Long Hydrocarbon Chain Keto Diols and Diacids that Favorably Alter Lipid Disorders in Vivo

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Keto-substituted hydrocarbons with 11−19 methylene and bis-terminal hydroxyl and carboxyl groups have been synthesized and evaluated in both in vivo and in vitro assays for their potential to favorably alter lipid disorders including metabolic syndrome. Compounds were assessed for their effects on the de novo incorporation of radiolabeled acetate into lipids in primary cultures of rat hepatocytes as well as for their effects on lipid and glycemic variables in obese female Zucker fatty rats [Crl:(ZUC)-faBR] following 1 and 2 weeks of oral administration. The most active compounds were found to be symmetrical with four to five methylene groups separating the central ketone functionality 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 (e.g., **10c**, **10g**, **14c**), and the least active were shown to be the bis(arylmethyl) derivatives (e.g., **10e**, **10f**, **14f**). Compound **14c** dose-dependently elevated HDL-cholesterol, reduced triglycerides, and reduced NEFA, with a minimum effective dose of 30 mg/kg/day. Compound **10g** dose-dependently modified non-HDL-cholesterol, triglycerides, and nonesterified fatty acids, with a minimum effective dose of 10 mg/kg/day. At this dose, compound **10g** elevated HDL-cholesterol levels 2−3 times higher than pretreatment levels, and a dose-dependent reduction of fasting insulin and glucose levels was observed.

Introduction

Epidemiological studies have demonstrated a strong correlation between elevated serum cholesterol and coronary artery disease (CAD).[1,2] Specifically, the level of blood cholesterol carried in the low density lipoproteins (LDL-C) is positively correlated with increased risk of CAD in the human population. Conversely, several epidemiological studies have demonstrated an inverse relationship between blood high-density lipoprotein cholesterol (HDL-C) levels and the risk of developing CAD.[3] Elevated blood triglyceride levels are also independently associated with increased risk for CAD.[4−6] In the light of these data, intensive effort over the last 30 years has focused on identifying pharmacologic agents that can alter blood lipid levels. The 1960s were marked by the discovery that clofibrate possessed hypolipidemic activity. Subsequent work in the 1970s resulted in the synthesis of other hypolipidemic fibrates, including bezafibrate, ciprofibrate, fenofibrate, and gemfibrozil. Elucidation of the cholesterol de novo synthetic pathway,[7] coupled with the discovery of the low-density lipoprotein receptor and the metabolic basis of its regulation,[8] led to rapid development in the late 1970s and 1980s of the statin class of drugs targeted at inhibiting HMG-CoA reductase. Clinical trials demonstrated that the statins markedly reduced LDL-C and morbidity and mortality in humans.[9] In addition, both the Helsinki Heart Study[10] and the Veterans Affairs-HDL-Cholesterol Intervention Trial (VA-HIT) showed that gemfibrozil-treatment-related increases in HDL-C predicted a significant reduction in secondary coronary events.[11] In addition, the VA-HIT trial showed that the gemfibrozil treatment reduced the incidence of stroke.[12]

While the fibrate and statin discovery efforts were ongoing, several groups were pursuing alternative chemical and biological approaches to identify lipid-regulating agents. For example, Sircar and co-workers[13] described a series of phenylenebis(oxy)bis[2,2,-dimethylpentanoic acid]s that blunted the HDL-C reduction induced in rats fed a peanut oil, cholesterol, and cholic acid containing diet. Furthermore, Bar-Tana and co-workers[14,15] initiated a program to design nonmetabolizable long-chain fatty acid analogues as potential hypolipidemic agents. The resultant series of compounds was termed "MEDICA" for *β,β′-me*thyl-α,*ω-dic*arboxylic *a*cids, and a prototype member of this family, 3,3,14,-14-tetramethylhexadecanedioic acid (MEDICA 16), was selected for biological evaluation. The biochemical design for this series was based on the idea that it would mimic long-chain fatty acids and thus inhibit lipid synthesis. Other structural features included (1) the *ω*-carboxyl function, which was expected to interfere with incorporation of fatty acids into neutral lipids and phospholipids, and (2) the *β,β′*-substitution to prevent the *β*-oxidative catabolism of MEDICA compounds by either mitochondrial or peroxisomal *β*-oxidative systems.

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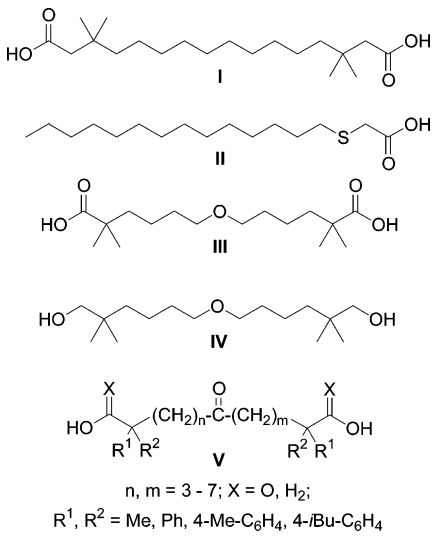


Figure 1.

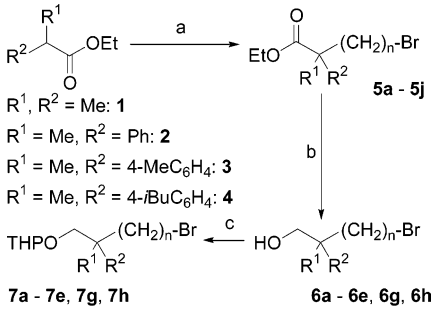
Bar-Tana and co-workers have described in detail the effects of MEDICA compounds (e.g., **I**, Figure 1) on lipid disorders including metabolic syndrome related disorders.[16−19] These studies have shown that, indeed, MEDICA compounds are hypolipidemic, antidiabetic, and antiatherosclerotic in addition to possessing antiobesity properties in relevant animal models. Another series of compounds with similar biological activity to the MEDICA series are 3-thia fatty acids (e.g., **II**, Figure 1) developed and studied by Berge, Bremer, and colleagues.[20−23] Finally, carboxyl- and hydroxylalkyl ether compounds **III**[24−26] and **IV**[27] (Figure 1) were shown to significantly raise HDL-C in rats in contrast to MEDICA 16 and 3-thia fatty acid compounds that tend to lower HDL-C or HDL-associated proteins in that species. However, the effect of Gemcabene (**III**, Figure 1), a dialkyl ether (dicarboxylic acid), on serum HDL-C and triglyceride levels (TG) was shown to be dependent upon baseline TG levels and Gemcabene dose in patients with low levels of HDL-C.[26]

To identify new compounds that may be useful for the treatment of human dyslipidemias and associated disorders such as metabolic syndrome, we synthesized ketone derivatives of long-chain hydrocarbons by varying chain length, symmetry, terminal groups, and quaternary carbon substitutions. To assess biological activity, compounds were tested in both a short-term (hours) in vitro assay and a long-term (2 weeks) in vivo animal model. Since some long-chain hydrocarbon compounds (e.g., **I** and **II**) have been shown to inhibit fatty acid and sterol synthesis,[20,28,29] we tested the ability of compounds to inhibit lipid synthesis by assessing their effects on the de novo incorporation of radiolabeled acetate into lipids in primary cultures of rat hepatocytes. In addition to the short-term lipid synthesis assay, the compounds were also tested for their ability to alter serum lipid variables over a 2-week period of oral administration in the obese female Zucker rat line Crl: (ZUC)-faBR, a model of diabetic dyslipidemia.

Results and Discussion

Drug Design. Studies related to compounds **I**−**IV** suggested that certain structural features of the polyfunctionalized long hydrocarbon chains conferred lipid regulating activity.[14,21,30] The central group appeared to be particularly important, since a central ether moiety conferred HDL-C elevating properties to alkyl ethers, while a methylene spacer chain of equivalent length did not.[24] Beginning with modifications of the central moiety, we determined that substitution of an ether with a ketone in compounds with terminal hydroxyl moieties resulted in nearly equivalent HDL-C elevating activity in various models of dyslipidemia.[27c] We then investigated a ketone series having the general formula **V** and examined the influence of chain length and symmetry, terminal groups, and substitution pattern at the quaternary carbons α to the terminal carboxyl and β to the terminal hydroxy moieties. It should be noted that pharmacokinetic studies have shown the interconversion between the ketone diols and ketone diacids in vivo (unpublished observation). Since a single, specific molecular target has not been positively identified for long-chain hydrocarbon compounds in general, their lipid-regulating activity could be explained by cumulative effects on multiple biological targets with emphasis on the fatty acid synthesis inhibition at the acetyl-CoA carboxylase (ACC) step via an allosteric mechanism.[27d] For this reason, lipid synthesis in primary rat hepatocytes and lipid serum regulation in the dyslipidemic obese female Zucker rat were tested to ensure efficacy through biochemical pathways in complex systems (cells and whole animals).

Scheme 1. Synthesis of Ethyl ω-Bromoalkanoates and ω-Bromoalkyloxy THP Ethers[a]



[a] Reagents: (a) LDA, $Br(CH_2)_nBr$, [THF/DMPU]; (b) $LiBH_4$, MeOH, [CH_2Cl_2]; (c) DHP, *p*TosOH, [CH_2Cl_2].

Chemistry. A series of long hydrocarbon chain keto diols and diacids was synthesized using as starting templates bromides of types **5** and **7** (Scheme 1 and Table 1).[31] The side chains connected to the central ketone functionality varied both in length (n, $m = 3-7$) and in the attached geminal modifying groups (R^1, R^2 = Me, Ph, 4-Me-C_6H_4, 4-*i*Bu-C_6H_4). The majority of target compounds fell in the category of either symmetrical keto diacids (**10b**−**10g**, **10i**, **10j**, Scheme 2) or symmetrical keto diols (**14a**−**14i**, Scheme 3). A series of unsymmetrical keto diols and diacids with chains of different lengths or with a different substitution pattern (**17**−**19**, Scheme 4; **25**, **26**, Scheme 5) was included in this study as well. In addition, the aryl-bridged compounds **31** and **32** with a benzophenone backbone (Scheme 6) were prepared and examined for comparison.

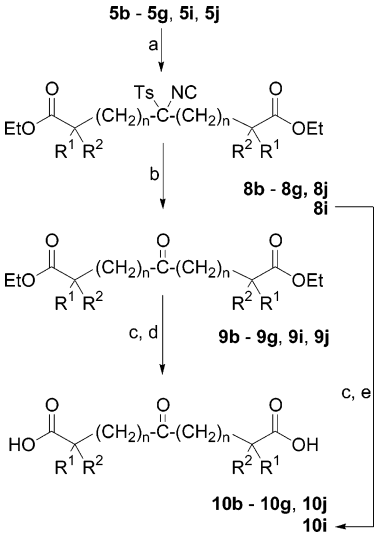
The key step in the syntheses of all ketones with aliphatic chains was the alkylation of tosylmethyl isocyanide (TosMIC)[32,33] with appropriately substituted alkyl bromides (Schemes 2−5). These alkyl bromide building blocks were generally synthesized via lithiation of commercially available or readily accessible ethyl

Table 1. Synthesis of Ethyl ω-Bromoalkanoates and ω-Bromoalkyloxy THP Ethers

no.	n	R^1	R^2	yield (%)	no.	n	R^1	R^2	yield (%)
2	–	Me	Ph	72	**6b**	3	Me	Ph	98
3	–	Me	4-Me-C_6H_4	86	**6c**	4	Me	Me	99[e]
4	–	Me	4-*i*BuC_6H_4	96	**6d**	4	Me	Ph	84
5a	3	Me	Me	85[a]	**6e**	4	Me	4-Me-C_6H_4	96
5b	3	Me	Ph	59[b]	**6g**	5	Me	Me	98
5c	4	Me	Me	98,[a] 72[c]	**6h**	5	Me	Ph	98
5d	4	Me	Ph	99	**7a**	3	Me	Me	90
5e	4	Me	4-Me-C_6H_4	90	**7b**	3	Me	Ph	95
5f	4	Me	4-*i*Bu-C_6H_4	88	**7c**	4	Me	Me	83
5g	5	Me	Me	44	**7d**	4	Me	Ph	70
5h	5	Me	Ph	57	**7e**	4	Me	4-Me-C_6H_4	93
5i	6	Me	Me	52	**7g**	5	Me	Me	46
5j	7	Me	Me	45[d]	**7h**	5	Me	Ph	76
6a	3	Me	Me	100					

[a] As described in ref 53. [b] (+)-Enantiomer described in ref 54. [c] As described in ref 36a. [d] Reaction performed at 0 °C and without cosolvent. [e] Also prepared with DIBAL according to ref 36a in 82% yield.

Scheme 2. Synthesis of Symmetrical Keto Diacids[a]



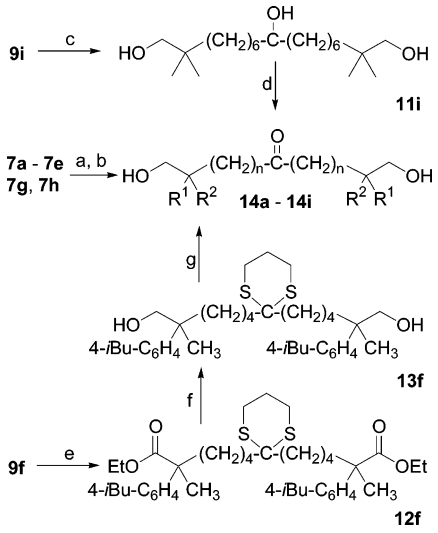
[a] Reagents: (a) TosMIC, NaH, NBu_4I, [DMSO]; (b) aq HCl, [CH_2Cl_2]; (c) KOH, [EtOH/H_2O]; (d) aq HCl; (e) aq H_2SO_4.

esters **1**, **2**,[34] **3**,[35] and **4** with LDA in anhydrous THF in the presence of *N*,*N*′-dimethylpropyleneurea (DMPU) at −78 °C, followed by subsequent reaction with an α,ω-dibromoalkane[36] of the required chain length (Scheme 1). Thus, bromo esters **5a**−**5j** were obtained in moderate to good yields (Table 1). Reduction of bromo esters with $LiBH_4$ and MeOH[37] in refluxing CH_2Cl_2 afforded the bromo alcohols **6a**−**6e**, **6g**, and **6h** in excellent yields and purities without affecting the bromide moiety.[38] Reduction with $LiAlH_4$ or $NaBH_4$ on the other hand was not chemoselective, and the reactions were not reproducible. Another chemoselective reducing agent was diisobutylaluminum hydride.[36a] Bromo alcohols were treated with 3,4-dihydro-2*H*-pyran (DHP) and catalytic amounts of *p*-toluenesulfonic acid (*p*TosOH)[36a] to give the THP ethers **7a**−**7e**, **7g**, and **7h** (Scheme 1, Table 1) in moderate to good yields.

The synthesis of symmetrical keto diacids **10b**−**10g**, **10i**, and **10j** from bromo esters **5b**−**5g**, **5i**, and **5j** was accomplished by employing TosMIC methodology[33] (Scheme 2). Accordingly, TosMIC was deprotonated with NaH in either DMSO or in a DMSO/Et_2O mixture[32a] at room temperature and then reacted with suitable bromo esters **5b**−**5g**, **5i**, and **5j** in the presence of catalytic amounts of tetrabutylammonium iodide (NBu_4I)[39] to give the corresponding dialkylated TosMIC intermediates **8b**−**8g**, **8i**, and **8j**. In most cases, these intermediates were not purified or characterized but directly treated with concentrated aqueous HCl in CH_2Cl_2[32a] to give keto diesters **9b**−**9g**, **9i**, and **9j** in good yields after chromatographic purification (Table 2). Finally, hydrolysis of the ester groups with KOH in aqueous EtOH and subsequent acidification with concentrated HCl (steps c, d) provided the target diacids **10b**−**10g** and **10j** in variable yields ranging from 31 to 87%. According to a different protocol, keto diacid **10i** was prepared by simultaneous hydrolysis of the tosyl isocyanide and the ester groups in **8i** with KOH in aqueous EtOH followed by acidification with dilute H_2SO_4 (steps c, e) in 57% yield.

