Synthesis and Hypolipidemic and Antidiabetogenic Activities of β,β,β′,β′-Tetrasubstituted, Long-Chain Dioic Acids

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β,β,β′,β′-Tetrasubstituted, long-chain dioic acids of the general formula HOOC–C(XY)–C(R_2)–Q–C(R_2)–C(XY)–COOH have been synthesized and evaluated as hypotriglyceridemic–hypocholesterolemic agents in rats and as antidiabetogenic agents in ob/ob diabetic mice. The free carboxyl function of analogues of the series was mandatory for their hypolipidemic–antidiabetogenic effect while nonhydrolyzable diesters were inactive. Other structure–activity relationships were determined as a function of the overall chain length (C_{12}–C_{22}), α,α′-substitutions (X, Y = H, F, Cl, Br, OH, CN), β,β′-substitutions (R = CH_3, C_6H_5), and core subtitutions [Q = $(CH_2)_{10}$, $(CH_2)_4CH{=}CH(CH_2)_4$, 1,4-$C_6H_{10}[(CH_2)_3]_2$, 1,4-$C_6H_4[(CH_2)_3]_2$, 1,4-$C_6H_4(CH{=}CHCH_2)_2$, $CH_2(OCH_2CH_2)_3OCH_2$)]. The most effective hypolipidemic–antidiabetogenic members of the series were α,α′-nonsubstituted, β,β′-methyl-substituted analogues of 14–18-carbon chains having either a saturated aliphatic core or a 1,4-bis(propenyl)benzene core in the cis/trans configuration. The hypotriglyceridemic rather than the hypocholesterolemic capacity of members of the series was found to correlate with their respective capacities as liver peroxisomal proliferators in rats.

The capacity of long-chain fatty acids and their respective CoA thioesters to act as inhibitors of the lipogenic pathway[1,2] has initiated the design of nonmetabolizable long-chain fatty acid analogues as potential hypolipidemic effectors. Long-chain β,β′-methyl-substituted α,ω-dicarboxylic acids (MEDICA)[3] appear to fulfill this role, since the terminal carboxyl function interferes with the esterification of dioic acids into neutral and phospholipids, and the β,β′-substitution prevents the β-oxidative catabolism of MEDICA compounds by either mitochondrial or peroxisomal β-oxidative systems. A prototype member of this family of compounds is 3,3,14,14-tetramethylhexadecanedioic acid (MEDICA 16, **4d**) [$HOOCCH_2C(CH_3)_2(CH_2)_{10}C(CH_3)_2CH_2COOH$], which was recently reported to act as a potent hypolipidemic and antidiabetogenic drug in the rat.[3-10] Thus, treatment of normal or puromycin aminonucleoside nephrotic rats kept on a balanced purina chow diet with **4d** resulted in an acute hypolipidemic effect which was sustained as long as the drug was administered.[3,5,6] The hypolipidemic effect in normal and nephrotic rats consisted of 70–80% decrease in plasma chylomicrons- and VLDL–triacylglycerols as well as 40–60% decrease in plasma VLDL–cholesterol while HDL–cholesterol remained unaffected. The hypolipidemic effect induced by **4d** treatment was accompanied by an acute reduction in adiposity which was already established during the first week of treatment, and consisted of 30–80% decrease in the perirenal, omental, epididymal, parametrial, and subcutaneous fat with a concomitant 50% decrease in total body neutral lipid mass.[7,8] The reduction in adiposity was accounted for by a respective decrease in the lipid content of individual adipocytes together with a transient or sustained decrease in the number of adipocytes of selected adipose tissues. The reduction in adiposity induced by **4d** was extensively pronounced in sand rats (*Psammomys obesus*) serving as an animal model for obesity-induced diabetes and resulted in amelioration of the tolerance of glucose with normalization of plasma insulin.[7,9] The weight-reductive and antidibetogenic effect of **4d** in sand rats was essentially similar in that of forced caloric restriction but could not be ascribed to an anorectic or cathartic effect of the drug.[9]

The hypolipidemic effect of **4d** in rats was accompanied by liver peroxisomal proliferation, with a concomitant increase in peroxisomal enoyl-CoA hydratase and cyanide-insensitive palmitoyl-CoA oxidation,[11] similar in character to that induced by fibrate drugs, phthalate esters, and others.

The marked hypolipidemic effect of **4d** and the apparent mutual relationship between hypolipidemia and peroxisomal proliferation in rodents[12] initiated the evaluation of MEDICA analogues for their differential capacities as hypolipidemic–antidiabetogenic drugs on one hand and as peroxisomal proliferators on the other. The concerned structure–activity relationships was evaluated by considering the general structural formula

$$HOOC\text{–}C(XY)\text{–}C(CH_3)_2\text{–}Q\text{–}C(CH_3)_2\text{–}C(XY)\text{–}COOH$$

where X and Y may each represent independently a hydrogen, halogen, hydroxy, or cyano function and Q represents either a saturated or an unsaturated aliphatic hydrocarbon chain that may incorporate also a cyclohexane, benzene, or polyether moiety. In addition, some analogues were investigated in which the β-CH_3 groups had been replaced by either a bulky C_6H_5 or lactonizable CH_2OH functions.

Results

Chemistry. The various tetramethyl dioic acids **4a–h** were prepared according to eq 1 by reacting 2 equiv of diethyl isopropylidenemalonate (**1**) with 1 equiv of the bis-Grignard reagent of the respective α,ω-dibromoalkane

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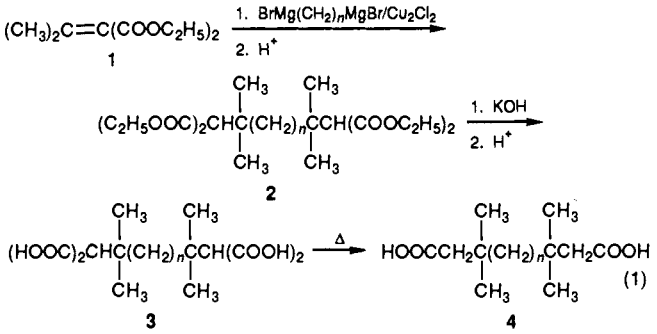
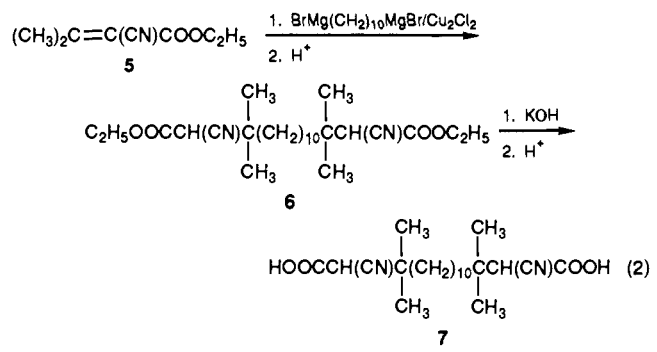
in the presence of Cu_2Cl_2,[13] followed by hydrolysis and decarboxylation of the resulting Michael adduct **2**.[3]



a, $n = 6$; **b**, $n = 8$; **c**, $n = 9$; **d**, $n = 10$; **e**, $n = 11$; **f**, $n = 12$; **g**, $n = 14$; **h**, $n = 16$

When the diethyl isopropylidenemalonate was substituted by diethyl isopropylidenecyanoacetate (**5**), the corresponding α,α'-dicyano dioic acids resulted as shown:



The introduction of a bromine or a chlorine atom in each of the α and α' positions was best accomplished by *N*-bromosuccinimide (NBS) bromination and *N*-chlorosuccinimide chlorination, respectively, of the desired acid chloride of **4**. Treatment of **4d** with $SOCl_2$ followed by bromination afforded a mixture of highly stable acid chlorides that could be separated by column chromatography. Hydrolysis of the dibromo acid chloride by prolonged heating in boiling water afforded 2,15-dibromo-3,3,14,14-tetramethylhexadecanedioic acid (**8**).

$R^1OOCC(R^2R^3)C(CH_3)_2(CH_2)_{10}C(CH_3)_2C(R^2R^3)COOR^1$

8: $R^1 = R^2 = H$; $R^3 = Br$
9: $R^1 = (CH_3)_2CH$; $R^2 = H$; $R^3 = Cl$
10: $R^1 = R^2 = H$, $R^3 = Cl$
11: $R^1 = (CH_3)_2CH$; $R^2 = R^3 = Cl$
12: $R^1 = H$; $R^2 = R^3 = Cl$
13: $R^1 = R^2 = H$, $R^3 = OH$

Chlorination of the acid chloride of **4d** also gave a mixture of halogenated compounds.[14] However, the dichloro acid **10** could be separated only after conversion of the acid chlorides into the diisopropyl esters. The separated isopropyl as well as the respectively methyl esters proved refractory to simple acid and base hydrolysis but could be transformed to the di-, tri-, and tetrachlorinated free acids by Newman's method for hydrolysis of sterically hindered compounds.[15] As the tetrachlorodioic acid **12** amounted only to a small percentage of the mixture, **11** was prepared by the interaction of **9** with CCl_4 in the presence of lithium diisopropylamide (LDA).[14]

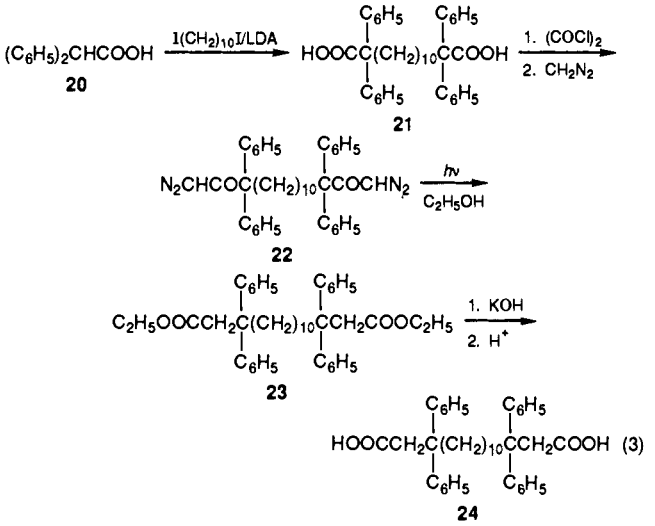
Although aqueous KOH failed to hydrolize the esters of the α,α'-dihalogenated dioic acids **8** and **10**, the base was found to affect the halogen atoms. Thus, **8** gave after 20-h reflux in 10% aqueous KOH 2,15-dihydroxy-3,3,14,14-tetramethylhexadecanedioic acid (**13**) in 62% yield.

Several methods have recently been published for the synthesis of α-fluorocarboxylic acids[16] which proved, however, unsatisfactory for the introduction of fluorine in the α and α' positions of **4d**. Positive results were obtained only when dimethyl 2,15-dibromo-3,3,14,14-tetramethylhexadecanedioate (**14**) was reacted with "dried" tetrabutylammonium fluoride.[17] Under optimized conditions, the reagent[18] converted the dibromo ester into a mixture of acids **13**, **15**, and **17–19** from which the difluoro compound **15** could be separated after reesterification. Pure **15** was obtained by tetrabutylammonium fluoride mediated hydrolysis of **16** at 60 °C.

$R^1OOCCHR^2C(CH_3)_2(CH_2)_{10}C(CH_3)_2CHR^3COOR^1$

14: $R^1 = CH_3$; $R^2 = R^3 = Br$
15: $R^1 = H$; $R^2 = R^3 = F$
16: $R^1 = CH_3$; $R^2 = R^3 = F$
17: $R^1 = H$; $R^2 = Br$; $R^3 = F$
18: $R^1 = H$; $R^2 = Br$; $R^3 = OH$
19: $R^1 = H$; $R^2 = F$; $R^3 = OH$

The synthesis of the tetraphenyl analogue of **4d**, 3,3,14,14-tetraphenylhexadecandioic acid (**24**), could not be accomplished as outlined in eq 1, but it was prepared by LDA-assisted condensation of 2 equiv of diphenylacetic acid (**20**) with 1 equiv of 1,10-diiododecane. The 2,2,13,13-tetraphenyltetradecanedioic acid (**21**) was, in turn, bis-homologized by a modified Arndt–Eistert reaction:[19]



The lactone analogue of **4d** (**29**) was synthesized by replacing one CH_3 at position 3 and one at position 13 of **4d** with CH_2OH functions. One equivalent of 1,1-diiododecane was condensed with 2 equiv of α-methylbutyrolacone (**25**) (eq 4), and the resulting bis(α-lactone) **26** was converted into the bis(β-lactone) of 3,14-bis(hy-

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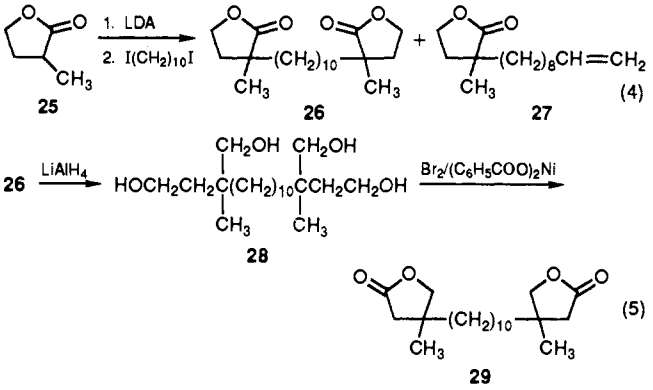
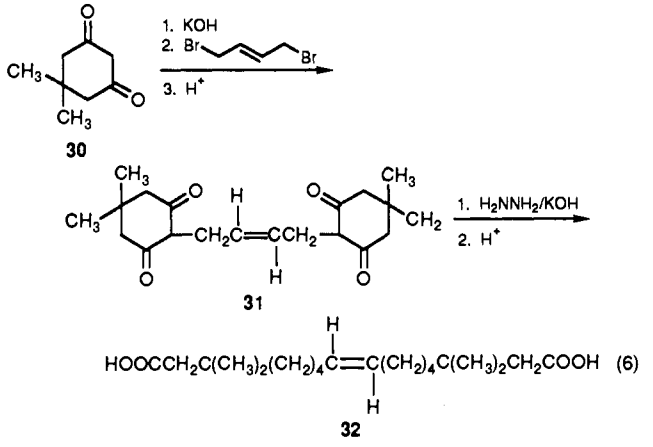
droxymethyl)-3,14-dimethylhexadecanedioic acid (**29**) via the tetraol **28** by the method of Doyle [lithium aluminum hydride reduction followed by $Br_2/(C_6H_5COO)_2Ni$ oxidation] for transformation of mono-α- to mono-β-lactones[20] (eq 5).



