Long Hydrocarbon Chain Ether Diols and Ether Diacids That Favorably Alter Lipid Disorders in Vivo

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Long hydrocarbon chain ethers with bis-terminal hydroxyl or carboxyl groups have been synthesized and evaluated 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 female obese Zucker fatty rats following 1 and 2 weeks of daily oral administration. The most active compounds were found to be symmetrical with four to five methylene groups separating the central ether functionality and the *gem* dimethyl or methyl/aryl substituents. Biological activity was found to be greatest for tetramethyl-substituted ether diols (e.g., **28** and **31**), while bis(arylmethyl) derivatives (e.g., **10**, **11**, and **27**), diethers (e.g., **49**, **50**, and **56**), and diphenyl ethers (e.g., **35** and **36**) were the least active. For the most biologically active compound **28**, we observed as much as a 346% increase in serum HDL-cholesterol and a 71% reduction in serum triglycerides at the highest dose administered (100 mg/kg) after 2 weeks of treatment. For compound **31** we observed a 69% reduction in non-HDL-cholesterol, accompanied by a 131% increase in HDL-cholesterol and an 84% reduction in serum triglycerides under the same treatment conditions.

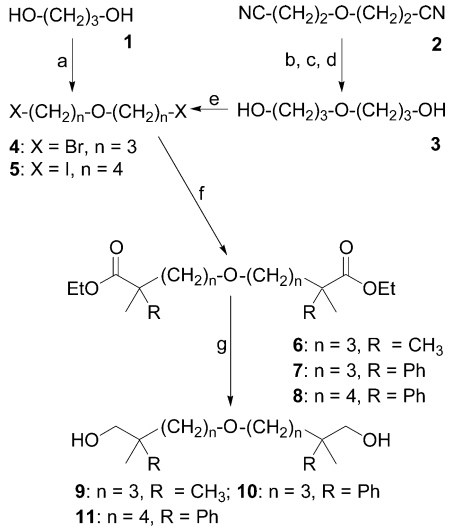
Introduction

We have previously shown that keto-substituted hydrocarbons with hydroxyl or carboxyl termini can favorably alter lipids in an animal model of metabolic syndrome.[1a,b] Here, we have extended those studies to ether derivatives of long-chain hydrocarbons with 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 total lipid synthesis assay and a long-term (weeks) in vivo animal model in which we determined serum lipid changes over a 2-week period in the obese female Zucker rat, a model of diabetic dyslipidemia.

Results and Discussion

Drug Design. We have investigated a series of ethers and examined the influence of chain length, aromatic rings, symmetry, terminal groups, and substitution pattern at the quaternary carbons α to the terminal carboxyl or β to the hydroxyl moieties. 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 targets. For this reason, biological activity was tested in cell-based as well as in animal models in order to ensure a full complement of operative biochemical pathways.

Scheme 1. Synthesis of Symmetrical Ether Diols Starting from Dihalo Ethers[a]



[a] Reagents: (a) HBr, H_2SO_4, 13%; (b) HCl; (c) EtOH, H_2SO_4; (d) $LiAlH_4$ [THF], 66%; (e) PBr_3, 55%; (f) for **6**, ethyl isobutyrate, LDA [THF/DMPU], 69%; for **7**, ethyl 2-phenylpropionate, LDA [THF/DMPU], 27%; for **8**, ethyl 2-phenylpropionate, LDA [THF/DMPU], 94%; (g) for **9**, $LiAlH_4$ [Et_2O], 79%; for **10**, $LiAlH_4$ [THF], 82%; for **11**, $LiBH_4$, MeOH [CH_2Cl_2], 95%.

Chemistry. A series of long hydrocarbon chain ether diols was synthesized. The side chains connected to the central ether functionality varied both in the number of methylene spacer units ($n = 3-5$) and in the attached geminal modifying groups (R = Me, Ph), resulting in ether diols of either the symmetrical (**9**−**11**, Scheme 1; **28** and **31**, Scheme 2) or the unsymmetrical (**26**, **27**, **29**,

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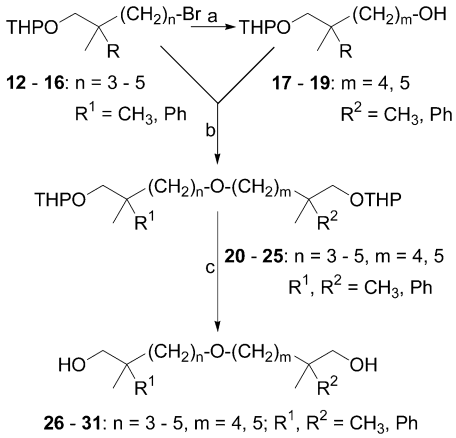
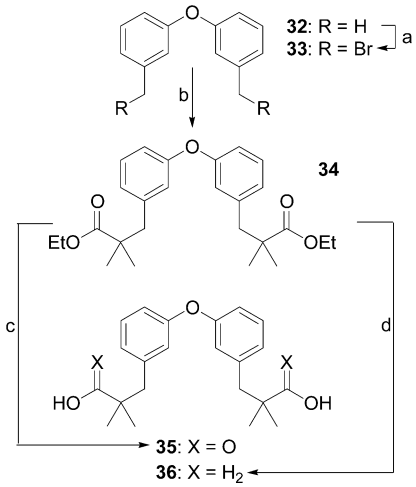
Scheme 2. Symmetrical and Unsymmetrical Ether Diols via Williamson Ether Synthesis[a]



[a] Reagents: (a) K_2CO_3 [DMSO/H_2O]; (b) NaH [THF]; (c) concentrated HCl [MeOH].

Scheme 3. Synthesis of Diaryl Ethers[a]

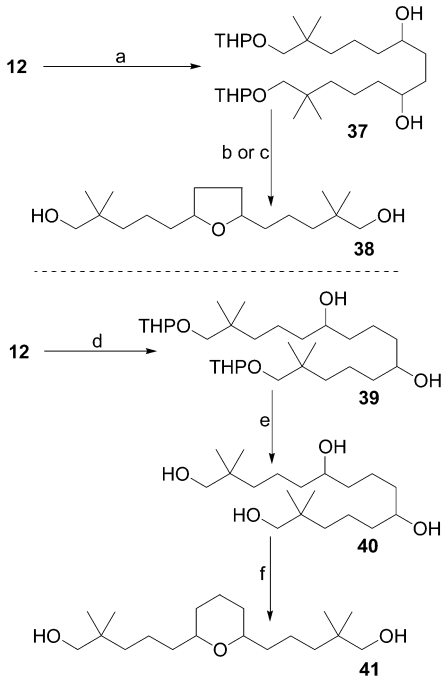


[a] Reagents: (a) NBS, benzoyl peroxide [CCl_4]; (b) ethyl isobutyrate, LDA [THF/DMPU]; (c) KOH [EtOH/H_2O]; (d) $LiAlH_4$ [THF].

and **30**, Scheme 2) category. In addition, the aryl-bridged diacid **35** and diol **36** (Scheme 3) as well as the diols **38** and **41** with cyclic ether structures (Scheme 4) were synthesized and examined for comparison. Also included in this study were the ether diacid **45** (Scheme 5) with $\gamma,\gamma,\gamma',\gamma'$-tetramethyl substitution, the THP-protected derivatives **22** and **46** (Scheme 6), compounds **49**, **50**, **55**, and **56** with a diether structural element (Schemes 7, 8), and finally the hydrocarbon chain analogues **61**−**63** (Scheme 9).

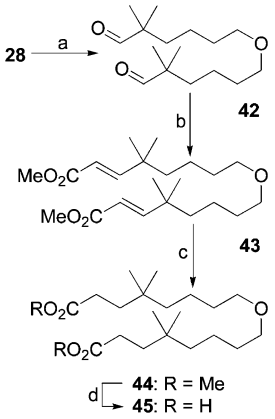
The synthesis of long hydrocarbon chain ether diols was accomplished by two different methods.[1c,d] According to the first procedure (Scheme 1), bis(ω-haloalkyl) ethers were reacted with lithiated ethyl esters and the resulting diesters were reduced to the target diols. For $n = 3$, the starting dibromo ether **4** was first prepared by condensing 1,3-propanediol (**1**) with 48% aqueous HBr and concentrated H_2SO_4.[2] However, the yield for this reaction was only 13%, and purification of **4** was difficult (fractional distillation). A better overall yield (36%) was obtained when dinitrile **2** was converted via a three-step reaction sequence consisting of saponification (concentrated HCl),[3] esterification (EtOH, concentrated H_2SO_4),[4] and reduction ($LiAlH_4$) to diol **3** (66%),[4] which was then transformed to **4** with PBr_3 (55%).[5] Bromide substitution in **4** with lithio ethyl isobutyrate and lithio ethyl 2-phenylpropionate[1,6] in THF and cosolvent dimethylpropyleneurea (DMPU) gave diesters **6** and **7** in 69% and 27% yield, respectively. Reduction

Scheme 4. Synthesis of Cyclic Ether Diols[a]



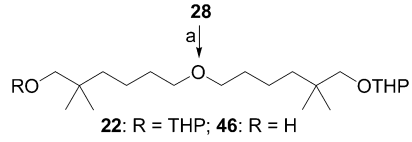
[a] Reagents: (a) Mg [THF], succinaldehyde, 92%; (b) *p*TosOH [toluene], H_2SO_4 [MeOH/H_2O], 35%; (c) TsCl, pyridine [CH_2Cl_2], Δ [pyridine/HMPA], H_2SO_4 [MeOH/H_2O], 38%; (d) Mg [THF], glutaric aldehyde, 55%; (e) H_2SO_4 [MeOH/H_2O], 80%; (f) *p*TosOH [toluene], 55%.

Scheme 5. Synthesis of Ether Diacid **45** via Wittig−Horner Reaction[a]



[a] Reagents: (a) SO_3−Py, NEt_3 [DMSO], 63%; (b) $(EtO)_2P(O)$-CH_2CO_2Me, NaH [DMF]; (c) H_2, 10% Pd−C [EtOH]; (d) KOH [MeOH/H_2O], 56%.

Scheme 6. Synthesis of THP-Protected Ether Diols **22** and **46**[a]



[a] Reagents: (a) *p*TosOH, 3,4-dihydro-2*H*-pyran [CH_2Cl_2]; **22**, 21%; **46**, 32%.

Table 1. Symmetrical and Unsymmetrical Ether Diols via Williamson Ether Synthesis

compd	*n*	*m*	R^1	R^2	yield (%)
12	3		CH_3		*a*
13	3		Ph		*a*
14	4		CH_3		*a*
15	4		Ph		*a*
16	5		CH_3		*a*
17		4		CH_3	99[b]
18		4		Ph	38
19		5		CH_3	83[b]
20	3	4	CH_3	CH_3	63
21	3	4	Ph	Ph	*c*
22	4	4	CH_3	CH_3	*c*
23	4	4	Ph	CH_3	*c*
24	5	4	CH_3	CH_3	34
25	5	5	CH_3	CH_3	*c*
26	3	4	CH_3	CH_3	51 (32[d])
27	3	4	Ph	Ph	44[d]
28	4	4	CH_3	CH_3	37[d]
29	4	4	Ph	CH_3	24[d]
30	5	4	CH_3	CH_3	90 (31[d])
31	5	5	CH_3	CH_3	30[d]

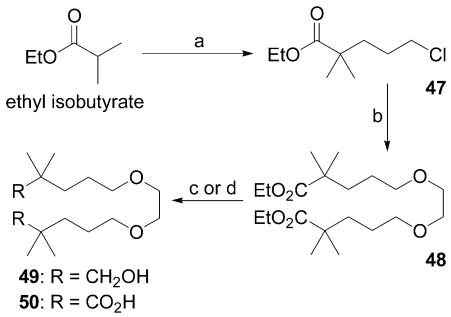
[a] Synthesis described in ref 1. [b] Used without purification for step b. [c] Directly used for step c. [d] Overall yield for steps b and c.

of the esters with $LiAlH_4$ afforded ether diols **9**[7] and **10** (79% and 82%) after purification by distillation or chromatography. For $n = 4$, the same methodology starting with diiodide **5**[8] via diester **8** was used and ether diol **11** was obtained by reduction with $LiBH_4$ and MeOH in CH_2Cl_2 [9] (86% over both steps).

According to the second method, symmetrical and unsymmetrical ether diols **26**−**31** were prepared via Williamson reaction[10] of THP-protected bromo alcohols **12**−**16**[1] with the sodium salts of alcohols **17**−**19** (Scheme 2, Table 1). Therefore, bromides **14**−**16** were hydrolyzed with K_2CO_3 in a DMSO/water mixture at reflux[11] to afford alcohols **17**−**19** in varying yields (38−99%). Alcohol **17** was deprotonated with NaH in THF at reflux temperature and condensed with bromo-THP ethers **12** and **16**, leading to protected ether intermediates **20** and **24** (60% and 34%), respectively, which were both purified by column chromatography. Deprotection of **20** and **24** with concentrated HCl in MeOH at reflux furnished the two unsymmetrical ether diols **26** (51%) and **30** (90%). The yields over both steps for these compounds, however, were similar (32% and 31%, Table 1). The synthesis of ethers **27**−**29** and **30** from alcohols **17**−**19** and bromides **13**−**16** followed the same protocol; however, the protected intermediates **21**−**23** and **25** were not purified but directly deprotected to the final ether diols. The moderate yields obtained over both steps (24−44%) were in the same range as those with purification of the THP-protected intermediates, and the differences in the synthesis of symmetrical (**28** and **31**) and unsymmetrical (**26**, **27**, **29**, and **31**) ether diols were not significant.

