×), 72.8, 60.4, 42.2, 40.2, 28.4, 26.0, 25.35, 25.30, 24.2, 22.0, 14.5. Anal. Calcd for $C_{19}H_{27}NO_4S$: C, 62.44; H, 7.45; N, 3.83, found: C, 62.57; H, 7.57; N, 3.96.

6.1.14. {8-Ethoxy-7,7-dimethyl-1-[(4-methylphenyl)sulfonyl]-8-oxooctyl}(methylidyne)ammonium (8b). Under a N_2 atmosphere, TosMIC (10.01 g, 51.3 mmol) and **3d**[1] (20.41 g, 77.0 mmol) were dissolved in dry DMF (100 mL) and Bu_4NI (1.89 g, 5.12 mmol) and K_2CO_3 (10.62 g, 76.8 mmol) were added while stirring vigorously. After 5 d, the reaction mixture was poured in an ice/H_2O mixture (500 mL) and extracted with Et_2O (1 × 200 mL, 2 × 100 mL). The combined organic layers were washed with brine (2 × 50 mL) and dried. The remaining residue was purified by column chromatography (silica, heptane/EtOAc = 3:1) to give in order of elution **3d** (5.67 g, 90% pure by GC), an impure batch of **8b** (0.94 g), and pure **8b** (11.83 g, 61%) as a colorless oil. ^{1}H NMR: δ 7.86 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 4.45 (dd, J = 10.9, 3.5 Hz, 1H), 4.11 (q, J = 7.2 Hz, 2H), 2.49 (s, 3H), 2.22–2.11 (m, 1H), 1.90–1.77 (m, 1H), 1.67–1.57 (m, 1H), 1.53–1.42 (m, 3H), 1.24 (t, J = 7.2 Hz, 3H), 1.39–1.20 (m, 4H), 1.15 (s, 6H). ^{13}C NMR: δ 177.8, 164.8, 146.5, 131.1, 130.1 (2×), 130.0 (2×), 72.8, 60.2, 42.0, 40.3, 29.0, 28.3, 25.12, 25.06 (2×), 24.5, 21.7, 14.2. HRMS calcd for $C_{20}H_{29}NNaO_4S$ (MNa^+): 402.1715, found: 402.1736.

6.2. General procedures for alkylation of TosMIC

6.2.1. Method A. *t*-Butyl 1-[9-[1-(*tert*-butoxycarbonyl)cyclopropyl]-5-oxononyl]-1-cyclopropanecarboxylate (6d). Under a N_2 atmosphere, NaH (60% (w/w) in mineral oil, 2.91 g, 72.8 mmol) was added portion wise to a solution of TosMIC (5.85 g, 30.0 mmol) and Bu_4NI (1.10 g, 2.98 mmol) in dry DMSO (100 mL) while stirring vigorously and cooling with a water bath. After 10 min, **3b** (16.56 g, 94% pure by GC, 56.2 mmol) was added drop wise in 20 min and stirring was continued for 1 h and 50 min. Then, H_2O (100 mL) was added drop wise and the resultant mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL) and dried. The remaining oil was purified by column chromatography (silica, heptane/EtOAc = 6:1) to give *t*-butyl 1-{9-[1-(*t*-butoxycarbonyl)cyclopropyl]-5-isocyano-5-[(4-methylphenyl)sulfonyl]nonyl}-1-cyclopropanecarboxylate (10.00 g) as a slightly yellow oil.

6.2.2. Acidic hydrolysis of alkylated TosMIC intermediate. The above mentioned oil (10.00 g) was dissolved in CH_2Cl_2 (200 mL) and concd aqueous HCl (4 mL) was added. After stirring vigorously for 1 h, H_2O (100 mL) was added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (100 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (3 × 100 mL) and dried. The remaining residue was purified by column chromatography (silica, heptane/EtOAc = 10:1) to give **6d** (5.80 g, 49%) as a colorless oil. ^{1}H NMR: δ 2.39 (t, J = 7.3 Hz, 4H), 1.63–1.38 (m, 30H), 1.10 (dd, J = 6.6, 3.9 Hz, 4H), 0.59 (dd, J = 6.7, 3.9 Hz, 4H). ^{13}C NMR: δ 211.1, 174.4 (2×), 79.9 (2×), 42.7 (2×), 33.9 (2×), 28.0 (6×), 27.4 (2×), 24.1 (2×), 24.0 (2×), 15.2 (4×). HRMS calcd for $C_{25}H_{43}O_5$ (MH^+): 423.3111, found: 423.3111.

