Structure−Activity Relationships of (4-Acylpyrrol-2-yl)alkanoic Acids as Inhibitors of the Cytosolic Phospholipase A_2: Variation of the Substituents in Positions 1, 3, and 5

Matthias Lehr

Institute of Pharmacy and Food Chemistry, Ludwig-Maximilians-University, Sophienstr. 10, D-80333 Munich, Germany

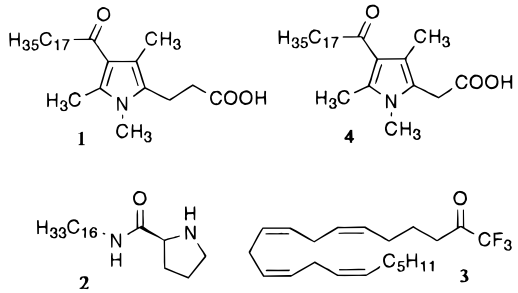
Received January 21, 1997[⊗]

Derivatives of 3-(1,3,5-trimethyl-4-octadecanoylpyrrol-2-yl)propionic acid (**1**) and (1,3,5-trimethyl-4-octadecanoylpyrrol-2-yl)acetic acid (**4**) were prepared and evaluated for their ability to inhibit the cytosolic phospholipase A_2 of intact bovine platelets. While replacement of one of the methyl groups in position 1, 3, or 5 of the acetic acid **4** by a benzyl residue did not influence the inhibitory potency significantly, the introduction of a dodecyl chain led to compounds which even enhanced the enzymatic activity. Stepwise elongation of the alkyl substituent in position 1 showed that the ability to inhibit the enzyme was lost when the alkyl chain exceeded a length of five carbons in case of compound **1** or six carbons in case of compound **4**. Introduction of a polar functional group at the end of the 1-alkyl chain of these inactive pyrroles, however, restored or even elevated inhibitory potency. The most preferable of the polar terminal functions investigated was the carboxylic acid moiety. 6-[2-(2-Carboxyethyl)-4-dodecanoyl-3,5-dimethylpyrrol-1-yl]hexanoic acid (**65c**) and 6-[2-(carboxymethyl)-4-dodecanoyl-3,5-dimethylpyrrol-1-yl]nonanoic acid (**66f**) were the synthesized inhibitors with the greatest potency. With IC_{50} values of 3.4 and 3.3 μM, respectively, they were about 3-fold more active than the standard $cPLA_2$ inhibitor arachidonyl trifluoromethyl ketone (IC_{50}: 11 μM).

Introduction

The cytosolic phospholipase A_2 plays the key role in the generation of several bioactive lipid mediators by cleaving the *sn*-2 acyl ester bond of membrane phospholipids and thus releasing arachidonic acid and lysophospholipids.[1,2] Further metabolism of arachidonic acid leads to the generation of proinflammatory prostaglandins[3] and proasthmatic leukotrienes.[4] Lysophospholipids, which are cell damaging compounds,[5] can serve as precursor for the platelet-activating factor (PAF), another potent mediator of inflammation.[6] Therefore, inhibitors of $cPLA_2$ might become useful drugs for inflammatory diseases and asthma. Probably their therapeutical effect is better than that of the nonsteroidal antiinflammatory drugs (NSAID) used today (*e.g.* indomethacin), since $cPLA_2$ inhibitors not only block the prostaglandin biosynthesis like the applied NSAIDs but moreover also inhibit the formation of the cytotoxic lysophospholipids and the PAF. The results of first *in vivo* experiments with such agents support this presumption.[7]

Recently we found that 3-(1,3,5-trimethyl-4-octadecanoylpyrrol-2-yl)propionic acid (**1**) is an inhibitor of $cPLA_2$.[8] It reduced the arachidonic acid release from bovine platelets after stimulation with calcium ionophore A23187 to about the same extent (IC_{50}: 13 μM) as the known $cPLA_2$ inhibitors (*S*)-*N*-hexadecylpyrrolidine-2-carboxamide[9−11] (Wy-48,489) (**2**) and arachidonyl trifluoromethyl ketone[12] ($AACOCF_3$) (**3**) (IC_{50}: 13 and 11 μM, respectively). Variation of the alkanoic acid group and the acyl residue of the lead compound **1** showed that inhibition of $cPLA_2$ was best by compounds which contain an acetic acid or propionic acid group and an acyl chain of 12 or more carbons.[13] We now investigated the relationships between the inhibitory activity against $cPLA_2$ and the chemical structure of the substituents in positions 1, 3, and 5 of the lead **1** and of its acetic acid derivative **4** (IC_{50}: 10 μM), respectively.



Chemistry

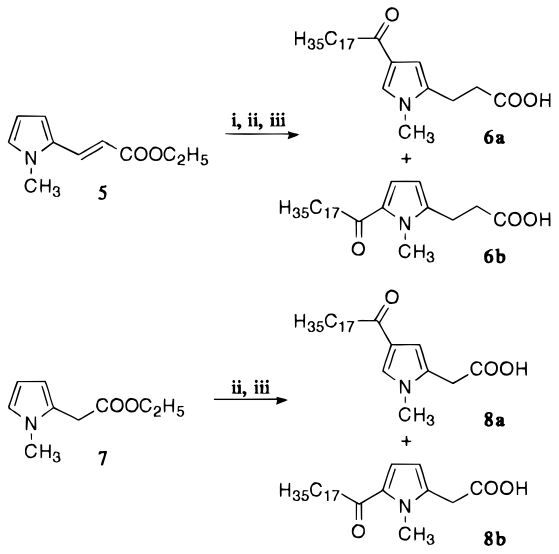
The synthesis of the 3-(1-methyl-4-octadecanoylpyrrol-2-yl)propionic acid (**6a**) started from ethyl 3-(1-methylpyrrol-2-yl)acrylate (**5**)[14] (Scheme 1). This was hydrogenated catalytically and than acylated with *N*,*N*-dimethyloctadecanamide−$POCl_3$ to yield a mixture of the 4-octadecanoyl and the 5-octadecanoyl derivatives of ethyl 3-(1-methylpyrrol-2-yl)propionate. Separation of the isomers was achieved by silica gel chromatography. KOH hydrolysis of the esters afforded the two propionic acid derivatives **6a** and **6b**. The configuration of the compounds was confirmed by comparing their ^{1}H-NMR spectra. The proton at C-5 of **6a** showed the greatest chemical shift ($\delta = 7.20$) of all aromatic protons of **6a** and **6b** because of its close proximity to the pyrrole nitrogen and to the 4-acyl residue. The signals of the vicinal protons at C-3 and C-4 of the pyrrole **6b** appeared as doublets (J = 4 Hz), while the isolated protons at the pyrrole cycle of **6a** gave singlets in the ^{1}H-NMR spectrum.

The analogous acetic acids **8a** and **8b** were prepared from ethyl (1-methylpyrrol-2-yl)acetate[15] in a similar manner (Scheme 1).

[⊗] Abstract published in *Advance ACS Abstracts,* September 1, 1997.

S0022-2623(97)00045-9 CCC: $14.00 © 1997 American Chemical Society

Scheme 1[a]



[a] (i) H_2, Pd/C, THF, EtOH; (ii) *N,N*-dimethyloctadecanamide, $POCl_3$, benzene; (iii) aqueous KOH, EtOH.

The three derivatives of **4** obtained by replacing one of the methyl groups in position 1, 3, or 5 of the pyrrole by a benzyl substituent were prepared as illustrated in Scheme 2. The synthesis of the 1-benzyl isomer **11** started from 2,4-dimethyl-3-octadecanoylpyrrole (**9**).[8] This was benzylated in position 1 by phase transfer reaction with benzyl bromide to give **10**. Subsequently, the acetic acid side chain was introduced by copper-assisted coupling with ethyl diazoacetate,[15] followed by KOH hydrolysis of the resulting ester intermediate. In order to prepare the isomeric acetic acid with a benzyl residue in position 3 (**14**), 4-benzoyl-1-methylpyrrole-2-carbaldehyde (**12**)[16] was reduced by the Wolff−Kishner reaction. The obtained 4-benzyl-1,2-dimethylpyrrole (**13**) was treated with ethyl diazoacetate−copper powder followed by acylation with *N,N*-dimethyloctadecanamide−$POCl_3$ and saponification to provide the desired product **14**. The 5-benzyl isomer **18** was synthesized starting from 2-benzoyl-1-methylpyrrole (**15**).[17] Formylation with dichloromethoxymethane and $AlCl_3$[18] led to 5-benzoyl-1-methylpyrrole-3-carbaldehyde (**16**). From this the target **18** was afforded using the same reaction sequence as described above for the synthesis of **14**.

The derivatives of **4** in which one of the three pyrrole-fixed methyl groups was substituted by a dodecyl chain (**20**, **23**, **26**) were synthesized analogously to the benzyl compounds **11**, **14**, and **18** using the corresponding starting materials (Scheme 3). 4-Dodecanoyl-1-methylpyrrole-2-carbaldehyde (**22**), which was required for the synthesis of **23**, was obtained by acylating the Vilsmeier−Haack intermediate, formed from 1-methylpyrrole, DMF, and oxalyl chloride, under normal Friedel−Crafts conditions with dodecanoyl chloride as described for the preparation of the 4-acetyl derivative of **22**.[19] 2-Dodecanoyl-1-methylpyrrole (**24**), necessary for the synthesis of **26**, was afforded from 1-methylpyrrole by reaction with *N,N*-dimethyldodecanamide and $POCl_3$.

The dibenzyl compound **29** was prepared starting from 4-benzoylpyrrole-2-carbaldehyde (**27**)[19] (Scheme 4). This was benzylated in position 1 in a phase transfer reaction with benzyl bromide, and the obtained intermediate was reduced to 1,4-dibenzyl-2-methylpyrrole (**28**) by the Wolff−Kishner reaction. Friedel−Crafts acylation of **28** with octadecanoyl chloride gave a mixture of the two possible acylation products, which could be separated chromatographically. The structure of the two isomers was assigned by comparing their ^{1}H-NMR spectra. Because of the closer proximity to the electron-withdrawing carbonyl group, the signal for the methylene protons of the *N*-benzyl group of the compound with an acyl residue in the α-position of the pyrrole nitrogen should appear at lower field ($\delta = 5.59$ ppm) than that of the corresponding compound with an acyl residue in the *β*-position ($\delta = 4.98$ ppm). This suggestion was strengthened by the fact that the chemical shift of the *N*-methyl group of 2-acetyl-1-methylpyrrole ($\delta = 3.93$ ppm)[20] is greater than that of the 3-acetyl-1-methylpyrrole ($\delta = 3.62$ ppm).[21]

The dibenzyl isomer with the acyl residue in the *β*-position was converted to the acetic acid derivative **29**, utilizing reaction conditions described for the synthesis of **11**.

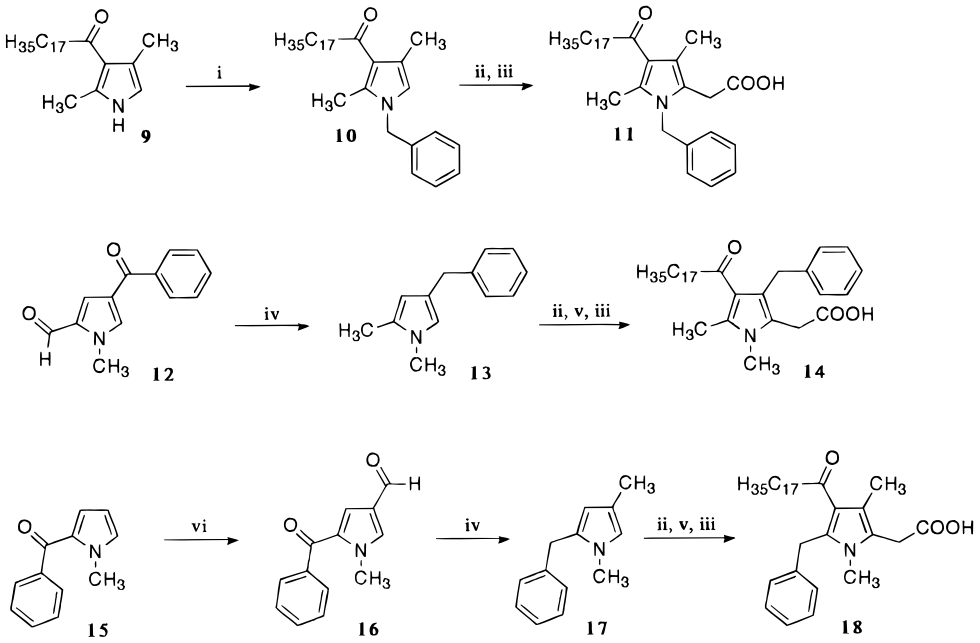
(3,5-Dimethyl-4-octadecanoylpyrrol-2-yl)acetic acids with different 1-alkyl chains (**32a**,**b**,**d**,**e**) or a 1-(4-methylbenzyl) residue (**33**) were synthesized from **9** similarly to **11**, employing the appropriate 1-bromoalkanes or 4-methylbenzyl bromide (Scheme 5). The homologous propionic acids **34a**−**d**, **35**, and **36** were afforded by reaction of the 1-substituted intermediates **30a**−**d**, **10**, and **31** with methyl acrylate in the presence of $BF_3{\cdot}Et_2O$[22] followed by KOH hydrolysis of the resulting ester intermediates.