The synthesis of diaryl ethers **35** and **36** is depicted in Scheme 3. Dibromide **33**[12] (prepared from diphenyl ether **32**[13] via bromination with NBS and benzoyl peroxide in CCl_4) was reacted with lithio ethyl isobutyrate in THF/DMPU to give diester **34** (59%). Saponification of **34** with KOH in aqueous EtOH led to diacid **35**, which was purified by crystallization from heptane (72%). Reduction of **34** with $LiAlH_4$ afforded ether diol **36** as an oil (80%).

Scheme 7. Synthesis of Diether Compounds **49** and **50**[a]



[a] Reagents: (a) 1-bromo-3-chloropropane, LDA [THF/DMPU], 64%; (b) (1) $HO(CH_2)_2OH$, KO*t*Bu [DMAc]; (2) KO*t*Bu, 18-crown-6, **47**, 65−85 °C, 23%; (c) $LiAlH_4$ [MTBE], 52%; (d) KOH [EtOH/H_2O], 44%.

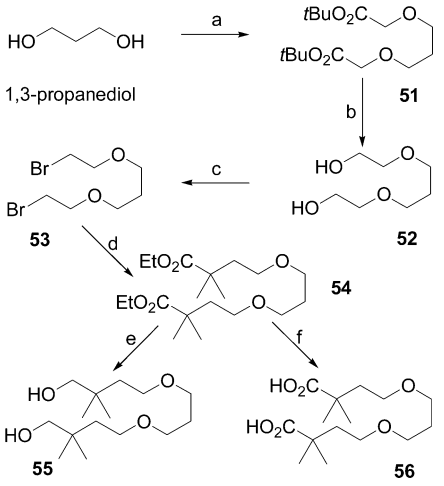
Scheme 4 illustrates the synthesis of cyclic ether diols **38** and **41**. Reaction of the Grignard reagent of bromo-THP ether **12** with freshly prepared succinaldehyde[14,15] in THF gave diol **37** (92%).[16] The cyclodehydration[17] and deprotection to tetrahydrofuran derivative **38** were then accomplished by two different methods: first, **37** was condensed by treatment with *p*-toluenesulfonic acid (*p*TosOH) in toluene under azeotropic removal[18] of the reaction water. Subsequent removal of the THP groups (aqueous H_2SO_4/MeOH) furnished cyclic ether diol **38** in moderate yield (35%). Alternatively, **37** was monotosylated (1.1 equiv of TsCl, Py)[19] and then cyclized under basic conditions (Py, HMPA). After deprotection of the terminal alcohols (aqueous H_2SO_4/MeOH) and purification by chromatography, **38** was obtained in 38% yield. A methodology similar to the one used for the synthesis of **38** was utilized to access tetrahydropyranyl diol **41**. Reaction of the Grignard reagent of **12** with glutaric aldehyde[15] gave compound **39** (55%). Deprotection (aqueous H_2SO_4/MeOH) furnished tetraol **40** that could conveniently be purified by crystallization from CH_2Cl_2/hexanes (80%). Finally, dehydration of **40** under acidic conditions (*p*TosOH, toluene, Dean-Stark) led to **41** in 55% yield.

The synthesis of the $\gamma,\gamma,\gamma',\gamma'$-tetramethyl-substituted ether diacid **45** began with the oxidation of diol **28** to dialdehyde **42** using SO_3−pyridine complex and NEt_3 in DMSO (63%, Scheme 5).[20] The α,β-unsaturated ester **43** was then prepared from **42** by the Wittig−Horner reaction with methyl diethylphosphonoacetate in the presence of NaH in DMF.[21,22] Subsequent hydrogenation to **44** (Pd−C)[22] followed by saponification of the ester groups (KOH, MeOH/H_2O)[23] furnished the target compound **45** (yield 56% from **42**).

The mono- and bis-THP ethers **22** and **46** (Scheme 6) were found as trace impurites in the kilogram-scale synthesis of ether diol **28** (Scheme 2).[9] Pure samples of these compounds were required in order to evaluate their biological properties. Treatment of **28** with 3,4-dihydro-2*H*-pyran (DHP, 1 equiv) and catalytic amounts of *p*TosOH in CH_2Cl_2 [24] produced a mixture of **22**, **28**, and **46** that was separated by chromatography to yield THP ethers **22** (21%) and **46** (32%).

The synthesis of diether diol **49** and diether diacid **50** is shown in Scheme 7. Alkylation of lithiated ethyl isobutyrate with 1-bromo-3-chloropropane in THF/DMPU gave chloro ester **47** (64%). Ethylene glycol was then deprotonated with potassium *tert*-butoxide (KO*t*-

Scheme 8. Synthesis of Diether Compounds **55** and **56**[a]



[a] Reagents: (a) *tert*-butyl bromoacetate, NBu_4HSO_4 [aqueous NaOH/toluene], 72%; (b) $LiAlH_4$ [MTBE], 62%; (c) PBr_3, Py [toluene], 61%; (d) ethyl isobutyrate, LDA [THF/DMPU], 66%; (e) $LiAlH_4$ [MTBE], 91%; (f) KOH [aqueous EtOH], 98%.

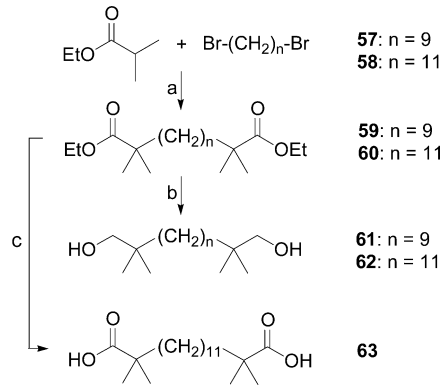
Bu, 1.5 equiv) in dimethylacetamide (DMAc) and reacted with **47** (1.5 equiv) at 65 °C.[25] Further reaction of this mixture with **47** (1.5 equiv), KO*t*Bu (1.5 equiv), and catalytic amounts of 18-crown-6 at 65−85 °C afforded diester **48** (23%). Subsequent reduction of **48** with $LiAlH_4$ in MTBE led to diol **49** (52%), while its saponification (KOH, aqueous EtOH) produced diacid **50** (44%).

A different approach was chosen for the synthesis of the related diether compounds **55** and **56** (Scheme 8). Alkylation of 1,3-propanediol with an excess of *tert*-butyl bromoacetate under phase-transfer conditions[26] (NBu_4HSO_4, aqueous NaOH/toluene) furnished diester **51** in 72% yield. Reduction of **51** with $LiAlH_4$ gave diol **52** (62%),[27] which was subsequently transformed to dibromide **53** by reaction with PBr_3 and pyridine (61%).[28] Substitution of the bromides in **53** with lithio ethyl isobutyrate[24] led to diethyl ester **54** (66%), which was reduced ($LiAlH_4$, 91%) to diether diol **55** as well as saponified (KOH, aqueous EtOH, 98%) to afford diether dicarboxylic acid **56**.

The hydrocarbon chain analogues to the ether compounds described in this work were synthesized by reaction of lithio ethyl isobutyrate with dibromides **57** and **58** in THF/DMPU to furnish diesters **59** and **60** (79% and 94%), respectively (Scheme 9). Reduction of the shorter chain homologue **59** with $LiAlH_4$ in Et_2O produced diol **61** (62%), whereas the longer chain homologue **60** was reduced with $LiBH_4$ and MeOH in CH_2Cl_2 to **62** (51%).[9] The tetramethyl-substituted diacid **63**, finally, was synthesized from **60** via ester hydrolysis with KOH in aqueous EtOH (69%).

Biological Activity. The structure-based drug design initiated earlier[1a,b] has been extended here to the ether series. The influence of structural modifications on biological activity has been examined. Specifically, the effects of the methylene spacer length from the central ether oxygen to the *gem* substitutions on the quarternary carbons, symmetry around the central ether, kind of the *gem* substitutions (methyl or phenyl) and of the terminal functional groups (diols or diacids) were studied. Tables 2−5 present in vitro and in vivo biological data in connection with lipid regulating

Scheme 9. Synthesis of Hydrocarbon Chain Analogues[a]



[a] Reagents: (a) for $n = 9$, 1,9-dibrononane, LDA [THF/DMPU], 79%; for $n = 11$, 1,11-dibromoundecane, LDA [THF/DMPU], 94%; (b) for $n = 9$, $LiAlH_4$ [Et_2O], 62%; for $n = 11$, $LiBH_4$/MeOH [CH_2Cl_2], 51%; (c) KOH [EtOH/H_2O], 69%.

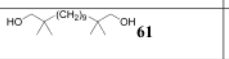
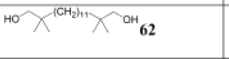
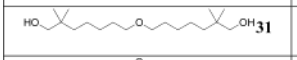
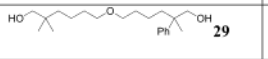
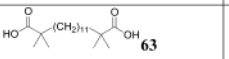
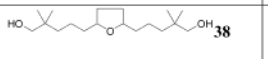
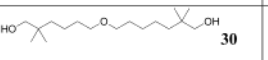
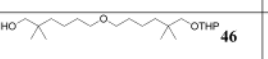
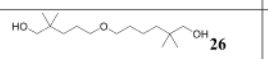
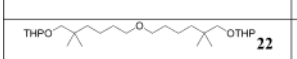
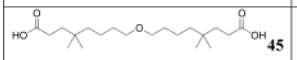
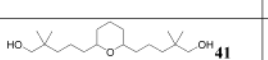
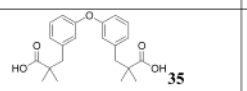
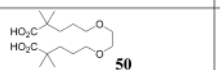
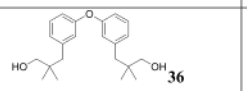
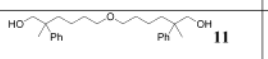
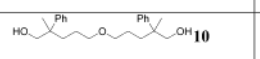
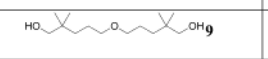
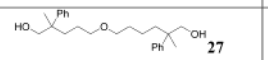
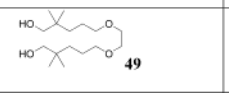
properties for the ether diols and ether diacids described above as well as for their hydrocarbon analogues. In vitro studies tested the ability of the compounds to inhibit the incorporation of ^{14}C-acetate into total cellular lipids of primary rat hepatocytes over a 4-h time period (Table 2). The compounds were also tested for their ability to alter serum lipid variables in an animal model of diabetic dyslipidemia, the obese Zucker rat, over a 2-week period at a single daily dose of 30 or 100 mg/kg (Table 3). Selected compounds (**28** and **31**) were further evaluated in the Zucker rat by performing a full dose response and measuring additional serum variables including markers for diabetes (Tables 4 and 5).

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 ether type compounds and their analogues on total lipid synthesis activity in that model using ^{14}C-acetate as the metabolic precursor.[29,30] Table 2 summarizes the biological effects of the compounds in primary rat hepatocyte cultures.

All of the hydrocarbon chain analogues (**61**−**63**) with 9 or 11 methylene spacers between the *gem* substitutions proved to be very active by inhibiting lipid synthesis with IC_{50} values of ≤ 7 μM. When the central methylene moiety was replaced with an oxygen atom, the resulting ethers, **28** and **31**, were also quite active with IC_{50} values of 11 and 4 μM, respectively; the shorter chain homologue **9**, which contains three methylenes on both sides of the oxygen, was inactive. The unsymmetrical ethers **30** and **26** showed activity with IC_{50} values of 11 and 17 μM, respectively. These data indicate that at least nine bonds between the two carbons with the *gem* substitutions are needed in order to induce lipid synthesis inhibition; there is little difference in the inhibitory activity between ethers and aliphatic compounds with *gem* dimethyl substitutions. Previous studies have indicated no difference in inhibitory activity between terminal diols and diacids in a related series of ketone compounds.[1a,b]

The cyclic ethers (**38** and **41**) and the aryl-bridged ethers (**35** and **36**) displayed IC_{50} values ranging from

Table 2. Effect of Ether Diols and Ether Diacids on Lipid Synthesis in Primary Rat Hepatocytes

Compound	IC_{50} (μM)	95% Confidence Interval		R^2 [b]
		Lower	Upper	
 **61**	4	3	7	0.99
 **62**	4	2	10	0.99
 **31**	4	2	6	0.99
 **29**	5	2	12	0.97
 **63**	7	5	9	0.99
 **38**	9			0.99
 **28**	11	9	12	0.99
 **30**	11	8	15	0.99
 **46**	11	5	22	0.98
 **26**	17	11	28	0.99
 **22**	20	9	45	0.98
 **45**	22	3	200	0.99
 **41**	39	15	106	0.99
 **35**	53	32	86	0.90
 **50**	72	24	219	0.79
 **36**	98			0.90
 **11**	106	66	168	0.99
 **10**	130			0.99
 **9**	NA[a]			
 **27**	NA[a]			
 **49**	NA[a]			

[a] Not active; inhibition of ^{14}C-acetate incorporation into total lipids is less than 50% at 300 μM. [b] r^2 is the goodness of fit of the data to the nonlinear sigmoidal model.