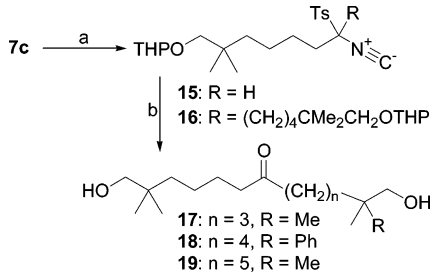
Scheme 3 illustrates three different strategies that were studied for the synthesis of symmetrical keto diols. The standard procedure used in most cases employed the dialkylation protocol of TosMIC as described above. Bromo THP ethers **7a**−**7e**, **7g**, and **7h** were used as electrophiles, and the resulting TosMIC intermediates were directly hydrolyzed to give the keto diols **14a**−**14e**, **14g**, and **14h** in acceptable yields after purification by column chromatography (Table 3). An alternative pathway was elected for the synthesis of keto diol **14i**. In

Scheme 3. Synthesis of Symmetrical Keto Diols[a]



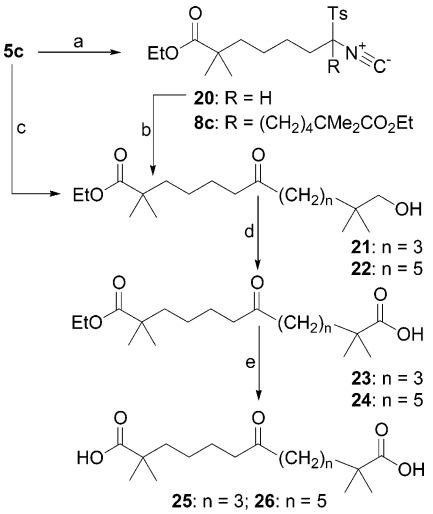
[a] Reagents: (a) TosMIC, NaH, NBu_4I, [DMSO]; (b) aq HCl, [MeOH/H_2O]; (c) $LiAlH_4$, [MTBE]; (d) aq NaOCl, [HOAc]; (e) 1,3-propanedithiol, BF_3−Et_2O, [CH_2Cl_2]; (f) $LiAlH_4$, [THF]; (g) concd HCl, DMSO, dimethoxyethane.

Scheme 4. Synthesis of Unsymmetrical Keto Diols[a]



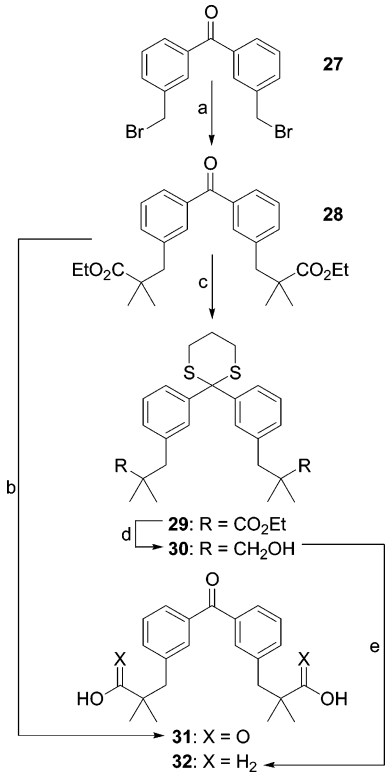
[a] Reagents: (a) TosMIC, NaH, NBu_4I, [DMSO], 27%, or K_2CO_3, NBu_4I, [DMF], 69%; (b) for **17**, **7a**, NaH, NBu_4I, [DMSO], then concd HCl, [MeOH], 58%; for **18**, **7d**, NaH, NBu_4I, [DMSO], then concd HCl, [MeOH], 71%; for **19**, **7g**, NaH, NBu_4I, [DMSO], then concd HCl, [MeOH], 48%.

Scheme 5. Synthesis of Unsymmetrical Keto Diacids[a]



[a] Reagents: (a) TosMIC, NaH, NBu_4I, [DMSO], 12%; (b) for $n = 3$, **7a**, NaH, NBu_4I, [DMSO], then aq H_2SO_4, [MeOH], 60%; (c) for $n = 5$, (1) TosMIC, NaH, NBu_4I, [DMSO]; (2) **7g**, NaH; (3) aq H_2SO_4, [MeOH], 36%; (d) PDC, [DMF]; $n = 3$, 79%; $n = 5$, 68%; (e) KOH, [EtOH/H_2O]; $n = 3$, 60%; $n = 5$, 43%.

Scheme 6. Synthesis of Aryl-Bridged Compounds[a]



[a] Reagents: (a) Ethyl isobutyrate, LDA, [THF/DMPU], 89%; (b) KOH, [EtOH/H_2O], quantitative; (c) 1,3-propanedithiol, BF_3-Et_2O, [CH_2Cl_2], 87%; (d) $LiBH_4$, MeOH, [CH_2Cl_2], 85%; (e) CuO, $CuCl_2$, [acetone/DMF], 71%.

this case, keto diester **9i** was first reduced to triol **11i** by treatment with $LiAlH_4$ (66%). Selective oxidation of the secondary alcohol moiety in **11i** with aqueous NaOCl solution in acetic acid[40] then produced **14i** in low yield (35%). Better results were obtained when the ketone functionality in the keto diester was protected prior to the reduction of the esters. Thus, protection of **9f** with 1,3-propanedithiol and BF_3-Et_2O[41] led to formation of **12f**, which was subsequently reduced with $LiAlH_4$ to **13f**. Removal of the 1,3-dithiane protective group with DMSO in dimethoxyethane and concentrated HCl[42] afforded keto diol **14f** (63% from **5f**). Despite the superior yields attained, this method was not generally applied for the synthesis of **14a**−**14i** because of the malodorous reagent involved.

Table 2. Synthesis of Symmetrical Keto Diacids

no.	n	R^1	R^2	yield (%)	no.	n	R^1	R^2	yield (%)
9b	3	Me	Ph	61	**10b**	3	Me	Ph	31
9c	4	Me	Me	67	**10c**	4	Me	Me	86
9d	4	Me	Ph	66	**10d**	4	Me	Ph	87
9e	4	Me	4-Me-C_6H_4	54	**10e**	4	Me	4-Me-C_6H_4	39
9f	4	Me	4-*i*Bu-C_6H_4	82	**10f**	4	Me	4-*i*Bu-C_6H_4	86
9g	5	Me	Me	61	**10g**	5	Me	Me	57
9i	6	Me	Me	40	**10i**	6	Me	Me	57[b]
9j	7	Me	Me	61[a]	**10j**	7	Me	Me	74

[a] Intermediate **8j** was purified by column chromatography; [b] Prepared by direct base hydrolysis of **8i**.

Table 3. Synthesis of Symmetrical Keto Diols

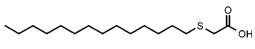
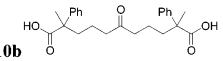
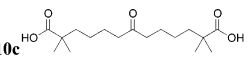
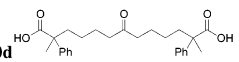
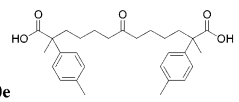
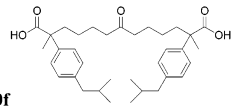
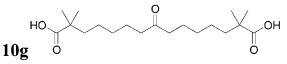
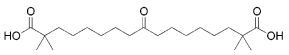
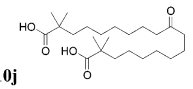
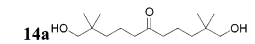
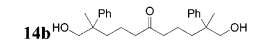
no.	n	R^1	R^2	yield (%)	no.	n	R^1	R^2	yield (%)
11i	5	Me	Me	66	**14d**	4	Me	Ph	61
12f	4	Me	4-iBu-C_6H_4	98	**14e**	4	Me	4-Me-C_6H_4	21
13f	4	Me	4-*i*Bu-C_6H_4	94	**14f**	4	Me	4-*i*Bu-C_6H_4	83
14a	3	Me	Me	30	**14g**	5	Me	Me	79
14b	3	Me	Ph	38	**14h**	5	Me	Ph	56
14c	4	Me	Me	68	**14i**	6	Me	Me	35

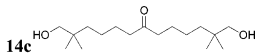
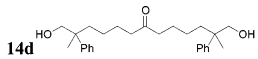
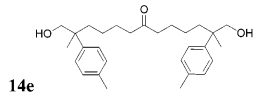
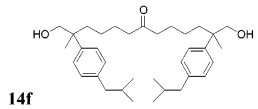
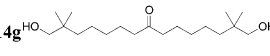
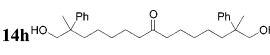
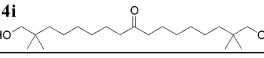
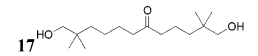
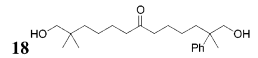
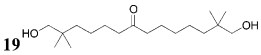
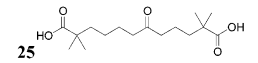
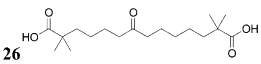
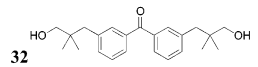
Unsymmetrical keto diols **17**−**19** were prepared via the mono-alkylated TosMIC derivative **15** (Scheme 4). However, reaction of TosMIC with 1 equiv of **7c** under the previously utilized reaction conditions (NaH and NBu_4I in DMSO) gave a mixture of mono- and dialkylated products **15** and **16**, which were separated by chromatography.[43] Consequently, formation in the next step of mixtures of **17** or **19**, respectively, with **14c**, practically impossible to separate, was prevented, but the yield remained low (27%). When using K_2CO_3 in DMF, compound **15** was produced in 69% yield without formation of **16**, even when an excess of **7c** was used. Further alkylation of **15** with bromo THP ethers **7a**, **7d**, and **7g**, followed by deprotection with concentrated HCl in refluxing MeOH furnished the unsymmetrical products **17**−**19**.

Similar problems with an unwanted dialkylated byproduct (**8c**, Scheme 5) were also encountered in the synthetic route to diacids **25** and **26**. Alkylation of TosMIC with **5c** by treatment with NaH and NBu_4I in DMSO led to a mixture of compounds **20** and **8c** that was very difficult to separate chromatographically.[44] As a result, the yield of pure **20** was only 12%. To ensure the complete removal of the symmetrical keto diester **9c** that results from intermediate **8c**, compound **20** was reacted with bromo THP ether **7a** and subsequently hydrolyzed to give hydroxy ester **21**. Purification of **21** from traces of **9c** was now easily accomplished by chromatography (60% yield). Subsequent oxidation of this alcohol with pyridinium dichromate (PDC) in DMF[45] afforded diacid monoester **23** (79%), which was further saponified to provide **25** in 60% yield after crystallization from Et_2O/hexanes.

The same strategy was applied for the synthesis of unsymmetrical keto diacid **26**. In this case, intermediate **20** was not isolated but further alkylated in situ with

Table 4. Effect of Keto Diacids and Diols on Lipid Synthesis in Primary Rat Hepatocytes

Compound	IC_{50} (μM)	95% Confidence Interval		r^2
		Lower	Upper	
 **3-thia fatty acid**	43	28	64	0.99
 **10b**	NA[a]			
 **10c**	3	2	4	0.93
 **10d**	NA[a]			
 **10e**	100-300[b]			
 **10f**	100-300[b]			
 **10g**	3	3	3	0.99
 **10i**	9	8	9	1
 **10j**	5	2	11	0.98
 **14a**	27	21	35	0.94
 **14b**	100-300[b]			

Compound	IC_{50} (μM)	95% Confidence Interval		r^2
		Lower	Upper	
 **14c**	4	3	7	0.91
 **14d**	100-300[b]			
 **14e**	100-300[b]			
 **14f**	NA[a]			
 **14g**	3	3	5	0.94
 **14h**	93	60	144	0.88
 **14i**	2	1	8	0.97
 **17**	3-10[b]			
 **18**	1	1	2	0.84
 **19**	2	2	3	0.94
 **25**	8	7	11	0.97
 **26**	3	3	4	0.96
 **32**	52	32	83	0.91

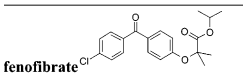
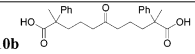
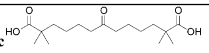
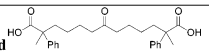
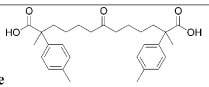
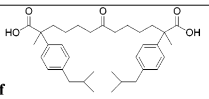
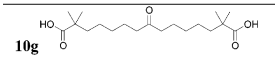
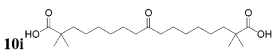
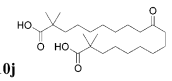
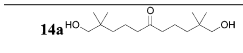
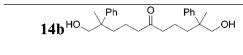
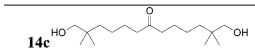
[a] Not active; inhibition of [^{14}C]acetate incorporation into total lipids is less than 50% at 300 μM. [b] The confidence of the IC_{50} estimate is insufficient to assign a value. However, the compound's IC_{50} is between the stated concentrations.

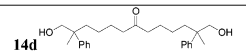
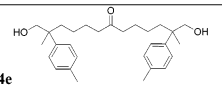
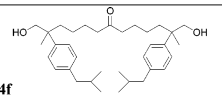
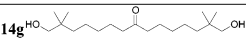
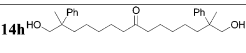
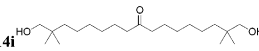
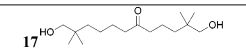
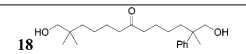
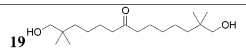
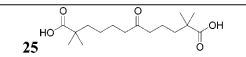
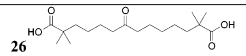
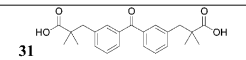
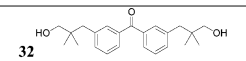
bromo THP ether **7g**. After deprotecting the ketone group by acid treatment and purification of the crude product by chromatography, hydroxy ester **22** was isolated in 36% yield. In analogy to its shorter chain homologue **21**, oxidation of compound **22** with PDC in DMF led to keto diacid monoester **24** (68%). Subsequent hydrolysis of **24** with KOH in aqueous EtOH followed by chromatographic purification and crystallization furnished **26** in 43% yield.

Benzophenone derivative **27**[46] was used as starting material for the synthesis of aryl-bridged ketones **31** and **32**. Bromide displacement in **27** by reaction with lithio ethyl isobutyrate in THF/DMPU at −78 °C produced the diester **28** in 89% yield. Conversion of **28** to diacid **31** performed by saponification with KOH resulted in practically quantitative yield. For the synthesis of the relalated diol **32**, the ketone moiety in intermediate **28** was first protected as *S*,*S*-acetal **29** (87%).[41] Reduction with $LiBH_4$ and MeOH[37b] gave diol **30** in 85% yield. Finaally, deprotection with CuO and $CuCl_2$ in a refluxing acetone/DMF solvent mixture[47] afforded keto diol **32** in 71% yield.

