Synthesis and Immunosuppressive Activity of 2-Substituted 2-Aminopropane-1,3-diols and 2-Aminoethanols[1,2]

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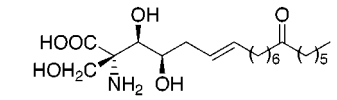
A series of 2-substituted 2-aminopropane-1,3-diols was synthesized and evaluated for their lymphocyte-decreasing effect and immunosuppressive effect on rat skin allograft. A phenyl ring was introduced into the alkyl chain of the lead compound **3**, which is an immunosuppressive agent structurally simplified from myriocin (**1**, ISP-I) via compound **2**. The potency of the various compounds was dependent upon the position of the phenyl ring within the alkyl side chain. The most suitable length between the quaternary carbon atom and the phenyl ring was two carbon atoms. 2-Substituted 2-aminoethanols were successively synthesized and evaluated for their T-cell-decreasing effect and immunosuppressive effect using a popliteal lymph node gain assay in rats. The absolute configuration at the quaternary carbon affected the activity, and the (*pro-S*)-hydroxymethyl group of compound **6** was essential for potent immunosuppressive activity. Favorable substituents for the (*pro-R*)-hydroxymethyl group of **6** were hydroxyalkyl (hydroxyethyl and hydroxypropyl) or lower alkyl (methyl and ethyl) groups. 2-Amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride (**6**, FTY720) was found to possess considerable activity and is expected to be useful as an immunosuppressive drug for organ transplantation.

Introduction

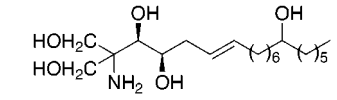
Immunosuppressants have important clinical roles in organ transplantation and the treatment of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and psoriasis. Both cyclosporin A (CsA)[3] and tacrolimus (FK506)[4] suppress immune responses by inhibiting the production of interleukin-2 (IL-2) in antigen-stimulated helper T-cells[5−7] and are standard medicines for preventing graft rejection after transplant surgery. Since their clinical use is restricted by severe side effects, notably renal and liver toxicities,[8] they are used in combination with glucocorticoids or other immunosuppressants such as azathioprine[9] and mizoribine.[10] Novel immunosuppressants should therefore not only be safer but also possess unique mechanisms of action.

In the late 1980s Fujita et al.[11] of our group isolated a unique immunosuppressant, ISP-I (**1**), from the fermentation broth of *Isaria sinclairii* (ATCC24400), and the structure was determined as shown in Chart 1. ISP-I is identical with antifungal antibiotic myriocin[12,13] and thermozymocidin,[14,15] which are produced by *Myriococcum albomyces* and *Mycelia sterilia*, respectively. It has been reported that myriocin inhibits serine palmitoyltransferase of an IL-2-dependent mouse cytotoxic T-cell line, CTLL-2, at picomole concentrations[16,17] and that sphingofungins,[18−20] which are myriocin analogues isolated from *Aspergillus fumigatus* or *Paecilomyces variotii*, inhibit yeast serine palmitoyltransferase.[20,21] These inhibitory activities appear to be responsible for their immunosuppressive and antifungal activity.

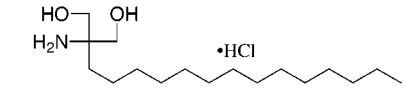
Chart 1. Structures of Myriocin and Related Immunosuppressive Compounds



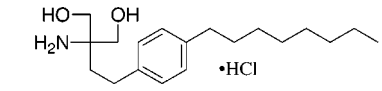
1: myriocin (thermozymocidin, ISP-I)



2



3



FTY720 (**6**)

Myriocin showed a potent inhibitory effect on mouse allogeneic mixed lymphocyte reaction (MLR).[11] Furthermore, we isolated mycestericins A−G,[22−24] which are the minor components of the myriocin-producing fungus *M. sterilia*, and established the structure−activity relation-

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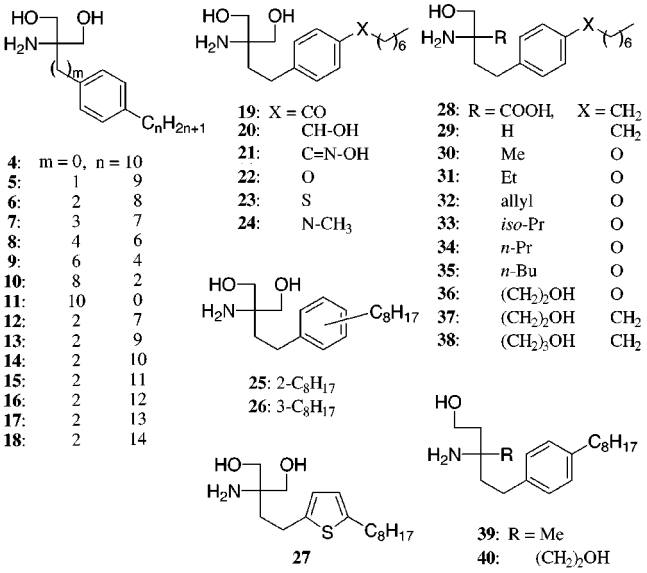
Chart 2. Structures of Target Compounds



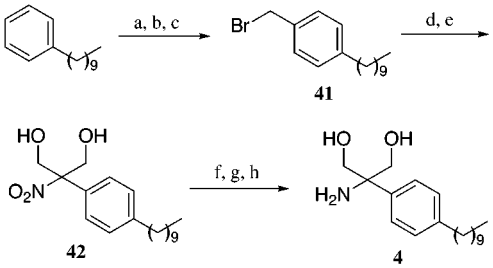
ships (SAR) of chemically modified derivatives of myriocin and mycestericins.[22,24,25] Interestingly, most of the functionalities in the hydrocarbon chain of **1** such as the 14-ketone, the 6-double bond, and the 4-hydroxy group, as well as the configuration of the 3-hydroxy group, are not essential for its activity. However, no candidates for clinical development were obtained from either the natural products or the semisynthetic compounds owing to their toxicity and unfavorable physicochemical properties such as insolubility.

As the next step, we simplified the structure of **1** in order to reduce its toxicity, to improve its physicochemical properties, and to identify the structure essential for immunosuppressive activity.[26,27] Compound **1** has a hydrophilic zwitterion on one side and a hydrophobic hydrocarbon long chain on the other side of the molecule. We reduced the carboxylic acid of **1** to a hydroxymethyl group to delete the zwitterion functionality presumably responsible for its poor solubility and asymmetric center at position 2 to afford compound **2**. The inhibitory activity of **2** on mouse allogeneic MLR in vitro was weaker than that of **1**. However, it is noteworthy that the 2-substituted 2-aminopropane-1,3-diols such as **2** prolonged survival time of rat skin allograft in vivo more effectively than **1** and that they were approximately 30-fold less toxic.[27] This observation suggested that the conversion of the carboxylic group of **1** to a hydroxymethyl group was effective in increasing in vivo activity and reducing toxicity. The SAR of a series of myriocin and mycestericin derivatives indicated that simplification of the hydrophobic long chain of **1** was possible. As a result of simplification of **2**, we obtained the lead compound **3** for the development of new immunosuppressants. In the present research, we modified the structure of **3** in order to obtain an immunosuppressant with acceptable potency and safety for clinical use (Chart 2).

Compound **3** consists of a hydrophilic part (2-aminopropane-1,3-diol) and a lipophilic part (hydrocarbon chain). First, we took interest in the lipophilic part because the double bonds in the hydrophobic long chain of **1** and **2** were favorable for potent activity.[24,26] On the assumption that introducing a π bond or restricting the conformation of the hydrocarbon chain would produce a favorable result, we substituted a 1,4-phenylene group for a part of the alkyl chain of **3** because the phenyl group not only has π bonds but is also considered an effective template for restricting the conformation of hydrocarbon chains.[28] To do this, we prepared and evaluated a series of compounds possessing a phenyl ring at a variety of positions within the side chain of **3**, keeping the chain length constant ($m + n = 10$) (compounds **4**−**11**, Chart 2) in order to identify the optimum position. Of the resulting compounds, compound **6** displayed excellent activity. The results prompted us to attempt to improve **6** by the synthesis of analogues. Compounds **12**−**18** were synthesized to confirm the optimal length of the side chain of **6**. The methylene group next to the phenyl ring in the side chain of **6** was displaced with other groups or atoms such as a carbonyl and an oxygen (compounds **19**−**24**) to investigate the most favorable linkage between the phenyl ring and the alkyl group extending from it. We also examined regioisomers on the phenyl ring (compounds **25** and **26**) and a thiophene analogue, where the thiophene ring has been considered to be a bioisoster of the phenyl ring (compound **27**).

Next, we modified the hydrophilic part of **6**. We synthesized 2-substituted 2-aminoethanols (compounds **28**−**38**), with various substituents replacing one of the hydroxymethyl groups of compounds **6** or **22**, and 3-substituted 3-aminopropanol (compounds **39** and **40**). We describe herein the discovery of the novel immunosuppressant FTY720 (**6**) and the synthesis and SAR of analogues of **6**.