9 to 98 μM. The aryl-bridged ethers **35** and **36** were very weak inhibitors with IC_{50} values of 53 and 98 μM, respectively, as was the dihydropyran **41** (IC_{50} = 39 μM). The tetrahydrofuran **38** showed relatively potent activity with an IC_{50} of 9 μM compared to the tetrahydropyran analogue **41** with an IC_{50} of 39 μM, while the compounds containing a diether in the backbone (**49** and **50**) were relatively weak or inactive in this assay.

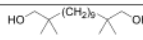
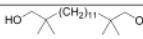
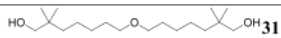
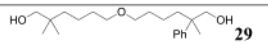
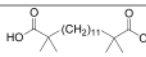
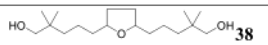
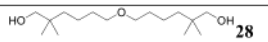
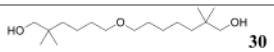
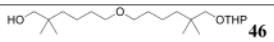
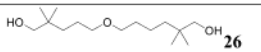
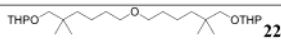
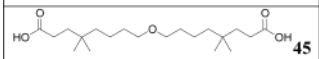
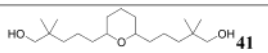
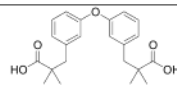
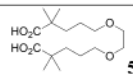
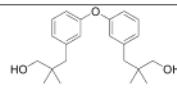
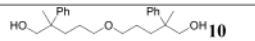
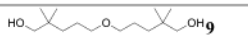
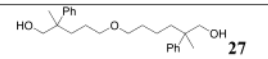
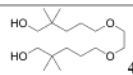
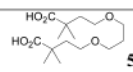
Regarding *gem* substitutions, the diphenyl-substituted ethers (**10** and **27**) with three methylenes on one or both sides of the central ether were essentially inactive in vitro, while the monophenyl-substituted compound **29** was quite active (IC_{50} = 5 μM). The diacid with *gem* dimethyl substitutions in γ-positions (**45**) was active with an IC_{50} of 22 μM. Mono- and bis-THP ethers **46** and **22** were also active, displaying IC_{50} values of 11 and 20 μM, respectively.

To demonstrate that the decreased incorporation of acetate into lipids is not due to a general compound effect on the cell, we assayed the culture medium for the release of the cytosolic enzyme lactate dehydrogenase (LDH).[31] Release of LDH into the media correlates with plasma membrane damage, an early event in loss of cell function. Compound-dependent increases in media LDH are compared to vehicle-treated cultures. The data for compounds active for inhibition of [1-^{14}C] acetate incorporation into lipids did not show general effects on membrane integrity.

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 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 non-insulin-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. Initially, the lipid-regulating activities of the ether compounds in this model were assessed by administering a single dose of 30 or 100 mg/kg 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 3 summarizes those serum lipid changes induced by the ether derivatives and their analogues.

The alkyl compounds (**61**−**63**) were all very effective at lowering serum triglyceride levels as evidenced by the >70% reductions compared to pretreatment values. Both **61** and **63** consistently reduced non-HDL-C levels, while only **61** elevated HDL-C. Thus, it appears that nine methylene spacers are optimum for favorably affecting all three lipid variables. In the corresponding ethers, both **28** and **31** markedly reduced serum triglycerides >70% while also significantly elevating HDL-C. In fact, **28** elevated HDL-C about 5-fold compared to pretreatment levels. Compound **31** markedly lowered non-HDL-C, while **28** did not appear to have much effect on that variable. A direct comparison of compounds with identical chain topology of the aliphatic or ether variety (**62** vs **31** and **61** vs **28**) indicated that of the compounds with 10 spacer bonds between the two quarternary carbons, compound **61** with nine methylene groups was more effective at lowering non-HDL-C than compound **28** in which the central methylene is replaced by oxygen; however, **28** was significantly more effective at elevating HDL-C. With respect to compounds with 12 bonds between the two quarternary carbons, ether **31** was effective at favorably altering all three lipid variables while the aliphatic compound **62** only lowered triglycerides. The unsymmetrical 9-bond spacer ether **26** was

Table 3. Effect of Ether Diols and Ether Diacids in Female Obese Zucker Rats

Compound	Dose (mg/kg)	n	Serum Variables: Percent Change from Pre-Treatment[a]					
			NonHDL-Cholesterol		HDL-Cholesterol		TG	
			1wk	2wk	1wk	2wk	1wk	2wk
 **61**	100	4	-67	-75	189	137	-83	-82
 **62**	100	4	-20	48	-5	-1	-70	-35
 **31**	100	4	-82	-68	99	133	-91	-82
 **29**	100	3	-55	-13	26	52	-61	-45
 **63**	100	3	-66	-60	-14	-6	-89	-87
 **38**	97	3	11	31	287	140	-49	-13
 **28**	100	4	-38	11	234	366	-77	-71
 **30**	30	4	-26	17	71	105	-66	-77
 **46**	100	4	-28	-14	130	152	-69	-63
 **26**	30	4	44	74	24	40	21	32
 **22**	100	4	46	92	43	79	-1	22
 **45**	100	3	-50	-30	13	39	-80	-73
 **41**	100	3	-70	-31	75	127	-74	-46
 **35**	100	4	-59	-21	20	16	-46	-27
 **50**	100	4	-38	-13	-6	-4	-24	-13
 **36**	100	4	-50	-50	17	25	-32	-54
 **10**	100	3	-32	-26	7	5	-27	-18
 **9**	30	3	7	58	-13	-8	21	77
 **27**	30	4	16	45	-2	-20	-1	21
 **49**	100	4	33	45	3	10	-9	6
 **56**	80	3	-10	15	-18	-5	5	46

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

weakly active in vivo in our animal model. Altogether, these data indicate that within the ether compounds, a spacer of 12 bonds between quarternary carbons (**31**) was more effective at lowering non-HDL-C and triglycerides, while a 10-bond spacer (**28**) was better at elevating HDL-C. Furthermore, a minimum spacer length of 10 bonds is required for activity. Diacid **45**, however, did not affect the HDL-C dramatically but

Table 4. Effect of Daily **28** Oral Treatment on Serum Lipid and Glycemic Control Variables in Female Obese Zucker Rats

		non-HDL-C (mg/dL)			HDL-C (mg/dL)			TG (mg/dL)			NEFA (mg/dL)			glucose (mg/dL)			insulin (ng/mL)		
dose (mg/kg)	*n*	pre	1 week	2 weeks	pre	1 week	2 weeks	pre	1 week	2 weeks	pre	1 week	2 weeks	pre	1 week	2 weeks	pre	1 week	2 weeks
0	4	20 ± 2	27 ± 3[a] (+35)	30 ± 2[a] (+50)	48 ± 9	37 ± 7[a] (−23)	40 ± 8[a] (−17)	1005 ± 169	1120 ± 131	1214 ± 122	1.1 ± 0.14	1.3 ± 0.12	1.3 ± 0.15	119 ± 3	115 ± 6	114 ± 5	9.2 ± 0.9	10.4 ± 0.9	6.7 ± 0.4[a] (−27)
3	3	21 ± 3	26 ± 5	29 ± 3[a] (+38)	59 ± 10	70 ± 9[a] (+19)	79 ± 5[a] (+34)	769 ± 73	770 ± 93	934 ± 54[a] (+21)	1.2 ± 0.05	1.7 ± 0.23	1.5 ± 0.22	117 ± 5	114 ± 5	119 ± 1	12.9 ± 3	15.1 ± 2.4	9.9 ± 1.3
10	4	25 ± 3	30 ± 5	43 ± 9	56 ± 8	100 ± 20[a] (+79)	134 ± 21[a] (+139)	943 ± 274	629 ± 123	706 ± 132	1.3 ± 0.17	1.2 ± 0.13	1.1 ± 0.13	112 ± 3	110 ± 8	117 ± 1	8.2 ± 0.8	8.9 ± 0.7	9.0 ± 1.1
30	4	31 ± 2	20 ± 2[a] (−35)	33 ± 6	42 ± 2	149 ± 19[a] (+255)	222 ± 34[a] (+429)	1240 ± 119	271 ± 42[a] (−78)	324 ± 37[a] (−74)	1.3 ± 0.09	0.76 ± 0.11[a] (−42)	0.75 ± 0.02[a] (−42)	109 ± 6	140 ± 7	123 ± 11	9.3 ± 1.5	14.2 ± 3.5	17.4 ± 2.6[a] (+87)
100	4	23 ± 4	14 ± 4	26 ± 8	59 ± 6	192 ± 19[a] (+225)	263 ± 21[a] (+346)	746 ± 122	174 ± 34[a] (−77)	219 ± 49[a] (−71)	1.1 ± 0.04	0.76 ± 0.03[a] (−31)	0.83 ± 0.07[a] (−25)	105 ± 2	107 ± 8	101 ± 7	12.7 ± 3.1	14.5 ± 6.2	12.8 ± 4.1

[a] $p < 0.05$ compared to pretreatment. Data are represented as the mean ± SEM. Numbers in parentheses are the percent increases (+) or decreases (−) of the pretreatment control values. 100% represents a 2-fold increase over pretreatment values.

Table 5. Effect of Daily **31** Oral Treatment on Serum Lipid and Glycemic Control Variables in Female Obese Zucker Rats

		non-HDL-C (mg/dL)			HDL-C (mg/dL)			TG (mg/dL)			NEFA (mg/dL)			glucose (mg/dL)			insulin (ng/mL)		
dose (mg/kg)	*n*	pre	1 week	2 weeks	pre	1 week	2 weeks	pre	1 week	2 weeks	pre	1 week	2 weeks	pre	1 week	2 weeks	pre	1 week	2 weeks
0	4	20 ± 2	27 ± 3[a] (+35)	30 ± 2[a] (+50)	48 ± 9	37 ± 7[a] (−23)	40 ± 8[a] (−17)	1005 ± 169	1120 ± 131	1214 ± 122	1.1 ± 0.14	1.3 ± 0.12	1.3 ± 0.15	119 ± 3	115 ± 6	114 ± 5	9.2 ± 0.9	10.4 ± 0.9	6.7 ± 0.4[a] (−27)
3	4	29 ± 5	26 ± 4	29 ± 8	57 ± 8	55 ± 8	56 ± 8	1111 ± 157	1031 ± 109	1116 ± 166	1.1 ± 0.13	1.3 ± 0.12	1.5 ± 0.10	115 ± 3	11 ± 2	114 ± 3	13.3 ± 5.5	12.2 ± 3.9	11.4 ± 2.6
10	4	33 ± 8	40 ± 8[a] (+21)	53 ± 10[a] (+61)	61 ± 7	92 ± 9[a] (+51)	110 ± 10[a] (+80)	1185 ± 276	1159 ± 267	1420 ± 239	1.4 ± 0.05	1.3 ± 0.21	1.5 ± 0.21	110 ± 3	100 ± 4	119 ± 3	8.8 ± 0.6	14.8 ± 3.4	8.7 ± 0.4
30	4	26 ± 4	15 ± 4	32 ± 8	49 ± 7	128 ± 8[a] (+161)	138 ± 10[a] (+181)	1004 ± 181	191 ± 45[a] (−81)	424 ± 109	1.2 ± 0.08	0.89 ± 0.15	0.82 ± 0.05[a] (−32)	106 ± 5	113 ± 10	141 ± 16	9.0 ± 0.7	12.4 ± 4.2	10.4 ± 2.7
100	4	32 ± 5	5 ± 3[a] (−84)	10 ± 3[a] (−69)	58 ± 5	115 ± 12[a] (+98)	134 ± 14[a] (+131)	1068 ± 269	83 ± 21[a] (−92)	167 ± 31[a] (−84)	1.2 ± 0.04	1.2 ± 0.13	0.70 ± 0.07	105 ± 0.9	72 ± 4[a] (−31)	104 ± 2	8.6 ± 2.0	3.5 ± 0.5[a] (−59)	4.4 ± 1.0

[a] $p < 0.05$ compared to pretreatment. Data are represented as the mean ± SEM. Numbers in parentheses are the percent increases (+) or decreases (−) of the pretreatment control values. 100% represents a 2-fold increase over pretreatment values.

showed significant triglyceride lowering. Compounds **38** and **41** (in which the central ether is part of a ring that induces restricted rotation of the hydrocarbon chain) showed significant HDL-C elevation, but relevant lipid lowering activity is only shown in tetrahydropyran **41**.

In this animal model, compounds **49**, **50**, and **56** with two ether moieties placed symmetrically in the hydrocarbon chain showed a weak triglyceride lowering but no HDL-C elavation. When the ether moiety connects two aromatic rings as in compounds **35** and **36**, a modest HDL-C elevation and triglyceride lowering were observed compared to compound **28**. There are no significant differences between the activities of the diacid/diol pairs (e.g., **35** vs **36**, **49** vs **56**, and **62** vs **63**).

A comparison of activities in the in vitro lipid synthesis assay (Table 2) and the Zucker rat model (Table 3) indicated that all compounds that lowered non-HDL-C or triglycerides by about 70% had $IC_{50} < 39\ \mu M$ in the lipid synthesis inhibition assay. However, some compounds active in the in vitro assay (**26**, $IC_{50} = 17\ \mu M$; **22**, $IC_{50} = 20\ \mu M$) were poorly active in vivo in the Zucker rat model.