Biological Activity. The aim of our structure-based drug design in the ketone series was to determine the influence of structural modifications on biological activity. Several specific structural features were explored to determine their effects on biological activity, including methylene spacer length from the central ketone to the *gem*-dialkyl or *gem*-alkylaryl substituents, symmetry around the central ketone, variation of *gem* substituents, and terminal functional groups (diacids and diols). Tables 4−8 present in vitro and in vivo biological data in

Table 5. Effect of Keto Diacids and Diols in Obese Female Zucker Rats[a]

Compound	Dose (mg/kg/day)	n	Serum Variables: Percent Change from Pre-Treatment ± SEM					
			Non-HDL-Cholesterol		HDL-Cholesterol		TG	
			1wk	2wk	1wk	2wk	1wk	2wk
 **fenofibrate**	100	3	19.8 ±24	11.6 ±25	-41 ±9	-14 ±14	6 ±25	-8 ±21
 **10b**	100	3	36 ±2	65 ±41	-4 ±4	12 ±9	10 ±5	27 ±15
 **10c**	100	5	-62 ±5	-41 ±1	54 ±29	78 ±28	-75 ±4	-69 ±3
 **10d**	100	3	36 ±14	79 ±27	43 ±1	45 ±3	-36 ±5	-8 ±15
 **10e**	30	4	0 ±23	47 ±30	0 ±11	10 ±14	-11 ±8	12 ±16
 **10f**	100	3	-40 ±5	-44 ±24	11 ±3	62 ±10	-63 ±3	-66 ±15
 **10g**	100	4	-98 ±1	-99 ±0	72 ±23	168 ±28	-93 ±1	-94 ±0
 **10i**	ND							
 **10j**	100	3	-81 ±5	-45 ±16	44 ±21	86 ±16	-85 ±1	-63 ±12
 **14a**	100	3	-22 ±7	28 ±6	24 ±6	2 ±7	-31 ±16	10 ±12
 **14b**	100	4	-18 ±10	-32 ±12	-14 ±2	-11 ±13	-20 ±9	-17 ±15
 **14c**	100	4	-23 ±21	-10 ±13	111 ±30	126 ±48	-54 ±12	-29 ±19

Compound	Dose (mg/kg/day)	n	Serum Variables: Percent Change from Pre-Treatment ± SEM					
			Non-HDL-Cholesterol		HDL-Cholesterol		TG	
			1wk	2wk	1wk	2wk	1wk	2wk
 **14d**	30	2	-30 ±31	31 ±0	0 ±27	-27 ±25	-25 ±21	
 **14e**	30	4	61 ±36	46 ±28	-3 ±10	-2 ±8	15 ±15	0 ±13
 **14f**	100	3	27 ±14	34 ±24	-5 ±7	6 ±8	-10 ±4	-15 ±19
 **14g**	100	3	-91 ±4	-88 ±7	77 ±22	135 ±14	-92 ±2	-92 ±2
 **14h**	100	5	29 ±15	9 ±9	2 ±6	10 ±9	24 ±16	1 ±9
 **14i**	30	4	-50 ±7	-32 ±8	85 ±15	61 ±16	-58 ±4	-33 ±7
 **17**	100	2	-26 ±8	4 ±7	47 ±4	48 ±3	-40 ±11	-12 ±7
 **18**	30	4	17 ±8	-8 ±7	-18 ±4	-5 ±3	18 ±11	-8 ±7
 **19**	100	2	-70 ±19	-78 ±35	78 ±5	78 ±10	-85 ±3	-87 ±15
 **25**	30	4	-17 ±19	93 ±35	7 ±5	4 ±10	-2 ±3	23 ±15
 **26**	100	3	-30 ±24	-51 ±1	240 ±80	72 ±77	-65 ±11	-62 ±5
 **31**	59	3	-43 ±15	34 ±18	2 ±7	7 ±0	-24 ±6	7 ±4
 **32**	100	4	-14 ±15	-5 ±17	1 ±10	-11 ±12	-29 ±7	-8 ±14

[a] ND = Compound not tested.

connection with lipid-regulating properties for the keto diols and keto diacids described above. In vitro studies tested the ability of compounds to inhibit the incorporation of [^{14}C]acetate into total cellular lipids of primary rat hepatocytes over a 4-h time period (Table 4). The compounds were also tested for their ability to alter serum lipid variables in an animal model of diabetic dyslipidemia, the obese female Zucker rat, over a 2-week period at a single daily dose of 30 or 100 mg/kg/day (Table 5). Select compounds (**14c**, **10c**, and **10g**) were further evaluated in the same Zucker rat model by performing a full dose−response study and measuring additional serum variables including markers for diabetes (Tables 6−8).

Effect on Lipid Synthesis In Vitro. The rat hepatocyte culture is a useful model for assessing de novo lipid synthesis activity. Key hepatic functions include the de novo synthesis of both cholesterol and triglycerides from fatty acids that are incorporated into nascent very low-density lipoprotein (VLDL). Therefore, we studied the effects of the ketone series on total lipid synthesis activity in that model using [^{14}C]acetate as the metabolic precursor.[48,49] Table 4 summarizes the biological effects of the keto diacid and keto diol analogues in primary rat hepatocyte cultures.

Compounds with three methylene spacers on each side of the central ketone moiety were inactive (**10b**) or showed only marginal activity (**14a**, **14b**). As the methylene spacer chain length was increased to four or five, the activity of keto diacids (**10c** and **10g**) and keto diols (**14c** and **14g**) increased markedly (i.e., $IC_{50} = 3-4$ μM). The activity of compounds with six or seven

methylene spacers (**10i**, **10j**, **14i**) was only slightly lower (i.e., IC_{50} = 2−9 μM). By replacing the methylene spacers in the chain with aryl groups (such as in benzophenone **32**), lipid synthesis inhibitory activity was reduced significantly (IC_{50} = 52 μM).

Symmetry around the central ketone did not appear to markedly affect biological activity. For example, the unsymmetrical compounds **19** (keto diol) and **26** (keto diacid) possessing chains of four and five methylene spacer groups flanking the central ketone had activities similar to the symmetrical compounds with two chains of four or five methylene spacers (compounds **10c**, **10g**, **14c**, **14g**).

Regarding *gem* substitutions, the addition of a single phenyl substituent to one of the *gem* sites on the quaternary carbon (**18**) did not markedly change the activity (IC_{50} = 1 μM) compared to the tetramethyl-substituted keto diol (**14c**, IC_{50} = 4 μM). However, substituting one of the methyl groups with aryl (**10d**−**10f**, **14d**−**14f**, **14h**) on both quaternary carbons markedly reduced activities (IC_{50} > 100 μM) compared to the corresponding tetramethyl-substituted compounds (**10c**, **10g**, **14c**, **14g**).

Regarding the terminal functional groups, there was no significant difference in the in vitro activity between diacids or diols (e.g., **10c** vs **14c** and **10g** vs **14g**).

Effect on Lipid Variables in the Obese Female Zucker Rat. To test the lipid regulating activity of these compounds, we used the obese Zucker fatty rat [Crl:(Zuc)-faBR] as a model of diabetic dyslipidemia. The Zucker rat has a mutation in the leptin receptor that leads to a metabolic disorder similar to human noninsulin dependent diabetes mellitus (NIDDM) or type II diabetes. Animals develop an age-dependent progression of disease that includes hypertriglyceridemia, increased VLDL-cholesterol (VLDL-C), decreased HDL-C, impaired insulin sensitivity, hyperphagia, and marked weight gain leading to obesity. The non-HDL-C in this model is mainly VLDL-C with essentially no LDL-C. It is worthwhile to mention that, unlike a normal rat, these animals have markedly elevated plasma triglycerides and a significant amount of cholesterol as VLDL-C. Their lipoproteins are also distinct from humans, where most of the non-HDL-C is carried in the LDL fraction.

Initially, the lipid-regulating activities of the ketone compounds in this model were assessed by administering a single dose of 30 or 100 mg/kg/day every day for up to 2 weeks. Compounds were evaluated for their ability to produce a less atherogenic serum lipid profile, that is, reduce non-HDL-C, elevate HDL-C, and reduce triglycerides. Table 5 summarizes those serum lipid changes induced by the keto diols and keto diacids.

Rather than favorably changing only one or two lipid variables and maintaining marked changes throughout the entire 2-week time course, active compounds favorably altered all three serum lipid variables while sustaining the effect for two weeks (**10c**, **10g**, **10j**, **14c**, **14g**, **19**, **26**). We generally defined active compounds as those that markedly reduced non-HDL-C and triglycerides while elevating HDL-C. Common features of these compounds included methylene spacer chain lengths equal to or greater than four and a *gem* dimethyl substitution pattern at the quaternary carbon. Symmetrical ketones with two chains of five methylene spacers (**10g**, **14g**) were superior to symmetrical ketones with two chains of four (**10c**, **14c**) and unsymmetrical ketones with chains of four and five (**19**, **26**) methylene spacers. Furthermore, compounds with six (**14i**) or seven (**10j**) methylene spacers displayed a reduction in activity compared to the five-methylene spacer compounds (**10g**, **14g**). No marked differences between the corresponding diacid or diol forms of the active compounds were noticed. Virtually all the aromatic substitutions at the quaternary carbon rendered the compounds relatively inactive with the exception of diacid **10f**. However, the corresponding diol **14f** was not active in this particular set of experiments. Additional dose−response studies are needed to confirm these differences.

A comparison of activities in the in vitro lipid synthesis assay (Table 4) and the Zucker rat model (Table 5) indicated that 8 out of the 12 compounds with an IC_{50} below 10 μM in the lipid synthesis assay favorably altered non-HDL-C, HDL-C, and triglycerides in the Zucker rat (**10c**, **10g**, **10j**, **14c**, **14g**, **14i**, **19**, **26**). Three compounds showed discordance between the in vitro and in vivo assays: diol **17** and diacid **25** are both unsymmetrical ketones with chains of three and four methylene spacers flanking the central ketone; compound **18** contains two chains consisting of four methylene spacer groups each and a phenyl substituent on one of the two quaternary carbons. In addition, keto diacid **10f**, which has two four-methylene spacers and aromatic substituents on both quaternary carbons, was not active in the lipid synthesis assay but did display activity in the Zucker rat model. These data demonstrate that the in vitro lipid synthesis assay cannot predict all active compounds in vivo but does show concordance with respect to certain structural features (e.g., *gem*-dimethyl substitutions and hydrocarbon chains but not α-(arylmethyl) substitution to the carboxyl).

Effect on Lipid Variables in the Obese Female Zucker Rat: Dose−Response for Selected Compounds. As noted previously, some long chain hydrocarbon compounds (e.g., **I** and **II**, Figure 1) possess insulin-sensitizing activity as well as lipid-regulating properties. To confirm our single dose findings with respect to lipids and determine ketone compound effects on diabetes variables, a dose−response study for some of the most active compounds (**10c**, **10g**, **14c**) was performed. In regard to lipid variables, we specifically focused on agents that lowered non-HDL-C, elevated HDL-C, and lowered serum triglycerides with additional measurements of glucose, insulin, and nonesterified fatty acids (NEFA). It should be noted that animals used to initiate these studies were between 10 and 12 weeks of age, hyperinsulinemic, and generally mildly hyperglycemic, that is, they expressed symptoms of impaired glucose tolerance. Data for **14c**, **10c**, and **10g** are presented in Tables 6, 7, and 8, respectively.

Both diacid **10c** and diol **14c** have two chains of four methylene spacers attached to the central ketone and *gem*-dimethyl substitution on both quaternary carbons. As noted previously (Tables 4 and 5), our initial assessment indicated little difference between diacids and diols in the in vitro and in vivo assays. Indeed, both compounds had similar activities in the dose−response study (Tables 6 and 7). The only observed difference was

Table 6. Effect of Daily **14c** Oral Treatment on Serum Lipid and Glycemic Control Variables in Obese Female Zucker Rats

dose		non-HDL-C (mg/dL)			HDL-C (mg/dL)			TG (mg/dL)			NE FA (mg/dL)			glucose (mg/dL)			insulin (ng/mL)		
(mg/kg/day)	n	pre	1 wk	2 wk	pre	1 wk	2 wk	pre	1 wk	2 wk	pre	1 wk	2 wk	pre	1 wk	2 wk	pre	1 wk	2 wk
0	32	25 ± 3	36 ± 5[a] (+44)	30 ± 4[a] (+20)	48 ± 2	39 ± 2[a] (−19)	41 ± 2[a] (−15)	933 ± 69	1114 ± 97[a] (+19)	1099 ± 86[a] (+18)	1.2 ± 0.08	1.3 ± 0.06	1.6 ± 0.12[a] (+33)	125 ± 2	118 ± 3	116 ± 3	9.1 ± 0.6	8.7 ± 0.5	7.7 ± 0.5
3	9	24 ± 3	25 ± 3	22 ± 2	48 ± 3	43 ± 4 [a] (−10)	39 ± 4 [a] (−19)	755 ± 89	800 ± 75	781 ± 65	1.1 ± 0.08	1.2 ± 0.05	1.6 ± 0.13[a] (+45)	118 ± 4	106 ± 2	103 ± 3	8.8 ± 1.5	7.5 ± 0.8	7.8 ± 0.6
10	18	25 ± 3	21 ± 2	25 ± 2	46 ± 3	52 ± 3 [a] (+13)	53 ± 4 [a] (+15)	777 ± 70	602 ± 37[a] (-23)	730 ± 52	1.2 ± 0.05	0.98 ± 0.08[a] (−18)	1.0 ± 0.10	112 ± 3	110 ± 2	110 ± 3	8.4 ± 0.6	7.5 ± 0.4	7.8 ± 0.5
30	26	30 ± 3	28 ± 2	38 ± 5[a] (+27)	43 ± 2	60 ± 3 [a] (+40)	61 ± 4 [a] (+42)	998 ± 85	726 ± 49[a] (−27)	985 ± 110	1.4 ± 0.06	1.1 ± 0.05[a] (−21)	1.2 ± 0.10	111 ± 1	112 ± 13	120 ± 3	9.3 ± 0.8	9.1 ± 0.6	9.8 ± 0.7
100	29	31 ± 3	23 ± 1	32 ± 2	45 ± 3	78 ± 5 [a] (+73)	79 ± 6 [a] (+76)	1051 ± 80	485 ± 29[a] (−54)	702 ± 53[a] (−33)	1.4 ± 0.10	0.98 ± 0.04[a] (−30)	0.94 ± 0.04[a] (−33)	114 ± 2	120 ± 5	118 ± 3	9.6 ± 0.8	10.9 ± 1.0	11.0 ± 0.9

[a] $p < 0.05$ compared to pretreatment. Data are represented as mean ± SEM. Numbers in parentheses are the percent increases (+) or decreases (−) of the pretreatment control values.

Table 7. Effect of Daily **10c** Oral Treatment on Serum Lipid and Glycemic Control Variables in Obese Female Zucker Rats

dose		non-HDL-C (mg/dL)			HDL-C (mg/dL)			TG (mg/dL)			NEFA (mg/dL)			glucose (mg/dL)			insulin (ng/mL)		
(mg/kg/day)	n	pre	1 wk	2 wk	pre	1 wk	2 wk	pre	1 wk	2 wk	pre	1 wk	2 wk	pre	1 wk	2 wk	pre	1 wk	2 wk
0	12	40 ± 11	43 ± 10	29 ± 3	39 ± 3	39 ± 5	38 ± 4	130 ± 261	1333 ± 231	1140 ± 124	1.5 ± 0.12	1.5 ± 0.09	1.4 ± 0.10	134 ± 6	124 ± 7	118 ± 3	9.8 ± 0.9	8.4 ± 0.6	6.8 ± 0.7[a] (−31)
3	4	32 ± 4	24 ± 2	24 ± 3	31 ± 3	36 ± 1	33 ± 1	996 ± 188	775 ± 92	857 ± 103	1.5 ± 0.14	1.2 ± 0.16	1.5 ± 0.27	108 ± 6	99 ± 4	103 ± 3	10.4 ± 1.3	10.7 ± 0.8	8.6 ± 0.5
10	4	40 ± 8	26 ± 4[a] (−35)	27 ± 4	37 ± 10	47 ± 7	39 ± 5	1143 ± 373	692 ± 180	814 ± 205	1.6 ± 0.15	0.92 ± 0.09[a]	1.5 ± 0.28	113 ± 7	105 ± 3	113 ± 3	10.6 ± 1.5	7.7 ± 1.0[a] (−27)	8.9 ± 1.3
30	4	48 ± 4	37 ± 4[a] (−23)	43 ± 5	34 ± 5	53 ± 8[a] (+56)	50 ± 9[a] (+47)	1242 ± 144	826 ± 92[a] (-33)	962 ± 118	1.4 ± 0.15	1.0 ± 0.11[a] (−29)	1.1 ± 0.20	103 ± 2	115 ± 4	1188	7.7 ± 1.6	9.2 ± 1.3	8.5 ± 1.8
100	11	31 ± 4	18 ± 3[a] (−42)	22 ± 3[a] (−29)	38 ± 3	66 ± 9[a] (+74)	68 ± 10[a] (+79)	964 ± 90	383 ± 49[a] (−60)	440 ± 58[a] (−54)	1.2 ± 0.06	0.81 ± 0.07[a] (−33)	0.66 ± 0.06[a] (−45)	110 ± 3	113 ± 6	122 ± 7	8.1 ± 0.9	9.0 ± 1.0	9.5 ± 0.9

[a] $p < 0.05$ compared to pretreatment. Data are represented as mean ± SEM. Numbers in parentheses are the percent increases (+) or decreases (−) of the pretreatment control values.