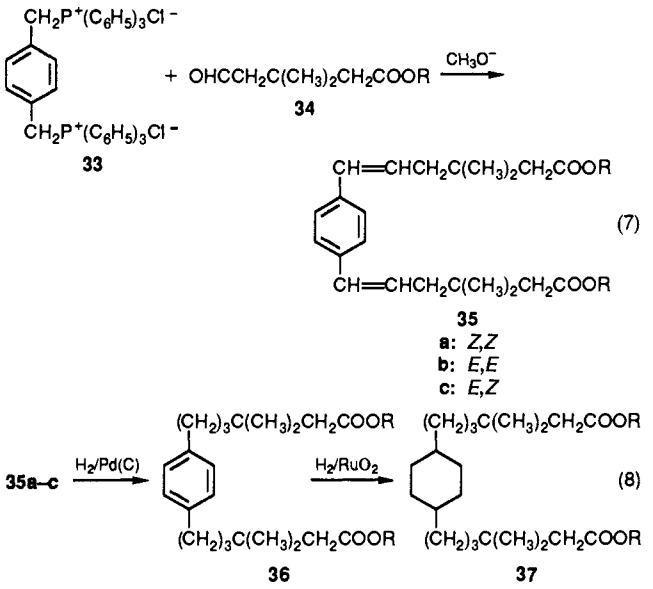
The introduction of one double bond into the core of the dioic acids was accomplished by alkylation of 5,5-dimethyl-1,3-cyclohexanedione (dimedone) (**30**) with an unsaturated dibromide followed by reductive cleavage of the two cyclohexanedione rings.[21] Thus, the reaction of 1 equiv of *trans*-1,4-dibromo-2-butene with 2 equiv of **30** yielded the unsaturated tetraone **31** which, in turn, could be transformed to 3,3,14,14-tetramethyl-8-hexadecenedioic acid (**32**) by a modified Wolff–Kishner reaction:



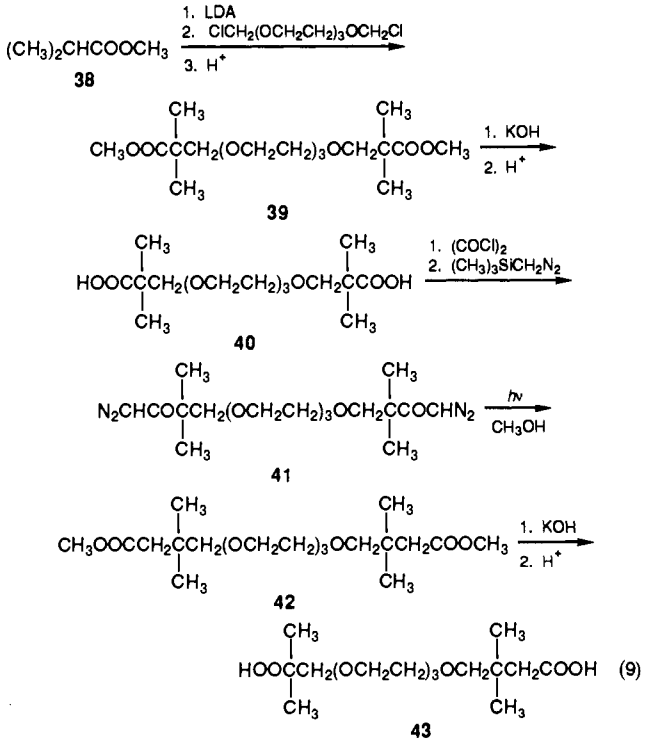
An analog of **4d** in which the four central CH_2 groups are replaced by a benzene ring was prepared by two alternative routes. The first method followed the general scheme outlined in eq 1 by starting with the bis-Grignard reagent of 1,4-bis(3-bromopropyl)benzene. The second method consisted of a Wittig condensation of 1 equiv of (1,4-phenylenedimethylene)bis[triphenylphosphonium] dichloride (**33**) with 2 equiv of methyl 4-formyl-3,3-dimethylbutanoate (**34**, R = CH_3) (eq 7) followed by palladium-catalyzed hydrogenation of the mixture of isomeric methyl esters of 6,6′-(1,4-phenylene)bis[3,3-dimethyl-5-hexenoic acid] (**35a–c**, R = CH_3) (eq 8).

Further hydrogenation of **36**, R = CH_3, at 90 °C and 80 bar in the presence of ruthenium dioxide resulted in the formation of dimethyl cyclohexanedi[(3,3-dimethyl)hexanoate] (**37**, R = CH_3). Base-mediated hydrolysis of the esters **35a–c**, **36**, and **37** afforded the respective free dioic acids.

The mixture of isomers **35a–c** was separated by a combination of fractional crystallization and column chromatography (see Experimental Section).



A MEDICA analogue with ether linkages in the central core, 2,2,15,15-tetramethyl-4,7,10,14-tetraoxahexadecenedioic acid (**43**), was prepared by LDA-assisted condensation of 1,12-dichloro-2,5,8,11-tetraoxadodecane[22] and methyl isobutyrate (**38**), followed by hydrolysis and bis-homologation of the dicarboxylic acid **40** via the Shioiri modification of the Arndt–Eistert reaction.[23] Monitoring of the latter reaction by IR and ^1H NMR revealed that the initially formed bis(trimethylsilyldiazo) ketone was gradually converted into the silicon-free diazo compound **41**. Irradiation of **41** at 254 nm in a 1:1 dioxane–methanol mixture gave the dimethyl ester **42** by the Wolff rearrangement:



Biological Effects. Representative MEDICA compounds have been evaluated for their hypolipidemic effect

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Table I. Hypolipidemic Effect and Peroxisomal Proliferation Induced by $HOOCCH_2C(CH_3)_2(CH_2)_nC(CH_3)_2CH_2COOH$ Homologues of Varying Chain Lengths

MEDICA homologue	liver lipogenesis in culture,[a] I_{50}, mM	liver cholesterogenesis in culture,[a] I_{50}, mM	liver lipogenesis in vivo,[b] %	liver cholesterogenesis in vivo,[b] %	K_i for ATP-citrate lyase,[c] mM	plasma triacylglycerols,[d] mg %	plasma cholesterol,[d] mg %	peroxisomal enoyl-CoA hydratase,[e] μmol/(mg·min)
4a: $n = 6$	0.30	0.20	80	120	310			7.5 ± 0.5
4b: $n = 8$	0.10	0.10	66	75	56	126 ± 14	70 ± 4	16.3 ± 1.5
4c: $n = 9$						112 ± 8	72 ± 2	
4d: $n = 10$	0.08	0.08	29	25	16	111 ± 8	58 ± 3	31.0 ± 1.0
4e: $n = 11$						113 ± 8	73 ± 4	
4f: $n = 12$	0.15	0.15	48	40	46	130 ± 9	73 ± 4	17.5 ± 2.5
4g: $n = 14$	0.30	0.30	113	73	260			5.0 ± 0.5
4h: $n = 16$	0.40	0.40	158	94	320			3.5 ± 0.5

[a] Inhibition of liver lipid synthesis by MEDICA homologues in culture was evaluated by following the incorporation of ^3H_2O into saponified fatty acids and 3-β-hydroxysterols in cultured rat hepatocytes incubated in the presence of varying concentrations of the respective homologues. The efficacy of each homologue was determined by the concentration required for 50% inhibition of ^3H_2O incorporation into saponified fatty acids (I_{50} lipogenesis) and 3-β-hydroxysterols (I_{50} cholesterogenesis). [b] Inhibition of liver lipid synthesis by MEDICA homologues in vivo was evaluated by following the incorporation of ^3H_2O into liver saponified fatty acids and 3-β-hydroxysterols in rats fed for 3 consecutive days with a carbohydrate-rich fat-free diet supplemented with 0.25% (w/w) of each of the respective MEDICA homologues. The incorporation of ^3H_2O into the respective lipid fractions in nontreated animals amounted to 89 ± 10 and 2.0 ± 0.1 μmol/(g of liver·60 min) (mean ± SD; $n = 4$), respectively, and the values determined in treated animals were expressed as a percentage of those observed in nontreated rats. [c] Inhibition of liver ATP-citrate lyase by MEDICA homologues was evaluated by following the citrate lyase activity in the presence of varying concentrations of the respective homologues. The K_i value for each homologue was determined by a Dixon plot. [d] The hypolipidemic effect of MEDICA homologues was evaluated by measuring plasma triacylglycerols and cholesterol in rats fed purina chow diet and treated for 7 days with 10 mg/kg of body weight of the respective homologue. Plasma triacylglycerols and cholesterol in nontreated rats amounted to 141 ± 7 and 78 ± 3 mg %, respectively (mean ± SEM; $n = 6$). [e] The peroxisome-proliferative capacity of MEDICA homologues in vivo was evaluated by measuring liver peroxisomal enoyl-CoA hydratase activity [μmol/(mg of protein·min)] in rats fed for 3 days with a carbohydrate-rich fat-free diet supplemented with 0.25% (w/w) of the respective homologue. The hydratase activity in nontreated rats amounted to 3.5 ± 0.5 μmol/(mg of protein·min) (mean ± SD; $n = 4$).

in rats by following their capacity as inhibitors of liver lipogenesis and cholesterogenesis in vivo and in culture, as well as their capacity for lowering plasma triacylglycerol and cholesterol. The antidiabetogenic effect was studied in ob/ob mice serving as an animal model for obesity-induced diabetes. The peroxisome-proliferative capacity was evaluated by following the induction of liver peroxisomal activities in the rat in vivo.

A. Chain Length. The optimal chain length of MEDICA compounds acting as inhibitors of liver lipogenesis and cholesterogenesis was studied by evaluating the inhibitory efficacy of C_{12}–C_{22} members of the homologous series $HOOCCH_2C(CH_3)_2(CH_2)_nC(CH_3)_2CH_2COOH$ (n = 6–16, **4a–h**). As shown in Table I, **4d** proved to be the most potent member of the homologous series since it had the lowest I_{50} value for inhibition of ^3H_2O incorporation into liver saponified fatty acids of 3-β-hydroxysterols in the rat in vivo as well as in cultured rat hepatocytes. The correlated inhibition of the lipogenic and cholesterogenic pathways by homologues of varying chain length implicated an intersection of the two pathways in the mechanism of action of MEDICA compounds. Indeed, the highest efficacy of **4d**, as compared to other members of the homologous series, could be accounted for by its lowest K_i value as an inhibitor of liver ATP-citrate lyase (Table I). As further shown in Table I, the antilipogenic and anticholesterogenic effects of MEDICA homologues resulted in a decrease in plasma triacylglycerol and cholesterol. The hypolipidemic effect of MEDICA homologues of odd-numbered carbon atoms was similar to that of the closest even-numbered members of the series. The correlation observed between the hypotriglyceridemic and hypocholesterolemic efficacies of the respective homologues and their capacity as inhibitors of liver lipogenesis and cholesterogenesis may indicate that the hypolipidemic effect of members of the homologous series may be accounted for by inhibition of liver lipid synthesis.

The hypolipidemic effect of MEDICA homologues of varying chain length was accompanied by induction of liver peroxisomal activities in vivo (Table I) as well as in cultured rat hepatocytes (not shown). The peroxisome proliferative capacity of respective MEDICA homologues was correlated with their respective capacities both as inhibitors of liver lipid synthesis and as hypolipidemic agents.

In light of the observed efficacy of **4d** as a hypolipidemic agent, its antidiabetogenic effect was verified in ob/ob mice serving as model animals for obesity-induced diabetes. Treatment of ob/ob mice with **4d** resulted in a significant decrease in weight gain which amounted to 0.18, 0.11, and 0.10 g/day in nontreated and ob/ob mice treated with 0.1 and 0.3% (w/w) of **4d**, respectively. The observed decrease in weight gain was accompanied by amelioration of the tolerance of glucose as long as the drug was administered (Figure 1). Upon elimination of the drug from the diet, the animals became again resistant to the glucose load and the level of plasma glucose attained in previously treated animals which have been further maintained in the absence of **4d** was even higher than that of nontreated animals. The overall antidiabetogenic effect of **4d** in ob/ob mice was essentially similar to that previously reported in sand rats.[9]

B. α,α′-Substitutions. The effect of α,α′-substituents was evaluated by studying the inhibition of lipogenesis and cholesterogenesis by analogues **15**, **10**, **8**, **13**, and **7** of **4d** in which F, Cl, Br, OH, or CN atoms have been introduced into the α and α′ positions. As shown in Table II, the I_{50} values for lipogenesis, as measured by the incorporation of ^3H_2O into liver saponified fatty acids in vivo, amounted to 0.06% (w/w) for **4d** and increased as a function of increasing the van der Waals radii with a concomitant decrease in the electronegativities of the respective α,α′-substituents. Since the incorporation of ^3H_2O into liver fatty acids constitutes a major fraction of that incorporated into total liver lipids, the I_{50} values for liver total lipids correlates well with that for liver saponified fatty acids. The consistently higher concentrations required for inhibition of ^3H_2O incorporation into liver total lipids as compared to those required for inhibition of lipogenesis may reflect the specificity of MEDICA inhibition of the lipogenic flux while in the presence of premade fatty acids the esterification of glycerol 3-phosphate into liver neutral lipids or phospholipids remains unaffected.[4] It is note-