Scheme 1[a]



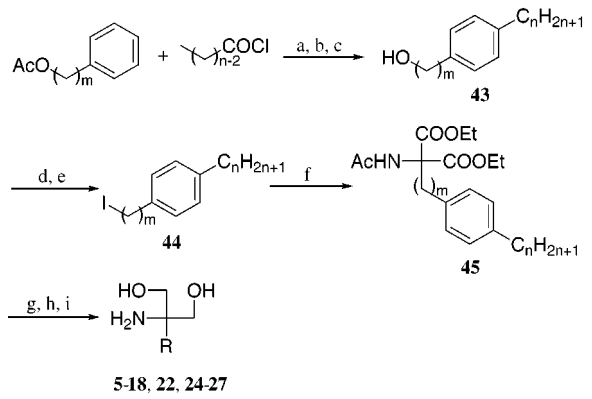
[a] (a) Cl_2HCOCH_3, $TiCl_4$, CH_2Cl_2; (b) $NaBH_4$, MeOH, 2-propanol; (c) 48% HBr, toluene; (d) $AgNO_2$, ether; (e) 37% HCHO, 1 N aq NaOH, EtOH; (f) H_2, Raney Ni, EtOH; (g) AcCl, Et_3N, EtOH/$CHCl_3$; (h) 1 N aq NaOH, EtOH.

Chemistry

The synthesis of compound **4** was carried out as shown in Scheme 1. Decylbenzene was formylated, and the formyl group was converted to a bromomethyl group. Nitration of the bromide **41** with silver nitrite[29] followed by hydromethylation gave the 2-nitropropane-1,3-diol **42**. The nitro group was reduced with hydrogen and Raney Ni, and the resulting crude target compound was purified by acetylation followed by hydrolysis to give **4**.

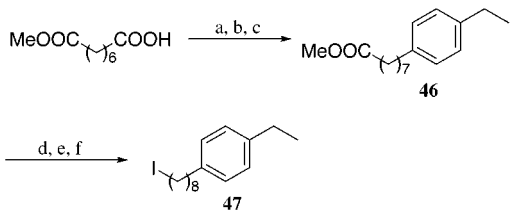
The synthesis of compounds **5**−**18** is presented in Scheme 2. Friedel−Crafts acylation of phenylalkyl acetates followed by reduction with triethylsilane in trifluoroacetic acid gave 4-alkylated phenylalkyl acetates. The acetates were deprotected to give intermediates **43**. The alcohols **43** were converted into iodides **44**

Scheme 2[a]



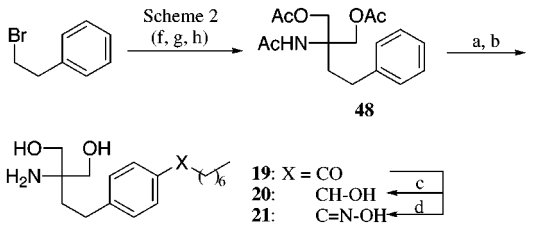
[a] (a) $AlCl_3$, 1,2-dichloroethane; (b) Et_3SiH, TFA; (c) NaOMe, MeOH; (d) MsCl, Et_3N, CH_2Cl_2; (e) NaI, 2-butanone; (f) diethyl acetamidomalonate, NaOEt, EtOH; (g) $LiAlH_4$, THF; (h) Ac_2O, pyridine; (i) 2 N aq LiOH, MeOH.

Scheme 3[a]



[a] (a) $SOCl_2$, 1,2-dichloroethane; (b) ethylbenzene, $AlCl_3$, 1,2-dichloroethane; (c) Et_3SiH, TFA; (d) $LiAlH_4$, THF; (e) MsCl, Et_3N, CH_2Cl_2; (f) NaI, 2-butanone.

Scheme 4[a]



[a] (a) Octanoyl chloride, $AlCl_3$, 1,2-dichloroethane; (b) aq LiOH, MeOH; (c) $NaBH_4$, MeOH; (d) $NH_2OH{\cdot}HCl$, EtOH, $CHCl_3$.

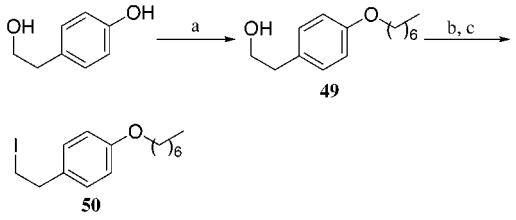
and subsequently condensed with diethyl acetamidomalonate using a standard method to give **45**. Reduction of **45** with lithium aluminum hydride and successive acetylation provided triacetylated target compounds, which were hydrolyzed to give compounds **5**−**18**. For the preparation of compound **10**, the iodide **47** (Scheme 3) was used instead of **44**. 10-Phenyldecyl bromide[30] was adopted instead of iodide **44** for the synthesis of compound **11**.

Next, target compounds **19**−**21** were prepared as outlined in Scheme 4. Phenethyl bromide was converted to intermediate **48** by the same method as in Scheme 2. Friedel−Crafts acylation of **48** followed by hydrolysis gave the target compound **19**. The ketone **19** was treated with sodium borohydride or hydroxylamine hydrochloride to give the target compounds **20** and **21**, respectively.

The ether **22** was synthesized by a method similar to that in Scheme 2, except that iodide **50** (Scheme 5) was used instead of **44**. The synthesis of the sulfide **23** was accomplished by the route shown in Scheme 6. 4-Methylthiobenzaldehyde underwent Knoevenagel-type condensation with methyl methylsulfinylmethyl sulfide in the presence of Triton B.[31] The acid-catalyzed degradation of the condensation product gave an ester **51**. The ester group of **51** was reduced, and the sulfide group was successively oxidized to the sulfoxide. Mesylation followed by iodination gave iodide **52**. Condensation of **52** with diethyl acetamidomalonate followed by Pummerer rearrangement using trifluoroacetic anhydride and triethylamine[32] gave intermediate **53**, which was converted into the desired compound **23** in three steps. The synthesis of amine **24** was carried out according to the procedure described in Scheme 2, except that the iodide **55** (Scheme 7) was used instead of **44**.

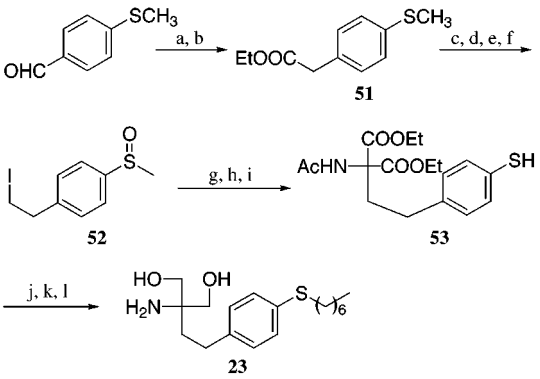
The *ortho*-substituted analogue **25** was synthesized using a method similar to that in Scheme 2, except that the iodide **58** (Scheme 8) was used instead of **44**. 2-Bromobenzaldehyde underwent Grignard coupling with heptyl bromide. Dehydration with P_2O_5 followed by formylation gave aldehyde **56**. The double bond was saturated, and the resulting aldehyde was transformed

Scheme 5[a]



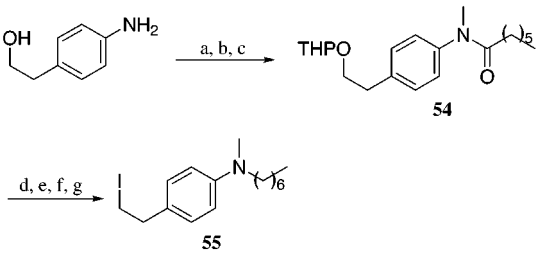
[a] (a) Heptyl bromide, NaOEt, EtOH; (b) MsCl, Et_3N, CH_2Cl_2; (c) NaI, 2-butanone.

Scheme 6[a]



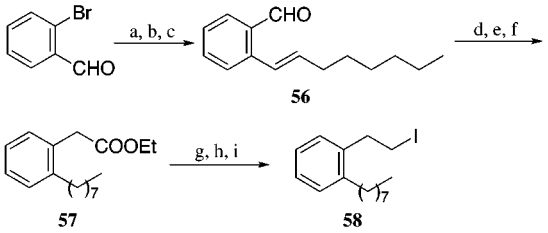
[a] (a) $CH_3SCH_2SOCH_3$, Triton B, 1,4-dioxane; (b) HCl, EtOH; (c) $LiAlH_4$, THF; (d) *m*-CPBA, $CHCl_3$; (e) MsCl, Et_3N; (f) NaI, 2-butanone; (g) diethyl acetamidomalonate, NaOEt, EtOH; (h) TFA, CH_2Cl_2; (i) Et_3N, EtOH; (j) heptyl bromide, K_2CO_3, DMF; (k) $LiAlH_4$, THF; (l) $LiOH{\cdot}H_2O$, MeOH/THF/H_2O.