Table 8. Effect of Daily **10g** Oral Treatment on Serum Lipid and Glycemic Control Variables in Obese Female Zucker Rats

dose (mg/kg/day)	n	non-HDL-C (mg/dL)			HDL-C (mg/dL)			TG (mg/dL)			NEFA (mg/dL)			glucose (mg/dL)			insulin (ng/mL)		
		pre	1 wk	2 wk	pre	1 wk	2 wk	pre	1 wk	2 wk	pre	1 wk	2 wk	pre	1 wk	2 wk	pre	1 wk	2 wk
0	27	20 ± 2	29 ± 3[a] (+45)	28 ± 3[a] (+40)	76 ± 5	66 ± 5[a] (−13)	69 ± 5[a] (−9)	950 ± 55	1119 ± 82[a] (+18)	1189 ± 92[a] (+25)	1.3 ± 0.06	1.3 ± 0.07	1.3 ± 0.07	129 ± 4	123 ± 2	120 ± 2	9.1 ± 0.5	10.1 ± 0.6	8.1 ± 0.6
3	18	22 ± 2	23 ± 2	25 ± 2	77 ± 5	75 ± 6	77 ± 8	905 ± 57	995 ± 50	833 ± 57	1.3 ± 0.09	1.1 ± 0.07[a] (−15)	1.0 ± 0.10[a] (−23)	114 ± 3	117 ± 4	124 ± 4[a] (+8)	8.6 ± 0.9	10.0 ± 1.0	7.3 ± 0.5
10	22	22 ± 1	22 ± 2	34 ± 3[a] (+55)	86 ± 10	136 ± 11[a] (+58)	138 ± 8[a] (+60)	863 ± 63	553 ± 35[a] (−36)	865 ± 69	1.2 ± 0.08	1.0 ± 0.07[a] (−17)	0.95 ± 0.08[a] (−21)	120 ± 4	122 ± 3	125 ± 4	9.9 ± 0. 9	10.5 ± 1.1	9.1 ± 0.7
30	18	27 ± 3	14 ± 2[a] (−48)	30 ± 2	62 ± 5	159 ± 12[a] (+156)	208 ± 14[a] (+235)	982 ± 75	213 ± 19[a] (−78)	475 ± 38[a] (−52)	1.3 ± 0.07	0.88 ± 0.06[a] (−32)	0.66 ± 0.03[a] (−49)	119 ± 5	108 ± 4	130 ± 4	9.8 ± 0.9	6.4 ± 0.6[a] (−35)	7.7 ± 0.9[a] (−21)
100	15	26 ± 2	2 ± 1[a] (−92)	3 ± 1[a] (−88)	66 ± 5	100 ± 8[a] (+51)	141 ± 12[a] (+113)	937 ± 77	69 ± 5[a] (−93)	78 ± 10[a] (−92)	1.4 ± 0.06	0.98 ± 0.08[a] (−30)	0.66 ± 0.06[a] (−52)	117 ± 3	92 ± 4[a] (−21)	105 ± 3[a] (−10)	11.9 ± 1.0	6.4 ± 1.3[a] (−46)	6.0 ± 0.8[a] (−50)

[a] $p < 0.05$ compared to pretreatment. Data are represented as mean ± SEM. Numbers in parentheses are the percent increases (+) or decreases (−) of the pretreatment control values.

that **10c** appeared to dose-dependently reduce non-HDL-C, with greater effects after 1 week than after 2 weeks, while **14c** displayed little activity toward non-HDL-C. However, both compounds dose-dependently elevated HDL-C, reduced triglycerides, and reduced NEFA. Neither compound affected fasting insulin or glucose in the Zucker rat.

The extended chain length in **10g** compared to **10c** significantly increased compound potency and efficacy. Compound **10g** dose-dependently modified non-HDL-C, triglycerides, and NEFA with reductions of 88%, 92%, and 52%, respectively, after 2 weeks of dosing at 100 mg/kg/day (Table 8). Furthermore, **10g** elevated HDL-C in a time- and dose-dependent manner, reaching HDL-C levels that were 2−3 times higher than pretreatment levels. In addition, the compound dose-dependently reduced fasting insulin levels while only moderately affecting fasting glucose levels, suggesting improved insulin-sensitization in this diabetic model. Weight gain was also measured in this experiment. Control animals ($n = 27$) gained 7.9 ± 0.4% of their initial body weight (401.7 ± 5.7 g) over the 2-week study period. Animals treated with compound **10g** at doses of 10, 30, and 100 mg/kg/day gained 7.1 ± 0.5%, 4.6 ± 0.5%, and 1.1 ± 0.9% of their initial body weights (407.9 ± 8.1 g, $n = 22$; 396.4 ± 5.8 g, $n = 18$; and 413.3 ± 5.3 g, $n = 15$), respectively. The percent weight gain with compound **10g** was significantly less at 30 ($p < 0.005$; $n = 18$) and 100 mg/kg/day ($p < 0.0001$; $n = 15$) compared to the control group.

It is unclear why non-HDL-C is elevated at the 30 mg/kg/day dose for **14c** and at 10 mg/kg/day for **10g**. However, since both compounds inhibit cholesterol synthesis, the effect may be due to the well-known cholesterol synthesis compensation mechanism earlier described for statins as being operative in rodents.[50]

Conclusions

Our research effort was focused on identifying compounds for the treatment of dyslipidemia, diabetes, and obesity, all of which are major medical problems related to premature development of cardiovascular diseases. Common elements of these conditions include elevated levels of triglycerides and low levels of HDL-C. The current discovery effort has generated a series of novel keto diol and keto diacid compounds with biological properties that suggest utility for controlling these serum variables in appropriate preclinical models. Symmetrical compounds possessing five methylene spacer chains proved to be the most promising candidates for further development. Overall, we have discovered a series of novel agents that may have beneficial effects on serum lipids while enhancing glycemic control without causing weight gain. The combination of these effects within a single agent may be highly desirable to treat a host of diverse but related metabolic disorders.

Experimental Section

Chemistry. Chemical reagents from Sigma-Aldrich or Lancaster were used without further purification. Ibuprofen and silica gel for column chromatography (0.035−0.070 mm, pore diameter ca. 6 nm) were obtained from Acros Organics. ACS grade solvents from Fisher Scientific or Mallinckrodt were routinely used for chromatographic purifications and extractions. Melting points (uncorrected) were determined on either

a Thomas-Hoover capillary or Haake-Buchler melting point apparatus. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz and ambient temperature on Varian NMR spectrometers. Chemical shifts for proton NMR are given in parts per million downfield from an internal tetramethylsilane standard, and ^{13}C chemical shifts are calibrated on the $CDCl_3$ resonance at 77.23 ppm, unless otherwise specified. Coupling constants (*J*) are given in Hz. The purity of target compounds was analyzed using Shimadzu HPLC systems equipped with UV and/or RI detection.

Representative Procedure for the Synthesis of Keto Diesters: 2,2,12,12-Tetramethyl-7-oxotridecanedioic Acid Diethyl Ester (9c). Under N_2-atmosphere, to a solution of **5c** (22.4 g, 89.2 mmol) in anhydrous DMSO (300 mL) was added TosMIC (8.71 g, 44.6 mmol), NaH (60% w/w in mineral oil, 4.28 g, 107.0 mmol), and NBu_4I (3.30 g, 8.9 mmol) under cooling with an ice bath. After the addition, the reaction mixture was stirred for 23 h at room temperature, cooled with an ice bath, and carefully hydrolyzed with water (300 mL). The solution was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were washed with water (100 mL) and half-saturated aqueous NaCl solution (100 mL), dried over anhydrous $MgSO_4$, concentrated in vacuo, and dried in high vacuo to give the crude intermediate **8c** (26.2 g) as an oil [^{1}H NMR ($CDCl_3$): δ 7.85 (d, 2 H, J = 8.3), 7.42 (d, 2 H, J = 8.3), 4.12 (q, 4 H, J = 7.0), 2.49 (s, 3 H), 1.94 (m, 4 H), 1.60−1.34 (m, 8 H), 1.30−1.15 (m, 4 H), 1.25 (t, 6 H, J = 7.0), 1.15 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 177.77, 164.08, 146.43, 131.20, 130.34, 129.96, 81.78, 60.37, 42.12, 40.27, 33.21, 25.25, 25.19, 24.97, 24.26, 21.86, 14.34]. To a solution of **8c** (26.0 g) in CH_2Cl_2 (400 mL) was added concentrated HCl (100 mL) and the reaction mixture was stirred for 45 min at room temperature. The solution was diluted with water (400 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (300 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (100 mL) and saturated aqueous NaCl solution (100 mL). The organic phases were dried over anhydrous $MgSO_4$, concentrated in vacuo, and dried in high vacuo. The residue was purified by flash chromatography (silica gel; hexanes/EtOAc = 95/5, then 90/10) to give **9c** (11.0 g, 67%) as an oil. ^{1}H NMR ($CDCl_3$): δ 4.03 (q, 4 H, J = 7.1), 2.31 (t, 4 H, J = 7.5), 1.45 (m, 8 H), 1.20−1.08 (m, 4 H), 1.16 (t, 6 H, J = 7.1), 1.07 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 211.14, 178.05, 60.34, 42.69, 42.20, 40.52, 25.24, 24.71, 24.30, 14.35. HRMS (LSIMS, nba): calcd for $C_{21}H_{39}O_5$ (MH^+) 371.2797, found 371.2763.

2,10-Dimethyl-6-oxo-2,10-diphenylundecanedioic Acid Diethyl Ester (9b). According to the procedure described for the synthesis of **9c**, **5b** (25.0 g, 76.4 mmol), NBu_4I (2.78 g, 7.5 mmol), and TosMIC (7.34 g, 37.6 mmol) in anhydrous DMSO (400 mL) and Et_2O (150 mL) were reacted with NaH (60% dispersion in mineral oil, 3.80 g, 95.0 mmol) first under cooling with an ice bath and then at room temperature for 24 h. Hydrolysis and extraction afforded the intermediate **8b** (28.0 g) as a brown oil. A portion of this crude intermediate (25.0 g) was then treated with concentrated aqueous HCl (140 mL) in CH_2Cl_2 (500 mL) for 2 h at room temperature. Aqueous workup, extraction, and purification by flash chromatography (silica gel; EtOAc/hexanes = 1/20, 1/10) furnished **9b** (9.5 g, 61%) as a light yellowish oil. ^{1}H NMR ($CDCl_3$): δ 7.40−7.10 (m, 10 H), 4.20−4.05 (m, 4 H), 2.38 (m, 4 H), 2.05−1.80 (m, 4 H), 1.60 (s, 6 H), 1.50−1.20 (m, 4 H), 1.22 (m, 6 H). ^{13}C NMR ($CDCl_3$): δ 210.24, 176.06, 143.71, 128.42, 126.72, 125.97, 60.83, 50.13, 42.97, 38.91, 22.73, 22.47, 19.09, 14.13. HRMS (LSIMS, nba): calcd for $C_{29}H_{39}O_5$ (MH^+) 467.2797, found 467.2772.

7-Oxo-2,12-dimethyl-2,12-diphenyltridecanedioic Acid Diethyl Ester (9d). In analogy to the procedure described for the synthesis of **9c**, **5d** (9.59 g, 30.6 mmol) in anhydrous DMSO (50 mL) was reacted with TosMIC (3.02 g, 15.5 mmol), NaH (60% w/w in mineral oil, 1.44 g, 36.0 mmol), and NBu_4I (1.10 g, 3.0 mmol), first under cooling with a water bath and then for 96 h at room temperature. Hydrolysis and extraction afforded the crude intermediate **8d** (30.0 g) as an oil. A solution of this oil (30.0 g) in CH_2Cl_2 (300 mL) and concentrated aqueous HCl (40 mL) was stirred for 2 h at room temperature. After extractive workup and flash chromatography (silica gel; hexanes/EtOAc = 10/1), **9d** (5.0 g, 66%) was obtained as a clear oil together with a less pure fraction (1.17 g, 16%). ^{1}H NMR ($CDCl_3$): δ 7.40−7.10 (m, 10 H), 4.11 (q, 4 H, J = 7.0), 2.34 (t, 4 H, J = 7.1), 2.10−1.70 (m, 4 H), 1.6−1.4 (m, 4 H), 1.52 (s, 6 H), 1.30−1.00 (m, 10 H). ^{13}C NMR ($CDCl_3$): δ 210.7, 176.0, 143.8, 128.2, 126.5, 125.8, 60.6, 50.0, 42.4, 38.9, 24.3, 24.1, 22.6, 14.0. HRMS (LSIMS, nba): calcd for $C_{31}H_{43}O_5$ (MH^+) 495.3110, found 495.3106. HPLC: Alltima C-18 column, 250 × 4.6 mm, 5 μm; 80% acetonitrile/20% 0.05 M KH_2PO_4, flow rate 1.2 mL/min; RI, t_R 13.00 min, 94.8% pure.

2,12-Dimethyl-7-oxo-2,12-di-*p*-tolyltridecanedioic Acid Diethyl Ester (9e). In analogy to the procedure described for the synthesis of **9c**, **5e** (21.0 g, 64.2 mmol) was reacted with NBu_4I (2.37 g, 6.4 mmol), TosMIC (6.26 g, 32.1 mmol), and NaH (60% dispersion in mineral oil, 3.24 g, 81.0 mmol) in anhydrous DMSO (320 mL) and Et_2O (110 mL) for 24 h at room temperature. After hydrolysis and extraction, the crude intermediate **8e** was stirred in CH_2Cl_2 (500 mL) and concentrated HCl (140 mL) for 2 h at room temperature. Extraction and purification by flash chromatography (silica gel; EtOAc/hexanes = 1/20, 1/9) afforded **9e** (9.0 g, 54%) as a light yellowish oil. ^{1}H NMR ($CDCl_3$): δ 7.10 (d, 4 H, J = 7.9), 7.02 (d, 4 H, J = 7.9), 4.05 (q, 4 H, J = 7.0), 2.25 (t, 4 H, J = 7.3), 2.20 (s, 6 H), 1.95−1.70 (m, 4 H), 1.42 (s, 6 H), 1.50−1.05 (m, 8 H), 1.08 (t, 6 H, J = 7.0). ^{13}C NMR ($CDCl_3$): δ 211.10, 176.00, 141.00, 135.80, 128.50, 124.51, 60.50, 49.50, 42.01, 39.50, 24.28, 24.05, 22.10, 20.50, 13.00. HRMS (LSIMS, nba): calcd for $C_{33}H_{47}O_5$ (MH^+) 523.3423, found 523.3405.

2,12-Bis(4-isobutylphenyl)-2,12-dimethyl-7-oxotridecanedioic Acid Diethyl Ester (9f). Similar to the procedure given for **9c**, **5f** (14.13 g, 38.3 mmol) was reacted with TosMIC (3.73 g, 19.1 mmol), NBu_4I (1.30 g, 3.5 mmol), and NaH (2.0 g, 60%, 50.0 mmol) in freshly distilled DMSO (200 mL) for 18 h at room temperature. The crude intermediate **8f** obtained after hydrolysis and extraction was stirred in CH_2Cl_2 (100 mL) and concentrated HCl (50 mL) for 1 h at room temperature. Extractive workup and purification by flash chromatography (silica gel; EtOAc/hexanes = 10/90, then 20/80) yielded **9f** (9.49 g, 82%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.18 (d, 4 H, J = 8.0), 7.07 (d, 4 H, J = 8.0), 4.10 (q, 4 H, J = 7.0), 2.43 (d, 4 H, J = 7.0), 2.34 (t, 4 H, J = 7.6), 2.10−1.92 (m, 2 H), 1.92−1.78 (m, 4 H), 1.60−1.50 (m, 4 H), 1.50 (s, 6 H), 1.19−1.11 (m, 5 H), 1.17 (t, 3 H, J = 7.0), 0.88 (d, 12 H, J = 6.6). ^{13}C NMR ($CDCl_3$): δ 211.06, 176.39, 141.36, 140.04, 129.16, 125.71, 60.77, 49.90, 45.06, 42.66, 39.18, 30.27, 24.59, 24.35, 22.86, 22.56, 14.23. HRMS (LSIMS, nba): calcd for $C_{39}H_{59}O_5$ (MH^+) 607.4362, found 607.4337.