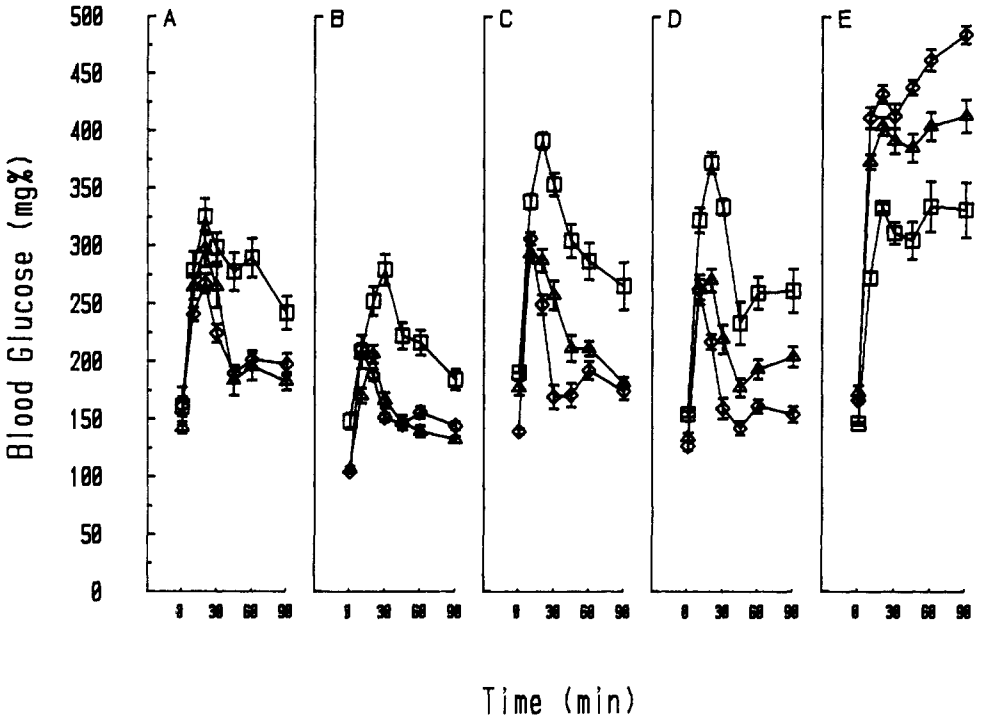

Figure 1. Tolerance of glucose in ob/ob mice treated with **4d**. The tolerance to an oral load of glucose was determined as described under Experimental Section in nontreated ob/ob mice (□), ob/ob mice treated with 0.1% (w/w) of **4d** (△), and ob/ob mice treated with 0.3% (w/w) of **4d** (◇) added to the diet. Pretreatment values of blood glucose for the three respective groups amounted to 190 ± 20, 204 ± 27, and 202 ± 22 mg %. The tolerance to glucose was evaluated as described under Experimental Section following 14 days (A), 28 days (B), 41 days (C), and 48 days (D) of treatment as well as in mice treated for 48 days and which were further maintained for 28 days in the absence of added **4d** (E). Mean ± SEM, n = 8.

Table II. Antilipogenic–Anticholesterogenic Effect of α,α'-Substituted Analogues of $HOOCC(R^1R^2)C(CH_3)_2(CH_2)_{10}C(CH_3)_2C(R^1R^2)COOH$[a]

MEDICA analogue	total liver lipids, I_{50}	liver saponified fatty acids, I_{50}	liver 3-β-hydroxysterols I_{50}
4d: R^1 = H; R^2 = H	0.08	0.06	0.05
15: R^1 = H; R^2 = F	0.12[b]	0.07[b]	0.5
10: R^1 = H; R^2 = Cl	0.15	0.12	0.16
8: R^1 = H; R^2 = Br	0.23	0.18	0.25
13: R^1 = H; R^2 = OH	0.20	0.17	0.23
7: R^1 = H; R^2 = CN	0.20	0.18	0.20
12: R^1 = Cl; R^2 = Cl	0.10	0.09	0.13

[a] Inhibition of liver lipid synthesis in vivo was determined by following the incorporation of ^3H_2O into liver total lipids, liver saponified fatty acids, and liver 3-β-hydroxysterols in rats fed for 3 consecutive days with varying concentrations of the respective MEDICA analgoues. The efficacy of each analogue was determined by the concentration required in the diet (% w/w) for 50% inhibition of ^3H_2O incorporation into liver total lipids, saponified fatty acids and 3-β-hydroxysterols. [b] The I_{50} values were derived from the initial slopes observed. Maximal inhibition of the incorporation of ^3H_2O into liver total lipids and saponified fatty acids amounted however to 35%.

worthy that the lower efficacy of α,α'-substituted analogues as inhibitors of lipogenesis as compared to the nonsubstituted parent compound **4d** could not be accounted by their respective inhibition of the ATP-citrate lyase. Thus, the K_i values for **15**, **8**, and **7** amounted to 6, 12, and 9 μM as compared with 16 μM for **4d**.

In contrast to the structure–activity pattern observed with respect to inhibition of lipogenesis, inhibition of ^3H_2O incorporation into liver 3-β-hydroxysterols by α,α'-substiututed MEDICA analogues was correlated neither with the van der Waals radii or the electronegativities of the concerned substituents nor with the efficacy of the respective analogues as inhibitors of lipogenesis. Thus, the α,α'-difluoro derivative **15** proved to be a potent inhibitor of liver lipogenesis similarly to **4d**, but practically did not inhibit liver cholesterogenesis. Furthermore, while the efficacy of *non*substituted MEDICA homologues of varying chain length as inhibitors of liver cholesterogenesis was observed to be similar to or better than their efficacies as inhibitors of liver lipogenesis (Table I), the α,α'-substituted analogues proved in general to be less inhibitory for liver cholesterogenesis than for liver lipogenesis. It is noteworthy that the $\alpha,\alpha,\alpha',\alpha'$-tetrachloro-substituted analogue **12** proved to be a better inhibitor for lipogenesis and cholesterogenesis than the respective α,α'-dichloro-substituted analogue **10** (Table II). However, in spite of approaching the capacity of **4d** as inhibitor of lipogenesis, its capacity as an inhibitor of cholesterogenesis was significantly lower as compared to that of **4d**.

The differential efficacies of α,α'-substituted MEDICA analogues as inhibitors of the lipogenic and cholesterogenic pathways were further confirmed by evaluating their hypotriglyceridemic and hypocholesterolemic effects, respectively. As shown in Figure 2A, treatment of rats with either **4d** or some of its α,α'-substituted derivatives resulted in a prompt and sustained hypotriglyceridemic effect which was maximal with the parent compound. However, in contrast to the combined hypotriglyceridemic–hypocholesterolemic effect of **4d**, treatment with the α,α'-substituted analogues did not result in a sustained decrease in plasma cholesterol (Figure 2B), but only in a transient hypocholesterolemic effect. The differential efficacies of

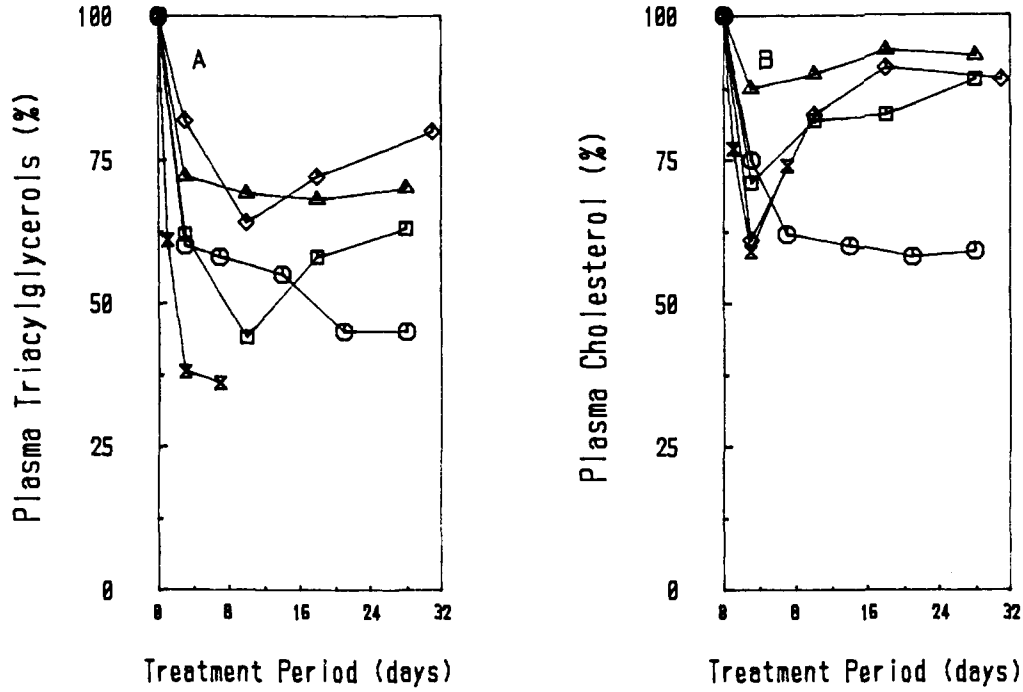

Figure 2. Hypolipidemic effect of α,α'-substituted MEDICA analogues. Plasma triacylglycerol (A) and plasma cholesterol (B) were determined as described under Experimental section in groups of 10 rats each treated with 100 mg/kg of **4d** (○), 8 (◇), **10** (□), 12 (×), and **13** (△) for the time periods as indicated. Plasma triacylglycerol and cholesterol values are presented as percentages of those of nontreated rats. Individual values within each group were within a range of ±5% of the mean.

α,α'-substituted MEDICA analogues as inhibitors of lipogenesis and cholesterogenesis, or as hypotriglyceridemic and hypocholesterolemic effectors, may thus indicate that the overall hypolipidemic effect of MEDICA compounds cannot be solely accounted for by inhibition of the ATP-citrate lyase reaction with a concomitant reduction in the availability of acetyl-CoA as a precursor for fatty acids and sterol synthesis.

The hypotriglyceridemic effect of the bromo and chloro analogues (**8** and **10**, respectively) in ob/ob mice was essentially similar to that observed in albino rats and was accompanied by a decrease in the content of neutral lipids in adipose tissues, with a concomitant decrease in body weight gain and amelioration of the tolerance of glucose. Thus, treatment of ob/ob mice with 0–0.45% (w/w) of the α,α'-dibromo compound **8** resulted in a dose-dependent decrease in weight gain which amounted to 0.32, 0.28, 0.23, 0.16, and −0.10 g/day for nontreated mice and ob/ob mice treated with 0.017, 0.050, 0.15, and 0,45% (w/w in the diet) of the drug, respectively. The morning plasma glucose levels following 28 days of treatment with the respective doses amounted to 341, 205, 204, 168, and 130 mg %, respectively, and the characteristic pathological tolerance of glucose of nontreated ob/ob mice was totally normalized by **8** (Figure 3). The amelioration of the diabetic trait was characterized by a dose-dependent decrease in the plasma level of insulin (100.9 ± 42.1, 71.2 ± 35.5, and 45.4 ± 14.8 μunits/mL (mean ± SD, n = 10) in nontreated mice and ob/ob mice treated with 0.05 and 0.15% (w/w) of **8**, respectively, thus indicating that the antidiabetogenic effect was accounted for by a decrease in the peripheral resistance to insulin rather than an increase in pancreatic insulin secretion.

In light of the differential efficacies of the α,α'-substituted MEDICA analogues as hypotriglyceridemic and hypocholesterolemic agents, it became of interest to evaluate their peroxisome proliferative capacities. As shown in Figure 4, α,α'-substitution resulted in general in a decrease in the capacity of MEDICA analogues as inducers of liver peroxisomal enoyl-CoA hydratase. Within the α,α'-substituted class, the peroxisome proliferative capacities of the fluoro (**15**), chloro (**10**), bromo (**8**), and hydroxy (**13**) derivatives were similar while the α-cyano (**7**) derivative was significantly less effective. The tetrachloro-substituted analogue **12** was found to have a higher capacity as a peroxisomal proliferator than the respectively α,α'-dichloro-substituted analogue **10**. The order observed with respect to induction of peroxisomal CN-insensitive palmitoyl-CoA oxidation was essentially similar to that observed for the induction of peroxisomal enoyl-CoA hydratase. It is noteworthy that the capacity of α,α'-substituted analogues as liver peroxisomal proliferators correlated with their respective antilipogenic (r^2 = 0.70) rather

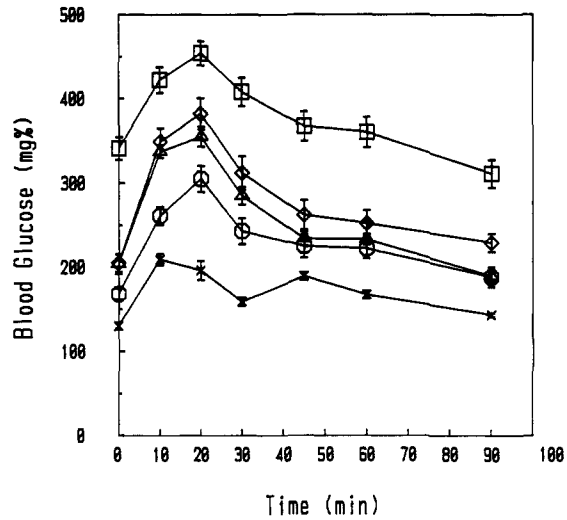

Figure 3. Antidiabetogenic effect of $\beta,\beta,\beta',\beta'$-tetramethyl-$\alpha,\alpha'$-dibromohexadecanedioic acid (**8**) in ob/ob mice. The tolerance to an oral load of glucose was determined as described under Expeimental Section in nontreated ob/ob mice (□) and in ob/ob mice treated for 28 days with 0.017 (◇), 0.05 (△), 0.15 (○), and 0.45% (w/w) (×) of **8** added to the diet. Mean ± SEM, n = 8.

Table III. Hypolipidemic Effect of β,β,β′,β′-Tetraphenyl-Substituted Hexadecanedioic Acid[a]

dose in diet, % w/w	plasma triacylglycerols, mg %	plasma cholesterol, mg %	^3H_2O incorpn into liver saponified fatty acids, μmol/(g of liver·75 min)	^3H_2O incorpn into liver cholesterol, μmol/(g of liver·75 min)	peroxisomal enoyl-CoA hydratase μmol/(mg of protein·min)	peroxisomal palmitoyl-CoA oxidation, nmol/(mg of protein·min)
0.00	131 ± 19	70.5 ± 1.3	118.2 ± 23.4	3.9 ± 0.4	0.45 ± 0.07	4.8 ± 1.0
0.15	127 ± 16	70.0 ± 7.0	100.5 ± 15.7	4.3 ± 1.0	0.59 ± 0.17	4.4 ± 1.0
0.30	101 ± 4	58.0 ± 1.9	123.2 ± 17	3.4 ± 0.8	0.60 ± 0.20	7.2 ± 0.5

[a] Plasma lipid content, the incorporation of ^3H_2O into saponified fatty acids and 3-β-hydroxysterols and liver peroxisomal enoyl-CoA hydratase and CN-insensitive palmitoyl-CoA oxidation activities were determined as described under Experimental Section in rats fed for 3 consecutive days with the indicated doses of **24**. Mean ± SD; $n = 4$.