6.2.3. Method B. Ethyl 1-9-[1-(ethoxycarbonyl)cyclobutyl]-5-oxononyl-1-cyclobutanecarboxylate (6f). Under a N_2 atmosphere at 0 °C, KO*t*Bu (8.61 g, 76.7 mmol) was added portion wise to a solution of **5b** (24.83 g, 80.1 mmol) and TosMIC (7.26 g, 36.4 mmol) in *N*,*N*-dimethylacetamide (DMAc, 150 mL). After 30 min, the

reaction mixture was allowed to warm to rt, stirred for 1.5 h, and diluted with DMAc (10 mL). Then, **5b** (2.01 g, 6.5 mmol) and KO*t*Bu (0.81 g, 7.2 mmol) were added followed by another portion of **5b** (1.00 g, 3.2 mmol) and KO*t*Bu (0.86 g, 7.7 mmol) after 1 h. After 1 h, the reaction mixture was poured into a mixture of Et_2O (700 mL) and aqueous NaCl (10%, 500 mL) and the layers were separated. The organic layer was washed with brine (1 × 500 mL, 1 × 300 mL) and dried. The remaining residue was purified by column chromatography (silica, heptane/EtOAc = 6:1) to give ethyl 1-9-[1-(ethoxycarbonyl)cyclobutyl]-5-isocyano-5-[(4-methylphenyl)sulfonyl]nonyl-1-cyclobutanecarboxylate (18.35 g) as a slightly yellow oil. Part of this oil (15.62 g, 27.9 mmol) was hydrolyzed with concd aqueous HCl (75 mL) according to the procedure described for **6d** to give, after purification by column chromatography (silica, heptane/EtOAc = 6:1), **6f** (9.99 g, 82%) as a slightly yellow liquid, after evaporation from CH_2Cl_2 (100 mL). ^{1}H NMR: δ 4.12 (q, J = 7.1 Hz, 4H), 2.44–2.32 (m, 8H), 1.93–1.79 (m, 8H), 1.77–1.72 (m, 4H), 1.55 (quintet, J = 7.5 Hz, 4H), 1.25 (t, J = 7.1 Hz, 6H), 1.21–1.10 (m, 4H). ^{13}C NMR: δ 210.2, 176.7 (2×), 60.2 (2×), 47.6 (2×), 42.6 (2×), 37.9 (2×), 30.1 (4×), 24.7 (2×), 24.1 (2×), 15.7 (2×), 14.4 (2×). HRMS calcd for $C_{23}H_{38}O_5$ (M^+): 394.2719, found: 394.2703.

6.2.4. Method C. Ethyl 13-[1-(*t*-butoxycarbonyl)cyclopropyl]-2,2-dimethyl-8-oxotridecanoate (6k). Under a N_2 atmosphere at 0 °C, a solution of **8b** (28.4 g, 75.0 mmol) in *N*,*N*-dimethylacetamide (DMAc, 125 mL) followed by a solution of **5d** (25.4 g, 75.0 mmol) in DMAc (125 mL) were added drop wise in 60 and 30 min, respectively, to a solution of KO*t*Bu (8.83 g, 79.0 mmol) in DMAc (250 mL). The mixture was allowed to reach rt and stirring was continued for 2 h. Then, the reaction mixture was quenched by the drop wise addition of H_2O (250 mL) while cooling with an ice-bath. The resultant mixture was extracted with Et_2O (3 × 250 mL) and the combined organic layers were washed with brine (2 × 250 mL) and dried to give a yellow oil (43.02 g). Part of this oil (42.50 g) was hydrolyzed with concd aqueous HCl (34 mL) according to the procedure described for **6d** to give, after purification by column chromatography (silica, heptane/EtOAc = 8:1), **6k** (19.0 g, 95% pure by ^{1}H NMR, 57%) as a slightly yellow oil. ^{1}H NMR: δ 4.09 (q, J = 7.2 Hz, 2H), 2.37 (t, J = 7.2 Hz, 2H), 2.36 (t, J = 7.2 Hz, 2H), 1.62–1.35 (m, 10H), 1.41 (s, 9H), 1.30–1.21 (m, 6H), 1.24 (t, J = 7.2 Hz, 3H), 1.14 (s, 6H), 1.09 (dd, J = 6.6, 3.9 Hz, 2H), 0.58 (dd, J = 6.3, 3.6 Hz, 2H). ^{13}C NMR: δ 210.8, 177.6, 174.1, 79.8, 60.2, 42.9. 42.8, 42.2, 40.6, 34.1, 29.8, 29.6, 28.2 (3×), 27.6, 25.3 (2×), 24.9, 24.3, 23.9, 23.8, 15.3 (2×), 14.4. HRMS calcd for $C_{25}H_{45}O_5$ (MH^+): 425.3267, found: 425.3267.