2,2,14,14-Tetramethyl-8-oxopentadecanedioic Acid Diethyl Ester (9g). According to the procedure described for the synthesis of **9c**, a solution of **5g** (32.3 g, 115.3 mmol), NBu_4I (3.69 g, 10.0 mmol), and TosMIC (9.80 g, 50.2 mmol) in anhydrous DMSO (300 mL) was treated with NaH (4.80 g, 120.0 mmol, 60% in mineral oil) at room temperature for 20 h. The intermediary dialkylated TosMIC derivative **8g** obtained after aqueous workup (36.8 g) was then hydrolyzed with concentrated HCl (110 mL) in CH_2Cl_2 (450 mL) at room temperature for 1 h. Extractive workup and purification by column chromatography (silica gel; hexanes/EtOAc = 11/1) afforded **9g** (12.20 g, 61%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 4.11 (q, 4 H, J = 6.9 Hz), 2.37 (t, 4 H, J = 7.5), 1.58−1.47 (m, 8 H), 1.35−1.10 (m, 8 H), 1.24 (t, 6 H, J = 7.2), 1.15 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 211.6, 178.3, 60.5, 43.1, 42.5, 40.9, 30.1, 25.5, 25.1, 24.1, 14.7. HRMS (LSIMS, gly): calcd for $C_{23}H_{43}O_5$ (MH^+) 399.3110, found 399.3129.

2,2,18,18-Tetramethyl-10-oxononadecanedioic Acid Diethyl Ester (9j). Under N_2 atmosphere, NaH (60% w/w in mineral oil, 1.21 g, 30.2 mmol) was added in portions to a solution of TosMIC (2.43 g, 12.5 mmol) and NBu_4I (0.462 g, 1.25 mmol) in dry DMSO (100 mL) while being vigorously stirred and cooled with a water bath. After 15 min, **5j** (7.65 g, 26.1 mmol) was added dropwise in 20 min. After 1 h, H_2O (100

mL) was added dropwise and the resulting mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (silica, heptane:EtOAc = 6:1) to give **8j** (5.41 g) as a yellow oil. To a portion of this oil (5.03 g), dissolved in CH_2Cl_2 (100 mL), was added aqueous HCl (concd, 30 mL) and the resulting mixture was stirred vigorously for 17.5 h. Water (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 $NaHCO_3$ solution (2 × 100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by column chromatography (silica, heptane:EtOAc = 7:1) to give **9j** (3.21 g, 61%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 4.11 (q, J = 7.2, 4 H), 2.37 (t, J = 7.4, 4 H), 1.57−1.46 (m, 8 H), 1.28−1.23 (m, 16 H), 1.24 (t, J = 7.1, 6 H), 1.15 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 211.5, 178.0, 60.08, 60.07, 42.7, 42.1, 40.7, 29.9, 29.21, 29.15, 25.1, 24.8, 23.8, 14.2. HRMS: calcd for $C_{27}H_{50}O_5$ (MH^+) 454.3658, found 454.3663.

9-Isocyano-2,2,16,16-tetramethyl-9-(tolyl-4-sulfonyl)-heptadecanedioic Acid Diethyl Ester (8i). To a solution of **5i** (35.0 g, 125.4 mmol), NBu_4I (4.6 g, 12.5 mmol), and TosMIC (12.2 g, 62.5 mmol) in anhydrous DMSO (450 mL) was added NaH (60% dispersion in mineral oil, 6.3 g, 158 mmol) under cooling with an ice−water bath and under N_2 atmosphere. The reaction mixture was stirred for 23 h at ambient temperature and then carefully hydrolyzed with ice−water (500 mL) and extracted with MTBE (3 × 200 mL). The organic layers were washed with water (300 mL) and brine (150 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to give crude **8i** (37.0 g, 100%) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.88 (d, J = 7.9, 2 H), 7.42 (d, J = 7.9, 2 H), 4.10 (q, J = 7.5, 4 H), 2.48 (s, 3 H), 2.05−1.75 (m, 3 H), 1.65−1.20 (m, 21 H), 1.15 (t, J = 7.5, 6 H), 1.10 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 177.89, 163.75, 146.23, 131.08, 130.28, 129.82, 81.79, 60.17, 42.09, 40.57, 33.09, 29.68, 29.31, 25.17, 24.78, 23.66, 21.08, 14.31. HRMS (LSIMS, gly): calcd for $C_{37}H_{54}NO_6S$ (MH^+) 592.3672, found 592.3667.

2,2,16,16-Tetramethyl-9-oxoheptadecanedioic Acid Diethyl Ester (9i). To a solution of **8i** (12.0 g, 20.3 mmol) in CH_2Cl_2 (200 mL) was added concentrated HCl (47 mL). The reaction mixture was stirred for 80 min at room temperature and diluted with water (200 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 70 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (3 × 40 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to yield the crude product (7.52 g). Purification by column chromatography (silica gel, EtOAc/hexanes = 1/9) gave **9i** (3.5 g, 40.0%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 4.14 (q, J = 7.1, 4 H), 2.41 (t, J = 7.0, 4 H), 1.66−1.45 (m, 8 H), 1.35−1.20 (m, 12 H), 1.25 (t, J = 7.1, 6 H), 1.17 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 211.24, 177.89, 60.01, 42.69, 42.07, 40.64, 29.86, 29.07, 25.13, 24.73, 23.74, 14.24. HRMS (LSIMS, gly): calcd for $C_{25}H_{47}O_5$ (MH^+) 427.3423, found 427.3430.

Representative Procedure for the Saponification of Keto Diesters: 2,12-Bis(4-isobutylphenyl)-2,12-dimethyl-7-oxotridecanedioic Acid (10f). A solution of **9f** (3.0 g, 4.95 mmol) and KOH (85%, 4.4 g, 66.7 mmol) in EtOH (40 mL) and water (10 mL) was heated to reflux for 6 h. The EtOH was removed under reduced pressure and the mixture was diluted with water (200 mL). The solution was extracted with Et_2O (100 mL) and the aqueous layer was acidified with concentrated HCl (10 mL) to pH 1. The product was extracted with Et_2O (2 × 100 mL). The ether fractions were combined, dried over Na_2SO_4, concentrated, and dried in high vacuo to yield **10f** (2.35 g, 86%) as a light yellow foam. ^{1}H NMR ($CDCl_3$): δ 10.02 (br, 2 H), 7.24 (d, 4 H, J = 8.0), 7.09 (d, 4 H, J = 8.0), 2.43 (d, 4 H, J = 7.0), 2.33 (t, 4 H, J = 7.3), 2.05−1.88 (m, 2 H), 1.96−1.77 (m, 4 H), 1.55−1.42 (m, 10 H), 1.22−1.08 (m, 4 H), 0.88 (d, 12 H, J = 6.6). ^{13}C NMR ($CDCl_3$): δ 211.48, 182.94, 140.43, 140.24, 129.27, 125.94, 49.71, 45.06, 42.58, 42.58, 38.91, 30.25, 24.45, 24.24, 22.58, 22.40. HRMS (LSIMS, nba): calcd for $C_{35}H_{50}O_5Na$ (MNa^+): 573.355, found 573.3459. HPLC: Alltima phenyl column, 250 × 4.6 mm, 5 μm; 80% acetonitrile/20% 0.05 M KH_2PO_4, flow rate 1.2 mL/min; RI, t_R 6.33 min, 86.9% pure. Anal. ($C_{35}H_{50}O_5$): C, H.

2,10-Dimethyl-6-oxo-2,10-diphenylundecanedioic Acid (10b). According to the procedure given for **10f**, **9b** (14.5 g, 31.1 mmol) was saponified with KOH (85%, 7.2 g, 108.6 mmol) in water (15 mL) and EtOH (45 mL) at reflux for 6 h. After the usual extractive workup, the crude material was purified by flash chromatography (silica gel; EtOAc/hexanes = 1/20, 1/10, 1/2) to give **10b** (4.0 g, 31%) as a white solid. Mp: 44−46 °C. ^{1}H NMR ($CDCl_3$): δ 10.25 (br, 2 H), 7.35−7.22 (m, 10 H), 2.32 (m, 4 H), 1.94−1.86 (m, 4 H), 1.57 (s, 6 H), 1.51−1.22 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ 210.64, 182.66, 142.69, 128.66, 127.18, 126.29, 50.07, 42.97, 38.62, 22.20, 19.11. HRMS (LSIMS, gly): calcd for $C_{25}H_{31}O_5$ (MH^+) 411.2171, found 411.2144. HPLC: Alltima C-18 column, 250 × 4.6 mm, 5 μm; 60% acetonitrile/40% 0.05 M KH_2PO_4, flow rate 1.2 mL/min; UV, t_R 5.50 min, 95.2% pure.

7-Oxo-2,2,12,12-tetramethyltridecanedioic Acid (10c). According to the procedure given for **10f**, **9c** (30.0 g, 81.0 mmol) was saponified with KOH (85%, 18.9 g, 286 mmol) in EtOH (143 mL) and water (48 mL) at reflux for 5 h. The solid product obtained after extraction and drying was purified by flash chromatography (silica; hexanes/EtOAc = 90/10) to afford **10c** (22.0 g, 86%) as a white solid. Mp: 60−61.5 °C. ^{1}H NMR ($CDCl_3$): δ 11.40 (br, 2 H), 2.41 (t, 4 H, J = 7.3), 1.62−1.48 (m, 8 H), 1.32−1.18 (m, 4 H), 1.18 (s, 12 H). ^{13}C NMR ($CDCl_3$ = 77.0 ppm): δ 211.11, 184.74, 42.49, 42.14, 40.42, 24.92, 24.62, 23.99. HRMS (LSIMS, gly): calcd for $C_{17}H_{31}O_5$ (MH^+) 315.2171, found 315.2183. HPLC: Alltima phenyl column, 250 × 4.6 mm, 5 μm; 60% acetonitrile/40% 0.05 M KH_2PO_4, flow rate 1.2 mL/min; RI, t_R 5.08 min, 94.5% pure. Anal. ($C_{17}H_{30}O_5$): C, H.

2,12-Dimethyl-7-oxo-2,12-diphenyltridecanedioic Acid (10d). According to the procedure given for **10f**, **9d** (3.93 g, 7.9 mmol) was hydrolyzed with KOH (85%, 4.0 g, 60.6 mmol) in EtOH (60 mL) and water (10 mL) at reflux for 3 h and at room temperature overnight. After the usual workup and drying, **10d** (3.0 g, 87%) was obtained as an oil. ^{1}H NMR ($CDCl_3$): δ 7.40−7.10 (m, 10 H), 2.32 (t, 4 H, J = 7.2), 2.10−1.80 (m, 4 H), 1.60−1.45 (m, 4 H), 1.54 (s, 6 H), 1.25−1.10 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ 211.1, 182.5, 142.8, 128.4, 126.9, 126.0, 49.9, 42.3, 38.7, 24.2, 24.0, 22.3. HRMS (LSIMS, nba): calcd for $C_{27}H_{35}O_5$ (MH^+) 439.2484, found 439.2497. HPLC: Alltima C-18 column, 250 × 4.6 mm, 5 μm; 60% acetonitrile/40% 0.05 M KH_2PO_4, flow rate 1.2 mL/min; RI, t_R 7.67 min, 93.7% pure.

2,12-Dimethyl-7-oxo-2,12-di-*p*-tolyltridecanedioic Acid (10e). According to the procedure given for **10f**, **9e** (9.0 g, 17.2 mmol) was hydrolyzed with KOH (85%, 4.0 g, 60.6 mmol) in water (10 mL) and EtOH (30 mL) at reflux for 6 h. After the usual extractive workup, the crude material was purified by flash chromatography (silica gel; EtOAc/hexanes = 1/10, 1/6, 1/2) to give **10e** (3.1 g, 39%) as a white solid. Mp: 48−50 °C. ^{1}H NMR ($CDCl_3$): δ 10.8−8.8 (br, 2 H), 7.22 (d, 4 H, J = 8.1), 7.12 (d, 4 H, J = 8.1), 2.36 (t, 4 H, J = 7.5), 2.31 (s, 6 H), 1.98−1.80 (m, 4 H), 1.56−1.44 (m, 4 H), 1.51 (s, 6 H), 1.24−1.15 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ 211.63, 183.07, 140.40, 137.00, 129.58, 126.43, 50.02, 42.82, 39.10, 24.74, 24.50, 22.82, 21.39. HRMS (LSIMS, gly): calcd for $C_{29}H_{39}O_5$ (MH^+) 467.2797, found 467.2785. HPLC: Alltima C-18 column, 250 × 4.6 mm, 5 μm; 60% acetonitrile/40% 0.05 M KH_2PO_4, flow rate 1.2 mL/min; RI, t_R 15.17 min, 92.4% pure. Anal. ($C_{29}H_{38}O_5$): C, H.

2,2,14,14-Tetramethyl-8-oxopentadecanedioic Acid (10g). According to the procedure given for **10f**, **9g** (8.54 g, 21.4 mmol) was saponified with KOH (85%, 4.53 g, 68.6 mmol) in EtOH (13 mL) and water (5 mL) at reflux for 4 h. The solid product obtained after usual workup was recrystallized from Et_2O/hexanes (50 mL/50 mL), affording **10g** (4.16 g, 57%) as colorless needles. Mp: 82−83 °C. ^{1}H NMR ($CDCl_3$): δ 11.53 (br, 2H), 2.39 (t, 4H, J = 7.3), 1.60−1.50 (m, 8 H), 1.30−1.20 (m, 8 H), 1.18 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 211.7, 185.0, 42.8, 42.3, 40.4, 29.7, 25.1, 24.8, 23.8. HRMS (LSIMS, gly): calcd

for $C_{19}H_{35}O_5$ (MH^+) 343.2484, found 343.2444. HPLC: Alltima C-8 column, 250 × 4.6 mm, 5 μm; 60% acetonitrile/40% 0.05 M KH_2PO_4, flow rate 1.0 mL/min; RI, t_R 6.50 min, 92.6% pure. Anal. ($C_{19}H_{34}O_5$): C, H.

2,2,16,16-Tetramethyl-9-oxoheptadecanedioic Acid (10i). To a solution of KOH (85%, 8.4 g, 127.3 mmol) in deionized water (3.6 mL) and EtOH (11.5 mL) was added **8i** (15.0 g, 25.3 mmol) and the mixture was heated to reflux for 7 h. The reaction mixture was diluted with water (40 mL) and extracted with MTBE (2 × 30 mL). The aqueous layer was cooled with an ice bath and the pH was adjusted to 1 by addition of 5 N H_2SO_4 (45 mL). The aqueous layer was extracted with MTBE (3 × 30 mL), and the combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to give a crude oil (12.5 g). Purification by chromatography (silica gel, EtOAc/hexanes = 10% to 100%) and recrystallization from MTBE/hexanes (4 mL/50 mL) yielded **10i** (5.37 g, 57%) as a white powder. Mp: 74.5−76.0 °C. ^{1}H NMR ($CDCl_3$): δ 12.40−11.20 (br, 2 H), 2.39 (t, J = 7.3, 4 H), 1.62−1.48 (m, 8 H), 1.38−1.22 (m, 12 H), 1.11 (s, 12 H). ^{13}C NMR ($CDCl_3$ = 77.02 ppm): δ 211.88, 184.93, 42.70, 42.19, 40.63, 29.63, 29.09, 24.96, 24.83, 23.83. HRMS (LSIMS, gly): calcd for $C_{21}H_{39}O_5$ (MH^+) 371.2797, found 371.2804. HPLC: Inertsil ODS2 column, 250 × 4.6 mm, 5 μm; 60% acetonitrile/40% 0.05 M KH_2PO_4, flow rate 1.0 mL/min; RI, t_R 10.95 min, 96.9% pure. Anal. ($C_{21}H_{38}O_5$) C, H.

2,2,18,18-Tetramethyl-10-oxononadecanedioic Acid (10j). To a solution of **9j** (11.63 g, 25.6 mmol) in EtOH and H_2O (3:1, 200 mL) was added powdered KOH (85%, 4.31 g, 65.3 mmol). The resulting mixture was refluxed for 19 h and concentrated in vacuo until all of the EtOH was removed. Water (200 mL) was added and the resulting mixture was extracted with Et_2O (2 × 200 mL). The aqueous phase was acidified with aqueous HCl (4 M) to pH ∼1 and extracted with Et_2O (3 × 200 mL). The combined Et_2O layers of the latter extraction were dried over anhydrous Na_2SO_4 and evaporated in vacuo. The remaining white solid was recrystallized from heptane/iPr$_2$O to give **10j** (7.56 g, 74%) as white crystals. Mp: 74.3−77.3 °C. ^{1}H NMR (CD_3OD): δ 2.43 (t, J = 7.3, 4 H), 1.57−1.50 (m, 8 H), 1.33−1.21 (m, 16 H), 1.14 (s, 12 H). ^{13}C NMR (CD_3OD): δ 214.5, 182.1, 43.6, 43.2, 42.0, 31.2, 30.4, 30.38, 26.2, 25.9, 25.0. HRMS: calcd for $C_{23}H_{42}O_5$ (M^+): 398.3028, found 398.3032. Anal. ($C_{23}H_{42}O_5$): C, H.