Acylpyrrolylpropionic acids with various terminal functional groups at the 1-alkyl residue (**39**,**41**,**45**−**47**) were prepared by the routes shown in Scheme 5. The synthesis of the derivative with a 6-hydroxyhexyl residue in position 1 (**39**) started from compound **9**. Phase transfer reaction with an excess of 1,6-dibromohexane yielded **37**. The methyl propionate side chain was introduced in position 2 by reaction with methyl acrylate−$BF_3{\cdot}Et_2O$.[22] Substitution of the terminal bromine with an acetate residue by reaction with silver acetate followed by ester hydrolysis led to the test compound **39**. The corresponding pyrrolylpropionic acid containing a 6-(dimethylamino)hexyl moiety in position 1 (**41**) was afforded using a similar reaction sequence.

The pyrrole derivatives with a terminal nitrile or a carboxylic acid functionality at the 1-alkyl residue (**45**, **46**) were obtained by *t*−BuOK-DMSO alkylation of **9** with 6-bromohexanenitrile and ethyl 6-bromohexanoate, respectively, and subsequent introduction of the propionic acid side chain using the method described above. In order to synthesize the target with a 1-(*N,N*-dimethylcarbamoyl)pentyl residue (**47**) (Scheme 5), prior to this last reaction the ethyl ester group of the intermediate **43** was converted to a *N,N*-dimethylamide moiety (**44**) by KOH hydrolysis and by coupling of the resulting carboxylic acid with dimethylamine using carbonyldiimidazole as the coupling agent.

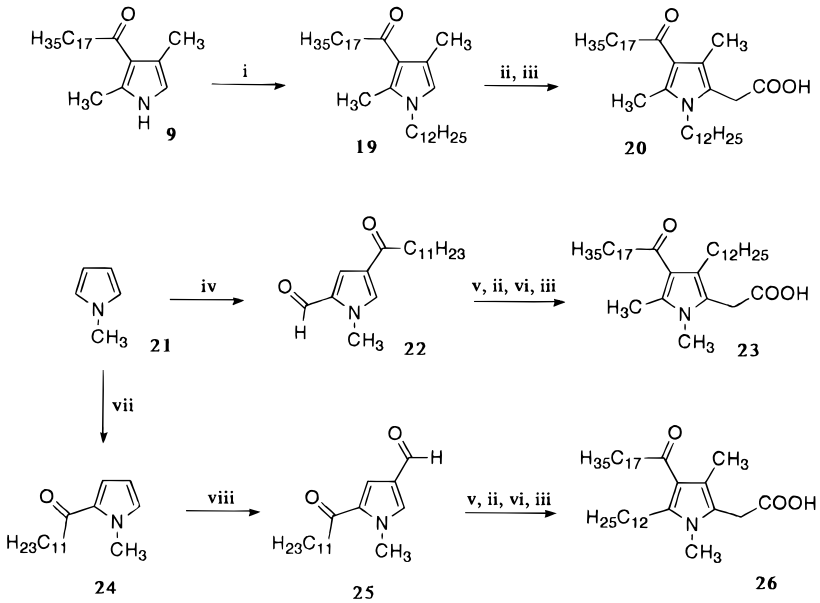
The propionic acid derivatives with various 4-substituted benzyl residues in position 1 of the pyrrole were prepared by applying procedures similar to those described above (Scheme 5). From the intermediate **52**, both the 4-cyanobenzyl-(**57**) and the 4-carbamoylbenzyl-(**58**) substituted compounds could be obtained in dependence on the duration of the final KOH hydrolysis. The propionic acid with a 4-hydroxybenzyl residue (**59**) was

Scheme 2[a]



[a] (i) Benzyl bromide, $(C_4H_9)_4N^+Br^-$, 50% aqueous NaOH, Et_2O, CH_2Cl_2; (ii) ethyl diazoacetate, Cu^0, toluene; (iii) aqueous KOH, EtOH; (iv) hydrazine hydrate, triethylene glycol, KOH; (v) *N*,*N*-dimethyloctadecanamide, $POCl_3$, benzene; (vi) $CHCl_2(OCH_3)$, $AlCl_3$, CH_2Cl_2.

Scheme 3[a]



[a] (i) 1-Bromododecane, $(C_4H_9)_4N^+Br^-$, 50% aqueous NaOH, Et_2O; (ii) ethyl diazoacetate, Cu^0, toluene; (iii) aqueous KOH, EtOH; (iv) oxalyl chloride, DMF, CH_2Cl_2, $AlCl_3$, dodecanoyl chloride; (v) hydrazine hydrate, triethylene glycol, KOH; (vi) *N*,*N*-dimethyloctadecanamide, $POCl_3$, benzene; (vii) *N*,*N*-dimethyldodecanamide, $POCl_3$, benzene; (viii) $CHCl_2(OCH_3)$, $AlCl_3$, CH_2Cl_2.

afforded from the corresponding 4-methoxybenzyl derivative **55** by ether cleavage with BBr_3. The 4-(*N*,*N*-dimethylcarbamoyl)benzyl derivative **60** was synthesized from **51** in a manner similar to the preparation of **47**.

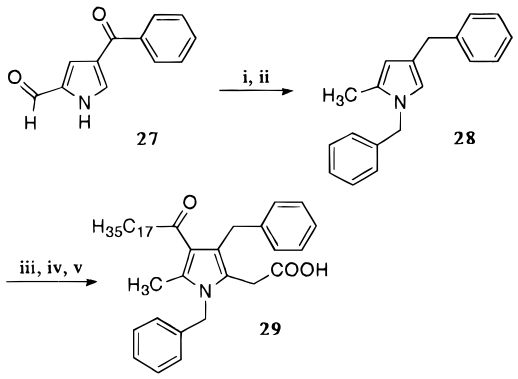
The acetic acid derivative **63** and the dicarboxylic acids **65a**−**e** and **66c**−**f** were synthesized using reaction sequences already mentioned above (Scheme 6).

Biological Evaluation

The $cPLA_2$ inhibitory potency of the test compounds was evaluated by measuring the calcium ionophore A23187-induced arachidonic acid release from bovine platelets with HPLC/UV detection.[23] In our opinion, such a cellular assay better correlates with the conditions prevailing *in vivo* than a test system using the isolated enzyme. However, when using A23187 as stimulant it has to be considered that the decrease of arachidonic acid release caused by a test compound may not only be the result of an affection of $cPLA_2$, but can also depend on an interference with the A23187-induced activation mechanism.

For the acylpyrrolylalkanoic acids the latter possibility of action could be ruled out, because the lead compound **1** also inhibited arachidonic acid liberation after stimulation the platelets with 12-*O*-tetrade-

Scheme 4[a]



[a] (i) Benzyl bromide, $(C_4H_9)_4N^+Br^-$, powdered NaOH, Et_2O, $CHCl_3$, H_2O; (ii) hydrazine hydrate, triethylene glycol, KOH; (iii) octadecanoyl chloride, $AlCl_3$, CH_2Cl_2; (iv) ethyl diazoacetate, Cu^0, toluene; (v) aqueous KOH, EtOH.

canoylphorbol 13-acetate (TPA),[8,24] which activates the $cPLA_2$ in a different way than does A23187.[25−27]

Since $cPLA_2$ inhibition is faked when a substance leads to lysis of the platelets,[28] the cell lytic potency of each test compound was determined besides by turbidimetry.

Platelets also contain type II $sPLA_2$.[29] However, this PLA_2 is not involved in the release of arachidonic acid.[2,24,30−32] Therefore, in combination with the determination of the cell lytic potency and the evaluation of the inhibition of the TPA-induced arachidonic acid liberation, the cellular test system applying A23187 as stimulant is specific for the evaluation of $cPLA_2$ inhibitors.

Results and Discussion

Recently we have found that a *N*-demethylation of the leads **1** and **4** led to a slight decrease of activity.[13] We then explored the effect of a simultaneous removal of the methyl groups in positions 3 and 5 of the pyrroles (**6a**, **8a**) on inhibitory potency. Since this modification did not significantly affect activity (Table 1), it could be assumed that the methyl groups in positions 3 and 5 of **1** and **4** were not necessary for enzyme inhibition.

Next the consequence of the replacement of one of the methyl groups in position 1, 3, or 5 of the acetic acid **4** by a benzyl residue was investigated. The three monobenzyl derivatives **11**, **14**, and **18** showed about the same activity as the lead **4** (Table 1), so in general a benzyl residue was well tolerated in all three positions. However, the benzyl derivatives differ in their cell lytic potencies. While **18** did not destroy the cells at 33 μM, compound **14** caused 22% and compound **11** even 32% cell lysis at this concentration.

On the other hand, the introduction of a dodecyl substituent in position 1, 3, or 5 of the lead **4** resulted in a total loss of $cPLA_2$ inhibition. The compounds **20**, **23**, and **26** even enhanced arachidonic acid liberation from the platelets after A23187 stimulation at 33 μM (Table 1). Likewise, the dibenzylpyrrole **29** led to an increase of the enzyme rate at a concentration of 10 μM. The effect of this compound on $cPLA_2$ could not be determined at 33 μM because of the occurrence of cell lysis.

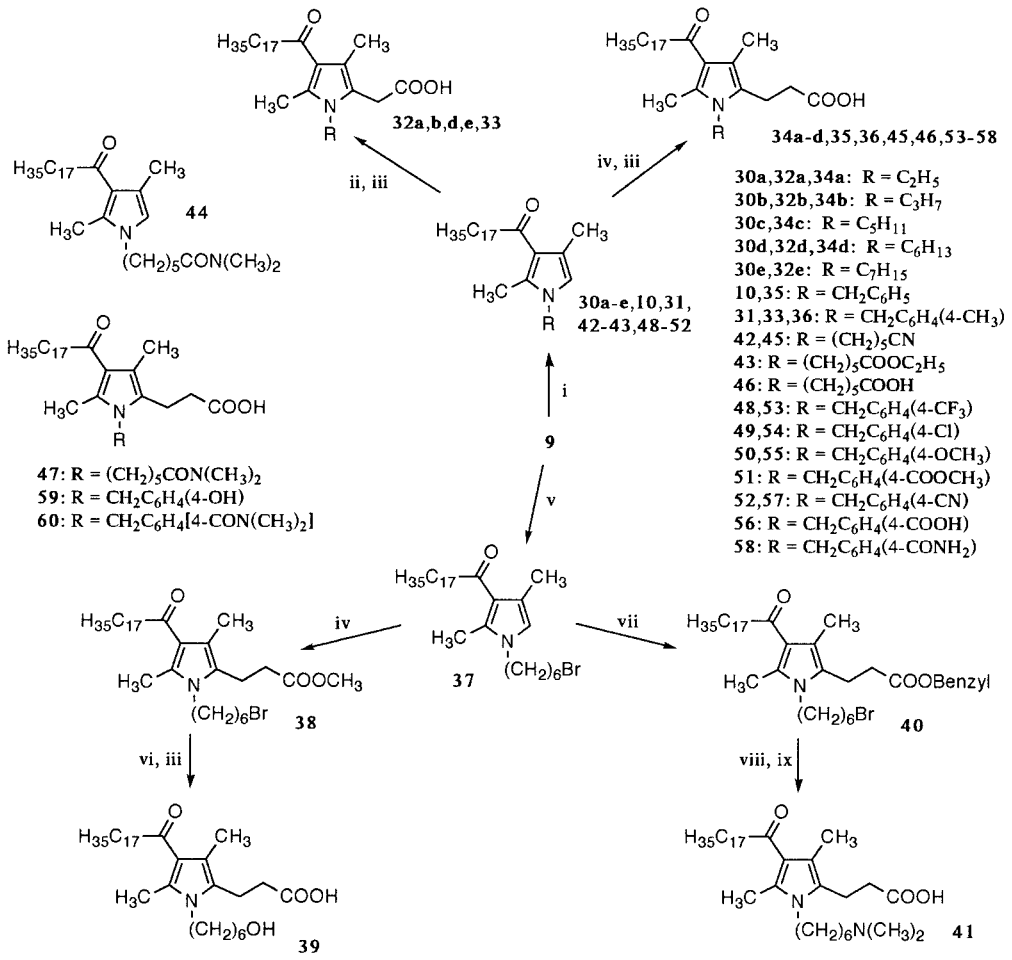
In order to evaluate the bulk of the 1-alkyl chain which leads to the loss of inhibitory activity, the length of the alkyl residue of the leads **1** and **4** was elongated stepwise. While the pyrrolylacetic acids with an ethyl (**32a**), propyl (**32b**), and hexyl (**32d**) substituent in position 1 inhibited the enzyme to about 50% at 10 μM (Table 2), the compound with a heptyl chain (**32e**) was inactive at 10 μM. In case of the pyrrolylpropionic acids, the introduction of a hexyl residue resulted in inactivity. Compound **34d** showed no enzyme inhibition at 20 μM opposed to the propionic acids with a shorter 1-alkyl residue (**34a**−**c**), which had an IC_{50} of about 10 μM. The result that for the pyrrolylacetic acids a slightly bulkier lipophilic substituent is tolerated in position 1 compared to the pyrrolylpropionic acids was confirmed by the following findings. While replacement of the 1-methyl group of the acetic acid **4** and the propionic acid **1** by a benzyl substituent (**11**, **35**) did not significantly change activity, the introduction of a 4-methylbenzyl residue retained activity only in case of the acetic acid (**33**). On the contrary, the 1-(4-methylbenzyl)-substituted pyrrolylpropionic acid **36** proved to be inactive (Tables 1 and 2).