Table IV. Hypolipidemic Effect and Peroxisomal Proliferation of $HOOCCH_2C(CH_3)_2$–Q–$C(CH_3)_2CH_2COOH$ MEDICA Analogues

Q	liver lipogenesis in vivo,[a] %	liver cholesterogenesis in vivo,[a] %	plasma triacylglycerols,[b] mg %	plasma cholesterol,[b] mg %	liver peroxisomal enoyl-CoA hydratase,[c] μmol/(min·mg of protein)
$(CH_2)_{10}$ (**4d**)	48	40	49 ± 17	32 ± 5	10.7 ± 0.2
1,4-$C_6H_{10}[(CH_2)_3]_2$ (**37**)	79	71	63 ± 14	42 ± 5	14.0 ± 1.0
1,4-$C_6H_4[(CH_2)_3]_2$ (**36**)	63	65	84 ± 8	36 ± 5	12.0 ± 1.0
1,4-$C_6H_4(CH{=}CHCH_2)_2$, *Z,Z* (**35a**)	72	97	98 ± 16	47 ± 1	4.5 ± 0.5
1,4-$C_6H_4(CH{=}CHCH_2)_2$, *E,E* (**35b**)	57	57	41 ± 1	28 ± 3	18.6 ± 0.9
1,4-$C_6H_4(CH{=}CHCH_2)_2$, *Z,E* (**35c**)[d]	50	37	25 ± 4	37 ± 9	10.5 ± 1.1

[a] Inhibition of liver lipid synthesis by core-substituted MEDICA analogues in vivo was evaluated by following the incorporation of ^3H_2O into liver saponified fatty acids and 3-β-hydroxysterols in rats fed for 3 consecutive days with 0.1% (w/w) of each of the respective analogues. The incorporation of ^3H_2O into the respective lipid fractions in nontreated animals amounted to 93.5 ± 15.5 and 0.35 ± 0.4 μmol/(g of liver·60 min) (mean ± SD; $n = 3$), respectively, and the values determined in treated animals were expressed as a percentage of those observed in nontreated rats. [b] The hypolipidemic effect of core-substituted MEDICA analogues was evaluated by measuring plasma triacylglycerols and cholesterol in rats treated for 3 days with 0.1% (w/w) of each of the respective analogues. Plasma triacylglycerols and cholesterol in nontreated rats amounted to 158 ± 21 and 74 ± 2 mg %, respectively (mean ± SD; $n = 3$). [c] The peroxisome-proliferative capacity of core-substituted MEDICA analogues was evaluated by measuring liver peroxisomal enoyl-CoA hydratase in rats fed for 3 consecutive days with a carbohydrate-rich fat-free diet supplemented with 0.1% (w/w) of the respective analogue. The hydratase activity in nontreated rats amounted to 1.5 ± 0.4 mol/(mg of protein·min) (mean ± SD; $n = 3$). [d] The "*Z,E*" preparation consisted of 35.8% of the *Z,Z* analogue **35a**, 1.9% of the *E,E* analogue **35b**, and 61.1% of the *Z,E* analogue **35c**. The efficacy of **35c** was evaluated indirectly from its relative abundance within the available mixture, the apparent overall efficacy of the mixture, and the known efficacies of the other two isomers with respect to liver lipogenesis, liver cholesterogenesis, plasma lipids and liver peroxisomal enoyl-CoA hydratase.

than anticholesterogenic ($r^2 = 0.10$) capacities.

C. β,β′-Substitutions. As pointed out previously, the β,β′-dimethyl substituents were introduced into MEDICA compounds in order to eliminate their β-oxidative catabolism. Indeed, the lipid-lowering effect of hexadecanedioic acid in vivo was about 10-fold lower than the respective efficacy of the β,β′-tetramethyl derivative **4d**. The difference between the two compounds was, however, masked when compared for their antilipogenic and anticholesterogenic effects in cultured rat hepatocytes (not shown) rather than in vivo, presumably as a result of the relatively limited β-oxidative capacity of cultured liver cells as compared to that effected in vivo by liver and muscle.

The effect of bulky substituents at the β,β′ positions was evaluated by studying the hypolipidemic effect of tetraphenyl-substituted hexadecanedioic acid (**24**). As shown in Table III, the antilipogenic, anticholesterogenic, and hypolipidemic effects of **24** were significantly lower than those of **4d**, thus indicating that the preferable β,β′-substitution should consist of a relatively small alkyl blocking group. The peroxisome proliferative capacity of **24** was correlated with its overall low hypolipidemic efficacy.

D. Core Substitutions. The structure–activity relationship of core-substituted MEDICA analogues was evaluated by studying analogues of **4d** in which the central aliphatic saturated core was replaced either by an unsaturated or a polyether aliphatic moiety or, alternatively, by a cyclohexyl or phenyl moiety. The trans monounsaturated acid **32** was significantly less effective as an inhibitor of lipogenesis and cholesterogenesis as compared to **4d**, while the polyether analogue **43** was practically noninhibitory, thus indicating that the efficacy of MEDICA analogues may depend on the relative positioning of the two symmetric halves of MEDICA compounds.

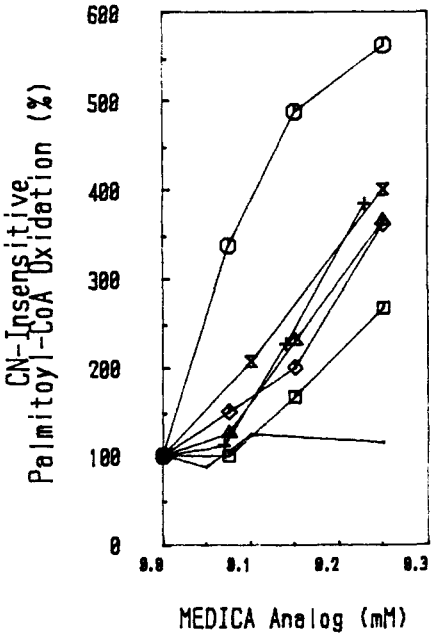

Figure 4. Liver peroxisomal proliferation by α,α′-substituted MEDICA analogues. Conditions as in Table II. The CN-insensitive palmitoyl-CoA oxidase activity was determined as described under Experimental Section. The induced peroxisomal activity is presented as a percentage increase of that of nontreated rats (100%). **4d** (○); **7** (●); **8** (◇); **10** (□); **12** (×); **13** (△); **15** (+).

The role played by the relative positioning of the two carboxyl terminals could be further probed by studying MEDICA analogues in which the central core consisted of a phenylene or a cyclohexylene moiety. As shown in Table

IV, the overall efficacy of the 1,4-phenylenebis[hexanoic acid] analogue **36** was somewhat better than that of the respective cyclohexylene analogue **37**. The efficacy of the phenylene compound was however significantly increased upon replacing the bis(propyl) moiety by the respective unsaturated propylene moiety. The increase in efficacy was specific for the *E,E* compound **35b** and the *Z,E* compound **35c**.

The peroxisomal proliferative capacity of core-substituted MEDICA analogues was well correlated with their respective hypolipidemic efficacy. Thus, the *Z,Z* analogue **35a** and the *E,E* analogue **35b** were found to act as the less and more effective members of the core-substituted class, both as hypolipidemic agents and as inducers of peroxisomal activities. The efficacy of core-substituted analogues as peroxisomal proliferators was well correlated with both their hypocholesterolemic ($r^2 = 0.78$) and hypotriglyceridemic ($r^2 = 0.70$) capacities.

E. Diesters of MEDICA Analogues. The hypolipidemic efficacy of the diethyl ester of **4d** was essentially similar to that of the free dioic acid. The stable bis(β-lactone) **29** was, however, not effective as a hypolipidemic agent. Neither did the various diethyl esters of the α,α′-di- and tetrahalogenated dioic acids show any hypolipidemic activity. In contrast to the diethyl ester of **4d**, the diethyl esters of α,α′-halo MEDICA analogues were resistant to enzymatic hydrolysis by pig pancreatic lipase.

The diethyl esters of the α,α′-halo analogues as well as the bis(β-lactone) **29** did not induce liver peroxisomal activities.

Discussion

The structure–activity relationship of MEDICA compounds as hypolipidemic agents may be defined by analyzing the hypolipidemic effect of members of the MEDICA series in light of the detailed mechanistic data previously established with **4d** (MEDICA 16).[3-8]

The role played by the inhibition of ATP-citrate lyase in the overall hypolipidemic effect of MEDICA compounds[3,4] was in fact confirmed here by the pattern of inhibition exerted by MEDICA analogues of varying chain lengths and core substitutions. Indeed, the correlated inhibition of both the lipogenic and cholesterogenic pathways by each member of the homologous series (Table I) as well as by most core-substituted analogues (Table IV) implicates an intersecting step of the two synthetic pathways as the site of action of MEDICA compounds. This indeed could be further corroborated by the correlation observed between the efficacies of homologues of varying chain lengths as inhibitors of the two pathways and as inhibitors of the ATP-citrate lyase step (Table I). However, in addition to the ATP-citrate lyase, some other steps, not shared by the two intersecting pathways, appear to be involved in the overall inhibition of liver lipid synthesis by MEDICA compounds. Thus, **4d** proved to be a better inhibitor of lipogenesis as compared to α,α′-substituted analogues (Table II), but its better efficacy could not be ascribed to a more potent inhibition of the lyase. Moreover, since most of the acetyl-CoA generated by the ATP-citrate lyase reaction is channeled into fatty acids rather than sterol synthesis, inhibition of the ATP-citrate lyase by MEDICA compounds was expected to affect the lipogenic more than the cholestereogenic pathway, in contrast to the observed respective efficacies of **4d** and related chain length homologues as inhibitors of fatty acid and 3-β-hydroxysterol synthesis (Table I). Furthermore, some of the α,α′-halo-substituted analogues proved to be efficient inhibitors of the lipogenic pathway but relatively poor inhibitors of cholesterogenesis (e.g., **15**), thus indicating that the overall efficacy of MEDICA compounds as inhibitors of liver lipid synthesis could not be solely accounted for by inhibition of the ATP-citrate lyase step. Indeed, the CoA thioester of **4d** was recently found to act as a potent acetyl-CoA-competitive inhibitor while the free dioic acid acted as a citrate-competitive inhibitor of liver acetyl-CoA carboxylase,[10] thus limiting specifically the lipogenic flux by inhibiting its rate-limiting step. The better efficacy of **4d** as inhibitor of lipogenesis as compared to α,α′-substituted analogues could thus reflect either its better availability for ATP-dependent CoA thioesterification[10,11] or the efficacy of its CoA thioester as inhibitor of acetyl-CoA carboxylase compared to that of the CoA thioesters of α,α′-substituted analogues. Similarly, **4d** was previously reported to inhibit specifically and irreversibly the cholesterogenic pathway at a site that follows the HMG-CoA reductase step, thus limiting specifically the synthesis of 3-β-hydroxysterols.[4] The differential efficacies of α,α′-substituted analogues as inhibitors of lipogenesis and cholesterogenesis could thus reflect their relatively lower efficacy as inhibitors of the putative specific cholesterogenic step.

The correlation observed between inhibition of liver lipid synthesis and the respective hypolipidemic effect of members of the MEDICA series may help in evaluating the role played by inhibition of liver lipid synthesis in the overall hypolipidemic effect observed. In general, analogues that did not inhibit liver lipid synthesis (e.g., **24**, **29**) also did not act as hypolipidemic agents, thus indicating that the hypolipidemic efficacy of MEDICA compounds was primarily determined by their efficacy as inhibitors of liver lipid synthesis. Moreover, MEDICA analogues that proved as potent inhibitors of the lipogenic pathway while not inhibiting (e.g., **15**) or inhibiting less (e.g., **10**, **12**) the cholesterogenic pathway proved also as efficient hypotriglyceridemic agents whereas their hypocholesterolemic effect was limited. Hence, the hypolipidemic effect with respect to plasma VLDL is due in the first place to inhibition of liver lipid synthesis while activation of plasma VLDL clearance[5] could be of importance during the transient shift from the normolipemic state of nontreated animals to the hypolipemic state of MEDICA-treated animals. It should be noted, however, that in contrast to plasma VLDL, the hypolipidemic effect of MEDICA compounds with respect to plasma chylomicrons appears to be exclusively accounted for by activation of their clearance, while their production and secretion remained unaffected.[6]

The structure–activity relationships of MEDICA analogues as reported here may help in defining the structural constraints required for the hypolipidemic effect exerted by members of this series. In light of the null efficacy of nonhydrolyzable esters of the series (e.g., methyl esters of α,α′-halo-substituted analogues **8**, **10**, and **12**, the stable β-lactone **29**), the free carboxyl function of MEDICA analogues is presumably mandatory for their hypolipidemic effect. The free acid may either be assumed to function as the immediate effector or, alternatively, may have to be transformed first into the respective CoA thioester by an ATP-dependent CoA thioesterification. The two proposed inhibitory species are not mutually exclusive, and the overall efficacy of various MEDICA analogues may indeed relfect the resultant of the efficacies of the two inhibitory species with respect to the multiple sites involved in the overall hypolipidemic effect (e.g., ATP-citrate lyase and lipogenic- and cholesterogenic-specific sites). α,α′- and β,β′-substituents are thus proposed to determine the efficacy of MEDICA analogues by mod-

ulating the electronic states or imposing a steric hindrance for the interaction of the terminal carboxyl functions with their target sites. Fine tuning could, however, depend on the overall three-dimensional configuration of MEDICA inhibitors as determined by their respective core structures.