Effect on Lipid Variables in the Obese Female Zucker Rat: Dose Response for Selected Compounds. To further investigate the active ether compounds **28** and **31**, we performed a complete dose response study in the Zucker rat (Tables 4 and 5). The 10-bond spacer compound **28** dose-dependently elevated HDL-C at a minimum effective daily dose of 3 mg/kg. Compound **28** also reduced serum triglycerides and nonesterified fatty acids (NEFA) at daily doses of 30 and 100 mg/kg. The compound had no effect on fasting serum glucose or insulin levels. The 12-bond spacer compound **31** dose-dependently elevated HDL-C as well, with a minimal effective daily dose of 10 mg/kg. The compound also lowered non-HDL-C (100 mg/kg/day) and triglycerides (30 and 100 mg/kg/day); minimal effects on NEFA were observed, while glucose and insulin were not altered.

The mechanism of action (MoA) is clearly a key component of drug discovery, and our in vivo structure optimization approach implies that multiple MoAs could be responsible for the biological activity in the whole animal. A similar approach has been reported recently by other research groups.[32] We have determined that a major MoA in this class of compounds is inhibition of fatty acid synthesis (FAS) at the acetyl-CoA carboxylase (ACC) step (within minutes of dosing) via an allosteric mechanism.[33] We have also found that these compounds rapidly block de novo cholesterol synthesis at a step between acetoacetyl-CoA formation and HMG-CoA,[33] inferring that the compounds are dual inhibitors of lipid synthesis.

Conclusions

Our research was focused on identifying compounds for the treatment of dyslipidemia, a major medical problem related to premature development of cardiovascular diseases. A common dyslipidemic patient presents elevated levels of triglycerides and low levels of HDL-C. The current discovery effort has generated a series of novel ether compounds with biological properties that suggest utility for controlling these serum variables. The most promising ether compound in this study is **28**, which contains a spacer of 10 bonds between the *gem* dimethyl substitutions and hydroxyl terminal groups. This compound was exceptional at elevating HDL-C and also lowered serum triglycerides and nonesterified fatty acids.

Experimental Section

Chemistry. Chemical reagents were purchased from Sigma-Aldrich or Lancaster and were used without further purification. Silica gel for column chromatography (0.035−0.070 mm, pore diameter ca. 6 nm) was obtained from Acros Organics. ACS grade solvents from Fisher Scientific or Mallinckrodt were routinely used for chromatographic purifications and extractions. Melting points were determined on either a Thomas-Hoover capillary or Haake-Buchler melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra were recorded 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 purities of target compounds were analyzed using Shimadzu HPLC systems with UV and RI detection.

Bis(3-bromopropyl) Ether (4). Under N_2 atmosphere, PBr_3 (7.2 mL, 20.5 g, 75.8 mmol) was added dropwise over 1 h to **3**[4] (10.14 g, 75.6 mmol), causing self-heating to reflux. The reaction mixture was stirred overnight at room temperature, then distilled in vacuo to give an oil. This oil was dissolved in CH_2Cl_2 (100 mL), washed with water (100 mL), dried over Na_2SO_4, and concentrated in vacuo, affording **4** (10.9 g, 55%) as a clear, colorless oil. Bp 68−70 °C/0.2 mmHg. ^{1}H NMR ($CDCl_3$): δ 3.56 (t, 4 H, $J = 5.8$), 3.51 (t, 4 H, $J = 6.4$), 2.10 (m, 4 H). ^{13}C NMR ($CDCl_3 = 77.00$ ppm): δ 68.17, 32.68, 30.59.

5-(4-Ethoxycarbonyl-4-methylpentyloxy)-2,2-dimethylpentanoic Acid Ethyl Ester (6). Under N_2 atmosphere and at −78 °C, to a stirred solution of ethyl isobutyrate (6.5 g, 55.9 mmol) in anhydrous THF (30 mL) was added dropwise a solution of LDA (30 mL, 60.0 mmol, 2.0 M in heptane/THF/ethylbenzene). After 1 h, a solution of **4**[2] (6.76 g, 26.0 mmol) and DMPU (2 mL) in THF (15 mL) was added dropwise, and the reaction temperature was kept at −78 °C for an additional 30 min. The reaction mixture was allowed to warm to room temperature and stirred overnight, then quenched with a mixture of ice (10 g) and concentrated HCl (10 mL). The product was extracted with Et_2O (2 × 30 mL). The combined ether phases were washed with 5% aqueous $NaHCO_3$ solution (30 mL), dried over $MgSO_4$, and concentrated in vacuo to furnish the crude product (10.9 g), which was distilled in high vacuo to give pure **6** (5.96 g, 69%) as an oil. Bp 115−120 °C/0.5 mmHg. ^{1}H NMR ($CDCl_3$): δ 4.11 (q, 4 H, $J = 7.0$), 3.37 (m, 4 H), 1.62−1.43 (m, 8 H), 1.25 (t, 4 H, $J = 7.0$), 1.17 (s, 12 H). ^{13}C NMR ($CDCl_3 = 77.00$ ppm): δ 177.62, 70.85, 60.06, 41.75, 36.89, 25.14, 24.96, 14.09.

5-(5-Hydroxy-4,4-dimethylpentyloxy)-2,2-dimethylpentan-1-ol (9). Under N_2 atmosphere, to a solution of $LiAlH_4$ in Et_2O (55 mL, 1.0 M, 55 mmol) was added dropwise a solution of **6** (5.62 g, 17.0 mmol) in anhydrous Et_2O (25 mL) at such a rate as to prevent the ether from boiling. The mixture was stirred for 30 min, then hydrolyzed by subsequent slow addition of distilled water (30 mL) and 25% H_2SO_4 (35 mL). The product was extracted with Et_2O (5 × 75 mL). The combined ether extracts were washed with 5% $NaHCO_3$ solution (2 × 25 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give an oil (4.95 g). Purification by vacuum distillation afforded **9** (3.3 g, 79%) as an almost colorless, very viscous oil. Bp 130−140 °C/0.5 mmHg (lit.[7] mp 30−32 °C). ^{1}H NMR ($CDCl_3$): δ 3.41 (t, 4 H, $J = 6.3$), 3.28 (s, 4 H), 3.11 (br s, 2 H), 1.60−1.48 (m, 4 H), 1.33−1.24 (m, 4 H), 0.86 (s, 12 H). ^{13}C NMR ($CDCl_3 = 77.00$ ppm): δ 71.65, 70.55, 34.78, 34.34, 24.06, 23.88. HRMS (CI) Calcd for $C_{14}H_{31}O_3$ (MH^+): 247.2273. Found: 247.2265. HPLC: Alltima C-8

column, 250 mm × 4.6 mm, 5 μm; 58% acetonitrile, 42% water, flow rate 1.0 mL/min; RI, retention time 4.95 min, 86.3% pure.

5-(5-Hydroxy-4-methyl-4-phenylpentyloxy)-2-methyl-2-phenylpentan-1-ol (10). According to the procedure given for the synthesis of **9**, **7** (4.2 g, 9.2 mmol) was reduced with $LiAlH_4$ (1.7 g, 44.8 mmol) in anhydrous Et_2O (100 mL) at room temperature overnight. Hydrolysis with acid, extraction, and drying afforded pure **10** (2.8 g, 82%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.45−7.10 (m, 10 H), 3.70 (d, 2 H, J = 11.0), 3.58 (d, 2 H, J = 11.0), 3.28 (t, 4 H, J = 6.3), 1.90−1.15 (m, 10 H), 1.34 (s, 6 H). ^{13}C NMR ($CDCl_3$ = 77.00 ppm): δ 144.75, 128.41, 126.62, 126.11, 71.91, 71.21, 43.09, 34.60, 24.16, 21.87. HRMS (LSIMS, gly) Calcd for $C_{24}H_{35}O_3$ (MH^+): 371.2586. Found: 371.2581. HPLC: Alltima C-8 column, 250 mm × 4.6 mm, 5 μm; 60% acetonitrile, 40% water, flow rate 1.0 mL/min; RI, retention time 8.50 min, 93.9% pure.

6-(6-Hydroxy-5-methyl-5-phenylhexyloxy)-2-methyl-2-phenylhexan-1-ol (11). Under N_2 atmosphere and at room temperature, to a suspension of $LiBH_4$ (6.3 g, 289 mmol) in CH_2Cl_2 (210 mL) was added dropwise MeOH (8.8 g, 275 mmol) over 30 min. The reaction mixture was heated to reflux, and **8** (44.0 g, 91.2 mmol) was added. After the mixture was refluxed overnight and cooled to room temperature, saturated NH_4Cl solution (100 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with 2 N HCl (100 mL) and saturated NaCl solution (100 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by flash chromatography (silica; hexanes/EtOAc = 80/20), affording **11** (34.4 g, 95%) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.36−7.14 (m, 10 H), 3.67 (d, 2 H, J = 10.7), 3.52 (d, 2 H, J = 10.7), 3.27 (t, 4 H, J = 6.6), 1.82−1.70 (m, 2 H), 1.60−1.10 (m, 10 H), 1.33 (s, 6 H), 1.05−0.95 (m, 2 H). ^{13}C NMR ($CDCl_3$ = 77.00 ppm): δ 144.84, 128.37, 126.63, 126.05, 72.35, 70.57, 43.34, 38.21, 30.25, 21.56, 20.44. HRMS (LSIMS, nba) Calcd for $C_{26}H_{39}O_3$ (MH^+): 399.2899. Found: 399.2903.

General Procedure for the Hydrolysis of ω-Bromo- to ω-Hydroxyalkyl THP Ethers: 6,6-Dimethyl-7-(tetrahydropyran-2-yloxy)heptan-1-ol (19). A mixture of **16** (11.0 g, 35.8 mmol), K_2CO_3 (10.0 g, 72.4 mmol), water (100 mL), and DMSO (50 mL) was heated to reflux for 24 h. After cooling to room temperature, the mixture was diluted with water (150 mL) and neutralized by addition of concentrated HCl (5 mL) and 1 N HCl (15 mL). The solution was extracted with Et_2O (4 × 100 mL). The combined organic layers were washed with saturated NH_4Cl solution (100 mL) and saturated NaCl solution (100 mL), dried over $MgSO_4$, and concentrated in vacuo to furnish **19** (7.3 g, 83%) as a colorless oil, which was used without further purification for the next step. ^{1}H NMR ($CDCl_3$): δ 4.55 (m, 1 H), 3.84 (m, 1 H), 3.61 (t, 2 H, J = 6.5), 3.51−3.30 (m, 1 H), 3.45 (d, 1 H, J = 9.1), 2.98 (d, 1 H, J = 9.1), 2.26 (br s, 1H), 1.98−1.40 (m, 8 H), 1.40−1.10 (m, 6 H), 0.88 (s, 6 H). ^{13}C NMR ($CDCl_3$ = 77.20 ppm): δ 99.17, 76.61, 62.89, 61.95, 39.38, 34.28, 32.87, 30.75, 26.79, 25.66, 24.65, 23.81, 19.50. HRMS (LSIMS, nba) Calcd for $C_{14}H_{29}O_3$ (MH^+): 245.2117. Found: 245.2119.

General Procedure for the Williamson Ether Synthesis: 2-{6-[4,4-Dimethyl-5-(tetrahydropyran-2-yloxy)pentyloxy]-2,2-dimethylhexyloxy}tetrahydropyran (20). Under Ar atmosphere, to a suspension of NaH (95%, 0.76 g, 30 mmol) in anhydrous THF (80 mL) was added dropwise **17** (7.93 g, 34.4 mmol) over 10 min at room temperature. The reaction mixture was heated to reflux overnight before **12** (9.30 g, 33.3 mmol) was added dropwise, and heating to reflux was continued for 4 h. After cooling to room temperature, the mixture was hydrolyzed by adding ice (20 g) and saturated NH_4Cl solution (30 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated NH_4Cl solution (3 × 50 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (silica gel, EtOAc/hexanes = 20/80) furnished **20** (9.0 g, 63%) as a yellowish oil. ^{1}H NMR ($CDCl_3$): δ 4.49 (m, 2 H), 3.79 (m, 2 H), 3.39 (m, 8 H), 2.94 (m, 2 H), 1.90−1.38 (m, 14 H), 1.28−1.16 (m, 8 H), 0.84 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 99.23, 76.68, 76.58, 71.95, 71.04, 62.03, 39.35, 35.56, 34.40, 34.20, 30.83, 25.75, 24.71, 24.63, 20.78, 19.60. HRMS (LSIMS, nba) Calcd for $C_{25}H_{47}O_5$ [(M − 2H) + H^+]: 427.3423. Found: 427.3428.

General Procedure for the Deprotection of THP Ethers: 6-(5-Hydroxy-4,4-dimethylpentyloxy)-2,2-dimethylhexan-1-ol (26). A solution of **20** (8.0 g, 18.7 mmol) in MeOH (80 mL) and concentrated HCl (8 mL) was heated to reflux for 4 h, then poured into ice−water (40 mL). The solution was neutralized with saturated $NaHCO_3$ solution (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with saturated NH_4Cl solution (100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue (7.4 g) was purified by chromatography (silica gel; EtOAc/hexanes = 20/80) to furnish **26** (2.5 g, 51%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.35 (m, 4 H), 3.23 (s, 4 H), 2.54 (br, 2 H), 1.47 (m, 4 H), 1.22 (m, 6 H), 0.79 (s, 12 H). ^{13}C NMR ($CDCl_3$ = 77.23 ppm): δ 71.77, 71.43, 71.07, 70.98, 38.25, 35.18, 35.06, 34.68, 30.45, 24.23, 20.63. HRMS (LSIMS, gly) Calcd for $C_{15}H_{33}O_3$ (MH^+): 261.2430. Found: 261.2413. HPLC: Alltima C-8 column, 250 mm × 4.6 mm, 5 μm; 50% acetonitrile, 50% water, flow rate 1.0 mL/min; RI, retention time 7.43 min, 96.4% pure.