Two explanations can be found for these results: First, the 1-alkyl residue of the pyrroles may be bound in a hydrophobic pocket of the enzyme which can accommodate carbon chains with up to five atoms in propionic acids or six atoms in acetic acids; elongation of the 1-alkyl substituents by one more carbon results in a loss of activity because of sterical interference. On the other hand, it could be possible that lipophilic 1-alkyl residues with more than five and six carbons, respectively, come into close proximity with a hydrophilic part of the enzyme, resulting in inactivity because of electronic incompatibility. To obtain evidence for one of these two assumptions, the terminal methyl group of the 1-hexyl residue of the pyrrolylpropionic acid **34d** was replaced with different polar functionalities. As shown in Table 3, inhibitory potency could be restored by these transformations. The compounds with a terminal nitrile, carboxylic acid, or *N*,*N*-dimethylamide moiety (**45**−**47**) were significantly more active than even the pyrroles with a C_1−C_5 alkyl substituent (**4**, **34a**−**c**). The most potent compound of this series was the derivative with a hexanoic acid residue in position 1 (**46**). With an IC_{50} of 3.2 μM it was about 3−4-fold more active compared with the lead **1**.

Similar results were obtained when replacing the lipophilic methyl group of the 4-methylbenzyl residue of the inactive compound **36** by other substituents (Table 3). The derivatives with a lipophilic trifluoromethyl (**53**) or chloro (**54**) substituent were also not active at 3.3 and 10 μM. On the contrary, the introduction of polar functionalities such as methoxy, hydroxy, carbamoyl, or carboxy led to compounds which inhibited the enzyme at 3.3 μM. Also in this series the carboxylic acid group was the substituent which caused the highest increase of activity (IC_{50} of **56**: 3.5 μM).

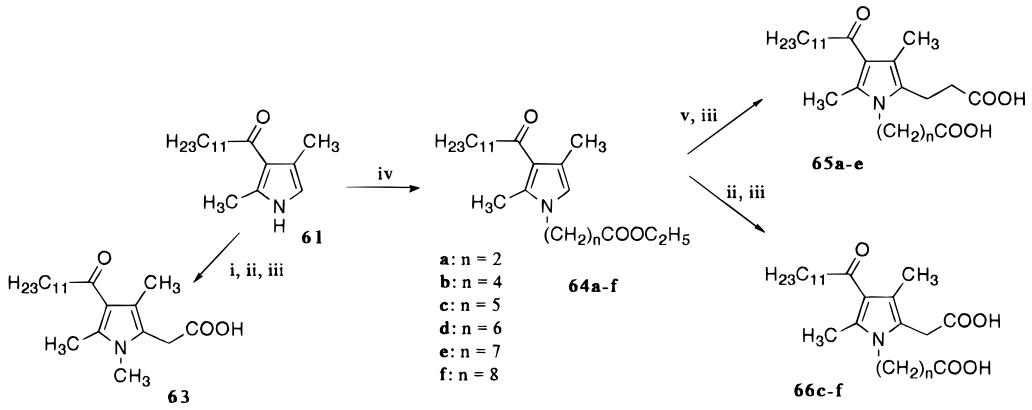
Unfortunately, the most active dicarboxylic acid **46** exhibited a high cytotoxicity (54% cell lysis at 33 μM). However, this cell lytic potency disappeared when reducing the chain length of the 4-acyl residue of **46** from 18 to 12 carbons. Since the afforded compound **65c** (IC_{50}: 3.4 μM) (Table 4) was about as active as **46** (IC_{50}: 3.2 μM), it can be assumed that perturbation of the physicochemical properties of the cell membrane, which may lead to cell lysis, and the evaluated inhibition of A23187-induced arachidonic acid release are two

Scheme 5[a]



[a] (i) 1-Bromoalkane or benzyl bromide or 4-substituted benzyl bromide/chloride, $(C_4H_9)_4N^+Br^-$, 50% aqueous NaOH or powdered NaOH, Et_2O, or $Et_2O-CH_2Cl_2$; in case of **42**−**43**: 6-bromohexanenitrile or ethyl 6-bromohexanoate, *t*-BuOK, DMSO; (ii) ethyl diazoacetate, Cu^0, toluene; (iii) aqueous KOH, EtOH; (iv) methyl acrylate, $BF_3{\cdot}Et_2O$, nitrobenzene; (v) 1,6-dibromohexane, $(C_4H_9)_4N^+Br^-$, 50% aqueous NaOH, Et_2O; (vi) silver acetate, DMSO; (vii) benzyl acrylate, $BF_3{\cdot}Et_2O$, nitrobenzene; (viii) aqueous dimethylamine, DMSO; (ix) H_2, Pd/C, THF, EtOH.

Scheme 6[a]

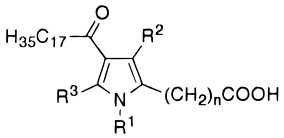


[a] (i) Methyl *p*-toluenesulfonate, $(C_4H_9)_4N^+Br^-$, 50% aqueous NaOH, Et_2O, CH_2Cl_2; (ii) ethyl diazoacetate, Cu^0, toluene; (iii) aqueous KOH, EtOH; (iv) ethyl *ω*-bromoalkanoate, *t*-BuOK, DMSO; (v) methyl acrylate, $BF_3{\cdot}Et_2O$, CH_2Cl_2.

distinct properties of the compounds. So these findings indicate that the pyrroles affect the activity of $cPLA_2$ more likely by a specific interaction with the enzyme than by an unspecific perturbation or disintegration of the cell membrane.

Finally, we varied the bulk of the 1-alkanoic acid substituent of 3-(4-dodecanoyl-3,5-dimethylpyrrol-2-yl)-propionic acid (**62**)[13] and (4-dodecanoyl-3,5-dimethylpyrrol-2-yl)acetic acid (**63**) (Table 4). When the carboxylate chain exceeded a certain length, in both cases compounds were obtained which were about 3−4-fold more active (IC_{50}: 3−4 μM) than the corresponding 1-methylated derivatives **62** (IC_{50}: 13 μM)[13] and **63** (IC_{50}: 11 μM), respectively. However, also some differences between the propionic acid derivatives (**65a**−**e**) and the acetic acid derivatives (**66c**−**f**) were noticeable. The propionic acid **1** lost its inhibitory potency when the 1-methyl group was replaced by a C_6-residue (**34d**)

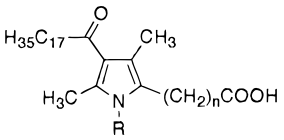
Table 1. *In Vitro* Inhibition of Platelet $cPLA_2$



compd	R^1	R^2	R^3	n	cell lysis at 33 μM (%)	IC_{50} (μM)[a]
1	CH_3	CH_3	CH_3	2	0	13
4	CH_3	CH_3	CH_3	1	0	10
6a	CH_3	H	H	2	0	14
8a	CH_3	H	H	1	0	15
11	benzyl	CH_3	CH_3	1	32	7
14	CH_3	benzyl	CH_3	1	22	10
18	CH_3	CH_3	benzyl	1	0	12
20	$C_{12}H_{25}$	CH_3	CH_3	1	0	Act[b]
23	CH_3	$C_{12}H_{25}$	CH_3	1	0	Act[b]
26	CH_3	CH_3	$C_{12}H_{25}$	1	0	Act[b]
29	benzyl	benzyl	CH_3	1	24	Act[c]
Wy-48,489 (**2**)					0	13
$AACOCF_3$ (**3**)					31	11

[a] IC_{50} values are the means of at least two independent determinations. Errors are within ±20%. [b] Act: 1.5-fold activation of arachidonic acid release at 33 μM. [c] Act: 1.3-fold activation of arachidonic acid release at 10 μM.

Table 2. *In Vitro* Inhibition of Platelet $cPLA_2$



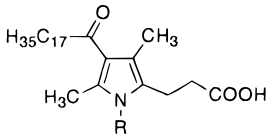
compd	R	*n*	cell lysis at 33 μM (%)	IC_{50} (μM)[a]
32a	C_2H_5	1	10	9
32b	C_3H_7	1	34	8
32d	C_6H_{13}	1	37	>10[b]
32e	C_7H_{15}	1	19	NA[c]
33	$CH_2C_6H_4(4\text{-}CH_3)$	1	29	9
34a	C_2H_5	2	0	11
34b	C_3H_7	2	0	11
34c	C_5H_{11}	2	13	10
34d	C_6H_{13}	2	10	NA[d]
35	$CH_2C_6H_5$	2	19	12
36	$CH_2C_6H_4(4\text{-}CH_3)$	2	14	NA[d]

[a] IC_{50} values are the means of at least two independent determinations. Errors are within ±20%. [b] 45% inhibition at 10μM. [c] NA: not active at 10 μM. [d] NA: not active at 20 μM.

(Table 2). A maximal active dicarboxylic acid was already obtained with an 1-alkanoic acid substituent having one carbon less (**65b**) (Table 4). On the contrary, to attain a compound with an IC_{50} of 3−4 μM, in case of the acetic acids **66c**−**f** the length of the carboxylic acid residue in position 1 had to exceed the length of the 1-heptyl chain, whose introduction had led to the loss of activity (**32e**), by one carbon (**66e**). The reasons for these differences remain to be elucidated.

Although several inhibitors of $cPLA_2$ have been described in the literature,[9−12] little is known about the way these substances affect the enzyme activity. For $AACOCF_3$ (**3**) a direct interaction with the active site of the enzyme was demonstrated by NMR experiments and a crude model for the structure of an enzyme−inhibitor complex was postulated.[12] On basis of this, of a model for the catalytic mechanism of the $cPLA_2$[1] and of the inhibition data for several indole-2-carboxylic acids,[33] we have proposed a hypothesis in which manner our $cPLA_2$ inhibitor 1-(7-carboxyheptyl)-3-dodecanoylindole-2-carboxylic acid[33,34] (IC_{50}: 1.6 μM) might be bound to the active site of the enzyme (Figure 1).

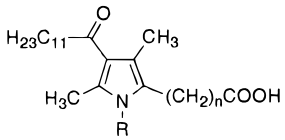
Table 3. *In Vitro* Inhibition of Platelet cPLA



compd	R	cell lysis at 33 μM (%)	$cPLA_2$ inhibition at 3.3 μM (%)
34c	C_5H_{11}	13	23
34d	C_6H_{13}	10	NA[a]
35	$CH_2C_6H_5$	19	20
36	$CH_2C_6H_4(4\text{-}CH_3)$	14	NA[a]
39	$(CH_2)_6OH$	0	20
41	$(CH_2)_6N(CH_3)_2$	0	33
45	$(CH_2)_5CN$	39	40
46	$(CH_2)_5COOH$	54	52[b]
47	$(CH_2)_5CON(CH_3)_2$	67	38
53	$CH_2C_6H_4(4\text{-}CF_3)$	13	NA[a]
54	$CH_2C_6H_4(4\text{-}Cl)$	13	NA[a]
55	$CH_2C_6H_4(4\text{-}OCH_3)$	12	31
56	$CH_2C_6H_4(4\text{-}COOH)$	57	47[c]
57	$CH_2C_6H_4(4\text{-}CN)$	26	15
58	$CH_2C_6H_4(4\text{-}CONH_2)$	0	44
59	$CH_2C_6H_4(4\text{-}OH)$	0	30
60	$CH_2C_6H_4[4\text{-}CON(CH_3)_2]$	42	34

[a] NA: 0% inhibition at 3.3 and 10 μM. [b] IC_{50}: 3.2 μM. [c] IC_{50}: 3.5 μM.

Table 4. *In Vitro* Inhibition of Platelet $cPLA_2$



compd	R	*n*	cell lysis at 33 μM (%)	IC_{50} (μM)[a]
62	CH_3	2	0	13
63	CH_3	1	0	11
65a	$(CH_2)_2COOH$	2	0	8
65b	$(CH_2)_4COOH$	2	0	3.9
65c	$(CH_2)_5COOH$	2	0	3.4
65d	$(CH_2)_6COOH$	2	0	3.8
65e	$(CH_2)_7COOH$	2	0	3.6
66c	$(CH_2)_5COOH$	1	0	11
66d	$(CH_2)_6COOH$	1	0	5.6
66e	$(CH_2)_7COOH$	1	0	3.7
66f	$(CH_2)_8COOH$	1	21	3.3

[a] IC_{50} values are the means of at least two independent determinations. Errors are within ±20%.