Scheme 7[a]



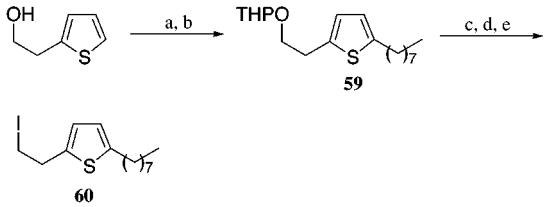
[a] (a) Hexanoyl chloride, Et_3N, THF; (b) DHP, *p*-TsOH·H_2O, CH_2Cl_2; (c) MeI, *t*-BuOK, 1,2-dimethoxyethane; (d) BH_3·THF, THF; (e) *p*-TsOH·H_2O, MeOH; (f) MsCl, Et_3N, CH_2Cl_2; (g) NaI, 2-butanone.

Scheme 8[a]



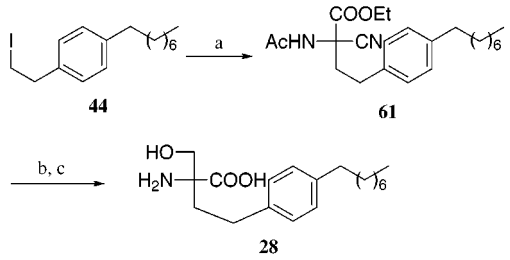
[a] (a) Heptyl bromide, Mg, THF; (b) P_2O_5, benzene; (c) Mg, DMF, THF; (d) H_2, Pd/C, EtOH; (e) $CH_3SCH_2SOCH_3$, Triton B, 1,4-dioxane; (f) HCl, EtOH; (g) $LiAlH_4$, THF; (h) MsCl, Et_3N; (i) NaI, 2-butanone.

Scheme 9[a]



[a] (a) DHP, *p*-TsOH·H_2O, CH_2Cl_2; (b) *n*-BuLi, octyl bromide, THF; (c) *p*-TsOH·H_2O; (d) MsCl, Et_3N; (e) NaI, 2-butanone.

Scheme 10[a]

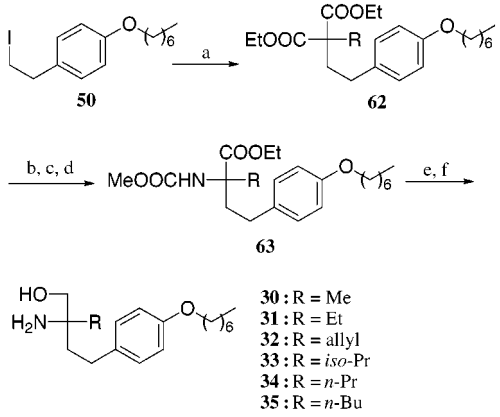


[a] (a) AcNHCH(CN)COOEt, NaH, DMF; (b) $LiBH_4$, THF; (c) HCl, AcOH, H_2O.

into the ester **57** using the same method as for the synthesis of **51**. The desired **58** was obtained from **57** in three steps. The *meta*-substituted analogue **26** was synthesized by a similar route to that used for **25**. Thiophene **27** was prepared according to Scheme 2. The iodide **60** used for the synthesis instead of **44** was obtained by the procedure shown in Scheme 9.

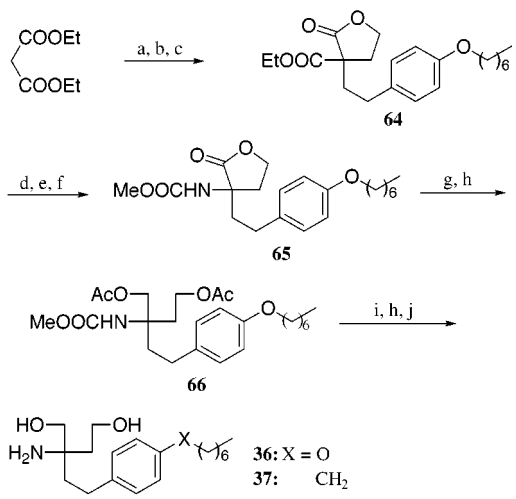
Compound **28**, which has an α-substituted serine skeleton like myriocin, was synthesized from phenethyl acetate as a starting material by the route shown in Scheme 10. The synthesis of compound **29** was reported in the previous paper.[33] Compounds **30**−**35**, having hydrophobic groups in place of one of the hydroxymethyl groups of **22**, were synthesized from 2-substituted diethyl malonates as the starting materials (Scheme 11). Iodide **50** and 2-substituted diethyl malonates were condensed using NaH to give diesters **62**. The diesters were treated with potassium hydroxide in ethanol to give half-esters, which were converted to acyl azides. The acyl azides underwent Curtius rearrangement, and the resulting isocyanates were trapped with methanol to afford methylcarbamates **63**. Reduction with lithium borohydride followed by hydrolysis yielded compounds **30**−**35**. Compound **36**, having a hydroxyethyl group in place of one of the hydroxymethyl groups of compound **22**, was synthesized by the route shown in Scheme 12. Diethyl malonate was dialkylated followed by treatment with aqueous hydrogen chloride to give the γ-lactone

Scheme 11[a]



[a] (a) $RCH(COOEt)_2$, NaH, DMF; (b) (1) KOH, EtOH, (2) HCl, H_2O; (c) (1) ClCOOEt, Et_3N, THF, (2) NaN_3; (d) (1) benzene, reflux, (2) benzene/MeOH; (e) $LiBH_4$, THF; (f) 5 N aq KOH, THF/MeOH.

Scheme 12[a]

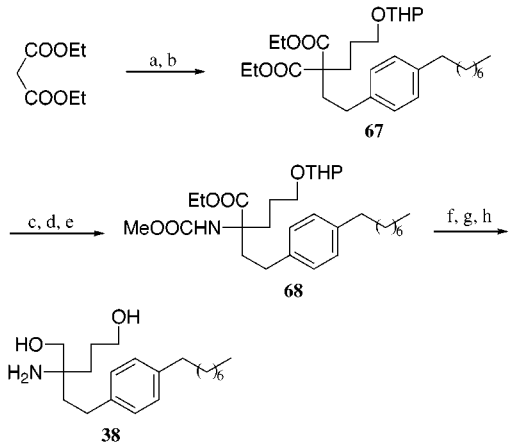


[a] (a) $I(CH_2)_2OTHP$, NaH, DMF; (b) **50**, NaH, DMF; (c) 1 N aq HCl, MeOH; (d) 0.25 N aq NaOH, acetone; (e) (1) ClCOOEt, Et_3N, THF, (2) NaN_3; (f) (1) benzene, reflux, (2) benzene/MeOH; (g) $LiBH_4$, THF; (h) Ac_2O, pyridine; (i) TMSI, CH_2Cl_2; (j) 2 N aq LiOH, THF/MeOH.

ethyl ester **64**. Hydrolysis of **64** followed by Curtius rearrangement afforded an isocyanate, which was trapped with methanol to give the methylcarbamate **65**. Compound **65** was reduced and successively acetylated to give **66**, which was deprotected into compound **36**. Compound **37** was synthesized using iodide **44** instead of **50** as in Scheme 12. The synthesis route of compound **38** is shown in Scheme 13. This route is similar to that for compound **36**, except that the tetrahydropyranyl group (THP) is removed in the last step, since, unlike in **64**, the deprotection of **67** did not yield a δ-lactone ethyl ester. Compounds **39** and **40** were prepared in a totally different way (Scheme 14) containing a Ritter reaction.[34,35]

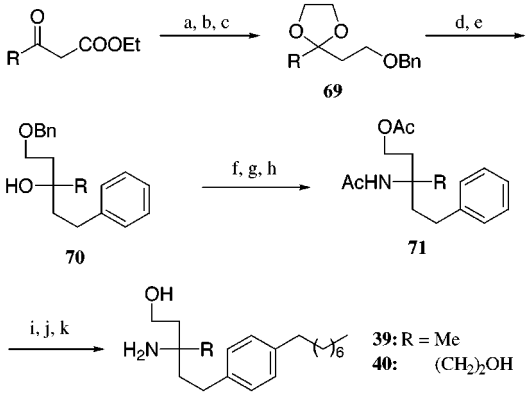
The enantiomers of compounds **30**, **34**, and **36** were obtained by optical resolution of their *N*-(3,5-dinitrobenzoyl) derivatives using chiral column HPLC (Scheme 15). The absolute configuration of the (−)-enantiomer of compound **34** was determined to be *S* by X-ray analysis.[2] The absolute configuration of compound **30** was assumed by comparing the optical rotation and retention time on the chiral HPLC of the optically active compounds **72a** and **72b**. (*R*)-(−)-**72a** and (*R*)-(−)-**72b**,

Scheme 13[a]



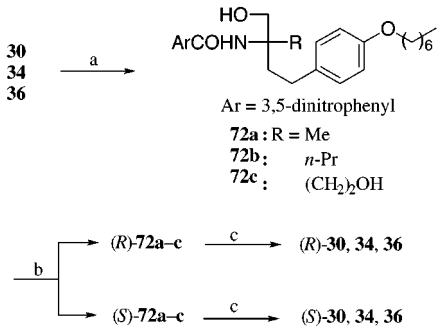
[a] (a) $Br(CH_2)_3OTHP$, NaH, DMF; (b) **44**, NaH, DMF; (c) (1) KOH, EtOH, (2) HCl, H_2O; (d) (1) ClCOOEt, Et_3N, THF, (2) NaN_3; (e) (1) benzene, reflux, (2) benzene/MeOH; (f) $LiBH_4$, THF; (g) 5 N aq KOH, THF/MeOH; (h) 1 N aq HCl, MeOH.