The induction of peroxisomal marker activities by members of the MEDICA series was verified here in vivo and in cultured rat hepatocytes incubated in the presence of the added compounds. Potent hypolipidemic members of the series were also found to induce peroxisomal proliferation (e.g., **4d**, **12**, **35b**), whereas MEDICA analogues that proved to be inefficient as hypolipidemic drugs [e.g., ethyl esters of α,α'-halo-substituted analogues, β,β'-phenyl-substituted hexadecanedioic acid (**24**), and the β-lactone **29**] were also found to lack peroxisome-proliferative capacity. The apparent correlation observed here between the two phenomena corroborates previous reports with respect to the hypolipidemic effect of peroxisomal proliferators of varying structural characteristics.[12] However, it is noteworthy that the concerned correlation does not necessarily implicate the hypolipedemic state as the driving force of the inductive sequel nor the proliferation of peroxisomes in effectuating the hypolipidemic state. The observed correlation could rather imply that the same structural constraints may be required for both initiating the hypolipidemic state and the induction of peroxisomal proliferation. Furthermore, the induction of peroxisomal activities in culture may indeed indicate that the capacity for inducing peroxisomal proliferation should be ascribed by the direct cellular effect exerted by the drug rather than the accompanying hypolipidemic effect observed under in vivo conditions.

The differential efficacies of some MEDICA analogues as hypotriglyceridemic and hypocholesterolemic effectors make it possible to correlate between the capacity of each as either a hypotriglyceridemic or a hypocholesterolemic agent and its capacity as an inducer of peroxisomal proliferation. Thus, the peroxisome-proliferative capacities of nonsubstituted or core-substituted analogues was correlated to a similar extent with both their hypotriglyceridemic and hypocholesterolemic capacities (Tables I and IV). However, the peroxisome-proliferative capacity of α,α'-substituted analogues was correlated significantly better with their antilipogenic (r^2 = −0.70) than anticholesterogenic (r^2 = −0.10) capacities. The example of the α,α'-substituted analogues may thus indicate that the inductive sequel leading to peroxisomal proliferation could perhaps be mediated at the molecular level by a mechanism of action similar in principle to that which mediates the antilipogenic–hypotriglyceridemic effect, whereas additional independent modes of action could be involved in the hypocholesterolemic effect of MEDICA compounds.

The relative structural simplicity of MEDICA analogues as compared with other common peroxisomal proliferators (e.g., fibrate drugs, phthalate plasticizers) may help in defining the common structural denominator of peroxisomal proliferators. Indeed, in spite of the apparent diversity of chemicals that induce peroxisomal proliferation, all appear to consist of an hydrophobic backbone carrying a carboxylic function to yield an amphipathic carboxylate. The carboxylic function may be present initially or derived either by in vivo hydrolysis of respective esters or amides or by in vivo oxidation of respective aldehydes or alcohols. The acylation of a putative signal protein by the concerned xenobiotic amphipathic carboxylates[32] could perhaps initiate the inductive sequel of peroxisomal proliferation.

The antidiabetogenic effect of MEDICA compounds in ob/ob mice as reported here is similar in general to that previously reported for **4d** in sand rats[7,9] and is due to the dramatic adipose reduction effected by members of the series.[7,8] In both species the amelioration of the glucose tolerance is accompanied by a decrease in circulating insulin and may thus be ascribed to a decrease in the peripheral resistance to insulin, resulting in improving the peripheral handling of glucose. Indeed, treatment of sand rats with **4d** was found to result in an increase in the number of insulin receptors with a concomitant activation of adipose glycogen synthase. It is remarkable that, in both sand rats and ob/ob mice, the antidiabetogenic effect of MEDICA compounds required the continuous treatment of the animals, and elimination of the drug resulted after a while in exacerbation of the fulminant diabetic state.

In conclusion, nonmetolizable analogues of long-chain dioic acids may be considered as potential pharmacological agents for treating hyperlipoproteinemic–obesity–diabetic pathological syndromes.

Experimental Section

Chemistry. 3,3,10,10-Tetramethyldodecanedioic acid (**4a**), 3,3,12,12-tetramethyltetradecanedioic acid (**4b**), 3,3,14,14-tetramethylhexadecanedioic acid (**4d**), 3,3,15,15-tetramethylheptadecanedioic acid (**4e**), and 3,3,16,16-tetramethyloctadecanedioic acid (**4f**) have been prepared as previously described.[3]

3,3,13,13-Tetramethylpentadecanedioic Acid (4c). A Grignard solution, prepared under argon from 1 g (42 mmol) of Mg and 1.3 g (45 mmol) of 1,9-dibromononane in 50 mL of THF, was added dropwise at −50 to −20 °C to a stirred mixture of 2.1 g (10.5 mmol) of diethyl isopropylidenemalonate (**1**)[24] and 38.3 mg (0.9 mmol) of freshly prepared dry Cu_2Cl_2. The temperature was raised to 25 °C and the mixture stirred for 36 h. Addition of 10% cold hydrochloric acid followed by the usual workup afforded 1.68 g of the tetracarboxylic ester **2** [200-MHz ^{1}H NMR ($CDCl_3$) δ 1.037 (s, 12, CCH_3), 1.203 (m, 30 CH_2, CH_2CH_3), 3.264 (s, 2, CH), 4.215 (q, 8, J = 7 Hz, CH_2CH_3)] admixed with some of the starting malonate. Hydrolysis of the mixture of esters with 120 mL of boiling 15% ethanolic KOH solution gave after 20 h 0.5 g of 3,3,13,13-tetramethylpentadecanetetraoic acid (**3**) [200-MHz ^{1}H NMR ($CDCl_3$) δ 1.119 (s, 12, CCH_3) 1.270 (m, 18, CH_2), 3.058 (s, 2, CH), 8.050 (br s, 4, $COOH$)]. Decarboxylation was performed at 180–190 °C. When the calculated amount of CO_2 (54 mL) was evolved, the reaction mixture was cooled and worked up in the usual manner to give **4c** as a tan oil that was purified by column chromatography on silica gel, using a 1:1 mixture of hexane and CH_2Cl_2 as eluent, to give colorless crystals: yield 350 mg (23%); mp 92–94 °C; IR ($CHCl_3$) 3000 (OH), 1700 cm^{-1} (C=O); 200-MHz ^{1}H NMR ($CDCl_3$) δ 0.999 (s, 12, CH_3), 1.247 (m, 18, CH_2), 2.210 (s, 4, CH_2COOH); EI MS (70 eV, 60 °C) m/z (rel intensity) 311 [$(M-OH)^+$, 6], 270 ($C_{17}H_{34}O_2^{\cdot+}$, 25), 269 ($C_{17}H_{33}O_2^+$, 61), 268 ($C_{17}H_{32}O_2^{\cdot+}$, 42), 168 ($C_{10}H_{16}O_2^{\cdot+}$, 12), 139 ($C_9H_{15}O^+$, 25), 129 ($C_7H_{13}O_2^+$, 18), 127 ($C_7H_{11}O_2^+$, 20), 126 ($C_8H_4O^{\cdot+}$, 55), 115 ($C_6H_{11}O_2^+$, 16), 113 ($C_7H_{13}O^+$, 28), 112 ($C_7H_{12}O^{\cdot+}$, 92), 101 ($C_5H_9O_2^+$, 100). Anal. ($C_{19}H_{36}O_4$) C, H.

3,3,18,18-Tetramethyleicosanedioic Acid (4g). Similarly, the bis-Grignard reagent of 1,14-dibromotetradecane[25] and **1** gave tetraethyl 3,3,18,18-tetramethyleicosanetetraoate (**2g**) as a colorless oil [IR ($CHCl_3$) 1730 cm^{-1} (C=O); 200-MHz ^{1}H NMR ($CDCl_3$) δ 1.081 (s, 6, CCH_3), 1.240 (m, 40, CH_2, CH_2CH_3), 3.311, (s, 2, CH), 4.161 (q, 8, J = 7 Hz, CH_2CH_3)]. Hydrolysis, which yielded the corresponding tetracarboxylic acid [yellow oil; IR ($CHCl_3$) 2900 (OH), 1700 cm^{-1} (C=O); 200-MHz ^{1}H NMR (C_5D_5N) δ 0.962 (m, 36, CH_2, CCH_3), 1.255 (m, 4, CCH_2), 3.214 (s, 2, CH)], was followed by decarboxylation at 180–190 °C to form **4g** in an overall yield of 38%: colorless crystals; mp 111–112 °C (from $CHCl_3$–hexane); 200-MHz ^{1}H NMR ($CDCl_3$) δ 0.995 (s, 12, CCH_3), 1.250 (m, 28, CH_2), 2.217 (s, 4, CH_2COOH); EI MS (70 eV, 170 °C) m/z (rel intensity), 381 [$(M-OH)^+$, 5], 362 [$(M-2H_2O)^{\cdot+}$, 21], 340 ($C_{22}H_{44}O_2^{\cdot+}$, 13) 339 ($C_{22}H_{43}O_2^+$, 56), 338 ($C_{22}H_{42}O_2^{\cdot+}$, 32), 321

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($C_{22}H_{41}O^+$, 36), 320 ($C_{22}H_{40}O^{\cdot+}$, 28), 125 ($C_8H_{13}O^+$, 73), 111 ($C_7H_{11}O^+$, 100), 110 ($C_7H_{10}O^{\cdot+}$, 46); 101 ($C_5H_9O_2^+$, 100). Anal. ($C_{24}H_{46}O_4$) C, H.

3,3,20,20-Tetramethyldocosanedioic Acid (4h). The reaction of 1,16-dibromohexadecane[25] and 1 gave tetraethyl 3,3,20,20-tetramethyldocosanetetraoate (**2h**) as a colorless oil [IR ($CHCl_3$) 1715 cm^{-1} (C=O); 200-MHz ^1H NMR ($CDCl_3$) δ 1.069 (s, 12, CCH_3), 1.228 (m, 44, CH_2, CH_2CH_3), 3.293 (s, 2, CH), 4.193 (q, 8, J = 7 Hz, CH_2CH_3)] that formed the tetracarboxylic acid upon hydrolysis [semisolid material; IR ($CHCl_3$) 2850 (OH), 1700 cm^{-1} (C=O); 200-MHz ^1H NMR ($CDCl_3$) δ 1.238 (m, 44, CH_2, CCH_3), 3.409 (s, 2, CH)]. Decarboxylation at 180–190 °C afforded **4h** in 47% yield: mp 105 °C (2 × from hexane); 300-MHz ^1H NMR ($CDCl_3$) δ 0.999 (s, 12, CCH_3); 1.252 (m, 32, CH_2), 2.219 (s, 4, CH_2COOH); EI MS (70 eV, 150 °C) m/z (rel intensity) 427 [(M + H)$^+$, 3], 426 ($M^{\cdot+}$, 1), 391 ($C_{26}H_{47}O_2^+$, 15), 368 ($C_{22}H_{44}O_3^{\cdot+}$, 40), 367 ($C_{24}H_{47}O_2^+$, 23), 137 ($C_9H_{15}O^+$, 21), 126 ($C_8H_{14}O^{\cdot+}$, 60), 112 ($C_7H_{12}O^{\cdot+}$, 74), 111 ($C_7H_{11}O^+$, 74), 101 ($C_5H_9O_2^+$, 100), 98 ($C_6H_{10}O^{\cdot+}$, 35). Anal. ($C_{26}H_{50}O_4$) C, H.

2,15-Dicyano-3,3,14,14-tetramethylhexadecanedioic Acid (7). To a stirred suspension of 1.1 g (7.2 mmol) of ethyl isopropylidenecyanoacetate (**5**)[26] and 43 mg (0.44 mmol) of freshly prepared cuprous chloride in 25 mL of dry THF was added dropwise between −50 and −20 °C a Grignard solution prepared from 1 g (3.3 mmol) of 1,10-dibromodecane, excess magnesium, and 15 mL of THF. The mixture was allowed to warm up to 25 °C and stirred at this temperature for 48 h. Decomposition with ice-cold 10% hydrochloric acid followed by the usual workup yielded 1.16 g of a tan oil that was purified by column chromatography on silica gel, using first a 1:4 ether–hexane mixture for elution of 1.622 g of the mono adduct followed by a 3:2 ether–hexane mixture for elution of the pure diesters **6** as a colorless oil: yield 417 mg (28%); IR (neat) 2220 (C≡N), 1740 cm^{-1} (C=O); 200-MHz ^1H NMR ($CDCl_3$) δ 1.078 (s, 6, CCH_3), 1.114 (s, 6, CCH_3), 1.255 (m, 16, CH_2), 1.291 (t, 6, J = 7.2 Hz, CH_2CH_3), 1.386 (m, 4, CCH_2), 3.36 (s, 2, $CHC{\equiv}N$), 4.227 (q, 4, J = 7.2 Hz, CH_2CH_3). Hydrolysis of the diester by stirring with 360 mg (6.4 mmol) of KOH in 25 mL of H_2O at 60 °C for 20 h followed by reflux for 3 h afforded after acidification 354 mg (97%) of **7** as a colorless oil that solidified on standing: IR ($CHCl_3$) 3000 (OH), 2220 (C≡N), 1715 cm^{-1} (C=O); 200-MHz ^1H NMR ($CDCl_3$) δ 1.147 (s, 6, CCH_3), 1.166 (s, 6, CCH_3), 1.275 (m, 16, CH_2), 1.445 (m, 4, CCH_2), 5.287 (s, 2, $CHCN$), 9.522 (br s, 2, $COOH$). Anal. ($C_{22}H_{36}N_2O_4$) C, H, N.