It may be possible that the pyrroles bind to the enzyme in a similar way as the indoles, since structure−activity relationship investigations of acylindoles and acylpyrroles showed several parallels. Therefore:

1. In both substance classes enzyme inhibition reached a maximum when the acyl residue had a length of 12 or more carbons.[13,33]

2. Esterification of the carboxylic acid in position 2 of the indole or of the alkanoic acid in position 2 of the pyrrole led to a loss of activity.[13,33]

3. Reduction of the carbonyl function of the acyl chains of indole or pyrrole to a methylene resulted in inactive compounds.[13,33]

4. The inhibitory potency was lost when a longer alkyl chain was introduced in position 1 of the indole or pyrrole (hexyl in case of the pyrrolylpropionic acids, heptyl in case of the pyrrolylacetic acids, and octyl in

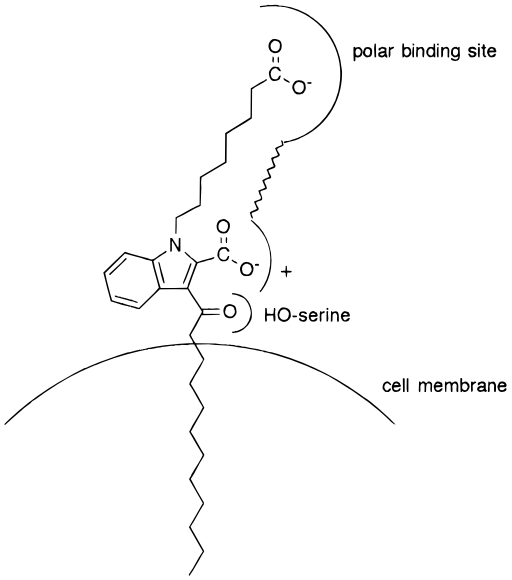


Figure 1. Model for the interaction of 1-(7-carboxyheptyl)-3-dodecanoylindole-2-carboxylic acid with the $cPLA_2$.[33]

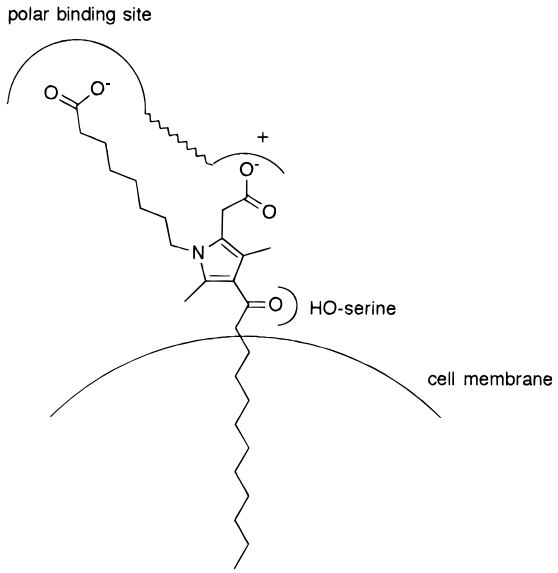


Figure 2. Model for the interaction of 6-[2-(carboxymethyl)-4-dodecanoyl-3,5-dimethylpyrrol-1-yl]octanoic acid (**66e**) with the $cPLA_2$.

case of the indole-2-carboxylic acids[33]), so enzyme inhibition was lost in each case when the sum of the carbons of the alkyl chain, of the carboxylic acid residue, and of the two atoms of the heterocycle to which these were affixed exceeded the value of 10. Introduction of a carboxylic acid functionality at the end of the 1-alkyl chain, however, restored or even elevated inhibitory potency.

However, there is one striking difference in the structure of the indoles and the pyrroles which does not allow that the pyrroles reach all the proposed binding sites of the enzyme when they are arranged as shown in Figure 1: The distance between the carbonyl of the acyl group and the carboxylic acid moiety in position 2 is much greater in case of the pyrroles than in case of the indoles. Nevertheless, in our opinion the model for the indoles (Figure 1) can be expanded to the pyrroles (*e.g.* **66e**) when making the following assumption. The enzyme has at least one flexible part, which can shift away from the rest of the enzyme bound to the membrane interface. The binding sites for the two carboxylic acid functionalities could lie on this flexible region. For binding of the pyrroledicarboxylic acids it tilts about 70° away from the position it occupies when interacting with the indoledicarboxylic acids (Figure 2).

As indicated in the model by the waved line, nothing can be said about the distance between the binding sites for the two carboxylic acid functions. In order to get informations about this, some more derivatives with conformationally constrained carboxylic acid side chains in position 1 of the pyrrole shall be synthesized.

Experimental Section

Chemistry. All organic extracts were dried over Na_2SO_4. Melting points were determined in open capillary tubes with a Büchi melting point apparatus and are uncorrected. ^{1}H nuclear magnetic resonance spectra were recorded on a JEOL JNM-GX 400 spectrometer (400 MHz); chemical shifts (δ) are expressed in ppm, relative to internal tetramethylsilane. Mass spectra were obtained on a Varian CH7 apparatus; electron beam ionization at 70 eV (EI) was applied. Elemental analyses were determined on a Heraeus CHN Rapid instrument and were within ±0.4%. Column chromatography was performed with Kieselgel 60 (70−230 mesh) silica gel (Merck, Darmstadt).

The starting materials were obtained from commercial suppliers (Aldrich, Steinheim; Lancaster Synthesis, Mühlheim) and used without further purification or they were synthesized in the same or a similar manner as described in the literature cited. Reference compounds for the biological assays: arachidonyl trifluoromethyl ketone was purchased from Biomol (Hamburg); (*S*)-*N*-hexadecylpyrrolidine-2-carboxamide was synthesized by known procedures.[9]

3-(1-Methyl-4-octadecanoylpyrrol-2-yl)propionic Acid (6a). A solution of ethyl 3-(1-methylpyrrol-2-yl)acrylate[14] (**5**) (448 mg, 2.5 mmol) in a mixture of THF (5 mL) and EtOH (5 mL) was treated with a catalytic amount of 10% Pd/C, and the mixture was hydrogenated at atmospheric pressure for 1 h. After addition of kieselguhr, the mixture was filtered and the solvent evaporated. The residue was dissolved in dry benzene (6 mL) and added to the refluxing solution of *N*,*N*-dimethyloctadecanamide (779 mg, 2.5 mmol) and $POCl_3$ (368 mg, 2.4 mmol) in dry benzene (10 mL). The resulting solution was refluxed for 2 h. After addition of the solution of sodium acetate (2 g) in water (8 mL), the mixture was heated to reflux for a further 15 min with vigorous stirring. The reaction mixture was cooled, diluted with water, and extracted twice with CH_2Cl_2. The organic phases were dried and evaporated. The residue was chromatographed on silica gel. Elution with petroleum ether−ethyl acetate (9 + 1) first gave ethyl 3-(1-methyl-5-octadecanoylpyrrol-2-yl)propionate (yield 47%) and then ethyl 3-(1-methyl-4-octadecanoylpyrrol-2-yl)propionate (yield 33%). To the latter compound were added EtOH (15 mL) and 10% aqueous KOH (5 mL), and the resulting mixture was refluxed for 15 min, cooled, diluted with water, acidified with dilute HCl, and extracted with Et_2O. The organic phase was washed with dilute HCl and dried, and most of the solvent was removed *in vacuo*. After addition of petroleum ether, **6a** precipitated: yield 24%; mp 101−102 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.15−1.41 (m, 28H), 1.67 (quint, 2H), 2.66 (t, 2H), 2.74 (t, 2H), 2.86 (t, 2H), 3.59 (s, 3H), 6.35 (s, 1H), 7.20 (s, 1H). Anal. ($C_{26}H_{45}NO_3$) C, H, N.

3-(1-Methyl-5-octadecanoylpyrrol-2-yl)propionic Acid (6b). Ethyl 3-(1-methyl-5-octadecanoylpyrrol-2-yl)propionate (270 mg, 0.60 mmol) was saponified with KOH using a method similar to that for the synthesis of **6a**: yield 75%; mp 108−110 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.15−1.41 (m, 28H), 1.68 (quint, 2H), 2.70−2.76 (m, 4H), 2.92 (t, 2H), 3.89 (s, 3H), 5.96 (d, 1H, J = 4 Hz), 6.92 (d, 1H, J = 4 Hz).

(1-Methyl-4-octadecanoylpyrrol-2-yl)acetic Acid (8a). Ethyl (1-methylpyrrol-2-yl)acetate[15] (**7**) (167 mg, 1 mmol) was acylated with *N*,*N*-dimethyloctadecanamide−$POCl_3$ analogously to the procedure described for **6a**. Chromatography on silica gel first gave ethyl (1-methyl-5-octadecanoylpyrrol-2-

yl)acetate (yield 23%) and then ethyl 3-(1-methyl-4-octadecanoylpyrrol-2-yl)acetate (yield 18%). The latter intermediate was saponified with KOH using the same method as for the synthesis of **6a**: yield 29%; mp 91−93 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.15−1.41 (m, 28H), 1.67 (quint, 2H), 2.67 (t, 2H), 3.62 (s, 3H), 3.66 (s, 2H), 6.52 (s, 1H), 7.24 (s, 1H). Anal. ($C_{25}H_{43}NO_3$) C, H, N.

(1-Methyl-5-octadecanoylpyrrol-2-yl)acetic Acid (8b). Ethyl (1-methyl-5-octadecanoylpyrrol-2-yl)acetate (100 mg, 0.23 mmol) was saponified with KOH using the same method as for the synthesis of **6a**: yield 65%; mp 103−104 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.15−1.40 (m, 28H), 1.68 (quint, 2H), 2.74 (t, 2H), 3.71 (s, 2H), 3.89 (s, 3H), 6.11 (d, 1H, J = 4 Hz), 6.94 (d, 1H, J = 4 Hz).

1-Benzyl-2,4-dimethyl-3-octadecanoylpyrrole (10). The mixture of 2,4-dimethyl-3-octadecanoylpyrrole (**9**)[8] (362 mg, 1 mmol), benzyl bromide (188 mg, 1.1 mmol), tetrabutylammonium bromide (161 mg, 0.5 mmol), Et_2O (10 mL), CH_2Cl_2 (5 mL), and 50% aqueous NaOH (5 mL) was refluxed for 1.5 h with vigorous stirring. The reaction mixture was cooled and the organic phase separated. The aqueous layer was extracted with Et_2O−CH_2Cl_2 (3 + 1), and the combined organic phases were dried and evaporated to dryness. The residue was chromatographed on silica gel with petroleum ether−ethyl acetate (14 + 1) and the obtained **10** precipitated from MeOH: yield 54%; mp 61−63 °C; EI-MS m/e 451 (M^+); ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.16−1.39 (m, 28H), 1.69 (quint, 2H), 2.27 (s, 3H), 2.41 (s, 3H), 2.72 (t, 2H), 4.98 (s, 2H), 6.34 (s, 1H), 7.01 (d, 2H), 7.26−7.34 (m, 3H).

(1-Benzyl-3,5-dimethyl-4-octadecanoylpyrrol-2-yl)acetic Acid (11). The solution of **10** (226 mg, 0.5 mmol) in dry toluene was treated with the solution of ethyl diazoacetate (86 mg, 0.75 mmol) in dry toluene (3 mL) and with powdered copper (about 0.4 g) in an oil bath at 115−120 °C until development of nitrogen ceased (about 15 min). The cooled reaction mixture was chromatographed on silica gel with petroleum ether−ethyl acetate, (1) 19 + 1 and (2) 9 + 1. The obtained ethyl ester of **11** was saponified with KOH using the same method as described for **6a**: yield 17%; mp 115−117 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.16−1.40 (m, 28H), 1.69 (quint, 2H), 2.23 (s, 3H), 2.42 (s, 3H), 2.74 (t, 2H), 3.48 (s, 2H), 5.13 (s, 2H), 6.86 (d, 2H), 7.19−7.31 (m, 3H). Anal. ($C_{33}H_{51}NO_3$) C, H, N.

4-Benzyl-1,2-dimethylpyrrole (13). The mixture of 4-benzoyl-1-methylpyrrole-2-carbaldehyde[16] (**12**) (4.26 g, 20 mmol), triethylene glycol (35 mL), and hydrazine hydrate 80% (7 mL) was refluxed for 1 h. The reaction mixture was allowed to cool to room temperature. Then KOH pellets (8.5 g) were added, the reflux condensor was replaced by a distilling link, and the mixture was heated in an oil bath at 210−220 °C until the development of nitrogen ceased (about 45 min). After cooling to room temperature, the reaction mixture and the distillate were combined, diluted with water, and extracted with Et_2O. The organic layer was washed with dilute HCl and dried. Evaporation of the solvent gave **13** as oil: yield 81%; ^{1}H-NMR ($CDCl_3$) δ 2.16 (s, 3H), 3.44 (s, 3H), 3.76 (s, 2H), 5.72 (s, 1H), 6.26 (s, 1H), 7.15−7.29 (m, 5H).