6.2.5. Ethyl 11-[1-(*t*-butoxycarbonyl)cyclopropyl]-2,2-dimethyl-7-oxoundecanoate (6c). Compound **6c** was prepared likewise Method C starting from **8a** (20.5 g, 55.9 mmol), **5a** (18.11 g, 55.9 mmol)[19] and KO*t*Bu (6.57 g, 58.7 mmol) to give a yellow oil (31.79 g). Part of this oil (30.63 g) was treated with concd aqueous HCl (23 mL), as described for **6d**, to give, after purification by column chromatography (silica, heptane/EtOAc = 40:1), **6c** (9.83 g, >90% pure by NMR, 43%) as a colorless oil. ^{1}H NMR: δ 4.09 (q, J = 7.2 Hz, 2H), 2.38 (t, J = 7.2 Hz, 4H), 1.62–1.35 (m, 10H), 1.41 (s, 9H), 1.26–1.17 (m, 2H), 1.24 (t, J = 7.2 Hz, 3H), 1.14 (s, 6H), 1.09 (dd, J = 6.9, 4.2 Hz, 2H), 0.59 (dd, J = 6.3, 3.6 Hz, 2H). ^{13}C NMR: δ 210.5, 177.4, 174.0, 79.8, 60.2, 42.8, 42.6, 42.1, 40.5, 34.0, 28.2 (3×), 27.5, 25.2 (2×), 24.7, 24.3, 24.2, 24.1, 15.3 (2×), 14.4. HRMS calcd for $C_{23}H_{41}O_5$ (MH^+): 397.2954, found: 397.2956.

6.2.6. Ethyl 11-[1-(ethoxycarbonyl)cyclobutyl]-2,2-dimethyl-7-oxoundecanoate (6e). Compound **6e** was prepared likewise Method C starting from **8a** (11.01 g, 30.1 mmol), **5b** (10.28 g, 33.1 mmol), and KO*t*Bu (4.06 g, 36.2 mmol) to give, after purification by column chromatography (silica, heptane/EtOAc = 6:1; a layer of $NaHCO_3$ was put on the base of the column), ethyl 1-[11-ethoxy-5-isocyano-10,10-dimethyl-5-[(4-methylphenyl)sulfonyl]-11-oxoundecyl]-1-cyclobutanecarboxylate (14.11 g) as a colorless oil. Part of this oil (13.86 g, 25.3 mmol) was treated with concd aqueous HCl (50 mL), as described for **6d**, to give crude **6e**, which was stirred up in heptane (50 mL) and the resultant precipitate was filtered off and washed with heptane (3 × 50 mL). The combined filtrates were washed with aqueous NaOH (1 M, 2 × 50 mL) and brine (50 mL) and dried to give **6e** (9.44 g, >90% pure by ^{1}H NMR, 75%) as a slightly yellow oil. ^{1}H NMR: δ 4.12 (q, J = 7.1 Hz, 2H), 4.09 (q, J = 7.1 Hz, 2H), 2.50–2.29 (m, 2H), 2.37 (t, J = 7.4 Hz, 4H), 1.95–1.70 (m, 6H), 1.61–1.44 (m, 6H), 1.30–1.09 (m, 4H), 1.25 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.14 (s, 6H). ^{13}C NMR: δ 210.1, 177.3, 176.6, 60.1 (2×), 47.5, 42.57 (2×), 42.1, 40.4, 37.8, 30.0 (2×), 25.2 (2×), 24.7, 24.6, 24.2, 24.1, 15.7, 14.4, 14.3. HRMS calcd for $C_{22}H_{39}O_5$ (MH^+): 383.2797, found: 383.2798.

6.2.7. Ethyl 1-9-[1-(ethoxycarbonyl)cyclopentyl]-5-oxononyl-1-cyclopentanecarboxylate (6g). Compound **6g** was prepared likewise Method B starting from TosMIC (4.27 g, 21.4 mmol), **5c** (18.18 g, 95% pure by ^{1}H NMR, 53.3 mmol), and KO*t*Bu (5.14 g, 45.8 mmol and after 3 h, and another 1.5 h, respectively, 0.98 g, 8.7 mmol and 0.48, 4.3 mmol) at 0 °C to give, after purification by column chromatography and coevaporation from CH_2Cl_2 (silica, heptane/EtOAc = 6:1) ethyl 1-9-[1-(ethoxycarbonyl)cyclopentyl]-5-isocyano-5-[(4-methylphenyl)sulfonyl]nonyl-1-cyclopentanecarboxylate (11.63 g, containing ~11% (w/w) CH_2Cl_2, 82%) as a slightly yellow oil. Part of this oil (11.00 g, containing ~11% (w/w) CH_2Cl_2, 16.7 mmol) was dissolved in CH_2Cl_2 (150 mL) and treated with concd aqueous HCl (15 mL) for 4 h. Then, the reaction mixture was washed with brine (100 mL) and aqueous NaCl (10% (w/w), 100 mL). On addition of saturated aqueous $NaHCO_3$ (100 mL), CH_2Cl_2 (50 mL), and H_2O (100 mL) a milky suspension was formed, which was concentrated to approximately 75 mL. The resultant mixture was extracted with Et_2O (1 × 150 mL, 2 × 50 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (150 mL) and brine (100 mL and 50 mL) and dried to give **6g** (6.51 g, >90% pure by ^{1}H NMR, 83%)

as a slightly yellow oil. ^{1}H NMR: δ 4.10 (q, J = 7.1 Hz, 4H), 2.35 (t, J = 7.4 Hz, 4H), 2.14–2.03 (m, 4H), 1.66–1.38 (m, 20H), 1.27–1.13 (m, 4H), 1.24 (t, J = 7.2 Hz, 6H). ^{13}C NMR: δ 210.4, 177.3 (2×), 60.2 (2×), 54.0 (2×), 42.6 (2×), 39.1 (2×), 36.1 (4×), 25.8 (2×), 25.0 (4×), 24.3 (2×), 14.4 (2×). HRMS calcd for $C_{25}H_{42}O_5$ (M^+): 422.3032, found: 422.3035.

