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Highly Potent Inhibitors of TNF-α Production. Part I: Discovery of New Chemical Leads and Their Structure–Activity Relationships

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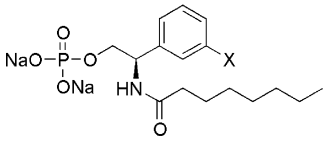
Abstract—Discovery of new chemical leads of inhibitors for TNF-α production starting from the chemical modification of **1** is reported. Further biological studies of **1** to disclose the site of its action strongly suggested that **1** inhibits LPS-induced TNF-α expression in the liver and spleen of mice. Structure–activity relationships (SARs) are also discussed and full details including the chemistry are reported.

Introduction

As one of the key cytokines in diseases such as rheumatoid arthritis (RA), multiple sclerosis, cachexia, sepsis, ulcerative colitis, congestive heart failure, inflammatory bowel disease and Crohn's disease, TNF-α[1–3] is thought to be at or near the top of hierarchy of all cytokines that play a role in these diseases.[4–9] This important role has been demonstrated by studies illustrating that blockage of TNF-α activity in synovial cells from rheumatoid arthritis (RA) patients inhibits the production of another important cytokines (IL-1 and other cytokines) which promote inflammation. Thus, TNF-α plays a central role in the initiation and maintenance of the diseases as described above. Because of its therapeutic potential, much attention has been paid to the development of a small molecule, which inhibits TNF-α production.[10–13] In one of our preceding papers,[14,15] we reported on 2-(octanoylamino)-2-phenylethyl disodium phosphates **1**–**2** as a new class of chemical lead (Fig. 1). We report here the full details of the discovery process for the chemical leads and further biological studies of **1** to disclose its site of action. Structure–activity relationships (SARs) are also discussed.



1: X = H (ID_{50} 3.0 mg/kg, iv in rats)

2: X = OMe (ID_{50} 0.26 mg/kg, iv in rats)

Figure 1. New inhibitors of TNF-α production.

Chemistry

Synthesis of all the compounds listed in the Tables 1–7 are described in Schemes 1–11. As outlined in Scheme 1, *N*-[(1*R*)-2-hydroxy-1-phenylethyl]acylamides **60a**–**r,t** and *N*-[(1*R*)-2-hydroxy-1-phenylethyl]octane-1-sulfonamide **60s** prepared from their corresponding aminoalcohols, were converted to dibenzyl phosphates **61a**–**t**, deprotection of which provided **62a**–**t**. Disodium phosphates **1**, **3**–**20** and **22** were prepared from their corresponding

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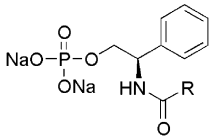
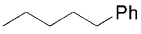
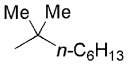
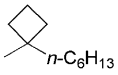
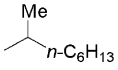
Table 1. Optimization of the *N*-acyl moiety

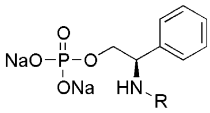


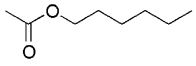
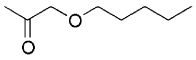
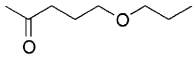
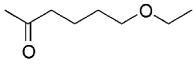
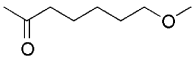
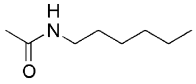
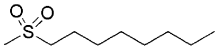
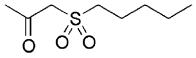
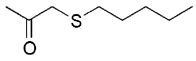
Compd	R	Inhibition of TNF-α production: ID_{50} (mg/kg, iv)	
		Mice	Rats
3	Me	(28)[a]	(21)[b]
4	*n*-Pr	(17)[a]	(37)[b]
5	*n*-C_5H_{11}	30	50
6	*n*-C_6H_{13}	2.8	4.5
1	*n*-C_7H_{15}	0.8	3.0
7	n-$C_{10}H_{21}$	(50)[a]	N.T.[c]
8	–Ph	(32)[a]	N.T.[c]
9		(36)[b]	N.T.[c]
10		(27)[a]	N.T.[c]
11		(56)[a]	N.T.[c]
12		(59)[a]	N.T.[c]
13a (less polar)		4.2	8.0
13b (more polar)		2.4	17

[a]Inhibition % at 10 mg/kg, iv.
[b]Inhibition % at 30 mg/kg, iv.
[c]N.T.: not tested.

free acid forms, respectively by treatment with NaOH aq in EtOH. The (2*R*)-pentylsulfonylethanoyl derivative **21** was prepared from its sulfide derivative **62t** by an oxidation reaction with OXONE® followed by treatment with NaOH aq in EtOH. As described in Scheme 2, **23a**–**26c** and **47** were synthesized from their corresponding methyl aminophenylacetate **63a**–**k**.[16] *N*-Acylation of **63a**–**k** with an octanoyl chloride followed by the reduction with $LiBH_4$ in THF provided **64a**–**k**. Protected phosphates **65a**–**k** were prepared from their corresponding *N*-acylaminoalchols **64a**–**k**, respectively. Deprotection of **65a**–**k** afforded the free acid forms **66a**–**k**, which were converted to their disodium phosphates **23a**–**26c** and **47**, respectively. As outlined in Scheme 3, compounds **53**–**57** were prepared from **67a**–**e** according to essentially the same procedures as described in Scheme 2. As described in Scheme 4, compounds **27**–**40** were synthesized from a common starting material **70**. *O*-Alkylation of the phenolic alcohol of **70** followed by the reduction with $LiBH_4$ in THF afforded intermediates **71a**–**m**, which were converted to **27**–**38** and **40** according to the same procedures as described before. Catalytic hydrogenation of the *O*-benzyl moiety of **71m** followed by *O*-alkylation with ethyl bromoacetate afforded **72**, which was converted to **39** by the following

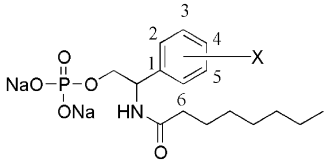
Table 2. Biological evaluation of hetero atom-containing *N*-acyl derivatives **14**–**22**



Compd	R	Inhibition of TNF-α production ID_{50} (mg/kg, iv)	
		Mice	Rats
14		1.1	3.2
15		(14)[a]	N.T.[c]
16		(12)[a]	N.T.[c]
17		(1)[a]	N.T.[c]
18		(34)[a]	N.T.[c]
19		(58)[a]	N.T.[c]
20		(−10)[a]	N.T.[c]
21		N.T.[c]	(38)[b]
22		N.T.[c]	10.5

[a]Inhibition % at 30 mg/kg, iv.
[b]Inhibition % at 10 mg/kg, iv.
[c]N.T.: Not tested.

Table 3. Biological evaluation of compounds **23a–26** possessing a substituted phenyl moiety

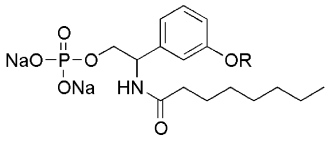


Compd	X	Inhibition of TNF-α production in rats ID_{50} (mg/kg. iv)
23a	2-OMe	(55)[a]
23b	3-OMe	0.5
23c	4-OMe	(34)[a]
24a	2-Me	2.0
24b	3-Me	5.3
24c	4-Me	(44)[a]
25a	2-Cl	(46)[a]
25b	3-Cl	5.2
25c	4-Cl	(−118)[a]
26	3.5-OMe	3.8

[a]Inhibition % at 10 mg/kg, iv.

successive procedures: (1) treatment with *i*-$Pr_2NP(OBn)_2$[17a,b] followed by an oxidation reaction with *m*-CPBA; and (2) deprotection by hydrogenation followed by treatment with $NaHCO_3$ aq. As described in Scheme 5, compounds **41** and **42** were prepared from **71m**. Compound **71m** was converted to **73** by the following successive procedures: (1) protection of the hydroxy group; (2) hydrogenolysis of the benzyl ether moiety; (3) trifluoromethane sulfonylation; and (4) palladium-catalyzed carbonylation by the conventional

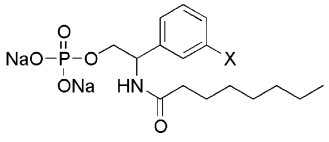
Table 4. Biological evaluation of *meta*-alkoxy phenyl derivatives **27–40**



Compd	R	Inhibition of TNF-α production in rats ID_{50} (mg/kg, iv)
27	H	1.4
28	Et	0.2
29	^{n}Pr	0.7
30	*i*Pr	0.1
31	^{n}Bu	(25)[a]
32	^{i}Bu	3.3
33		(24)[a]
34	^{n}Pentyl	(23)[a]
35	^{n}Hex	(−6)[a]
36		0.9
37		(7)[a]
38	$CH_2CON(Me)_2$	(36)[a]
39	CH_2COOEt	(19)[a]
40	CH_2OCH_3	1.5

[a]Inhibition % at 10 mg/kg, iv.

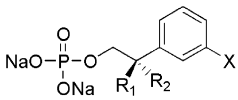
Table 5. Biological evaluation of compounds **41–50** possessing a miscellaneous meta-substituent



Compd	X	Inhibition of TNF-α production in rats ID_{50} (mg/kg, iv)
41	CH_2OH	3.0
42	CH_2OCH_3	4.1
43	COONa	(37)[a]
44	$COOCH_3$	0.4
45	CH_2COONa	(26)[a]
46	CH_2COOCH_3	4.2
47	SMe	0.3
48	S^{i}Pr	0.2
49	SO_2CH_3	(31)[a]
50	$N(Na)SO_2CH_3$	(36)[a]

[a]Inhibition % at 10 mg/kg, iv.

Table 6. Biological evaluation of the optically active forms **1–2** and **51–52**



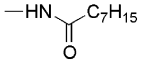
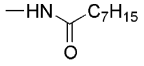
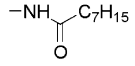
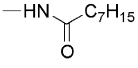
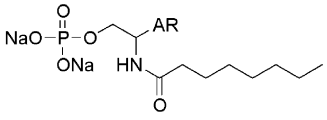
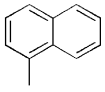
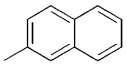
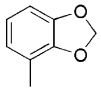
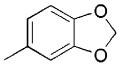
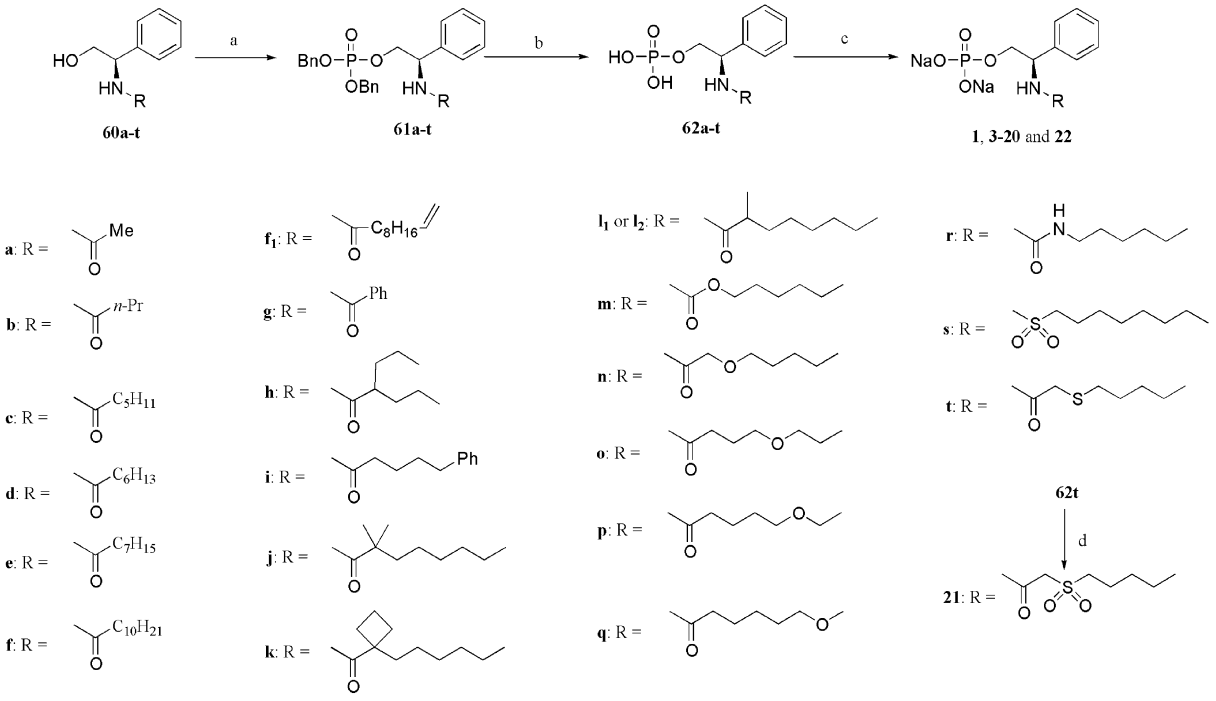
Compd	R_1	R_2	X	Inhibition of TNF-α production ID_{50} (mg/kg, iv) rats
1		H	H	3.0
2		H	OMe	0.26
51	H		H	10.0
52	H		OMe	1.6

Table 7. Biological evaluation of the miscellaneous aromatic derivatives **53–59**

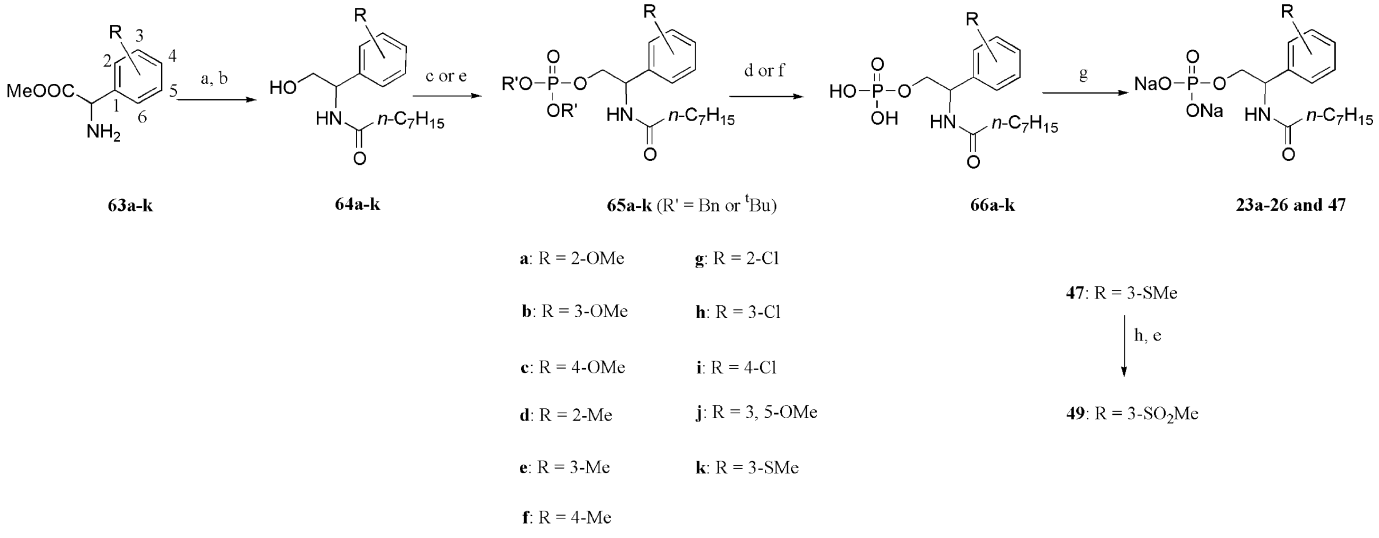


Compd	AR	Inhibition of TNF-α production in rats ID_{50} (mg/kg, iv)
53		3.9
54		(6.5)[a]
55		3.8
56		(16)[a]
57		(−5)[a]
58		(17)[a]
59		(56)[a]

[a]Inhibition % at 10 mg/kg, iv.

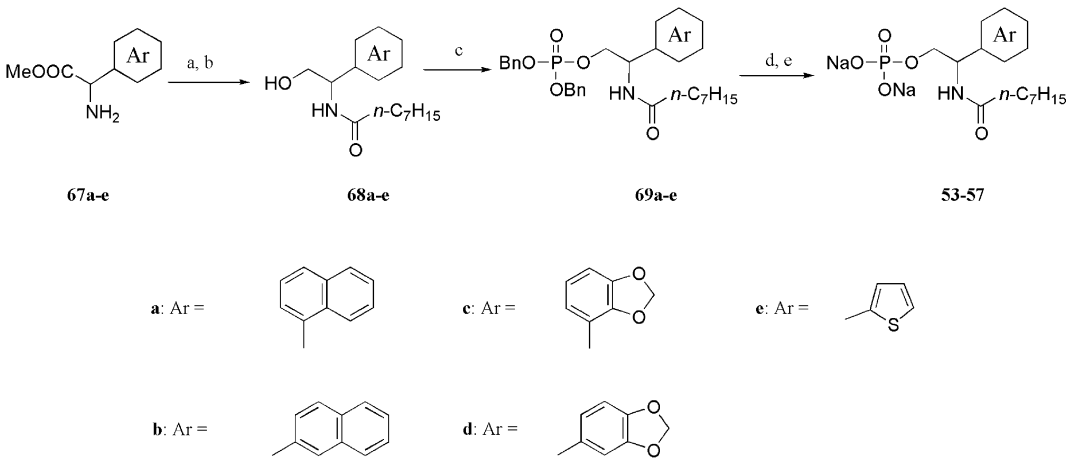


Scheme 1. Synthesis of compound **1** and **3**–**22**. Reagents: Method A: (a) (i) *n*-BuLi, THF; (ii) $(BnO)_2P(O)Cl$; (b) H_2, Pd–C, MeOH; (c) NaOHaq, EtOH; Method B: (a) (i) LDA, THF; (ii) $[(BnO)_2P(O)]_2O$; (b) H_2, Pd–C, MeOH; (c) NaOHaq, EtOH; Method C: (a) (i) NaH, THF; (ii) $(^tBuO)_2P(O)Br$; (b) TFA; (c) NaOHaq, EtOH; Preparation of **21**: (d) (i) TFA; (ii) OXONE®; (iii) NaOHaq, EtOH.

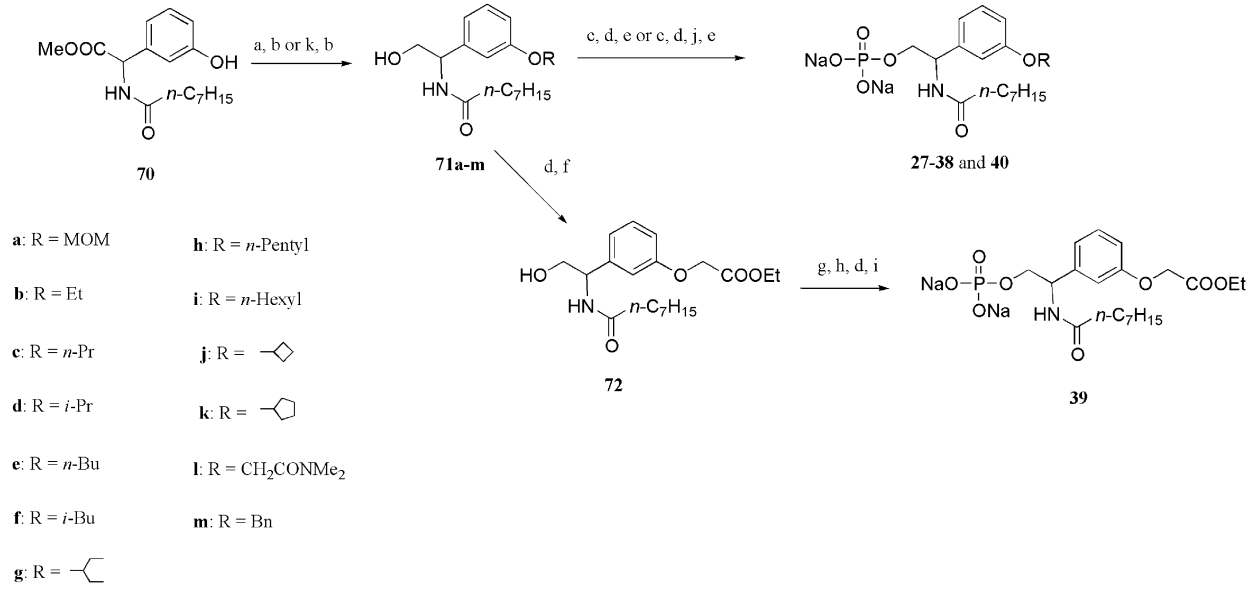


Scheme 2. Synthesis of compounds **23a–26** and **47**. Reagents: (a) n-$C_7H_{15}COCl$, Py, or Et_3N, CH_2Cl_2, or n-$C_7H_{15}COCl$, satd $NaHCO_3$, dioxane; (b) $LiBH_4$, THF; Method A (c–g): (c) (i) *n*-BuLi, THF, (ii) $(BnO)_2P(O)Cl$; (d) H_2, Pd–C, MeOH; (e) NaOHaq, EtOH; Method C (f, g, e): (f) (i) NaH, benzene-THF, (ii) $(^tBuO)_2P(O)Br$; (g) TFA; (h) OXONE®, MeOH.

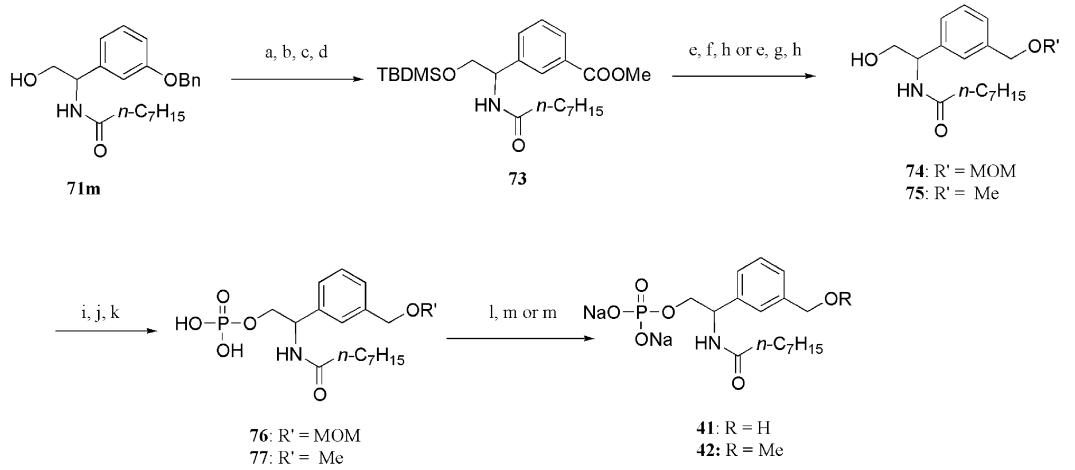
method.[18] Lithium borohydride reduction of the ester moiety of **73** followed by the protection of the formed hydroxymethyl moiety with chloromethyl methyl ether (MOMCl) and desilylation with tetrabutylammonium fluoride (TBAF) provided **74**. Lithium borohydride reduction of the ester moiety of **73** followed by *O*-methylation and deprotection afforded **75**. Phosphates **76** and **77** were prepared from **74** and **75**, respectively by the following successive procedures: (1) phosphinylation;[19] (2) oxidation with *m*-CPBA; (3) deprotection with 50% Me_2NH in EtOH; and (4) acidification. Compounds **76** and **77** were converted to **41** and **42**, respectively according to the same procedures as described before. Synthesis of **43**–**46** is described in Scheme 6. Deprotection of the TBDMS group in **73** gave **78**, which was phosphorylated to **43** and **44** by the following successive procedures: (1) phosphinylation; (2) oxidation with *m*-CPBA; (3) deprotection with DBU; and (4) treatment with NaOH aq or $NaHCO_3$ aq. *O*-Benzylation of **78** followed by the alkaline hydrolysis afforded **79**, which was converted to **80** by the Arndt-Eistert C1 homologation reaction.[20] Hydrogenolysis of the benzyl ether of **80** followed by essentially the same procedures as described above provided **45** and **46**. Compound **48** was prepared



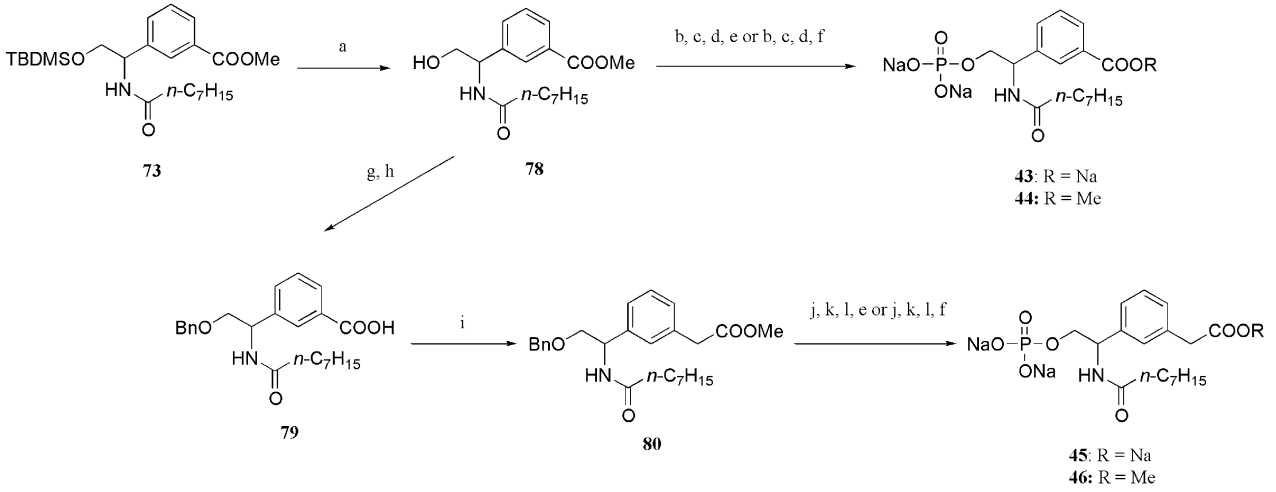
Scheme 3. Synthesis of compounds **53**–**57**. Reagents: (a) n-$C_7H_{15}COCl$, Py, CH_2Cl_2; (b) $LiBH_4$, THF; Method A (c–e): (c) (i) n-BuLi, THF, (ii) $(BnO)_2P(O)Cl$; (d) H_2, Pd–C, MeOH; (e) NaOHaq, EtOH.



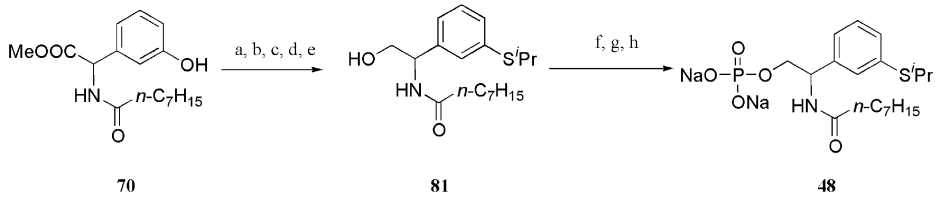
Scheme 4. Synthesis of compounds **27**–**40**. Reagents: (a) RX, K_2CO_3, DMF or acetone; (b) $LiBH_4$, THF; Method A (c–e): (c) (i) n-BuLi, THF, (ii) $(BnO)_2P(O)Cl$; (d) H_2, Pd-C, MeOH; (e) NaOHaq, EtOH; (f) $BrCH_2COOEt$, KI, K_2CO_3, DMF; Method D (g, h, d, i): (g) i-$Pr_2NP(OBn)_2$, tetrazole, CH_3CN; (h) m-CPBA, CH_2Cl_2; (i) $NaHCO_3$aq, EtOH; (j) 6M HCl, MeOH; Preparation of **71j** and **71g**: (k) ROH, DEAD, Ph_3P, THF.