Scheme 14[a]



[a] (a) $HO(CH_2)_2OH$, *p*-TsOH−H_2O, benzene; (b) $LiAlH_4$, THF; (c) BnBr, NaH, DMF; (d) 1 N aq HCl, acetone/THF; (e) phenethyl bromide, Mg, THF; (f) H_2SO_4, CH_3CN; (g) H_2, Pd−C, AcOH; (h) Ac_2O, pyridine; (i) octanoyl chloride, $AlCl_3$, 1,2-dichloroethane; (j) Et_3SiH, TFA; (k) 2 N aq LiOH, THF/MeOH.

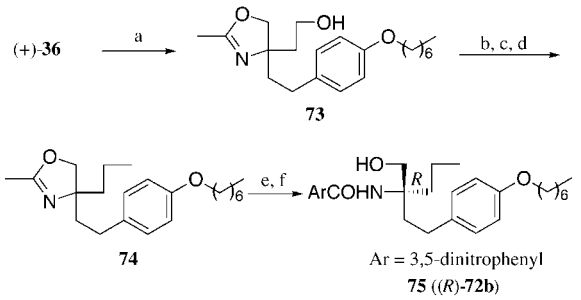
Scheme 15[a]



[a] (a) 3,5-Dinitrobenzoyl chloride, $KHCO_3$, EtOAc/H_2O; (b) separation by HPLC; (c) 2 N aq LiOH, THF/MeOH.

as well as (*S*)-(+)-**72a** and (*S*)-(+)-**72b**, had the same retention time on the chiral HPLC and a similar optical rotation, respectively. The (+)-enantiomer of compound **36** was converted into **75** to determine the absolute configuration as shown in Scheme 16. The compound **75** derived from (+)-**36** had the same optical rotation and retention time on the chiral HPLC as the *R*-enantiomer of **72b**. The absolute configuration of (+)-enantiomer of **36** was thus determined to be *S*.

Scheme 16[a]



[a] (a) $CH_3CH(OC_2H_5)_3$, DIPEA, DMF; (b) (1) $(COCl)_2$, DMSO, CH_2Cl_2, (2) Et_3N; (c) Zn, CH_2I_2, Me_3Al, THF; (d) H_2, Pd−C, EtOH; (e) concd HCl, EtOH; (f) 3,5-dinitrobenzoyl chloride, $KHCO_3$, H_2O/EtOAc.

Results and Discussion

From the beginning of our search for immunosuppressive compounds, we had evaluated the compounds for their in vitro immunosuppressive activity using mouse allogeneic MLR. However, 2-alkyl-2-aminopropane-1,3-diols such as **3** prolonged rat skin allograft survival markedly compared to **1**, despite having only comparable activity on mouse allogeneic MLR.[27] This result prompted us to investigate the mechanism of action of compounds **1** and **3**. We found that 2-alkyl-2-aminopropane-1,3-diols such as **3** drastically decrease the number of circulating lymphocytes (T-cells and B-cells) in peripheral blood and that compound **3**, unlike **1**, has no inhibitory effect on serine palmitoyltransferase.[27] Myriocin (**1**), on the other hand, did not decrease the number of circulating lymphocytes, suggesting that the immunosuppressive mechanism of 2-alkyl-2-aminopropane-1,3-diols such as **3** would be different from that of **1**. We assume that the lymphocyte-decreasing effect of **3** contributes to its immunosuppressive activity in vivo. In the early stage of this study (compounds **4**−**27**), all compounds were initially screened for their lymphocyte-decreasing effect. Most compounds were also tested for their immunosuppressive activity in rat skin allograft using LEW donors and F344 recipients (Table 1). In these experiments, the compounds were administered intraperitoneally.

Our attention focused first on the most favorable position for introducing a phenyl ring into the lipophilic side chain of **3**. We synthesized a series of compounds having the same length of the side chain containing a phenyl ring ($m + n = 10$, compounds **4**−**11**). This indicates that the position of the phenyl ring markedly affected the activities. Compound **6**, which has two carbon atoms between the quaternary carbon atom and the phenyl ring ($m = 2$), decreased the number of lymphocytes 3 times more effectively than the lead compound **3** and prolonged allograft survival in a dose-dependent manner. Moving the phenyl ring of **6** by just one carbon in either direction resulted in a great loss of potency, suggesting that the position of the phenyl ring is of critical importance for the potency of activity. This finding suggests that the introduction of the phenyl ring can modify their pharmacological properties presumably by sterical restriction on the alkyl chain and/or favorable interaction with target molecules. All compounds except **6** showed weaker activity than the lead compound **3**.

Table 1. Lymphocyte-Decreasing Effect (ID_{50} and ID_{80}, mg/kg) and Immunosuppressive Activity on Rat Skin Allograft (MST ± SE, days) of 2-Substituted 2-Aminopropane-1,3-diols

			MST ± SE[b]				
compd	ID_{50}[a]	ID_{80}[a]	0.1 mg/kg	0.3 mg/kg	1 mg/kg	3 mg/kg	10 mg/kg
control	>3	>3			8.5 ± 0.3		
3	0.3	0.3	13.8 ± 0.3	26.5 ± 1.8	37.3 ± 1.1	45.5 ± 2.4	toxic[c]
4	0.3	>3			NT[d]		
5	>3	>3				9.8 ± 0.5	11.8 ± 0.5
6	0.03	0.1	25.3 ± 0.6	31.3 ± 0.9	39.5 ± 2.8	52.0 ± 6.2	toxic
7	>3	>3				9.0 ± 0.6	10.5 ± 1.0
8	>3	>3				13.8 ± 1.8	18.8 ± 1.5
9	0.3	1				9.8 ± 0.5	13.5 ± 0.3
10	>3	>3				8.5 ± 0.3	8.6 ± 0.3
11	0.3	1	11.5 ± 0.9	21.5 ± 3.1	27.0 ± 2.1	toxic	
12	0.1	0.3			NT		
13	0.03	0.1		23.0 ± 3.9	32.0 ± 1.5	toxic	
14	0.1	0.1	20.0 ± 1.8	37.8 ± 2.1	48.0 ± 3.3	toxic	
15	0.1	0.1		23.3 ± 2.1	39.3 ± 3.5	toxic	
16	0.1	1	12.0 ± 0.7	22.8 ± 3.7	40.5 ± 3.8	53.0 ± 3.5	toxic
17	0.03	1			NT		
18	1	>3			NT		
19	0.03	0.3	19.8 ± 1.3	25.5 ± 1.7	32.5 ± 1.2	toxic	
20	0.1	0.3			NT		
21	0.03	1			NT		
22	0.03	0.1	15.0 ± 1.1	23.5 ± 1.6	33.8 ± 0.5	39.5 ± 1.6	toxic
23	0.03	0.03	22.3 ± 2.2	36.0 ± 1.5	44.5 ± 2.0	toxic	
24	1	1			21.3 ± 1.1	29.0 ± 1.1	toxic
25	>3	>3			NT		
26	>3	>3			NT		
27	1	>3		13.0 ± 1.1	17.3 ± 0.6	21.0 ± 1.8	
CsA	>30	>30	8.0 ± 0.4 (1 mg/kg)	10.8 ± 0.3 (3 mg/kg)	15.0 ± 0.4 (10 mg/kg)	19.8 ± 0.5 (30 mg/kg)	toxic (100 mg/kg)

[a] The indicated dose (mg/kg) is the lowest dose required to decrease the number of lymphocytes by 50% or 80% of vehicle-treated control. [b] MST: mean survival time (days). Each group consisted of four animals. [c] Animals died. [d] NT, not tested.

Next we focused on the refinement of the length of the alkyl chain containing the phenyl ring. When the length between the quaternary carbon atom and the phenyl ring was two carbon atoms ($m = 2$), most compounds (**12**−**17**) except **18** showed comparable activity to **3**, suggesting that the activities were not so sensitive to the length of the alkyl chain attached to the phenyl ring. This finding contrasts with the case of alkyl compounds reported previously.[27] In the reported study, we found that the activity of alkyl compounds containing no phenyl ring was significantly influenced by the length of the alkyl side chain. When the length of the alkyl chain was eight ($n = 8$, compound **6**) or nine ($n = 9$, compound **13**) carbon atoms, activity in terms of lymphocyte-decreasing effect was excellent. On the other hand, compound **14**, of which the alkyl chain had ten carbon atoms ($n = 10$), showed the most potent immunosuppressive activity on rat skin allograft at a dose of 1 mg/kg but was toxic at a dose of 3 mg/kg. The toxicity of the compounds of this series was greatest when the length of the alkyl chain attached to the phenyl ring was nine to eleven carbon atoms ($n = 9-11$, compounds **13**−**15**). Although compound **16** with its longer alkyl chain ($n = 12$) effectively prolonged rat skin allograft survival at high doses (1 and 3 mg/kg), its activity at low doses (0.1 and 0.3 mg/kg) was weaker than that of **6**. This weak immunosuppressive activity at low doses is associated with its weak activity on the lymphocyte-decreasing effect. Since a sufficient separation of immunosuppressive activity and toxicity has been achieved with compound **6**, we concluded that compound **6** is superior to **16** as the candidate drug.