6.2.8. Tetraethyl 7-oxo-2,2,12,12-tridecanetetracarboxylate (6h). Compound **6h** was prepared likewise Method A starting from TosMIC (10.63 g, 53.4 mmol), Bu_4NI (3.99 g, 10.7 mmol), NaH (60% (w/w) in mineral oil, 4.27 g, 107 mmol), and **3c**[20] (30.0 g, 97.0 mmol) to give, after filtration through silica (elute: heptane/EtOAc = 2:1), 7-ethoxy-6-(ethoxycarbonyl)-1-[6-ethoxy-5-(ethoxycarbonyl)-5-methyl-6-oxohexyl]-6-methyl-1-[(4-methylphenyl)sulfonyl]-7-oxoheptyl(methylidyne)ammonium (27.9 g) as a yellow oil. Part of this oil (26.9 g) was treated with concd aqueous HCl (50 mL), as described for **6d**, to give, after purification by column chromatography (silica, heptane/EtOAc = 4:1), **6h** (16.21 g, 71%) as a yellow oil. ^{1}H NMR: δ 4.17 (q, J = 7.1 Hz, 8H), 2.40 (t, J = 7.4 Hz, 4H), 1.87–1.82 (m, 4H), 1.58 (quintet, J = 7.4 Hz, 4H), 1.38 (s, 6H), 1.28–1.18 (m, 4H), 1.25 (t, J = 7.2 Hz, 12H). ^{13}C NMR: δ 210.0, 172.0 (4×), 60.8 (4×), 53.3 (2×), 42.1 (2×), 35.0 (2×), 23.6 (4×), 19.5 (2×), 13.8 (4×). HRMS calcd for $C_{25}H_{43}O_9$ (MH^+): 487.2907, found: 487.2944.

6.2.9. Ethyl 2,2-dimethyl-8-oxo-10-phenyldecanoate (6j). Compound **6j** was prepared likewise Method A starting from **8b** (19.0 g, 50.1 mmol), Bu_4NI (1.85 g, 5.01 mmol), NaH (60% (w/w) in mineral oil, 2.40 g, 60.0 mmol), and (2-bromoethyl)benzene (8.24 mL, 60.1 mmol) to give an oil, which was treated with concd aqueous HCl (50 mL), as described for **6d**, to give, after purification by column chromatography (silica, heptane/EtOAc = 6:1), **6j** (10.84 g, 68%) as a yellow oil. ^{1}H NMR: δ 7.30–7.23 (m, 2H), 7.21–7.14 (m, 3H), 4.10 (q, J = 7.2 Hz, 2H), 2.89 (t, J = 7.5 Hz, 2H), 2.71 (t, J = 7.8 Hz, 2H), 2.36 (t, J = 7.4 Hz, 2H), 1.60–1.44 (m, 4H), 1.28–1.16 (m, 4H), 1.23 (t, J = 7.1 Hz, 3H), 1.14 (s, 6H). ^{13}C NMR: δ 210.0, 177.8, 141.1, 128.4 (2×), 128.2 (2×), 126.0, 60.0, 44.1, 42.8, 42.0, 40.4, 29.7, 29.5, 25.0 (2×), 24.6, 23.5, 14.2. HRMS calcd for $C_{20}H_{30}O_3$ (M^+): 318.2195, found: 318.2201.

6.2.10. *t*-Butyl 1-11-[1-(*t*-butoxycarbonyl)cyclopropyl]-6-oxoundecyl-1-cyclopropanecarboxylate (6l). Compound **6l** was prepared likewise Method B starting from TosMIC (13.84 g, 70.9 mmol), **5d** (24.0 g and 24.0 g after 1.5 h in 15 min, 71.0 and 71.0 mmol), and KO*t*Bu (8.35 g and 8.35 g after 1.5 h, 74.6 mmol and 74.6 mmol) to give, after dissolving the crude product in EtOAc (100 mL) and filtration through silica (elute: heptane/EtOAc = 1:1, 5 × 80 mL) an oil (42.38 g). This oil (42.38 g) was treated with concd aqueous HCl (11.4 mL), as described for **6d**, to give, after purification by column chromatography (silica, heptane/EtOAc = 12:1), **6l** (16.3 g, >90% pure by ^{1}H NMR, 46%) as a colorless oil. ^{1}H NMR: δ 2.37 (t, J = 7.4 Hz, 4H), 1.62–1.49 (quintet, J = 7.4 Hz, 4H), 1.48–1.36 (m, 8H), 1.41 (s, 18H), 1.33–1.20 (m, 4H) 1.09 (dd, J = 6.5, 3.8 Hz, 4H), 0.58 (dd, J = 6.6, 3.9 Hz, 4H). ^{13}C NMR: δ 210.9, 174.1 (2×), 79.8 (2×), 42.9 (2×), 34.1 (2×), 29.6 (2×), 28.2 (6×), 27.7 (2×), 24.4 (2×), 24.0 (2×), 15.4 (4×). HRMS calcd for $C_{27}H_{46}NaO_5$ (MNa^+): 473.3243, found: 473.3233.