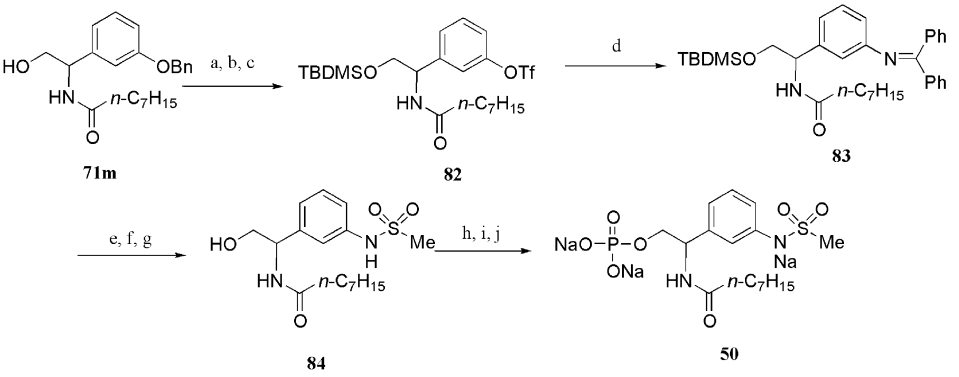
Scheme 5. Synthesis of compounds **41** and **42**. Reagents: (a) TBDMSCl, imidazole, DMF; (b) H_2, Pd–C, MeOH; (c) Tf_2O, Py; (d) $Pd(OAc)_2$, DPPP, CO, Et_3N, MeOH, DMSO; (e) $LiBH_4$, THF; (f) MOMCl, i-Pr_2NEt, CH_2Cl_2; (g) NaH, MeI, THF; (h) TBAF, THF; Method E (i–m): (i) i-$Pr_2NP(OCH_2CH_2CN)_2$, tetrazole, CH_3CN; (j) m-CPBA, CH_2Cl_2; (k) 50% Me_2NH, EtOH; (l) c-HCl; (m) NaOHaq, EtOH.



Scheme 6. Synthesis of compounds **43**–**46**. Reagents: (a) TBAF, THF; Method C (b–e or b–d, f): (b) *i*-$Pr_2NP(OCH_2CH_2CN)_2$, tetrazole, CH_3CN; (c) *m*-CPBA, CH_2Cl_2; (d) DBU, THF; (e) NaOHaq; (f) satd $NaHCO_3$, EtOH; (g) Ag_2O, BnBr, DMF; (h) 2N-NaOH, THF, EtOH; (i) (i) $(COCl)_2$, DMF, toluene; (ii) CH_2N_2, Et_2O; (iii) AgOAc, Et_3N, MeOH; (j) H_2, Pd–C, MeOH, Method D (k–l, e or k–l, f): (k) *i*-$Pr_2NP(OBn)_2$, tetrazole, CH_3CN; (l) *m*-CPBA, CH_2Cl_2.

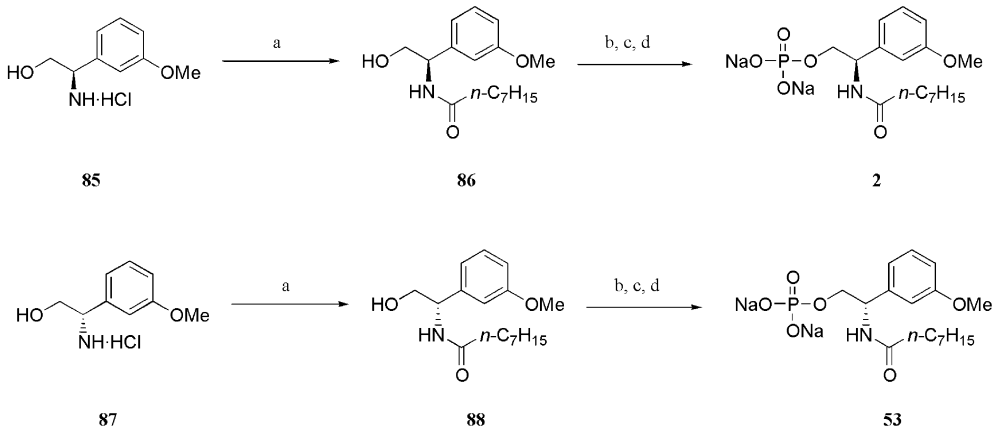


Scheme 7. Synthesis of compound **48**. Reagents: (a) NaH, $ClC(S)NMe_2$, DMF; (b) 235 °C, Ph_2O; (c) $LiBH_4$, THF; (d) KOH, MeOH; (e) ^iPrI, K_2CO_3, DMF; Method C (f–h): (f) NaH, $(^tBuO)_2P(O)Br$, THF; (g) TFA, CH_2Cl_2; (h) NaOHaq, EtOH.

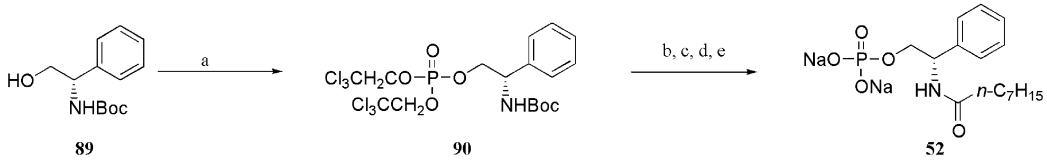


Scheme 8. Synthesis of compound **50.** Reagents: (a) TBDMSCl, imidazole, DMF; (b) H_2, Pd–C, MeOH; (c) Tf_2O, Py; (d) Ph_2CNH, $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene; (e) $HONH_2{\cdot}HCl$, AcONa, MeOH; (f) MsCl, Py; (g) TBAF, THF; Method D (h–j): (h) *i*-$Pr_2NP(OBn)_2$, tetrazole, CH_3CN; (i) *m*-CPBA, CH_2Cl_2; (j) NaOHaq, EtOH.

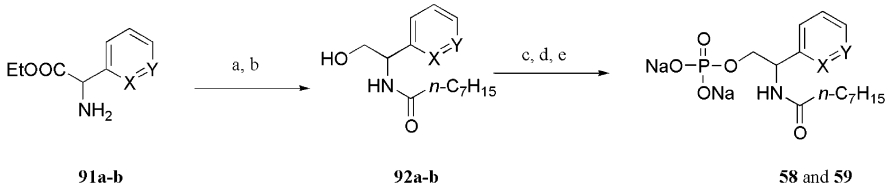
from **70** as outlined in Scheme 7. Compound **70** was converted to **81** by the following successive procedures: (1) replacement of the phenol group with a thiol group by the conventional method;[21] (2) lithium borohydride reduction of the ester group; and (3) alkaline hydrolysis followed by *S*-alkylation. Compound **81** was converted to **48** by the same procedures as described before. Compound **50** was prepared from **71m** as described in Scheme 8. Compound **71m** was transformed to **82** according to the same procedures as described in Scheme 5. Compound **82** was converted to **83** by the reported method.[22] Compound **83** was converted to **84** by the following successive procedures: (1) selective hydrolysis of the imino moiety followed by *N*-methanesulfonylation; and (2) desilylation with TBAF. Conversion of **84** to **50** was accomplished by the above-mentioned procedures. As outlined in Scheme 9, compounds **2** and **53** were prepared from the optically active aminoalcohols,[23a,b] **85** and **87**, respectively according to the same procedure as described before. As described in Scheme 10, compound **52** was prepared from **89**, which was transformed to a phosphate **90** by the conventional method.[24] Compound



Scheme 9. Synthesis of compounds **2** and **53**. Reagents; (a) n-$C_7H_{15}COCl$, satd $NaHCO_3$aq, THF; Method A (b–d): (b) (i) n-BuLi, THF; (ii) $(BnO)_2P(O)Cl$; (c) H_2, Pd–C, MeOH; (d) NaOHaq, EtOH.



Scheme 10. Synthesis of compound **52**. Reagents: Method F (a–e): (a) $(Cl_3CCH_2O)_2P(O)Cl$, Py; (b) TFA, CH_2Cl_2; (c) n-$C_7H_{15}COCl$, Py, CH_2Cl_2; (d) Zn, Py, AcOH; (e) NaOHaq, EtOH.



a: X = N, Y = CH

b: X = CH, Y = N

Scheme 11. Synthesis of compounds **58** and **59**. Reagents: (a) n-$C_7H_{15}COCl$, $NaHCO_3$aq, THF; (b) $LiBH_4$, THF; Method A (c–e): (c) (i) n-BuLi, THF; (ii) $(BnO)_2P(O)Cl$; (d) H_2, Pd-C, MeOH; (e) NaOHaq, EtOH.

90 was converted to **52** according to the following successive procedures: (1) deprotection of the *N*-*tert*-butyloxycarbonyl group; (2) *N*-acylation with octanoyl chloride; (3) reductive deprotection of the trichloroethyl group; and (4) treatment under alkaline conditions. As outlined in Scheme 11, heteroaromatic derivatives **58** and **59** were prepared from **91a**[25] and **91b**,[26] respectively. *N*-Acylation followed by reduction afforded **92a** and **92b**, which were converted to **58** and **59** by the usual methods, respectively.

Results and Discussion

A series of 2-(acylamino)-2-phenylethyl disodium phosphates was synthesized and biologically evaluated for their ability to inhibit LPS-induced plasma TNF-α production in mice and rats. Plasma TNF-α production was determined 90 min after LPS injection by ELISA using a commercially available kit. Test compounds were intravenously (iv) administered prior to the iv injection of LPS. Potency of the test compounds was evaluated by their ID_{50} values (the dosage required to inhibit plasma TNF-α production by 50%) or percentage of inhibition at the maximum dosages administered (10 mg/kg or 30 mg/kg, iv).

As described below, optimization of the *N*-acyl moiety (Tables 1 and 2), the substituent on the aromatic moiety (Tables 3 and 5) and biological evaluation of the optically active forms (Table 6) were studied. An attempt to find another aromatic moiety which could be substituted for the phenyl moiety of **1** was also carried out, the result of which is described in Table 7.

In the course of our screening program for the TNF-α inhibitors, a new class of compounds, 2-(acylamino)-2-phenylethyl disodium phosphate derivatives **1** and **2**

were discovered to be highly potent inhibitors of TNF-α production. Our chemical modification was started with the optimization of the *N*-acyl chain in **1** followed by the introduction of an alkoxy group into the *meta*-position of the phenyl moiety. Due to the effectiveness of the screening process, the biological evaluations were carried out in mice in the earlier stages of the project and in rats in the later stages.

As described in Table 1, good ID_{50} values were obtained with **6**, **1** and **13a**–**b**. The importance of the role played by the *N*-acyl moiety in the potency of these compounds was clarified by the marked reduction in the inhibitory activity of **3**–**5** and **7**–**10**. As illustrated in **1** and **3**–**7**, the length of the *N*-acyl side chain was optimized at the *N*-octanoyl moiety. Compounds **8**–**10** possessing benzoyl, branched alkanoyl and 5-phenylpentanoyl moieties, respectively afforded a marked reduction in their inhibitory activity compared with **1**. To block a predicted inactivation by rapid hydrolysis of the *N*-acyl chain, a 2,2-dimethyl group and a 2,2-trimethylene group were introduced into the optimized *N*-octanoyl moiety of **1** afforded **11** and **12** with a reduced activity. Introduction of a methyl group into the same position afforded two diastereomers **13a** (less polar isomer) and **13b** (more polar isomer). The inhibitory activity of the more polar isomer **13b** was more potent than that of the less polar isomer **13a**. Thus, the SARs obtained in mice were roughly retained with the evaluation in rats.

Introduction of a heteroatom into the *N*-acyl chain provided compounds **14**–**22** as illustrated in Table 2. The *n*-hexyloxycarbonyl derivative **14** showed nearly same potency as **1** on its evaluation in both mice and rats. Other oxygen-containing *N*-acyl derivatives **15**–**18** showed less than 50% inhibition at a dose of 30 mg/kg, iv (mice). The urea derivative **19** demonstrated less potent activity compared with the corresponding urethane derivative **14**. *N*-Sulfonyl derivative **20** did not show any activity at 30 mg/kg, iv (mice). The 2-pentylsulfonylmethyl derivative **21** showed less than 50% inhibition at 10 mg/kg, iv (rats) while the 2-pentylthioethanoyl derivative **22** had an ID_{50} value of 10.5 mg/kg (rats). Thus, the *N*-carbonyl moiety is one of the structural requirements for potent inhibitory activity as illustrated in **1** and **14**.

Replacement of one of the *N*-acyl carbons with an oxygen atom provided **14**–**18**. The increased hydrophilicity in the *N*-acyl side chains of **15**–**18** was thought to be deleterious for their potent inhibitory activity. The *N*-hexyloxycarbonyl moiety of **14** was thought to be an isoster of the *N*-octanoyl moiety of **1**. The lower activity of the urea derivative **19** was thought to be due to the more polar property of its urea moiety compared with that of the urethane moiety of **14**. Replacement of the carbon atom at position-3 with sulfonyl or sulfide was also found to be deleterious for the inhibitory activity.

According to the data obtained so far, the ID_{50} values of these compounds were normally more potent in the evaluations with mice than with rats.

Optimization of the substituents on the phenyl moiety was carried out using racemic compounds for their synthetic reasons as illustrated in Tables 3–5. As described in Table 3, introduction of a methoxy group into the phenyl moiety of (±)-**1** afforded **23a**–**c**. Of these, the *meta*-isomer **23b** exhibited the most potent activity in the evaluation with rats. The inhibitory activity of the *ortho*-isomer **23a** was more potent than that of *para*-isomer **23c**. Introduction of a methyl group into the phenyl moiety of (±)-**1** instead of a methoxy group afforded **24a**–**c**. Among them, the *ortho*-isomer **24a** exceptionally demonstrated the most potent activity. The *meta*-isomer **24b** showed more potent inhibitory activity than *para*-isomer **24c** but less potent activity than **24a**. Introduction of a chloro group into the phenyl moiety in (±)-1 provided **25a**–**c**. Of these, the *meta*-isomer **25b** again demonstrated the most potent activity. The *ortho*-isomer **25a** also showed more potent activity than the *para*-isomer **25c**. Thus, *meta*-isomer tended to show the most potent activity among the each of the classes. The *ortho*-isomers **23a**, **24a** and **25a** always showed more potent activity than their corresponding *para*-isomers **23c**, **24c** and **25c**, respectively. Introduction of another *meta*-methoxy group into the phenyl moiety of **23b** afforded **26** with a nearly eight times less potent ID_{50} value.

As described in Table 4, further optimization of the *meta*-alkoxy moiety was carried out. The *meta*-hydroxy derivative **27** demonstrated an ID_{50} value of 1.4 mg/kg, iv. The ID_{50} values of the ethoxy derivative **28** and isopropyloxy derivative **30** were the most potent among the test compounds **27**–**40**. Although the ID_{50} values for **29** and **36** showed that they were still potent. The isobutyl derivative **32** demonstrated moderate potency, however compounds **31**, **33**–**35** and **37** showed a marked decrease in inhibitory activity presumably because of the more bulky *meta*-alkoxy groups. Heteroatom-containing *meta*-alkoxy derivatives **38**–**40** were also synthesized and biologically evaluated. Of these, the methoxymethyl derivative **40** exhibited the most potent ID_{50} value.

As described in Table 5, other *meta*-substituted derivatives **41**–**50**, the *meta*-position of which was substituted with carbon, sulfur and nitrogen atoms, were also synthesized and biologically evaluated. Of these, a methyl ester, as well as methylthio and isopropylthio derivatives **44**, **47** and **48** demonstrated very potent ID_{50} values. Hydroxymethyl, methoxymethyl and methoxycarbonylmethyl derivatives **41**, **42** and **46** demonstrated moderate ID_{50} values (3–4 mg/kg, iv). The remaining compounds **43**, **45**, **49** and **50** showed less than 50% inhibition at the dose of 10 mg/kg, iv. Carboxyl, carboxylmethyl, methyl sulfonyl and methylsulfonyl amino groups were found to be deleterious for increasing the inhibitory activity.

As described in Table 6, optically active derivatives **1**–**2** and **51**–**52** were synthesized and biologically evaluated. The inhibitory activity of the newly discovered chemical lead **1** exhibited inhibitory activity for TNF-α production

at 3.0 mg/kg, iv in rats. The *meta*-methoxy derivative **2** showed a nearly ten times more potent ID_{50} value (0.26 mg/kg, iv in rats) than **1**. Their corresponding enantiomers **51** and **52** demonstrated nearly three times and six times less potent ID_{50} values, respectively. Thus the (*R*)-configuration of **1** and **2** was thought to be a structural requirement for their more potent activity compared with the (*S*)-configuration of **51** and **52**.

A biological evaluation of the miscellaneous aromatic derivatives **53**–**59** is outlined in Table 7. Replacement of the phenyl moiety in (±)-**1** with a 1-naphtyl moiety afford **53** which retained the potent activity while the potency was markedly decreased in the evaluation of the corresponding 2-naphthyl derivative **54**. A similar tendency to the above-mentioned result was obtained in the biological evaluation of **55** and **56**. As such, **55** demonstrated nearly the same potency as **53** while **56**, which corresponds to **54**, demonstrated much less potency than **55**. The 2-thienyl derivative **57** did not exhibit any inhibitory activity at the dose of 10 mg/kg, iv although a thienyl moiety is very often used as an isoster of a phenyl moiety in medicinal chemistry.

Pyridine derivatives **58**–**59** tended to show inhibitory activity although their potency was not so high. Compound **59** showed more than 50% inhibition at 10 mg/kg, iv while **58** exhibited 17% inhibition at the same dose.

LPS, an inflammatory inducer, stimulates TNF-α mRNA and protein expression. It has been reported that significant increases of TNF-α mRNA expression were seen in spleens and livers of LPS-treated animals.[27a–c] As described in Table 1, compound **1** showed a potent inhibitory effect on increase of plasma TNF-α production in LPS-treated mice. To elucidate mechanism of the inhibitory effect of **1** on TNF-α protein expression we investigated an effect of **1** on TNF-α mRNA induction in spleens and livers of LPS-treated mice. As shown in Figures 2 and 3, compound **1** (line 3) significantly suppresses LPS-induced increase of TNF-α production at the mRNA level as well as PGE_2 (line 4), which was used as the positive control. The mechanism leading to inhibition on plasma TNF-α production in LPS-treated mice likely depends on suppression of TNF-α mRNA induction.

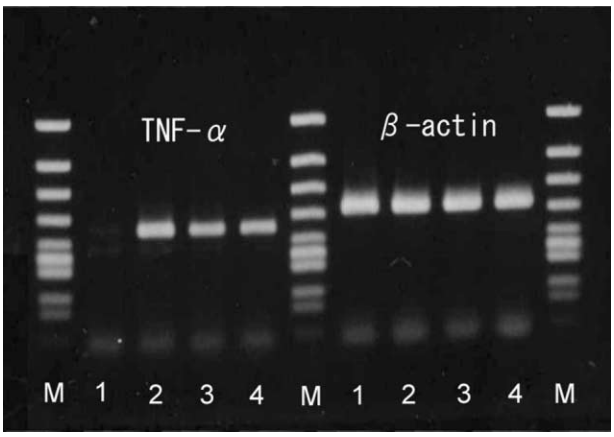


Figure 2. Evaluation of TNF-α expression in mouse liver by RT-PCR. M: DNA molecular weight markers. Lane 1: saline; lane 2: LPS (5 mg/kg, ip); lane 3: LPS (5 mg/kg, ip) + compound **1** 30 mg/kg, ip (1 min before LPS injection); lane 4: LPS (5 mg/kg, ip) + PGE_2 1 mg/kg, ip (1 min before LPS injection).

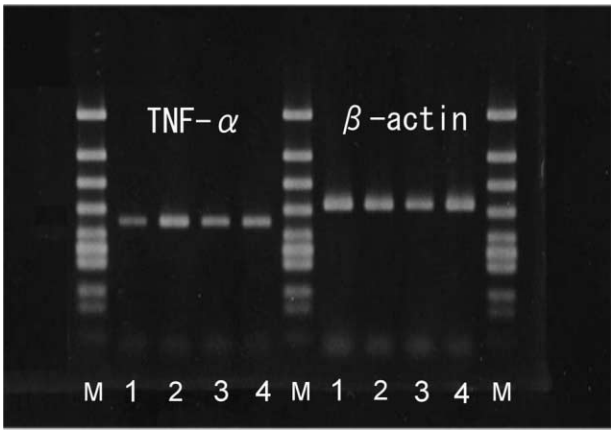


Figure 3. Evaluation of TNF-α expression in mouse spleen by RT-PCR. M: DNA molecular weight markers. Lane 1: saline; lane 2: LPS (5 mg/kg, ip); lane 3: LPS (5 mg/kg, ip) + compound **1** 30 mg/kg, ip (1 min before LPS injection); lane 4: LPS (5 mg/kg, ip) + PGE_2 1 mg/kg, ip (1 min before LPS injection).

Conclusion

In summary, we have discovered a new series of inhibitors of TNF-α production. A number of the compounds, 2-(acylamino)-2-phenylethyl phosphate derivatives, most notably **2**, **23b**, **28**, **30**, **44**, **47** and **48**, were excellent inhibitors. Biological evaluation of the optically active derivatives clearly shows that (*R*)-enantiomers **1** and **2** are more potent inhibitors than their corresponding (*S*)-enantiomers **51** and **52**, respectively. According to the biological evaluation of the miscellaneous aromatic derivatives **53**–**59**, **53** and **55** exhibited nearly the same potency as **1**. Based on this result, the 2-naphtyl and 2,3-methylenedioxyphenyl moieties could be a surrogate for the phenyl moiety of **1**. Our further biological evaluation of **1** strongly suggested that the inhibitory activity of **1** in LPS-induced TNF-α production takes place at the level of TNF-α expression in the liver and spleen of mice. The findings from the present study will be useful for further optimization of the newly discovered chemical lead **2**. Lead optimization and oral activity of representative test compounds will be reported in the following paper in this journal.

Experimental

General directions

Analytical samples were homogeneous as confirmed by TLC, and afforded spectroscopic results consistent with the assigned structures. All ^1H NMR spectra were taken on a Varian Gemini-200, VXR-200s or Mercury 300 spectrometer. MS spectra were obtained on a Hitachi M1200H, JMS-DX303HF or PerSeptive Voyager

Elite spectrometer. Matrix assisted laser desorption ionization-time of flight high-resolution mass spectra (MALDI-TOF HRMS) were obtained on a PerSeptive Voyager Elite spectrometer. IR spectra were measured on a Perkin–Elmer FT-IR 1760X or Jasco FT/IR-430 spectrometer. Melting points were uncorrected. Optical rotations were measured on a Jasco DIP-1000 polarimeter. Column chromatography was carried out on silica gel (Merck silica gel 60 (0.063–0.200 mm) or Fuji Silysia FL60D). Thin layer chromatography was performed on silica gel (Merck TLC plate, silica gel 60 F_{254}). HPLC analyses were performed with a LaChrom (L-7400 UV Detector, L-7100 pump: HITACHI). The following abbreviations for solvents and reagents are used: THF, tetrahydrofuran; EtOAc, ethyl acetate; MeOH, methanol; EtOH, ethanol; DMF, dimethylformamide; CH_2Cl_2, dichloromethane; $CHCl_3$, chloroform; EDC·HCl, 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride; HOBt·H_2O, *N*-hydroxybenzotriazole hydrate; *m*-CPBA, *meta*-chloroperbenzoic acid; DEAD, diethyl azodicarboxylate; TBDMSCl, *tert*-butylchlorodimethylsilane; MOMCl, chloromethylmethyl ether; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; TBAF, tetrabutylammonium fluoride.

***N*-[(1*R*)-2-Hydroxy-1-phenylethyl]octanamide (60e).** To a stirred mixture of (2*R*)-2-amino-2-phenylethanol (4.93 g, 36 mmol) in dioxane (180 mL) and 0.5 M $NaHCO_3$ aq (220 mL) was added dropwise a solution of octanoyl chloride (5.85 g, 36 mmol) in dioxane (20 mL) at 0 °C. After the reaction mixture was stirred for 2 h at that temperature, it was diluted with EtOAc. The organic layer was successively washed with 1 M HCl, 1 M NaOH and brine before being dried over $MgSO_4$. Removal of the solvent by evaporation afforded a white solid, which was washed with Et_2O/*n*-hexane and dried under reduced pressure to obtain **60e** as a white powder (8.0 g, 85%): TLC R_f = 0.21 (*n*-hexane/EtOAc, 1/2); MS (MALDI-TOF, Pos.) *m*/*z* 286 $(M+Na)^+$, 264 $(M+H)^+$; IR (KBr) 3316, 1647, 1541, 1466, 1418, 1039, 702 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 6.15 (d, *J* = 6.2 Hz, 1H), 5.07 (m, 1H), 3.88 (dd, *J* = 6.6, 4.6 Hz, 2H), 2.81 (brt, *J* = 6.0 Hz, 1H), 2.24 (brt, *J* = 7.6 Hz, 2H), 1.66 (m, 2H), 1.40–1.20 (m, 8H), 0.87 (brt, *J* = 6.6 Hz, 3H).

Preparation of **60a**–**d**, **g**, **j**, **k**, $\mathbf{l_{1,\ 2}}$ and **m**. The following compounds were prepared from (2*R*)-2-amino-2-phenylethanol according to the same procedure as described for the preparation of **60e** from (2*R*)-2-amino-2-phenylethanol.

***N*-[(1*R*)-2-Hydroxy-1-phenylethyl]acetamide (60a).** Yield, 88%; TLC R_f = 0.20 (CH_2Cl_2/MeOH, 15/1); ^1H NMR (200 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 6.28 (brs, 1H), 5.06 (m, 1H), 3.87 (brs, 2H), 2.86 (brs 1H), 2.04 (s, 3H).

***N*-[(1*R*)-2-Hydroxy-1-phenylethyl]butanamide (60b).** Yield, 93%; TLC R_f = 0.28 (*n*-hexane/EtOAc, 1/2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 6.29 (brs, 1H), 5.05 (m, 1H), 3.85 (brd, *J* = 5.1 Hz, 2H), 3.04 (brs, 1H), 2.20 (t, *J* = 7.5 Hz, 2H), 1.67 (tq, *J* = 7.5, 7.5 Hz, 2H), 0.94 (t, *J* = 7.5 Hz, 3H).

***N*-[(1*R*)-2-Hydroxy-1-phenylethyl]hexanamide (60c).** Yield, 70%; TLC R_f = 0.40 (*n*-hexane/EtOAc, 1/2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 6.23 (brd, *J* = 6.3 Hz, 1H), 5.05 (m, 1H), 3.86 (brd, *J* = 4.8 Hz, 2H), 2.23 (t, *J* = 7.5 Hz, 2H), 1.67–1.58 (m, 2H), 1.41–1.25 (m, 4H), 0.88 (brt, *J* = 6.9 Hz, 3H).

***N*-[(1*R*)-2-Hydroxy-1-phenylethyl]heptanamide (60d).** Yield, 99%; TLC R_f = 0.46 (*n*-hexane/EtOAc, 1/2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 6.26 (brd, *J* = 6.6 Hz, 1H), 5.05 (m, 1H), 3.86 (brd, *J* = 5.1 Hz, 2H), 2.23 (t, *J* = 7.5 Hz, 2H), 1.67–1.58 (m, 2H), 1.41–1.25 (m, 6H), 0.87 (brt, *J* = 6.9 Hz, 3H).

***N*-[(1*R*)-2-Hydroxy-1-phenylethyl]benzamide (60g).** Yield, 68%; TLC R_f = 0.40 (*n*-hexane/EtOAc, 1/2); ^1H NMR (200 MHz, DMSO-d_6) δ 8.67 (brd, *J* = 8.0 Hz, 1H), 7.92–7.87 (m, 2H), 7.52–7.21 (m, 8H), 5.07 (m, 1H), 4.91 (brt, *J* = 8.7 Hz, 1H), 3.78–3.60 (m, 2H).

***N*-[(1*R*)-2-Hydroxy-1-phenylethyl]-2,2-dimethyloctanamide (60j).** 2,2-Dimethyloctanoyl chloride was prepared by the conventional method.[28] 73% yield; TLC R_f = 0.64 (*n*-hexane/EtOAc, 1/2); ^1H NMR (200 MHz, $CDCl_3$) δ 7.400–7.25 (m, 5H), 6.28 (brd, *J* = 6.6 Hz, 1H), 5.05 (m, 1H), 3.88 (brd, *J* = 5.2 Hz, 2H), 1.51 (m, 2H), 1.24 (m, 8H), 1.96 (s, 6H), 0.86 (brt, *J* = 6.6 Hz, 3H).

***N*-[(1*R*)-2-Hydroxy-1-phenylethyl]-2-trimethyleneoctanamide (60k).** 2-Trimethyleneoctanoyl chloride was prepared by the conventional method.[29] 65% yield; TLC R_f = 0.64 (*n*-hexane/EtOAc, 1/2); ^1H NMR (200 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 6.15 (brd, *J* = 6.6 Hz, 1H), 5.06 (ddd, *J* = 7.4, 5.0, 5.0 Hz, 1H), 3.90 (brs, 2H), 2.82 (brs, 1H), 2.45–2.30 (m, 2H), 1.95–1.70 (m, 6H), 1.40–1.10 (m, 8H), 0.86 (brt, *J* = 6.6 Hz, 3H).