(3-Benzyl-1,5-dimethyl-4-octadecanoylpyrrol-2-yl)acetic Acid (14). **13** (0.93 g, 5 mmol) was reacted with ethyl diazoacetate in a similar way as described for the synthesis of **11**. The obtained intermediate was acylated with *N*,*N*-dimethyloctadecanamide−$POCl_3$ and then saponified with KOH analogously as described for **6a**: yield 2%; mp 90−92 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.05−1.34 (m, 28H), 1.50 (quint, 2H), 2.49 (s, 3H), 2.54 (t, 2H), 3.48 (s, 3H), 3.61 (s, 2H), 4.09 (s, 2H), 7.09 (d, 2H), 7.11 (t, 1H), 7.21 (t, 2H). Anal. ($C_{33}H_{51}NO_3$) C, H, N.

5-Benzoyl-1-methylpyrrole-3-carbaldehyde (16). The stirred mixture of 2-benzoyl-1-methylpyrrole[17] (**15**) (2.04 g, 11 mmol), $AlCl_3$ (4.40 g, 33 mmol), and dry CH_2Cl_2 (20 mL) was treated in an ice bath with dichloromethoxymethane (1.49 g, 13 mmol) as fast as the exothermic reaction allowed. The resulting mixture was stirred for 15 min, poured onto ice/water, and extracted twice with CH_2Cl_2. The organic phases were dried, the solvent was evaporated, the residue was chromatographed on silica gel with petroleum ether−ethyl acetate, (1) 8 + 2 and (2) 7 + 3, and the product **16** precipitated from petroleum ether: yield 26%; mp 110−112 °C; EI-MS m/e 213 (M^+); ^{1}H-NMR ($CDCl_3$) δ 4.09 (s, 3H), 7.17 (d, 1H), 7.49 (t, 2H), 7.52 (d, 1H), 7.59 (t, 1H), 7.82 (d, 2H), 9.79 (s, 1H).

2-Benzyl-1,4-dimethylpyrrole (17). The synthesis started from **16** (0.60 g, 2.8 mmol) using an analogous method as for the preparation of **13**. The product was afforded as an oil: yield 93%; ^{1}H-NMR ($CDCl_3$) δ 2.06 (s, 3H), 3.37 (s, 3H), 3.89 (s, 2H), 5.71 (s, 1H), 6.34 (s, 1H), 7.16 (d, 2H), 7.20 (t, 1H), 7.29 (t, 2H).

(5-Benzyl-1,3-dimethyl-4-octadecanoylpyrrol-2-yl)acetic Acid (18). The synthesis started from **17** (278 mg, 1.5 mmol) using a method analogous to that for the preparation of **14**: yield 10%; mp 93−95 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.13−1.34 (m, 28H), 1.64 (quint, 2H), 2.27 (s, 3H), 2.71 (t, 2H), 3.33 (s, 3H), 3.63 (s, 2H), 4.37 (s, 2H), 7.07 (d, 2H), 7.16 (t, 1H), 7.24 (t, 2H). Anal. ($C_{33}H_{51}NO_3$) C, H, N.

1-Dodecyl-2,4-dimethyl-3-octadecanoylpyrrole (19). The mixture of 2,4-dimethyl-3-octadecanoylpyrrole (**9**)[8] (323 mg, 2 mmol), 1-bromododecane (548 mg, 2.2 mmol), tetrabutylammonium bromide (322 mg, 1 mmol), Et_2O (30 mL), and 50% aqueous NaOH was refluxed for 7 h with vigorous stirring. The reaction mixture was cooled and the organic phase separated. The aqueous layer was extracted with Et_2O, and the combined organic phases were dried and evaporated to dryness. The residue was chromatographed on silica gel with petroleum ether−ethyl acetate (14 + 1), and the obtained **19** was precipitated from MeOH: yield 61%; mp 45−46 °C; EI-MS m/e 530 (M^+); ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.18−1.42 (m, 46H), 1.63−1.71 (m, 4H), 2.25 (s, 3H), 2.46 (s, 3H), 2.69 (t, 2H), 3.72 (t, 2H), 6.28 (s, 1H).

(1-Dodecyl-3,5-dimethyl-4-octadecanoylpyrrol-2-yl)acetic Acid (20). The synthesis started from **19** using the same method as for the preparation of **11** (deviation: for chromatography of the ester intermediate petroleum ether−ethyl acetate, 17 + 1, was used as eluent): yield 24%; mp 65−67 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.18−1.42 (m, 46H), 1.52−1.63 (m, 2H), 1.67 (quint, 2H), 2.22 (s, 3H), 2.47 (s, 3H), 2.70 (t, 2H), 3.61 (s, 2H), 3.79 (t, 2H). Anal. ($C_{38}H_{69}NO_3$) C, H, N.

4-Dodecanoyl-1-methylpyrrole-2-carbaldehyde (22). The solution of oxalyl chloride (10.5 g, 82.5 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise to a stirred solution of DMF (6.0 g, 82.5 mmol) in dry CH_2Cl_2 (25 mL) at 0 °C during 20 min. Then the mixture was stirred at room temperature for 15 min, cooled again (ice bath), and treated with the solution of 1-methylpyrrole (**21**) (5.1 g, 63 mmol) in dry CH_2Cl_2 (15 mL) during 15 min. After the mixture was stirred at room temperature for another 15 min, $AlCl_3$ (9.7 g, mmol) and dodecanoyl chloride (16.0 g, 73 mmol) were added and stirring was continued for 21 h at room temperature. To the cooled mixture (5 °C) was added carefully the solution of 39 g of sodium acetate in 120 mL of water, and the mixture was stirred for 15 min. Then water, dilute NaOH, and Et_2O were added, and stirring was continued for a further 15 min. After NaCl was added, the organic phase was separated, filtered, and dried and the solvent evaporated. Chromatography of the residue on silica gel with petroleum ether−ethyl acetate (9 + 1) gave the product as solid: yield 5%; mp 37−38 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.16−1.39 (m, 16H), 1.70 (quint, 2H), 2.74 (t, 2H), 3.99 (s, 3H), 7.31 (s, 1H), 7.45 (s, 1H), 9.61 (s, 1H).

(3-Dodecyl-1,5-dimethyl-4-octadecanoylpyrrol-2-yl)acetic Acid (23). **22** (0.87 g, 3 mmol) was reduced to 4-dodecyl-1,2-dimethylpyrrole, applying a method similar to the synthesis of **13**. The obtained intermediate was reacted with ethyl diazoacetate in a similar way as described for the synthesis of **11** followed by acylation with *N*,*N*-dimethyloctadecanamide−$POCl_3$ and saponification with KOH analogously as described for the synthesis of **6a**: yield 0.6%; mp 100−102 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.11−1.71 (m, 50H), 2.44 (s, 3H), 2.60 (t, 2H), 2.70 (t, 2H), 3.44 (s, 3H), 3.63 (s, 2H). Anal. ($C_{38}H_{69}NO_3$) C, H, N.

2-Dodecanoyl-1-methylpyrrole (24). 1-Methylpyrrole (**21**) (2.43 g, 30 mmol) was acylated with *N*,*N*-dimethyldodecanamide−$POCl_3$ in an analogous way as described for the synthesis of **6a**. The crude product was chromatographed on

silica gel with petroleum ether−ethyl acetate, (1) 9 + 1 and (2) 6 + 4, to give **24** as oil: yield 46%; EI-MS *m/e* 263 (M^+); ^{1}H-NMR (DMSO-d_6) δ 0.86 (t, 3H), 1.10−1.35 (s, 16H), 1.56 (quint, 2H), 2.71 (t, 2H), 3.84 (s, 3H), 6.08 (t, 1H), 7.03 (d, 1H), 7.08 (1H).

5-Dodecanoyl-1-methylpyrrole-3-carbaldehyde (25). 24 (2.1 g, 8 mmol) was reacted with dichloromethoxymethane−$AlCl_3$ in a similar way as described for the preparation of **16** to give **25** as solid: yield 32%; mp 53−54 °C; EI-MS *m/e* 291 (M^+); ^{1}H-NMR (DMSO-d_6) 0.85 (t, 3H), 1.14−1.36 (m, 16H), 1.57 (quint, 2H), 2.81 (t, 2H), 3.90 (s, 3H), 7.50 (s, 1H), 7.90 (s, 1H), 9.72 (s, 1H).

(5-Dodecyl-1,3-dimethyl-4-octadecanoylpyrrol-2-yl)acetic Acid (26). The synthesis started from **25** (0.58 g, 2 mmol) using the same methods as for the synthesis of **23**. The product was precipitated from MeOH: yield 5%; mp 95−97 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.13−1.43 (m, 46H), 1.51 (m, 2H), 1.67 (quint, 2H), 2.23 (s, 3H), 2.70 (t, 2H), 2.85 (t, 2H), 3.46 (s, 3H), 3.63 (s, 2H). Anal. ($C_{38}H_{69}NO_3$) C, H, N.

1,4-Dibenzyl-2-methylpyrrole (28). The mixture of **27**[19] (1.6 g, 8 mmol), benzyl bromide (1.5 g, 8.8 mmol), tetrabutylammonium bromide (258 mg, 0.8 mmol), Et_2O (40 mL), $CHCl_3$ (60 mL), and powdered NaOH (800 mg, 20 mmol) was stirred at room temperature. After 3 h water (5 drops) was added and the mixture was stirred for a further 2 h. Then it was filtered, the filter cake was washed with $CHCl_3$, and the filtrates were dried and concentrated. The residue was chromatographed on silica gel with petroleum ether−ethyl acetate (9 + 1). An aliquot (0.49 g, 1.7 mmol) of the obtained 1-benzyl-4-benzoylpyrrole-2-carbaldehyde (yield: 1.25 g) was treated with hydrazine hydrate in an analogous way as described for the preparation of **13** to yield **28** as oil: yield 66%; ^{1}H-NMR ($CDCl_3$) δ 2.08 (s, 3H), 3.78 (s, 2H), 4.94 (s, 2H), 5.77 (s, 1H), 6.37 (s, 1H), 6.99 (d, 2H), 7.11−7.32 (m, 8H).

(1,3-Dibenzyl-5-methyl-4-octadecanoylpyrrol-2-yl)acetic Acid (29). The solution of **28** (260 mg, 1 mmol) and octadecanoyl chloride (364 mg, 1.2 mmol) in dry CH_2Cl_2 (10 mL) was treated under stirring at room temperature with $AlCl_3$ (173 mg, 1.3 mmol). After 15 min water was added and the mixture was extracted with Et_2O. The organic phase was washed with dilute NaOH, dried, and concentrated. The residue was chromatographed on silica gel with petroleum ether−ethyl acetate (19 + 1), first yielding 1,3-dibenzyl-5-methyl-2-octadecanoylpyrrole (25%) and then 1,4-dibenzyl-2-methyl-3-octadecanoylpyrrole (19%). The latter compound was dissolved in dry toluene (3 mL) and treated with the solution of ethyl diazoacetate (40 mg, 0.35 mmol) in dry toluene (1 mL) and with powdered copper (about 0.4 g) in an oil bath at 115−120 °C until development of nitrogen ceased (about 10 min). The addition of ethyl diazoacetate and copper powder was repeated in the same way. After 30 min the reaction mixture was cooled and chromatographed on silica gel with petroleum ether−ethyl acetate (9 + 1). The ester intermediate was saponified with KOH similarly as described for the synthesis of **6a** (deviation: reaction time 30 min). The product was precipitated from MeOH−water: yield 3%; mp 104−105 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 6H), 1.08−1.34 (m, 28H), 1.52 (quint, 2H), 2.44 (s, 3H), 2.57 (t, 2H), 3.47 (s, 2H), 4.13 (s, 2H), 5.17 (s, 2H), 6.99 (d, 2H), 7.09−7.34 (m, 8H). Anal. ($C_{39}H_{55}NO_3$) C, H, N.

Compounds **30a**−**e** were synthesized from **9**[8] using the appropriate 1-bromoalkanes, utilizing the synthetic procedure described for the synthesis of **19**.

1-Ethyl-2,4-dimethyl-3-octadecanoylpyrrole (30a): yield 33%; mp 49−50 °C.

2,4-Dimethyl-3-octadecanoyl-1-propylpyrrole (30b): yield 30%; mp 54−55 °C.

2,4-Dimethyl-3-octadecanoyl-1-pentylpyrrole (30c): yield 25%; mp 49−50 °C.

1-Hexyl-2,4-dimethyl-3-octadecanoylpyrrole (30d): yield 30%; mp 40−42 °C.

1-Heptyl-2,4-dimethyl-3-octadecanoylpyrrole (30e): yield 54%; mp 47−48 °C.