6.2.11. Ethyl 1-{11-[1-(ethoxycarbonyl)cyclopentyl]-6-oxoundecyl}-1-cyclopentanecarboxylate (6m). Compound **6m** was prepared likewise Method B starting from TosMIC (5.38 g, 27.0 mmol), **5e** (24.21 g, 94% pure by GC, 67.3 mmol), and KO*t*Bu (6.40 g, 57.0 mmol and after 1 h, and another 1 h, respectively, 1.20 g, 10.7 mmol and 0.60, 5.3 mmol) at 0 °C to give, after purification by column chromatography (silica, heptane/EtOAc = 6:1) and coevaporation form CH_2Cl_2, ethyl 1-11-[1-(ethoxycarbonyl)cyclopentyl]-6-isocyano-6-[(4-methylphenyl)-sulfonyl]undecyl-1-cyclopentanecarboxylate (11.18 g, containing ~4% (w/w) CH_2Cl_2, 65%) as a slightly yellowish oil. Part of this oil (10.78 g, 16.7 mmol) was dissolved in CH_2Cl_2 (150 mL) and treated with concd aqueous HCl (15 mL) for 1.5 h. Then, the reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with H_2O (150 mL), and aqueous NaCl (10% (w/w), 2 × 150 mL), and dried. The remaining residue was suspended in heptane (100 mL) and filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried, and coevaporation form CH_2Cl_2 to give **6m** (7.26 g, 90% pure by ^{1}H NMR, 87%) as a thin slightly yellow oil. ^{1}H NMR: δ 4.10 (q, J = 7.0 Hz, 4H), 2.35 (t, J = 7.4 Hz, 4H), 2.13–2.03 (m, 4H), 1.66–1.38 (m, 20H), 1.29–1.13 (m, 8H), 1.24 (t, J = 7.1 Hz, 6H). ^{13}C NMR: δ 210.7, 177.4 (2×), 60.1 (2×), 54.0 (2×), 42.7 (2×), 39.1 (2×), 36.1 (4×), 29.8 (2×), 25.9 (2×), 25.0 (4×), 23.8 (2×), 14.4 (2×). HRMS calcd for $C_{27}H_{46}O_5$ (M^+): 450.3345, found 450.3347.

6.2.12. Diethyl 10-oxo-2,2,18,18-tetramethyl-nonadecanedioate (6n). Compound **6n** was prepared likewise Method A starting from TosMIC (2.43 g, 12.5 mmol), Bu_4NI (0.462 g, 1.25 mmol), NaH (60% (w/w) in mineral oil, 1.21 g, 30.3 mmol) and **3e** (7.65 g, 88% pure by GC, 23.0 mmol) to give, after purification by column chromatography (silica, heptane/EtOAc = 6:1), {10-ethoxy-1-(9-ethoxy-8,8-dimethyl-9-oxononyl)-9,9-dimethyl-1-[(4-methylphenyl)sulfonyl]-10-oxodecyl}(methylidyne)ammonium (5.41 g) as a yellow oil. Part of this oil (5.03 g) was treated with concd aqueous HCl (30 mL), as described for **6d**, to give, after purification by column chromatography (silica, heptane/EtOAc = 7:1), **6n** (3.21 g, 57%) as a colorless oil. ^{1}H NMR: δ 4.11 (q, J = 7.2 Hz, 4H), 2.37 (t, J = 7.4 Hz, 4H), 1.57–1.46 (m, 8H), 1.28–1.23 (m, 16H), 1.24 (t, J = 7.1 Hz, 6H), 1.15 (s, 12H). ^{13}C NMR: δ 211.5, 178.0 (2×), 60.08 (2×), 60.07 (2×), 42.7 (2×), 42.1 (2×), 40.7 (2×), 29.9 (2×), 29.21 (2×), 29.15 (2×), 25.1 (2×), 24.8 (2×), 23.8 (2×), 14.2 (2×). HRMS calcd for $C_{27}H_{50}O_5$ (M^+): 454.3658, found: 454.3663.

6.2.13. Dimethyl 6,6-dimethoxyundecanedioate (15). To a solution of **7b**[13] (9.21 g, 40.0 mmol) in MeOH (50 mL) was added trimethyl orthoformate (100 mL, 0.91 mol) and TsOH (0.60 g, 3.14 mmol). The solution was heated to reflux and stirred for 2 d. Et_2O (250 mL) and

saturated aqueous $NaHCO_3$ (250 mL) were added and the layers were separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (250 mL) and brine (250 mL) and dried to give **15** (11.48 g, 90% pure by GC, 85%) as a dark brown oil, which was used without further purification in the next reaction. ^{1}H NMR: δ 3.67 (s, 6H), 3.13 (s, 6H), 2.33 (t, $J = 7.5$ Hz, 4H), 1.69–1.53 (m, 8H), 1.32–1.21 (m, 4H).