2,15-Dibromo-3,3,14,14-tetramethylhexadecanedioic Acid (8). A mixture of 5 g (14.6 mmol) of **4d**[3] and 10 mL (0.137 mol) of thionyl chloride was heated for 60 min at 75 °C. The acid chloride solution [IR (neat) 1800 cm^{-1} (C=O)] was treated with 7.5 mL (0.141 mol) of Br_2 in 45 mL of CCl_4 and the mixture irradiated with a 250-W tungsten lamp under reflux for 20 h. Excess thionyl chloride and bromine were removed under reduced pressure to give 9 g of yellow dibromo acid chloride that was purified by chromatography on silica gel (hexane was used as eluent). The yield of the purified acid chloride was 84%: 300-MHz ^1H NMR ($CDCl_3$) δ 1.111 (s, 6, CH_3), 1.580 (s, 6, CH_3), 1.265 (m, 16, CH_2), 1.429 (m, 4, CCH_2), 4.469 (s, 2, $CHBr$). Hydrolysis of the acid chloride with boiling water for 20 h yielded after the usual workup 60% of 8 as pale yellow crystals: mp 95–96 °C; IR ($CHCl_3$) 3100 (OH), 1710 cm^{-1} (C=O); 300-MHz ^1H NMR ($CDCl_3$) δ 1.093 (s, 6, CH_3), 1.097 (s, 6, CH_3), 1.253 (m 16, CH_2), 1.405 (m, CCH_2), 4.172 (s, 1, $CHBr$), 4.180 (s, 1, $CHBr$); EI MS (70 eV, 115 °C) m/z (rel intensity) 403 ($C_{20}H_{34}{}^{81}BrO_3^+$, 42), 401 ($C_{20}H_{34}{}^{79}BrO_3^+$, 42), 363 ($C_{18}H_{34}{}^{81}BrO_2^+$, 100), 361 ($C_{18}H_{34}{}^{79}BrO_2^+$, 100), 181 ($C_5H_8{}^{81}BrO_2^+$, 27), 179 ($C_5H_8{}^{79}BrO_2^+$, 27), 141 ($C_{10}H_{21}^+$, 43), 140 ($C_5H_3{}^{81}BrO_2^{\cdot+}$, 30), 139 ($C_2H_2{}^{81}BrO_2^+$, 55), 138 ($C_2H_3{}^{79}BrO_2^{\cdot+}$, 30), 137 ($C_2H_2{}^{79}BrO_2^+$, 55). Anal. ($C_{20}H_{36}Br_2O_4$) C, H.

2,15-Dichloro-3,3,14,14-tetramethylhexadecanedioic Acid (10). A mixture of 24 g of concentrated H_2SO_4 and 24 g of oleum (containing 20% of SO_3) was added dropwise at 0 °C to 2.64 g (5.3 mmol) of bis(1-methylethyl) 2,15-dichloro-3,3,14,14-tetramethylhexadecanedioate (**9**) (obtained by separation of the mixtures of chlorinated esters described previously[14]). The mixture was stirred at 0 °C for 75 min, cooled to −10 °C and digested, under vigorous stirring, with excess ice and ether. When the purple mixture warmed up to room temperature, the color disappeared. Phase separation followed by the usual workup gave, after trituration with hexane, 1.72 g (79%) of colorless **10**: mp 117 °C; IR (KBr) 3000–3350 (OH), 1717 cm^{-1} (C=O); 200-MHz ^1H NMR ($CDCl_3$) δ 1,088 (s, 6, CH_3), 1.108 (s, 6, CH_3), 1.264 (m, 16, CH_2), 1.364 [m, 4, $CH_2C(CH_3)_2$], 4.190 (s, 2, $CHCl$). Anal. ($C_{20}H_{36}Cl_2O_4$) C, H, Cl.

Bis(1-methylethyl) 2,2,15-trichloro-3,3,14,14-tetramethylhexadecanedioate that accompanied **9** in the synthesis from 4d[14] was hydrolyzed in the same manner to yield 92% of **2,2,15-trichloro-3,3,14,14-tetramethylhexadecanedioic acid** as colorless crystals: mp 123–124 °C; IR (KBr) 3000–3680 (OH), 1715, 1725 cm^{-1} (C=O); 200-MHz ^1H NMR ($CDCl_3$) δ 1.073 (s, 3, CH_3), 1.093 (s, 3, CH_3), 1.263 (m, 2, CCH_2), 1.338 (m, 2, CCH_2), 2.420 (m, 22, CH_2, CH_3), 4.183 (s, 1, $CHCl$). Anal. ($C_{20}H_{35}Cl_3O_4$) C, H, Cl.

2,2,15,15-Tetrachloro-3,3,14,14-tetramethylhexadecanedioic acid (12) was obtained by H_2SO_4–oleium hydrolysis of the bis-(1-methylethyl) ester **11**[14] as described above. The acid was purified by flash chromatography on silica gel using a mixture of CH_2Cl_2 and 5% acetic acid in THF as eluent: yield 78%; mp 154–154.5 °C; IR (KBr) 3000–3670 (OH), 1725 cm^{-1} (C=O); 200-MHz ^1H NMR ($CDCl_3$) δ 1.267 (m, 28, CH_2 and CH_3), 1.252 [m, 4, $CH_2C(CH_3)_2$]. Anal. ($C_{20}H_{34}Cl_4O_4$) C, H, Cl.

2,15-Dihydroxy-3,3,14,14-tetramethylhexadecanedioic Acid (13). A mixture of 880 mg (1.76 mmol) of the dibromo acid 8, 3 g (53.6 mmol) of KOH, and 30 mL of water was refluxed and stirred for 20 h. The usual workup yielded 108 mg (62%) of **13** as a colorless oil that solidified upon standing: mp 84–89 °C dec; IR ($CHCl_3$) 3000–3420 (OH), 1710 cm^{-1} (C=O); 200-MHz ^1H NMR (CDC_3) δ 0.974 (s, 12, CCH_3), 1.256 (m, 20, CH_2), 3.961 (s, $CHOH$); EI MS (68 eV, 100 °C) m/z (rel intensity) 312 ($C_{18}H_{32}O_4^{\cdot+}$, 34), 299 ($C_{18}H_{35}O_3^+$, 16), 255 ($C_{15}H_{27}O_3^+$, 39), 253 ($C_{17}H_{33}O^+$, 93), 237 ($C_{16}H_{29}O^+$, 38), 225 ($C_{16}H_{33}^+$, 16), 125 ($C_7H_9O_2^+$, 6), 117 ($C_5H_9O_3^+$, 100). Anal. ($C_{20}H_{38}O_6$) C, H.

When the solvolysis of 1.210 g (2.42 mmol) of 8 was carried out for 4 days with 0.249 g (10.8 mmol) of MeONa in 50 mL of boiling MeOH, 0.574 g (59%) of **2,15-dimethoxy-3,3,14,14-tetramethylhexadecanedioic acid** was obtained as a colorless oil: IR (neat) 3000 (OH), 1710 (C=O), 1120 cm^{-1} (C–O); 300-MHz ^1H NMR ($CDCl_3$) δ 0.947 (s, 6, CCH_3), 0.958 (s, 6, CCH_3), 1.243 (m, 20, CH_2), 3.393 (s, 6, OCH_3), 3.472 (s, 2, CH_2OCH_3); EI MS (70 eV, 100 °C) m/z (rel intensity) 314 ($C_{19}H_{37}O_3^+$, 47), 270 ($C_{16}H_{30}O_3^{\cdot+}$, 10), 268 ($C_{16}H_{28}O_3^{\cdot+}$, 53), 131 ($C_6H_{11}O_3^+$, 27), 123 ($C_8H_{11}O^+$, 60), 115 ($C_5H_7O_3^+$, 30), 113 ($C_6H_9O_2^+$, 77), 111 ($C_7H_{11}O^+$, 86), 109 ($C_7H_9O^+$, 100). Anal. ($C_{22}H_{42}O_6$) C, H.

2,15-Difluoro-3,3,14,14-tetramethylhexadecanedioic Acid (15). A mixture of 34 g (6.4 mmol) of dimethyl 2,15-dibromo-3,3,14,14-tetramethylhexadecanedioate (**14**) [prepared from the acid chloride of 8 and MeOH; IR ($CHCl_3$) 1735 cm^{-1} (C=O); 200-MHz ^1H NMR ($CDCl_3$) δ 1.060 s, 6, CCH_3), 1.079 (s, 6, CCH_3), 1.247 (m, 20, CH_2), 3.732 (s, 6, OCH_3), 4.175 (s, 2, $CHBr$); anal. ($C_{22}H_{40}Br_2O_4$) C, H] and 9.2 g (29 mmol) of "predried" tetrabutylammonium fluoride (freshly dried for 48 h at 50 °C and 1 mm) was stirred under argon at 60 °C for 20 h. After cooling, the reaction mixture was diluted with water. Extraction of the organic material with ether and workup in the usual manner gave 2.3 g of a mixture of 8, **13**, **15**, **17**, **18**, and **19** in the ratio 50:25:100:5:5:2 (determined by NMR). The acids were esterified by refluxing with 50 mL of MeOH and 0.4 mL of concentrated H_2SO_4. Flash chromatography of the resulting esters on silica gel afforded 325 mg (13%) of **dimethyl 2,15-difluoro-3,3,14,14-tetramethylhexadecanedioate (16)** as a colorless oil: IR (neat) 1750 cm^{-1} (C=O); 200-MHz ^1H NMR ($CDCl_3$) δ 0.959 (d, 6, J_{CHCHF} = 1 Hz, CCH_3), 0.975 (d, 6, J_{CHCHF} = 1 Hz, CCH_3), 1.249 (m, 20, CH_2), 3.776 (s, 6, OCH_3), 4.615 (d, 2, J_{HF} = 48 Hz, CHF); 282-MHz ^{19}F NMR ($CDCl_3$, 1,4-$C_6H_4F_2$) δ 202.79 (d, J_{HF} = 48 Hz, CHF); 75-MHz ^{13}C NMR ($CDCl_3$) δ 93.8 (d, J_{CF} = 187 Hz, CF), 170.1 (d, J_{CCF} = 20 Hz, CO), 170.4 (d, J_{CCF} = 20 Hz, CO). Anal. ($C_{22}H_{40}F_2O_4$) C, H.

The hydrolysis of the dimethyl ester was accomplished by stirring 120 mg (0.296 mmol) with 2.5 g (7.9 mmol) of tetrabutylammonium fluoride at 60 °C for 16 h. Dilution with water followed by the usual workup afforded 42 mg (38%) of **15** as colorless crystals: mp 91–92 °C; IR (Nujol) 2900 (OH), 1720 cm^{-1} (C=O); 200-MHz ^1H NMR ($CDCl_3$) δ 1.024 (d, 6, J_{CHCHF} = 1 Hz,

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CH_3C), 1.031 (s, 6, CCH_3), 1.251 (m, 20, CH_2) 4.643 (d, 2, J_{HF} = 48.5 Hz, CHF), 7.350 (br s, 2, OH); 282-MHz ^{19}F NMR ($CDCl_3$, 1,4-$C_6H_4F_2$) δ 196.8 (d, J_{HF} = 48.5 Hz, CHF); 75-MHz ^{13}C NMR ($CDCl_3$) δ 95.5 (d, J_{CF} = 188.4 Hz, CF), 174.7 (d, J_{CCF} = 25.6 Hz, CO), 174.8 (d, J_{CCF} = 25.6 Hz, CO); EI MS (70 eV, 105 °C) m/z (rel intensity) 337 [$(M - H)^+$, 17], 314 ($C_{19}H_{35}FO^{\cdot+}$, 22), 302 ($C_{18}H_{35}FO_2^{\cdot+}$, 25), 301 ($C_{18}H_{34}FO_2^+$, 100), 283 ($C_{18}H_{32}FO^+$, 20). Anal. ($C_{20}H_{36}F_2O_4$) C, H.

2,2,13,13-Tetraphenyltetradecanedioic Acid (21). A quantity of 10 mmol of *n*-butyllithium in hexane was syringed dropwise under N_2 at 0 °C into a stirred solution of 1.01 g (10 mmol) of diisopropylamine in 50 mL of dry THF. The mixture was stirred for 30 min at 0 °C and then cooled to −10 °C. A solution of 1.06 g (5 mmol) of diphenylacetic acid (**20**) in 20 mL of THF was then added, followed by 0.9 mL (5 mmol) of HMPT. The red reaction mixture was stirred at −10 °C for 15 min and then allowed to warm up to 0 °C. After 30 min a solution of 830 mg (2.1 mmol) of freshly prepared 1,10-diiododecane (from 1,10-dibromodecane and NaI in acetone) in 30 mL of THF was added. The temperature was allowed to rise to 25 °C during 2.5 h. After 20 h at this temperature the mixture was quenched with a minimum quantity of ice; the THF was removed under reduced pressure and excess water was added. The HMPT was extracted with CH_2Cl_2 and the aqueous layer acidified with 32% hydrochloric acid to pH 1. Ether extraction afforded 1.07 g (quantitative yield) of **21** as colorless fluffy crystals: mp 164.5 °C (from a benzene–hexane mixture); IR (KBr) 3150 (OH), 1697 cm^{-1} (C=O); 300-MHz ^1H NMR ($CDCl_3$) δ 1.129 (m, 16, CH_2) 2.343 [m, 4, $CH_2C(C_6H_5)_2$], 7.287 (m, 20, ArH). Anal. ($C_{38}H_{42}O_4$) C, H.

3,3,14,14-Tetraphenylhexadecanedioic Acid (24). A quantity of 3.1 g (5.5 mmol) of **21** was converted into the acid dichloride by treatment with 1 mL of oxalyl chloride in 100 mL of dry benzene. After careful removal of the excessive reagent, the residue [IR (C_6H_6) 1773 cm^{-1} (C=O)] was divided into three equal parts that were dissolved separately in portions of 20 mL of dry ether. Each solution was added dropwise separately in portions of 20 mL of dry ether. Each solution was added dropwise at 4 °C to a freshly prepared solution of 12 mmol of CH_2N_2 in ether.[19] After 1 h the mixture was allowed to warm up to 25 °C and left at that temperature for 20 h. The excessive CH_2N_2 was removed with a stream of N_2. Evaporation of the ether afforded 2.9 g of the yellow bis-diazo ketone **22** [IR (neat) 2100 cm^{-1} (CN_2)], which was immediately dissolved in 500 mL of a 4:3 mixture of EtOH–dioxane, and the solution was irradiated for 6 h in a Pyrex well with the aid of a 125-W medium-pressure Hanovia mercury lamp. Flash chromatography of the photoproducts on silica gel, using hexane–CH_2Cl_2 mixtures (gradient from 3:2 to pure CH_2Cl_2) as eluent, gave 1.3 g (37%) of **diethyl 3,3,14,14-tetraphenylhexadecanedioate (23)** as a colorless oil: IR (neat) 1728 cm^{-1} (C=O); 200'MHz ^1H NMR ($CDCl_3$) δ 0.901 (t, 6, J = 7 Hz, CH_2CH_3), 1.124 (m, 16, CH_2), 2.289 [m, 4, $CH_2C(C_6H_5)_2$], 3.099 (s, 4, $CH_2COOC_2H_5$), 3.803 (q, 4, J = 7 Hz, CH_2CH_3), 7.246 (m, 20, ArH). Anal. ($C_{44}H_{54}O_4$) C, H.