Our third focus of attention was the most favorable linkage between the phenyl ring and the alkyl group extending from it. Replacement of the methylene group with a carbonyl or hydroxymethylene (compounds **19** and **20**, respectively) resulted in slightly weaker activity on the lymphocyte-decreasing effect compared with that of compound **6**. Compound **19** was toxic at a dose of 3 mg/kg. Compound **22**, which has an oxygen atom, was equipotent to **6** in terms of lymphocyte-decreasing effect but did not significantly prolong allograft survival compared to **6**. Introduction of a sulfur atom was favorable for potent activity on the lymphocyte-decreasing effect and rat skin allograft survival. Unfortunately, the sulfide **23** combined strong toxicity with its potent activity. Attempts to replace the methylene group with nitrogen functional groups (compounds **21** and **24**) resulted in a loss in activity. These findings verify that hydrophilic groups next to the phenyl ring are unfavorable for activity.

The *ortho*- and *meta*-substituted derivatives **25** and **26**, respectively, showed notably reduced activity. This finding together with that in the *para*-substituted derivative **6** indicates that the phenyl ring affects activity by restricting the conformation of molecules. Replacement of the phenyl ring with a thiophene ring (compound **27**) led to a great loss of activity.

On the whole, marked decrease in the number of peripheral blood lymphocytes was associated with significant prolongation of allograft survival. This suggests that a decrease in peripheral lymphocytes is closely related to immunosuppressive activity. Among the compounds described above, we selected **6** (FTY720) as the candidate drug for clinical trial in view of its marked lymphocyte-decreasing effect, potent immunosuppressive activity, and low toxicity. FTY720 prolonged rat skin allograft survival more effectively than CsA and showed activity in other administration routes (mean survival time: 24.8 days/0.1 mg/kg, 46.3 days/3 mg/kg,

Table 2. T-Cell-Decreasing Activity and Immunosuppressive Activity of 2-Substituted 2-Amino Alcohols and Related Amino Alcohols

compd	ID_{50} values[a] (mg/kg, po, $n = 4$)	
	T-cells	lymph node
6	0.024 (0.016−0.035)	0.0097 (0.032−0.28)
22	0.014 (0.012−0.018)	0.049 (0.019−0.15)
28	>10	>10
29	>10	>10
30	0.016 (0.013−0.021)	0.031 (0.018−0.053)
(*R*)-**30**	0.0092 (0.0068−0.010)	0.088 (0.032−0.22)
(*S*)-**30**	>1[b]	>1[b]
31	0.044 (0.039−0.050)	0.059 (0.029−0.11)
32	3.1 (2.1−4.7)	1.9 (0.70−4.9)
33	4.5 (3.8−5.6)	2.7 (1.5−4.7)
34	7.3 (4.6−12)	3.1 (1.6−5.7)
(*R*)-**34**	4.4 (3.6−4.7)	0.63 (0.14−1.9)
(*S*)-**34**	>10	>10
35	>10	>10
36	0.055 (0.035−0.085)	0.038 (0.025−0.058)
(*R*)-**36**	4.2 (2.8−6.5)	4.2 (1.8−10)
(*S*)-**36**	0.018 (0.015−0.021)	0.017 (0.0068−0.035)
37	0.12 (0.079−0.19)	0.009 (0.0040−0.021)
38	0.021 (0.015−0.028)	0.085 (0.048−0.14)
39	>10	>10
40	>10	>10
CsA	>30	2.8 (1.2−6.5)

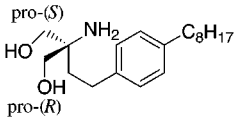
[a] 95% confidence limits are given in parentheses. [b] No activity at 1 mg/kg, the highest dose tested for this compound.

and 53.5 days/10 mg/kg, iv; 19.3 days/0.1 mg/kg, 41.0 days/3 mg/kg, and 57.8 days/30 mg/kg, po). From our study on the mechanism of action of FTY720, we concluded that FTY720 sequesters circulating mature lymphocytes into peripheral lymph nodes, mesenteric lymph nodes, and Peyer's patches by acceleration of lymphocyte homing and thereby decreases the number of lymphocytes in peripheral blood.[36−39] Meanwhile, we confirmed that FTY720, like **3**, had no inhibitory effect on serine palmitoyltransferase at a concentration of 1000 nM or less.

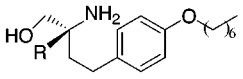
During the research to elucidate the mechanism of action of compound **6**, it was proved that the decrease of T-cells in peripheral blood caused by **6** was more remarkable than the decrease of B-cells or other cells.[37] We presumed that the T-cell-decreasing effect is the essence of immunosuppressive activity of **6** because T-cells perform pivotal functions on allograft rejection. Therefore, we investigated the T-cell-decreasing effect (Table 2) instead of the lymphocyte-decreasing effect in the late stage of this study (compounds **28**−**40**) to obtain an improved compound. Furthermore, we adopted a popliteal lymph node gain assay[40] to evaluate the immunosuppressive activity. This assay represents one of the simplest models of graft rejection in transplantation and is able to express the results as simpler numerals (e.g. ID_{50}, Table 2) than those of skin allograft. Compound **6** markedly decreased the number of T-cells (ID_{50} = 0.024 mg/kg) and showed potent immunosuppressive activity (ID_{50} = 0.0097 mg/kg) on the popliteal lymph node gain assay.

An α-substituted serine **28**, the structure of which is similar to that of myriocin (**1**), was not active probably due to its poor solubility. Although we previously reported that compound **29**, which has a hydrogen in place of one of the hydroxymethyl groups of **6**, had a similar activity to **6** in mouse allogeneic MLR,[33] **29** was inactive in vivo at doses of 10 mg/kg or less presumably

Chart 3. Comparison of Configuration at Quaternary Carbon Atoms



6 (FTY720)



(*R*)-**30** (R = CH_3)
(*R*)-**34** (R = $CH_2CH_2CH_3$)
(*S*)-**36** (R = CH_2CH_2OH)

because of its rapid metabolic change. We also found that the hydroxy groups of **6** are not always both necessary for in vivo activity, as compounds **30** and **31**, having a lower alkyl group, showed potent T-cell-decreasing activity (**30**: 0.016 mg/kg, **31**: 0.044 mg/kg) and immunosuppressive activity (**30**: 0.031 mg/kg, **31**: 0.059 mg/kg). However, activity weakened with increasing bulkiness of the alkyl group (compounds **32**−**34**). No activity was observed at larger size (compound **35**). Interestingly, compounds **36**−**38**, which retain two hydroxy groups such as **6**, show a tendency distinct from that observed in the alkyl derivatives **30**−**35**. Compounds **36**−**38** showed potent activity despite the increasing volume of the substituent attached to the quaternary carbon. For example, the bulkiness of the hydroxyethyl group of compound **36** is similar to that of the propyl group of compound **34**. However, **36** showed potent activity in contrast to the weak activity of compound **34**. These results suggest that, when the substituent attached to the quaternary carbon is bigger than an ethyl group, the hydroxyalkyl groups are more favorable for potent activity than the corresponding alkyl groups.

3-Substituted 3-aminopropanols (compounds **39** and **40**) showed no activity, whether the substituent binding to the quaternary carbon was methyl or hydroxyethyl. When the results for **39** and **40** were compared with those for **30** and **36**, it became clear that a 2-aminoethanol moiety, that is, a hydroxymethyl group attached to the quaternary carbon, is essential for the immunosuppressive activity.

Marked differences in activity were observed between the enantiomers of three compounds (**30**, **34**, and **36**). For example, (*R*)-**30** showed potent T-cell-decreasing activity and immunosuppressive activity (ID_{50} = 0.0092 and 0.088 mg/kg, respectively), whereas (*S*)-**30** showed no activity at a dose of 1 mg/kg. (*R*)-**30**, (*R*)-**34**, and (*S*)-**36** were more potent than the corresponding enantiomers, (*S*)-**30**, (*S*)-**34**, and (*R*)-**36**, respectively. (*S*)-**36** has the same configuration for the quaternary carbon as (*R*)-**30** and (*R*)-**34**, as the priority of the groups attached to the chiral center is changed. The active enantiomers have the (*pro*-*S*)-hydroxymethyl group of **6** (Chart 3), indicating that the two hydroxymethyl groups of **6** play different roles for showing immunosuppressive activity and that the (*pro*-*S*)-hydroxymethyl group of **6** is essential for immunosuppressive activity. On the other hand, it is able to replace the (*pro*-*R*)-hydroxymethyl group by other substituents, and the favorable substituents are lower alkyl (methyl and ethyl) or hydroxyalkyl (hydroxyethyl and hydroxypropyl) groups shown by compounds **30**, **31**, and **36**−**38**. This result suggests that the binding site of the (*pro*-*R*)-hydroxymethyl group in the targeting molecule is constituted by a lipophilic entrance and a hydrophilic inner site.