***N*-[(1*R*)-2-Hydroxy-1-phenylethyl]-2-methyloctanamide ($\mathbf{60l_1}$ and $\mathbf{60l_2}$).** 2-Methlyoctanoyl chloride was prepared by the conventional method.[30] Purification was performed by column chromatography on silica gel (FL60D, *n*-hexane/EtOAc, 3/1–2/1) to afford $\mathbf{60l_1}$ and $\mathbf{60l_2}$. $\mathbf{60l_1}$ (less polar, 32% yield): TLC R_f = 0.64 (*n*-hexane/EtOAc, 1/2); ^1H NMR (200 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 6.13 (brd, *J* = 6.6 Hz, 1H), 5.06 (ddd, *J* = 7.4, 5.0, 5.0 Hz, 1H), 3.90 (brs, 2H), 2.82 (brs, 1H), 2.35–2.15 (m, 1H), 1.80–1.20 (m, 10H), 1.17 (d, *J* = 6.6 Hz, 3H), 0.86 (brt, *J* = 6.6 Hz, 3H). $\mathbf{60l_2}$ (more polar, 28% yield): TLC R_f = 0.55 (*n*-hexane/EtOAc, 1/2); ^1H NMR (200 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 6.13 (brd, *J* = 6.6 Hz, 1H), 5.06 (ddd, *J* = 7.4, 5.0, 5.0 Hz, 1H), 3.90 (brd, *J* = 5.0 Hz, 2H), 2.80 (brs, 1H), 2.35–2.17 (m, 1H), 1.70–1.10 (m, 10H), 1.15 (d, *J* = 6.6 Hz, 3H), 0.87 (brt, *J* = 6.6 Hz, 3H)

Hexyl (1*R*)-2-hydroxy-1-phenylethylcarbamate (60m). Yield, 99%; TLC R_f = 0.47 (*n*-hexane/EtOAc, 2/1); ^1H NMR (200 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 5.41 (brd, *J* = 7.0 Hz, 1H), 4.82 (m, 1H), 4.05 (t, *J* = 6.8 Hz, 2H), 3.86 (brs, 2H), 2.25 (brs, 1H), 1.58 (brs, 2H), 1.40–1.20 (m, 6H), 0.87 (brt, *J* = 6.6 Hz, 3H).

***N*-[(1*R*)-2-Hydroxy-1-phenylethyl]-2-propylpentanamide (60h).** To a stirred solution of (2*R*)-2-amino-2-phenyl-

ethanol (500 mg, 3.65 mmol), 2-propylpentanoic acid (0.63 mL, 4.02 mmol) and HOBt·H_2O (1.18 g, 7.7 mmol) in DMF (5 mL) was added EDC·HCl (840 mg, 4.38 mmol) at 0 °C and the mixture was stirred for 18 h. The reaction mixture was diluted with EtOAc (20 mL). The organic layer was successively washed with 1 M HCl, saturated $NaHCO_3$ aq and brine before being dried over Na_2SO_4. Removal of the solvent by evaporation gave an oily residue, which was solidified by *n*-hexane to afford **60h** (744 mg, 78%) as a white powder. TLC R_f = 0.47 ($CHCl_3$/MeOH, 9/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.22 (m, 5H), 6.11 (d, J = 6.6 Hz, 1H), 5.15–5.02 (m, 1H), 4.00–3.80 (m, 2H), 2.84 (t, J = 6.0 Hz, 1H), 2.20–2.00 (m, 1H), 1.70–1.50 (m, 2H), 1.50–1.20 (m, 6H), 0.92 (t, J = 7.2 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H).

Preparation of **60f$_1$**, **i**, **n**, **o**–**q**, and **t**. The following compounds were prepared according to the same procedure as described for the preparation of **60h** from (2*R*)-2-amino-2-phenylethanol.

***N*-[(1*R*)-2-Hydroxy-1-phenylethyl]undec-10-enamide (60f$_1$).** Yield, 70%; TLC R_f = 0.13 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 6.17 (d, J = 7.0 Hz, 1H), 5.80 (dddd, J = 17.5, 10.4, 5.6, 5.6 Hz, 1H), 5.10–4.90 (m, 5H), 3.88 (m, 2H), 3.30 (m, 1H), 2.23 (brt, J = 7.6 Hz, 2H), 2.10–1.96 (m, 2H), 1.70–1.50 (m, 2H), 1.40–1.20 (m, 10H).

***N*-[(1*R*)-2-Hydroxy-1-phenylethyl]-5-phenylpentanamide (60i).** Yield, 53%; TLC R_f = 0.35 (CH_2Cl_2/MeOH, 19/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.10 (m, 10H), 6.13 (brd, J = 5.2 Hz, 1H), 5.05 (m, 1H), 3.86 (d, J = 4.8 Hz, 2H), 2.62 (t, J = 7.2 Hz, 2H), 2.25 (t, J = 7.2 Hz, 2H), 1.80–1.55 (m, 4H).

***N*-[(1*R*)-2-Hydroxy-1-phenylethyl]-2-(pentyloxy)acetamide (60n).** (Pentyloxy)acetic acid was prepared by the conventional method.[31] Purification was performed by column chromatography on silica gel (FL60D, *n*-hexane/EtOAc, 2/1–1/1–1/2) to afford **60n**: 50% yield; TLC R_f = 0.64 (*n*-hexane/EtOAc, 1/2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45–7.25 (m, 5H), 7.21 (brd, J = 6.2 Hz, 1H), 5.10 (ddd, J = 7.4, 5.2, 5.2 Hz, 1H), 4.01 (d, J = 15.0 Hz, 1H), 3.93 (d, J = 15.0, 1H), 3.93–3.87 (m, 2H), 3.55–3.48 (m, 2H), 2.82 (brt, J = 6.0 Hz, 1H), 1.70–1.50 (m, 2H), 1.40–1.20 (m, 4H), 0.89 (brt, J = 7.2 Hz, 3H).

***N*-[(1*R*)-2-Hydroxy-1-phenylethyl]-4-propoxybutanamide (60o).** 4-Propoxybutanoic acid was prepared by the conventional method.[32] Purification was performed by column chromatography on silica gel (Merck 7734, $CHCl_3$/MeOH, 9/1) to afford **60o**: 58% yield; a slightly yellow oil: TLC R_f = 0.40 ($CHCl_3$/MeOH, 9/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42–7.22 (m, 5H), 6.55 (d, J = 7.0 Hz, 1H), 5.06 (td, J = 7.0, 5.0 Hz, 1H), 3.87 (t, J = 5.0 Hz, 2H), 3.45 (t, J = 6.0 Hz, 2H), 3.39–3.28 (m, 2H), 3.00 (t, J = 5.8 Hz, 1H), 2.37 (t, J = 7.2 Hz, 2H), 2.05–1.80 (m, 2H), 1.65–1.40 (m, 2H), 0.88 (t, J = 7.2 Hz, 3H).

5-Ethoxy-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]pentanamide (60p). 5-Ethyloxypentanoic acid was prepared by the conventional method.[33] Purification was performed by column chromatography on silica gel (FL60D, CH_2Cl_2/MeOH, 40/1–35/1–30/1) to afford **60p**: 32% yield; slightly yellow oil; TLC R_f = 0.64 (*n*-hexane/EtOAc, 1/2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 6.39 (brd, J = 6.6 Hz, 1H), 5.06 (ddd, J = 7.4, 5.0, 5.0 Hz, 1H), 3.86 (brt, J = 5.0 Hz, 1H), 3.45 (q, J = 7.0, 2H), 3.43 (t, J = 7.0 Hz, 2H), 2.99 (brs, 1H), 2.29 (t, J = 6.8 Hz, 1H), 1.80–1.55 (m, 4H), 1.17 (brt, J = 7.0 Hz, 3H).

***N*-[(1*R*)-2-Hydroxy-1-phenylethyl]-6-methoxyhexanamide (60q).** 6-Methoxyhexanoic acid was prepared by the conventional method.[34] Purification was performed by column chromatography on silica gel (Merck 7734, $CHCl_3$/MeOH, 9/1) to afford **60q**: 56% yield; TLC R_f = 0.42 ($CHCl_3$/MeOH, 9/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42–7.22 (m, 5H), 6.19 (d, J = 7.4 Hz, 1H), 5.07 (td, J = 7.4, 5.0 Hz, 1H), 3.88 (t, J = 5.0 Hz, 2H), 3.37 (t, J = 6.4 Hz, 2H), 3.32 (s, 3H), 2.90–2.80 (m, 1H), 2.26 (t, J = 7.2 Hz, 2H), 1.80–1.50 (m, 4H), 1.50–1.30 (m, 2H).

***N*-[(1*R*)-2-Hydroxy-1-phenylethyl]-2-(pentylthio)acetamide (60t).** Yield, 85%; TLC R_f = 0.12 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (brd, J = 6.9 Hz, 1H), 7.40–7.30 (m, 5H), 5.09 (ddd, J = 7.8, 4.8, 4.8 Hz, 1H), 3.90 (brd, J = 4.8 Hz, 2H), 3.30 (d, J = 16.8 Hz, 1H), 3.23 (d, J = 16.8 Hz, 1H), 2.53 (m, 1H), 2.53 (brt, J = 6.9 Hz, 2H), 1.65–1.50 (m, 2H), 1.40–1.20 (m, 4H), 0.87 (brt, J = 7.2 Hz, 3H).

***N*-Hexyl-*N*′-[(1*R*)-2-hydroxy-1-phenylethyl]urea (60r).** To a stirred solution of (2*R*)-2-amino-2-phenylethanol (960 mg, 7 mmol) in CH_2Cl_2 (20 mL) was added dropwise hexyl isocyanate (1.0 mL, 6.86 mmol) at 0 °C and the stirring was continued for 1 h at room temperature. The reaction mixture was diluted with CH_2Cl_2. The organic layer was successively washed with 1 M HCl and brine before being dried over $MgSO_4$. Removal of the solvent by evaporation gave a solid, which was washed with Et_2O and dried under reduced pressure to afford **60r**: 50% yield; TLC R_f = 0.30 (CH_2Cl_2/MeOH, 19/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.25 (m, 5H), 5.75 (brs, 1H), 4.72 (brt, J = 5.0 Hz, 1H), 3.78 (m, 2H), 3.11 (m, 2H), 2.75 (brs, 1H), 1.50–1.10 (m, 8H), 0.85 (t, J = 7.0 Hz, 3H).

***N*-[(1*R*)-2-Hydroxy-1-phenylethyl]octane-1-sulfonamide (60s).** To a stirred mixture of (2*R*)-2-amino-2-phenylethanol (960 mg, 7 mmol) and Et_3N (2.0 mL, 14 mmol) in CH_2Cl_2 (20 mL) was added chlorotrimethylsilane (0.90. mL, 7 mmol) at −78 °C. Stirring was continued at that temperature for 3 h and at 0 °C for 1 h. To the mixture was added dropwise 1-octanesulfonyl chloride (1.4 mL, 7 mmol) at −78 °C. The reaction mixture was then stirred at that temperature for 2 h and at 0 °C for 1.5 h. The reaction mixture was diluted with EtOAc (100 mL) and the organic layer was successively washed with 1 M HCl, satd $NaHCO_3$ aq and brine before being dried over $MgSO_4$. Removal of the solvent by evaporation gave an oily residue, purification of which was performed by column chromatography on silica gel (Merck

7734, *n*-hexane/EtOAc, 2/1–3/2) to afford **60s**: 78% yield; TLC R_f = 0.50 (CH_2Cl_2/MeOH, 19/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45–7.30 (m, 5H), 5.33 (d, J = 7.0 Hz, 1H), 4.60 (m, 1H), 3.89 (dd, J = 11.4, 4.4 Hz, 1H), 3.77 (dd, J = 11.4, 7.0 Hz, 1H), 2.81 (ddd, J = 13.8, 10.0, 6.2 Hz, 1H), 2.66 (ddd, J = 13.8, 9.6, 6.0 Hz, 1H), 1.80–1.50 (m, 2H), 1.40–1.00 (m, 10H), 0.87 (t, J = 7.0 Hz, 3H).

General method A. (2*R*)-2-(Octanoylamino)-2-phenylethyl disodium phosphate (1). To a stirred solution of **60e** (7.89 g, 30 mmol) in THF (200 mL) was added dropwise *n*-butyllithium in *n*-hexane (1.53 M, 40 mL, 61 mmol) at −78 °C under an argon atmosphere. To the resulting mixture was added dropwise a solution of dibenzlyphosphorochloridate[35] in THF (1 M, 90 mL, 90 mmol) at −60 °C and the stirring was continued for 1 h at −78 °C. The reaction was quenched with 1 M NaOH (100 mL). The resulting mixture was warmed to room temperature before being diluted with EtOAc (100 mL). After the organic layer was successively washed with 1 M NaOH, saturated $NaHCO_3$ aq and brine, it was dried over $MgSO_4$. Removal of the solvent by evaporation gave **61e**, which was used for the next reaction without further purification. A mixture of **61e** in MeOH (200 mL) and 10% Pd–C (1 g) was stirred at room temperature under an atmospheric pressure of hydrogen for 2 h. Removal of the catalyst by filtration through a pad of Celite followed by evaporation afforded an oily residue which was dissolved in CH_2Cl_2 (50 mL) and extracted with 2 M NaOH (50 mL). The aqueous layer was washed with CH_2Cl_2 (50 mL×2), acidified with 2 M HCl (100 mL) and extracted with EtOAc (100 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give **62e** (4.67 g, 45% in 2 steps): ^{1}H NMR (200 MHz, CD_3OD) δ 7.40–7.20 (m, 5H), 5.18 (brdd, J = 7.2, 5.6 Hz, 1H), 4.15–4.07 (m, 2H), 2.25 (brt, J = 7.4 Hz, 2H), 1.70–1.50 (m, 2H), 1.40–1.20 (m, 8H), 0.88 (brt, J = 6.6 Hz, 3H). To a stirred solution of **62e** (4.67 g, 13.6 mmol) in EtOH (200 mL) was added 1 M NaOH (27.2 mL, 27.2 mmol) at 0 °C. Removal of the solvent by evaporation followed by the dissolution of the residue in EtOH was repeated several times to remove H_2O azeotropically. Next addition of Et_2O followed by evaporation afforded **1** as an off-white powder (5.18 g, 98%): TLC R_f = 0.17 ($CHCl_3$/MeOH/H_2O, 65/35/4); IR (KBr) 3291, 1636, 1547, 1455, 1378, 1378, 1095, 987, 700 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 7.36–7.13 (m, 5H), 4.85 (m, 1H), 3.95 (m, 2H), 2.35 (dd, J = 13.8, 8.0 Hz, 1H), 2.21 (dd, J = 13.8, 7.0 Hz, 1H), 1.59 (m, 2H), 1.40–1.20 (m, 8H), 0.88 (brt, J = 7.6 Hz, 3H); MS (FAB, Pos.) m/z 410 $(M+Na)^+$, 388 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{16}H_{24}NO_5P{\cdot}2Na+H^+$: 388.1266; found: 388.1222; optical rotation for free acid form $[\alpha]_D^{25}$ −41.4 (*c* 1.17, MeOH).

(2*R*)-2-Acetylamino-2-phenylethyl disodium phosphate (3). Compound **61a** was obtained from **60a** according to the same procedure as described for the preparation of **61e** from **60e** and was purified by column chromatography on silica gel (Merck 7734, CH_2Cl_2/MeOH, 50/1–45/1–40/1) to afford **61a**: 39% yield; TLC R_f = 0.40 (CH_2Cl_2/MeOH, 15/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.20 (m, 15H), 6.69 (brd, J = 7.6 Hz, 1H), 5.20 (m, 1H), 4.97 (d, J = 8.4 Hz, 2H), 4.94 (dd, J = 11.8, 8.4 Hz, 1H), 4.87 (dd, J = 11.8, 8.4 Hz, 1H), 4.18 (dd, J = 8.4, 5.2 Hz, 2H), 1.96 (s, 3H). The title compound **3** was prepared from **61a** according to the same procedure as described for the preparation of **1** from **61e**: 78% yield; off-white powder; TLC R_f = 0.23 ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3404, 1656, 1629, 1558, 1455, 1378, 1306, 1100 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.40–7.15 (m, 5H), 4.85 (m, 1H), 3.96 (m, 2H), 2.00 (s, 3H); MS (FAB, Pos.) m/z 326 $(M+Na)^+$, 304 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{10}H_{12}NO_5P{\cdot}2Na+H^+$: 304.0327; found: 304.0334.

(2*R*)-2-Hexanoylamino-2-phenylethyl disodium phosphate (5). Compound **61c** was obtained from **60c** according to the same procedure as described for the preparation of **61e** from **60e** and was purified by column chromatography on silica gel (Merck 7734, *n*-hexane/EtOAc, 2/1–3/2–1/1) to afford **61c**: 58% yield; TLC R_f = 0.51 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.20 (m, 15H), 6.65 (brd, J = 7.5 Hz, 1H), 5.22 (m, 1H), 4.97 (d, J = 8.4 Hz, 2H), 4.94 (dd, J = 11.7, 8.4 Hz, 1H), 4.88 (dd, J = 11.7, 8.4 Hz, 1H), 4.21–4.16 (m, 2H), 2.17 (t, J = 7.5 Hz, 2H), 1.65–1.55 (m, 2H), 1.40–1.20 (m, 4H), 0.86 (t, J = 6.9 Hz, 3H). The title compound **5** was prepared from **61c** according to the same procedure as described for the preparation of **1** from **61e**: 83% yield; off-white powder; TLC R_f = 0.15 ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3407, 1636, 1549, 1455, 1092, 984, 701 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.10 (m, 5H), 4.90 (m, 1H), 3.95 (m, 2H), 2.33 (ddd, J = 14.0, 7.2, 7.2 Hz, 1H), 2.23 (ddd, J = 14.0, 7.2, 7.2 Hz, 1H), 1.60 (m, 2H), 1.31 (m, 4H), 0.89 (brt, J = 7.2 Hz, 3H); MS (FAB, Pos.) m/z 382 $(M+Na)^+$, 360 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{14}H_{20}NO_5P{\cdot}2Na+H^+$: 360.0944; found; 360.0953.

(2*R*)-2-Heptanoylamino-2-phenylethyl disodium phosphate (6). Compound **61d** was obtained from **60d** according to the same procedure as described for the preparation of **61e** from **60e** and was purified by column chromatography on silica gel (Merck 7734, *n*-hexane/EtOAc, 2/1–3/2–1/1) to afford **61d**: 55% yield; TLC R_f = 0.54 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.20 (m, 15H), 6.65 (brd, J = 7.8 Hz, 1H), 5.22 (m, 1H), 4.98 (d, J = 8.4 Hz, 2H), 4.94 (dd, J = 11.7, 8.4 Hz, 1H), 4.88 (dd, J = 11.7, 8.4 Hz, 1H), 4.21–4.16 (m, 2H), 2.17 (t, J = 7.5 Hz, 2H), 1.65–1.55 (m, 2H), 1.35–1.20 (m, 6H), 0.86 (brt, J = 6.6 Hz, 3H). The title compound **6** was prepared from **61d** according to the same procedure as described for the preparation of **1** from **61e**: 75% yield; off-white powder; TLC R_f = 0.16 ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3304, 1636, 1548, 1455, 1092 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 7.40–7.10 (m, 5H), 4.90 (m, 1H), 3.95 (m, 2H), 2.33 (ddd, J = 14.0, 7.2, 7.2 Hz, 1H), 2.23 (ddd, J = 14.0, 7.2, 7.2 Hz, 1H), 1.60 (m, 2H), 1.31 (m, 6H), 0.88 (brt, J = 7.2 Hz, 3H); MS (FAB, Pos.) m/z 396 $(M+Na)^+$, 374 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{15}H_{22}NO_5P{\cdot}2Na+H^+$: 374.1109; found: 374.1113.

(2*R*)-2-Phenyl-2-undecanoylaminoethyl disodium phosphate (7). Compound **61f$_1$** was obtained from **60f$_1$** according to the same procedure as described for the preparation of **61e** from **60e**: 57% yield; The product was used for the next reaction without further purification. The title compound **7** was prepared from **61f$_1$** according to the same procedure as described for the preparation of **1** from **61e**: 87% yield; off-white powder; TLC R_f = 0.27 ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3300, 1631, 1544, 1466, 1103 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 7.36–7.16 (m, 5H), 4.80 (m, 1H), 3.96 (m, 2H), 2.29 (m, 2H), 1.58 (m, 2H), 1.40–1.15 (m, 14H), 0.88 (brt, J = 6.4 Hz, 3H); MS (FAB, Pos.) m/z 452 $(M+Na)^+$, 430 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{19}H_{30}NO_5P{\cdot}2Na+H^+$: 430.1735; found: 430.1686.

(2*R*)-2-Phenyl-2-phenoxyaminoethyl disodium phosphate (8). Compound **61g** was obtained from **60g** according to the same procedure as described for the preparation of **61e** from **60e** and was used for the next reaction without further purification. Compound **62g** was obtained from **61g** according to the same procedure as described for the preparation of **62e** from **61e** and was purified by column chromatography on silica gel (Merck 7734, $CHCl_3$/MeOH/NH_4OH, 65/25/1–$CHCl_3$/MeOH/H_2O, 65/25/4). The fraction including the desired product was collected and evaporated to give an oily residue, which was dissolved in EtOAc and washed with 1 M HCl. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give **62g** (35% yield in 2 steps). The title compound **8** was prepared from **62g** with as 92% yield according to the same procedure as described for the preparation of **1** from **62e**: off-white powder; TLC R_f = 0.21 ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3364, 1629, 1579, 1529, 1492, 1098 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 8.00 (dd, J = 8.0, 2.0 Hz, 2H), 7.50–7.39 (m, 5H), 7.32–7.15 (m, 3H), 5.10 (brt, J = 8.4 Hz, 1H), 4.08 (m, 2H); MS (FAB, Pos.) m/z 366 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{15}H_{14}NO_5P{\cdot}2Na+H^+$: 366.0483; found: 366.0470.

(2*R*)-2-Phenyl-2-(2-propylpentanoylamino)ethyl disodium phosphate (9). White powder; TLC R_f = 0.31 ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3304, 2957, 2933, 2873, 1628, 1540, 1496, 1456, 1380, 1258, 1217, 1106 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 7.40–7.10 (m, 5H), 5.00–4.78 (m, 1H), 4.05–3.90 (m, 2H), 2.50–2.30 (m, 1H), 1.70–1.10 (m, 8H), 0.90 (t, J = 6.8 Hz, 3H), 0.87 (t, J = 6.8 Hz, 3H); MS (FAB, Pos.) m/z 410 $(M+Na)^+$, 388 $(M+H)^+$, 366; HRMS (MALDI-TOF, Pos.) calcd for $C_{16}H_{24}NO_5P{\cdot}2Na+H^+$: 388.1266; found: 388.1302.

(2*R*)-2-Phenyl-2-(5-phenylpentanoylamino)ethyl disodium phosphate (10). Compound **61i** was obtained from **60i** according to the same procedure as described for the preparation of **61e** from **60e** and was purified by column chromatography on silica gel (Merck 7734, CH_2Cl_2/MeOH, 50/1) to afford **61i**: 54% yield; ^1H NMR (200 MHz, $CDCl_3$) δ 7.40–7.10 (m, 20H), 6.65 (brd, J = 7.6 Hz, 1H), 5.21 (m, 1H), 4.95 (d, J = 8.4 Hz, 2H), 4.93 (dd, J = 11.6, 8.4 Hz, 1H), 4.86 (dd, J = 11.6, 8.4 Hz, 1H), 4.18 (dd, J = 8.6, 5.0 Hz, 2H), 2.58 (t, J = 7.0 Hz, 2H), 2.19 (t, J = 7.0 Hz, 2H), 1.80–1.55 (m, 4H). The title compound **10** was prepared from **61i** according to the same procedure as described for the preparation of **1** from **61e**: 92% yield; colorless powder; TLC R_f = 0.21 ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3316, 1637, 1544, 1496, 1454, 1094, 986 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.32 (d, J = 7.5 Hz, 2H), 7.25–7.10 (m, 8H), 4.85 (m, 1H), 3.95 (m, 2H), 2.59 (brt, J = 5.7 Hz, 2H), 2.38–2.25 (m, 2H), 1.62 (m, 4H); MS (FAB, Pos.) m/z 444 $(M+Na)^+$, 422 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{19}H_{22}NO_5P{\cdot}2Na+H^+$: 422.1109; found: 422.1141.

(2*R*)-2-(2,2-Dimethylheptanoylamino)-2-phenylethyl disodium phosphate (11). Yield, 60%; colorless powder; TLC R_f = 0.18 ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3385, 1632, 1523, 1456, 1102 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 7.36–7.14 (m, 5H), 4.85 (m, 1H), 3.97 (brt, J = 6.2 Hz, 2H), 1.53–1.46 (m, 2H), 1.40–1.00 (m, 8H), 1.25 (s, 3H), 1.14 (s, 3H), 0.86 (brt, J = 6.6 Hz, 3H); MS (FAB, Pos.) m/z 416 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{18}H_{28}NO_5P{\cdot}2Na+H^+$: 416.1579; found: 416.1578.

(2*R*)-2-Phenyl-2-(2-trimethyleneheptanoylamino)ethyl disodium phosphate (12). Yield, 43%; colorless powder; TLC R_f = 0.18 ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3376, 1629, 1522, 1106 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 7.38–7.16 (m, 5H), 4.90 (m, 1H), 3.97 (brt, J = 6.2 Hz, 2H), 2.60–2.30 (m, 2H), 2.05–1.65 (m, 6H), 1.35–1.00 (m, 8H), 0.86 (brt, J = 6.6 Hz, 3H); MS (FAB, Pos.) m/z 450 $(M+Na)^+$, 428 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{19}H_{28}NO_5P{\cdot}2Na+H^+$: 428.1579; found: 428.1614.

(2*R*)-2-(2-Methyloctanoylamino)-2-phenylethyl disodium phosphate (13a). Yield, 33%; colorless powder; TLC R_f = 0.25 ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3329, 1625, 1533, 1466, 1112 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.34 (brd, J = 6.9 Hz, 2H), 7.25 (brt, J = 7.2 Hz, 2H), 7.16 (m, 1H), 4.85 (m, 1H), 4.03–3.88 (m, 2H), 2.44 (m, 1H), 1.60 (m, 1H), 1.40–1.20 (m, 9H), 1.10 (d, J = 6.9 Hz, 3H), 0.88 (brt, J = 6.6 Hz, 3H); MS (FAB, Pos.) m/z 402 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{17}H_{26}NO_5P{\cdot}2Na+H^+$: 402.1422; found: 402.1420.

(2*R*)-2-(2-Methyloctanoylamino)-2-phenylethyl disodium phosphate (13b). Yield, 91%; pinkish powder; TLC R_f = 0.20 ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3315, 1631, 1540, 1455, 1377, 1108 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.36 (brd, J = 7.2 Hz, 2H), 7.25 (brt, J = 7.2 Hz, 2H), 7.17 (m, 1H), 4.85 (m, 1H), 4.00–3.90 (m, 2H), 2.48 (m, 1H), 1.55 (m, 1H), 1.40–1.15 (m, 9H), 1.08 (d, J = 6.6 Hz, 3H), 0.88 (brt, J = 6.6 Hz, 3H); MS (FAB, Pos.) m/z 424 $(M+Na)^+$, 402 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{17}H_{26}NO_5P{\cdot}2Na+H^+$: 402.1422; found: 402.1461.

(2*R*)-2-(Hexanoyloxycarbonylamino)-2-phenylethyl disodium phosphate (14). Yield, 52%; colorless powder; TLC R_f = 0.16 ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3409, 1696, 1455, 1421, 1341, 1104 cm^{-1}; ^1H NMR

(200 MHz, CD_3OD) δ 7.36–7.14 (m, 5H), 4.70 (m, 1H), 3.97–3.78 (m, 4H), 1.65–1.10 (m, 8H), 0.88 (m, 3H); MS (FAB, Pos.) m/z 412 $(M+Na)^+$, 390 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{15}H_{22}NO_6P{\cdot}2Na+H^+$: 390.1058; found: 390.1067.

(2*R*)-2-Phenyl-2-(pentyloxyethanoylamino)ethyl disodium phosphate (15). Yield, 80%; colorless powder; TLC $R_f=0.18$ ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3405, 1662, 1542, 1454, 1102, 987, 699 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.36 (d, $J=7.5$ Hz, 2H), 7.30–7.19 (m, 3H), 5.03 (dd, $J=8.1$, 7.2 Hz, 1H), 4.03 (d, $J=16.5$ Hz, 1H), 4.00 (m, 2H), 3.95 (d, $J=16.5$ Hz, 1H), 3.50 (t, $J=6.9$ Hz, 2H), 1.70–1.55 (m, 2H), 1.50–1.30 (m, 4H), 0.90 (brt, $J=6.0$ Hz, 3H); MS (FAB, Pos.) m/z 412 $(M+Na)^+$, 390 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{15}H_{22}NO_6P{\cdot}2Na+H^+$: 390.1058; found: 390.1104.