2,2,16,16-Tetramethylheptadecane-1,9,17-triol (11i). Under N_2 atmosphere, MTBE (80 mL) was added to $LiAlH_4$ (0.67 g, 17.65 mmol) and the suspension was stirred under cooling with an ice−water bath. A solution of **9i** (3.0 g, 7.03 mmol) in MTBE (20 mL) was added dropwise, followed by additional MTBE (40 mL). After 2 h at 0 °C, the reaction mixture was carefully quenched by addition of EtOAc (8 mL) and allowed to warm to room temperature overnight. The mixture was cooled with an ice−water bath and carefully hydrolyzed by addition of crushed ice (15 g) and water (15 mL). The pH was adjusted to 1 by addition of 2 N H_2SO_4 (28 mL) and the solution was stirred at room temperature for 15 min. The layers were separated, and the aqueous layer was extracted with MTBE (40 mL). The combined organic layers were washed with deionized water (50 mL), saturated $NaHCO_3$ solution (40 mL), and brine (40 mL), dried over anhydrous $MgSO_4$, concentrated in vacuo, and dried in high vacuo. The crude product (2.65 g) was purified by recrystallization from hot CH_2Cl_2 (20 mL). The crystals were filtered, washed with ice-cold CH_2Cl_2 (20 mL), and dried in high vacuo to furnish **11i** (1.59 g, 66%) as a white solid. Mp: 75−77 °C. ^{1}H NMR ($CDCl_3$): δ 3.57 (m, 1 H), 3.30 (s, 4 H), 1.72 (br, 2 H), 1.50−1.16 (m, 25 H), 0.85 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 72.09, 38.79, 37.61, 35.21, 30.70, 29.85, 25.78, 24.06, 23.92. HRMS (LSIMS, gly): calcd for $C_{21}H_{45}O_3$ (MH^+) 345.3369, found 345.3364. HPLC: Alltima C-18 column, 250 × 4.6 mm, 5 μm; 60% acetonitrile/40% water, flow rate 1.0 mL/min; RI, t_R 17.88 min, 95.0% pure.

Representative Procedure for the Dialkylation of TosMIC and Deprotection to Keto Diols: 1,15-Dihydroxy-2,2,14,14-tetramethylpentadecan-8-one (14g). Under an argon atmosphere, to a solution of **7g** (26.0 g, 84.6 mmol) and TosMIC (7.8 g, 40.0 mmol) in anhydrous DMSO (200 mL) and THF (10 mL) was added NaH (3.8 g, 95.0 mmol, 60% in mineral oil) in five portions at 20−30 °C under cooling with a water bath. After the addition of NBu_4I (3.0 g, 8.1 mmol), the reaction mixture was stirred at room temperature for 20 h and then hydrolyzed with water (400 mL). The mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with saturated aqueous NaCl solution (100 mL), dried over $MgSO_4$, and concentrated in vacuo to yield the crude dialkylated intermediate (28.2 g) as an orange oil, which was used without purification. To a solution of this crude product (28.0 g) in MeOH (115 mL) was added dilute H_2SO_4 (46 g, 12 mL of concd H_2SO_4 in 24 mL of water) over a period of 10 min, and the mixture was stirred for 80 min at room temperature. The solution was diluted with water (120 mL) and extracted with CH_2Cl_2 (150 mL, 100 mL, 50 mL). The combined organic layers were washed with saturated aqueous Na_2CO_3 solution (2 × 100 mL), saturated aqueous $NaHCO_3$ solution (100 mL), water (200 mL), and saturated aqueous NaCl solution (150 mL). The organic extract was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue (18.4 g) was purified by column chromatography (silica gel; hexanes, then CH_2Cl_2, then hexanes/EtOAc = 4/3) to give **14g** (9.97 g, 79%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.30 (s, 4 H), 2.39 (t, 4 H, J = 7.2), 2.07 (br. s, 2 H), 1.60−1.55 (m, 4 H), 1.28−1.17 (m, 12 H), 0.85 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 212.0, 72.0, 43.0, 38.6, 35.2, 30.3, 24.0, 23.8. HRMS (LSIMS, gly): calcd for $C_{19}H_{39}O_3$ (MH^+) 315.2899, found 315.2886. HPLC: Alltima C-18 column, 250 × 4.6 mm, 5 μm; 70% acetonitrile/30% water, flow rate 1.0 mL/min; RI, t_R 8.10 min, 94.7% pure.

1,11-Dihydroxy-2,2,10,10-tetramethylundecan-6-one (14a). In analogy to the procedure described for the synthesis of **14g**, **7a** (40.0 g, 143.3 mmol) was reacted with TosMIC (13.99 g, 71.7 mmol), NBu_4I (5.28 g, 14.3 mmol), and NaH (6.86 g, 171.5 mmol) in anhydrous DMSO (400 mL). After extractive workup and drying, the crude intermediate (47.9 g) was dissolved in MeOH (200 mL) and water (40 mL) and treated with concentrated sulfuric acid (20 mL) at room temperature. Workup and purification by chromatography (silica gel; hexanes/EtOAc = 90/10, 70/30, and then 50/50) afforded **14a** (5.6 g, 30%) as an oil. ^{1}H NMR ($CDCl_3$): δ 3.30 (s, 4 H), 2.68 (br. s, 2 H), 2.40 (t, 4 H, J = 7.2), 1.53 (m, 4 H), 1.20 (m, 4 H), 0.86 (s, 12 H). ^{13}C NMR ($CDCl_3$ = 77.0 ppm): δ 212.25, 70.99, 43.15, 37.69, 34.94, 23.89, 17.91. HRMS (LSIMS, gly): calcd for $C_{15}H_{29}O_2$ ($MH^+ - H_2O$) 241.2168, found 241.2169. HPLC: Alltima C-8 column, 250 × 4.6 mm, 5 μm; 50% acetonitrile/50% water, flow rate 1.0 mL/min; RI, t_R 6.05 min, 96.7% pure.

1,11-Dihydroxy-2,10-dimethyl-2,10-diphenylundecan-6-one (14b). In analogy to the procedure given for **14g**, to a solution of **7b** (25.0 g, 73.3 mmol), NBu_4I (3.0 g, 8.2 mmol), and TosMIC (7.23 g, 37.0 mmol) in anhydrous DMSO (350 mL) was added NaH (60% dispersion in mineral oil, 3.73 g, 93.3 mmol) while the temperature was controlled with an ice bath. After the addition of Et_2O (100 mL), the mixture was stirred at room temperature for 24 h, hydrolyzed, extracted, and dried to afford the dialkylated TosMIC intermediate (28.0 g) as a brown oil. This crude intermediate was heated to reflux for 3 h in MeOH (500 mL), concentrated HCl (60 mL), and water (120 mL). Extractive workup and purification by flash chromatography (silica gel; hexanes, then EtOAc/hexanes = 1/20, 1/10, 1/2, 1/1) gave **14b** (5.3 g, 38%) as a light yellowish oil. ^{1}H NMR ($CDCl_3$): δ 7.38−7.30 (m, 8 H), 7.26−7.18 (m, 2 H), 3.62 (d, 2 H, J = 10.5 Hz), 3.48 (d, 2 H, J = 10.5 Hz), 2.25 (m, 6 H) 1.76−1.64 (m, 2 H), 1.58−1.16 (m, 6 H), 1.32 (s, 6 H). ^{13}C NMR ($CDCl_3$): δ 211.43, 144.84, 128.32, 126.58, 126.03, 71.79, 43.11, 42.89, 37.61, 21.68, 18.12. HRMS (LSIMS, nba): calcd for $C_{25}H_{33}O_2$ ($MH^+ - H_2O$) 365.2481, found 365.2482. HPLC: Alltima C-8 column, 250 × 4.6 mm, 5 μm; 50% acetonitrile/50% water, flow rate 1.0 mL/min; RI, t_R 14.00 min, 89.5% pure.

1,13-Dihydroxy-2,2,12,12-tetramethyltridecan-7-one (14c). Similar to the procedure given for the synthesis of **14g**, **7c** (13.0 g, 44.3 mmol) was treated with TosMIC (4.33 g, 22.17 mmol), NaH (60% dispersion in mineral oil, 2.13 g, 53.2 mmol),

and NBu_4I (1.64 g, 4.4 mmol) in anhydrous DMSO (100 mL) and anhydrous Et_2O (50 mL) at room temperature overnight. Hydrolysis and extraction afforded the dialkylated TosMIC intermediate (15.5 g) as an oil that was dissolved in MeOH (180 mL), concentrated HCl (20 mL), and water (40 mL) and heated to reflux for 2 h. Extractive workup and purification by flash chromatography (silica gel; hexanes/EtOAc = 50/50) furnished **14c** (4.3 g, 68%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.28 (s, 4 H), 2.80 (br. m, 2 H), 2.42 (t, 4 H, J = 7.3), 1.54 (m, 4 H), 1.25 (m, 8 H), 0.84 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 212.06, 71.24, 42.47, 38.11, 34.76, 24.45, 23.72, 23.25. HRMS (LSIMS, gly): calcd for $C_{17}H_{35}O_5$ (MH^+) 287.2556, found 287.2585. HPLC: Alltima C-8 column, 250 × 4.6 mm, 5 μm; 58% acetonitrile/42% water, flow rate 1.0 mL/min; RI, t_R 7.02 min, 97.5% pure. Anal. ($C_{17}H_{34}O_5$): C, H.

1,13-Dihydroxy-2,12-dimethyl-2,12-diphenyltridecan-7-one (14d). According to the procedure described for the synthesis of **14g**, **7d** (10.0 g, 28.2 mmol) was reacted with NBu_4I (1.06 g, 2.9 mmol), TosMIC (2.34 g, 12.0 mmol), and NaH (60% dispersion in mineral oil, 1.42 g, 35.5 mmol) in anhydrous DMSO (100 mL) and anhydrous Et_2O (50 mL) at room temperature for 24 h. After aqueous workup and extraction, the dialkylated TosMIC intermediate (11.0 g) was heated to reflux in a mixture of MeOH (180 mL), concentrated HCl (20 mL), and water (40 mL) for 3 h. After extraction, the crude oil was purified by flash chromatography (silica gel; hexanes/EtOAc = 80/20, then 60/40), affording **14d** (3.0 g, 61%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.37−7.28 (m, 8 H), 7.24−7.17 (m, 2 H), 3.69 (dd, 2 H, J = 10.9, 5.2), 3.52 (dd, 2 H, J = 10.9, 7.5), 2.26 (t, 4 H, J = 7.3), 1.75 (m, 2 H), 1.61 (s, 2 H), 1.57−1.40 (m, 6 H), 1.33 (s, 6 H), 1.29−1.06 (m, 2 H), 1.04−0.80 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ 211.21, 144.72, 128.23, 126.50, 125.92, 72.17, 43.14, 42.38, 38.06, 24.27, 23.34, 21.42. HRMS (LSIMS): calcd for $C_{27}H_{39}O_3$ (MH^+) 411.2899, found 411.2899. HPLC: Alltima phenyl column, 250 × 4.6 mm, 5 μm; 70% acetonitrile/30% water, flow rate 1.0 mL/min; UV, t_R 8.10 min, 92.7% pure.

1,13-Dihydroxy-2,12-dimethyl-2,12-di-*p*-tolyltridecan-7-one (14e). According to the procedure for the synthesis of **14g**, **7e** (21.5 g, 75.3 mmol) was reacted with NBu_4I (2.36 g, 6.4 mmol), TosMIC (5.68 g, 29.1 mmol), and NaH (60% dispersion in mineral oil, 2.94 g, 73.5 mmol) in anhydrous DMSO (300 mL) and anhydrous Et_2O (100 mL) at room temperature for 24 h. The crude intermediate (18.4 g) obtained after aqueous workup and extraction was then heated to reflux in MeOH (300 mL), concentrated HCl (36 mL), and water (70 mL) for 3 h. Extractive workup and purification by flash chromatography (silica gel; hexanes/EtOAc = 20/1, 15/1, 10/1, 5/1, and 1/1) gave **14e** (2.72 g, 21%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.18 (d, 4 H, J = 8.1), 7.12 (d, 4 H, J = 8.1), 3.61 (d, 2H, J = 11.0), 3.48 (d, 2 H, J = 11.0 Hz), 2.31 (s, 6 H), 2.26 (t, 4 H, J = 7.8), 1.78−1.40 (m, 10 H), 1.29 (s, 6 H), 1.24−0.82 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ 211.51, 141.75, 135.64, 129.23, 126.64, 72.54, 43.06, 42.65, 38.28, 24.53, 23.59, 21.66, 20.98. HRMS (LSIMS, gly): calcd for $C_{29}H_{43}O_3$ (MH^+) 439.3212, found 439.3222. HPLC: Alltima C-8 column, 250 × 4.6 mm, 5 μm; 60% acetonitrile/40% water, flow rate 1.0 mL/min; RI, t_R 15.32 min, 95.4% pure.

1,15-Dihydroxy-2,14-dimethyl-2,14-diphenylpentadecan-8-one (14h). In analogy to the procedure of **14g**, to a solution of **7h** (18.0 g, 63.1 mmol), NBu_4I (2.0 g, 5.4 mmol), and TosMIC (4.8 g, 24.6 mmol) in anhydrous DMSO (250 mL) and Et_2O (80 mL) was added NaH (60% dispersion in mineral oil, 2.5 g, 62.5 mmol) while being cooled with an ice bath under N_2 atmosphere. After 24 h at room temperature, the mixture was hydrolyzed and worked up by extraction to give the crude intermediate (18.0 g) as a brown oil. This crude material was heated to reflux in MeOH (300 mL), concentrated HCl (36 mL), and water (70 mL) for 3 h. Extractive workup and purification by flash chromatography (silica gel; hexanes/EtOAc/hexanes = 10/1, 5/1, 2/1) yielded **14h** (6.1 g, 56%) as a yellowish oil. ^{1}H NMR ($CDCl_3$): δ 7.32−7.19 (m, 10 H), 3.68 (d, 2 H, J = 10.8), 3.50 (d, 2 H, J = 10.8), 2.26 (t, 4 H, J = 7.50 H), 1.88−1.42 (m, 10 H), 1.25 (s, 6 H), 1.22−0.85 (m, 8 H). ^{13}C NMR ($CDCl_3$): δ 211.68, 144.94, 128.56, 126.82, 126.23, 72.68, 43.50, 42.79, 38.42, 30.01, 23.74, 23.68, 21.62. HRMS (LSIMS, nba): calcd for $C_{29}H_{43}O_3$ (MH^+) 439.3212, found 439.3207. HPLC: Alltima C-8 column, 250 × 4.6 mm, 5 μm; 75% acetonitrile/25% water, flow rate 1.0 mL/min; RI, t_R 5.78 min, 95.3% pure.

2,12-*Bis*(4-isobutylphenyl)-2,12-dimethyl-7-([1,3]dithianyl)tridecanedioic Acid Diethyl Ester (12f). Compound **9f** (5.50 g, 9.06 mmol) was dissolved in CH_2Cl_2 (freshly distilled from CaH_2, 60 mL) with BF_3−Et_2O (0.45 mL, 0.50 g, 3.55 mmol) and 1,3-propanedithiol (1.0 mL, 1.08 g, 9.99 mmol). The solution was stirred for 3 h at room temperature under a nitrogen atmosphere. An additional volume of CH_2Cl_2 (100 mL) was added and the solution was extracted with 5% NaOH solution (2 × 50 mL) and water (100 mL). After drying with anhydrous Na_2SO_4, filtration, and concentration, the product was purified by flash chromatography (silica gel; EtOAc/hexanes = 10/90), affording **12f** (6.16 g, 98%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.20 (d, 4 H, J = 8.0), 7.07 (d, 4 H, J = 8.0), 4.10 (q, 4 H, J = 7.0), 2.76 (t, 4 H, J = 5.3), 2.43 (d, 4 H, J = 7.0), 2.09−1.95 (m, 2 H), 1.94−1.78 (m, 10 H), 1.51 (s, 6 H), 1.46−1.36 (m, 4 H), 1.25−1.12 (m, 4 H), 1.18 (t, 6 H, J = 7.0), 0.88 (d, 12 H, J = 6.5). ^{13}C NMR ($CDCl_3$): δ 176.42, 141.43, 140.00, 129.14, 125.74, 60.74, 53.30, 49.97, 45.05, 39.22, 38.29, 30.26, 26.10, 25.64, 25.17, 24.76, 22.99, 22.56, 14.26. HRMS (EI): calcd for $C_{42}H_{64}O_4S_2$ (M^+) 696.4246, found 696.4234. HPLC: Alltima C-18 column, 250 × 4.6 mm, 5 μm; 95% acetonitrile/5% water, flow rate 1.0 mL/min; UV, t_R 7.33 min, 96.2% pure.