Hydrolysis of 2.5 g (3.7 mmol) of the ester with boiling KOH (3.5 g 62.5 mmol) solution in 250 mL of 90% aqueous EtOH afforded after 8.5 h and the usual workup 1.7 g (78%) of **24** as colorless crystals: mp 214 °C; IR ($CHCl_3$) 3340 (OH), 1700 cm^{-1} (C=O); 200-MHz ^1H NMR ($CDCl_3$) δ 1.222 (m, 16, CH_2), 2.292 [m, 4, $CH_2C(C_6H_5)_2$], 3.143 (s, 4, CH_2COOH), 7.182 (m, 20, ArH). Anal. ($C_{40}H_{46}O_4$) C, H.

1,10-Bis[tetrahydro-3-methyl-2-oxofuran-3-yl]decane (26). A solution of 10 g (10 mmol) of α-methylbutyrolactone (**25**) in 12 mL of dry THF was added under N_2 at −78 °C to a stirred solution of 12 mmol of LDA in 100 mL of the same solvent. After 30 min there was added a solution of 1.3 g (3.3 mol, to minimize formation of the monolactone derivative) of 1,10-diiododecane and 2.2 mL of HMPT in 8 mL of THF. After 15 min, the temperatures was allowed to rise during 30 min to −35 °C, and the mixture was stirred at this temperature for 40 h. Brief heating to −15 °C was followed by quenching of the reaction mixture with saturated aqueous NH_4Cl and with concentrated HCl to pH 1. The THF was evaporated under reduced pressure, water was added, and the mixture was extracted 5 times with 50-mL portions of petroleum ether (40–60 °C). The organic solution was washed with H_2O, dried, and concentrated (<25 °C) to give 380 mg (34%) of analytically pure **26**. A further amount of 55 mg of the dilactone was obtained when the petroleum ether was evaporated to dryness and the residual semisolid (534 mg) flash chromatographed on silica gel (eluents: hexane–ether gradient from 2:1 to pure ether): total yield 39%; mp 60–61 °C; IR (KBr) 1762 cm^{-1} (C=O); 200-MHz ^1H NMR ($CDCl_3$) δ 1.241 (m, 20, CH_2), 1.266 (s, 6, CH_3), 2.135 (m, 4, CH_2CH_2CO), 4.255 (t, 4, J = 6.9 Hz, CH_2CO). Anal. ($C_{20}H_{34}O_4$) C, H.

The compound eluted first by flash chromatography proved to be **27**: yield 458 mg (58%); colorless oil; IR (neat) 1767 cm^{-1} (C=O); 200-MHz ^1H NMR ($CDCl_3$) δ 1.239 (m, 1, CH_2), 1.284 (s, 3, CH_3), 1.564 (m, 2, CH_2), 2.035 (m, 2, $CH_2CH{=}CH_2$), 2.160 (m, 2, ring CH_2CH_2), 4.256 (t, 2, J = 7 Hz, ring CH_2O), 4.970 (m, 2, $CH{=}CH_2$), 5.816 (m, 1, $CH{=}CH_2$). Anal. ($C_{15}H_{26}O_2$) C, H.

1,10-Bis[tetrahydro-4-methyl-2-oxofuran-4-yl]decane (29). Reduction of 4.563 g (13.5 mmol) of **26** with 1.635 g (43 mmol) of $LiAlH_4$ in 60 mL of THF yielded 2,13-bis(2-hydroxyethyl)-2,13-bis(hydroxymethyl)tetradecane (**28**) in quantitative yield as a colorless oil: IR (neat) 3300 cm^{-1} (OH); 200-MHz ^1H NMR ($CDCl_3$) δ 0.851 (s, 6, CH_3), 1.264 (m, 20, CH_2), 1.562 (m, 4, CH_2CH_2OH), 3.373 (s, 4, CH_2OH), 3.717 (t, 4, J = 5.6 Hz, CH_2OH).

A solution of 34.9 g (0.218 mol) of bromine in 140 mL of acetonitrile (freshly distilled over CaH_2) was added dropwise, at −20 °C, to a mixture of anhydrous nickel benzoate [prepared by dehydration of 41 g (135 mmol) of commercial $(C_6H_5COO)_2Ni\cdot 3H_2O$ at 108 °C and 0.2 mmHg for 60 h] and 4.676 g (135 mmol) of **28**, at a rate that permitted immediate decoloration at −20 °C. The mixture was brought to 23 °C and stirred at this temperature for 6 h. The solvent was removed in vacuo and the residue treated with cold (0 °C) hydrochloric acid. Extraction with ether and washing with aqueous $KHSO_3$, aqueous KOH, and water afforded, after solvent removal, **29** as a viscous oil that solidified upon trituration with cold ether: yield 2.36 g (52%); colorless crystals; mp 75.5–76.5 °C; IR (KBr) 1780 cm^{-1} (C=O); 200-MHz ^1H NMR ($CDCl_3$) δ 1.172 (s, 6, CH_3), 1.285 (m, 16, CH_2), 1.439 (m, 4, CH_2), 2.338 (ABq, 4, J_{AB} = 17 Hz, CH_2CO), 4.011 (ABq, 4, J_{AB} = 8 Hz, CH_2O). Anal. ($C_{20}H_{34}O_4$) C, H.

***trans*-3,3,14,14-Tetramethyl-8-hexadecenedioic Acid (32).** A solution of 40 g (0.286 mol) of 5,5-dimethyl-1,3-cyclohexanedione (**30**) (freshly recrystallized from acetone) in 60 mL of 20% aqueous KOH was added to a stirred mixture of 33 g (0.15 g) of *trans*-1,4-dibromo-2-butene and 1.4 g (22 mmol) of copper powder. When the pH dropped to 7, another portion of 14 mL of aqueous KOH was added. After 5 days the orange semisolid reaction mixture was dissolved in 10% NaOH. Unreacted dibromobutene (10 g) was extracted with ether, and the aqueous layer was acidified to give 40 g of yellow **31** contaminated with some **30**. Recrystallization from acetone afforded pure **31** as colorless crystals: mp 205–206 °C; IR (Nujol) 3150 (OH), 1700 (C=O), 1590 cm^{-1} (C=C); 300-MHz ^1H NMR (C_5D_5N and $CDCl_3$) δ 0.975 (s, 12, CCH_3), 2.326 (s, 8, $COCH_2$), 3.390 (m, 4, $CHCH_2$), 5.948 (m, 2, CH_2CH). Anal. ($C_{20}H_{28}O_4$) C, H.

A mixture of 8 g of *crude* **31**, 5 g of KOH, 50 mL triethylene glycol, 6 mL of hydrazine hydrate (85%), and 5 mL of MeOH was heated on an oil bath at 120 °C for 36 h. The water formed was removed by heating the reaction mixture to 195 °C. After 20 h at this temperature the mixture was cooled and diluted with water. Extraction with ether, phase separation, acidification of the aqueous layer, extraction with CH_2Cl_2, and workup of the organic phase afforded 3.77 g of a tan oily mixture that was separated by chromatography on silica gel, using a 1:20 mixture of MeOH and CH_2Cl_2 as eluent. The initial fraction of 3,3-dimethylcaproic acid was followed by the unsaturated dicarboxylic acid **32**. Recrystallization from hexane (2×) gave 175 mg (2% overall yield) of colorless crystals: mp 100–101 °C; IR ($CHCl_3$) 3100 (OH), 1710 cm^{-1} (C=O); 300-MHz ^1H NMR ($CDCl_3$) δ 1.014 (s, 12, CCH_3), 1.298 (m, 12, CH_2), 1.984 (m, 4, $CHCH_2$), 2.213 (s, 4, CCH_2), 5.361 (m, 2, CH); EI MS (70 eV, 200 °C) m/z (rel intensity) 341 [$(M + H)^+$, 10), 340 ($M^{\cdot+}$, 21), 322 ($C_{20}H_{34}O_3^{\cdot+}$, 65), 307 ($C_{21}H_{36}O_2^{\cdot+}$, 34), 303 ($C_{20}H_{32}O_2^{\cdot+}$, 99), 281 ($C_{18}H_{33}O_2^+$, 24), 280 ($C_{18}H_{32}O_2^{\cdot+}$, 20), 140 ($C_9H_{16}O^{\cdot+}$, 42), 124 ($C_8H_{12}O^{\cdot+}$, 64), 115 ($C_4H_{11}O_2^+$, 22), 112 ($C_7H_{12}O^{\cdot+}$, 88), 101 ($C_5H_9O_2^+$, 100). Anal. ($C_{20}H_{36}O_4$) C, H.

Isomers of 6,6′-(1,4-Phenylene)bis[3,3-dimethyl-5-hexenoic acid] (35a–c, R = H). A solution of MeONa [prepared from 1.00 g (44 mequiv) of Na] in 50 mL of MeOH was added dropwise at room temperature to a stirred solution of 6.96 g (44 mmol) of methyl 4-formyl-3,3-dimethylbutanoate (**34**, R = CH_3)[27] (Dynamit

Nobel) and 14.0 g (20 mmol) of (1,4-phenylenedimethylene)bis-[triphenylphosphonium] dichloride (**33**) in 60 mL of the same solvent. After 3 h the solvent was evaporated under reduced pressure and the residue extracted with Et_2O to which 2N H_2SO_4 had been added. The organic phase was separated, and the aqueous layer was extracted with Et_2O. The combined ether phases were washed with water, dried, and evaporated to dryness. The residue was extracted (2×) with petroleum ether, filtered, and evaporated to give 7.6 g (98%) of crude esters. Chromatography on silica gel (CH_2Cl_2 as eluent) afforded 5.5 g (71% of a mixture of the three isomeric esters (**35a–c**, R = CH_3, as a colorless oil. [GC analysis indicated the presence of 29.1% **35a**, R = CH_3, 17.3% **35b**, R = CH_3, and 46.1% **35c**, R = CH_3: 60-MHz ^1H NMR ($CDCl_3$) δ 1.02 [m, 12, C(CH_3)], 2.00–2.55 (m, 8, CH_2), 3.58 (m, 3, OCH_3), 3.63 (m, 3, OCH_3), 5.23–6.83 (m, 4, C*H*), 7.27 (m, 4, Ar*H*); EI MS (70 eV) m/z 386 ($M^{\cdot+}$).] A quantity of 1.3 g (3.36 mmol) of the mixture of methyl esters was refluxed with 13 mL of 2 N aqueous NaOH and 13 mL of MeOH for 3 h. The MeOH was distilled off, 5 mL of H_2O was added, and the solution was acidified with HCl. The semisolid that formed was triturated with H_2O and dried to yield 0.82 g (68%) of a mixture of carboxylic acids that consisted of 30.0% **35a**, R = H, 18.8% **35b**, R = H, and 48.9% **35c**, R = H: mp 118–160 °C; 300-MHz ^1H NMR (DMSO-d_6) δ 1.00 (m, 12, CH_3), 2.10 (m, 4, COCH_2), 2.38 (m, 4, CHCH_2), 5.47–5.92 (m, 2, CH_2C*H*), 6.24–6.57 (m, 2, C_6H_4C*H*), 7.27 (m, 4, Ar*H*). Anal. ($C_{22}H_{30}O_4$) C, H.

The three isomeric acids were separated by stirring a suspension of 23.0 g of the mixture in 50 mL of hot acetone (bath temperature 70 °C) for 60 min. The mixture was filtered while hot, and the resulting solid cake was resuspended in 50 mL of fresh hot acetone. This procedure was repeated for a third time, and the resulting product was recrystallized from acetone to give 3.0 g (13%) of the *E,E*-isomer **35b**, R = H, of 98.5% purity (by GC): mp 197–199 °C; 300-MHz ^1H NMR (DMSO-d_6) δ 1.01 (s, 12, CH_3), 2.14 (s, 4, COCH_2), 2.20 (d, 4, J = 6.9 Hz, CHCH_2), 6.30 (dt, 2, J_1 = 6.9 Hz, J_2 = 15.6 Hz, CH_2C*H*), 6.37 (d, 2, J = 15.6 Hz, C_6H_4C*H*), 7.33 (br s, 4, Ar*H*), 11.85 (s, 2, COO*H*). Anal. ($C_{22}H_{30}O_4$) C, H.

The combined filtrates of the previous operation were evaporated to dryness, and the residue was dissolved in the *minimum* volume of boiling AcOEt. Petroleum ether (bp 45–60 °C) was then added until the liquid became turbid. After cooling to room temperature and filtering off a residual amount of **35b**, R = H, the 10-fold volume of petroleum ether was added and the flask cooled in a refrigerator. The precipitate was separated and subjected to the same procedure again. The resulting solid cake was recrystallized from a AcOEt–heptane mixture (1:3) to give 4.98 g (21.7%) of the *E,Z*-isomer **35c** of 98.2% purify (by GC): mp 67–70 °C; 300-MHz ^1H NMR (DMSO-d_6) δ 0.98 (s, 6, CH_3), 1.01 (s, 6, CH_3), 2.14 (s, 2, COCH_2), 2.15 (s, 2, COCH_2), 2.21 (d, 2, J = 6.6 Hz, CHCH_2), 2.37 (dd, J_1 = 1.9 Hz, J_2 = 7.3 Hz, CHCH_2), 5.73 (dt, 1, J_1 = 7.3 Hz, J_2 = 12.0 Hz, CH_2C*H*), 6.30 (dt, 2, J_1 = 6.6 Hz, J_2 = 15.7 Hz, CH_2C*H*), 6.38 (d, 1, J = 15.7 Hz, C_6H_4C*H*), 6.47 (d, 1, J = 12.0 Hz, C_6H_4C*H*), 7.23 (d, 2, J = 8.4 Hz, Ar*H*), 7.37 (d, 2, J = 8.4 Hz, Ar*H*), 11.85 (s, 2, COO*H*). Anal. ($C_{22}H_{30}O_4$) C, H.