(2*R*)-2-Phenyl-2-(propyloxybutanoylamino)ethyl disodium phosphate (16). Yield, 87%; white powder; TLC $R_f=0.28$ ($CHCl_3$/MeOH/H_2O, 65/25/8); IR (KBr) 3290, 2960, 2874, 1646, 1549, 1496, 1455, 1379, 1276, 1110 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 7.40–7.10 (m, 5H), 5.02–4.85 (m, 1H), 4.10–3.90 (m, 2H), 3.42 (t, $J=6.5$ Hz, 2H), 3.36 (t, $J=6.8$ Hz, 2H), 2.50–2.20 (m, 2H), 1.98–1.78 (m, 2H), 1.70–1.45 (m, 2H), 0.91 (t, $J=7.5$ Hz, 3H); MS (FAB, Pos.) m/z 412 $(M+Na)^+$, 390 $(M+H)^+$, 368; HRMS (MALDI-TOF, Pos.) calcd for $C_{15}H_{22}NO_6P{\cdot}2Na+H^+$: 390.1058; found: 390.1073.

(2*R*)-2-Ethyloxypentanoylamino-2-phenylethyl disodium phosphate (17). Yield, 82%; colorless powder; TLC $R_f=0.13$ ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3298, 1639, 1548, 1455, 1378, 1108 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.36 (d, $J=7.5$ Hz, 2H), 7.30–7.15 (m, 3H), 4.90 (m, 1H), 3.95 (m, 2H), 3.45 (q, $J=7.2$ Hz, 2H), 3.41 (t, $J=6.0$ Hz, 2H), 2.31 (m, 2H), 1.70–1.50 (m, 4H), 1.15 (t, $J=7.2$ Hz, 3H); MS (FAB, Pos.) m/z 412 $(M+Na)^+$, 390 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{15}H_{22}NO_6P{\cdot}2Na+H^+$: 390.1058; found: 390.1085.

(2*R*)-2-Methoxyhexanoylamino-2-phenylethyl disodium phosphate (18). Yield, 57%; white powder; TLC $R_f=0.26$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3284, 2935, 2865, 1634, 1549, 1496, 1455, 1119 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.40–7.14 (m, 5H), 4.98–4.82 (m, 1H), 4.02–3.85 (m, 2H), 3.37 (t, $J=6.5$ Hz, 2H), 3.30 (s, 3H), 2.40–2.20 (m, 2H), 1.70–1.50 (m, 4H), 1.50–1.30 (m, 2H); MS (FAB, Pos.) m/z 412 $(M+Na)^+$, 390 $(M+H)^+$, 368; HRMS (MALDI-TOF, Pos.) calcd for $C_{15}H_{22}NO_6P{\cdot}2Na+H^+$: 390.1058; found: 390.1101.

(2*R*)-2-(*N*-Hexylureido)-2-phenylethyl disodium phosphate (19). Yield, 63%; off-white powder; TLC $R_f=0.23$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3323, 1648, 1560, 1454, 1100 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 7.37–7.11 (m, 5H), 4.73 (dd, $J=8.0$, 4.0 Hz, 1H), 4.03–3.80 (m, 2H), 3.05 (t, $J=6.8$ Hz, 2H), 1.50–1.20 (m, 8H), 0.88 (brt, $J=7.0$ Hz, 3H); MS (FAB, Pos.) m/z 411 $(M+Na)^+$, 389 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{15}H_{23}NO_5P{\cdot}2Na+H^+$: 389.1218; found: 389.1211.

(2*R*)-2-phenyl-2-(octylsulfonylamino)ethyl disodium phosphate (20). Yield, 25%; colorless powder; TLC $R_f=0.25$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 1656, 1455, 1303, 1145 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 7.45–7.23 (m, 5H), 4.57 (dd, $J=7.4$, 5.6 Hz, 1H), 3.92 (m, 2H), 2.77 (m, 2H), 1.65 (m, 2H), 1.40–1.10 (m, 10H), 0.88 (brt, $J=7.0$ Hz, 3H); MS (FAB, Pos.) m/z 460 $(M+Na)^+$, 438 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{16}H_{26}NO_6P{\cdot}2Na+H^+$: 438.1092; found: 438.1079.

General method B

(2*R*)-2-Butanoylamino-2-phenylethyl disodium phosphate (4). To a stirred solution of **60b** (207 mg, 1 mmol) in THF (10 mL) was added dropwise lithium diisopropylamide in THF (2 M, 0.53 mL, 1.06 mmol) at −78 °C under an argon atmosphere. To the resulting mixture was added tetrabenzylpirophosphate[36] (646 mg, 1.2 mmol) in a single portion. Stirring was continued for 1 h at −78 °C and at 0 °C for 30 min. The reaction was quenched with saturated $NaHCO_3$ aq (10 mL) and extracted with EtOAc (50 mL). The organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent by evaporation gave an oily residue. The product was purified by column chromatography on silica gel (Merck 7734, CH_2Cl_2/MeOH, 40/1) to afford **61b** (343 mg, 73%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.20 (m, 15H), 6.64 (brd, $J=7.5$ Hz, 1H), 5.22 (m, 1H), 4.97 (d, $J=8.4$ Hz, 2H), 4.94 (dd, $J=11.7$, 8.4 Hz, 1H), 4.87 (dd, $J=11.7$, 8.4 Hz, 1H), 4.19 (dd, $J=8.4$, 5.1 Hz, 2H), 2.15 (t, $J=7.5$ Hz, 2H), 1.70–1.57 (m, 2H), 0.91 (t, $J=7.5$ Hz, 3H). The title compound **4** was obtained from **61b** according to the same procedure as described for the preparation of **1** from **61e** as an off-white powder: TLC $R_f=0.12$ ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3306, 1637, 1548, 1456, 1093 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.40–7.15 (m, 5H), 4.85 (m, 1H), 3.96 (m, 2H), 2.26 (m, 2H), 1.63 (ddq, $J=7.2$, 7.2, 7.2 Hz, 2H), 0.93 (t, $J=7.2$ Hz, 3H); MS (FAB, Pos.) m/z 354 $(M+Na)^+$, 332 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{12}H_{16}NO_5P{\cdot}2Na+H^+$: 332.0640; found: 332.0624.

General method C

(2*R*)-2-(2-Pentylthioethanoylamino)-2-phenylethyl disodium phosphate (22). To a stirred solution of **60t** (281 mg, 1 mmol) in benzene (2 mL) was added NaH (60% dispersion in mineral oil, 80 mg, 2 mmol) at room temperature under an argon atmosphere. The resulting mixture was heated under reflux for 30 min. After cooling, the mixture was diluted with THF (2 mL) and then di-*tert*-butyl phosphorobromidate[37] (272 mg, 1 mmol) was added. Stirring was continued at 30 °C for 2 h. The reaction mixture was diluted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ aq and brine before being dried over $MgSO_4$. Removal of the solvent by evaporation gave **61t** as an oil, which was used for the next reaction without further purification. To a stirred solution of **61t** in benzene (5 mL) was added CF_3COOH (1 mL) and the mixture stirred at room temperature for 15 h. Removal of the solvent by evaporation gave an oily

residue, which was partitioned between CH_2Cl_2 (5 mL) and 2 M NaOH (5 mL). The aqueous layer was washed with CH_2Cl_2 (×3), acidified by adding 2 M HCl (10 mL) and extracted with EtOAc. The organic layer was dried over $NaSO_4$. Removal of the solvent by evaporation gave **62t** as an oil (74% in 2 steps), which was converted to the disodium salt according to the same procedure as described for preparation of **1** from **62e**: 75% yield; orange powder; TLC R_f = 0.35 ($CHCl_3$/MeOH/H_2O, 65/25/8); IR (KBr) 3342, 1640, 1543, 1454, 1100 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.37 (brd, J = 7.5 Hz, 2H), 7.26 (brt, J = 7.5 Hz, 2H), 7.18 (m, 1H), 4.92 (dd, J = 8.1, 4.5 Hz, 1H), 3.97 (m, 2H), 3.36 (d, J = 13.8 Hz, 1H), 3.13 (d, J = 13.8 Hz, 1H), 2.52 (brt, J = 7.2 Hz, 2H), 1.54 (m, 2H), 1.30 (m, 4H), 0.87 (brt, J = 7.2 Hz, 3H); MS (FAB, Pos.) m/z 428 $(M+Na)^+$, 406 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{15}H_{22}NO_5PS{\cdot}2Na+H^+$: 406.0830; found: 406.0873.

(2*R*)-2-(2-Pentylsulfonylethanoylamino)-2-phenylethyl disodium phosphate (21). To a stirred solution of **62t** (166 mg, 0.45 mmol) in MeOH (2.5 mL) was added dropwise a solution of OXONE® ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$, 311 mg, 0.505 mmol) in H_2O (2.5 mL) at 0 °C. Stirring was continued at 0 °C for 3 h and at room temperature for 15 h. A precipitate which formed was removed by filtration. The solid was washed with MeOH. The filtrate was combined and concentrated to give an oily residue, which was dissolved in EtOAc. The organic layer was washed with 1 M HCl and dried over Na_2SO_4. Removal of the solvent by evaporation gave (2*R*)-2-(2-pentylsulfonylamino)-2-phenylethyl dihydrogen phosphate as an oil (75%), which was converted to the disodium salt according to the same procedure as described for preparation of **1** from **62e**: 85% yield; orange powder; TLC R_f = 0.16 ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3212, 1668, 1564, 1455, 1298, 1123 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.40 (brd, J = 7.2 Hz, 2H), 7.30–7.15 (m, 3H), 4.91 (dd, J = 8.1, 3.9 Hz, 1H), 4.05–3.90 (m, 2H), 3.17 (m, 2H), 1.78 (m, 2H), 1.45–1.30 (m, 4H), 0.89 (brt, J = 7.2 Hz, 3H); MS (FAB, Pos.) m/z 438 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{15}H_{22}NO_7PS{\cdot}2Na+H^+$: 438.0728; found: 438.0692.

***N*-[2-Hydroxy-1-(2-methoxyphenyl)ethyl]octanamide (64a).** To a stirred suspension of **63a**[16] (4.73 g, 24.3 mmol) in CH_2Cl_2 (32 mL) were added a solution of octanoyl chloride (4.72 g, 29 mmol) in CH_2Cl_2 (8 mL) and pyridine (16 mL) at 0 °C. Stirring was continued for 18 h at room temperature. The reaction mixture was diluted with EtOAc. The organic layer was successively washed with 1 M HCl, satd $NaHCO_3$ aq and brine before being dried over Na_2SO_4. Removal of the solvent by evaporation afforded a crude product which was purified by column chromatography on silica gel (Merck 7734, *n*-hexane/EtOAc, 2/1) and solidified with *n*-hexane to give methyl (2-methoxyphenyl)(octanoylamino)acetate as a slightly yellow powder: 65% yield; TLC R_f = 0.21 (*n*-hexane/EtOAc, 1/1); ^1H NMR (200 MHz, $CDCl_3$) δ 7.40–7.25 (m, 2H), 7.00–6.85 (m, 2H), 6.54 (d, J = 8.5 Hz, 1H), 5.80 (d, J = 8.5 Hz, 1H), 3.84 (s, 3H), 3.68 (s, 3H), 2.30–2.15 (m, 2H), 1.70–1.50 (m, 2H), 1.40–1.15 (m, 8H), 0.86 (t, J = 6.6 Hz, 3H). To a stirred suspension of $LiBH_4$ (549 mg, 25 mmol) in THF (25 mL) was added dropwise a solution of methyl (2-methoxyphenyl)(octanoylamino)acetate (4.0g, 12.5 mmol) in THF (10 mL) at 0 °C and stirring was continued for 20 h at room temperature. The reaction was quenched by adding satd NH_4Cl aq and the mixture was diluted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Removal of the solvent by evaporation gave an oily residue, which was solidified with *n*-hexane to afford **64a** as a white powder: 98% yield; TLC R_f = 0.52 ($CHCl_3$/MeOH, 9/1); ^1H NMR (200 MHz, $CDCl_3$) δ 7.38–7.20 (m, 2H), 7.00–6.85 (m, 2H), 6.53 (d, J = 7.6 Hz, 1H), 5.40–5.28 (m, 1H), 4.00–3.70 (m, 5H), 2.55 (t, J = 5.6 Hz, 1H), 2.30–2.20 (m, 2H), 1.75–1.50 (m, 2H), 1.40–1.15 (m, 8H), 0.87 (t, J = 6.6 Hz, 3H).

Preparation of **64b–k** and **68a–e**: the following compounds were prepared according to essentially the same procedures as described for the preparation of **64a** from **63a**.

***N*-[2-Hydroxy-1-(3-methoxyphenyl)ethyl]octanamide (64b).** Yield, 94%; white powder; TLC R_f = 0.53 ($CHCl_3$/MeOH, 9/1); ^1H NMR (200 MHz, $CDCl_3$) δ 7.35–7.22 (m, 1H), 6.95–6.80 (m, 3H), 6.13 (d, J = 6.4 Hz, 1H), 5.10–4.98 (m, 1H), 3.95–3.81 (m, 2H), 3.81 (s, 3H), 2.80–2.65 (br, 1H), 2.30–2.20 (m, 2H), 1.80–1.50 (m, 2H), 1.50–1.18 (m, 8H), 0.87 (t, J = 6.6 Hz, 3H).

***N*-[2-Hydroxy-1-(4-methoxyphenyl)ethyl]octanamide (64c).** Methyl (4-methoxylphenyl)(octanoylamino)acetate was prepared from **63c** according to the same procedure as described for the preparation of **64a** from **63a** using $NaHCO_3$ as a base instead of pyridine and the product was used for the next reaction without further purification: TLC R_f = 0.30 (CH_2Cl_2/MeOH, 19/1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 9.0 Hz, 2H), 6.20 (d, J = 6.6 Hz, 1H), 4.99 (m, 1H), 3.83 (m, 2H), 3.79 (s, 3H), 3.40–2.80 (brs, 1H), 2.22 (t, J = 7.2 Hz, 2H), 1.63 (m, 2H), 1.40–1.20 (m, 8H), 0.87 (t, J = 6.9 Hz, 3H).

***N*-[2-Hydroxy-1-(2-methylphenyl)ethyl]octanamide (64d).** Methyl (2-methylphenyl)(octanoylamino)acetate was prepared from **63d** according to the same procedure as described for the preparation of **64a** from **63a** using Et_3N as a base instead of pyridine and the product was used for the next reaction without further purification: TLC R_f = 0.43 (*n*-hexane/EtOAc, 3/1); ^1H NMR (200 MHz, $CDCl_3$) δ 7.23–7.16 (m, 4H), 6.30 (brd, J = 7.4 Hz, 1H), 5.81 (d, J = 7.4 Hz, 1H), 3.71 (s, 3H), 2.48 (s, 3H), 2.26–2.19 (m, 2H), 1.63–1.52 (m, 2H), 1.30–1.15 (m, 8H), 0.95–0.82 (m, 3H). The title compound **64d** was prepared from methyl(2-methylphenyl)(octanoylamino)acetate according to the same procedure as described for the preparation of **64a** from methyl (2-methoxyphenyl)(octanoylamino)acetate. The product was washed with Et_2O/*n*-hexane and used for the next reaction without further purification.

***N*-[2-Hydroxy-1-(3-methylphenyl)ethyl]octanamide (64e).** Methyl (3-methylphenyl)(octanoylamino)acetate was prepared from **63e** according to the same procedure as

described for the preparation of **64a** from **63a** using Et_3N as a base instead of pyridine and the product was used for the next reaction without further purification: TLC $R_f = 0.35$ (*n*-hexane/EtOAc, 3/1); ^1H NMR (200 MHz, $CDCl_3$) δ 7.29–7.21 (m, 1H), 7.16–7.12 (m, 3H), 6.38 (brd, $J = 6.8$ Hz, 1H), 3.73 (s, 3H), 2.27–2.20 (m, 2H), 1.63–1.52 (m, 2H), 1.31–1.15 (m, 8H), 0.96–0.80 (m, 3H). The title compound **64e** was prepared from methyl (3-methylphenyl)(octanoylamino)acetate according to the same procedure as described for the preparation of **64a** from methyl (2-methoxyphenyl)(octanoylamino)acetate. The product was washed with Et_2O/*n*-hexane and used for the next reaction without further purification.

***N*-[2-Hydroxy-1-(4-methylphenyl)ethyl]octanamide (64f).** Yield, 89%; TLC $R_f = 0.28$ (*n*-hexane/EtOAc, 1/3); ^1H NMR (200 MHz, $CDCl_3$) δ 7.16 (s, 4H), 6.10 (d, $J = 6.3$ Hz, 1H), 5.05–4.99 (m, 1H), 3.88 (dd, $J = 11.4$, 5.7 Hz, 1H), 3.83 (dd, $J = 11.4$, 4.5 Hz, 1H), 2.33 (s, 3H), 2.25–2.20 (m, 2H), 1.66–1.58 (m, 2H), 1.29–1.26 (m, 8H), 0.89–0.84 (m, 3H).

***N*-[1-(2-Chlorophenyl)-2-hydroxyethyl]octanamide (64g).** Yield, 84%; TLC $R_f = 0.45$ (*n*-hexane/EtOAc, 1/3); ^1H NMR (200 MHz, $CDCl_3$) δ 7.40–7.37 (m, 1H), 7.32–7.22 (m, 3H), 6.32 (d, $J = 6.3$ Hz, 1H), 5.47–5.42 (m, 1H), 3.91 (d, $J = 4.5$ Hz, 2H), 2.25 (t, $J = 6.6$ Hz, 2H), 1.69–1.59 (m, 2H), 1.30–1.26 (m, 8H), 0.89–0.85 (m, 3H).

***N*-[1-(3-Chlorophenyl)-2-hydroxyethyl]octanamide (64h).** Yield, 73%; TLC $R_f = 0.43$ (*n*-hexane/EtOAc, 1/3); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.23 (m, 3H), 7.17–7.14 (m, 2H), 6.38–6.36 (d, $J = 7.2$ Hz, 1), 5.03–4.97 (m, 1H), 3.87–3.77 (m, 2H), 2.22 (t, $J = 7.2$ Hz, 2H), 1.68–1.57 (m, 2H), 1.31–1.22 (m, 8H), 0.86 (t, $J = 7.2$ Hz, 3H).

***N*-[1-(4-Chlorophenyl)-2-hydroxyethyl]octanamide (64i).** Yeild, 90%; TLC $R_f = 0.25$ (*n*-hexane/EtOAc, 1/3); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, $J = 8.7$ Hz, 2H), 7.24 (d, $J = 8.7$ Hz, 2H), 6.12 (d, $J = 6.9$ Hz, 1H), 5.07–5.02 (m, 1H),3.87 (d, $J = 8.1$ Hz,2H), 2.24 (t, $J = 7.5$ Hz, 2H), 1.67–1.62 (m, 2H),1.28–1.25 (m, 8H), 0.89–0.85 (m, 3H).

***N*-[1-(3,5-Dimethoxyphenyl)-2-hydroxyethyl]octanamide (64j).** Methyl (3,5-dimethoxylphenyl)(octanoylamino) acetate was prepared from **63j** according to the same procedure as described for the preparation of **64a** from **63a** using Et_3N as a base instead of pyridine and the reaction product was washed with Et_2O/*n*-hexane: yellow powder; 50% yield; TLC $R_f = 0.36$ (*n*-hexane/EtOAc, 2/1); ^1H NMR (200 MHz, $CDCl_3$) δ 6.50 (d, $J = 3.3$ Hz, 2H), 6.41 (t, $J = 3.3$ Hz, 1H), 5.51 (d, $J = 7.4$ Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 2.28–2.20 (m, 2H), 1.70–1.55 (m, 2H), 1.30–1.25 (m, 8H), 0.85–0.83 (m, 3H). The title compound **64j** was prepared from methyl (3,5-dimethoxylphenyl)(octanoylamino)acetate according to the same procedure as described for the preparation of **64a** from methyl (2-methoxyphenyl)(octanoylamino)acetate. The product was washed with Et_2O/*n*-hexane and used for the next reaction without further purification.

***N*-{2-Hydroxy-1-[3-(methylthio)phenyl]ethyl}octanamide (64k).** Methyl (3-methylthiophenyl)(octanoylamino) acetate was prepared from **63k** according to the same procedure as described for the preparation of **64a** from **63a** using Et_3N as a base instead of pyridine and the product was washed with Et_2O/*n*-hexane: yellow powder; 38% yield; TLC $R_f = 0.26$ (*n*-hexane/EtOAc, 3/1). The title compound **64k** was prepared from methyl (3-methylthiophenyl)(octanoylamino)acetate according to the same procedure as described for the preparation of **64a** from methyl (2-methoxyphenyl)(octanoylamino) acetate. The product was washed with Et_2O/*n*-hexane and used for the next reaction without further purification.

***N*-[2-Hydroxy-1-(1-naphthyl)ethyl]octanamide (68a).** Ivory powder; 73% yield; TLC $R_f = 0.27$ (*n*-hexane/EtOAc, 1/3); ^1H NMR (300 MHz, $CDCl_3$) δ 8.08–8.05 (m, 1H), 7.90–7.80 (m, 2H), 7.58–7.44 (m, 4H), 6.13 (d, $J = 6.3$ Hz, 1H), 5.93–5.87 (m, 1H), 4.14–4.04 (m, 2H), 2.89 (brs, 1H), 2.37–2.17 (m, 2H), 1.70–1.60 (m, 2H), 1.28–1.25 (m, 8H), 0.88–0.84 (m, 3H).

***N*-[2-Hydroxy-1-(2-naphthyl)ethyl]octanamide (68b).** Ivory powder; 77% yield; TLC $R_f = 0.24$ (*n*-hexane/EtOAc, 1/3); ^1H NMR (300 MHz, $CDCl_3$) δ 7.84–7.73 (m, 4H), 7.51–7.46 (m, 2H), 7.38 (dd, $J = 8.4$ Hz, 1.8 Hz, 1H), 6.29 (d, $J = 6.9$ Hz, 1H), 5.24–5.19 (m, 1H), 4.01–3.90 (m, 2H), 2.26 (t, $J = 7.2$ Hz, 2H), 1.70–1.60 (m, 2H), 1.29–1.26 (m, 8H), 0.88–0.84 (m, 3H).

***N*-[1-(1,3-Benzodioxol-4-yl)-2-hydroxyethyl]octanamide (68c).** Off-white powder; 57% yield; TLC $R_f = 0.25$ (*n*-hexane/EtOAc, 1/1); ^1H NMR (200 MHz, $CDCl_3$) δ 6.90–6.75 (m, 3H), 6.35 (d, $J = 7.5$ Hz, 1H), 6.00 (m, 2H), 5.23 (m, 1H), 4.00–3.78 (m, 2H), 2.62–2.38 (m, 1H), 2.25 (t, $J = 7.5$ Hz, 2H), 1.78–1.45 (m, 2H), 1.40–1.20 (m, 8H), 0.85 (m, 3H).

***N*-[1-(1,3-Benzodioxol-5-yl)-2-hydroxyethyl]octanamide (68d).** Methyl (1,3-dioxaindan-5-yl)(octanoylamino) acetate was prepared from **67d** according to the same procedure as described for the preparation of **64a** from **63a** using Et_3N as a base instead of pyridine and the product was washed with Et_2O/*n*-hexane; white powder; 82% yield; TLC $R_f = 0.46$ (*n*-hexane/EtOAc, 2/1). The title compound **68d** was prepared from methyl (1,3-dioxaindan-5-yl)(octanoylamino)acetate according to the same procedure as described for the preparation of **64a** from methyl (2-methoxyphenyl)(octanoylamino) acetate. The product was washed with Et_2O/*n*-hexane and used for the next reaction without further purification.

***N*-(2-Hydroxy-1-thien-2-ylethyl)octanamide (68e).** Methyl (octanoylamino)(thiophen-2-yl)acetate was prepared from **67e** according to the same procedure as described for the preparation of **64a** from **63a** using Et_3N as a base instead of pyridine and purified by column chromatography on silica gel (Merck 7734, *n*-hexane/EtOAc, 4/1): 71% yield; TLC $R_f = 0.45$ (*n*-hexane/EtOAc, 2/1); ^1H NMR; (200 MHz, $CDCl_3$) δ 7.26 (dd, $J = 5.2$, 1.2 Hz, 1H), 7.07–7.04 (m, 1H), 6.97 (dd, $J = 5.2$, 3.8 Hz, 1H), 6.38 (brd, $J = 7.8$ Hz, 1H), 5.89 (dd, $J = 7.8$, 0.8 Hz, 1H), 3.79 (s, 3H), 2.27–2.21 (m, 2H), 1.71–1.55

(m, 2H), 1.37–1.22 (m, 8H), 0.92–0.82 (m, 3H). The title compound **68e** was prepared from methyl (octanoylamino)(thiophen-2-yl)acetate according to the same procedure as described for the preparation of **64a** from methyl (2-methoxyphenyl)(octanoylamino)acetate. The product was purified by column chromatography on silica gel (Merck 7734, *n*-hexane/EtOAc, 3/1).

Preparation of **23a**–**24c** and **26**: the following compounds were prepared according to the same procedures as described for the preparation of **1** from **60e** (general method A).

2 - (2 - Methoxyphenyl) - 2 - octanoylaminoethyl disodium phosphate (23a). White powder; TLC $R_f = 0.28$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3274, 2929, 2857, 1630, 1555, 1494, 1462, 1375, 1289, 1247, 1098, 1029 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.26 (d, $J = 7.5$ Hz, 1H), 7.17 (dd, $J = 7.5$, 7.5 Hz, 1H), 6.90 (d, $J = 7.5$ Hz, 1H), 6.85 (dd, $J = 7.5$, 7.5 Hz, 1H), 5.29 (dd, $J = 7.8$, 3.6 Hz, 1H), 4.08–3.95 (m, 1H), 3.95–3.80 (m, 4H), 2.40–2.20 (m, 2H), 1.70–1.50 (m, 2H), 1.40–1.20 (m, 8H), 0.89 (t, $J = 6.6$ Hz, 3H); MS (FAB, Pos.) m/z 440 $(M + Na)^+$, 418 $(M + H)^+$, 396; HRMS (MALDI-TOF, Pos.) calcd for $C_{17}H_{26}NO_6P \cdot 2Na + H^+$: 418.1371; found: 418.1375.

2 - (3 - Methoxyphenyl) - 2 - octanoylaminoethyl disodium phosphate (23b). White powder; TLC $R_f = 0.28$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3278, 2955, 2930, 2858, 1632, 1551, 1491, 1466, 1436, 1377, 1262, 1103 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.18 (dd, $J = 8.1$, 8.1 Hz, 1H), 6.95–6.88 (m, 2H), 6.78–6.72 (m, 1H), 4.95–4.80 (m, 1H), 4.02–3.85 (m, 2H), 3.77 (s, 3H), 2.40–2.20 (m, 2H), 1.70–1.50 (m, 2H), 1.40–1.20 (m, 8H), 0.89 (t, $J = 6.3$ Hz, 3H); MS (FAB, Pos.) m/z 440 $(M + Na)^+$, 418 $(M + H)^+$, 396; HRMS (MALDI-TOF, Pos.) calcd for $C_{17}H_{26}NO_6P \cdot 2Na + H^+$: 418.1371; found: 418.1355.

2 - (4 - Methoxyphenyl) - 2 - octanoylaminoethyl disodium phosphate (23c). White powder; TLC $R_f = 0.28$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3285, 2930, 2858, 1631, 1550, 1515, 1465, 1250, 1102 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.26 (d, $J = 8.7$ Hz, 2H), 6.82 (d, $J = 8.7$Hz, 2H), 4.92–4.80 (m, 1H), 4.00–3.85 (m, 1H), 3.75 (s, 3H), 2.38–2.18 (m, 2H), 1.68–1.50 (m, 2H), 1.40–1.20 (m, 8H), 0.89 (t, $J = 6.5$ Hz, 3H); MS (FAB, Pos.) m/z 440 $(M + Na)^+$, 418 $(M + H)^+$, 396; HRMS (MALDI-TOF, Pos.) calcd for $C_{17}H_{26}NO_6P \cdot 2Na + H^+$: 418.1371; found: 418.1323.