7-(6-Hydroxy-5,5-dimethylhexyloxy)-2,2-dimethylheptan-1-ol (30). According to the method given for the synthesis of **26**, **24** (5.0 g, 10.9 mmol) was heated to reflux in MeOH (60 mL) and concentrated HCl (6 mL) for 4 h. Extractive workup gave a crude product that was purified by chromatography (silica gel; EtOAc/hexanes = 20/80), affording **30** (2.85 g, 90%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.34 (m, 4 H), 3.21 (s, 4 H), 2.26 (br, 2 H), 1.60−1.40 (m, 4 H), 1.34−1.10 (m, 10 H), 0.78 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 71.83, 71.67, 71.06, 70.86, 38.68, 38.42, 35.17, 30.53, 29.73, 27.22, 24.02, 23.76, 20.58. HRMS (LSIMS, gly) Calcd for $C_{17}H_{37}O_3$ (MH^+): 289.2743. Found: 289.2739. HPLC: Alltima C-8 column, 250 mm × 4.6 mm, 5 μm; 60% acetonitrile, 40% water, flow rate 1.0 mL/min; RI, retention time 7.63 min, 95.7% pure.

General Procedure for the Williamson Ether Synthesis Followed by THP Deprotection: 6-(5-Hydroxy-4-methyl-4-phenylpentyloxy)-2-methyl-2-phenylhexan-1-ol (27). Under Ar atmosphere, to a suspension of NaH (60%, 600 mg, 15 mmol) in anhydrous THF (100 mL) was added dropwise a solution of **18** (3.3 g, 11.3 mmol) in anhydrous THF (25 mL). After 30 min of stirring at room temperature, the mixture was heated to reflux for 1 h and cooled to room temperature, and a solution of **13**[1b] (3.8 g, 11.1 mmol) in anhydrous THF (25 mL) was added dropwise. The reaction mixture was heated to reflux for 22 h and hydrolyzed by addition of ice (100 g) and saturated NH_4Cl solution (200 mL). The mixture was extracted with EtOAc (3 × 300 mL). The combined organic layers were washed with saturated NH_4Cl solution (3 × 300 mL), dried over $MgSO_4$, and concentrated in vacuo to give **21** (10.6 g). A solution of this residue in MeOH (200 mL) and concentrated HCl (20 mL) was heated to reflux for 6 h. The reaction mixture was diluted with water (50 mL), and the MeOH was evaporated under reduced pressure. The solution was extracted with CH_2Cl_2 (4 × 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (3 × 400 mL), dried over $MgSO_4$, and evaporated to give the crude product (6.5 g). Purification by flash chromatography (silica gel; hexanes/EtOAc = 50/50) afforded **27** (1.88 g, 44%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.36−7.15 (m, 10 H), 3.68 (m, 2 H), 3.55 (m, 2 H), 3.27 (m, 4 H), 1.85−1.30 (m, 10 H), 1.36 (s, 3 H), 1.33 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 145.07, 144.97, 128.61, 126.85, 126.31, 126.28, 72.52, 72.24, 71.40, 70.75, 43.55, 43.33, 38.38, 34.84, 30.44, 24.36, 22.03, 21.84, 20.70. HRMS (LSIMS, gly) Calcd for $C_{25}H_{37}O_3$ (MH^+): 385.2743. Found: 385.2749. HPLC: Alltima C-18/cation column, 250 mm × 4.6 mm, 5 μm; 60% acetonitrile, 40% water, flow rate 1.0 mL/min; RI, retention time 9.10 min, 90.1% pure.

6-(6-Hydroxy-5-methyl-5-phenylhexyloxy)-2,2-dimethyl-hexan-1-ol (29). According to the procedure provided for the synthesis of **27**, **17** (10.57 g, 45.9 mmol) was treated with NaH (95%, 1.01 g, 40.0 mmol) and **15** (14.95 g, 42.1 mmol) in

anhydrous THF (105 mL). After workup by hydrolysis and extraction, the crude intermediate **23** (21.8 g) was heated to reflux in MeOH (80 mL) and concentrated HCl (8 mL) overnight. After extractive workup, the volatile impurities were distilled off (195 °C/0.5 mmHg) and the residue was purified by column chromatography (silica; CH_2Cl_2/acetone = 15:1) to furnish **29** (3.2 g, 24%) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.38−7.16 (m, 5H), 3.70 (dd, 1 H, J = 10.7, 4.4), 3.55 (dd, 1 H, J = 10.7, 7.7), 3.42−3.18 (m, 6 H), 1.76 (m, 2 H), 1.64−0.95 (m, 15 H), 0.85 (s, 6 H). ^{13}C NMR ($CDCl_3$ = 77.00 ppm): δ 144.86, 128.31, 126.60, 125.98, 72.23, 71.58, 70.69, 70.58, 43.32, 38.20, 34.97, 30.35, 30.22, 23.88, 21.62, 20.42. HRMS (LSIMS, gly) Calcd for $C_{21}H_{37}O_3$ (MH^+): 337.2743. Found: 337.2751. HPLC: Alltima C-18 column, 250 mm × 4.6 mm, 5 μm; 70% acetonitrile, 30% 0.05 M KH_2PO_4, flow rate 1.2 mL/min; UV, retention time 5.83 min, 94.8% pure.

7-(7-Hydroxy-6,6-dimethylheptyloxy)-2,2-dimethylheptan-1-ol (31). According to the procedure provided for the synthesis of **27**, **19** (1.83 g, 7.5 mmol) was treated with NaH (60% w/w dispersion in mineral oil, 0.6 g, 15 mmol) and **16** (2.3 g, 7.5 mmol) in anhydrous THF (50 mL). The residue obtained after extractive workup was heated to reflux in MeOH (20 mL) and concentrated HCl (2 mL) for 4 h. Workup and purification by column chromatography (silica; hexanes/EtOAc = 10/1 to 3/1) afforded **31** (0.68 g, 30%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 3.40 (t, 4 H, J = 6.6), 3.31 (s, 4 H), 1.71−1.50 (m, 6 H), 1.40−1.17 (m, 12 H), 0.86 (s, 12 H). ^{13}C NMR ($CDCl_3$ = 77.00 ppm): δ 71.90, 70.90, 38.60, 34.98, 29.66, 27.15, 23.84, 23.66. HRMS (LSIMS, gly) Calcd for $C_{18}H_{39}O_3$ (MH^+): 303.2899. Found: 303.2907. HPLC: Alltima C-18 column, 250 mm × 4.6 mm, 5 μm; 60% acetonitrile, 40% water, flow rate 1.0 mL/min; RI, retention time 15.73 min, 91.8% pure. Anal. ($C_{18}H_{38}O_3$) C, H.

6-(6-Hydroxy-5,5-dimethylhexyloxy)-2,2-dimethylhexan-1-ol (28). Under N_2 atmosphere, NaH (60% w/w dispersion in mineral oil, 150 g, 3.75 mol) was washed with hexanes (3 × 0.5 L) and anhydrous THF (3 × 0.5 L), then suspended in THF (2 L). A solution of **17** (496 g, 2.15 mol) in THF (1.5 L) was added, and the mixture was stirred for 30 min at room temperature. After heating to 60 °C for 17 h, the suspension was cooled to 0 °C and a solution of **14** (639 g, 2.18 mol) in THF (1.5 L) was added dropwise, keeping the internal temperature below 35 °C. The mixture was heated to reflux for 10 h, stirred at room temperature for 17 h, and hydrolyzed by addition of ice (0.5 L) and saturated NH_4Cl solution (1.5 L). The layers were separated, and the aqueous layer was extracted with EtOAc (2 L, 2 × 0.5 L). The combined organic phases were washed with saturated NH_4Cl solution (2 × 0.6 L), dried over Na_2SO_4, and concentrated in vacuo to give **22** as a yellow, oily residue. A solution of this residue in MeOH (2 L) and concentrated HCl (0.3 L) was heated to reflux for 48 h. The reaction mixture was cooled to room temperature, diluted with water (1 L), and neutralized with saturated $NaHCO_3$ solution (1.1 L). The mixture was extracted with EtOAc (3 × 0.7 L). The combined organic extracts were washed with saturated NH_4Cl solution (0.5 L) and saturated NaCl solution (0.5 L), dried over Na_2SO_4, and concentrated in vacuo. The volatiles were removed by distillation under high vacuum at 35−70 °C/5 mmHg. The residue was dissolved in MeOH (0.5 L) and concentrated HCl (50 mL) and heated to reflux for 17 h. The residual oil obtained after extractive workup as above was distilled in high vacuo, affording **28** (216 g, 37%) as a colorless oil. Bp 155−159 °C/0.03 mmHg; 160−162 °C/0.15 mmHg. ^{1}H NMR ($CDCl_3$): δ 3.42 (t, 4 H, J = 6.8), 3.32 (s, 4 H), 1.88 (br, 2 H), 1.55 (m, 4 H), 1.40−1.30 (m, 8 H), 0.86 (s, 12H). ^{13}C NMR ($CDCl_3$ = 77.00 ppm): δ 71.58, 70.70, 38.16, 34.99, 30.33, 23.90, 20.43. HRMS (LSIMS, nba) Calcd for $C_{16}H_{35}O_3$ (MH^+): 275.2586. Found: 275.2568. HPLC: Alltima C-8 column, 250 mm × 4.6 mm, 5 μm; 55% acetonitrile, 45% water, flow rate 1.0 mL/min; RI, retention time 8.83 min, 98.0% pure. Anal. ($C_{16}H_{34}O_3$) C, H.

3-{3-[3-(2-Ethoxycarbonyl-2-methylpropyl)-phenoxy]-phenyl}-2,2-dimethylpropionic Acid Ethyl Ester (34). Under Ar atmosphere, to a solution of ethyl isobutyrate (20.7 g, 178 mmol) in anhydrous THF (150 mL) was added dropwise a solution of LDA (2.0 M in heptane/THF/ethylbenzene, 89 mL, 178 mmol) over 50 min at − 78 °C. The mixture was stirred for 40 min, and a solution of **33** (prepared from diphenyl ether **32**[13] via bromination with NBS and benzoyl peroxide,[12] 25.4 g, 71.2 mmol) in THF (50 mL) was added dropwise over 20 min, keeping the reaction temperature below − 45 °C. DMPU (20 mL) was added dropwise over 10 min, and the reaction mixture was allowed to warm to room temperature overnight. The mixture was poured into half-saturated aqueous NH_4Cl solution (250 mL) and extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with 1 N aqueous HCl (250 mL) and saturated NaCl solution (2 × 100 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica, heptane/EtOAc = 90/10) to afford **34** (17.9 g, 59%) as a yellowish oil. ^{1}H NMR ($CDCl_3$): δ 7.20 (t, 2 H, J = 7.8), 6.83 (t, 4 H, J = 6.6), 6.76 (s, 2 H), 4.06 (q, 4 H, J = 7.2), 2.82 (s, 4 H), 1.20 (t, 6 H, J = 7.2), 1.17 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 176.95, 156.65, 139.73, 128.89, 124.82, 120.39, 116.62, 60.31, 45.98, 43.38, 24.95, 14.12. HRMS (LSIMS, nba) Calcd for $C_{26}H_{35}O_5$ (MH^+): 427.2484. Found: 427.2443.

3-{3-[3-(2-Carboxy-2-methylpropyl)phenoxy]phenyl}-2,2-dimethylpropionic Acid (35). A mixture of **34** (8.5 g, 19.9 mmol) and KOH (85%, 4.6 g, 69.8 mmol) in EtOH (30 mL) and water (30 mL) was heated to reflux for 4 h. The mixture was cooled to room temperature, diluted with deionized water (100 mL), and extracted with MTBE (50 mL). The aqueous layer was acidified with concentrated HCl (5 mL) to pH 1 and extracted with MTBE (2 × 50 mL). The organic layers were washed with saturated NaCl solution (50 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was recrystallized from hot heptane (40 mL) to furnish **35** (5.3 g, 72%) as a white powder. Mp 87 °C. ^{1}H NMR ($CDCl_3$): δ 11.0−9.0 (br, 2 H), 7.29 (t, 2 H, J = 8.1), 7.00 (m, 2 H), 6.91 (m, 2 H), 6.59 (s, 2 H), 2.77 (s, 4 H), 1.26 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 183.61, 156.72, 139.29, 129.14, 125.23, 118.35, 118.31, 47.46, 43.81, 24.82. HRMS (CI) Calcd for $C_{22}H_{26}O_5$ (M^+): 370.1780. Found: 370.1750. HPLC: Alltima phenyl column, 250 mm × 4.6 mm, 5 μm; 60% acetonitrile, 40% 0.05 M KH_2PO_4, flow rate 1.2 mL/min; RI, retention time 6.67 min, 92.5% pure. Anal. ($C_{22}H_{26}O_5$) C, H.