2,4-Dimethyl-1-(4-methylbenzyl)-3-octadecanoylpyrrole (31). Compound **31** was synthesized analogously to **10**: yield 39%; mp 50−51 °C.

The acetic acid derivatives **32a**,**b**,**d**,**e** and **33** were prepared from the appropriately substituted pyrroles by using a method similar to that described for **11**.

(1-Ethyl-3,5-dimethyl-4-octadecanoylpyrrol-2-yl)acetic acid (32a): yield 29%; mp 79−81 °C. Anal. ($C_{28}H_{49}NO_3$) C, H, N.

(3,5-Dimethyl-4-octadecanoyl-1-propylpyrrol-2-yl)acetic acid (32b): yield 22%; mp 95−97 °C. Anal. ($C_{29}H_{51}NO_3$) C, H, N.

(1-Hexyl-3,5-dimethyl-4-octadecanoylpyrrol-2-yl)acetic acid (32d): yield 22%; mp 83−84 °C. Anal. ($C_{32}H_{57}NO_3$) C, H, N.

(1-Heptyl-3,5-dimethyl-4-octadecanoylpyrrol-2-yl)acetic acid (32e): yield 8%; mp 75−76 °C. Anal. ($C_{33}H_{59}NO_3$) C, H, N.

[3,5-Dimethyl-1-(4-methylbenzyl)-4-octadecanoylpyrrol-2-yl]acetic acid (33): yield 28%; mp 90−91 °C. Anal. ($C_{34}H_{53}NO_3$) C, H, N.

General Procedure for the Synthesis of 1-Substituted 3-(3,5-Dimethyl-4-octadecanoylpyrrol-2-yl)propionic Acids (34a−d, 35, 36). The solution of the appropriate 1-substituted 2,4-dimethyl-3-octadecanoylpyrrole (**30a-d**,**10**,**31**) (0.25 mmol) and methyl acrylate (0.12 mL) in dry nitrobenzene (3 mL) was treated with $BF_3{\cdot}Et_2O$ (0.05 mL). After 3 days water was added and the mixture was extracted twice with Et_2O. The organic phases were dried and evaporated. The residue was chromatographed on silica gel with petroleum ether−ethyl acetate, (1) 19 + 1 and (2) 8 + 2, and the resulting methyl ester intermediate hydrolyzed with KOH as described for **6a**.

3-(1-Ethyl-3,5-dimethyl-4-octadecanoylpyrrol-2-yl)propionic acid (34a): yield 33%; mp 96−97 °C. Anal. ($C_{29}H_{51}NO_3$) C, H, N.

3-(3,5-Dimethyl-4-octadecanoyl-1-propylpyrrol-2-yl)-propionic acid (34b): yield 38%; mp 69−70 °C. Anal. ($C_{30}H_{53}NO_3$) C, H, N.

3-(3,5-Dimethyl-4-octadecanoyl-1-pentylpyrrol-2-yl)-propionic acid (34c): yield 36%; mp 61−62 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 0.97 (t, 3H), 1.16−1.42 (m, 32H), 1.54−1.70 (m, 4H), 2.21 (s, 3H), 2.46 (s, 3H), 2.48−2.52 (m, 2H), 2.69 (t, 2H), 2.88−2.92 (m, 2H), 3.77 (t, 2H). Anal. ($C_{32}H_{57}NO_3$) C, H, N.

3-(1-Hexyl-3,5-dimethyl-4-octadecanoylpyrrol-2-yl)propionic acid (34d): yield 27%; mp 59−61 °C. Anal. ($C_{33}H_{59}NO_3$) C, H, N.

3-(1-Benzyl-3,5-dimethyl-4-octadecanoylpyrrol-2-yl)-propionic acid (35): yield 27%; mp 97−99 °C. Anal. ($C_{34}H_{53}NO_3$) C, H, N.

3-[3,5-Dimethyl-1-(4-methylbenzyl)-4-octadecanoylpyrrol-2-yl]propionic acid (36): yield 30%; mp 99−100 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.14−1.39 (m, 28H), 1.69 (quint, 2H), 2.24 (s, 3H), 2.30−2.34 (m, 2H), 2.31 (s, 3H, CH_3), 2.39 (s, 3H), 2.73 (t, 2H), 2.80−2.84 (m, 2H), 5.03 (s, 2H), 6.75 (d, 2H), 7.10 (d, 2H). Anal. ($C_{35}H_{55}NO_3$) C, H, N.

1-(6-Bromohexyl)-2,4-dimethyl-3-octadecanoylpyrrole (37). The mixture of **9**[8] (542 mg, 1.5 mmol), 1,6-dibromohexane (2.93 g, 12 mmol), tetrabutylammonium bromide (192 mg, 0.6 mmol), Et_2O (30 mL), and 50% aqueous NaOH (15 mL) was refluxed for 1.5 h with vigorous stirring. The reaction mixture was cooled and the organic phase separated. The aqueous layer was extracted with Et_2O, and the combined organic phases were dried and evaporated to dryness. Chromatography on silica gel with petroleum ether−ethyl acetate (19 + 1) gave **37** as solid: yield 69%; mp 47−48 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.13−1.38 (m, 30H), 1.43−1.50 (m, 2H), 1.63−1.72 (m, 4H), 1.85 (quint, 2H), 2.25 (s, 3H), 2.46 (s, 3H), 2.69 (t, 2H), 3.40 (t, 2H), 3.74 (t, 2H), 6.28 (s, 1H).

Methyl 3-[1-(6-Bromohexyl)-3,5-dimethyl-4-octadecanoylpyrrol-2-yl]propionate (38). The solution of **37** (262 mg, 0.5 mmol) and methyl acrylate (0.26 mL) in dry nitrobenzene (4 mL) was treated with $BF_3{\cdot}Et_2O$ (0.11 mL). After 24 h water was added, and the mixture was extracted with Et_2O. The organic phases were dried and evaporated. The residue was chromatographed on silica gel with petroleum ether−ethyl acetate, (1) 19 + 1 and (2) 9 + 1, to give **38**: yield 68%; mp 47−48 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.16−1.42 (m, 30H),

1.48 (quint, 2H), 1.57−1.72 (m, 4H), 1.87 (quint, 2H), 2.19 (s, 3H), 2.43−2.46 (m, 2H), 2.46 (s, 3H), 2.69 (t, 2H), 2.85−2.89 (m, 2H), 3.41 (t, 2H), 3.70 (s, 3H), 3.77 (t, 2H).

3-[1-(6-Hydroxyhexyl)-3,5-dimethyl-4-octadecanoylpyrrol-2-yl]propionic Acid (39). The mixture of **38** (92 mg, 0.15 mmol), silver acetate (28 mg, 0.17 mmol), and dry DMSO (3 mL) was stirred at 150 °C for 15 min. The mixture was cooled, diluted with water and dilute HCl, and extracted with Et_2O. The organic phase was dried, and the solvent was evaporated. The residue was chromatographed on silica gel with petroleum ether−ethyl acetate, (1) 9 + 1 and (2) 17 + 3. An aliquot (24 mg, 0.04 mmol) of the obtained methyl 3-[1-(6-acetoxyhexyl)-3,5-dimethyl-4-octadecanoylpyrrol-2-yl]propionate (yield 34%, mp 48−50 °C) was hydrolyzed with KOH by using a procedure similar to that described for **6a** (reaction time: 2 h) to give **39** as solid: yield 75%; mp 69−70 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.12−1.47 (m, 32H), 1.55−1.70 (m, 6H), 2.20 (s, 3H), 2.46 (s, 3H), 2.50 (m, 2H), 2.69 (t, 2H), 2.90 (t, 2H), 3.66 (t, 2H), 3.77 (t, 2H). Anal. ($C_{33}H_{59}NO_4$) C, H, N.

Benzyl 3-[1-(6-Bromohexyl)-3,5-dimethyl-4-octadecanoylpyrrol-2-yl]propionate (40). The solution of **37** (525 mg, 1 mmol) and benzyl acrylate (0.90 mL) in dry nitrobenzene (8 mL) was treated with $BF_3 \cdot Et_2O$ (0.22 mL). After 48 h water was added, and the mixture was extracted with Et_2O. The organic phases were dried and evaporated. The residue was chromatographed on silica gel with petroleum ether−ethyl acetate, (1) 19 + 1 and (2) 9 + 1, to give **40** as oil: yield 26%; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.17−1.38 (m, 32H), 1.45 (quint, 2H), 1.57−1.73 (m, 4H), 2.18 (s, 3H), 2.44 (s, 3H), 2.48−2.52 (m, 2H), 2.68 (t, 2H), 2.87−2.91 (m, 2H), 3.39 (t, 2H), 3.74 (m, 2H), 5.12 (s, 2H), 7.28−7.38 (m, 5H).

3-[1-[6-(Dimethylamino)hexyl]-3,5-dimethyl-4-octadecanoylpyrrol-2-yl]propionic Acid (41). The mixture of **40** (82 mg, 0.12 mmol), DMSO (4 mL), and 40% aqueous dimethylamine (1 mL) was refluxed for 15 min. The mixture was cooled, diluted with water and dilute NaOH, and extracted with Et_2O. The organic phase was dried and the solvent evaporated. The residue was chromatographed on silica gel (eluents: (1) petroleum ether−ethyl acetate, 7 + 3, and (2) MeOH). An aliquot (24 mg, 0.04 mmol) of the obtained oily benzyl 3-[1-[6-(dimethylamino)hexyl]-3,5-dimethyl-4-octadecanoylpyrrol-2-yl]propionate (yield 40%) was dissolved in THF (2 mL) and EtOH (2 mL) and treated with a catalytic amount of 10% Pd/C. The mixture was hydrogenated at atmospheric pressure for 1 h. After addition of kieselguhr the mixture was filtered and the solvent evaporated. The residue was dissolved in a small amount of CH_2Cl_2. After addition of petroleum ether, **41** precipitated: yield 58%; mp 45−48 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.16-1.38 (m, 28H), 1.39−1.54 (m, 4H), 1.55−1.71 (m, 4H), 1.79−1.91 (m, 2H), 2.19 (s, 3H), 2.45 (s, 3H), 2.50−2.59 (m, 2H), 2.69 (t, 2H), 2.83 (s, 6H), 2.87−2.95 (m, 2H), 3.03 (t, 2H), 3.78 (t, 2H). Anal. ($C_{35}H_{64}N_2O_3$) C, H, N.

6-(2,4-Dimethyl-3-octadecanoylpyrrol-1-yl)hexanenitrile (42). The mixture of **9**[8] (362 mg, 1 mmol), *t*-BuOK (135 mg, 1.2 mmol), and dry DMSO (3 mL) was heated at 110−120 °C for 10 min. After addition of 6-bromohexanenitrile (211 mg, 1.2 mmol), the mixture was heated for an additional 10 min at the same temperature. After cooling, water and NaCl were added, and the mixture was extracted with Et_2O. The organic phase was dried and the solvent evaporated. The residue was chromatographed on silica gel with petroleum ether−ethyl acetate (17 + 3) to give **42** as solid: yield 67%; mp 60−61 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.18−1.39 (m, 28H), 1.34−1.50 (m, 2H), 1.64−1.75 (m, 6H), 2.25 (s, 3H), 2.35 (t, 2H), 2.46 (s, 3H), 2.70 (t, 2H), 3.77 (t, 2H), 6.28 (s, 1H).

Ethyl 6-(2,4-Dimethyl-3-octadecanoylpyrrol-1-yl)hexanoate (43). **9**[8] was alkylated with ethyl 6-bromohexanoate in a similar way as described for the synthesis of **42**. The product was precipitated from MeOH: yield 46%; mp 46−48 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.10−1.38 (m, 33H), 1.61−1.73 (m, 6H), 2.25 (s, 3H), 2.30 (t, 2H), 2.46 (s, 3H), 2.69 (t, 2H), 3.74 (t, 2H), 4.12 (q, 2H), 6.28 (s, 1H).

6-(2,4-Dimethyl-3-octadecanoylpyrrol-1-yl)-*N*,*N*-dimethylhexanamide (44). **43** (200 mg, 0.40 mmol) was hydrolyzed with KOH in a similar way as described for **6a** (reaction time: 1.5 h). An aliquot (119 mg, 0.25 mmol) of the obtained 6-(2,4-dimethyl-3-octadecanoylpyrrol-1-yl)hexanoic acid (yield 68%, mp 72−73 °C) was dissolved in dry CH_2Cl_2 (5 mL) and treated with *N*,*N*′-carbonyldiimidazole (227 mg, 1.4 mmol). After being stirred at room temperature for 1 h, the mixture was cooled (5 °C). Then 40% aqueos dimethylamine (2 mL) was added, and the resulting mixture was vigorously stirred for 1 h. The mixture was diluted with water and extracted with Et_2O. The organic phase was dried and the solvent evaporated. The residue was chromatographed on silica gel with petroleum ether−ethyl acetate (1 + 1) to give **44** as solid: yield 88%; mp 49−50 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.18−1.38 (m, 30H), 1.61−1.74 (m, 6H), 2.25 (s, 3H), 2.30 (t, 2H), 2.45 (s, 3H), 2.69 (t, 2H), 2.94 (s, 3H), 2.99 (s, 3H), 3.75 (t, 2H), 6.28 (s, 1H).