2-(2-Methylphenyl)-2-octanoylaminoethyl disodium phosphate (24a). White powder; TLC $R_f = 0.33$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3272, 2928, 1623, 1557, 1095, 988 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.33–7.28 (m, 1H), 7.13–7.05 (m, 3H), 5.12 (t, $J = 6.3$ Hz, 1H), 3.87 (t like, $J = 6.3$ Hz, 1H), 2.43 (s, 3H), 2.36–2.17 (m, 2H), 1.64–1.52 (m, 2H), 1.33–1.22 (m, 8H), 0.88 (brt, $J = 6.6$ Hz, 3H); MS (FAB, Pos.) m/z 402 $(M + H)^+$, 380, 358; HRMS (MALDI-TOF, Pos.) calcd for free acid form $C_{17}H_{28}NO_5P + Na^+$: 380.1603; found: 380.1611.

2-(3-Methylphenyl)-2-octanoylaminoethyl disodium phosphate (24b). Off-white powder; TLC $R_f = 0.33$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3259, 2925, 1625, 1557, 1459, 1099, 990 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.17–7.10 (m, 3H), 7.04–6.90 (m, 1H), 4.85 (dd, $J = 6.3$, 4.5 Hz, 1H), 4.00–3.86 (m, 2H), 2.38–2.18 (m, 2H), 2.92 (s, 3H), 1.68–1.52 (m, 2H), 1.38–1.20 (m, 8H), 0.88 (brt, $J = 6.3$ Hz, 3H); MS (FAB, Pos.) m/z 402 $(M + H)^+$, 380, 358; HRMS (MALDI-TOF, Pos.) calcd for free acid form $C_{17}H_{28}NO_5P + Na^+$: 380.1603; found: 380.1639.

2-(4-Methylphenyl)-2-octanoylaminoethyl disodium phosphate (24c). White powder; TLC $R_f = 0.30$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3258, 2927, 2857, 2360, 1625, 1554, 1462, 1377, 1276, 1104 cm^{-1}; ^1H NMR (300 MHz,CD_3OD) δ 7.22 (d, $J = 8.1$ Hz, 2H), 7.08 (d, $J = 8.1$ Hz, 2H), 4.90–4.85 (m, 1H), 3.99–3.86 (m, 2H), 2.36–2.17 (m, 2H), 2.27 (s, 3H), 1.67–1.52 (m, 2H), 1.38–1.24 (m,8H), 0.93–0.86 (m, 3H); MS (FAB, Pos.) m/z 402 $(M + H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{17}H_{26}NO_5P \cdot 2Na + H^+$: 402.1422; found: 402.1377.

2-(3,5-Dimethoxyphenyl)-2-octanoylaminoethyl disodium phosphate (26). Off-white amorphous powder; TLC $R_f = 0.50$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3291, 1609, 1549, 1464, 1206, 1155, 1102, 984 cm^{-1}; ^1H NMR (300 MHz,CD_3OD) δ 6.51 (d, $J = 2.4$ Hz, 2H), 6.30 (t, $J = 2.4$ Hz, 1H), 4.83 (dd, $J = 7.8$, 4.2 Hz, 1H), 4.01–3.87 (m, 2H), 3.73 (s, 6H), 2.39–2.18 (m, 2H), 1.70–1.52 (m, 2H), 1.37–1.24 (m, 8H), 0.92–0.85 (m, 3H); MS (FAB, Pos.) m/z 448 $(M + H)^+$, 427, 426, 405; HRMS (MALDI-TOF, Pos.) calcd for free acid form $C_{18}H_{30}NO_7P + Na^+$: 426.1658; found: 426.1705.

Preparation of **25a**–**c** and **47**: the following compounds were prepared according to the same procedures as described for the preparation of **22** from **60t** (general method C).

2-(2-Chlorophenyl)-2-octanoylaminoethyl disodium phosphate (25a). Ivory powder; TLC $R_f = 0.26$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3284, 3066, 2955, 2928, 2857, 2359, 1651, 1541, 1467, 1442, 1202, 1058 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 7.46–7.42 (m, 1H), 7.38–7.33 (m, 1H), 7.29–7.20 (m, 2H), 5.44 (dd, $J = 7.0$ Hz, 4.0 Hz, 1H), 4.15–3.90 (m, 2H), 2.32–2.24 (m, 2H), 1.65–1.54 (m, 2H), 1.36–1.22 (m, 8H), 0.88 (t, $J = 7.0$ Hz, 3H); MS (FAB, Pos.) m/z 422 $(M + H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{16}H_{23}ClNO_5P \cdot 2Na + H^+$: 422.0876; found: 422.0924.

2-(3-Chlorophenyl)-2-octanoylaminoethyl disodium phosphate (25b). Off-white powder; TLC $R_f = 0.33$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3429, 1645, 1550, 1465, 1204, 1058 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.37 (s, 1H), 7.30–7.20 (m, 3H), 5.02 (dd, $J = 6.9$, 4.2 Hz, 1H), 4.10–3.90 (m, 2H), 2.35–2.13 (m, 2H), 1.70–1.55 (m, 2H), 1.40–1.10 (m, 8H), 0.88 (t, $J = 6.6$ Hz, 3H); MS (FAB. Pos.) m/z 422 $(M + H)^+$, 400; HRMS (MALDI-TOF, Pos.) calcd for $C_{16}H_{23}ClNO_5P \cdot 2Na + H^+$: 422.0876; found: 422.0899.

2-(4-Chlorophenyl)-2-octanoylaminoethyl disodium phosphate (25c). White powder; TLC $R_f = 0.39$ ($CHCl_3$/

MeOH/H_2O, 65/35/8); IR (KBr) 3285, 2928, 2857, 1647, 1549, 1494, 1466, 1202, 1092, 1056, 1015 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.36–7.33 (m, 2H), 7.31–7.27 (m, 2H), 5.05–5.01 (m, 1H), 4.08–3.93 (m, 2H), 2.28–2.23 (m, 2H), 1.64–1.57 (m, 2H), 1.30–1.27 (m, 8H), 0.91–0.86 (m, 3H); MS (FAB, Pos.) *m*/*z* 422 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{16}H_{23}ClNO_5P{\cdot}2Na+H^+$: 422.0876; found: 422.0905.

2-(3-Methylthiophenyl)-2-octanoylaminoethyl disodium phosphate (47). White powder; TLC $R_f=0.37$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3261, 1625, 1553, 1093, 988 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 7.25 (m, 1H), 7.18 (d, $J=6.8$ Hz, 1H), 7.14–7.07 (m, 2H), 4.89–4.83 (m, 1H), 4.04–3.85 (m, 2H), 2.42–2.16 (m, 2H), 2.45 (s, 3H), 1.68–1.52 (m, 2H), 1.35–1.24 (m, 8H), 0.92–0.84 (m, 3H); MS (FAB, Pos.) *m*/*z* 434 $(M+H)^+$, 456, 412; HRMS (MALDI-TOF, Pos.) calcd for $C_{17}H_{26}NO_5PS{\cdot}2Na+H^+$: 434.1143; found: 434.1154.

Preparation of **53**–**57**: the following compounds were prepared according to the same procedures as described for the preparation of **1** from **60e** (general method A).

2-(Naphtalen-1-yl)-2-octanoylaminoethyl disodium phosphate (53). White powder; TLC $R_f=0.33$ ($CHCl_3$/MeOH/H_2O, 65/25/8); IR (KBr) 3418, 3051, 2955, 2930, 1645, 1540, 1465, 1212, 1057 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 8.21 (d, $J=8.4$ Hz, 1H), 7.88–7.76 (m, 2H), 7.59–7.41 (m, 4H), 5.95 (dd, $J=7.5$ Hz, 4.5 Hz, 1H), 4.31–4.23 (m, 1H), 4.14–4.06 (m, 1H), 2.37–2.22 (m, 2H), 1.68–1.55 (m, 2H), 1.29–1.26 (m, 8H), 0.89–0.85 (m, 3H); MS (FAB. Pos.) *m*/*z* 438 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{20}H_{26}NO_5P{\cdot}2Na+H^+$: 438.1422; found: 438.1412.

2-(Naphtalen-2-yl)-2-octanoylaminoethyl disodium phosphate (54). White powder; TLC $R_f=0.28$ ($CHCl_3$/MeOH/H_2O, 65/25/8); IR (KBr) 3851, 3428, 2954, 1626, 1555, 1464, 1300, 1105 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.80–7.75 (m, 4H), 7.50 (dd, $J=6.9$ Hz, 1.5 Hz, 1H), 7.45–7.37 (m, 2H), 5.06 (dd, $J=7.2$ Hz, 3.6 Hz, 1H), 4.15–3.98 (m, 2H), 2.43–2.23 (m, 2H), 1.68–1.57 (m, 2H), 1.31–1.26 (m, 8H), 0.88–0.84 (m, 3H); MS (FAB. Pos.) *m*/*z* 438 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{20}H_{26}NO_5P{\cdot}2Na+H^+$: 438.1422; found; 438.1378.

2-(1,3-Dioxaindan-4-yl)-2-octanoylaminoethyl disodium phosphate (55). Pale bitter orange powder; TLC $R_f=0.31$ ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3284, 2360, 1635, 1551, 1459, 1250, 1108 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 6.81 (dd, $J=7.5$, 1.5 Hz, 1H), 6.73 (t, $J=7.5$ Hz, 1H), 6.66 (dd, $J=7.5$, 1.5 Hz, 1H), 5.93 (dd, $J=3.9$, 1.2 Hz, 2H), 5.03 (t, $J=6.0$ Hz, 1H), 4.01 (t, $J=6.0$ Hz, 2H), 2.29 (m, 2H), 1.59 (m, 2H), 1.40–1.20 (m, 8H), 0.89 (t, $J=6.6$ Hz, 3H); MS (FAB. Pos.) *m*/*z* 454 $(M+Na)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{17}H_{24}NO_7P{\cdot}2Na+H^+$: 432.1164; found; 432.1137.

2-(1,3-Dioxaindan-5-yl)-2-octanoylaminoethyl disodium phosphate (56). Beige amorphous powder; TLC $R_f=0.35$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3285, 1631, 1550, 1505, 1491, 1249, 1101, 1044 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 6.86 (d, $J=1.4$ Hz, 1H), 6.81 (dd, $J=8.2$, 1.4 Hz, 1H), 6.70 (d, $J=8.2$ Hz, 1H), 5.87 (s, 2H), 4.80 (dd, $J=7.6$, 4.8 Hz, 1H), 4.00–3.81 (m, 2H), 2.38–2.14 (m, 2H), 1.70–1.50 (m, 2H), 1.35–1.20 (m, 8H), 0.95–0.83 (m, 3H); MS (FAB, Pos.) *m*/*z* 432 $(M+H)^+$, HRMS (MALDI-TOF, Pos.) calcd for $C_{17}H_{24}NO_7P{\cdot}2Na+H^+$: 432.1164; found; 432.1143.

2-Octanoylamino-2-(thiophen-2-yl)ethyl disodium phosphate (57). Beige amorphous powder; TLC $R_f=0.33$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3276, 1634, 1548, 1103, 989 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 7.20 (dd, $J=5.0$, 1.4 Hz, 1H), 7.03 (brd, $J=3.4$ Hz, 1H), 6.91 (dd, $J=5.0$, 3.4 Hz, 1H), 5.22 (dd, $J=7.4$, 4.8 Hz, 1H), 4.15–3.97 (m, 2H), 2.38–2.13 (m, 2H), 1.70–1.50 (m, 2H), 1.40–1.20 (m, 8H), 0.93–0.82 (m, 3H); MS (FAB, Pos.) *m*/*z* 394 $(M+H)^+$,416, 372; HRMS (MALDI-TOF, Pos.) calcd for $C_{14}H_{22}NO_5PS{\cdot}2Na+H^+$: 394.0830; found; 394.0801.

Methyl (3-hydroxyphenyl)(octanoylamino)acetate (70). Methyl amino(3-hydroxyphenyl)acetate was prepared from 3-benzyloxy benzaldehyde according to the conventional procedures.[16] To a stirred mixture of methyl amino(3-hydroxyphenyl)acetate (15.7 g, 86.7 mmol) and $NaHCO_3$ (21.8 g, 260 mmol) in THF (170 mL) was added dropwise *n*-octanoyl chloride (16.3 mL, 95.3 mmol) at 0 °C. Stirring was continued for 30 min at that temperature. The reaction mixture was poured into ice-water and extracted with EtOAc/THF. The organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent by evaporation afforded a crude product, which was washed with Et_2O/*n*-hexane to give **70**: beige powder; 88% yield; TLC $R_f=0.29$ (*n*-hexane/EtOAc, 2/1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (t, $J=7.8$ Hz, 1H), 6.91 (brs, 1H), 6.83–6.77 (m, 2H), 6.63 (brd, $J=7.5$ Hz, 1H), 5.53 (d, $J=7.5$ Hz, 1H), 3.73 (s, 3H), 2.26 (t, $J=8.1$ Hz, 2H), 1.70–1.55 (m, 2H), 1.31–1.23 (m, 8H), 0.88–0.80 (m, 3H).

***N*-[2-Hydroxy-1-(3-methoxymethoxyphenyl)ethyl]octanamide (71a).** To a stirred solution of **70** (922 mg, 3.0 mmol) and chloromethyl methyl ether (362 mg, 4.5 mmol) in THF (10 mL) was added NaH (60% dispersion in mineral oil, 132 mg, 3.3 mmol) at 0 °C and stirring was continued for 1 h at room temperature. The reaction mixture was poured into satd NH_4Cl aq and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent by evaporation gave methyl (3-methoxymethoxy) phenyl(octanoylamino)acetate as a pale yellow powder, to a stirred solution of which in THF (10 mL) was added $LiBH_4$ (131 mg, 6.0 mmol) at 0 °C. Stirring was continued for 18 h at room temperature. The reaction mixture was quenched by saturated NH_4Cl aq and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent by evaporation gave a residue, which was purified by column chromatography on silica gel (Merck 7734, *n*-hexane/EtOAc, 1/1) to afford **71a**: colorless oil; 80% yield; TLC $R_f=0.11$ (*n*-hexane/EtOAc, 1/1).

***N*-[2-Hydroxy-1-(3-ethoxyphenyl)ethyl]octanamide (71b).** To a stirred solution of **70** (1.23 g, 4 mmol) in acetone

(10 mL) were added K_2CO_3 (1.38 g, 10 mmol) and EtI (1.25 g, 8 mmol) at room temperature and stirring was continued for 8 h at the reflux temperature. After cooling, removal of the precipitates by filtration through a pad of Celite followed by evaporation of the filtrate gave an oily residue, which was dissolved in EtOAc. The organic layer was successively washed with H_2O and brine before being dried over $MgSO_4$ which was concentrated to afforded methyl (3-ethoxyphenyl)(octanoylamino)acetate (1.3 g, 96%). The product was used for the next reaction without further purification: TLC R_f = 0.46 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (dd, J = 8.4, 8.4 Hz, 1H), 6.92–6.82 (m, 3H), 6.38 (d, J = 7.2 Hz, 1H), 5.55 (d, J = 7.2 Hz, 1H), 4.02 (q, J = 7.2 Hz, 3H), 3.72 (s, 3H), 2.23 (brt, J = 8.4 Hz, 2H), 1.70–1.55 (m, 2H), 1.40 (t, J = 7.2 Hz, 3H), 1.35–1.20 (m, 8H), 0.86 (brt, J = 7.2 Hz, 3H). Compound **71b** was prepared according to the same procedure as described for the preparation of **71a** from **70** and purified by column chromatography on silica gel (FL60D, *n*-hexane/EtOAc, 1/1–2/3): 74% yield; TLC R_f = 0.10 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (dd, J = 8.4, 8.4 Hz, 1H), 6.86–6.80 (m, 3H), 6.11 (brd, J = 6.9 Hz, 1H), 5.02 (m, 1H), 4.02 (q, J = 7.2 Hz, 3H), 3.91–3.81 (m, 2H), 2.23 (brt, J = 7.5 Hz, 2H), 1.70–1.60 (m, 2H), 1.40 (t, J = 7.2 Hz, 3H), 1.30–1.20 (m, 8H), 0.87 (brt, J = 6.9 Hz, 3H).

Preparation of **71c**–**71i** and **71k**–**71m**: the following compounds were prepared according to the same procedures as described for the preparation of **71b** from **70**.

***N*-[2-Hydroxy-1-(3-propyloxyphenyl)ethyl]octanamide (71c).** Yield, 66%; TLC R_f = 0.40 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (dd, J = 7.5, 7.5 Hz, 1H), 6.85–6.80 (m, 3H), 6.12 (brd, J = 6.9 Hz, 1H), 5.02 (m, 1H), 3.90 (t, J = 7.2 Hz, 2H), 3.85 (m, 2H), 2.23 (brt, J = 7.8 Hz, 2H), 1.85–1.70 (m, 2H), 1.70–1.57 (m, 2H), 1.40–1.20 (m, 8H), 1.03 (t, J = 7.8 Hz, 3H), 0.87 (brt, J = 6.9 Hz, 3H).

***N*-[2-Hydroxy-1-(3-isopropyloxyphenyl)ethyl]octanamide (71d).** Yield, 68%; TLC R_f = 0.40 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (dd, J = 7.5, 7.5 Hz, 1H), 6.84–6.79 (m, 3H), 6.13 (brd, J = 6.6 Hz, 1H), 5.00 (m, 1H), 4.53 (m, 1H), 3.84 (m, 2H), 2.23 (brt, J = 8.1 Hz, 2H), 1.70–1.60 (m, 2H), 1.32 (d, J = 6.3 Hz, 6H), 1.32–1.22 (m, 8H), 0.86(t, J = 6.9 Hz, 3H).

***N*-{1-[3-(Butyloxy)phenyl]-2-hydroxyethyl}octanamide (71e).** Yield, 75%; TLC R_f = 0.24 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (dd, J = 7.8, 7.8 Hz, 1H), 6.86–6.81 (m, 3H), 6.10 (brd, J = 6.6 Hz, 1H), 5.03 (m, 1H), 3.95 (t, J = 6.3 Hz, 2H), 3.92–3.80 (m, 2H), 2.76 (brs, 1H), 2.24 (brt, J = 7.5 Hz, 2H), 1.80–1.40 (m, 6H), 1.40–1.20 (m, 8H), 0.98 (t, J = 7.5 Hz, 3H), 0.87 (brt, J = 6.9 Hz, 3H).

***N*-{2-Hydroxy-1-[3-(isobutyloxy)phenyl]ethyl}octanamide (71f).** Yield, 59%; TLC R_f = 0.40 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (dd, J = 7.2, 7.2 Hz, 1H), 6.86–6.81 (m, 3H), 6.11 (brd, J = 6.6 Hz, 1H), 5.02 (m, 1H), 3.92–3.80 (m, 2H), 3.70 (d, J = 6.3 Hz, 2H), 2.24 (brt, J = 8.1 Hz, 2H), 2.17–1.96 (m, 1H), 1.70–1.50 (m, 2H), 1.40–1.20 (m, 8H), 0.87 (brt, J = 6.6 Hz, 3H).

***N*-{2-Hydroxy-1-[3-(pentyloxy)phenyl]ethyl}octanamide (71h).** Yield, 69%; TLC R_f = 0.24 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (dd, J = 8.1, 8.1 Hz, 1H), 6.86–6.81 (m, 3H), 6.11 (brd, J = 6.6 Hz, 1H), 5.02 (m, 1H), 3.94 (t, J = 6.6 Hz, 2H), 3.92–3.80 (m, 2H), 2.77 (brs, 1H), 2.24 (brt, J = 7.5 Hz, 2H), 1.82–1.60 (m, 4H), 1.50–1.20 (m, 12H), 0.93 (t, J = 7.2 Hz, 3H), 0.87 (brt, J = 6.9 Hz, 3H).

***N*-{1-[3-(Hexyloxy)phenyl]-2-hydroxyethyl}octanamide (71i).** Yield 87%; TLC R_f = 0.28 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (dd, J = 8.1, 8.1 Hz, 1H), 6.86–6.81 (m, 3H), 6.10 (brd, J = 7.2 Hz, 1H), 5.03 (m, 1H), 3.94 (t, J = 6.6 Hz, 2H), 3.92–3.80 (m, 2H), 2.77 (brs, 1H), 2.24 (brt, J = 7.5 Hz, 2H), 1.82–1.60 (m, 4H), 1.50–1.20 (m, 12H), 0.91 (t, J = 6.9 Hz, 3H), 0.87 (brt, J = 7.2 Hz, 3H).

***N*-{1-[3-(Cyclopentyloxy)phenyl]-2-hydroxyethyl}octanamide (71k).** Yield, 61%; TLC R_f = 0.42 (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (dd, J = 7.5, 7.5 Hz, 1H), 6.84–6.78 (m, 3H), 6.11 (brd, J = 6.9 Hz, 1H), 5.01 (m, 1H), 4.74 (m, 1H), 3.92–3.80 (m, 2H), 2.83 (brs, 1H), 2.24 (brt, J = 8.1 Hz, 2H), 2.00–1.55 (m, 10H), 1.40–1.20 (m, 8H), 0.87 (brt, J = 6.9 Hz, 3H).

***N*-(1-{3-[2-(Dimethylamino)-2-oxoethoxy]phenyl}-2-hydroxyethyl) octanamide (71l).** Yield, 82%; TLC R_f = 0.14 (EtOAc/MeOH, 19/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (t, J = 8.1 Hz, 1H), 6.92–6.81 (m, 3H), 6.32 (d, J = 6.9 Hz, 1H), 5.04–4.99 (m, 1H), 4.67 (s, 2H), 3.85–383 (m, 2H), 3.07 (s. 3H), 2.96 (s, 3H), 2.23 (t, J = 7.2 Hz, 2H), 1.68–1.58 (m, 2H), 1.29–1.23 (m, 8H), 0.89–0.84 (m, 3H).

***N*-{1-[3-(3-Benzyloxy)phenyl]-2-hydroxyethyl}octanamide (71m).** Yield, 79%; white powder; TLC R_f = 0.25 (*n*-hexane/toluene, 3/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.25 (m, 6H), 6.92–6.87 (m, 3H), 6.07 (d, J = 6.9 Hz, 1H), 5.05 (s, 2H), 5.02 (t, J = 9.0 Hz, 1H), 3.92–3.80 (m, 2H), 2.23 (t, J = 7.8 Hz, 2H), 1.69–1.59 (m, 2H), 1.30–1.26 (m, 8H), 0.86 (t, J = 6.9 Hz, 3H).

***N*-{1-[3-(Cyclobutyloxy)phenyl]-2-hydroxyethyl}octanamide (71j).** To a stirred mixture of **70** (614 mg, 2 mmol), PPh_3 (524 mg, 2 mmol) and cyclobutyl alcohol (144 mg, 2 mmol) in THF (6 mL) was added dropwise DEAD (0.32 mL, 2 mmol) at 0 °C. Stirring was continued for 24 h at room temperature. Removal of the solvent by evaporation gave a residue, which was purified by column chromatography on silica gel (Merck 7734, *n*-hexane/EtOAc, 4/1–3/1) to afforded methyl [(3-cyclobutyloxyphenyl)](octanoylamino)acetate (400 mg, 55%): TLC R_f = 0.33 (*n*-hexane/EtOAc, 3/1); ^{1}H NMR (300 MHz, CD_3OD) δ 7.23 (dd, J = 7.8, 7.8 Hz, 1H), 6.90 (brd, J = 7.8 Hz, 1H), 6.80 (brt, J = 2.1 Hz, 1H), 6.75 (dd, J = 7.8, 2.1 Hz, 1H), 6.35 (brd, J = 7.5 Hz, 1H), 5.54 (d, J = 7.2 Hz, 1H), 4.62 (m, 1H), 3.72 (s, 3H),

2.50–2.37 (m, 2H), 2.25–2.10 (m, 4H), 1.90–1.55 (m, 4H), 1.35–1.20 (m, 8H), 0.87 (t, $J=6.9$ Hz, 3H). The compound **71j** was prepared from methyl (3-cyclobutyloxyphenyl)(octanoylamino)acetate according to the same procedures as described for the preparation of **71a** from methyl (3-methoxymethoxy)phenyl(octanoylamino) acetate: TLC $R_f=0.36$ (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (dd, $J=7.8$, 7.8 Hz, 1H), 6.84 (brd, $J=7.8$ Hz, 1H), 6.75–6.70 (m, 2H), 6.10 (brd, $J=6.6$ Hz, 1H), 5.01 (m, 1H), 4.62 (m, 1H), 3.91–3.82 (m, 2H), 2.50–2.35 (m, 2H), 2.25–2.10 (m, 4H), 1.90–1.60 (m, 4H), 1.40–1.20 (m, 8H), 0.87 (t, $J=6.9$ Hz, 3H).

***N*-{1-[3-(1-Ethylpropoxy)phenyl]-2-hydroxyethyl}octanamide (71g).** The title compound **71g** was prepared from **70** according to the same procedures as described for the preparation of **71j** from **70** and purified by column chromatography on silica gel (Merck 7734, *n*-hexane/EtOAc, 4/1–3/1) to give methyl [3-(3-pentyloxylphenyl)](octanoylamino)acetate: 48% yield; TLC $R_f=0.38$ (*n*-hexane/EtOAc, 3/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (dd, $J=8.1$, 8.1 Hz, 1H), 6.89–6.81 (m, 3H), 6.33 (brd, $J=7.2$ Hz, 1H), 5.55 (d, $J=7.2$ Hz, 1H), 4.10 (m, 1H), 3.73 (s, 3H), 2.23 (t, $J=8.4$ Hz, 2H), 1.70–1.57 (m, 6H), 1.35–1.20 (m, 8H), 0.94 (t, $J=7.2$ Hz, 6H), 0.86 (brt, $J=6.9$ Hz, 3H). Compound **71g**: 98% yield; TLC $R_f=0.45$ (*n*-hexane/EtOAc, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (dd, $J=9.0$, 7.5 Hz, 1H), 6.84–6.79 (m, 3H), 6.09 (brd, $J=6.6$ Hz, 1H), 5.03 (m, 1H), 4.11 (m, 1H), 3.90–3.83 (m, 2H), 2.24 (t, $J=7.5$ Hz, 2H), 1.70–1.60 (m, 6H), 1.40–1.20 (m, 8H), 0.95 (t, $J=7.5$ Hz, 6H), 0.87 (brt, $J=6.9$ Hz, 3H).

2-(3-Hydoxyphenyl)-2-octanoylaminoethyl disodium phosphate (27). 2-(3-Methoxymethoxyphenyl)-2-octanoylaminoethyl dihydrogen phosphate was prepared from **71a** according to essentially the same procedures as described for the preparation of **62e** from **60e**. To a solution of 2-(3-metoxymetylphenyl)-2-octanoylaminoethyl dihydrogen phosphate in MeOH (10 mL) was added a few drops of 6 M HCl and the mixture was stirred at room temperature for 18 h. Following the addition of H_2O, the mixture was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Removal of the solvent by evaporation gave 2-(3-hydroxyphenyl)-2-octanoylaminoethyl dihydrogen phosphate as a white amorphous powder (54% yield), which was converted to the disodium salt according to the same procedures as described for the preparation of **1** from **62e**: gray amorphous powder; TLC $R_f=0.22$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3398, 1621, 1544, 1460, 1089, 983 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.04 (t, $J=7.8$ Hz, 1H), 6.78 (brs, 1H), 6.74 (brd, $J=7.8$ Hz, 1H), 6.59 (dd, $J=7.8$, 2.4 Hz, 1H), 4.82 (dd, $J=8.1$, 3.9 Hz, 1H), 4.00–3.86 (m, 2H), 2.36–2.18 (m, 2H), 1.68–1.53 (m, 2H), 1.35–1.24 (m, 8H), 0.91–0.86 (m, 3H); MS (FAB, Pos.) *m*/*z* 404 $(M+H)^+$, 426, 382; HRMS (MALDI-TOF, Pos.) calcd for $C_{16}H_{24}NO_6P{\cdot}2Na+H^+$: 404.1215; found: 404.1255.

2-(3-Methoxymethoxyphenyl)-2-octanoylaminoethyl disodium phosphate (40). 2-[(3-Methoxymethoxyphenyl)]-2-octanoylaminoethyl dihydrogen phosphate was obtained from **70a** according to the same procedures as described for the preparation of **27** from **70a**, which was converted to the disodium salt according to the same procedures as described for the preparation of **1** from **62e**: off-white amorphous powder; TLC $R_f=0.28$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3407, 1628, 1559, 1099, 986 cm^{-1}; ^{1}H NMR; (300 MHz, CD_3OD) δ 7.18 (t, $J=7.8$ Hz, 1H), 7.01 (brs, 1H), 6.98 (brd, $J=7.8$ Hz, 1H), 6.86 (ddd, $J=7.8$, 2.1, 0.9 Hz, 1H), 5.16 (d, $J=6.6$ Hz, 1H), 5.13 (d, $J=6.6$ Hz, 1H), 4.88–4.82 (m, 1H), 4.01–3.87 (m, 2H), 3.42 (s, 3H), 2.38–2.18 (m, 2H), 1.69–1.53 (m, 2H), 1.36–1.24 (m, 8H), 0.91–0.86 (m, 3H); MS (FAB, Pos.) *m*/*z* 448 $(M+H)^+$, 426, 404; HRMS (MALDI-TOF, Pos.) calcd for $C_{18}H_{28}NO_7P{\cdot}2Na+H^+$: 448.1477; found: 448.1488.