3-{3-[3-(3-Hydroxy-2,2-dimethylpropyl)phenoxy]-phenyl}-2,2-dimethylpropan-1-ol (36). Under Ar atmosphere, to a solution of $LiAlH_4$ (1.0 M in THF, 41 mL, 41 mmol) was added dropwise a solution of **34** (8.76 g, 20.5 mmol) in anhydrous THF (50 mL) over 1 h under cooling with an ice bath. The solution was stirred at room temperature for 3 h, cooled with an ice bath, and carefully hydrolyzed with water (25 mL) and 25% aqueous H_2SO_4 (100 mL). The mixture was extracted with MTBE (3 × 50 mL). The combined organic layers were washed with water (100 mL), saturated $NaHCO_3$ solution (50 mL), and saturated NaCl solution (50 mL). The solution was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue (8.1 g) was purified by column chromatography (silica, heptane/EtOAc = 75/25, 70/30) to furnish **36** (5.65 g, 80%) as a very viscous, colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.21 (t, 2 H, J = 7.7), 6.89 (d, 2 H, J = 7.7), 6.80 (d, 2 H, J = 7.7), 6.82 (s, 2 H), 3.29 (s, 4 H), 2.53 (s, 4 H), 2.34 (s br, 2 H), 0.86 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 156.81, 140.89, 129.00, 125.47, 120.94, 116.38, 71.09, 44.70, 36.61, 24.25. HRMS (LSIMS, gly) Calcd for $C_{22}H_{31}O_3$ (MH^+): 343.2273. Found: 343.2257. HPLC: Alltima C-8 column, 250 mm × 4.6 mm, 5 μm; 80% acetonitrile, 20% water, flow rate 1.0 mL/min; RI, retention time 5.03 min, 94.6% pure.

1,14-Bis(tetrahydropyran-2-yloxy)-2,2,13,13-tetramethyltetradecan-6,9-diol (37). A mixture of 2,5-dimethoxytetrahydrofuran (26.4 g, 0.2 mol) and 0.6 N HCl (160 mL) was stirred at room temperature for 1.5 h. The mixture was neutralized with $NaHCO_3$ (8.4 g, 0.10 mol) and extracted with CH_2Cl_2 (3 × 50 mL). The aqueous phase was acidified with concentrated HCl (10 mL), stirred for 1.5 h, neutralized with $NaHCO_3$ (10.1 g), and extracted with CH_2Cl_2 (3 × 50 mL). This sequence of acidification, neutralization, and extraction was

repeated two more times. The combined organic extracts were dried over $MgSO_4$, and the solvent was distilled off under atmospheric pressure. Distillation of the residue under reduced pressure gave succinaldehyde[14] (5.71 g, 33%) as a foul-smelling, colorless liquid (bp 75−77 °C/15 mmHg; lit.[15] bp 55−60 °C/12 mmHg). Under N_2 atmosphere, to a suspension of Mg powder (3.65 g, 0.15 mol) in anhydrous THF (100 mL) was added dropwise a solution of **12**[1b] (27.9 g, 0.10 mol) in THF (100 mL). The reaction mixture was heated to reflux for 2 h. Under cooling with an ice bath, a solution of freshly distilled succinaldehyde (3.44 g, 40.0 mmol) in THF (30 mL) was added dropwise, and the reaction mixture was stirred at room temperature overnight. The solution was decanted from excess Mg and poured into aqueous saturated NH_4Cl solution (300 mL). After acidification to pH 1−2 with 2 N HCl, the reaction mixture was extracted with diethyl ether (2 × 100 mL). The combined organic extracts were washed with saturated NaCl solution (100 mL), dried over $MgSO_4$, and concentrated in vacuo to give a residue that was purified by flash column chromatography (silica, EtOAc/hexanes = 25/75, then 50/50), affording **37** (18.0 g, 92%) as an almost colorless, very viscous oil. ^{1}H NMR ($CDCl_3$): δ 4.54−4.50 (m, 2 H), 3.89−3.82 (m, 2 H), 3.66 (br s, 2 H), 3.48 (pseudo-t, 4 H, J = 9.6), 2.99 (dd, 2 H, J = 9.1, 3.5), 2.60 (br s, 2 H), 1.90−1.20 (m, 28 H), 0.90−0.88 (m, 12 H). ^{13}C NMR ($CDCl_3$ = 77.00 ppm): δ 99.38, 99.15, 76.40, 76.14, 72.14, 71.67, 71.29, 62.39, 62.05, 39.19, 38.77, 38.30, 38.17, 34.18, 33.35, 30.74, 30.64, 25.51, 24.93, 24.65, 24.48, 24.37, 20.04, 19.74, 19.51. HRMS (LSIMS, gly) Calcd for $C_{28}H_{55}O_6$ (MH^+): 487.3998. Found: 487.3995.

5-[5-(5-Hydroxy-4,4-dimethylpentyl)tetrahydrofuran-2-yl]-2,2-dimethylpentan-1-ol (38). Method A. A solution of **37** (6.18 g, 12.7 mmol) and *p*TosOH monohydrate (0.3 g, 1.6 mmol) in toluene (300 mL) was heated under reflux with azeotropic removal of water for 3 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in MeOH (100 mL) and 3 N H_2SO_4 (30 mL) and stirred at room temperature overnight. The MeOH was distilled under reduced pressure, and the aqueous phase was extracted with EtOAc (3 × 75 mL). The combined organic extracts were washed with water (75 mL) and saturated NaCl solution (75 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (twice; silica, EtOAc/hexanes = 75/25, then 50/50) to give **38** (1.35 g, 35%) as a light-yellow oil.

Method B. Under N_2 atmosphere, a solution of **37** (3.79 g, 7.8 mmol), tosyl chloride (1.64 g, 8.6 mmol), and pyridine (1.0 mL, 12.4 mmol) in CH_2Cl_2 (40 mL) was stirred at room temperature for 21 h. The solvent was removed under reduced pressure, and the residue was dissolved in pyridine (3 mL) and HMPA (5 mL). The mixture was heated to 70−75 °C for 4 h, cooled to room temperature, diluted with water (100 mL), and extracted with CH_2Cl_2 (3 × 50 mL). The organic extracts were washed with 2 N HCl (until the washings were acidic) and with water and dried over $MgSO_4$. The residue obtained after solvent removal was dissolved in MeOH (40 mL) and aqueous H_2SO_4 (2 mL of concentrated H_2SO_4/5 mL of water) and stirred at room temperature overnight. The MeOH was removed under reduced pressure. The residue was diluted with water (40 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica, EtOAc/hexanes = 25/75, then 50/50) to give **38** (0.9 g, 38%, mixture of diastereomers in a ratio of ca. 60/40) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 3.96 (m, 2 H), 3.86 (m, 2 H), 3.30 (m, 8 H), 2.41 (s br, 4 H), 2.05−1.91 (m, 4 H), 1.57−1.18 (m, 28 H), 0.86 (s, 12 H), 0.85 (s, 12 H). ^{13}C NMR ($CDCl_3$ = 77.00 ppm): δ 79.20, 78.53, 71.13, 37.99, 36.69, 36.48, 35.02, 32.16, 31.12, 24.23, 24.00, 23.95, 20.47. HRMS (LSIMS, gly) Calcd for $C_{18}H_{37}O_3$ (MH^+): 301.2743. Found: 301.2743. HPLC: Alltima C8 column, 250 mm × 4.6 mm, 5 μm; 50% acetonitrile, 50% water, flow rate 1.0 mL/min; RI, retention time 11.58 min, 53.3%, retention time 12.00 min, 43.8%; combined, 97.1% pure. Anal. ($C_{18}H_{36}O_3$) C, H.

1,15-Bis(tetrahydropyran-2-yloxy)-2,2,14,14-tetramethylpentadecan-6,10-diol (39). An aqueous solution of glutaric aldehyde (25 mL, 50% w/w) was extracted with CH_2Cl_2 (4 × 50 mL). The organic extracts were dried over $MgSO_4$, and the solvent was removed by distillation under atmospheric pressure. The residue was distilled in vacuo to give glutaric dialdehyde (7.97 g, 64%, bp 65−66 °C/5 mmHg; lit.[15] bp 68−69 °C/25 mmHg) as a malodorous, colorless liquid. According to the procedure given for the synthesis of **36**, the Grignard reagent prepared from **12**[1b] (36.9 g, 0.13 mol) and Mg powder (4.8 g, 0.20 mol) in anhydrous THF was reacted with a solution of freshly distilled glutaric aldehyde (6.0 g, 60 mmol) in THF. After workup and concentration, the residue was purified by flash column chromatography (silica, EtOAc/hexanes = 1/5 to 1/1) to afford **39** (16.67 g, 55%) as an almost colorless, very viscous oil. ^{1}H NMR ($CDCl_3$): δ 4.53 (m, 2 H), 3.85 (m, 2 H), 3.63 (br s, 2 H), 3.48 (pseudo-t, 4 H, J = 8.6), 3.00 (d, 1 H, J = 9.1), 2.99 (d, 1 H, J = 9.1), 1.90−1.20 (m, 32 H), 0.90 (s, 6 H), 0.89 (s, 6 H). ^{13}C NMR ($CDCl_3$ = 77.00 ppm): δ 99.34, 99.15, 76.26, 71.76, 71.47, 62.29, 62.03, 39.24, 38.93, 38.24, 37.38, 34.22, 30.66, 25.53, 24.83, 24.65, 24.44, 21.73, 19.99, 19.83, 19.68, 19.51. HRMS (LSIMS, gly) Calcd for $C_{29}H_{57}O_6$ (MH^+): 501.4155. Found: 501.4152.

2,2,14,14-Tetramethylpentadecane-1,6,10,15-tetraol (40). A solution of **39** (5.75 g, 11.5 mmol) in MeOH (100 mL) and diluted aqueous H_2SO_4 (1 mL of concentrated H_2SO_4/9 mL of water) was stirred at room temperature for 5 h. After dilution with water (20 mL), the MeOH was removed under reduced pressure. The obtained aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL). The combined aqueous extracts were saturated with NaCl and reextracted with EtOAc (3 × 50 mL). The organic phases were washed with water (20 mL) and brine (20 mL). Saturation with NaCl and reextraction of the aqueous layer were repeated, and the combined organic extracts were dried over $MgSO_4$. After solvent removal under reduced pressure, the residue was dissolved in the minimal amount of CH_2Cl_2, treated with hexanes for 15 min, and crystallized at room temperature. The crystals were filtered and washed with hexanes to afford **40** (3.06 g, 80%) as a white solid. Mp 85−86 °C. ^{1}H NMR (DMSO-d_6): δ 4.40 (t, 2 H, J = 5.3), 4.20 (d, 2 H, J = 5.5), 3.40−3.30 (m, 2 H), 3.06 (d, 4 H, J = 5.3), 1.50−1.05 (m, 18 H), 0.77 (s, 12 H). ^{13}C NMR (DMSO-d_6): δ 69.87, 69.72, 38.36, 37.52, 34.83, 24.10, 21.67, 19.72. HRMS (LSIMS, gly) Calcd for $C_{19}H_{41}O_4$ (MH^+): 333.3005. Found: 333.2997.

5-[6-(5-Hydroxy-4,4-dimethylpentyl)tetrahydropyran-2-yl]-2,2-dimethylpentan-1-ol (41). A suspension of **40** (3.06 g, 9.2 mmol) and *p*TosOH monohydrate (0.59 g, 3.1 mmol) in toluene (350 mL) was heated to reflux under azeotropic water removal for 7 h. The solvent was evaporated, and the residual oil was purified by column chromatography (silica, first, EtOAc/hexanes = 1/5 to 1/3; second, EtOAc/hexanes = 1/3), affording **41** (1.58 g, 55%) as a very viscous, colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.69 (br s, 2 H), 3.31 (s, 4 H), 2.10−2.00 (m, 2 H), 1.75−1.50 (m, 6 H), 1.50−1.18 (m, 12 H), 0.86 (s, 12 H). ^{13}C NMR ($CDCl_3$ = 77.00 ppm): δ 71.50, 70.61, 38.51, 35.02, 34.03, 30.28, 24.10, 23.91, 20.02, 18.72. HRMS (LSIMS, gly) Calcd for $C_{19}H_{39}O_3$ (MH^+): 315.2899. Found: 315.2899. HPLC: Alltima C-8 column, 250 mm × 4.6 mm, 5 μm; 50% acetonitrile, 50% water, flow rate 1.0 mL/min; RI, retention time 14.80 min, 88.3% pure. Anal. ($C_{19}H_{38}O_3$) C, H.