6.2.14. 2,12-Dihydroxy-2,12-dimethyl-7-tridecanone (7i). At 0 °C under a N_2 atmosphere, MeMgCl (22% (w/w) in THF, 41.5 mL, 0.126 mol) was added drop wise to a solution of **15** (8.5 g, 90% pure, 25.2 mmol) in Et_2O (100 mL) in 30 min. After stirring for 30 min, the reaction mixture was allowed to warm to rt, stirred for 2.5 h, and then cooled again to 0 °C. The reaction was quenched by careful addition of HCl (1 M, 125 mL) and the layers were separated. The aqueous phase was extracted with Et_2O (50 mL) and the combined organic layers were washed with brine (2×25 mL) and dried. The remaining residue was purified by column chromatography (silica, EtOAc) to give 6.91 g of a brown oil, which was taken up in EtOAc (25 mL). Norrit (0.5 g) was added and the suspension was filtered through kieselguhr and washed with EtOAc (50 mL). The combined filtrate and washings were evaporated in vacuo to give **7i** (6.73 g, 90% pure by GC, 93%)[14] as a dark yellow oil. ^{1}H NMR: δ 2.40 (t, $J = 7.3$ Hz, 4H), 1.51–1.61 (m, 4H), 1.40–1.48 (m, 4H), 1.27–1.38 (m, 4H), 1.18 (s, 12H). ^{13}C NMR: δ 211.6, 71.0 (2×), 43.8 (2×), 42.9 (2×), 29.4 (4×), 24.4 (2×), 24.1 (2×). HRMS calcd for $C_{15}H_{31}O_3$ (MH^+): 259.2273, found: 259.2278.

6.3. General procedures for ester hydrolysis

6.3.1. Method D. 1-[9-(1-Carboxy-cyclobutyl)-5-oxononyl]-1-cyclobutanecarboxylic acid (7f). $LiOH{\cdot}H_2O$ (3.94 g, 93.9 mmol) and H_2O (30 mL) were added to a solution of **6f** (9.20 g, 23.3 mmol) in EtOH (90 mL) and the resultant mixture was stirred at reflux temperature for 17 h, allowed to cool to rt, and concentrated in vacuo to a smaller volume. H_2O (150 mL) was added and the resultant mixture was extracted with Et_2O (50 mL), acidified with aqueous HCl (6 M, 25 mL), and extracted with Et_2O (1×100 mL, 2×50 mL). The latter organic layers were combined, washed with brine (50 mL), and dried. The remaining residue was recrystallized from iPr$_2$O/heptane to give **7f** (4.41 g, 56%) as small, white granules. Mp: 69–70 °C. ^{1}H NMR: δ 11.2 (br s, 2H), 2.50–2.37 (m, 4H), 2.39 (t, $J = 7.2$ Hz, 4H), 1.96–1.84 (m, 8H), 1.81–1.75 (m, 4H), 1.57 (quintet, $J = 7.4$ Hz, 4H), 1.26–1.12 (m, 4H). ^{13}C NMR: δ 210.6, 183.4 (2×), 47.6 (2×), 42.7 (2×), 37.8 (2×), 30.1 (4×), 24.7 (2×), 24.1 (2×), 15.7 (2×). Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.93. Found: C, 67.19; H, 8.97.

6.3.2. Method E. 1-[9-(1-Carboxy-cyclopropyl)-5-oxononyl]-1-cyclopropanecarboxylic acid (7d). A solution of **6d** (5.31 g, 12.6 mmol) in HCO_2H (50 mL) was stirred for 3 h, evaporated in vacuo, and coevaporated from toluene (3×25 mL) to give **7d** (3.89 g, 99%) as a white solid. An analytical sample was obtained after recrystallization from iPr$_2$O/heptane. Mp: 132–134 °C. ^{1}H NMR (CD_3OD): δ 2.45 (t, $J = 6.9$ Hz, 4H), 1.58–1.39 (m, 12H), 1.14 (dd, $J = 6.6$, 3.7 Hz, 4H), 0.70 (dd, $J = 6.8$, 3.9 Hz, 4H). ^{13}C NMR (CD_3OD): δ 214.4, 179.4 (2×), 43.5 (2×), 34.9 (2×), 28.5 (2×), 25.1 (2×), 24.2 (2×), 16.2 (4×). Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.40; H, 8.37.