Preparation of **28**–**37**: the following compounds were prepared according to the same procedure as described for the preparation of **1** from **60e** (general method A).

2-(3-Ethoxyphenyl)-2-octanoylaminoethyl disodium phosphate (28). Yield, 36%; colorless powder; TLC $R_f=0.22$ ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3286, 2928, 1637, 1547, 1261, 1116 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.15 (t, $J=8.1$ Hz, 1H), 6.89 (m, 2H), 6.72 (dd, $J=8.1$, 1.8 Hz, 1H), 4.83 (m, 1H), 4.05–3.87 (m, 4H), 2.38–2.18 (m, 2H), 1.61 (m, 2H), 1.35 (t, $J=7.2$ Hz, 3H), 1.30–1.20 (m, 8H), 0.88 (brt, $J=6.6$ Hz, 3H); MS (FAB, Pos.) *m*/*z* 432 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{18}H_{28}NO_6P{\cdot}2Na+H^+$: 432.1528; found: 432.1518.

2-Octanoylamino-2-(3-propyloxyphenyl)ethyl disodium phosphate (29). Colorless powder; TLC $R_f=0.22$ ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3278, 2928, 1632, 1550, 1452, 1264, 1111 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.15 (t, $J=8.1$ Hz, 1H), 6.89 (m, 2H), 6.72 (dd, $J=8.1$, 1.8 Hz, 1H), 4.83 (m, 1H), 4.00–3.87 (m, 4H), 2.38–2.18 (m, 2H), 1.76 (tq, $J=7.5$, 7.5 Hz, 2H), 1.61 (m, 2H), 1.38–1.20 (m, 8H), 1.02 (t, $J=7.5$ Hz, 3H), 0.88 (brt, $J=6.6$ Hz, 3H); MS (FAB, Pos.) *m*/*z* 446 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{19}H_{30}NO_6P{\cdot}2Na+H^+$: 446.1684; found: 446.1719.

2-(3-Isopropyloxyphenyl)-2-octanoylaminoethyl disodium phosphate (30). Colorless powder; TLC $R_f=0.22$ ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3281, 2928, 1634, 1550, 1489, 1259, 1117 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.14 (t, $J=8.1$ Hz, 1H), 6.89 (m, 2H), 6.72 (dd, $J=8.1$, 2.4 Hz, 1H), 4.83 (m, 1H), 4.56 (qq, $J=6.0$, 6.0 Hz, 1H), 4.00–3.87 (m, 2H), 2.38–2.18 (m, 2H), 1.62 (m, 2H), 1.38–1.20 (m, 8H), 1.28 (d, $J=6.0$ Hz, 3H), 1.26 (d, $J=6.0$ Hz, 3H), 0.84 (brt, $J=6.6$ Hz, 3H); MS (FAB, Pos.) *m*/*z* 446 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{19}H_{30}NO_6P{\cdot}2Na+H^+$: 446.1684; found: 446.1720.

2-(3-Butyloxyphenyl)-2-octanoylaminoethyl disodium phosphate (31). Colorless powder; TLC $R_f=0.35$ ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3260, 2930, 1658, 1626, 1555, 1460, 1097, 990 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.15 (t, $J=8.1$ Hz, 1H), 6.89 (m,

2H), 6.72 (dd, $J=8.1$, 2.4 Hz, 1H), 4.83 (m, 1H), 4.00–3.87 (m, 4H), 2.40–2.18 (m, 2H), 1.77–1.40 (m, 6H), 1.40–1.20 (m, 8H), 0.97 (t, $J=7.5$ Hz, 3H), 0.88 (brt, $J=6.3$ Hz, 3H); MS (FAB, Pos.) m/z 482 $(M+Na)^+$, 460 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{20}H_{32}NO_6P{\cdot}2Na+H^+$: 460.1841; found: 460.1837.

2-(3-Isobutyloxyphenyl)-2-octanoylaminoethyl disodium phosphate (32). Colorless powder; TLC $R_f=0.26$ ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3298, 2928, 1631, 1550, 1469, 1266, 1113, 988 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.15 (t, $J=7.8$ Hz, 1H), 6.89 (m, 2H), 6.73 (dd, $J=7.8$, 1.8 Hz, 1H), 4.84 (m, 1H), 4.00–3.88 (m, 2H), 3.75–3.65 (m, 2H), 2.39–2.18 (m, 2H), 2.09–1.95 (m, 1H), 1.70–1.50 (m, 2H), 1.40–1.20 (m, 8H), 1.01 (d, $J=6.9$ Hz, 6H), 0.88 (brt, $J=6.6$ Hz, 3H); MS (FAB, Pos.) m/z 482 $(M+Na)^+$, 460 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{20}H_{32}NO_6P{\cdot}2Na+H^+$: 460.1841; found: 460.1850.

2-[3-(3-Pentyloxyphenyl)]-2-octanoylaminoethyl disodium phosphate (33). Colorless powder; TLC $R_f=0.23$ ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3279, 2962, 2929, 1632, 1551, 1463, 1268, 1111 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.14 (t, $J=8.1$ Hz, 1H), 6.88 (m, 2H), 6.72 (dd, $J=8.1$, 1.8 Hz, 1H), 4.84 (m, 1H), 4.14 (m, 1H), 4.00–3.87 (m, 2H), 2.40–2.18 (m, 2H), 1.70–1.50 (m, 6H), 1.40–1.20 (m, 8H), 0.94 (t, $J=7.5$ Hz, 3H), 0.93 (t, $J=7.5$ Hz, 3H), 0.88 (brt, $J=6.9$ Hz, 3H); MS (FAB, Pos.) m/z 496 $(M+Na)^+$, 474 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{21}H_{34}NO_6P{\cdot}2Na+H^+$: 474.1997; found: 474.1992.

2-(3-*n*-Pentyloxyphenyl)-2-octanoylaminoethyl disodium phosphate (34). Colorless powder; TLC $R_f=0.35$ ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3259, 2928, 1656, 1625, 1556, 1460, 1098, 990 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.15 (t, $J=8.1$ Hz, 1H), 6.89 (m, 2H), 6.72 (dd, $J=8.1$, 1.8 Hz, 1H), 4.83 (m, 1H), 4.00–3.87 (m, 4H), 2.40–2.18 (m, 2H), 1.80–1.20 (m, 16H), 0.94 (t, $J=7.2$ Hz, 3H), 0.88 (brt, $J=6.3$ Hz, 3H); MS (FAB, Pos.) m/z 496 $(M+Na)^+$, 474 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{21}H_{34}NO_6P{\cdot}2Na+H^+$: 474.1997; found: 474.2013.

2-(3-*n*-Hexyloxyphenyl)-2-octanoylaminoethyl disodium phosphate (35). Colorless powder; TLC $R_f=0.35$ ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3259, 2927, 1657, 1625, 1556, 1459, 1099, 990 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.15 (t, $J=8.1$ Hz, 1H), 6.89 (m, 2H), 6.73 (dd, $J=8.1$, 2.4 Hz, 1H), 4.83 (m, 1H), 4.00–3.87 (m, 4H), 2.40–2.18 (m, 2H), 1.80–1.20 (m, 18H), 0.92 (t, $J=6.9$ Hz, 3H), 0.88 (brt, $J=6.6$ Hz, 3H); MS (FAB, Pos.) m/z 488 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{22}H_{36}NO_6P{\cdot}2Na+H^+$: 488.2154; found: 488.2179.

2-(3-Cyclobutyloxyphenyl)-2-octanoylaminoethyl disodium phosphate (36). Colorless powder; TLC $R_f=0.21$ ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3263, 2927, 1626, 1553, 1453, 1101, 989 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.13 (t, $J=7.8$ Hz, 1H), 6.89 (brd, $J=7.8$ Hz, 1H), 6.79 (brt, $J=1.8$ Hz, 1H), 6.63 (dd, $J=7.8$, 1.8 Hz, 1H), 4.84 (m, 1H), 4.64 (m, 1H), 3.98–3.86 (m, 2H), 2.50–2.00 (m, 6H), 1.85–1.50 (m, 4H), 1.40–1.20 (m, 8H), 0.88 (brt, $J=6.6$ Hz, 3H); MS (FAB, Pos.) m/z 480 $(M+Na)^+$, 458 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{20}H_{30}NO_6P{\cdot}2Na+H^+$: 458.1684; found: 458.1716.

2-(3-Cyclopentyloxyphenyl)-2-octanoylaminoethyl disodium phosphate (37). Colorless powder; TLC $R_f=0.26$ ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3288, 2928, 1636, 1550, 1450, 1112, 987 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.14 (t, $J=7.8$ Hz, 1H), 6.87 (m, 2H), 6.69 (dd, $J=7.8$, 1.8 Hz, 1H), 4.84 (m, 1H), 4.77 (m, 1H), 4.00–3.87 (m, 2H), 2.40–2.18 (m, 2H), 1.95–1.50 (m, 10H), 1.40–1.20 (m, 8H), 0.88 (brt, $J=6.6$ Hz, 3H); MS (FAB, Pos.) m/z 494 $(M+Na)^+$, 472 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{21}H_{32}NO_6P{\cdot}2Na+H^+$: 472.1841; found: 472.1838.

2-(3-Dimethylaminocarbonylmethyloxyphenyl)-2-octanoylaminoethyl disodium phosphate (38). Ivory powder; TLC $R_f=0.30$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3855, 3424, 2928, 1648, 1544, 1491, 1458, 1363, 1257, 1090 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.18 (t, $J=8.1$ Hz, 1H), 6.98–6.96 (m, 2H), 6.83–6.80 (m, 1H), 4.88–4.84 (m, 1H), 4.75 (s, 2H), 3.99–3.91 (m, 2H), 3.09 (s, 3H), 2.96 (s, 3H), 2.38–2.18 (m, 2H), 1.66–1.53 (m, 2H), 1.30–1.28 (m, 8H), 0.88 (t, $J=6.9$ Hz, 3H); MS (FAB. Pos.) m/z 489 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{20}H_{31}N_2O_7P{\cdot}2Na+H^+$: 489.1743; found: 489.1748.

Ethyl {3-[2-hydroxy-1-(octanoylamino)ethyl]phenoxy} acetate (72). A mixture of **71m** (1.2 g, 3.25 mmol) in EtOH (20 mL) and 10% Pd-C (120 mg) was stirred at room temperature under an atmospheric pressure of hydrogen for 2 h. Removal of the catalyst by filtration through a pad of Celite followed by evaporation of the filtrate afforded 2-(3-hydroxyphenyl)-2-octanoylaminoethanol as an oily residue which was used for the next reaction without further purification: TLC $R_f=0.50$ (EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.18 (m, 1H), 6.83–6.75 (m, 3H), 6.20 (d, $J=7.5$ Hz, 1H), 4.98 (dt, $J=7.5$, 4.0 Hz, 1H), 3.85 (d, $J=4.0$ Hz, 2H), 2.25 (t, $J=7.5$ Hz, 2H), 1.67 (m, 2H), 1.40–1.20 (m, 8H), 0.88 (t, $J=6.2$ Hz, 3H). To a stirred mixture of 2-(3-hydroxyphenyl)-2-octanoylaminoethanol (906 mg, 3.25 mmol), K_2CO_3 (897 mg, 6.5 mmol) and KI (647 mg, 3.9 mmol) in DMF (10 mL) was added ethyl bromoacetate (0.43 mL, 3.9 mmol) and stirring was continued at room temperature for 2 days. The reaction mixture was poured into ice-cooled 1 M HCl and extracted with EtOAc. The organic layer was successively washed with H_2O and brine before being dried over Na_2SO_4. Removal of the solvent by evaporation gave a residue which was purified by column chromatography on silica gel (Merck 7734, *n*-hexane/EtOAc, 1/1–1/2–1/3) to afford **72** as a colorless wax: 81% yield in 2 steps; TLC $R_f=0.55$ (EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (t, $J=8.0$ Hz, 1H), 6.92 (d, $J=8.0$ Hz, 1H), 6.88 (t, $J=2.7$ Hz, 1H), 6.80 (dd, $J=8.0$, 2.7 Hz, 1H), 6.21 (d, $J=6.6$ Hz, 1H), 5.03 (dt, $J=6.6$, 5.0 Hz, 1H), 4.61 (s,

2H), 4.27 (q, $J=7.0$ Hz, 2H), 3.85 (d, $J=5.0$ Hz, 2H), 2.24 (t, $J=7.2$ Hz, 2H), 1.64 (m, 2H), 1.40–1.20 (m) and 1.31 (t, $J=7.0$ Hz) total 11H, 0.88 (m, 3H).

General method D

2-(3-Ethoxycarbonylmethylphenyl)-2-octanoylaminoethyl disodium phosphate (39). To a stirred solution of **72** (960 mg, 2.6 mmol) and tetrazole (364 mg, 5.2 mmol) in CH_3CN (10 mL) was added dibenzyl diisopropylphosphoramidite (989 mg, 3.1 mmol) in CH_3CN (5 mL). Stirring was continued at room temperature for 3 h. The reaction mixture was poured into saturated $NaHCO_3$ aq and extracted with EtOAc. After the organic layer was successively washed with H_2O and brine, it was dried over Na_2SO_4. Removal of the solvent by evaporation gave dibenzyl 2-(3-ethoxycarbonylmethylphenyl)-2-octanoylaminoethyl phosphite which was used for the next reaction without further purification. To a stirred solution of dibenzyl 2-(3-ethoxycarbonylmethylphenyl)-2-octanoylaminoethyl phosphite (1.58 g, 2.6 mmol) in CH_2Cl_2 (10 mL) was added *m*-CPBA (70%, 767 mg, 3.12 mmol) at 0 °C and stirring was continued for 30 min at that temperature. Next saturated $Na_2S_2O_3$ aq was added to the mixture and the mixture was extracted with EtOAc. The organic layer was successively washed with saturated $NaHCO_3$ aq, H_2O and brine before being dried over Na_2SO_4. Removal of the solvent by evaporation gave a residue which was purified by column chromatography on silica gel (Merck 7734, *n*-hexane/EtOAc, 3/1–2/1–1/1) to afford dibenzyl 2-(3-ethoxycarbonylmethylphenyl)-2-octanolyaminoethyl phosphate as a colorless oil (80% yield in 2 steps). A mixture of dibenzyl 2-(3-ethoxycarbonylmethylphenyl)-2-octanolyaminoethyl phosphate (1.3 g, 2 mmol) in EtOH (10 mL) and 10% Pd-C (130 mg) was stirred at room temperature under an atmospheric pressure of hydrogen for 20 h. Removal of the catalyst by filtration through a pad of Celite followed by evaporation afforded 2-(3-ethoxycarbonylmethylphenyl)-2-octanolyamino phosphate as a colorless oil (89% yield). To a stirred solution of 2-(3-ethoxycarbonylmethylphenyl)-2-octanolyamino dihydrogen phosphate (390 mg, 0.87 mmol) in EtOH (5 mL) was added 1 M $NaHCO_3$ aq. Removal of the solvent by evaporation gave the title compound **39** as a white powder: 94% yield; TLC $R_f=0.50$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3258, 1765, 1625, 1557, 1461, 1025, 1098 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.19 (t, $J=7.8$ Hz, 1H), 6.98 (d, $J=7.8$ Hz, 1H), 6.94 (t, $J=2.1$ Hz, 1H), 6.76 (m, 1H), 4.85–4.83 (m, 1H), 4.67 (s, 2H), 4.24 (q, $J=7.2$ Hz, 2H), 4.04–3.86 (m, 2H), 2.40–2.18 (m, 2H), 1.65–1.55 (m, 2H), 1.40–1.20 (m) and 1.28 (t, $J=7.2$ Hz) total 11H, 0.89 (brt, $J=6.9$ Hz, 3H); MS (FAB. Pos.) *m/z* 512 $(M+Na)^+$, 490 $(M+H)^+$, 468; HRMS (MALDI-TOF, Pos.) calcd for $C_{20}H_{31}NO_8P{\cdot}2Na+H^+$: 490.1583; found: 490.1567.

1-(*tert*-Butyldimethylsilyl)-2-(3-methoxycarbonylphenyl)-2-octanoylaminoethyl ether (73). To a stirred solution of **71m** (10.0 g, 27.0 mmol) and TBDMSCl (4.88 g, 32.4 mmol) in DMF (30 mL) was added imidazole (4.59 g, 67.5 mmol) at 0 °C and stirring was continued for 18 h at room temperature. The reaction mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent by evaporation gave 2-(3-benzyloxyphenyl)-1-(*tert*-butyldimethylsilyl)-2-octanoylaminoethyl ether as a colorless oil (15.2 g, quant.): TLC $R_f=0.46$ (*n*-hexane/EtOAc, 2/1); ^1H NMR (200 MHz, $CDCl_3$) δ 7.46–7.30 (m, 6H), 7.27–7.19 (m, 1H), 6.96–6.82 (m, 2H), 6.17 (d, $J=7.8$ Hz, 1H), 5.05 (s, 2H), 5.06–4.94 (m, 1H), 3.89 (dd, $J=10.2$, 4.4 Hz, 1H), 3.78 (dd, $J=10.2$, 4.4 Hz, 1H), 2.27–2.19 (m, 2H), 1.40–1.20 (m, H), 0.86 (s, 9H), 0.90–0.80 (m, 3H), −0.03 (s, 3H), −0.06 (s, 3H). A mixture of 2-(3-benzyloxyphenyl)-1-(*tert*-butyldimethylsilyl)-2-octanoylaminoethyl ether (15.23 g, 27.0 mmol) in MeOH (200 mL) and 10% Pd–C (1.0 g) was stirred at room temperature under an atmospheric pressure of hydrogen for 2 h. Removal of the catalyst by filtration through a pad of Celite followed by evaporation afforded 1-(*tert*-butyldimethylsilyl)-2-(3-hydroxyphenyl)-2-octanoylaminoethyl ether as a white powder (10.6 g, quant.): TLC $R_f=0.33$ (*n*-hexane/EtOAc, 3/1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.11 (t, $J=7.6$ Hz, 1H), 6.80–6.66 (m, 3H), 6.35 (d, $J=7.6$ Hz, 1H), 4.96–4.88 (m, 1H), 3.87 (dd, $J=10.2$, 4.4 Hz, 1H), 3.72 (dd, $J=10.2$, 4.4 Hz, 1H), 2.30–2.22 (m, 2H), 1.40–1.20 (m, (H), 0.95–0.90 (m, 12H), −0.04 (s, 3H), −0.06 (s, 3H). To a stirred solution of 1-(*tert*-butyldimethylsilyl)-2-(3-hydroxyphenyl)-2-octanoylaminoethyl ether (8.26 g, 21.0 mmol) in pyridine (30 mL) was added dropwise Tf_2O (3.90 mL, 23.1 mmol) at 0 °C. Stirring was continued for 1 h at that temperature. The reaction mixture was poured into 1 M HCl and extracted with EtOAc. The organic layer was successively washed saturated $NaHCO_3$ aq and brine before being dried over $MgSO_4$. Removal of the solvent by evaporation gave 1-(*tert*-butyldimethylsilyl) - 2 - (3 - trifluoromethansulfonyloxyphenyl)-2-octanoylaminoethyl ether as a yellow oil (11.6 g, quant.): TLC $R_f=0.54$ (*n*-hexane/EtOAc, 3/1). To a stirred mixture of 1-(*tert*-butyldimethylsilyl) - 2 - (3 - trifluoromethansulfonyloxyphenyl)-2-octanoylaminoethyl ether (9.46 g, 18 mmol), Et_3N (6.30 mL, 45.0 mmol) and $Pd(OAc)_2$ (202 mg, 0.9 mmol) in MeOH (36 mL)/DMSO (54 mL) was added DPPP (371 mg, 0.9 mmol) at room temperature. Stirring was continued at 70 °C for 2 h under an atmospheric pressure of carbon monoxide. The reaction mixture was poured into 0.2 M HCl and extracted with EtOAc. The organic layer was successively washed with saturated $NaHCO_3$ aq and brine before being dried over $MgSO_4$. Removal of the solvent by evaporation gave an residue which was purified by column chromatography on silica gal (Merck 7734, *n*-hexane/EtOAc, 4/1) to afford **73** as a pale yellow oil: 93% yield; TLC $R_f=0.35$ (*n*-hexane/EtOAc, 3/1); ^1H NMR (200 MHz, $CDCl_3$) δ 8.00 (brs, 1H), 7.93 (brd, $J=7.6$ Hz, 1H), 7.50 (brd, $J=7.6$ Hz, 1H), 7.38 (t, $J=7.6$ Hz, 1H), 6.30 (brd, $J=7.6$ Hz, 1H), 5.12–5.04 (m, 1H), 3.92 (dd, $J=10.0$, 4.4 Hz, 1H), 3.91 (s, 3H), 3.80 (dd, $J=10.0$, 4.0 Hz, 1H), 2.25 (t, $J=7.2$ Hz, 2H), 2.30–2.20 (m, 2H), 1.40–1.20 (m, 8H), 0.95–0.90 (m, 12H), −0.04 (s, 3H), −0.08 (s, 3H).

***N*-(2-Hydroxy-1-{3-[(methoxymethoxy)methyl]phenyl}ethyl)octanamide (74).** To a stirred solution of **73** (3.00 g, 6.88 mmol) in THF (10 mL) and MeOH (20 mL) was

added $LiBH_4$ (300 mg, 13.8 mmol) at 0 °C and stirring was continued at room temperature for 20 h. Next $LiBH_4$ (150 mg, 6.88 mmol) was added to the resulting mixture and stirred at 45 °C for 2 h. The reaction mixture was poured into saturated NH_4Cl aq and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent by evaporation gave a residue which was purified by column chromatography on silica gel (Merck 7734, *n*-hexane/EtOAc, 1/1) to afford 1-(*tert*-butyldimethylsilyl)-2-(3-hydroxymethlyphenyl)-2-octanoylaminoethyl ether as a colorless oil (1.80 g, 62%): TLC $R_f = 0.53$ (*n*-hexane/EtOAc, 1/1). To a stirred solution of 1-(*tert*-butyldimethylsilyl)-2-(3-hydroxymethlyphenyl)-2-octanoylaminoethyl ether (1.42 g, 3.38 mmol) and $^{i}Pr_2NEt$ (3.0 mL) in CH_2Cl_2 (5.0 mL) was added MOMCl (0.385 mL, 5.07 mmol) at room temperature and stirring was continued at that temperature for 1 h. The reaction mixture was poured into 1 M HCl and extracted with EtOAc. The organic layer was successively washed with saturated $NaHCO_3$ aq and brine before being dried over $MgSO_4$. Removal of the solvent by evaporation gave 1-(*tert*-butyldimethylsilyl)-2-(3-methoxymethlyoxymethylphenyl)-2-octanoylaminoethyl ether as a yellow oil (1.39 g, 89%): TLC $R_f = 0.31$ (*n*-hexane/EtOAc, 3/1); ^1H NMR (200 MHz, $CDCl_3$) δ 7.35–7.20 (m, 4H), 6.20 (brd, $J = 7.6$ Hz, 1H), 5.09–5.01 (m, 1H), 4.70 (s, 2H), 4.58 (s, 2H), 3.91 (dd, $J = 10.2$, 4.2 Hz, 1H), 3.82 (dd, $J = 10.2$, 4.2 Hz, 1H), 2.27–2.20 (m, 2H), 1.75–1.60 (m, 2H), 1.40–1.20 (m, 8H), 0.90–0.80 (m, 12H), −0.04 (s, 3H), −0.07 (s, 3H). To a stirred solution of 1-(*tert*-butyldimethylsilyl)-2-(3-methoxymethlyoxymethylphenyl)-2-octanoylaminoethyl ether (1.39 g, 3.00 mmol) in THF (10 mL) was added TBAF (1.0 M THF, 3.00 mL, 3.00 mmol) at 0 °C and stirring was continued at that temperature for 30 min. The reaction mixture was poured into saturated NH_4Cl aq and extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent by evaporation gave **74** as a yellow oil: TLC $R_f = 0.34$ (EtOAc). The compound was used for the next reaction without further purification.

Method E

2-(3-Methoxymethyloxymethylphenyl)-2-octanoylaminoethyl phosphate (76). To a stirred solution of **74** (1.0 g, 3.0 mmol) and tetrazole (420 mg, 6.0 mmol) in CH_3CN (20 mL) was added bis(2-cyanoethyl) diisopropylamidophosphite[19] (819 mg, 3.30 mmol) at room temperature and stirring was continued at that temperature for 2 h. The reaction mixture was poured into saturated $NaHCO_3$ aq and extracted with EtOAc. The organic layer was successively washed with H_2O and brine before being dried over $MgSO_4$. Removal of the solvent by evaporation gave bis(2-cyanoethyl) 2-(3-methoxymethyloxymethylphenyl)-2-octanoylaminoethyl phosphite as a colorless oil which was used for the next reaction without further purification: TLC $R_f = 0.21$ (*n*-hexane/EtOAc, 1/2). To a stirred solution of bis(2-cyanoethyl) 2-(3-methoxymethyloxymethylphenyl)-2-octanoylaminoethyl phosphite (1.58 g, 3.0 mmol) in CH_2Cl_2 (15 mL) was added *m*-CPBA (57%, 908 mg, 3.0 mmol) at 0 °C and stirring was continued for 30 min at that temperature. Next satd $Na_2S_2O_3$ aq was added and the reaction mixture was extracted with EtOAc. The organic layer was successively washed with saturated $NaHCO_3$ aq, H_2O and brine before being dried over Na_2SO_4. Removal of the solvent by evaporation gave bis(2-cyanoethyl) 2-(3-methoxymethyloxymethylphenyl)-2-octanoylaminoethyl phosphate as a pale yellow oil which was used for the next reaction without further purification: TLC $R_f = 0.10$ (*n*-hexane/EtOAc, 1/3). To a stirred solution of bis(2-cyanoethyl) 2-(3-methoxymethyloxymethylphenyl)-2-octanoylaminoethyl phosphate in EtOH (10 mL) was added 50% Me_2NH aq (5.0 mL). Stirring was continued under reflux for 4 h. The reaction mixture was poured into 1 M HCl and extracted with EtOAc. The organic layer was successively washed with H_2O and brine before being dried over Na_2SO_4. Removal of the solvent by evaporation gave a residue, which was purified by column chromatography on silica gel (Merck 7734, $CHCl_3$/MeOH/NH_4OH, 65/25/1–$CHCl_3$/MeOH/H_2O, 65/25/4) to afford 2-(3-methoxymethyloxymethylphenyl)-2-octanoylaminoethyl diammonium phosphate which was acidified with 1 M HCl and then extracted with EtOAc. The organic layer was successively washed with H_2O and brine before being dried over Na_2SO_4. Removal of the solvent by evaporation gave a residue which was washed with Et_2O/*n*-hexane to obtain **76** as a white powder (473 mg, 38%): TLC $R_f = 0.40$ ($CHCl_3$/MeOH/H_2O, 65/35/8); ^1H NMR (200 MHz, CD_3OD) δ 7.37–7.25 (m, 4H), 5.21–5.17 (m, 1H), 4.68 (s, 2H), 4.57 (s, 2H), 4.18–4.05 (m, 2H), 3.37 (s, 3H), 2.26 (t, $J = 7.5$ Hz, 2H), 1.66–1.50 (m, 2H), 1.35–1.25 (m, 8H), 0.90–0.85 (m, 3H).