The combined filtrates of the latter operation were evaporated to dryness, and the residue was extracted with several portions of boiling petroleum ether (bp 45–60 °C). After filtering of the hot mixture, the combined filtrates were evaporated, and the residue was chromatographed on silica gel (MN-Kieselgel 60) (CH_2Cl_2–MeOH, 38:1) to give 4.07 g (17.7%) of the *Z,Z*-isomer **35a**, R = H, of 97.2% purity (by GC): mp 136–139 °C. Further purification was accomplished by preparative HPLC: mp 139–140 °C; 300-MHz ^1H NMR (DMSO-d_6) δ 1.00 (s, 12, CH_3), 2.12 (s, 4, OCH_2), 2.39 (dd, 4, J_1 = 2.1 Hz, J_2 = 7.2 Hz, CHCH_2), 5.75 (dt, 2, J_1 = 7.2 Hz, J_2 = 12.0 Hz, CH_2C*H*), 6.48 (dt, 2, J_1 = 1.8 Hz, J_2 = 12.0 Hz, C_6H_4C*H*), 7.27 (s, 4, Ar*H*), 11.85 (s, 2, COO*H*). Anal. ($C_{22}H_{30}O_4$) C, H.

6,6′-(1,4-Phenylene)bis[3,3-dimethylhexanoic acid] (36, R = H). Method A. A solution of 19.0 g (49.2 mmol) of the mixture of isomeric esters **35a–c**, R = CH_3, in 300 mL of MeOH was hydrogenated at 1 atm in the presence of 0.5 g of 10% palladium on carbon. The resulting 17.5 g (91%) of colorless oil of **36**, R = CH_3 [60-MHz ^1H NMR ($CDCl_3$) δ 0.97 (s, 12, CCH_3), 1.17–1.78 (m, 8, CH_2), 2.37–2.70 (m, 4, CH_2), 3.60 (s, 6, COCH_3), 7.07 s, 4, Ar*H*); EI MS (70 eV) m/z 390 ($M^{\cdot+}$)], was stirred for 3 h at 90 °C with 175 mL of 2 N aqueous NaOH and 175 mL of MeOH. The MeOH was distilled off, and the resulting solution was acidified. Extraction with Et_2O, phase separation, and evaporation of the solvent afforded, after recrystallization from cyclohexane, 13.33 g (82%) of **36**, R = H: mp 120–121 °C; 300-MHz ^1H NMR ($CDCl_3$) δ 0.998 (s, 12, CH_3), 1.207 (m, 4, CCH_2), 1.653 (m, 4, $C_6H_4CH_2CH_2$), 2.149 (s, 4, CH_2COOH), 2.587 (t, 4, J = 6.3 Hz, $C_6H_4CH_2$), 7.038 (s, 4, Ar*H*). Anal. ($C_{22}H_{34}O_4$) C, H.

Method B. A Grignard solution prepared from 3.0 g (125 mequiv) of Mg and 20.0 g (62.5 mmol) of 1,4-bis(3-bromopropyl)benzene in 150 mL of THF was added dropwise at −20 °C to a stirred solution of 25.6 g (1.24 mol) of **1** and of 220 mg of freshly prepared Cu_2Cl_2 in 250 mL of the same solvent. After reflux for 3 h the mixture was cooled and treated with ice-cold 10% hydrochloric acid. After the usual workup the residual tetramethyl ester was freed from some volatile compounds by heating at 150 °C at 10^{-2} mmHg. The yield of the crude viscous oily ester was 23.6 g (67%).

Hydrolysis of the tetramethyl ester was accomplished by heating of 2.5 g (4.4 mmol) with 1.0 g (25 mmol) of NaOH and 25 mL of MeOH under reflux for 60 h. Dilution with water, extraction of the neutral material with ether, and acidification afforded 1.8 g (90%) of the tetracarboxylic acid : mp 181–183 °C dec; 300-MHz ^1H NMR (DMSO-d_6) δ 1.03 (s, 12, CH_3), 1.40–1.60 (m, 8, CH_2), 2.48 (m, 4, CH_2), 3.12 (s, 2, C*H*), 7.07 (m, 4, Ar*H*).

Upon heating of the tetraoic acid for 2 h at 160 °C, there was obtained 0.44 g (31%) of **36**, R = H, with the same properties as the dioic acid obtained by method A.

6,6′-(Cyclohexane-1,4-diyl)bis[3,3-dimethylhexanoic acid] (37, R = H). Hydrogenation of 7.00 g (18 mmol) of **36**, R = CH_3, in 50 mL MeOH in the presence of 0.1 g of RuO_2 at 90 °C and 80 bar gave 0.7 g (98%) of **37**, R = CH_3, as a colorless oil: IR (neat) 1738 cm^{-1} (C=O); 60-MHz ^1H NMR ($CDCl_3$) δ 0.97 (s, 12, CH_3), 1.10–1.50 (m, 22, CH_2), 2.18 (s, 4, CCH_2), 3.65 (s, 6, OCH_3). Hydrolysis with a 10-fold 2 N methanolic NaOH gave after 3 h at reflux followed by acidification the free acid **37**, R = H, in 81% yield: mp 167–169 °C (ethyl acetate); 300-MHz ^1H NMR ($CDCl_3$) δ 1.008 (s, 12, CH_3), 1.090–1.520 (m, 22, CH_2), 2.218 (s, 4, CH_2COOH). Anal. ($C_{22}H_{40}O_4$) C, H.

3,3,16,16-Tetramethyl-5,8,11,14-tetraoxaoctadecanedioic Acid (43). To a LDA solution, prepared from 13.9 mL (97 mmol) of diisopropylamine, 96 mmol of 15% butyllithium in hexane, and 100 mL of dry THF at −20 °C, was added under argon 6 mL of HMPT. The solution was cooled to −78 °C and treated slowly with 10.62 g (0.1 mol) of methyl isobutyrate (**38**). After stirring for 1 h at −78 °C, a solution of 11 g (45 mmol) of 1,12-dichloro-2,5,8,11-tetraoxadodecane[22] in 50 mL of THF was added. The mixture was then allowed to warm up to 20 °C, and stirring was continued for 20 h. Acidification with dilute H_2SO_4, extration with hexane, and workup in the usual manner afforded 1.00 g (6%) of crude ester. After chromatography on silica gel (2:3 mixture of ether and hexane as eluent), 400 mg of pure dimethyl 2,2,15,15-tetramethyl-4,7,10,13-tetraoxahexadecanedioate (**39**) was obtained as a pale yellow oil:[28] IR ($CHCl_3$) 1720 (C=O), 1130 cm^{-1} (C–O); 200-MHz ^1H NMR ($CDCl_3$) δ 1.159 (s, 12, CCH_3), 3.451 (s, 4, OCH_2CO), 3.589 (m, 12, OCH_2), 3.649 (s, 6, OCH_3). Hydrolysis of the diester was accomplished by refluxing 380 mg (1 mmol) with a solution of 300 mg (5.4 mmol) of KOH in 8 mL of H_2O and 40 mL of MeOH. After workup and purification, there was obtained 175 mg (52%) of the dicarboxylic acid **40** as a pale yellow oil: IR ($CHCl_3$) 2950 (OH), 1700 (C=O), 1100 cm^{-1} (C–O); 200-MHz ^1H NMR ($CDCl_3$) δ 1.187 (s, 12, CCH_3), 3.425 (s, 4, OCH_2C), 3.615 (m, 12, CH_2O), 6.996 (br s, 2, COO*H*). A quantity of 175 mg (0.519 mmol) of the dicarboxylic acid was converted into the acid chloride by treatment with an excess of oxalyl chloride in benzene at 25 °C for 48 h [IR (neat) 1820, 1770 cm^{-1}

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(C=O)]. To a solution of the acid chloride in a mixture of 1.5 mL of acetonitrile and 1.5 mL of dry THF was added, at 0 °C, 371 mg (3.25 mmol) of (trimethylsilyl)diazomethane[23] in 2 mL of the same mixture of solvents. Stirring at room temperature for 15 h gave a solution of a silicon-containing diazo ketone [IR (THF-CH_3CN) 2100 (CHN_2), 1625 (C=O), 1110 (C-O) 1250, 845 cm^{-1} (SiC); the two latter peaks of the trimethylsilyl groups disappeared after further stirring of the mixture for 24 h]. Evaporation of the solvents under reduced pressure yielded **41** as a yellow oil [300-MHz ^1H NMR ($CDCl_3$) δ 1.114 (s, 12, CH_3), 3.403 (s, 4, OCH_2CO), 3.592 (m, 12, CH_2O)].

The yellow solution of 144 mg (0.36 mmol) of the diazo ketone **41** in 75 mL of degassed dioxane and 75 mL of degassed MeOH was irradiated under argon and cooling with ice water in a Pyrex well with a high-pressure 450-W mercury lamp. When the solution was decolorized, the solvent was removed under reduced pressure. The residue was dissolved in ether and purified by column chromatography on silica gel (ether-hexane mixtures as eluent) to give 104 mg (71%) of dimethyl 3,3,16,16-tetramethyl-5,8,11,14-tetraoxaoctadecanedioate (**42**) as a pale yellow oil: IR ($CHCl_3$) 1725 (C=O), 1115 cm^{-1} (C-O); 200-MHz ^1H NMR ($CDCl_3$) δ 0.972 (s, 12, CCH_3), 2.265 (s, 4, CCH_2CO), 3.206 (s, 4, OCH_2C), 3.616 (m, 18, OCH_3, OCH_2). Anal. ($C_{20}H_{38}O_8$) C, H.

Hydrolysis of **42** with boiling aqueous KOH gave 59% of the free dicarboxylic acid **43** as a pale yellow oil: IR ($CHCl_3$) 3000 (OH), 1700 (C=O), 1100 cm^{-1} (C-O); 200-MHz ^1H NMR ($CDCl_3$) δ 1.010 (s, 12, CCH_3), 2.303 (s, 4, CCH_2CO), 3.265 (s, 4, OCH_2C), 3.623 (m, 12, OCH_2), 7.822 (br s, 2, COOH); EI MS (70 eV, 75 °C) m/z (rel intensity) 319 ($C_{16}H_{31}O_6^+$, 24), 318 ($C_{16}H_{30}O_6^{\cdot+}$, 22) 263 ($C_{12}H_{23}O_6^+$, 6), 247 ($C_{12}H_{23}O_5^+$, 100), 219 ($C_{10}H_{19}O_5^+$, 51), 203 ($C_{10}H_{19}O_4^+$, 26), 202 ($C_{10}H_{13}O_4^+$, 40), 200 ($C_{10}H_{16}O_4^{\cdot+}$, 32). Anal. ($C_{18}H_{34}O_8$) C, H.

Biochemistry. Incorporation of ^3H_2O into Liver Total Lipids, Saponified Fatty Acids, and 3-β-Hydroxysterols; Induction of Liver Peroxisomal Activities. Rats of the Hebrew University strain weighing 140-160 g were starved for 48 h and pair-refed for 3 consecutive nights a 15-g meal of a high-carbohydrate fat-free powdered diet (Fat-free Test diet, ICN, Cleveland, OH) in the absence and in the presence of MEDICA analogues added to the diet as stated. In the morning following the last meal, the rats were injected intraperitoneally with 10 mCi of ^3H_2O in saline and were sacrificed by cervical dislocation 1 h later. The liver was quickly excised, rinsed in saline, and cooled in ice. The incorporation of ^3H_2O into liver total lipids, saponified fatty acids, and 3-β-hydroxysterols was evaluated as previously described.[3] The induction of liver peroxisomal proliferation was determined by evaluating the CN-insensitive palmitoyl-CoA oxidation or the peroxisomal enoyl-CoA hydratase activities in weighed samples of the liver as previously described.[11]

Incorporation of ^3H_2O into Total Lipids, Saponified Fatty Acids, and 3-β-Hydroxysterols in Cultured Rat Hepatocytes. This was determined as previously described.[4]

Induction of Liver Peroxisomal Activities in Cultured Rat Hepatocytes. This was determined as previously described.[11]

Liver ATP-Citrate Lyase Activity. This was determined as previously described.[4]

The Hypotriglyceridemic-Hypocholesterolemic Effect. Male Lewis rats weighing 150-180 g (SAND-Iwanovas, Kissleg, GFR) were fed ad libitum with standard chow. The test compounds were administered orally in 1% hydrous tylose suspension for the time periods as specified. Control animals were treated with the same amount of vehicle. Blood was drawn by puncture of the retrobulbar venous plexus 3 h following the application of the compounds. Plama cholesterol and triacylglycerols were determined spectrophotometrically by using the respective enzymatic kits (Boehringer Mannheim, GmBH).[29,30]

Blood Glucose and Glucose Tolerance in ob/ob Mice. Female diabetic ob/ob mice (C57BL/6J-ob obtained from Jackson Laboratory, Bar Harbor, ME 04609), aged 10-12 weeks and weighing ca. 40 g, were kept at room temperature of 23 ± 1 °C and relative humidity of 55 ± 5%. The animals had free access to water and standard chow (Sniff-R powder, Sniff Versuchsdiaten GmBH, Soest, FRG). The test compounds were mixed into the powder. Blood samples (5 μL) were taken from the tail tip. Blood glucose concentrations were measured in the hemolysate using the hexokinase/glucose-6-phosphate dehydrogenase method (Boehringer Mannheim GmBH).[31] The oral glucose tolerance was evaluated following the application by gavage of 1 g of glucose/kg of body weight (10% hydrous solution).

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Design of Potential Anti-HIV Agents. 1. Mannosidase Inhibitors

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A molecular orbital and molecular graphics study of 12 substrates, inhibitors, reaction intermediates, and substrate analogues of α-mannosidase was undertaken. The results indicated that potent inhibitors must be good topographical analogues of the mannopyranosyl cation, an intermediate in the reaction catalyzed by the enzyme. Enzyme recognition and strong binding by the inhibitors requires that they contain, as part of their structures, electronegative atoms which are the topographical equivalent of the mannosyl cation C_2 and C_3 hydroxyl groups and ring heteroatom. The absence of a topographical analogue of the C_4 hydroxyl group of the cation appeared to have little effect on the binding and activity of inhibitors. These results have been utilized in the design of potential anti-HIV drugs whose synthesis is now under consideration.

Inhibitors of glycosidases have the potential to produce a number of kinds of beneficial therapeutic effects. They have been used or suggested, as antihyperglycemic compounds,[1] inhibitors of tumour metastasis,[2] antiobesity drugs,[3,4] fungistatic compounds,[5] insect antifeedants,[6-8] and antivirals.[9-12]

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