6.3.3. Method F. 11-(1-Carboxy-cyclopropyl)-2,2-dimethyl-7-oxoundecanoic acid (7c). A solution of **6c** (9.27 g, >90% pure by ^{1}H NMR, 21.0 mmol) in HCO_2H (50 mL) was stirred for 1.5 h, evaporated in vacuo, and coevaporated from toluene (10 mL). The remaining residue was dissolved in EtOH/H_2O (2:1, 100 mL) and NaOH (5.33 g, 132 mmol) was added. The resultant clear solution was warmed to 80 °C and after 5 h, EtOH was evaporated in vacuo. The remaining solution was diluted with H_2O to ~100 mL, extracted with Et_2O (3×100 mL), acidified to pH ~1 with concd aqueous HCl (~9 mL) and extracted with Et_2O (3×100 mL). The latter organic layers were combined and dried. The remaining residue was purified by column chromatography (silica, heptane/EtOAc = 2:1 (containing 1% (v/v) HOAc)) to give **7c** (5.83 g, >90% pure by ^{1}H NMR, 80%) as a slightly yellow oil, which turns solid when stored at −18 °C for several days. Mp: 49–52 °C. ^{1}H NMR (CD_3OD): δ 2.44 (t, $J = 7.2$ Hz, 4H), 1.57–1.42 (m, 10H), 1.30–1.19 (m, 2H), 1.17–1.07 (m, 2H), 1.14 (s, 6H), 0.59 (dd, $J = 6.6$, 3.9 Hz, 2H). ^{13}C NMR (CD_3OD): δ 213.5, 181.4, 178.9, 43.5, 43.4, 43.0, 41.7, 34.9, 28.5, 25.9 (3×), 25.5, 25.2, 24.3, 16.4 (2×). Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.06; H, 9.02.

6.3.4. 11-(1-Carboxy-cyclobutyl)-2,2-dimethyl-7-oxoundecanoic acid (7e). Compound **7e** was prepared likewise Method D starting from **6e** (8.83 g, >90% pure by ^{1}H NMR, 20.8 mmol) and $LiOH{\cdot}H_2O$ (2.91 and 1.94 g after 18 h, 69.4 and 46.2 mmol) to give, after recrystallized from iPr$_2$O/heptane, **7e** (5.19 g, 76%) as a white solid. Mp: 53–55 °C. ^{1}H NMR: δ 10.80 (br s, 2H), 2.50–2.35 (m, 2H), 2.39 (t, $J = 7.2$ Hz, 4H), 1.98–1.74 (m, 6H), 1.65–1.49 (m, 6H), 1.31–1.11 (m, 4H), 1.18 (s, 6H). ^{13}C NMR: δ 210.6, 184.3, 183.4, 47.6, 42.7, 42.6, 42.2, 40.5, 37.8, 30.1 (2×), 25.1 (2×), 24.8, 24.7, 24.2, 24.1, 15.7. Anal. Calcd for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26. Found: C, 66.26; H, 9.37.

6.3.5. 1-[9-(1-Carboxy-cyclopentyl)-5-oxononyl]-1-cyclopentanecarboxylic acid (7g). Compound **7g** was prepared likewise Method D starting from **6g** (6.05 g, >90% pure by ^{1}H NMR, 12.9 mmol) and $LiOH{\cdot}H_2O$ (2.01 g, 47.9 mmol) to give, after crystallization from iPr$_2$O/heptane, **7g** (5.01 g, 93% pure by ^{1}H NMR, 99%) as white granules. An analytical sample was obtained after recrystallization from iPr$_2$O/heptane. Mp = 104–106 °C. ^{1}H NMR: δ 2.39 (t, $J = 6.9$ Hz, 4H), 2.18–2.10 (m, 4H), 1.69–141 (m, 20H), 1.27–1.14 (m, 4H). ^{13}C NMR: δ 211.1, 184.6 (2×), 53.9 (2×), 42.5 (2×), 39.0 (2×), 35.9 (4×), 25.7 (2×), 24.9 (4×), 24.0 (2×). Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 68.78; H, 9.47.

6.3.6. 2,12-Di(ethoxycarbonyl)-2,12-dimethyl-7-oxotridecanedioic acid (7h). A solution of KOH (2.44 g, >85%, >37.0 mmol) in EtOH (80 mL) was added to **6h** (9.00 g, 18.5 mmol). After stirring for 54 h, another portion of KOH (1.21 g, >85%, >18.5 mmol) was added and stirring was continued for 16 h. The reaction mixture was evaporated in vacuo and Et_2O (250 mL) and H_2O (250 mL) were added. The aqueous layer was separated, acidified with aqueous HCl (2 M, 50 mL), and extracted with Et_2O (250 mL) and CH_2Cl_2 (250 mL). The combined organic layers were dried and the remaining residue was purified by column chromatography (silica, heptane/EtOAc/HOAc = 3:2:0.01) and vacuum dried at 50 °C to give **7h** (6.43 g, 81%) as a yellow oil. ^{1}H NMR: δ 10.40 (br s, 2H), 4.21 (q, J = 7.1 Hz, 4H), 2.42 (t, J = 7.4 Hz, 4H), 1.90–1.84 (m, 4H), 1.59 (quintet, J = 7.4 Hz, 4H), 1.43 (s, 6H), 1.32–1.19 (m, 4H), 1.27 (t, J = 7.2 Hz, 6H). ^{13}C NMR: δ 210.9, 177.7 (2×), 172.1 (2×), 61.5 (2×), 53.5 (2×), 42.2 (2×), 35.3 (2×), 23.8 (2×), 23.7 (2×), 19.8 (2×), 13.9 (2×). HRMS calcd for $C_{21}H_{35}O_9$ (MH^+): 431.2281, found: 431.2298.