6-(5,5-Dimethyl-6-oxohexyloxy)-2,2-dimethylhexanal (42). Under N_2 atmosphere, to a solution of **28** (1.63 g, 5.9 mmol) and freshly distilled NEt_3 (2.8 mL) in anhydrous DMSO (10 mL) was added a solution of SO_3−pyridine complex (3.3 g, 20.7 mmol) in anhydrous DMSO (10 mL) at room temperature. The mixture was stirred for 4 h, and additional NEt_3 (5.6 mL) and SO_3−pyridine complex (3.3 g, 20.7 mmol) were added. The mixture was stirred at room temperature overnight, poured into ice−water (100 mL), and stirred for 20 min. The mixture was extracted with Et_2O (4 × 30 mL), and the combined organic layers were washed with 10% citric acid (2 × 20 mL), water (2 × 20 mL), and saturated $NaHCO_3$ solution (2 × 20

mL). Drying over $MgSO_4$, concentration under reduced pressure, and purification by column chromatography (silica; hexanes/EtOAc = 5/1 to 3/1) afforded **42** (1.0 g, 63%) as a colorless oil, which should be used as soon as possible for the next step. ^{1}H NMR ($CDCl_3$): δ 9.45 (s, 2 H), 3.38 (t, 4 H, J = 6.4), 1.62−1.38 (m, 8 H), 1.38−1.14 (m, 4 H), 1.05 (s, 1 2H). ^{13}C NMR ($CDCl_3$ = 77.00 ppm): δ 206.17, 70.36, 45.65, 36.89, 30.08, 21.11, 20.90. HRMS (LSIMS, gly) Calcd for $C_{16}H_{31}O_3$ (MH^+): 271.2273. Found: 271.2279.

4,4,14,14-Tetramethyl-9-oxaheptadecane-1,17-dioic Acid (45). To a solution of methyl diethylphosphonoacetate (12.0 g, 57.1 mmol) in anhydrous DMF (60 mL) was added NaH (60% w/w dispersion in mineral oil, 3.3 g, 82.5 mmol) at room temperature under N_2 atmosphere, resulting in an exothermic reaction. This mixture was stirred for 30 min, **42** (7.4 g, 24.7 mmol) was added, and stirring was continued overnight. The mixture was hydrolyzed by addition of deionized water (100 mL) and extracted with Et_2O (4 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo at 40−50 °C to give crude **43** (11.2 g) as an oil, which was used for the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 6.91 (d, 2 H, J = 16.1), 5.71 (d, 2 H, J = 16.1), 3.73 (s, 6 H), 3.36 (t, 4 H, J = 6.4), 1.65−1.15 (m, 12 H), 1.04 (s, 12 H). ^{13}C NMR ($CDCl_3$ = 77.00 ppm): δ 167.54, 158.54, 117.32, 70.68, 51.41, 42.10, 36.75, 30.26, 26.25, 21.28. HRMS (LSIMS, gly) Calcd for $C_{22}H_{39}O_5$ (MH^+): 383.2797. Found: 383.2789. A portion of crude **43** (2.0 g) was hydrogenated under elevated H_2 pressure (38 psi) on 10% Pd/C (0.5 g) in EtOH (50 mL) for 20 h. The catalyst was removed by filtration through Celite (1 cm bed) and washed with some EtOH. The filtrate was concentrated under reduced pressure to give crude **44** (1.76 g) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.66 (s, 6 H), 3.40 (t, 4 H, J = 6.4), 2.25 (m, 4 H), 1.63−1.45 (m, 6 H), 1.40−1.10 (m, 10 H), 0.85 (s, 12 H). ^{13}C NMR ($CDCl_3$ = 77.00 ppm): δ 174.67, 70.70, 51.38, 41.44, 36.34, 32.27, 30.43, 29.28, 26.60, 20.51. HRMS (LSIMS, nba) Calcd for $C_{22}H_{43}O_5$ (MH^+): 387.3110. Found: 387.3116. A solution of **44** (1.76 g) and KOH (85%, 1.5 g, 22.7 mmol) in MeOH (50 mL) and deionized water (10 mL) was stirred at room temperature overnight under N_2 atmosphere. MeOH was removed under reduced pressure, and the residue was diluted with deionized water (50 mL). The solution was extracted with Et_2O (4 × 20 mL), and the ethereal layers were discarded. The aqueous layer was acidified with 2 N HCl (11 mL) to pH 2 and extracted with Et_2O (4 × 20 mL). The combined organic layers were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$, and concentrated and dried in vacuo to afford **45** (0.89 g, 56%) as a colorless oil. A sample of 350 mg was further purified by flash chromatography (silica, heptane/EtOAc = 70/30, 50/50) to give a sample (220 mg) that was used for combustion analysis. ^{1}H NMR ($CDCl_3$): δ 9.8−8.8 (br, 2 H), 3.42 (t, 4 H, J = 6.4), 2.29 (m, 4 H), 1.67−1.40 (m, 8 H), 1.40−1.08 (m, 8 H), 0.86 (s, 12 H). ^{13}C NMR ($CDCl_3$ = 77.00 ppm): δ 180.59, 70.75, 41.45, 36.11, 32.37, 30.41, 29.42, 26.71, 20.55. HRMS (LSIMS, gly) Calcd for $C_{20}H_{39}O_5$ (MH^+): 359.2797. Found: 359.2788. HPLC: Inertsil ODS2 column, 250 mm × 4.6 mm, 5 μm; 50% acetonitrile, 50% water, flow rate 1.0 mL/min; RI, retention time 23.22 min, 93.6% pure. Anal. ($C_{20}H_{38}O_5$) C, H.

2-{6-[5,5-Dimethyl-6-(tetrahydropyran-2-yloxy)hexyloxy]-2,2-dimethylhexyloxy}tetrahydropyran (22) and 6-[5,5-Dimethyl-6-(tetrahydropyran-2-yloxy)hexyloxy]-2,2-dimethylhexan-1-ol (46). Under N_2 atmosphere and at 0 °C, to a solution of **28** (85.3 g, 0.31 mol) and *p*TosOH hydrate (0.35 g, 1.8 mmol) in CH_2Cl_2 (400 mL) was added dropwise DHP (26.3 g, 0.31 mol) over 1.5 h. The reaction mixture was stirred at room temperature for 20 h and concentrated in vacuo. The residue was purified twice by column chromatography (silica; CH_2Cl_2/acetone = 95/5) to afford **22** (29.0 g, 21%) and **46** (35.7 g, 32%) as colorless oils.

22. ^{1}H NMR ($CDCl_3$): δ 4.47 (t, 2 H, J = 3.3), 3.77 (m, 2 H), 3.44 (m, 2 H), 3.39 (d, 2 H, J = 9.1), 3.33 (t, 4 H, J = 6.6), 2.91 (d, 2 H, J = 9.1), 1.81−1.40 (m, 16 H), 1.30−1.19 (m, 8 H), 0.82 (s, 6 H), 0.81 (s, 6 H). ^{13}C NMR ($CDCl_3$ = 77.00 ppm): δ 99.03, 76.47, 70.87, 61.80, 39.14, 34.18, 30.62, 30.60, 25.53, 24.48, 24.41, 20.55, 19.37. HRMS (LSIMS, nba) Calcd for $C_{26}H_{49}O_5$ ($M - H^+$): 441.3567. Found: 441.3610. HPLC: Alltima phenyl column, 250 mm × 4.6 mm, 5 μm; 70% acetonitrile, 30% water, flow rate 1.0 mL/min; RI, retention time 7.40 min, 93.5% pure. Anal. ($C_{26}H_{50}O_5$) C, H.

46. ^{1}H NMR ($CDCl_3$): δ 4.53 (t, 1 H, J = 3.3), 3.88−3.78 (m, 1H), 3.52−3.44 (m, 1H), 3.45 (d, 1 H, J = 9.1), 3.41 (t, 2 H, J = 6.5), 3.39 (t, 2 H, J = 6.5), 3.30 (s br, 2 H), 2.99 (d, 1 H, J = 9.1), 1.90−1.40 (m, 12 H), 1.40−1.20 (m, 7 H), 0.89 (s, 3 H), 0.88 (s, 3 H), 0.84 (s, 6 H). ^{13}C NMR ($CDCl_3$ = 77.00 ppm): δ 98.48, 76.02, 70.94, 70.48, 70.38, 61.25, 38.84, 38.11, 34.65, 33.83, 30.24, 30.19, 25.22, 24.21, 24.17, 23.61, 20.22, 20.16, 18.92. HRMS (LSIMS, nba) Calcd for $C_{21}H_{42}O_4$ (M + 1): 359.3161. Found: 359.3161. HPLC: Alltima phenyl column, 250 mm × 4.6 mm, 5 μm; 70% acetonitrile, 30% water, flow rate 1.0 mL/min; RI, retention time 5.05 min, 93.6% pure. Anal. ($C_{21}H_{42}O_4$) C, H.

5-Chloro-2,2-dimethylpentanoic Acid Ethyl Ester (47). To a solution of ethyl isobutyrate (130 g, 1.13 mol) and DMPU (5 mL) in THF (160 mL) was added a solution of LDA (790 mL, 2 M in THF/heptane, 1.58 mol) at −50 to −78 °C. The mixture was stirred for 1 h at −78 °C. 1-Bromo-3-chloropropane (250 g, 1.58 mol) was added, and the mixture was stirred overnight, gradually warming to room temperature. The reaction mixture was poured into a mixture of aqueous HCl (6 N, 250 mL), water (500 mL), and ice (500 g) and diluted with saturated NH_4Cl solution (400 mL). The solution was extracted with MTBE (250 mL, 2 × 150 mL). The combined organic layers were washed with saturated NaCl solution (200 mL), dried over $MgSO_4$, and concentrated under vacuum to give **47** (248 g) as a colorless oil. Distillation under vacuum furnished pure product (140 g, 64%, bp 73−75 °C/2 mmHg) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 4.14 (q, 2 H, J = 7.1 Hz), 3.53 (t, 2 H, J = 6.1 Hz), 1.74−1.69 (m, 4 H), 1.27 (t, 3 H, J = 7.1 Hz), 1.21 (s, 6 H). ^{13}C NMR ($CDCl_3$): δ 177.2, 60.2, 45.1, 41.7, 37.8, 28.3, 25.1, 14.2. HRMS (EI) Calcd for $C_9H_{17}O_2Cl$ (M^+): 192.0917. Found: 192.0915.

5-[2-(4-Ethoxycarbonyl-4-methylpentyloxy)ethoxy]-2,2-dimethylpentanoic Acid Ethyl Ester (48). To a solution of ethylene glycol (13.6 g, 220 mmol) in anhydrous DMAc (250 mL) was added KO*t*Bu (40 g, 360 mmol) under N_2 atmosphere. The mixture was stirred at 80 °C for 18 h. A solution of **47** (70 g, 363 mmol) in DMAc (30 mL) and 18-crown-6 (0.35 g, 1.3 mmol) was added, and the mixture was stirred at 65 °C for 30 h. Second portions of KO*t*Bu (40 g, 360 mmol) and, 3 h later, of **47** (70 g, 363 mmol) were added, and stirring was continued, first at 65 °C for 63 h and then at 85 °C for 28 h. The reaction mixture was poured into ice−water (1300 mL), and the crude product was extracted with MTBE (4 × 250 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (100 mL) and saturated NaCl solution (100 mL) and dried over anhydrous $MgSO_4$. The solution was evaporated to yield the crude product as a colorless oil (112 g). The crude product (110 g) was subjected to column chromatography on silica gel, eluting with hexanes/EtOAc (9:1) to give **48** (19.1 g, 23%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 4.16 (q, 4 H, J = 7.1 Hz), 3.61 (s, 4 H), 3.49 (t, 4 H, J = 6.7 Hz), 1.61−1.58 (m, 8 H), 1.29 (t, 6 H, J = 7.1 Hz), 1.22 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 177.6, 71.5, 69.9, 60.1, 41.8, 36.8, 25.1, 25.0, 14.1. HRMS (EI) Calcd for $C_{20}H_{38}O_6$ (M^+): 374.2668. Found: 374.2664.

5-[2-(5-Hydroxy-4,4-dimethylpentyloxy)ethoxy]-2,2-dimethylpentan-1-ol (49). Under Ar atmosphere, $LiAlH_4$ (4.55 g, 120 mmol) was added in portions to MTBE (200 mL) and the suspension was stirred at room temperature for 1 h. A solution of **48** (11.2 g, 30 mmol) in MTBE (40 mL) was added slowly. The mixture was heated to 45 °C for 3 h, then stirred at room temperature for 60 h. The excess of $LiAlH_4$ was destroyed by dropwise addition of a solution of EtOAc (50 mL) in MTBE (50 mL) at 0−10 °C. The mixture was stirred at room temperature for 1 h, then hydrolyzed with aqueous HCl (6 N, 100 mL) and water (50 mL). The solution was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with saturated NaCl solution (2 × 200 mL), dried over

$MgSO_4$, and concentrated under vacuum to give the crude product (9.0 g) as a colorless oil. This residue was subjected to column chromatography on silica using hexanes/EtOAc (2:1, then 1:1) as eluent to afford **49** (4.52 g, 52%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.63 (br s, 2 H), 3.58 (s, 4 H), 3.46 (t, 4 H, J = 6.5 Hz), 3.27 (s, 4 H), 1.59−1.54 (m, 4 H), 1.31−1.21 (m, 4 H), 0.87 (s, 6 H), 0.86 (s, 6 H). ^{13}C NMR ($CDCl_3$): δ 72.0, 70.7, 69.8, 34.7, 34.3, 24.0, 23.9. HRMS (LSIMS, nba) Calcd for $C_{16}H_{35}O_4$ (MH^+): 291.2535. Found: 291.2534. HPLC: Alltima C-18, 4.6 mm × 250 mm; 60% acetonitrile, 40% water, flow rate 1.0 mL/min, 35 °C; RI detection at 254 nm, retention time 5.37 min, 99.1% pure. Anal. ($C_{16}H_{34}O_4$) C, H.