Conclusion

A phenyl ring was introduced into the alkyl side chain of lead compound **3**. The position of the phenyl ring was critical for the lymphocyte-decreasing effect and immunosuppressive activity. Activity was especially potent when the length between the quaternary carbon atom and the phenyl ring was two carbon atoms. The most suitable substitution pattern for the phenyl ring was *para*. Variation of the length of the alkyl side chain did not dramatically affect activity but caused the fluctuation of toxicity. Favorable substituents for one of the hydroxymethyl groups of **6** were hydroxyalkyl (hydroxyethyl and hydroxypropyl) or lower alkyl (methyl and ethyl) groups. Evaluation of three pairs of enantiomers revealed that the (*pro-S*)-hydroxymethyl group of **6** is indispensable, while the (*pro-R*)-hydroxymethyl group plays a supplementary role for the immunosuppressive activity. FTY720 (**6**) possesses potent immunosuppressive activity and unique mechanisms of action. It is therefore expected to be a promising immunosuppressive drug for organ transplantation.

Experimental Section

Chemistry. Organic extracts were dried over anhydrous Na_2SO_4. Silica gel chromatography was performed on Merck Kieselgel 60. HPLC was accomplished using a TOSOH SC-8010 controller, a CCPP-M pump, and a UV-8010 detector. Melting points were obtained on a Buchi 535 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL α400 spectrometer (400 MHz) or a HITACHI R-90H spectrometer (90 MHz) using tetramethylsilane (TMS) as an internal standard. Mass spectra were measured on a JEOL-JMS-DX300 instrument. Infrared spectra were recorded on a JASCO FT/IR-5300 spectrometer. Optical rotations were determined on a JASCO digital polarimeter DIP-360 in a 10-cm path length cell. Elemental analyses were performed on a Yanako CHN coder MT-5, and the results indicated by element symbols are within ±0.4% of the calculated values.

2-Amino-2-(4-decylphenyl)propane-1,3-diol Hydrochloride (4). A solution of **42** (337 mg, 1.00 mmol) in EtOH (10 mL) was hydrogenated at room temperature for 16 h using Raney Ni (500 mg) and 20 atm of hydrogen. The catalyst was removed by filtration and the filtrate was evaporated. To a solution of the residue in EtOH (20 mL) and $CHCl_3$ (5 mL) were added triethylamine (400 μL, 2.89 mmol) and acetyl chloride (120 μL, 1.69 mmol) at −60 °C. The mixture was stirred at room temperature for 30 min, evaporated, and diluted with EtOAc. The solution was washed with 1 N HCl, saturated $NaHCO_3$ and brine, dried, and evaporated. The residue was purified by preparative TLC, developing with $CHCl_3$−CH_3CN (4:1), to give 2-acetamido-2-(4-decylphenyl)-propane-1,3-diol (130 mg, 37%) as a white solid. To a solution of this intermediate (170 mg, 0.486 mmol) in MeOH (9 mL) was added 1 N NaOH (3 mL). The mixture was refluxed for 3 h, and the organic solvent was evaporated. The yielded white solid was the free base of **4** (142 mg, 95%): mp 136−137 °C; ^{1}H NMR (90 MHz, $CDCl_3$/CD_3OD) δ 7.33 (d, 2H, J = 10 Hz), 7.20 (d, 2H, J = 10 Hz), 4.20−3.50 (m, 4H), 2.70−2.30 (m, 6H), 1.80−1.40 (m, 2H), 1.40−1.10 (m, 14H), 0.88 (t, 3H, J = 8 Hz).

This product was converted to hydrochloride salt by treatment with HCl/MeOH and recrystallized from 2-propanol to give **4** (131 mg) as a white solid: mp 117−118 °C; IR (KBr) 3464, 3015, 2919, 2851 cm^{-1}; MS (EI) m/z 307 (M^+). Anal. ($C_{19}H_{33}NO_2$·HCl) C, H, N.

2-Amino-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol Hydrochloride (6). To a suspension of $LiAlH_4$ (3.03 g, 79.8 mmol) in THF (260 mL) at 0 °C was added dropwise a solution of **45** (11.6 g, 26.8 mmol) in THF (100 mL). After stirring at room temperature for 2 h, the reaction was quenched with saturated Na_2SO_4 (50 mL). The reaction mixture was filtered through Celite and evaporated. The residue was dissolved in pyridine (40 mL) and acetic anhydride (30 mL) and left at room temperature for 16 h. The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with 1 N HCl and saturated $NaHCO_3$ and brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (1:2), gave 2-acetamido-2-[2-(4-octylphenyl)ethyl]propane-1,3-diol diacetate (8.25 g, 88%) as a white solid. To a solution of this intermediate (8.25 g, 23.6 mmol) in MeOH (100 mL) was added 2 N LiOH (80 mL). The mixture was refluxed for 2 h, evaporated to remove the organic solvent, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. The residue was converted to hydrochloride salt by treatment with EtOH (50 mL) and 1 N HCl solution in Et_2O (50 mL) and recrystallized from EtOH/EtOAc to give **6** (4.20 g, 52%) as a white solid: mp 107−108 °C; ^{1}H NMR (90 MHz, DMSO-d_6) δ 7.94 (brs, 3H), 7.11 (s, 4H), 5.40 (t, 2H, J = 6 Hz), 3.50 (d, 4H, J = 6 Hz), 2.63−2.44 (m, 4H), 1.83−1.72 (m, 2H), 1.57−1.45 (m, 2H), 1.29−1.18 (m, 10H), 0.85 (t, 3H, J = 6 Hz); IR (KBr) 3371, 3265, 2924 cm^{-1}; MS (EI) m/z 307 (M^+). Anal. ($C_{19}H_{33}NO_2$·HCl) C, H, N.

Compounds **5** and **7**−**18** were synthesized as described for **6**.

2-Amino-2-(4-nonylbenzyl)propane-1,3-diol hydrochloride (5): mp 119−120 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (brs, 3H), 7.17 (d, 2H, J = 7.9 Hz), 7.12 (d, 2H, J = 7.9 Hz), 5.42 (t, 2H, J = 3.9 Hz), 3.37−3.29 (m, 4H), 2.82 (s, 2H), 2.52 (t, 2H, J = 7.3 Hz), 1.59−1.50 (m, 2H), 1.31−1.18 (m, 12H), 0.84 (t, 3H, J = 6.9 Hz); IR (KBr) 3362, 3279 cm^{-1}; MS (EI) m/z 308 (M + H) $^+$. Anal. ($C_{19}H_{33}NO_2$·HCl) C, H, N.

2-Amino-2-[3-(4-heptylphenyl)propyl]propane-1,3-diol hydrochloride (7): mp 124−126 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 (brs, 3H), 7.08 (s, 4H), 5.29 (t, 2H, J = 4.4 Hz), 3.46−3.38 (m, 4H), 2.53−2.48 (m, 4H), 1.59−1.48 (m, 6H), 1.29−1.18 (m, 8H), 0.84 (t, 3H, J = 6.8 Hz); IR (KBr) 3435, 3045 cm^{-1}; MS (EI) m/z 307 (M^+). Anal. ($C_{19}H_{33}NO_2$·HCl) C, H, N.

2-Amino-2-[4-(4-hexylphenyl)butyl]propane-1,3-diol hydrochloride (8): (free base) mp 89−90 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.09 (s, 4H), 3.58 (d, 2H, J = 12 Hz), 3.41 (d, 2H, J = 12 Hz), 2.61 (t, 4H, J = 6 Hz), 1.93−1.19 (m, 18H), 0.90 (t, 3H, J = 6 Hz); IR (KBr) 3347, 3331, 3288, 2927 cm^{-1}; MS (EI) m/z 307 (M^+); (HCl salt) mp 107−108 °C. Anal. ($C_{19}H_{33}NO_2$·HCl) C, H, N.

2-Amino-2-[6-(4-butylphenyl)hexyl]propane-1,3-diol hydrochloride (9): (free base) mp 70−71 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.08 (s, 4H), 3.57 (d, 2H, J = 12 Hz), 3.40 (d, 2H, J = 12 Hz), 2.59 (t, 4H, J = 6 Hz), 1.97 (brs, 4H), 1.83−1.11 (m, 14H), 0.92 (t, 3H, J = 6 Hz); IR (KBr) 3334, 3289, 3167, 2927 cm^{-1}; MS (EI) m/z 307 (M^+); (HCl salt) mp 97−98 °C. Anal. ($C_{19}H_{33}NO_2$·HCl) C, H, N.

2-Amino-2-[8-(4-ethylphenyl)octyl]propane-1,3-diol hydrochloride (10): synthesized as described for **6** using **47**; (free base) ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.09 (s, 4H), 3.82 (s, 4H), 2.58 (t, 2H, J = 7 Hz), 2.54 (t, 2H, J = 6 Hz), 1.88−1.17 (m, 14H), 1.22 (t, 3H, J = 7 Hz); IR (KBr) 3491, 3288, 2930 cm^{-1}; MS (EI) m/z 307 (M^+); (HCl salt) mp 84−86 °C. Anal. ($C_{19}H_{33}NO_2$·HCl·H_2O) C, H, N.