The compounds **45**, **46**, and **47** were synthesized from **42**, **43**, and **44** by using a procedure similar to that described for **34a**−**d** (reaction times: treatment with methyl acrylate, 24−48 h; hydrolysis with KOH, 5 min in case of **45**, 1 h in case of **46**). Compound **45** was purified by silica gel chromatography with Et_2O−acetic acid (100 + 1).

3-[1-(5-Cyanopentyl)-3,5-dimethyl-4-octadecanoylpyrrol-2-yl]propionic acid (45): yield 49%; mp 89−90 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.18−1.39 (m, 28H), 1.48−1.55 (m, 2H), 1.61−1.74 (m, 6H,), 2.20 (s, 3H), 2.37 (t, 2H), 2.46 (s, 3H), 2.50 (t, 2H), 2.69 (t, 2H), 2.89 (t, 2H), 3.88 (t, 2H). Anal. ($C_{33}H_{56}N_2O_3$) C, H, N.

6-[2-(2-Carboxyethyl)-3,5-dimethyl-4-octadecanoylpyrrol-1-yl]hexanoic acid (46): yield 18%; mp 105−106 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.14−1.38 (m, 28H), 1.45 (quint, 2H), 1.59−1.76 (m, 6H), 2.21 (s, 3H), 2.41 (t, 2H), 2.46 (s, 3H), 2.48−2.51 (m, 2H), 2.69 (t, 2H), 2.88−2.92 (m, 2H), 3.77 (t, 2H). Anal. ($C_{33}H_{57}NO_5$) C, H, N.

3-[1-[5-(Dimethylcarbamoyl)pentyl]-3,5-dimethyl-4-octadecanoylpyrrol-2-yl]propionic acid (47): yield 29%; mp 74−75 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.13−1.44 (m, 30H), 1.58−1.72 (m, 6H), 2.20 (s, 3H), 2.37 (t, 2H), 2.45 (s, 3H), 2.52 (t,2H), 2.69 (t, 2H), 2.92 (t, 2H), 2.96 (s, 3H), 3.02 (s, 3H), 3.77 (t, 2H). Anal. ($C_{35}H_{62}N_2O_4$) C, H, N.

Compounds **48**−**50** were synthesized by treating **9**[8] with the appropriately substituted (bromomethyl)benzene or (chloromethyl)benzene using a procedure similar to that described for **10**.

2,4-Dimethyl-3-octadecanoyl-1-[4-(trifluoromethyl)benzyl]pyrrole (48): yield 62%; mp 61−63 °C.

1-(4-Chlorobenzyl)-2,4-dimethyl-3-octadecanoylpyrrole (49): yield 61%; mp 62−63 °C.

1-(4-Methoxybenzyl)-2,4-dimethyl-3-octadecanoylpyrrole (50): yield 42%; mp 66−67 °C.

Methyl 4-[(2,4-Dimethyl-3-octadecanoylpyrrol-1-yl)-methyl]benzoate (51):

The mixture of **9**[8] (723 mg, 2 mmol), methyl 4-(bromomethyl)benzoate (473 mg, 2.2 mmol), tetrabutylammonium bromide (64 mg, 0.2 mmol), Et_2O (20 mL), CH_2Cl_2 (10 mL), and powdered NaOH (320 mg, 8 mmol) was refluxed for 4 h with vigorous stirring. The reaction mixture was filtered, the filter cake was washed with CH_2Cl_2, and the filtrates were concentrated. The residue was chromatographed on silica gel with petroleum ether−ethyl acetate (9 + 1) and the product precipitated from petroleum ether: yield 42%; mp 66−67 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.15−1.40 (m, 28H), 1.69 (quint, 2H), 2.28 (s, 3H), 2.38 (s, 3H), 2.72 (t, 2H), 3.91 (s, 3H), 5.03 (s, 2H), 6.35 (s, 1H), 7.05 (d, 2H), 7.99 (d, 2H).

4-[(2,4-Dimethyl-3-octadecanoylpyrrol-1-yl)methyl]benzonitrile (52). Compound **52** was prepared from **9**[8] and 4-(bromomethyl)benzonitrile by using a method similar to that described for **51** (reaction time: 1.5 h): yield 68%; mp 89−90 °C.

Compounds **53**−**58** were synthesized from **48**−**52** by using a procedure similar to that described for **34a**−**d** (reaction times: treatment with methyl acrylate, 24−36 h; hydrolysis with KOH, 1 h in case of **56**, 5 min in case of **57**, 2 h in case of **58**). Compound **57** was purified by silica gel chromatography with Et_2O−acetic acid (100 + 1).

3-[3,5-Dimethyl-4-octadecanoyl-1-[4-(trifluoromethyl)benzyl]pyrrol-2-yl]propionic acid (53): yield 28%; mp 99−100 °C. Anal. ($C_{35}H_{52}F_3NO_3$) C, H, N.

3-[1-(4-Chlorobenzyl)-3,5-dimethyl-4-octadecanoylpyrrol-2-yl]propionic acid (54): yield 27%; mp 85−87 °C. Anal. ($C_{34}H_{52}ClNO_3$) C, H, N.

3-[1-(4-Methoxybenzyl)-3,5-dimethyl-4-octadecanoylpyrrol-2-yl]propionic acid (55): yield 42%; mp 102−103 °C. Anal. ($C_{35}H_{55}NO_4$) C, H, N.

3-[1-(4-Carboxybenzyl)-3,5-dimethyl-4-octadecanoylpyrrol-2-yl]propionic acid (56): yield 46%; mp 152−154 °C. Anal. ($C_{35}H_{53}NO_5$) C, H, N.

3-[1-(4-Cyanobenzyl)-3,5-dimethyl-4-octadecanoylpyrrol-2-yl]propionic acid (57): yield 26%; mp 102−103 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.16−1.39 (m, 28H), 1.68 (quint, 2H), 2.24 (s, 3H), 2.35 (s, 3H), 2.36 (t, 2H), 2.73 (t, 2H), 2.78 (t, 2H), 5.15 (s, 2H), 6.95 (d, 2H), 7.60 (d, 2H). Anal. ($C_{35}H_{52}N_2O_3$) C, H, N.

3-[1-(4-Carbamoylbenzyl)-3,5-dimethyl-4-octadecanoylpyrrol-2-yl]propionic Acid (58). Synthesis started from **52**: yield 27%; mp 143−145 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.16−1.39 (m, 28H), 1.69 (quint, 2H), 2.25 (s, 3H), 2.35 (s, 3H), 2.36 (t, 2H), 2.74 (t, 2H), 2.83 (t, 2H), 5.16 (s, 2H), 6.08 (br, 1H), 6.21 (br, 1H), 6.94 (d, 2H), 7.72 (d, 2H). Anal. ($C_{35}H_{54}N_2O_4$) C, H, N.

3-[1-(4-Hydroxybenzyl)-3,5-dimethyl-4-octadecanoylpyrrol-2-yl]propionic Acid (59). The solution of **55** (0.05 mmol) in dry CH_2Cl_2 (3 mL) was treated at −20 °C with the solution of BBr_3 (0.025 mL) in dry CH_2Cl_2 (1 mL). The mixture was allowed to warm up to room temperature during 2 h, poured into dilute HCl, and extracted twice with Et_2O. The organic layers were dried and concentrated to some milliliters. Then petroleum ether was added and the product precipitated when evaporating a part of the solvent: yield 89%; mp 128−129 °C. Anal. ($C_{34}H_{53}NO_4$) C, H, N.

3-[1-[4-(Dimethylcarbamoyl)benzyl]-3,5-dimethyl-4-octadecanoylpyrrol-2-yl]propionic Acid (60). Compound **60** was synthesized starting from **51** using similar procedures as described for the preparation of **44** and **47** (reaction time for treatment with methyl acrylate, 7 days): yield 23%; mp 52−53 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.16−1.37 (m, 28H), 1.69 (quint, 2H), 2.24 (s, 3H), 2.30 (t, 2H), 2.39 (s, 3H), 2.73 (t, 2H), 2.81 (t, 2H), 2.96 (s, 3H), 3.10 (s, 3H), 5.10 (s, 2H), 6.89 (d, 2H), 7.36 (d, 2H). Anal. ($C_{37}H_{58}N_2O_4$) C, H, N.

3-Dodecanoyl-2,4-dimethylpyrrole (61). Starting from ethyl 3,5-dimethylpyrrole-2-carboxylate the synthesis was performed in an analogous way as the preparation of 2,4-dimethyl-3-octadecanoylpyrrole (**9**):[8] yield 31%; mp 59−60 °C; EI-MS *m*/*e* 277 (M^+).

(1,3,5-Trimethyl-4-octadecanoylpyrrol-2-yl)acetic Acid (63). Compound **61** (139 mg, 0.5 mmol) was *N*-methylated with methyl *p*-toluenesulfonate using a similar method as described for the synthesis of **10**. The acetic acid group was then introduced, applying the procedure described for the preparation of **66**: yield 10%; mp 99−100 °C. Anal. ($C_{21}H_{35}NO_3$) C, H, N.

Compounds **64a**−**f** were synthesized by treating **61** with the appropriately substituted methyl or ethyl ω-bromoalkanoate using a procedure similar to that described for **42**. Compound **64a** could not be separated from the remaining starting compound **61** and was used in the reaction with methyl acrylate without further purification.

Ethyl 5-(3-dodecanoyl-2,4-dimethylpyrrol-1-yl)pentanoate (64b): yield 63%; wax like substance.

Ethyl 6-(3-dodecanoyl-2,4-dimethylpyrrol-1-yl)hexanoate (64c): yield 65%; wax like substance; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.18−1.39 (m, 21H), 1.61−1.72 (m, 6H), 2.25 (s, 3H), 2.30 (t, 2H), 2.45 (s, 3H), 2.69 (t, 2H), 3.74 (t, 2H), 4.12 (q, 2H), 6.28 (s, 1H).

Ethyl 7-(3-dodecanoyl-2,4-dimethylpyrrol-1-yl)heptanoate (64d): yield 59%; wax like substance.

Ethyl 8-(3-dodecanoyl-2,4-dimethylpyrrol-1-yl)octanoate (64e): yield 68%; mp 37−38 °C.

Ethyl 9-(3-dodecanoyl-2,4-dimethylpyrrol-1-yl)nonanoate (64f): yield 48%; mp 39−40 °C.

Compounds **65a**−**e** were synthesized from **64a**−**e** by using a procedure similar to that described for **34a**−**d** (reaction times: treatment with methyl acrylate, 5 days using dry CH_2Cl_2 as solvent instead of nitrobenzene; hydrolysis with KOH, 1 h). Compound **65a** was purified by silica gel chromatography (eluents: (1) Et_2O and (2) Et_2O−acetic acid, 100 + 1). The products were precipitated from Et_2O−petroleum ether.

3-[2-(2-Carboxyethyl)-4-dodecanoyl-3,5-dimethylpyrrol-1-yl]propionic acid (65a): yield 9%; mp 117−119 °C. Anal. ($C_{24}H_{39}NO_5$) C, H, N.

5-[2-(2-Carboxyethyl)-4-dodecanoyl-3,5-dimethylpyrrol-1-yl]pentanoic acid (65b): yield 23%; mp 111−112 °C. Anal. ($C_{26}H_{43}NO_5$) C, H, N.

6-[2-(2-Carboxyethyl)-4-dodecanoyl-3,5-dimethylpyrrol-1-yl]hexanoic acid (65c): yield 20%; mp 101−102 °C. Anal. ($C_{27}H_{45}NO_5$) C, H, N.

7-[2-(2-Carboxyethyl)-4-dodecanoyl-3,5-dimethylpyrrol-1-yl]heptanoic acid (65d): yield 12%; mp 91−93 °C. Anal. ($C_{28}H_{47}NO_5$) C, H, N.

8-[2-(2-Carboxyethyl)-4-dodecanoyl-3,5-dimethylpyrrol-1-yl]octanoic acid (65e): yield 27%; mp 103−104 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.16−1.45 (m, 22H), 1.51−1.72 (m, 6H), 2.20 (s, 3H), 2.37 (t, 2H), 2.46 (s, 3H), 2.46−2.51 (m, 2H), 2.69 (t, 2H), 2.87−2.91 (m, 2H), 3.72 (t, 2H). Anal. ($C_{29}H_{49}NO_5$) C, H, N.

General Procedure for the Synthesis of [2-(Carboxymethyl)-4-dodecanoyl-3,5-dimethylpyrrol-1-yl]alkanoic Acids (66c−f). The solution of **64c**−**f** (0.5 mmol) in dry toluene (3 mL) was treated with the solution of ethyl diazoacetate (0.08 mL) in dry toluene (1 mL) and with powdered copper (about 0.4 g) in an oil bath at 115−120 °C until development of nitrogen ceased. The addition of ethyl diazoacetate and copper powder was repeated twice in the same way. The cooled reaction mixture was chromatographed on silica gel with petroleum ether−ethyl acetate (9 + 1). The obtained intermediate was hydrolyzed with KOH as described for **6a** (reaction time: 1 h). The product was precipitated from Et_2O−petroleum ether.