5-[2-(4-Carboxy-4-methylpentyloxy)ethoxy]-2,2-dimethylpentanoic Acid (50). A solution of **48** (15.1 g, 40.3 mmol) and KOH (85%, 9.4 g, 142.0 mmol) in EtOH (28 mL) and water (12 mL) was heated to reflux for 4 h. Most of the EtOH was evaporated under reduced pressure. The residue was diluted with water (50 mL). The solution was extracted with Et_2O (50 mL), and the ether extracts were discarded. The aqueous solution was acidified with aqueous 6 N HCl to pH 1 and extracted with MTBE (3 × 50 mL) and CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with saturated NaCl (50 mL), dried over $MgSO_4$, and concentrated in a vacuum to get the crude product (12.0 g) as a pale-yellow solid. The residue was subjected to column chromatography (silica gel, hexanes/EtOAc = 2:1, 1:1) to give **50** (5.6 g, 44%) as a colorless oil, which solidified upon standing to give a white solid. Mp 60−61 °C. ^{1}H NMR ($CDCl_3$): δ 11.93 (br s, 2 H), 3.60 (s, 4 H), 3.49 (br s, 4 H), 1.61−1.60 (m, 8 H), 1.21 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ 184.4, 71.5, 70.0, 41.8, 36.7, 25.1, 24.9. HRMS (LSIMS, gly) Calcd for $C_{16}H_{31}O_6$ (MH^+): 319.2121. Found: 319.2117. HPLC: Luna C-18, 4.6 mm × 250 mm; 55% acetonitrile, 45% 25 mM aqueous KH_2PO_4, 25 °C; RI detection at 224 nm, flow rate 1.0 mL/min, retention time 5.03 min, 99.3% pure. Anal. ($C_{16}H_{30}O_6$) C, H.

(3-*tert*-Butoxycarbonylmethoxypropoxy)acetic Acid *tert*-Butyl Ester (51). A mixture of 1,3-propanediol (2.69 g, 35.4 mmol), *tert*-butyl bromoacetate (58.0 g, 297.4 mmol), and NBu_4HSO_4 (1.2 g, 3.5 mmol) in aqueous NaOH solution (50% w/w, 175 mL, 265 g, 3.3 mol) and toluene (175 mL) was stirred at room temperature for 16 h. The reaction mixture was diluted with ice−water (750 mL), and the crude product was extracted with MTBE (3 × 150 mL). The combined organic layers were washed with saturated NaCl solution (2 × 150 mL) and dried over anhydrous $MgSO_4$. The solution was evaporated to yield the crude product as a colorless oil, which was purified by column chromatography (silica gel; heptane/EtOAc = 10:1) to give **51** (7.75 g, 72%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.96 (s, 4 H), 3.64 (t, 4 H, J = 6.3), 1.94 (quint, 2 H, J = 6.3), 1.48 (s, 18 H). ^{13}C NMR ($CDCl_3$): δ 169.6, 81.5, 68.9, 68.5, 30.2, 28.3.

2-[3-(2-Hydroxyethoxy)propoxy]ethanol (52).[28] Under Ar atmosphere, $LiAlH_4$ (3.87 g, 102 mmol) was added in portions to MTBE (150 mL). The mixture was stirred at room temperature for 1 h. A solution of **51** (7.75 g, 25.5 mmol) in MTBE (20 mL) was added slowly. The mixture was stirred at room temperature for 16 h and heated to reflux for 3 h. The excess of $LiAlH_4$ was destroyed at 0−10 °C by slowly adding water (4 mL), 20% aqueous NaOH solution (3 mL), and water (12 mL). The suspension was stirred at room temperature for 4 h. The ether solution was decanted and concentrated under vacuum to give **52** (2.60 g, 62%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.76−3.54 (m, 12 H), 3.58 (s, 2 H), 1.89 (quint, 2 H, J = 6.3). ^{13}C NMR ($CDCl_3$): δ 72.0, 68.1, 61.3, 29.6. HRMS (LSIMS, gly) Calcd for $C_7H_{17}O_4$ (MH^+): 165.1127. Found: 165.1127.

4-[3-(4-Hydroxy-3,3-dimethylbutoxy)propoxy]-2,2-dimethylbutan-1-ol (55). Under Ar atmosphere, to a suspension of $LiAlH_4$ (3.51 g, 92.4 mmol) in MTBE (100 mL) was added dropwise a solution of **54** (10.4 g, 28.8 mmol) in MTBE (50 mL). The reaction mixture was stirred at room temperature for 64 h, then heated to reflux for 2 h. The excess of $LiAlH_4$ was destroyed by adding water (3.7 mL), aqueous NaOH solution (20%, 2.8 mL), and water (13 mL). The reaction mixture was stirred vigorously for 1 h. The supernatant was decanted from the white granular residue and concentrated under vacuum to give pure **55** (7.20 g, 91%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.54−3.47 (m, 10H), 3.26 (d, 4H, J = 5.4), 1.84 (quint, 2 H, J = 6.3), 1.55 (t, 4H, J = 5.7), 0.90 (s, 12H). ^{13}C NMR ($CDCl_3$): δ 71.4, 68.1, 67.9, 39.4, 35.1, 30.0, 25.3. HRMS (LSIMS, gly) Calcd for $C_{15}H_{33}O_4$ (MH^+): 277.2379. Found: 277.2387. HPLC: Alltech Alltima C-8 column, 250 mm × 4.6 mm, 5 μm; 65% acetonitrile, 35% water, flow rate 1.0 mL/min; RI, retention time 4.30 min, 99.9% pure. Anal. ($C_{15}H_{32}O_4$) C, H.

4-[3-(4-Carboxy-3-methylbutoxy)propoxy]-2,2-dimethylbutyric Acid (56). A solution of **54** (8.06 g, 22.4 mmol) and KOH (85%, 5.90 g, 89.5 mmol) in EtOH (15 mL) and water (7 mL) was heated to reflux for 4 h. MTBE (100 mL) was added, and the mixture was stirred for 16 h. The aqueous solution was acidified with 6 N HCl (ca. 17 mL) to pH 1 and extracted with CH_2Cl_2 (3 × 80 mL). The organic extracts were washed with saturated NaCl solution (200 mL), dried over Na_2SO_4, and concentrated in a vacuum to give **56** (6.66 g, 98%) as a pale-yellow oil. ^{1}H NMR ($CDCl_3$): δ 11.25 (br s, 2H), 3.49 (t, 4H, J = 6.3), 3.42 (t, 4H, J = 6.3 Hz), 1.86 (t, 4H, J = 6.3), 1.75 (quint, 2H, J = 6.3), 1.22 (s, 12H). ^{13}C NMR ($CDCl_3$): δ 184.4, 67.9, 67.5, 40.7, 40.2, 30.4, 25.4. HRMS (LSIMS, gly) Calcd for $C_{15}H_{29}O_6$ (MH^+): 305.1964. Found: 305.1966. HPLC: Luna C-18 column, 4.6 mm × 250 mm; 55% acetonitrile, 45% 25 mM aqueous KH_2PO_4, flow rate 1.0 mL/min, 35 °C; RI detection at 224 nm, retention time 4.50 min, 99.2% pure. Anal. ($C_{15}H_{28}O_6$) C, H.

2,2,12,12-Tetramethyl-1,13-tridecanediol (61). Under N_2 atmosphere, to a stirred suspension of $LiAlH_4$ (0.80 g, 21.1 mmol) in Et_2O (20 mL) was added dropwise a solution of **59** (6.35 g, 17.8 mmol) in Et_2O (15 mL) at room temperature. The reaction mixture was heated to reflux for 3 h, cooled with an ice bath, and carefully hydrolyzed by addition of water (10 mL) and aqueous 2 N HCl (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 40 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was distilled in high vacuum to afford **61** (3.0 g, 62%) as an oil, which solidified upon standing. Bp 150−151 °C/0.08 mmHg. Mp 52−54 °C. ^{1}H NMR ($CDCl_3$): δ (ppm) 3.29 (s, 4 H), 1.50 (s, 2 H), 1.23 (m, 18 H), 0.85 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ (ppm) 72.0, 38.7, 35.0, 30.5, 29.6, 23.8. HRMS (LSIMS, nba) Calcd for $C_{17}H_{37}O_2$ (MH^+): 273.2794. Found: 273.2796. HPLC: Alltech Alltima C-8 column, 250 mm × 4.6 mm, 5 μm; 52% acetonitrile, 48% water, flow rate 1.0 mL/min; RI, retention time 39.40 min, 97.2% pure. Anal. ($C_{17}H_{36}O_2$) C, H.

2,2,14,14-Tetramethylpentadecane-1,15-diol (62). Under N_2 atmosphere, MeOH (4.2 g, 131.1 mmol) was added dropwise to a stirred suspension of $LiBH_4$ (2.9 g, 133.1 mmol) in methylene chloride (200 mL), followed by addition of **60** (17.0 g, 44.2 mmol). The reaction mixture was heated to reflux overnight. Water (80 mL) and saturated aqueous NH_4Cl solution (80 mL) were added. The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The organic solutions were combined, washed with saturated aqueous $NaHCO_3$ solution (50 mL) and brine (80 mL), and dried over $MgSO_4$. The solvent was partially evaporated, EtOAc (10 mL) was added, and the formed crystals were filtered, affording **62** (6.8 g, 51%). Mp 45−47 °C. ^{1}H NMR ($CDCl_3$): δ (ppm) 3.31 (br s, 4 H), 1.71 (br s, 2 H), 1.27−1.23 (m, 22 H), 0.86 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ (ppm) 72.0, 38.7, 35.0, 30.6, 29.6, 23.8. HRMS (LSIMS, nba) Calcd for $C_{19}H_{41}O_2$ $[M + 1]^+$: 301.3107. Found: 301.3106. HPLC: Alltech Alltima C-8 column, 250 mm × 4.6 mm, 5 μm; 70% acetonitrile, 30% water, flow rate 1.0 mL/min; RI, retention time 15.87 min, 100% pure. Anal. ($C_{19}H_{40}O_2$) C, H.

2,2,14,14-Tetramethylpentadecanedioic Acid (63). A solution of **60** (11.0 g, 28.6 mmol) and KOH (85%, 4.8 g, 72.7 mmol) in EtOH (70 mL) and water (30 mL) was heated to reflux for 20 h. The EtOH was evaporated in vacuo, and the remaining mixture was diluted with water (100 mL). After acidification with dilute aqueous HCl, crystals formed, which

were filtered and dissolved in EtOAc. The solution was dried over $MgSO_4$ and reduced in volume. The crystals formed were filtered and dried to give **63** (6.5 g, 69%). Mp 95−96 °C. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.57−1.52 (m, 4 H), 1.30−1.25 (m, 18 H), 1.20 (s, 12 H). ^{13}C NMR ($CDCl_3$): δ (ppm) 185.3, 42.2, 40.7, 30.0, 29.5, 29.5, 29.4, 25.0, 24.9. HRMS (LSIMS, gly) Calcd for $C_{19}H_{37}O_4$ $[M + 1]^+$: 329.2692. Found: 329.2678. Anal. ($C_{19}H_{36}O_4$) C, H.

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). Rat hepatocytes were isolated essentially as described by the method of Seglen.[34] 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 were 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} values of the compounds.

In Vivo Effects on Lipid Variables in Female Obese Zucker Fatty Rats. The 10−12 week old (400−500 g) female Zucker fatty rats Crl: (Zuc)-faBR were obtained from Charles River Laboratories. Animals were acclimated to the laboratory environment for 7 days. During the acclimation and study period, animals were housed by group in shoebox polycarbonate cages on Cellu-Dri bedding. The temperature and humidity in the animals' quarters (68−78 °F; 30−75% RH) were monitored, and the airflow in the room was sufficient to provide several exchanges per hour with 100% fresh filtered air. An automatic timing device provided an alternating 12 h cycle of light and dark. Rats received pelleted Purina Laboratory Rodent Chow (5001) prior to and during the drug intervention period except for a 6 h phase prior to blood sampling. Fresh water was supplied ad libitum via an automatic watering system. Compounds were dissolved, suspended by mixing in a dosing vehicle consisting of 20% 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. Prior to and after 7 days of dosing, a 1.0−2.0 mL sample of blood was collected by administering O_2/CO_2 anesthesia and bleeding from the orbital venous plexus. Following 14 days of dosing, blood was collected by cardiac puncture after euthanasia with CO_2. All blood samples were processed for separation of serum and stored at −80 °C until analysis. Commercially available kits were used to determine serum triglycerides (Roche Diagnostic Corporation, no. 148899, or Boehringer Mannheim, no. 1488872), total cholesterol (Roche Diagnostic Corporation, no. 450061), nonesterified fatty acids (Wako Chemicals, no. 994-75409), and β-hydroxybutyrate (Wako Chemicals, no. 417-73501 or Sigma, no. 310-0) on a Hitachi 912 automatic analyzer (Roche Diagnostic Corporation). In some instances, an in-house cholesterol reagent was used to determine total serum cholesterol levels. Serum lipoprotein cholesterol levels were determined by lipoprotein profile analysis. Lipoprotein profiles were analyzed using gel-filtration chromatography on a Superose 6HR (1 cm × 30 cm) column equipped with on-line detection of total cholesterol as described by Kieft et al.[35] 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 **7**, **8**, **17**, **18**, **24**, **53**, **54**, **59**, and **60** and elemental analysis results. This material is available free of charge via the Internet at http://pubs.acs.org.

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