2-Amino-2-(10-phenyldecyl)propane-1,3-diol hydrochloride (11): synthesized as described for **6** using 10-phenyldecyl bromide; (free base) mp 87−89 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.35−7.13 (m, 5H), 3.60 (d, 2H, J = 12 Hz), 3.42 (d, 2H, J = 12 Hz), 2.62 (t, 2H, J = 6 Hz), 1.93 (m, 4H), 1.80−1.46 (m, 2H), 1.43−1.19 (m, 14H); IR (KBr) 3347, 3223, 2920, 2852 cm^{-1}; MS (EI) m/z 307 (M^+); (HCl salt) mp 97−98 °C. Anal. ($C_{19}H_{33}NO_2$·HCl) C, H, N.

2-Amino-2-[2-(4-heptylphenyl)ethyl]propane-1,3-diol hydrochloride (12): mp 109−110 °C; ^{1}H NMR (90 MHz, DMSO-d_6) δ 7.47 (brs, 3H), 7.08 (s, 4H), 3.48 (s, 4H), 3.34 (brs, 2H), 2.62−2.48 (m, 4H), 1.79−1.69 (m, 2H), 1.58−1.45 (m, 2H), 1.33−1.17 (m, 8H), 0.85 (t, 3H, J = 6 Hz); IR (KBr) 3369, 2926 cm^{-1}; MS (EI) m/z 293 (M^+). Anal. ($C_{18}H_{31}NO_2$·HCl) C, H, N.

2-Amino-2-[2-(4-nonylphenyl)ethyl]propane-1,3-diol hydrochloride (13): mp 108−110 °C; ^{1}H NMR (400 MHz,

DMSO-d_6) δ 7.79 (brs, 3H), 7.09 (s, 4H), 5.36 (t, 2H, J = 5.3 Hz), 3.51 (d, 4H, J = 5.3 Hz), 2.57−2.49 (m, 4H), 1.79−1.74 (m, 2H), 1.55−1.51 (m, 2H), 1.28−1.21 (m, 12H), 0.84 (t, 3H, J = 6.9 Hz); IR (KBr) 3348, 2921 cm^{-1}; MS (EI) m/z 321 (M^+). Anal. ($C_{20}H_{35}NO_2$·HCl) C, H, N.

2-Amino-2-[2-(4-decylphenyl)ethyl]propane-1,3-diol hydrochloride (14): mp 107−109 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (brs, 3H), 7.09 (s, 4H), 5.32 (t, 2H, J = 5.2 Hz), 3.50 (d, 4H, J = 5.2 Hz), 2.56−2.49 (m, 4H), 1.79−1.74 (m, 2H), 1.55−1.50 (m, 2H), 1.29−1.21 (m, 14H), 0.84 (t, 3H, J = 6.8 Hz); IR (KBr) 3255, 2920 cm^{-1}; MS (EI) m/z 335 (M^+). Anal. ($C_{21}H_{37}NO_2$·HCl) C, H, N.

2-Amino-2-[2-(4-undecylphenyl)ethyl]propane-1,3-diol hydrochloride (15): mp 108−110 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (brs, 3H), 7.09 (s, 4H), 5.37 (t, 2H, J = 5.2 Hz), 3.51 (d, 4H, J = 5.2 Hz), 2.57−2.49 (m, 4H), 1.78−1.74 (m, 2H), 1.55−1.50 (m, 2H), 1.29−1.20 (m, 16H), 0.84 (t, 3H, J = 6.9 Hz); IR (KBr) 3345, 3249, 2916 cm^{-1}; MS (EI) m/z 349 (M^+). Anal. ($C_{22}H_{39}NO_2$·HCl) C, H, N.

2-Amino-2-[2-(4-dodecylphenyl)ethyl]propane-1,3-diol hydrochloride (16): mp 108−110 °C; ^{1}H NMR (90 MHz, DMSO-d_6) δ 8.07 (brs, 3H), 7.12 (d, 2H, J = 8 Hz), 7.06 (d, 2H, J = 6 Hz), 4.79 (brs, 2H), 3.65 (d, 2H, J = 11 Hz), 3.56 (d, 2H, J = 11 Hz), 2.68−2.56 (m, 4H), 2.02−1.94 (m, 2H), 1.58−1.52 (m, 2H), 1.30−1.20 (m, 18H), 0.87 (t, 3H, J = 6 Hz); IR (KBr) 3375, 3270, 2922 cm^{-1}; MS (EI) m/z 363 (M^+). Anal. ($C_{23}H_{41}NO_2$·HCl) C, H, N.

2-Amino-2-[2-(4-tridecylphenyl)ethyl]propane-1,3-diol hydrochloride (17): mp 109−110 °C; ^{1}H NMR (90 MHz, DMSO-d_6) δ 7.91 (brs, 3H), 7.08 (s, 4H), 5.38 (brs, 2H), 3.51 (s, 4H), 2.60−2.44 (m, 4H), 1.80−1.73 (m, 2H), 1.53−1.45 (m, 2H), 1.30−1.15 (m, 20H), 0.84 (t, 3H, J = 6 Hz); IR (KBr) 3265, 2922 cm^{-1}; MS (EI) m/z 377 (M^+). Anal. ($C_{24}H_{43}NO_2$·HCl) C, H, N.

2-Amino-2-[2-(4-tetradecylphenyl)ethyl]propane-1,3-diol hydrochloride (18): mp 109−111 °C; ^{1}H NMR (90 MHz, DMSO-d_6) δ 7.99 (brs, 3H), 7.07 (s, 4H), 4.90 (brs, 2H), 3.51 (s, 4H), 2.62−2.56 (m, 2H), 2.46 (t, 2H, J = 6 Hz), 1.80−1.72 (m, 2H), 1.53−1.45 (m, 2H), 1.30−1.12 (m, 22H), 0.83 (t, 3H, J = 6 Hz); IR (KBr) 3267, 2922 cm^{-1}; MS (EI) m/z 391 (M^+). Anal. ($C_{25}H_{45}NO_2$·HCl) C, H, N.

2-Amino-2-[2-(4-octanoylphenyl)ethyl]propane-1,3-diol (19). To a suspension of $AlCl_3$ (31.0 g, 232 mmol) in 1,2-dichloroethane (460 mL) was added dropwise octanoyl chloride (19.8 mL, 116 mmol). After stirring at room temperature for 1 h, a solution of **48** (9.34 g, 29.0 mmol) in 1,2-dichloroethane was added. The mixture was stirred for 12 h, poured into 1 N NaOH, and extracted with Et_2O. The extract was washed with brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (1:1), gave 2-acetamido-2-[2-(4-octanoylphenyl)ethyl]propane-1,3-diol diacetate (8.30 g, 64%) as a yellowish solid. To a solution of this intermediate (8.30 g, 19.0 mmol) in MeOH (200 mL) and THF (100 mL) was added 2 N LiOH (80 mL). The solution was refluxed for 3 h, evaporated to remove the organic solvent, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. Recrystallization from hexanes−EtOAc gave **19** (3.02 g, 51%) as a white solid: mp 116−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, 2H, J = 8.3 Hz), 7.27 (d, 2H, J = 8.3 Hz), 3.60 (d, 2H, J = 10.7 Hz), 3.52 (d, 2H, J = 10.7 Hz), 2.93 (t, 2H, J = 7.3 Hz), 2.73−2.69 (m, 2H), 1.72−1.68 (m, 4H), 1.32−1.26 (m, 8H), 0.88 (t, 3H, J = 6.9 Hz); IR (KBr) 3350, 2926, 1678 cm^{-1}; MS (EI) m/z 321 (M^+). Anal. ($C_{19}H_{31}NO_3$) C, H, N.

2-Amino-2-[2-[4-(1-hydroxyoctyl)phenyl]ethyl]propane-1,3-diol (20). To a solution of **19** (643 mg, 2.00 mmol) in EtOH (50 mL) was added $NaBH_4$ (151 mg, 4.0 mmol). After stirring at room temperature for 3 h, the mixture was evaporated, and diluted with EtOAc. The organic solution was washed with brine, dried, and evaporated. Silica gel chromatography, eluting with $CHCl_3$−MeOH (4:1), gave **20** (429 mg, 66%) as a yellowish oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, 2H, J = 7.8 Hz), 7.12 (d, 2H, J = 7.8 Hz), 4.59 (t, 1H, J = 6.1 Hz), 3.50 (d, 2H, J = 10.7 Hz), 3.40 (d, 2H, J = 10.7 Hz), 2.74 (brs, 5H), 2.56 (t, 2H, J = 8.0 Hz), 1.78−1.73 (m, 2H), 1.65−1.60 (m, 2H), 1.39−1.22 (m, 10H), 0.86 (t, 3H, J = 6.9 Hz); IR (KBr) 3338 cm^{-1}; MS (EI) m/z 323 (M^+). Anal. ($C_{19}H_{33}NO_3$·H_2O) C, H, N.