2-(3-Hydroxymethylphenyl)-2-octanoylaminoethyl disodium phosphate (41). To a stirred solution of **76** (406 mg, 0.973 mmol) in MeOH (10 mL) was added a few drops of 1 M HCl and stirring was continued at 60 °C for 6 h. The reaction mixture was poured into H_2O and then extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Removal of the solvent by evaporation gave a residue which was washed with Et_2O/EtOAc to afford 2-(3-Hydroxymethylphenyl)-2-octanoylaminoethyl dihydrogen phosphate as a white powder (279 mg, 77%): TLC $R_f = 0.30$ ($CHCl_3$/MeOH/H_2O, 65/35/8); ^{1}HNMR (200 MHz, CD_3OD) δ 7.40–7.20 (m, 4H), 5.23–5.15 (m, 1H), 4.59 (s, 2H), 4.20–4.05 (m, 2H), 2.25 (t, $J = 7.4$ Hz, 2H), 1.65–1.50 (m, 2H), 1.40–1.20 (m, 8H), 0.91–0.85 (m, 3H). The title compound **41** was obtained according to the same procedures as described for the preparation of **1** from **62e**: white amorphous powder; TLC $R_f = 0.30$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3254, 3074, 1641, 1560, 1115, 1100, 1020, 984 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.34 (brs, 1H), 7.25–7.18 (m, 3H), 4.90–4.87 (m, 1H), 4.56 (s, 2H), 4.03–3.88 (m, 2H), 2.37–2.19 (m, 2H), 1.65–1.53 (m, 2H), 1.34–1.25 (m, 8H), 0.91–0.86 (m, 3H); MS (FAB, Pos.) *m/z* 418 $(M+H)^+$, 440, 396; HRMS (MALDI-TOF, Pos.) calcd for $C_{17}H_{26}NO_6P{\cdot}2Na+H^+$: 418.1371; found: 418.1342.

2-(3-Methoxymethylphenyl)-2-octanoylaminoethyl dihydrogen phosphate (77). To a stirred solution of 1-(*tert*-butyldimethylsilyl)-2-(3-hydroxymethylyphenyl)-2-octa-

noylaminoethyl ether (800 mg, 1.91 mmol) and MeI (0.240 mL, 3.82 mmol) in THF (5.0 mL) was added NaH (60% dispersion in mineral oil, 92 mg, 2.29 mmol) at 0 °C and stirring was continued for 2 h. The reaction mixture was poured into saturated NH_4Cl aq and extracted with EtOAc. The organic layer was successively washed with brine and dried over $MgSO_4$. Removal of the solvent by evaporation gave a residue which was purified by column chromatography on silica gel (Merck 7734, *n*-hexane/EtOAc, 4/1) to afford 1-(*tert*-butyldimethylsilyl)-2-(3-methoxymethylphenyl)-2-octanoylaminoethyl ether as a colorless oil (740 mg, 89%): TLC $R_f = 0.38$ (*n*-hexane/EtOAc, 3/1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35–7.20 (m, 4H), 6.20 (brd, $J = 7.6$ Hz, 1H), 5.09–5.01 (m, 1H), 4.44 (s, 2H), 3.90 (dd, $J = 10.2$, 4.2 Hz, 1H), 3.80 (dd, $J = 10.2$, 4.2 Hz, 1H), 3.41 (s, 3H), 2.27–2.10 (m, 2H), 1.75–1.60 (m, 2H), 1.40–1.20 (m, 8H), 0.90–0.80 (m, 12H), −0.04 (s, 3H), −0.07 (s, 3H). *N*-{2-Hydroxy-1-[3-(methoxymethyl) phenyl]ethyl}octanamide **75** was obtained from 1-(*tert*-butyldimethylsilyl)-2-(3-methoxymethylphenyl)-2-octanoylaminoethyl ether according to the same procedures as described for the preparation of **74** from 1-(*tert*-butyldimethylsilyl)-2-(3-methoxymethyloxymethylphenyl)-2-octanoylaminoethyl ether, which was used for the next reaction without further purification: 85% yield; white powder; TLC $R_f = 0.34$ (EtOAc). The title compound **77** was obtained from **75** according to the same procedures as described for the preparation of **76** from **74**: 65% yield; colorless amorphous powder; TLC $R_f = 0.41$ ($CHCl_3$/MeOH/H_2O, 65/35/8); ^{1}H NMR (200 MHz, CD_3OD) δ 7.40–7.20 (m, 4H), 5.23–5.16 (m, 1H), 4.45 (s, 2H), 4.20–4.00 (m, 2H), 3.36 (s, 3H), 2.29–2.22 (m, 2H), 1.70–1.50 (m, 2H), 1.40–1.20 (m, 8H), 0.91–0.85 (m, 3H).

2-(3-Methoxymethylphenyl)-2-octanoylaminoethyl disodium phosphate (42). The title compound **42** was obtained from **27** according to the same procedures as described for the preparation of **1** from **62e**: white amorphous powder; TLC $R_f = 0.41$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3260, 1626, 1555, 1102, 989 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.32 (brs, 1H), 7.31–7.23 (m, 2H), 7.17 (brd, $J = 6.6$ Hz, 1H), 4.92–4.87 (m, 1H), 4.42 (s, 2H), 4.02–3.88 (m, 2H), 3.33 (s, 3H), 2.38–2.19 (m, 2H), 1.66–1.53 (m, 2H), 1.35–1.24 (m, 8H), 0.92–0.85 (m, 3H); MS (FAB, Pos.) *m*/*z* 432 $(M+H)^+$, 454, 410; HRMS (MALDI-TOF, Pos.) calcd for $C_{18}H_{28}NO_6P{\cdot}2Na + H^+$: 432.1479; found: 432.1528.

Methyl 3-[2-hydroxy-1-(octanoylamino)ethyl]benzoate (78). The title compound **78** was obtained from **73** according to the same procedures as described for the preparation of **74** from 1-(*tert*-butyldimethylsilyl)-2-(3-methoxymethlyoxy methylphenyl)-2-octanoylaminoethyl ether, which was washed with *n*-hexane to give a white powder: 93% yield; TLC $R_f = 0.25$ (*n*-hexane/EtOAc, 1/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00–7.94 (m, 2H), 7.51 (dt, $J = 6.0$ Hz, 1.5 Hz, 1H), 7.43 (t, $J = 8.1$ Hz, 1H), 6.26 (d, $J = 6.9$ Hz, 1H), 5.15–5.09 (m, 1H), 3.91 (s, 3H), 3.92–3.87 (m, 2H), 2.26 (t, $J = 7.5$ Hz, 2H), 1.67–1.62 (m, 2H), 1.30–1.26 (m, 8H), 0.86(t, $J = 6.6$ Hz, 3H).

2-(3-Methoxycarbonylphenyl)-2-octanoylaminoethyl disodium phosphate (44). Bis(2-cyanoethyl) 2-(3-methoxycarbonylphenyl)-2-octanolyaminoethyl phosphate was obtained from **78** according to the essentially same procedures as described for the preparation of **76** from **74** using DBU instead of 50% Me_2NH aq. To a stirred solution of bis(2-cyanoethyl) 2-(3-methoxycarbonylphenyl)-2-octanolyaminoethyl phosphate (2.18 mmol) in THF (10 mL) was added DBU (0.98 mL, 6.54 mmol) and stirring was continued at the reflux temperature for 3 h. The reaction mixture was poured into 1 M HCl and extracted with EtOAc. The organic layer was washed with brine and then dried over Na_2SO_4. Removal of the solvent by evaporation gave a residue, which was purified by column chromatography on silica gel (Merck 7734, $CHCl_3$/MeOH/NH_4OH, 65/25/1–$CHCl_3$/MeOH/H_2O, 65/25/4) to afford 2-(3-methoxycarbonylphenyl)-2-octanoylaminoethyl diammonium phosphate which was acidified with 1 M HCl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Removal of the solvent by evaporation gave a residue which was washed with Et_2O/*n*-hexane to obtain 2-(3-methoxycarbonylphenyl)-2-octanoylaminoethyl dihydrogen phosphate as a white powder (370 mg, 38%): TLC $R_f = 0.41$ ($CHCl_3$/MeOH/H_2O, 65/35/8); ^{1}H NMR; (200 MHz, CD_3OD) δ 8.04 (brs, 1H), 7,94 (brd, $J = 7.6$ Hz, 1H), 7.62 (brd, $J = 7.6$ Hz, 1H), 7.46 (t, $J = 7.6$ Hz, 1H), 5.24 (t, $J = 6.2$ Hz, 1H), 4.19–4.12 (m, 2H), 3.90 (s, 3H), 2.27 (t, $J = 5.8$ Hz, 2H), 1.70–1.50 (m, 2H), 1.35–1.20 (m, 8H), 0.90–0.84 (m, 3H). The title compound **44** was obtained from 2-(3-methoxycarbonylphenyl)-2-octanoylaminoethyl dihydrogen phosphate according to the same procedures as described for the preparation of **1** from **62e**: white amorphous powder: TLC $R_f = 0.34$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3267, 1729, 1626, 1552, 1292, 1202, 1097 cm^{-1}; ^{1}H NMR; (300 MHz, CD_3OD) δ 8.01 (brs, 1H), 7.86 (brd, $J = 8.1$ Hz, 1H), 7.61 (brd, $J = 8.1$ Hz, 1H), 7.39 (t, $J = 8.1$ Hz, 1H), 4.94 (dd, $J = 8.1$, 3.9 Hz, 1H), 4.06–3.93 (m, 2H), 3.88 (s, 3H), 2.39–2.20 (m, 2H), 1.66–1.53 (m, 2H), 1.34–1.22 (m, 8H), 0.91–0.84 (m, 3H); MS (FAB, Pos.) *m*/*z* 446 $(M+H)^+$, 468, 424; HRMS (MALDI-TOF, Pos.) calcd for $C_{18}H_{26}NO_7P{\cdot}2Na + H^+$: 446.1321; found: 446.1318.

Trisodium 3-[1-(octanoylamino)-2-(phosphonooxy)ethyl]-benzoate (43). To a stirred solution of 2-(3-methoxycarbonylphenyl)-2-octanoylaminoethyl dihydrogen phosphate (700 mg, 1.74 mmol) in THF (5.0 mL) and MeOH (5.0 mL) was added 2 M NaOH (3.48 mL, 6.96 mmol) at 0 °C and stirring was continued at room temperature for 3 h. The reaction mixture was poured into 1 M HCl and extracted with EtOAc. The organic layer was washed with brine and then dried over Na_2SO_4. Removal of the solvent by evaporation gave a residue which was washed with Et_2O/*n*-hexane to afford 2-(3-carboxylphenyl)-2-octanoylaminoethyl phosphate as a white powder (600 mg, 89%): TLC $R_f = 0.20$ ($CHCl_3$/MeOH/H_2O, 65/35/8); ^{1}H NMR; (200 MHz, CD_3OD) δ 8.05 (brs, 1H), 7.97–7.92 (m, 1H), 7.64–7.57 (m, 1H), 7.49–7.42 (m, 1H), 5.28–5.21 (m, 1H), 4.19–4.12 (m, 2H), 2.27 (t, $J = 7.6$ Hz, 2H), 1.70–1.50 (m, 2H),

1.40–1.20 (m, 8H), 0.90–0.84 (m, 3H). The title compound **43** was prepared from 2-(3-carboxylphenyl)-2-octanoylaminoethyl dihydrogen phosphate according to the same procedures as described for the preparation of **1** from **62e**: white amorphous powder: TLC $R_f = 0.20$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3422, 1637, 1560, 1390, 1096, 984 cm^{-1}; ^1H NMR; (300 MHz, CD_3OD) δ 7.96 (brs, 1H), 7.80 (dt, $J = 7.5$, 1.2 Hz, 1H), 7.42 (brd, $J = 7.5$ Hz, 1H), 7.26 (t, $J = 7.5$ Hz, 1H), 4.98–4.94 (m, 1H), 4.04–3.90 (m, 2H), 2.38–2.20 (m, 2H), 1.65–1.54 (m, 2H), 1.34–1.22 (m, 8H), 0.90–0.86 (m, 3H); MS (FAB, Pos.) m/z 454 $(M+H)^+$, 432; HRMS (MALDI-TOF, Pos.) calcd for disodium salt $C_{17}H_{24}NO_7P{\cdot}2Na + H^+$: 432.1164; found: 432.1134.

3-[2-(Benzyloxy)-1-(octanoylamino)ethyl]benzoic acid (79). To a stirred mixture of **78** (7.41 g, 23.08 mmol) and Ag_2O (6.42 g, 27.7 mmol) in DMF (23 mL) was added benzyl bromide (3.29 mL, 27.7 mmol) at room temperature and stirring was continued for 20 h at that temperature. The reaction mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Removal of the solvent by evaporation gave a residue which was purified by column chromatography on silica gel (Merck 7734, *n*-hexane/EtOAc, 85/15) to afford methyl 3-[2-(benzyloxy)-1-(octanoylamino)ethyl]benzoate, which was used for the next reaction without further purification: TLC $R_f = 0.39$ (*n*-hexane/EtOAc, 4/1). To a stirred solution of methyl 3-[2-(benzyloxy)-1-(octanoylamino)ethyl]benzoate (23.0 mmol) in THF (2 mL) and MeOH (14 mL) was added 2 M NaOH (14.8 mL, 29.6 mmol) at 0 °C and stirring was continued for 2 h at room temperature. The reaction mixture was poured into H_2O and extracted with Et_2O. The aqueous layer was acidified with 2 M HCl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Removal of the solvent by evaporation gave a residue which was washed with Et_2O/*n*-hexane to afford **79** (89 g, 53% yield in 2 steps): TLC $R_f = 0.50$ ($CHCl_3$/MeOH, 9/1); ^1H NMR (300 MHz, $CDCl_3$) δ 8.08–8.06 (m, 1H), 7.99 (dt, $J = 7.8$, 1.5 Hz, 1H), 7.58–7.54 (m, 1H), 7.42 (t, $J = 7.2$ Hz, 1H), 7.36–7.23 (m, 5H), 6.31 (d, $J = 7.2$ Hz, 1H), 5.27–5.22 (m, 1H), 4.54 (d, $J = 12.0$ Hz, 1H), 4.49 (d, $J = 12.0$ Hz, 1H), 3.78 (dd, $J = 9.9$, 4.5 Hz, 1H), 3.73 (dd, $J = 9.9$, 4.5 Hz, 1H), 2.24 (t, $J = 7.5$ Hz, 2H), 1.69–1.58 (m, 2H), 1.36–1.23 (m, 8H), 0.86 (t, $J = 7.3$ Hz, 3H).

Methyl {3-[2-(benzyloxy)-1-(octanoylamino)ethyl]phenyl} acetate (80). To a stirred solution of **79** (2.38 g, 6.0 mmol) in toluene (60 mL) and DMF (0.1 mL) was added dropwise $(COCl)_2$ (0.63 mL, 7.2 mmol) at 0 °C and stirring was continued at room temperature for 2 h. Removal of the solvent by evaporation gave an acid chloride which was used for the next reaction without further purification: TLC $R_f = 0.33$ (*n*-hexane/EtOAc, 2/1). To a stirred mixture of the acid chloride and $NaHCO_3$ (504 mg, 6.0 mmol) in Et_2O (60 mL) was added CH_2N_2/Et_2O(100 mL) at 0 °C and stirring was continued at that temperature for 2 h. Removal of the solvent by evaporation gave a residue which was poured into H_2O and extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford a residue, which was purified by column chromatography on silica gel (Merck 7734, *n*-hexane/EtOAc, 8/2–6/4) to afford a diazoketone derivative: TLC $R_f = 0.48$ (*n*-hexane/EtOAc, 1/1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (t, $J = 1.5$ Hz, 1H), 7.62 (dt, $J = 7.8$, 1.5 Hz, 1H), 7.51–7.48 (m, 1H), 7.39 (t, $J = 7.8$ Hz, 1H), 7.33–7.22 (m, 5H), 6.26 (d, $J = 7.8$ Hz, 1H), 5.83 (s, 1H), 4.53 (d, $J = 11.7$ Hz, 1H), 4.48 (d, $J = 11.7$ Hz, 1H), 3.78–3.69 (m, 2H), 2.2 1(t, $J = 7.2$ Hz, 1H), 1.65–1.56 (m, 2H), 1.28–1.23 (m, 8H), 0.86 (t, $J = 6.9$ Hz, 3H). To a stirred solution of the above-described diazoketone (1.53 g, 3.63 mmol) and Et_3N (0.52 mL) in MeOH (36 mL) was added silver acetate (121 mg, 7.27 mmol) and stirring was continued at 40 °C for 1 h. The reaction mixture was diluted with EtOAc. After the organic layer was successively washed with 1 M HCl and brine, it was dried over Na_2SO_4. Removal of the solvent by evaporation gave a residue which was purified by column chromatography on silica gel (Merck 7734, *n*-hexane/EtOAc, 7/3–6/4) to afford **79** (1.25 g, 49% in 3 steps): TLC $R_f = 0.53$ (*n*-hexane/EtOAc, 1/1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.17 (m, 9H), 6.15 (d, $J = 7.8$ Hz, 1H), 5.23–5.18 (m, 1H), 4.53 (d, $J = 12.0$ Hz, 1H), 4.48 (d, $J = 12.0$ Hz, 1H), 3.75 (dd, $J = 9.9$, 4.8 Hz, 1H), 3.71 (d, $J = 9.9$, 4.8 Hz, 1H), 3.67 (s, 3H), 3.60 (s, 2H), 2.23–2.18 (m, 2H), 1.68–1.57 (m, 2H), 1.29–1.24 (m, 8H), 0.87 (t, $J = 6.6$ Hz, 3H).

2-(3-Methoxyarboxylmethylphenyl)-2-octanoylaminoethyl disodium phosphate (46). A mixture of **80** (1.21 g, 2.85 mmol) and 10% Pd–C (1 g) was vigorously stirred at room temperature under an atmospheric pressure of hydrogen for 2 h. Removal of the catalyst by filtration through a pad of Celite followed by evaporation afforded 2-(3-methoxyarboxylmethylphenyl)-2-octanoylaminoethanol as an oily residue which was used for the next reaction without further purification: TLC $R_f = 0.21$ (*n*-hexane/EtOAc, 1/3); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (t, $J = 7.5$ Hz, 1H), 7.23–7.18 (m, 3H), 6.20 (d, $J = 5.7$ Hz, 1H), 5.08–5.00 (m, 1H), 3.87–3.85 (m, 2H), 3.69 (s, 3H), 3.62 (s, 2H), 2.28–2.19 (m, 2H), 1.71–1.60 (m, 2H), 1.29–1.23 (m, 8H), 0.87 (t, $J = 6.3$ Hz, 3H). The title compound **46** was prepared from 2-(3-methoxycarboxylmethylphenyl)-2-octanoylaminoethanol according to the same procedure as described in the preparation of **39** from **72**: ivory powder; TLC $R_f = 0.42$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3862, 3423, 2928, 2857, 1739, 1637, 1550, 1491, 1438, 1345, 1258, 1091, cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.25–7.19 (m, 3H), 7.13–7.10 (m, 1H), 4.90–4.85 (m, 1H), 4.02–3.87 (m, 2H), 3.65 (s, 3H), 3.60 (s, 2H), 2.37–2.18 (m, 2H), 1.63–1.55 (m, 2H), 1.37–1.25 (m, 8H), 0.88 (t, $J = 6.9$ Hz, 3H); MS (FAB. Pos.) m/z 460 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{19}H_{28}NO_7P{\cdot}2Na + H^+$: 460.1477; found: 460.1432.

Trisodium 2-(3-carboxymethlyphenyl)-2-octanoylaminoethyl phosphate (45). To a stirred solution of 2-(3-methoxycarboxylmethylphenyl)-2-octanoylaminoethyl dihydrogen phosphate (490 mg, 1.07 mmol) in THF (3.0 mL) and MeOH (3.0 mL) was added 1 M NaOH (1.61 mL, 1.61 mmol) and stirring was continued at that

temperature for 20 h. The reaction mixture was poured into 1 M HCl and extracted with EtOAc–MeOH. The organic layer was washed with brine and dried over Na_2SO_4. Removal of the solvent by evaporation gave a residue which was purified by column chromatography on silica gel (Merck 7734, $CHCl_3$/MeOH/NH_4OH, 65/25/1–$CHCl_3$/MeOH/H_2O, 65/35/8) to afford 2-(3-carboxyphenyl)-2-octanoylaminoethyl dihydrogen phosphate as a white amorphous powder (208 mg, 48%): TLC R_f = 0.28 ($CHCl_3$/MeOH/H_2O, 65/35/8); ^{1}H NMR (300 MHz, CD_3OD) δ 7.33–7.15 (m, 4H), 5.21–5.16 (m, 1H), 4.19–4.06 (m, 2H), 3.60 (s, 2H), 2.28–2.23 (m, 2H), 1.66–1.54 (m, 2H), 1.35–1.24 (m, 8H), 0.91–0.86 (m, 3H). The title compound **45** was obtained from 2-(3-carboxyphenyl)-2-octanoylaminoethyl phosphate according to essentially the same procedure as described for the preparation of **1** from **62e**: white powder: TLC R_f = 0.28 ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3423, 1637, 1577, 1388, 1093, 984 cm^{-1}; ^{1}H NMR; (300 MHz, CD_3OD) δ 7.26 (brs, 1H), 7.18 (brs, 3H), 4.92–4.88 (m, 1H), 4.02–3.88 (m, 2H), 3.45 (s, 2H), 2.34–2.18 (m, 2H), 1.66–1.54 (m, 2H), 1.36–1.24 (m, 8H), 0.90–0.86 (m, 3H); MS (FAB, Pos.) *m*/*z* 468 $(M+H)^+$, 446, 424; HRMS (MALDI-TOF, Pos.) calcd for $C_{18}H_{25}NO_7P{\cdot}3Na+H^+$: 468.1140; found: 468.1102.

***N*-{2-Hydroxy-1-[3-(isopropylthio)phenyl]ethyl}octanamide (81).** To a stirred solution of **70** (3.07 g, 10 mmol) in DMF (15 mL) was added NaH (60% dispersion in mineral oil, 420 mg, 10 mmol) at 0 °C. Dimethylthiocarbamoyl chloride (1.61 g, 13 mmol) was then added to the resulting mixture and stirring was continued at 80 °C for 1.5 h. The reaction mixture was poured into H_2O and extracted with EtOAc. The organic layer was successively washed with 1 M HCl, saturated $NaHCO_3$ aq and brine before being dried over Na_2SO_4. Removal of the solvent by evaporation gave a residue which was purified by column chromatography on silica gel (Merck 7734, toluene/EtOAc, 7/1–5/1) and (FL60D toluene/EtOAc, 10/1) to afford methyl (3-{[(dimethylamino)carbonothioyl]oxy}phenyl) (octanoylamino)acetate (2.55 g, 64%): TLC R_f = 0.37 (toluene/EtOAc, 3/1); MS (MALDI-TOF, Pos.) *m*/*z* 417 $(M+Na)^+$, 395 $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.28–7.04 (m, 3H), 6.40 (brd, *J* = 6.9 Hz, 1H), 5.59 (d, *J* = 6.9 Hz, 1H), 3.74 (s, 3H), 3.45 (s, 3H), 3.33 (s, 3H), 2.24 (brt, *J* = 7.5 Hz, 2H), 1.70–1.55 (m, 2H), 1.40–1.20 (m, 8H), 0.87 (brt, *J* = 6.9 Hz, 3H). A solution of methyl (3-{[(dimethylamino)-carbonothioyl]oxy}phenyl) (octanoylamino)acetate (2.07 g, 5.24 mmol) in diphenyl ether (35 mL) was heated with stirring to 235 °C and the stirring was continued for 10 h. After cooling, the reaction mixture was purified by column chromatography on silica gel (Merck7734, toluene/EtOAc, 5/1–3/1) to give methyl (3-{[(dimethylamino) carbonyl]thio}phenyl) (octanoylamino)acetate (1.62 g, 66%): TLC R_f = 0.18 (toluene/EtOAc, 3/1); MS (MALDI-TOF, Pos.) *m*/*z* 417 $(M+Na)^+$, 395 $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.35 (m, 4H), 6.42 (brd, *J* = 6.9 Hz, 1H), 5.59 (d, *J* = 6.9 Hz, 1H), 3.15–2.95 (brs, 6H), 2.24 (brt, *J* = 7.5 Hz, 2H), 1.70–1.55 (m, 2H), 1.40–1.20 (m, 8H), 0.87 (brt, *J* = 6.9 Hz, 3H). To a stirred solution of methyl (3-{[(dimethylamino)-carbonyl]thio}phenyl) (octanoylamino)acetate (1.62 g, 4.1 mmol) in THF (15 mL) was added $LiBH_4$ (179 mg, 8.2 mmol) and stirring was continued at room temperature for 2 h. The reaction was quenched with saturated NH_4Cl aq and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Removal of the solvent by evaporation gave 2-(3-dimethycarbonylthiophenyl)-2-octanoylaminoethanol which was used for the next reaction without further purification: TLC R_f = 0.16 (toluene/EtOAc, 3/1); MS (MALDI-TOF, Pos.) *m*/*z* 389 $(M+Na)^+$, 367 $(M+H)^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.26 (m, 4H), 6.37 (brd, *J* = 7.2 Hz, 1H), 5.04 (m, 1H), 3.86 (dd, *J* = 11.6, 4.6 Hz, 1H), 3.79 (dd, *J* = 11.6, 4.0 Hz, 1H), 3.20–2.95 (brs, 6H), 2.24 (brt, *J* = 7.6 Hz, 2H), 1.70–1.55 (m, 2H), 1.40–1.20 (m, 8H), 0.87 (brt, *J* = 6.8 Hz, 3H). To a stirred solution of 2-(3-dimethycarbonylthiophenyl)-2-octanoylaminoethanol (4.1 mmol) in MeOH (20 mL) was added KOH (2.0 g, 35.6 mmol) and stirring was continued under reflux for 40 min. The reaction mixture was poured into 1 M HCl (50 mL) and extracted with EtOAc. The organic layer was washed with brine and then dried over Na_2SO_4. Removal of the solvent by evaporation gave a solid which was washed with Et_2O/*n*-hexane to afford 2-(3-mercaptophenyl)-2-octanoylaminoethanol (820 mg, 67%): TLC R_f = 0.19 (*n*-hexane/EtOAc, 2/3); MS (MALDI-TOF, Pos.) *m*/*z* 318 $(M+Na)^+$, 296 $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.15 (m, 4H), 6.25 (brd, *J* = 7.2 Hz, 1H), 5.00 (m, 1H), 3.84 (m, 2H), 2.22 (brt, *J* = 7.6 Hz, 2H), 1.70–1.55 (m, 2H), 1.40–1.20 (m, 8H), 0.86 (brt, *J* = 6.8 Hz, 3H). To a stirred mixture of 2-(3-mercaptophenyl)-2-octanoylaminoethanol (590 mg, 2 mmol) and K_2CO_3 (691 mg, 5 mmol) was added 2-idopropane (510 mg, 3 mmol) and stirring was continued at 70 °C for 3 h. After cooling, the precipitates were removed by filtration through a pad of Celite. Evaporation of the filtrate gave an oily residue, which was dissolved in EtOAc. The organic layer was successively washed with H_2O and brine before being dried over $MgSO_4$ and concentrated to give an oily residue, which was purified by column chromatography on silica gel (Merck 7734, *n*-hexane/EtOAc, 1/1–2/3) to afford **81** (654 mg, 97%): TLC R_f = 0.38 (*n*-hexane/EtOAc, 2/3); MS (MALDI-TOF, Pos.) *m*/*z* 376 $(M+K)^+$, 360 $(M+Na)^+$, 338 $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.26 (m, 3H), 7.12 (m, 1H), 6.16 (brd, *J* = 6.6 Hz, 1H), 5.03 (m, 1H), 3.86 (m, 2H), 3.38 (m, 1H), 2.69 (brs, 1H), 2.24 (brt, *J* = 7.5 Hz, 2H), 1.70–1.55 (m, 2H), 1.40–1.20 (m, 8H), 0.87 (brt, *J* = 6.6 Hz, 3H).

2-(3-Isopropylthiophenyl)-2-octanoylaminoethyl disodium phosphate (48). The title compound **48** was prepared from **81** according to the same procedure as described for the preparation of **22** from **60t** (general method C): off-white powder; TLC R_f = 0.27 ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3264, 2926, 1659, 1625, 1555, 1464, 1097 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 7.36 (brs, 1H), 7.22 (m, 3H), 4.84 (m, 1H), 4.00–3.90 (m, 2H), 3.37 (m, 1H), 2.41–2.17 (m, 2H), 1.70–1.50 (m, 2H), 1.40–1.20 (m, 8H), 1.24 (d, *J* = 6.6 Hz, 6H), 0.88 (brt, *J* = 6.6 Hz, 3H); MS (FAB, Pos.) *m*/*z* 484 $(M+Na)^+$, 462 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{19}H_{30}NO_5PS{\cdot}2Na+H^+$: 462.1456; found: 462.1435.