2,12-Bis(4-isobutylphenyl)-2,12-dimethyl-7-([1,3]dithianyl)tridecane-1,13-diol (13f). A solution of **12f** (5.81 g, 8.33 mmol) in freshly distilled THF (50 mL) was added dropwise to a suspension of $LiAlH_4$ (1.0 g, 26.4 mmol) in THF (50 mL) at −78 °C under N_2 atmosphere. The solution was warmed to room temperature over 4 h, cooled back to −78 °C, and quenched with EtOAc (5.0 mL). After warming to room temperature, water (100 mL) was added and the product was extracted with Et_2O (2 × 100 mL). The ether extracts were combined, dried with sodium sulfate, filtered, and concentrated. After drying under high vacuum for 4 h, **13f** (4.80 g, 94%) was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.20 (d, 4 H, J = 8.0), 7.09 (d, 4 H, J = 8.0), 3.64 (d, 2 H, J = 10.7), 3.48 (d, 2 H, J = 10.7), 2.71 (t, 4 H, J = 5.1), 2.50−2.35 (m br, 2 H), 2.43 (d, 4 H, J = 7.0), 1.90−1.80 (m, 4 H), 1.80−1.68 (m, 6 H), 1.58−1.42 (m, 2 H), 1.38−1.25 (m, 4 H), 1.30 (s, 6 H), 1.26−1.10 (m, 2H), 1.10−0.95 (m, 2 H), 0.89 (d, 12 H, J = 6.6). ^{13}C NMR ($CDCl_3$): δ 141.94, 139.39, 129.20, 126.44, 72.48, 53.30, 44.97, 43.09, 38.45, 38.18, 30.21, 26.01, 25.64, 24.84, 24.09, 22.55, 21.64. HRMS (LSIMS, nba): calcd for $C_{38}H_{61}O_2S_2$ (MH^+) 613.4113, found 613.4075. HPLC: Alltima C-18 column, 250 × 4.6 mm, 5 μm; 90% acetonitrile/10% water, flow rate 1.0 mL/min; UV, t_R 8.37 min, 97.6% pure.

1,13-Dihydroxy-2,12-bis(4-isobutylphenyl)-2,12-dimethyltridecan-7-one (14f). To a mixture of **13f** (4.50 g, 7.34 mmol) in dimethoxyethane (50 mL) and concentrated HCl (10 mL) was added dropwise DMSO (5.0 mL) over 5 min. The solution was stirred for 30 min at room temperature and then slowly poured into saturated aqueous $NaHCO_3$ solution (100 mL) and extracted with Et_2O (2 × 100 mL). The ether fractions were combined, dried with anhydrous Na_2SO_4, filtered, and concentrated. The product was purified by flash chromatography (silica gel; EtOAc/hexanes = 30/70), affording **14f** (3.2 g, 83%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.19 (d, 4 H, J = 8.0), 7.09 (d, 4 H, J = 8.0), 3.63 (d, 2 H, J = 11.0), 3.49 (d, 2 H, J = 11.0), 2.43 (d, 4 H, J = 7.0), 2.26 (t, 4 H, J = 7.3), 1.88−1.66 (m, 4 H), 1.52−1.41 (m, 8 H), 1.29 (s, 6 H), 1.15−1.10 (m, 2 H), 0.98−0.88 (m, 2 H), 0.89 (d, 12 H, J = 6.6). ^{13}C NMR ($CDCl_3$): δ 211.47, 141.97, 139.51, 129.28, 126.45, 72.53, 45.02, 43.11, 42.69, 38.36, 30.26, 24.57, 23.63, 22.58, 21.72. HRMS (LSIMS, nba): calcd for $C_{35}H_{55}O_3$ (MH^+) 523.4151, found 523.4144. HPLC: Alltima C-8 column, 250 × 4.6 mm, 5 μm; 90% acetonitrile/10% water, flow rate 1.0 mL/min; UV, t_R 5.78 min, 96.3% pure.

1,17-Dihydroxy-2,2,16,16-tetramethylheptadecan-9-one (14i). To a solution of **11i** (2.42 g, 7.02 mmol) in acetic

acid (10 mL) was added dropwise NaOCl solution (1.76 mL, ca. 3.5 mmol) at 18 °C. Additional NaOCl solution (3 × 1.0 mL, ca. 6.0 mmol) was added after 20, 40, and 60 min under monitoring by TLC. The reaction was quenched with 2-propanol (4 mL) and diluted with deionized water (100 mL). The reaction mixture was extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (3 × 60 mL), water (60 mL), and brine (60 mL); dried over anhydrous $MgSO_4$; and concentrated in vacuo. Purification of the crude product (2.38 g) by column chromatography (silica gel, EtOAc/hexanes = 1/1) gave **14i** (0.83 g, 35%) as a colorless wax. ^{1}H NMR ($CDCl_3$): δ 3.33 (s, 4 H), 2.41 (t, J = 7.4, 4 H), 1.85 (br, 2 H), 1.62−1.45 (m, 4 H), 1.35−1.18 (m, 16 H), 0.87 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 212.09, 72.10, 42.99, 38.75, 35.20, 30.48, 29.42, 24.05, 23.99, 23.82. HRMS (LSIMS, gly): calcd for $C_{21}H_{43}O_3$ (MH^+) 343.3212, found 343.3208. HPLC: Alltima C-8 column, 250 × 4.6 mm, 5 μm; 90% acetonitrile/10% water, flow rate 1.0 mL/min; RI, t_R 26.91 min, 93.5% pure.

2-[7-Isocyano-2,2-dimethyl-7-(tolyl-4-sulfonyl)heptyloxy]-tetrahydropyran (15). Method A. To a solution of TosMIC (9.75 g, 49.9 mmol) and NBu_4I (1.69 g, 4.6 mmol) in anhydrous DMSO (240 mL) was added NaH (2.2 g, 55.0 mmol, 60% in mineral oil), while being cooled with an ice bath. **7c** (14.65 g, 50 mmol) was added dropwise over 1 h, and the reaction mixture was stirred at room temperature overnight. The mixture was quenched with water (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water (100 mL) and half-saturated aqueous NaCl solution (100 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford the crude product (30 g), which was purified by column chromatography (silica gel; hexanes/EtOAc = 90/10) to obtain **15** (5.4 g, 27%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.87 (d, 2 H, J = 8.2), 7.43 (d, 2 H, J = 8.2), 4.56−4.40 (m, 2 H), 3.83 (t, 1 H, J = 8.1), 3.58−3.38 (m, 1 H), 3.46 (d, 1 H, J = 9.2), 2.97 (d, 1 H, J = 9.2), 2.49 (s, 3 H), 2.30−1.20 (m, 16 H), 0.88 (s, 6 H). ^{13}C NMR ($CDCl_3$): δ 164.7, 146.5, 131.1, 130.1, 99.1, 76.2, 62.0, 38.7, 34.1, 30.6, 28.3, 26.2, 25.5, 24.5, 23.0, 21.8, 19.5. HRMS (LSIMS, nba): calcd for $C_{22}H_{34}NSO_4$ (MH^+) 408.2209, found 408.2205.

Method B. To a solution of TosMIC (3.9 g, 20.0 mmol) in anhydrous DMF (100 mL) was added K_2CO_3 (5.52 g, 39.9 mmol), **7c** (11.72 g, 40.0 mmol), and NBu_4I (0.74 g, 1.95 mmol). The reaction mixture was stirred at room temperature for 20 h and then heated to 50 °C for 4 h. The reaction mixture was poured into ice water (300 mL) and extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were washed with water (2 × 100 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to afford the crude product, which was purified by column chromatography (silica gel; hexanes/EtOAc = 90/10) to give **15** (5.6 g, 69%) as a colorless oil.

1,12-Dihydroxy-2,2,11,11-tetramethyldodecan-6-one (17). To a solution of **15** (6.5 g, 15.9 mmol) in anhydrous DMSO (70 mL) was added NaH (0.77 g, 19.3 mmol, 60% in mineral oil), **7a** (4.91 g, 17.6 mmol), and NBu_4I (0.59 g, 1.6 mmol). The reaction mixture was stirred at room temperature for 24 h and hydrolyzed with water (100 mL). The product was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water (3 × 100 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give the crude intermediate (14.0 g). This crude material was heated to reflux in concentrated HCl (17 mL) and MeOH (100 mL) overnight. The reaction mixture was poured into ice water (200 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with 5% NaOH solution (60 mL) and water (2 × 100 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; hexanes/EtOAc = 80/20), affording **17** (2.5 g, 58%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.31 (s, 2 H), 3.28 (s, 2 H), 2.42−2.37 (m, 4 H), 2.4−1.8 (m br, 2 H), 1.56−1.48 (m, 4 H), 1.22−1.14 (m, 6 H), 0.85 (s, 6 H), 0.84 (s, 6 H). ^{13}C NMR ($CDCl_3$): δ 212.0, 71.5, 71.1, 43.0, 42.7, 38.2, 37.7, 35.0, 34.9, 30.8, 24.6, 23.9, 23.8, 23.4, 17.8. HRMS (LSIMS, gly): calcd for $C_{16}H_{33}O_3$ (MH^+) 273.2430, found 273.2422. HPLC: Alltima C-18 column, 250 × 4.6 mm, 5 μm; 60% acetonitrile/40% water, flow rate 1.0 mL/min; RI, t_R 5.50 min, 91.4% pure.

1,13-Dihydroxy-2,2,12-trimethyl-12-phenyltridecan-7-one (18). To a solution of **15** (5.3 g, 13.0 mmol) in anhydrous DMSO (60 mL) was added NaH (0.62 g, 15.5 mmol, 60% in mineral oil), **7d** (4.6 g, 12.9 mmol), and NBu_4I (0.48 g, 1.3 mmol). The reaction mixture was stirred at room temperature overnight and hydrolyzed with water (100 mL). The product was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic phases were washed with water (100 mL) and half-saturated aqueous NaCl solution (100 mL), dried over Na_2SO_4, and concentrated in vacuo to get the crude intermediate (9.0 g). This crude material was heated to reflux in concentrated HCl (13.4 mL) and MeOH (60 mL) overnight. The reaction mixture was poured into water (200 mL) and the product was extracted with Et_2O (3 × 60 mL). The combined organic layers were washed with water (3 × 20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; hexanes/EtOAc = 2/1), affording **18** (3.2 g, 71%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.38−7.16 (m, 5 H), 3.67 (d, 1 H, J = 10.9), 3.52 (d, 1 H, J = 10.9), 3.26 (s, 2 H), 2.40−2.20 (m, 4 H), 1.85−1.60 (m, 3 H), 1.60−1.40 (m, 5 H), 1.33 (s, 3 H), 1.28−1.10 (m, 5 H), 1.10−0.90 (m, 1 H), 0.83 (s, 6 H). ^{13}C NMR ($CDCl_3$ = 77.0 ppm): δ 211.5, 144.6, 128.3, 126.6, 126.0, 72.3, 71.6, 43.3, 42.5, 38.2, 34.9, 24.6, 24.4, 23.8, 23.4, 21.5. HRMS (LSIMS, gly): calcd for $C_{22}H_{37}O_3$ (MH^+) 349.2743, found 349.2731. HPLC: Alltima C-8 column, 250 × 4.6 mm, 5 μm; 50% acetonitrile/50% water, flow rate 1.0 mL/min; RI, t_R 12.87 min, 84.9% pure.

1,14-Dihydroxy-2,2,13,13-tetramethyltetradecan-7-one (19). According to the procedure described for the synthesis of **17**, **15** (6.98 g, 17.1 mmol) was reacted with NaH (0.82 g, 20.5 mmol, 60% in mineral oil), **7g** (5.8 g, 18.9 mmol), and NBu_4I (0.63 g, 1.7 mmol) in anhydrous DMSO (100 mL) for 24 h at room temperature. The crude intermediate (10.9 g) obtained after aqueous workup was heated to reflux in concentrated HCl (18 mL) and MeOH (100 mL) overnight. After extraction and column chromatography (silica gel; hexanes/EtOAc = 80/20), **19** (2.3 g, 48%) was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.30 (s, 4 H), 2.48−2.34 (m, 4 H), 1.85 (br, 2 H), 1.66−1.46 (m, 4 H), 1.24−1.14 (m, 10 H), 0.85 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 211.8, 71.8, 71.6, 42.7, 42.6, 38.4, 38.2, 34.9, 30.1, 24.6, 23.8, 23.8, 23.7, 23.6, 23.4. HRMS (LSIMS, gly): calcd for $C_{18}H_{37}O_3$ (MH^+) 301.2743, found 301.2745. HPLC: Alltima C-8 column, 250 × 4.6 mm, 5 μm; 50% acetonitrile/50% water, flow rate 1.0 mL/min; RI, t_R 15.32 min, 97.4% pure.

7-Isocyano-2,2-dimethyl-7-(tolyl-4-sulfonyl)heptanoic Acid Ethyl Ester (20). Under N_2 atmosphere, to a stirred solution of NBu_4I (4.23 g, 11.5 mmol) and TosMIC (27.56 g, 141.2 mmol) in anhydrous DMSO (500 mL) was added NaH (60% w/w in mineral oil, 5.80 g, 145.0 mmol), while the internal temperature was kept between 10 and 15 °C. After the dropwise addition of **5c** (36.60 g, 145.7 mmol), the mixture was stirred at room temperature for 20 h and then cooled with an ice bath and carefully hydrolyzed with water (600 mL). The solution was extracted with CH_2Cl_2 (4 × 150 mL). The combined organic layers were washed with water (200 mL) and half-saturated aqueous NaCl solution (200 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to obtain the crude product mixture (40.9 g) as an orange oil. A portion of this crude product (13.0 g) was purified by column chromatography (silica gel; hexanes/EtOAc = 10/1, then 9/1), affording **20** (1.92 g, 12%) as a pale yellow oil, **8c** (0.70 g, 3%) as a colorless oil, and a mixture of both (2.50 g, ratio 9/1). ^{1}H NMR ($CDCl_3$): δ 7.86 (d, 2 H, J = 8.1), 7.43 (d, 2 H, J = 8.1), 4.48 (dd, 1 H, J = 7.2, 3.6), 4.11 (q, 2 H, J = 7.2), 2.49 (s, 3 H), 2.21−2.16 (m, 1 H), 1.90−1.78 (m, 1 H), 1.56−1.50 (m, 4 H), 1.35−1.20 (m, 2 H), 1.25 (t, 3 H, J = 7.2), 1.16 (s, 6 H). ^{13}C NMR ($CDCl_3$): δ 177.8, 165.0, 146.7, 131.3, 130.3, 130.2, 72.9, 60.5, 42.2, 40.2, 28.3, 25.8, 25.3, 25.2, 24.2, 21.9, 14.4. HRMS (LSIMS, nba): calcd for $C_{19}H_{28}NO_4S$ (MH^+) 366.1739, found 366.1746.