6.3.7. 13-(1-Carboxy-cyclopropyl)-2,2-dimethyl-8-oxotridecanoic acid (7k). Compound **7k** was prepared likewise Method F starting from **6k** (18.34 g, 95% pure by ^{1}H NMR, 41.0 mmol) to give 1-(11-ethoxy-10,10-dimethyl-5,11-dioxoundecyl)-1-cyclopropanecarboxylic-acid, which was treated with NaOH (9.68 g, 241 mmol) to give, after recrystallized from iPr$_2$O/heptane, **7k** (9.47 g, 68%) as a white solid. The mother liquor was evaporated in vacuo and the remaining residue was purified by column chromatography (heptane/EtOAc = 2:1 (containing 1% (v/v) HOAc)) and recrystallization from iPr$_2$O/heptane to give a second batch **7k** (2.23 g, 16%) as a white solid. Mp: 65–66 °C. ^{1}H NMR (CD_3OD): δ 2.43 (t, J = 7.2 Hz, 4H), 1.58–1.42 (m, 10H), 1.35–1.20 (m, 6H), 1.14 (s, 6H), 1.15–1.06 (m, 2H), 0.70 (dd, J = 6.6, 3.9 Hz, 2H). ^{13}C NMR (CD_3OD): δ 213.8, 181.6, 179.0, 43.6, 43.5, 43.1, 41.9, 35.1, 31.0, 30.6, 28.7, 26.2, 25.9 (2×), 25.02, 24.96, 24.4, 16.4 (2×). Anal. Calcd for $C_{19}H_{32}O_5$: C, 67.03; H, 9.47. Found: C, 66.86; H, 9.50.

6.3.8. 1-[11-(1-Carboxy-cyclopropyl)-6-oxoundecyl]-1-cyclopropanecarboxylic acid (7l). Compound **7l** was prepared likewise Method E starting from **6l** (7.50 g, >90% pure by ^{1}H NMR, 15.0 mmol) to give, after recrystallized from toluene, **7l** (5.06 g, 99%) as colorless crystals. Mp: 122–123 °C. ^{1}H NMR (DMSO-d_6): δ 11.96 (br s, 2H), 2.39 (t, J = 7.4 Hz, 4H), 1.50–1.33 (m, 12H), 1.25–1.15 (m, 4H), 1.03 (dd, J = 6.5, 3.5 Hz, 4H), 0.68 (dd, J = 6.6, 3.6 Hz, 4H). ^{13}C NMR (DMSO-d_6): δ 209.9, 175.7 (2×), 41.8 (2×), 33.2 (2×), 28.8 (2×), 27.2 (2×), 23.3 (2×), 22.9 (2×), 14.8 (4×). Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.93. Found: C, 67.20; H, 9.05.

6.3.9. 1-[11-(1-Carboxy-cyclopentyl)-6-oxoundecyl]-1-cyclopentanecarboxylic acid (7m). Compound **7m** was prepared likewise Method D starting from **6m** (7.1 g, 90% pure by ^{1}H NMR, 14.2 mmol) and $LiOH{\cdot}H_2O$ (3.3 g, 78.6 mmol) to give, after recrystallization from iPr$_2$O/heptane, **7m** (5.09 g, 91%) as white granules. Mp = 78–85 °C. ^{1}H NMR: δ 2.37 (t, J = 7.4 Hz, 4H), 2.18–2.10 (m, 4H), 1.65–1.45 (m, 20H), 1.29–1.25 (m, 8H). ^{13}C NMR: δ 211.5, 184.8 (2×), 54.0 (2×), 42.4 (2×), 38.9 (2×), 35.9 (4×), 29.2 (2×), 25.5 (2×), 24.9 (4×), 23.5 (2×). Anal. Calcd for $C_{23}H_{38}O_5$: C, 70.02; H, 9.71, Found: C, 70.37; H, 9.72.

6.3.10. 10-Oxo-2,2,18,18-tetramethyl-nonadecanedioic acid (7n). Compound **7n** was prepared likewise Method D starting from **6n** (11.63 g, 25.6 mmol) and KOH (4.31 g, 77.0 mmol) to give, after recrystallization from iPr$_2$O/heptane, **7n** (7.56 g, 74%) as white crystals. Mp: 74–77 °C. ^{1}H NMR (CD_3OD): δ 2.43 (t, J = 7.3 Hz, 4H), 1.57–1.50 (m, 8H), 1.33–1.21 (m, 16H), 1.14 (s, 12H). ^{13}C NMR: δ 214.5, 182.1 (2×), 43.6 (2×), 43.2 (2×), 42.0 (2×), 31.2 (2×), 30.4 (2×), 30.38 (2×), 26.2 (2×), 25.9 (4×), 25.0 (2×). Anal. Calcd for $C_{23}H_{42}O_5$: C, 69.31; H, 10.62, Found: C, 69.41; H, 10.73.

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