6-[2-(Carboxymethyl)-4-dodecanoyl-3,5-dimethylpyrrol-1-yl]hexanoic acid (66c): yield 20%; mp 144−145 °C. Anal. ($C_{26}H_{43}NO_5$) C, H, N.

7-[2-(Carboxymethyl)-4-dodecanoyl-3,5-dimethylpyrrol-1-yl]heptanoic acid (66d): yield 13%; mp 113−114 °C. Anal. ($C_{27}H_{45}NO_5$) C, H, N.

8-[2-(Carboxymethyl)-4-dodecanoyl-3,5-dimethylpyrrol-1-yl]octanoic acid (66e): yield 10%; mp 122−123 °C; ^{1}H-NMR ($CDCl_3$) δ 0.88 (t, 3H), 1.19−1.43 (m, 22H), 1.52−1.70 (m, 6H), 2.23 (s, 3H), 2.35 (t, 2H), 2.47 (s, 3H), 2.70 (t, 2H), 3.62 (s, 2H), 3.77 (t, 2H). Anal. ($C_{28}H_{47}NO_5$) C, H, N.

9-[2-(Carboxymethyl)-4-dodecanoyl-3,5-dimethylpyrrol-1-yl]nonanoic acid (66f): yield 9%; mp 110−111 °C. Anal. ($C_{29}H_{49}NO_5$) C, H, N.

Biochemistry. cPLA$_2$ Inhibition. Inhibition of cPLA$_2$ was determined by measuring calcium ionophore A23187-induced arachidonic acid release from bovine platelets with HPLC/UVdetection as previously described.[23] Briefly, to a solution of 5,8,11,14-eicosatetraynoic acid (ETYA), which inhibits formation of arachidonic acid metabolites in platelets, was added the test compound solution or the solvent (in case of the control tests) followed by the platelet suspension and a solution of calcium chloride at 37 °C. Then cPLA$_2$ was activated by calcium ionophore A23187. After termination of the enzyme reaction the produced arachidonic acid was cleaned up by solid-phase extraction and quantified with HPLC/UV detection at 200 nm. Compounds **20**, **23**, and **26** were dissolved in DMSO−0.05 M ethanolic NaOH (1 + 1), and all other test compounds were dissolved in DMSO, if necessary with heating. When DMSO−0.05 M NaOH in EtOH was used as solvent, the solution of the test compound (deviating from[23] 10 μL) was added after the platelet suspension to avoid degradation of ETYA. Each value is the average of at least two runs, and experimental error is within ±20%. The enzyme reactions were performed within 36 h after isolation of the platelets. The platelets were stored at 4 °C.

Cell lysis. Cell lysis was measured by turbidimetry as previously described.[28] Briefly, to a solution of ETYA was added the test compound solution or the solvent (in case of the control tests) followed by the platelet suspension and a solution of calcium chloride at 37 °C. After dilution with phosphate-buffered saline, the absorbance of the cell suspensions was measured at 800 nm. Cell lysis led to a decrease of absorbance. Compounds **20**, **23**, and **26** were dissolved in DMSO−0.05 M ethanolic NaOH (1 +1); all other test compounds were dissolved in DMSO, if necessary with heating. When DMSO−0.05 M ethanolic NaOH was used as solvent, the solution of the test compound (deviating from[28] 5 μL) was added after the platelet suspension to avoid degradation of ETYA. As reference substance, (1-benzyl-3,5-dimethyl-4-octadecanoylpyrrol-2-yl)acetic acid (**11**) was used. This compound caused a cell lysis of 32 ± 6% (mean ± sd; n = 5, different cell preparations were used). The cell lysis was determined within 36 h after isolation of the platelets. The platelets were stored at 4 °C.

Acknowledgment. I thank Prof. Dr. H.-D. Stachel for supporting this study and Mrs. Monika Klimt for technical assistance.

References

(1) Clark, J. D.; Schievella, A. R.; Nalefski, E. A.; Lin, L. L. Cytosolic phospholipase A_2. *J. Lipid Mediators Cell Signalling* **1995**, *12*, 83−117.
(2) Faili, A.; Emadi, S.; Vargaftig, B.; Hatmi, M. Dissociation between the phospholipases C and A_2 activities in stimulated platelets and their involvement in the arachidonic acid liberation. *Br. J. Haematol.* **1994**, *88*, 149−155.
(3) Moncada, S.; Higgs, E. A. Metabolism of arachidonic acid. *Ann. N.Y. Acad. Sci.* **1988**, *522*, 454−463.
(4) Samuelsson, B.; Dahlen, S. E.; Lindgren, J. A.; Rouzer, C. A.; Serhan, C. N. Leukotrienes and lipoxins: structures, biosynthesis, and biological effects. *Science* **1991**, *237*, 1171−1176.
(5) Weltzien, H. U. Cytolytic and membrane-perturbing properties of lysophosphatidylcholine. *Biochim. Biophys. Acta* **1979**, *559*, 259−287.
(6) Venable, M. E.; Zimmerman, G. A.; McIntyre, T. M.; Prescott, S. M. Platelet-activating factor: a phospholipid autacoid with diverse actions. *J. Lipid Res.* **1993**, *34*, 691−702.
(7) Tibes, U.; Vondran, A.; Rodewald, E.; Friebe, W.-G.; Schäfer, W.; Scheuer, W. Inhibition of allergic and non-allergic inflammation by phospholipase A_2 inhibitors. *Int. Arch. Allergy Immunol.* **1995**, *107*, 432−434.
(8) Lehr, M. 3-(3,5-Dimethyl-4-octadecanoylpyrrol-2-yl)propionic acids as inhibitors of 85 kDa cytosolic phospholipase A_2. *Arch. Pharm. Pharm. Med. Chem.* **1996**, *329*, 483−488.
(9) McGregor, W. H.; Chang, J. Y. Preparation of α-aminoalkanamides as phospholipase A_2 inhibitors. PCT Int. Appl. WO 88 06,885, 1988.
(10) Marshall, L. A.; Chang, J. Y. Pharmacological control of phospholipase A_2 activity *in vitro* and *in vivo*. In *Adv. Exp. Med. Biol. Phospholipase A_2: Role and Function in Inflammation*; Wong, P. Y. K., Dennis, E. A., Eds.; Plenum Press: New York, London, 1990; Vol. 275, pp 169−182.
(11) Märki, F.; Breitenstein, W.; Beriger, E.; Bernasconi, R.; Caravatti, G.; Francis, J. E.; Paioni, R.; Wehrli, H. U.; Wiederkehr, R. Differential inhibition of human secretory and cytosolic phospholipase A_2. *Agents Actions* **1993**, *38*, 202−211.
(12) Trimble, L. A.; Street, I. P.; Perrier, H.; Tremblay, N. M.; Weech, P. K.; Bernstein, M. A. NMR structural studies of the tight complex between a trifluoromethyl ketone inhibitor and the 85-kDa human phospholipase A_2. *Biochemistry* **1993**, *32*, 12560−12565.
(13) Lehr, M. Structure-activity relationship studies on (4-acylpyrrol-2-yl)alkanoic acids as inhibitors of the cytosolic phospholipase A_2: Variation of the alkanoic acid substituent, the acyl chain, and the position of the pyrrole nitrogen. *Eur. J. Med. Chem.*, in press.
(14) Sinisterra, J. V.; Moulounguí, Z.; Delmas, M.; Gaset, A. Barium hydroxide as catalyst in organic reactions; V. Application in the Horner reaction under solid-liquid phase-transfer conditions. *Synthesis* **1985**, 1097−1100.
(15) Nenitzescu, C. D.; Solomonica, E. Action of aliphatic diazo compounds on pyrrole and its homologs. *Ber. Dtsch. Chem. Ges.* **1931**, *64*, 1924−1931.
(16) Massa, S.; Artico, M.; Corelli, F.; Mai, A.; Di Santo, R.; Cortes, S.; Marongiu, M. E.; Pani, A.; La Colla, P. Synthesis and antimicrobial and cytotoxic activities of pyrrole-containing analogs of trichostatin A. *J. Med. Chem.* **1990**, *33*, 2845−2849.
(17) Hess, K.; Wissing, F. New transformations in the pyrrole series. *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 1416−1428.
(18) Loader, C. E.; Anderson, H. J. Pyrrole Chemistry - IX A new synthesis of 3-acylpyrroles from 4-acyl-2-pyrrolethiolcarboxylates using a catalytic decarbonylation reaction. *Tetrahedron* **1969**, *25*, 3879−3885.
(19) Anderson, H. J.; Loader, C. E.; Foster, A. Pyrrole chemistry. XXII. A "one-pot" synthesis of some 4-acylpyrrole-2-carboxaldehydes from pyrrole. *Can. J. Chem.* **1980**, *58*, 2527−2530.
(20) Jurch, G. R.; Tatum, J. H. Degradation of D-glucose with acetic acid and methyl-amine. *Carbohydr. Res.* **1970**, *15*, 233−239.
(21) Ermili, A.; Castro, A. J.; Westfall, P. A. Products from attempted Vilsmeier-Haack acylations of pyrroles with selected amides. *J. Org. Chem.* **1965**, *30*, 339−343.
(22) Treibs, A.; Michl, K. H. Substitution reactions of the pyrroles. IV. Addition of acrylic acid and its derivatives to pyrroles. *Justus Liebigs Ann. Chem.* **1954**, *589*, 163−173.
(23) Lehr, M. In-vitro assay for the evaluation of phospholipase A_2 inhibitors using bovine platelets and HPLC with UV-detection. *Pharm. Pharmacol. Lett.* **1992**, *2*, 176−179.
(24) Lehr, M. *In vitro* assay for the evaluation of inhibitors of 85 kDa cytosolic phospholipase A_2 by measuring phorbol ester-induced arachidonic acid release from bovine platelets with HPLC/UV-detection. *Pharm. Pharmacol. Lett.* **1995**, *5*, 108-111.
(25) Urata, C.; Siraganian, R. P. Pharmacologic modulation of the IgE or calcium ionophore A23187 mediated calcium influx, phospholipase A_2 activation, and histamine release in rat basophilic leukemia cells. *Arch. Allergy Appl. Immunol.* **1985**, *78*, 92−100.
(26) Qiu, Z. H.; Leslie, C. C. Protein kinase C-dependent and -independent pathways of mitogen-activated protein kinase activation in macrophages by stimuli that activate phospholipase A_2. *J. Biol. Chem.* **1994**, *269*, 19480- 19487.
(27) Visnjic, D.; Batinic, D.; Lasic, Z.; Knotek, M.; Marusic, M.; Banfic, H. Phorbol 12-myristate 13-acetate-mediated signalling in murine bone marrow cells. *Biochem. J.* **1995**, *310*, 163−170.
(28) Lehr, M. 3-(Octadecanoylaminomethyl)indole-2-carboxylic acid derivatives and 1-methyl-3-octadecanoylindole-2-carboxylic acid as inhibitors of cytosolic phospholipase A_2. *Arch. Pharm. Pharm. Med. Chem.* **1996**, *329*, 386−392.
(29) Murakami, M.; Kudo, I.; Inoue, K. Secretory phospholipase A_2. *J. Lipid Mediators Cell Signalling* **1995**, *12*, 119−130.
(30) Mounier, C.; Faili, A.; Vargaftig, B. B.; Bon, C.; Hatmi, M. Secretory phospholipase A_2 is not required for arachidonic acid liberation during platelet activation. *Eur. J. Biochem.* **1993**, *216*, 169−175.
(31) Mounier, C.; Vargaftig, B. B.; Franken, P. A.; Verheij, H. M.; Bon, C.; Touqui, L. Platelet secretory phospholipase A_2 fails to induce rabbit platelet activation and to release arachidonic acid in contrast with venom phospholipases A_2. *Biochim. Biophys. Acta* **1994**, *1214*, 88−96.
(32) Bartoli, F.; Lin, H.-K.; Ghomashchi, F.; Gelb, M. H.; Jain, M. K.; Apitz-Castro, R. Tight binding inhibitors of 85-kDa phospholipase A_2 but not 14-kDa phospholipase A_2 inhibit release of free arachidonate in thrombin-stimulated human platelets. *J. Biol. Chem.* **1994**, *269*, 15625−15630.
(33) Lehr, M. Synthesis, biological evaluation and structure-activity relationships of 3-acylindole-2-carboxylic acids as inhibitors of the cytosolic phospholipase A_2. *J. Med. Chem.* **1997**, *40*, 2694−2705.
(34) Laufer, S.; Lehr, M.; Tries, S. Effects of ML 3116, an inhibitor of $cPLA_2$, on zymosan- and carrageenan-induced paw edema. *Prostaglandins, Leukotrienes Essent. Fatty Acids* **1996**, *55* (Suppl. 1), 91.

JM970045J