2-(3-Methylsulfonylphenyl)-2-octanoylaminoethyl disodium phosphate (49). 2-(3-Methylthiophenyl)-2-octanoylaminoethyl dihydrogen phosphate was prepared according to the same procedure as described for the preparation of **47** from **64k**. To a stirred solution of 2-(3-methylthiophenyl)-2-octanoylaminoethyl dihydrogen phosphate (320 mg, 0.823 mmol) in MeOH was added OXONE® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, 556 mg, 0.905 mmol) at 0 °C and stirring was continued at room temperature for 6 h. The reaction mixture was poured into 0.5 M HCl and extracted with EtOAc. The organic layer was successively washed with H_2O and brine before being dried over $MgSO_4$. Removal of the solvent by evaporation gave 2-(3-methylsulfonylphenyl)-2-octanoylaminoethyl dihydrogen phosphate as a beige amorphous powder (246 mg, 71%): TLC $R_f = 0.31$ ($CHCl_3$/MeOH/H_2O, 65/35/8); ^{1}H NMR (300 MHz, CD_3OD) δ 7.97 (brs, 1H), 7.88 (brd, $J = 7.8$ Hz, 1H), 7.72 (brd, $J = 7.8$ Hz, 1H), 7.62 (t, $J = 7.8$ Hz, 1H), 5.30–5.20 (m, 1H), 4.20–4.16 (m, 2H), 3.11 (s, 3H), 2.28 (t, $J = 7.5$ Hz, 2H), 1.65–1.55 (m, 2H), 1.35–1.20 (m, 8H), 0.90–0.85 (m, 3H). The title compound **49** was prepared from 2-(3-methylsulfonylphenyl)-2-octanoylaminoethyl phosphate according to the same procedure for as described the preparation of **1** from **62e**: beige amorphous powder; TLC $R_f = 0.31$($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3375, 1644, 1546, 1299, 1147, 1094, 983 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 7.95 (brs, 1H), 7.80 (brd, $J = 7.8$ Hz, 1H), 7.74 (brd, $J = 7.8$ Hz, 1H), 7.55 (t, $J = 7.8$ Hz, 1H), 5.00–4.95 (m, 1H), 4.14–3.89 (m, 2H), 3.10 (s, 3H), 2.43–2.18 (m, 2H), 1.68–1.52 (m, 2H), 1.36–1.22 (m, 8H), 0.93–0.84 (m, 3H); MS (FAB, Pos.) m/z 466 $(M + Na)^+$, 444 $(M + H)^+$, 422; HRMS (MALDI-TOF, Pos.) calcd for $C_{17}H_{26}NO_7PS \cdot 2Na + H^+$: 466.1041; found: 466.1026.

1-(*tert*-Butyldimethylsilyl)-2-{3-[(diphenylmethylene)amino]-phenyl}-2-octanoylaminoethyl ether (83). To a stirred solution of **82** (3.57 g, 6.79 mmol) and 1,1-diphenylmethanimine (1.85 g, 10.2 mmol) in toluene (15 mL) were added Cs_2CO_3 (3.10 g, 9.51 mmol), $Pd(OAc)_2$ (15 mg, 0.0679 mmol) and (±)-BINAP (64 mg, 0.102 mmol) and stirring was continued at 80 °C for 20 h. The reaction mixture was diluted with Et_2O. Removal of the catalyst by filtration through a pad of Celite followed by evaporation of the filtrate afforded **83** as a brown oil (6.10 g) which was used for the next reaction without further purification: TLC $R_f = 0.70$ (*n*-hexane/EtOAc, 3/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74–7.71 (m, 2H), 7.50–7.37 (m, 4H), 7.28–7.20 (m, 3H), 7.12–7.05 (m, 3H), 6.86 (d, $J = 7.8$ Hz, 1H), 6.67–6.60 (m, 2H), 5.91 (d, $J = 7.8$ Hz, 1H), 4.91–4.86 (m, 1H), 3.74 (dd, $J = 10.2$, 4.5 Hz, 1H), 3.60 (dd, $J = 10.2$, 4.8 Hz, 1H), 2.25–2.20 (m, 2H), 1.70–1.60 (m, 2H), 1.40–1.20 (m, 8H), 0.88–0.86 (m, 12H), −0.04 (s, 3H), −0.06 (s, 3H).

1-(*tert*-Butyldimethylsilyl)-2-[(3-methylsulfonylamino)-phenyl]-2-octanonylamino ether (84). To a stirred solution of **83** (6.10 g, 6.79 mmol) in MeOH (100 mL) were added CH_3CO_2Na (3.94 g, 48.0 mmol) and $NH_2OH \cdot HCl$ (2.50 g, 36.0 mmol). Stirring was continued at room temperature for 30 min. The reaction mixture was evaporated and extracted with EtOAc. The organic layer was successively washed with 1 M NaOH and brine before being dried over Na_2SO_4. Removal of the solvent by evaporation gave a residue which was purified by column chromatography on silica gel (Merck 7734, *n*-hexane/EtOAc, 2/1) to afford 2-(3-aminophenyl)-1-(*tert*-butyldimethylsilyl)-2-octanonylaminoethyl ether as a yellow oil (961 mg, 36% yield in 2 steps): TLC $R_f = 0.29$ (*n*-hexane/EtOAc, 1/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (t, $J = 7.8$ Hz, 1H), 6.71 (d, $J = 7.8$ Hz, 1H), 6.66 (brs, 1H), 6.61–6.58 (m, 1H), 6.14 (d, $J = 7.8$ Hz, 1H), 4.97–4.91 (m, 1H), 3.87 (dd, $J = 10.2$, 4.5 Hz, 1H), 3.78 (dd, $J = 10.2$, 4.5 Hz, 1H), 2.25–2.20 (m, 2H), 1.70–1.60 (m, 2H), 1.40–1.20 (m, 8H), 0.88–0.86 (m, 12H), −0.03 (s, 3H), −0.06 (s, 3H). To a stirred solution of 2-(3-aminophenyl)-1-(*tert*-butyldimethylsilyl)-2-octanonylaminoethyl ether (426 mg, 1.08 mmol) in pyridine (5.0 mL) was added dropwise $MeSO_2Cl$ (0.125 mL, 1.62 mmol) at 0 °C and stirring was continued at that temperature for 30 min. The reaction mixture was poured into 1 M HCl and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Removal of the solvent by evaporation gave a residue, which was purified by column chromatography on silica gel (Merck 7734, *n*-hexane/EtOAc, 1/1) to afford methyl {3-[(methylsulfonyl)amino]phenyl}(octanoylamino)acetate as a yellow oil (508 mg, quant.): TLC $R_f = 0.52$ (*n*-hexane/EtOAc, 1/1); MS (APCI, Pos., 20eV) m/z 471 $(M + H)^+$; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32–7.24 (m, 1H), 7.15–7.06 (m, 3H), 6.96 (brs, 1H), 6.34 (d, $J = 7.2$ Hz, 1H), 5.03–4.95 (m, 1H), 3.90 (dd, $J = 10.2$, 4.0 Hz, 1H), 3.78 (dd, $J = 10.2$, 4.4 Hz, 1H), 2.94 (s, 3H), 1.80–0.85 (m, 3H), 0.85 (s, 9H), −0.04 (s, 3H), −0.07 (s, 3H).

Trisodium 2-{3-[(methylsulfonyl)amino]phenyl}-2-(octanoylamino)ethyl phosphate (50). 3-[(Methylsulfonylamino)-phenyl]-2-octanonylaminoethanol was prepared from methyl {3-[(methylsulfonyl)amino]phenyl}(octanoylamino)acetate according to the essentially same procedure as described for the preparation of **74** from 1-(*tert*-butyldimethylsilyl) - 2 - [(3 - methoxymethlyoxymethyl)-phenyl]-2-octanoylaminoethyl ether: yellow viscous oil; 75% yield; TLC $R_f = 0.42$ (EtOAc). The title compound **50** was prepared from **84** according to the same procedure as described for the preparation of **39** from **72** (General Method D): 84% yield; white powder; TLC $R_f = 0.29$ ($CHCl_3$/MeOH/H_2O, 65/35/8); IR (KBr) 3299, 1636, 1550, 1484, 1283, 1216, 1110, 982 cm^{-1}; ^{1}HNMR (300 MHz, CD_3OD) δ 7.08 (brs, 1H), 7.05 (t, $J = 7.5$ Hz, 1H), 6.93 (brd, $J = 7.5$ Hz, 1H), 6.79 (brd, $J = 7.5$ Hz, 1H), 4.84–4.81 (m, 1H), 4.00–3.87 (m, 2H), 2.79 (s, 3H), 2.36–2.18 (m, 2H), 1.66–1.54 (m, 2H), 1.35–1.25 (m, 8H), 0.91–0.86 (m, 3H); MS (FAB, Pos.) m/z 503 $(M + H)^+$, 481, 525; HRMS (MALDI-TOF, Pos.) calcd for free acid form $C_{17}H_{29}N_2O_7PS \cdot + Na^+$: 459.1331; found: 459.1344.

***N*-[(1*R*)-2-Hydroxy-1-(3-methoxyphenyl)ethyl]octanamide (86).** The compound **85** was prepared from 1-methoxy-3-vinylbenzene according to the known procedure:[23] (>99% ee); white powder; TLC $R_f = 0.53$ (EtOAc/AcOH/H_2O 3/1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65–8.50 (br, 3H), 7.34–7.26 (m, 1H), 7.15 (brs, 1H), 7.04 (d, $J = 7.8$ Hz, 1H), 6.92 (dd, $J = 8.1$, 2.7 Hz, 1H), 5.25 (t,

$J=4.8$ Hz, 1H), 4.21 (t, $J=6.3$ Hz, 1H), 3.76 (s, 3H), 3.74–3.68 (m, 2H); ee determination: the corresponding 4-nitro benzoate prepared from **85** was analyzed by HPLC: DAICEL CHIRALCEL OD (0.46×25 cm); column temperature, 25 °C; eluent, EtOH/*n*-hexane = 30/70; flow rate, 0.5 mL /min; UV 260 nm; the retention times of 4-nitro benzoate and its enantiomer were 19.7 and 11.7 min, respectively. The title compound **86** was prepared quantitatively from **85** according to essentially the same procedure as described for the preparation of **60e** from (2*R*)-2-amino-2-phenylethanol. Compound **86** was then used for the next reaction without further purification: quant.; white solid; TLC $R_f=0.40$ (*n*-hexane/EtOAc 1/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.26 (m, 1H), 6.90–6.80 (m, 3H), 6.09 (d, $J=6.3$ Hz, 1H), 5.05–5.00 (m, 1H), 3.95–3.82 (m, 2H), 3.81 (s, 3H), 2.75–2.60 (br, 1H), 2.28–2.21 (m, 2H), 1.70–1.50 (m, 2H), 1.40–1.20 (m, 8H), 0.88 (t, $J=6.8$ Hz, 3H).

(2*R*)-2-(3-Methoxyphenyl)-2-octanoylaminoethyl disodium phosphate (2). The title compound **2** was prepared from **86** according to the same procedure as described for the preparation of **1** from **60e** (general method A): light brown powder, TLC $R_f=0.51$ ($CHCl_3$/MeOH/H_2O 65/35/8); IR (KBr) 3399, 2956, 2929, 2858, 1638, 1548, 1492, 1466, 1437, 1262, 1092 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.18 (dd, $J=8.1$, 8.1 Hz, 1H), 6.95–6.88 (m, 2H), 6.78–6.72 (m, 1H), 4.95–4.80 (m, 1H), 4.02–3.85 (m, 2H), 3.77 (s, 3H), 2.40–2.20 (m, 2H), 1.70–1.50 (m, 2H), 1.40–1.20 (m, 8H), 0.89 (t, $J=6.8$ Hz, 3H); optical rotation $[\alpha]_D^{25}$-43.82 (*c* 1.01, H_2O); MS (FAB, pos.) *m*/*z* 440 $(M+Na)^+$, 418 $(M+H)^+$, 396; HRMS (MALDI-TOF, Pos.) calcd for $C_{17}H_{26}NO_6P{\cdot}2Na+H^+$: 418.1371; found; 418.1413.

***N*-[(1*S*)-2-Hydroxy-1-(3-methoxyphenyl)ethyl]octanamide (88).** The title compound **88** was prepared from 1-methoxy-3-vinylbenzene according to the same procedure as described for the preparation of **86** from 1-methoxy-3-vinylbenzene. Compound **88** was then used for the next reaction without further purification: white powder; TLC $R_f=0.27$ (*n*-hexane/EtOAc 1/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.26 (m, 1H), 6.89–6.82 (m, 3H), 6.07 (d, $J=6.3$ Hz, 1H), 5.7–5.01 (m, 1H), 3.91–3.85 (m, 2H), 3.80 (s, 3H), 2.65 (t, $J=6.6$ Hz, 1H), 2.24 (t, $J=7.8$ Hz, 2H), 1.67–1.58 (m, 2H), 1.29–1.27 (m, 8H), 0.87 (t, $J=6.6$ Hz, 3H); ee determination: the corresponding 4-nitro benzoate prepared from **87** was analyzed by HPLC: DAICEL CHIRALCEL OD (0.46×25 cm); column temperature, 25 °C; eluent, EtOH/*n*-hexane = 30/70; flow rate, 0.5 mL/min; UV 260 nm; the retention times of 4-nitro benzoate and its enantiomer were 11.7 and 19.7 min, respectively.

(2*S*)-2-(3-Methoxyphenyl)-2-octanoylaminoethyl disodium phosphate (53). The title compound **53** was prepared from **88**, which was obtained from 1-methoxy-3-vinylbenzene, according to the same procedure as described for the preparation of **1** from **60e** (general method A): beige powder, TLC $R_f=0.26$ ($CHCl_3$/MeOH/H_2O 65/35/8); IR (KBr) 3390, 2929, 2857, 2213, 1637, 1547, 1491, 1466, 1437, 1262, 1092 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.17 (t, $J=8.0$ Hz, 1H), 6.92–6.89 (m, 2H), 6.76–6.71 (m, 1H), 4.89–4.83 (m, 1H), 3.98–3.90 (m, 2H), 3.76 (s, 3H), 2.42–2.17 (m, 2H), 1.67–1.55 (m, 2H), 1.29–1.25 (m, 8H), 0.88 (t, $J=7.0$ Hz, 3H); MS (FAB, pos.) *m*/*z* 418 $(M+H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{17}H_{26}NO_6P{\cdot}2Na+H^+$: 418.1371; found; 418.1347.

Method F

(2*S*)-2-Octanoylamino-2-phenylethyl disodium phosphate (52). To a stirred solution of **89** (3.0 g, 12.7 mmol) in pyridine (30 mL) was added bis(2,2,2-trichloroethyl)-chloridophosphate (5.76 g, 15.2 mmol) at 0 °C and stirring was continued at that temperature for 1.5 h. The reaction mixture was poured into ice-cold 1 M HCl and extracted with EtOAc. The organic layer was successively washed with 1 M HCl, H_2O and brine before being dried over Na_2SO_4. Removal of the solvent by evaporation gave a residue, which was washed with Et_2O to afford **90** as a white solid (1.14 g). The filtrate was concentrated to give a reside, which was purified by column chromatography on silica gel (Merck 7734, *n*-hexane/EtOAc, 4/1) to afford additional **90** (5.36 g). In total 6.5 g (89%) of compound **90** was obtained: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42–7.20 (m, 5H), 5.28 (m, 1H), 5.03 (m, 1H), 4.60–4.30 (m, 6H), 1.43 (s, 9H). To a solution of **90** (4.23 g, 7.33 mmol) in CH_2Cl_2 (20 mL) was added trifluoroacetic acid (10 mL) at 0 °C and stirring was continued for 1 h at room temperature. Removal of the solvent by evaporation gave (2*S*)-2-amino-2-phenylethyl bis(2,2,2-trichloroethyl) phosphate hydrochloride which was used for the next reaction without further purification. To a stirred solution of (2*S*)-2-amino-2-phenylethyl bis(2,2,2-trichloroethyl) phosphate hydrochloride (7.33 mmol) in CH_2Cl_2 (10 mL) were added octanoyl chloride (1.43 g, 8.8 mmol) and pyridine (1.78 mL, 22 mmol) at 0 °C and stirring was continued at room temperature for 15 min. Removal of the solvent by evaporation gave (2*S*)-2-phenyl-2-(octanoylamino)ethyl bis(2,2,2-trichloroethyl) phosphate which was used for the next reaction without further purification. To a stirred solution of (2*S*)-2-phenyl-2-(octanoylamino)ethyl bis(2,2,2-trichloroethyl) phosphate (7.33 mmol) in pyridine (25 mL)/AcOH (5 mL) was added Zn powder (4.2 g, 64.5 mmol) at 0 °C and stirring was continued at room temperature for 2.5 h. Removal of the Zn powder by filtration through a pad of Celite followed by evaporation afforded an oily residue, which was dissolved in 5 M NaOH and extracted with EtOAc. The aqueous layer was acidified by 2 M HCl and extracted with EtOAc. The organic layer was successively washed with H_2O and brine before being dried over Na_2SO_4. Removal of the solvent by evaporation gave a residue, which was purified by column chromatography on silica gel (Merck 7734, $CHCl_3$/MeOH/NH_4OH, 65/25/2-$CHCl_3$/MeOH/H_2O, 65/25/4) to afford a solid. The solid was dissolved in 1 M HCl/EtOAc. After the organic layer was successively washed with H_2O and brine, it was dried over Na_2SO_4. Removal of the solvent by evaporation gave (2*S*)-2-octanoylamino-2-phenylethyl dihydrogen phosphate (1.7 g, 68% yield from **90**) which was converted to the

disodium salt **52**: white powder; TLC $R_f = 0.33$ ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3368, 2923, 1645, 1562, 1467, 1048, 963 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.40–7.20 (m, 5H), 5.19 (dd, $J = 7.5$, 5.7 Hz, 1H), 4.20–4.05 (m, 2H), 2.26 (t, $J = 7.5$ Hz, 2H), 1.61 (quint, $J = 7.5$ Hz, 2H), 1.40–1.20 (m, 8H), 0.89 (t, $J = 6.6$ Hz, 3H); $[\alpha]_D^{25} + 41.2$ (c1.1, MeOH); MS (FAB, Pos.) m/z 366 $(M + Na)^+$, 344 $(M + H)^+$, 246; HRMS (MALDI-TOF, Pos.) calcd for $C_{16}H_{26}NO_5P + Na^+$: 366.1446; found; 366.1401.

***N*-(2-Hydroxy-1-pyridin-2-ylethyl)octanamide (92a).** To a stirred mixture of **91a**[25] (3.28 g, 10 mmol) and *N*-methylmorpholine (3.3 mL, 30 mmol) in CH_2Cl_2 (30 mL) was added dropwise octanoyl chloride (1.62 g, 10 mmol) at 0 °C and stirring was continued at that temperature for 2 h. The reaction mixture was quenched with 1 M NaOH and extracted with CH_2Cl_2 (3 times). The combined organic layers were dried over $MgSO_4$. Removal of the solvent by evaporation afforded a residue, which was purified by column chromatography on silica gel (Merck 7734, *n*-hexane/EtOAc, 3/2–1/1–1/2–1/3) to afford ethyl 2-octanonylamino-2-(pyridin-2-yl)acetate (1.16 g, 38% in 2 steps): TLC $R_f = 0.25$ (*n*-hexane/EtOAc, 2/1); ^1H NMR (300 MHz, $CDCl_3$) δ 8.55 (ddd, $J = 4.8$, 1.8, 0.9 Hz, 1H), 7.73 (ddd, $J = 7.5$, 7.5, 1. 8 Hz, 1H), 7.50 (brd, $J = 7.5$ Hz, 1H), 7.28–7.24 (m, 2H), 5.68 (d, $J = 6.6$ Hz, 1H), 4.25–4.10 (m, 2H), 2.33–2.28 (m, 2H), 1.70–1.60 (m, 2H), 1.40–1.20 (m, 8H), 1.23 (t, $J = 7.2$ Hz, 3H), 0.86 (brt, $J = 6.6$ Hz, 3H). The title compound **92a** was prepared from 2-octanonylamino-2-(pyridin-2-yl)ethyl acetate according to the same procedure as described for the preparation of **64a** from methyl (2-methoxyphenyl)(octanoylamino)acetate: 46% yield, TLC $R_f = 0.18$ (*n*-hexane/EtOAc, 1/2); ^1H NMR (200 MHz, $CDCl_3$) δ 8.51 (ddd, $J = 5.2$, 1.8, 1.0 Hz, 1H), 7.72 (ddd, $J = 7.6$, 7.6, 1.8 Hz, 1H), 7.40 (ddd, $J = 7.6$, 1.0, 1.0 Hz, 1H), 7.25 (ddd, $J = 7.6$, 5.2, 1.0 Hz, 1H), 7.07 (brd, $J = 7.0$ Hz, 1H), 5.16 (ddd, $J = 7.0$, 4.2, 4.2 Hz, 1H), 4.04 (dd, $J = 11.0$, 4.2 Hz, 1H), 3.88 (dd, $J = 11.0$, 4.2 Hz, 1H), 3.20 (brs, 1H), 2.26 (dd, $J = 8.4$, 6.2 Hz, 2H), 1.64 (m, 2H), 1.40–1.10 (m, 8H), 0.86 (brt, $J = 6.6$ Hz, 3H).

***N*-(2-Hydroxy-1-pyridin-3-ylethyl)octanamide (92b).** The title compound **92b** was prepared from **91b**[26] according to the same procedure as described for the preparation of **92a** from **91a**: 42% yield; TLC $R_f = 0.38$ (*n*-hexane/EtOAc, 1/2); ^1H NMR (300 MHz, $CDCl_3$) δ 8.63 (brd, $J = 1.8$ Hz, 1H), 8.56 (dd, $J = 4.8$, 1.8 Hz, 1H), 7.69 (ddd, $J = 8.1$, 1.8, 1.8 Hz, 1H), 7.29 (dd, $J = 8.1$, 4.8 Hz, 1H), 6.65 (brd, $J = 6.6$ Hz, 1H), 5.62 (d, $J = 6.6$ Hz, 1H), 4.30–4.15 (m, 2H), 2.26 (brt, $J = 8.1$ Hz, 2H), 1.70–1.60 (m, 2H), 1.40–1.20 (m, 8H), 1.11 (t, $J = 7.2$ Hz, 3H), 0.86 (brt, $J = 7.2$ Hz, 3H).

2-Octanoylamino-2-(pyridin-2-yl)ethyl disodium phosphate (58). The title compound **58** was prepared from **92a** according to essentially the same procedure as described for the preparation on **1** from **60e** (general method A). 64% yield; colorless powder; TLC $R_f = 0.12$ ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3282, 2928, 1650, 1596, 1547, 1469, 1094, 985 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 8.42 (brd, $J = 5.1$ Hz, 1H), 7.73 (ddd, $J = 7.5$, 7.5, 1.5 Hz, 1H), 7.47 (brd, $J = 7.8$ Hz, 1H), 7.23 (ddd, $J = 7.5$, 5.1, 1.2 Hz, 1H), 4.94 (dd, $J = 6.3$, 3.6 Hz, 1H), 4.17 (ddd, $J = 10.8$, 6.6, 3.6 Hz, 1H), 4.08 (ddd, $J = 10.8$, 7.2, 6.3 Hz, 1H), 2.40–2.24 (m, 2H), 1.61 (m, 2H), 1.40–1.20 (m, 8H), 0.89 (brt, $J = 6.6$ Hz, 3H); MS (FAB, Pos.) m/z 411 $(M + Na)^+$, 389 $(M + H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{15}H_{23}N_2O_5P{\cdot}2Na + H^+$: 389.1218; found; 389.1245.

2-Octanoylamino-2-(pyridin-3-yl)ethyl disodium phosphate (59). The title compound **59** was prepared from **92b** according to essentially the same procedure as described for the preparation on **1** from **60e** (general method A): 48% yield; colorless powder; TLC $R_f = 0.11$ ($CHCl_3$/MeOH/H_2O, 65/25/4); IR (KBr) 3280, 2927, 1650, 1547, 1467, 1093 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 8.54 (d, $J = 1.6$ Hz, 1H), 8.36 (dd, $J = 5.0$, 1.6 Hz, 1H), 7.88 (brd, $J = 8.2$ Hz, 1H), 7.36 (dd, $J = 8.2$, 5.0 Hz, 1H), 4.93 (dd, $J = 6.4$, 3.8 Hz, 1H), 4.18–3.89 (m, 2H), 2.33–2.24 (m, 2H), 2.40–2.24 (m, 2H), 1.70–1.50 (m, 2H), 1.40–1.15 (m, 8H), 0.87 (brt, $J = 6.6$ Hz, 3H); MS (FAB, Pos.) m/z 389 $(M + H)^+$; HRMS (MALDI-TOF, Pos.) calcd for $C_{15}H_{23}N_2O_5P{\cdot}2Na + H^+$: 389.1218; found; 389.1220.

Biological assay method

Inhibition of LPS-induced plasma TNF-α production in rats. LPS from *Escherichia coli* strain 055 B5 (Difco laboratories) and the test compounds were dissolved in saline. Male Sprague–Dawley (CD)/IGS rats (Charles River Inc., Japan) aged 6–8 weeks ($n = 5$) were injected intravenously with the test compounds (0.01–0.1 mg/ 10 mL/kg), and then immediately given an intraperitoneal injection of LPS (30 μg/kg). Plasma TNF-α production was determined 90 min after the LPS challenge by ELISA using a commercial kit (R&D Systems). ID_{50} values were determined by log-linear regression analysis (3–4 doses per compound). ID_{50} = The dosage required to inhibit plasma TNF-α production by 50%. The data were expressed as the mean ± SEM of 5 animals per group or ID_{50} values.

% Inhibition = 100- (C-S)/(L-S)×100.
C: Plasma TNF-α concentration of LPS-treated animals pretreated with a test compound.
L: Plasma TNF-α concentration of LPS-treated animals pretreated with saline.
S: Plasma TNF-α concentration of saline-treated animals also pretreated with saline.

Inhibition of LPS-induced plasma TNF-α production in mice. Male BALB/c mice aged 8 weeks ($n = 5$) were injected intravenously with the test compounds (0.01–0.1 mg/ 10 mL/kg), and then immediately given an intraperitoneal injection of LPS (5 mg/10 mL/kg). Plasma TNF-α production was determined 90 min after the LPS challenge by ELISA using a commercial kit (GENZYME). ID_{50} values were determined by log-linear regression analysis (3–4 doses per compound).

ID_{50} = the dosage required to inhibit plasma TNF-α production by 50%. The data were expressed as the mean ± SEM of 5 animals per group or ID_{50} values.

% Inhibition = 100- (C-S)/(L-S)×100
C: Plasma TNF-α concentration of LPS-treated animals pretreated with a test compound.
L: Plasma TNF-α concentration of LPS-treated animals pretreated with saline
S: Plasma TNF-α concentration of saline-treated animals also pretreated with saline.

Evaluation of TNF-α expression in mouse liver and spleen by RT-PCR.[38] The expression of TNF-α and β-actin in the liver and spleen of BALB/c female mice was evaluated by the RT-PCR method. BALB/c mice were obtained from Charles River (Shizuoka, Japan). Mouse TNF-α and β-actin primers (Nihon bio-service, Asaka City, Saitama, Japan) were used as specified by the vendor. After 90 min of LPS (from W *E. Coli* O55:B5, DIFCO LABORATORIES, Detroit, MI, USA) and drug administration, each animal was decapitated. PGE_2 was used as the positive control (1 mg/kg, ip, 1 min before LPS injection). Their liver and spleen were then removed, rinsed in sterile saline, and immediately stored at −80 °C. Total RNA was extracted with RNAzol B (TEL-TEST, INC., Friendswood, TX, USA) according to the manufacturer's instructions. Reverse transcription followed by 32 cycles (94 °C for 1 min, 55 °C for 1 min and 72 °C for 3 min) of PCR were carried out with the first-strand cDNA synthesis kit (TaKaRa, Otsu, Shiga, Japan), the TaKaRa Taq kit (TaKaRa, Otsu, Shiga, Japan) and a GeneAmp PCR System 9600 thermal controller (PERKIN ELMER, Foster City, Calif., USA), according to the manufacturer's instructions. The PCR products were electrophoresed on a 1.5% agarose gel, stained with a 0.5 mg/mL solution of ethidium bromide, and photographed under UV transillumination.

References and Notes

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30. 2-Methyloctanoyl chloride was prepared from propionic acid by following successive procedures: (i) LDA, $C_6H_{13}I$, (ii) $SOCl_2$.
31. (Pentyloxy)acetic acid was prepared from ethylene glycol by following successive procedures: (i) DHP, $TsOH{\cdot}H_2O$, (ii) NaH, $C_5H_{11}I$, (iii) TsOH, MeOH, (iv) Jone's oxidation.
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34. 6-Methoxyhexanoic acid from hexane-1,6-diol by following successive procedures: (i) DHP, $TsOH{\cdot}H_2O$, (ii) NaH, C_2H_5Br, (iii) TsOH, MeOH, (iv) Jone's oxidation.
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