Ethyl 12-Hydroxy-2,2,11,11-tetramethyl-7-oxododecanoate (21). Under N_2 atmosphere, to a solution of **20** (1.72 g, 4.68 mmol), NBu_4I (0.17 g, 0.46 mmol), and **7a** (1.45 g, 5.19 mmol) in anhydrous DMSO (20 mL) was added NaH (60% w/w in mineral oil, 0.19 g, 4.75 mmol), while the internal temperature was kept between 10 and 15 °C. The reaction mixture was stirred for 20 h at room temperature and then carefully hydrolyzed with ice−water (100 mL). The mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with water (40 mL) and saturated aqueous NaCl solution (2 × 20 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to obtain the crude intermediate (3.50 g) as brown oil. A solution of this intermediate in 48% H_2SO_4 (6 mL) and MeOH (12 mL) was stirred for 100 min at room temperature. The mixture was diluted with water (50 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with water (100 mL) and saturated aqueous NaCl solution (100 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to obtain the crude product (2.70 g) as yellow oil. A portion of the crude product (2.50 g) was subjected to column chromatography (silica gel; hexanes/EtOAc = 80/20, then 75/25) to give **21** (0.82 g, 60%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 4.14−4.03 (m, 2 H), 3.31 (br s, 2 H), 2.42 (br, 1 H), 2.39 (m, 4 H), 1.54−1.48 (m, 6 H), 1.24−1.18 (m, 7 H), 1.14 (s, 6 H), 0.86 (s, 6 H). ^{13}C NMR ($CDCl_3$): δ 211.7, 178.0, 71.2, 60.3, 43.2, 42.7, 42.1, 40.4, 37.9, 35.1, 25.2, 24.6, 24.2, 24.1, 18.0, 14.3. HRMS (LSIMS, gly): calcd for $C_{18}H_{35}O_4$ (MH^+) 315.2535, found 315.2541.

Ethyl 14-Hydroxy-2,2,13,13-tetramethyl-7-oxotetradecanoate (22). According to the procedure for the synthesis of **20**, **5c** (45.6 g, 182 mmol) was reacted with TosMIC (35.2 g, 180 mmol), NBu_4I (4.3 g, 11.6 mmol), and NaH (60% w/w in mineral oil, 7.3 g, 183 mmol) in anhydrous DMSO (500 mL). To this solution were added NBu_4I (4.3 g, 11.6 mmol) and **7g** (43.8 g, 143 mmol) in anhydrous DMSO (20 mL) and then NaH (7.4 g, 185 mmol, 60% w/w in mineral oil) at 10 °C. The reaction mixture was stirred at room temperature for 20 h, cooled with an ice bath, and carefully hydrolyzed with ice−water (1000 mL). The product was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo to obtain the crude intermediate (115 g) as a red oil. This intermediate was dissolved in 48% H_2SO_4 (147 mL) and MeOH (480 mL) and the mixture was stirred for 100 min at room temperature. After dilution with water (1500 mL), the product was extracted with CH_2Cl_2 (2 × 150 mL, 100 mL, 50 mL). The combined organic layers were washed with saturated aqueous Na_2CO_3 solution (150 mL) and saturated aqueous NaCl solution (150 mL), dried over $MgSO_4$, filtered through a short column (aluminum oxide; EtOAc), and concentrated in vacuo to obtain the crude product (89 g) as a yellow oil. The crude product was subjected to column chromatography (silica gel; hexanes/EtOAc = 6:1, then 3:1) to give **22** (17.6 g, 36%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 4.10 (q, 2 H, J = 6.9), 3.30 (br. s, 2 H), 2.39 (t, 4 H, J = 6.9), 1.98 (br, 1 H), 1.56−1.48 (m, 6 H), 1.27−1.18 (m, 11 H), 1.14 (s, 6 H), 0.85 (s, 6 H). ^{13}C NMR ($CDCl_3$): δ 211.5, 178.0, 71.9, 60.3, 42.9, 42.7, 42.2, 40.5, 38.6, 35.1, 30.3, 25.2, 24.7, 24.2, 24.0, 23.8, 14.4. HRMS (LSIMS, gly): calcd for $C_{20}H_{39}O_4$ (MH^+) 343.2848, found 343.2846.

2,2,11,11-Tetramethyl-7-oxododecanedioic Acid 1-Ethyl Ester (23). A mixture of **21** (3.26 g, 10.4 mmol) and PDC (14.0 g, 37.2 mmol) in DMF (45 mL) was stirred at room temperature for 46 h. The solution was diluted with 48% H_2SO_4 (30 mL) and water (300 mL) and extracted with EtOAc (5 × 100 mL). The combined organic layers were washed with saturated aqueous NaCl solution (5 × 100 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to give the crude product (3.19 g) as greenish oil. The crude product was subjected to column chromatography (silica gel; hexanes/EtOAc = 3:1, 2:1), affording **23** (2.69 g, 79%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 11.30 (br, 1 H), 4.10 (q, 2 H, J = 7.2), 2.39 (t, 4 H, J = 7.2), 1.56−1.48 (m, 8 H), 1.25−1.15 (m, 2 H), 1.24 (t, 3 H, J = 7.2), 1.20 (s, 6 H), 1.15 (s, 6 H). ^{13}C NMR ($CDCl_3$): δ 210.9, 184.4, 178.1, 60.4, 43.1, 42.7, 42.2, 40.5, 39.8, 25.3, 25.0, 24.7, 24.3, 19.3, 14.4. HRMS (LSIMS, gly): calcd for $C_{18}H_{33}O_5$ (MH^+) 329.2328, found 329.2330.

2,2,13,13-Tetramethyl-7-oxotetradecanedioic Acid 1-Ethyl Ester (24). A mixture of **22** (10.53 g, 30.7 mmol) and PDC (32.5 g, 86.4 mmol) in DMF (120 mL) was stirred at 30 °C for 40 h. The mixture was poured into 48% H_2SO_4 (50 mL) and water (700 mL). The product was extracted with EtOAc (3 × 200 mL, 2 × 100 mL). The combined organic layers were washed with saturated aqueous NaCl solution (4 × 100 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to give the crude product (10.3 g) as a pale yellow oil. This crude material was purified by column chromatography (silica gel; hexanes/EtOAc = 75/25) to afford **24** (7.40 g, 68%) as a yellowish oil. ^{1}H NMR ($CDCl_3$): δ 4.10 (q, 2 H, J = 7.5), 2.39 (m, 4 H), 1.56−1.49 (m, 8 H), 1.26−1.21 (m, 10 H), 1.18 (s, 6 H), 1.15 (s, 6 H). ^{13}C NMR ($CDCl_3$): δ 211.4, 184.2, 178.0, 60.3, 42.8, 42.7, 42.1, 40.5, 40.4, 29.7, 25.2, 24.8, 24.7, 24.3, 23.7, 14.3. HRMS (LSIMS, gly): calcd for $C_{20}H_{37}O_5$ (MH^+) 357.2641, found 357.2641.

2,2,11,11-Tetramethyl-6-oxododecanedioic Acid (25). According to the procedure given for **9f**, **23** (2.50 g, 7.6 mmol) was saponified with KOH (1.80 g, 27.3 mmol) in water (3 mL) and EtOH (8 mL) at reflux for 4 h. After the usual workup, the crude product (2.17 g) was recrystallized from Et_2O/hexanes (15 mL/25 mL) to give **25** (1.36 g, 60%) as white needles. Mp: 72−73 °C. ^{1}H NMR ($CDCl_3$): δ 12.0−11.2 (br, 2 H), 2.41 (m, 4 H), 1.60−1.52 (m, 8 H), 1.29−1.24 (m, 2 H), 1.20 (s, 6 H), 1.18 (s, 6 H). ^{13}C NMR ($CDCl_3$): δ 211.2, 185.1, 184.9, 43.9, 42.7, 42.2, 40.3, 39.8, 25.1, 25.0, 24.7, 24.2, 19.3. HRMS (LSIMS, gly): calcd for $C_{16}H_{29}O_5$ (MH^+) 301.2015, found 301.2023. HPLC: Alltima C-8 column, 250 × 4.6 mm, 5 μm; 60% acetonitrile/40% water, flow rate 1.0 mL/min; RI, t_R 4.60 min, 95.8% pure. Anal. ($C_{16}H_{28}O_5$): C, H.

2,2,13,13-Tetramethyl-7-oxotetradecanedioic Acid (26). According to the procedure for the synthesis of **9f**, a solution of **24** (7.4 g, 20.8 mmol) and KOH (85%, 4.6 g, 69.6 mmol) in water (5 mL) and EtOH (15 mL) was heated to reflux for 4 h. The crude product (6.8 g) obtained after the usual workup was purified by repeated column chromatography (silica gel; first hexanes/EtOAc = 2/1 and then 1/1 and second hexanes/EtOAc = 1/) and crystallization (Et_2O/hexanes, 20 mL/10 mL), affording **26** (2.95 g, 43%) as colorless needles. Mp: 61−62 °C. ^{1}H NMR ($CDCl_3$): δ 11.91 (br, 2 H), 2.41 (t, 4 H, J = 6.9), 2.39 (t, 4 H, J = 6.9), 1.58−1.52 (m, 8 H), 1.30−1.22 (m, 6 H), 1.18 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 211.8, 184.5, 185.4, 43.0, 42.9, 42.5, 40.7, 40.6, 29.9, 25.4, 25.1, 25.0, 24.6, 23.9. HRMS (LSIMS, gly): calcd for $C_{18}H_{33}O_5$ (MH^+) 329.2328, found 329.2324. HPLC: Alltima C-8 column, 250 × 4.6 mm, 5 μm; 60% acetonitrile/40% water, flow rate 1.0 mL/min; RI, t_R 5.72 min, 93.5% pure. Anal. ($C_{18}H_{32}O_5$) C, H.

3-{3-[3-Ethoxycarbonyl-2-methylpropyl)benzoyl]phenyl}-2,2-dimethylpropionic Acid Ethyl Ester (28). Under inert gas atmosphere and at −78 °C, to a stirred solution of ethyl isobutyrate (9.78 g, 84.2 mmol) in anhydrous THF (30 mL) was added dropwise a solution of LDA (2.0 M, 42.2 mL, 84.4 mmol). After 1 h, **27**[46] (10.34 g, 28.1 mmol) was added, followed by addition of DMPU (2.7 g, 21.1 mmol). The mixture was stirred for 30 min and then allowed to warm to room temperature over 30 min. The THF was distilled off under reduced pressure. The residue was dissolved in saturated aqueous NH_4Cl solution (280 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with saturated aqueous NaCl solution (200 mL), 5% HCl (100 mL) and saturated aqueous $NaHCO_3$ solution (50 mL). Drying over anhydrous Na_2SO_4 and concentration in vacuo afforded **28** (11.0 g, 89%) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.8−7.2 (m, 8 H), 3.98 (q, 4 H, J = 6.9), 2.83 (s, 4 H), 1.2−0.8 (m, 18 H). ^{13}C NMR ($CDCl_3$ = 77.0 ppm): δ 196.5, 176.8, 138.1, 137.2, 134.0, 131.4, 128.1, 127.7, 60.3, 45.7, 43.3, 24.8, 13.9.

3-(3-{2-[3-(2-Ethoxycarbonyl-2-methylpropyl}phenyl]-[1,3]dithian-2-yl}phenyl)-2,2-dimethylpropionic Acid Ethyl Ester (29). To a solution of **28** (6.2 g, 14.1 mmol) and 1,3-propanedithiol (1.9 g, 17.6 mmol) in CH_2Cl_2 (100 mL) was added BF_3−Et_2O (0.52 mL, 0.58 g, 4.1 mmol). The solution

was stirred at room temperature overnight. After the addition of 5% NaOH solution (17.5 mL), the organic layer was separated, washed with water (50 mL), dried over anhydrous Na_2SO_4, and evaporated to afford **29** (6.5 g, 87%) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.58−6.96 (m, 8 H), 4.10 (q, 4 H, J = 7.2), 2.85 (s, 4 H), 2.76 (t, 4 H, J = 5.6), 1.98 (m, 2 H), 1.22 (t, 6 H, J = 7.2) 1.13 (s, 12 H). ^{13}C NMR ($CDCl_3$ = 77.0 ppm): δ 177.17, 142.18, 138.07, 131.12, 129.30, 127.84, 127.33, 60.35, 46.16, 43.48, 29.38, 24.90, 14.13.

3-(3-{2-[3-(3-Hydroxy-2,2-dimethylpropyl)phenyl][1,3]-dithian-2-yl}phenyl)-2,2-dimethylpropan-1-ol (30). To a suspension of $LiBH_4$ (0.78 g, 35.8 mmol) in CH_2Cl_2 (55 mL) was added MeOH (1.04 g, 32.5 mmol) at room temperature. After the addition of **29** (6.5 g, 12.3 mmol), the reaction mixture was heated to reflux for 6 h. After cooling to room temperature, saturated aqueous NH_4Cl solution (20 mL) and CH_2Cl_2 (15 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford **30** (4.66 g, 85%) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.42 (s br, 2 H), 7.17 (m, 4 H), 6.97 (m, 2 H), 3.63 (s, 4 H), 3.16 (s, 4 H), 2.69 (m, 2 H), 2.47 (m, 4 H), 1.88 (m, 2 H), 0.75 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 142.39, 139.18, 131.69, 129.88, 128.05, 127.01, 71.12, 44.89, 43.74, 36.70, 29.63, 24.22.

3-{3-[3-(2-Carboxy-2-methylpropyl)benzoyl]phenyl}-2,2-dimethylpropionic Acid (31). According to the procedure for the synthesis of **9f**, a mixture of **28** (4.38 g, 10.0 mmol) and KOH (85%, 1.57 g, 23.8 mmol) was heated to reflux in water (1.5 mL) and EtOH (5 mL) for 3 h. After extraction and drying in high vacuo, **31** (3.88 g, quantitative) was obtained as a white solid. Mp: 46−48 °C. ^{1}H NMR ($CDCl_3$): δ 11.2−10.6 (br, 2 H), 7.8−7.2 (m, 8 H), 2.83(s, 4 H), 1.25(s, 12 H). ^{13}C NMR ($CDCl_3$): δ 198.02, 183.86, 138.61, 137.73, 134.56, 130.54, 128.41, 128.10, 46.69, 43.77, 24.83. HRMS (LSIMS, nba): calcd for $C_{23}H_{27}O_5$ (MH^+) 383.1858, found 383.1858. HPLC: Alltima C-8 column, 250 × 4.6 mm, 5 μm; 55% acetonitrile/45% water, flow rate 1.0 mL/min; RI, t_R 8.62 min, 88.3% pure.

Bis[3-(3-hydroxy-2,2-dimethylpropyl)phenyl]methanone (32). A suspension of CuO (0.96 g, 12.1 mmol) and anhydrous $CuCl_2$ (3.2 g, 23.8 mmol) in acetone (80 mL) was heated to reflux. A solution of **30** (4.44 g, 10.0 mmol) in acetone (20 mL) and DMF (1.2 mL) was added dropwise over 5 min. After 90 min at reflux temperature, the reaction mixture was cooled to room temperature and filtered. The insoluble material was washed with CH_2Cl_2 (3 × 20 mL). The combined organic solutions were washed with aqueous 2 N Na_2CO_3 solution (50 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel; hexanes/acetone = 80/20) to give **32** (2.5 g, 71%) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.68−7.30 (m, 8 H), 3.31 (s, 4 H), 3.03 (s br, 2 H), 2.65 (s, 4 H), 0.88 (s, 12 H). ^{13}C NMR ($CDCl_3$ = 77.00 ppm): δ 197.42, 139.06, 136.96, 134.60, 131.88, 127.78, 127.55, 70.39, 44.07, 36.30, 23.80. HRMS (LSIMS, nba): calcd for $C_{23}H_{31}O_3$ (MH^+) 355.2273, found 355.2263. HPLC: Alltima C-18 column, 250 × 4.6 mm, 5 μm; 55% acetonitrile/45% water, flow rate 1.0 mL/min; RI, t_R 13.37 min, 94.5% pure.

Biological Methods. 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/day). Rat hepatocytes were isolated essentially as described by the method of Seglen.[51] 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 nonessential 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 of water were 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.

In Vivo Effects on Lipid Variables in Obese Female 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. Freshwater was supplied ad libitum via an automatic watering system. Compounds were dissolved and suspended by mixing in a dosing vehicle consisting of 20% EtOH and 80% poly(ethylene 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 a.m. Regarding blood sampling, animals were fasted for 6 h prior to all blood collections. To measure blood glucose levels, blood from tail-pricked, unanesthetized animals was spotted onto a glucometer (Bayer, Model 3952E). Subsequently, additional blood samples were collected as follows. 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 Corp., Kit No. 148899 or Boehringer Mannheim, Kit No. 1488872), total cholesterol (Roche Diagnostic Corp., Kit No. 450061), nonesterified 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 Corp.). Serum insulin was determined using a commercial ELISA kit (Alpco Diagnostics, Windham, NH). 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.[52] 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.

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Supporting Information Available: Details on the syntheses of intermediates **2**, **3**, **4**, **5a**−**5j**, **6a**−**6h**, and **7a**−**7h** and spectral and elemental analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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