2-Amino-2-[2-[4-(1-hydroxyiminooctyl)phenyl]ethyl]-propane-1,3-diol (21). A mixture of **19** (1.20 g, 3.73 mmol) and hydroxylamine hydrochloride (310 mg, 4.46 mmol) in EtOH (16 mL) and $CHCl_3$ (3 mL) was refluxed for 1.5 h. The mixture was evaporated, diluted with 1 N NaOH, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. Silica gel chromatography, eluting with $CHCl_3$−MeOH (9:1), followed by recrystallization from EtOAc−isopropyl ether, gave **21** (320 mg, 25%) as a yellowish solid: mp 90−93 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 7.50 (d, 2H, J = 8.3 Hz), 7.18 (d, 2H, J = 8.3 Hz), 4.49 (brs, 2H), 3.26 (d, 2H, J = 10.5 Hz), 3.22 (d, 2H, J = 10.5 Hz), 2.67 (t, 2H, J = 7.6 Hz), 2.60−2.56 (m, 2H), 1.78 (brs, 2H), 1.52−1.48 (m, 2H), 1.43−1.39 (m, 2H), 1.24−1.21 (m, 10H), 0.83 (t, 3H, J = 7.1 Hz); IR (KBr) 3341, 3180 cm^{-1}; MS (EI) m/z 336 (M^+). Anal. ($C_{19}H_{32}N_2O_3$·0.25H_2O) C, H, N.

2-Amino-2-[2-(4-heptyloxyphenyl)ethyl]propane-1,3-diol hydrochloride (22): synthesized as described for **6** using **50**; mp 111−112 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (brs, 3H), 7.08 (d, 2H, J = 8.3 Hz), 6.83 (d, 2H, J = 8.3 Hz), 5.36 (t, 2H, J = 4.9 Hz), 3.89 (t, 2H, J = 6.6 Hz), 3.50 (d, 4H, J = 4.9 Hz), 2.53−2.49 (m, 2H), 1.76−1.63 (m, 4H), 1.38−1.25 (m, 8H), 0.85 (t, 3H, J = 6.4 Hz); IR (KBr) 3355, 3274, 3033, 2924, 2855 cm^{-1}; MS (EI) m/z 309 (M^+). Anal. ($C_{18}H_{31}NO_3$·HCl) C, H, N.

2-Amino-2-[2-(4-heptylthiophenyl)ethyl]propane-1,3-diol (23). To a solution of **53** (1.80 g, 5.09 mmol) in DMF (20 mL) were added K_2CO_3 (829 mg, 6.00 mmol) and heptyl bromide (1.07 g, 6.00 mmol). After stirring at room temperature for 1 h, the mixture was diluted with EtOAc. The organic solution was washed with brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (4:1), gave diethyl 2-acetamido-2-[2-(4-heptylthiophenyl)ethyl]malonate (1.86 g, 81%) as a white solid. To a suspension of $LiAlH_4$ (380 mg, 10.0 mmol) in THF (15 mL) at 0 °C was added dropwise a solution of the malonate (1.13 g, 2.50 mmol) obtained above in THF (10 mL). After stirring at room temperature for 1 h, the reaction was quenched with saturated Na_2SO_4 (20 mL). The reaction mixture was filtered through Celite and evaporated. Silica gel chromatography, eluting with $CHCl_3$−MeOH (20:1), gave 2-acetamido-2-[2-(4-heptylthiophenyl)ethyl]propane-1,3-diol (560 mg, 61%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, 2H, J = 7.6 Hz), 7.11 (d, 2H, J = 7.6 Hz), 5.88 (s, 1H), 3.85 (dd, 2H, J = 11.2, 5.4 Hz), 3.71 (t, 2H, J = 5.4 Hz), 3.62 (dd, 2H, J = 11.2, 5.4 Hz), 2.87 (t, 2H, J = 7.4 Hz), 2.63−2.60 (m, 2H), 1.98 (s, 3H), 1.98−1.93 (m, 2H), 1.63−1.59 (m, 2H), 1.42−1.38 (m, 2H), 1.32−1.20 (m, 6H), 0.87 (t, 3H, J = 7.1 Hz).

A solution of this intermediate (500 mg, 1.36 mmol) and LiOH·H_2O (420 mg, 10.0 mmol) in MeOH (5 mL), THF (2 mL), and water (5 mL) was stirred at 50 °C for 4 h and diluted with EtOAc. The solution was washed with brine, dried, and evaporated. Recrystallization from EtOAc−hexane gave **23** (120 mg, 27%) as a white solid: mp 70−72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, 2H, J = 8.3 Hz), 7.10 (d, 2H, J = 8.3 Hz), 3.60 (d, 2H, J = 10.8 Hz), 3.50 (d, 2H, J = 10.8 Hz), 2.87 (t, 2H, J = 7.4 Hz), 2.63−2.59 (m, 2H), 2.20−1.80 (m, 4H), 1.70−1.66 (m, 2H), 1.62 (quint, 2H, J = 7.4 Hz), 1.43−1.34 (m, 2H), 1.34−1.20 (m, 6H), 0.87 (t, 3H, J = 6.8 Hz); IR (KBr) 3352, 3289, 2923 cm^{-1}; MS (EI) m/z 325 (M^+). Anal. ($C_{18}H_{31}NO_2S$) C, H, N.

2-Amino-2-[2-[4-(*N*-methylheptylamino)phenyl]ethyl]-propane-1,3-diol hydrochloride (24): synthesized as described for **6** using **55**; mp 128−129 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.97 (d, 2H, J = 8.3 Hz), 6.59 (d, 2H, J = 8.3 Hz), 5.35 (t, 2H, J = 5.0 Hz), 3.49 (d, 4H, J = 5.0 Hz), 3.23 (t, 2H, J = 7.4 Hz), 2.81 (s, 3H), 2.46−2.42 (m, 2H), 1.74−1.70 (m, 2H), 1.46−1.21 (m, 10H), 0.84 (t, 3H, J = 6.8 Hz); IR (KBr) 3277 cm^{-1}; MS (EI) m/z 322 (M^+). Anal. ($C_{19}H_{34}N_2O_2$·HCl·1.5H_2O) C, N; H: calcd, 9.92; found, 9.39.

2-Amino-2-[2-(2-octylphenyl)ethyl]propane-1,3-diol hydrochloride (25): synthesized as described for **6** using **58**;

mp 157−159 °C; ^{1}H NMR (90 MHz, DMSO-d_6) δ 7.89 (brs, 3H), 7.17−7.05 (m, 4H), 5.40 (t, 2H, J = 4 Hz), 3.59−3.49 (m, 4H), 2.63−2.52 (m, 4H), 1.78−1.68 (m, 2H), 1.54−1.43 (m, 2H), 1.37−1.22 (m, 10H), 0.85 (t, 3H, J = 6 Hz); IR (KBr) 3385, 3272, 2925 cm^{-1}; MS (EI) m/z 307 (M$^+$). Anal. ($C_{19}H_{33}NO_2$·HCl) C, H, N.

2-Amino-2-[2-(3-octylphenyl)ethyl]propane-1,3-diol hydrochloride (26): synthesized as described for **25**; mp 97−98 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (brs, 3H), 7.18 (t, 1H, J = 7.3 Hz), 7.01−6.97 (m, 3H), 5.33 (brs, 2H), 3.45 (s, 4H), 2.60−2.40 (m, 4H), 1.76−1.72 (m, 2H), 1.55−1.50 (m, 2H), 1.38−1.20 (m, 10H), 0.84 (t, 3H, J = 6.8 Hz); IR (KBr) 3366, 3178, 2924, 2853 cm^{-1}; MS (EI) m/z 307 (M$^+$). Anal. ($C_{19}H_{33}NO_2$·HCl) C, H, N.

2-Amino-2-[2-(5-octylthien-2-yl)ethyl]propane-1,3-diol hydrochloride (27): synthesized as described for **6** using **60**; mp 63−65 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 6.54 (d, 1H, J = 3.4 Hz), 6.47 (d, 1H, J = 3.4 Hz), 3.67 (d, 2H, J = 12.2 Hz), 3.61 (d, 2H, J = 12.2 Hz), 2.76−2.72 (m, 2H), 2.63 (t, 2H, J = 7.5 Hz), 1.97−1.94 (m, 2H), 1.55−1.51 (m, 2H), 1.29−1.15 (m, 10H), 0.79 (t, 3H, J = 6.9 Hz); IR (KBr) 3366, 3178, 2924, 2853 cm^{-1}; MS (EI) m/z 307 (M$^+$). Anal. ($C_{17}H_{31}NO_2S$·HCl) C, H, N.

2-Amino-2-hydroxymethyl-4-(4-octylphenyl)butanoic Acid (28). To a solution of **61** (17.9 g, 46.3 mmol) in THF (270 mL) was slowly added $LiBH_4$ (910 mg, 41.8 mmol). The mixture was refluxed for 6 h and cooled to 0 °C. The reaction mixture was acidified with 2 N HCl (20 mL), diluted with water, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. Silica gel chromatography, eluting with EtOAc, followed by recrystallization from EtOAc−diisopropyl ether gave *N*-[1-cyano-1-hydroxymethyl-3-(4-octylphenyl)propyl]acetamide (8.67 g, 54%) as a white solid. A solution of this intermediate (7.71 g, 22.4 mmol) in concentrated HCl (110 mL), AcOH (40 mL), and water (40 mL) was refluxed for 7 h and cooled to room temperature. The separated oil was collected, dispersed in water (100 mL), and neutralized with 2 N NaOH. The yielded white crystalline solid was collected and washed with MeOH to give **28** (4.76 g, 66%): mp 246−250 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.08 (s, 4H), 3.91−3.87 (m, 2H), 3.30 (brs, 4H), 2.56 (t, 4H, J = 7.8 Hz), 2.08 (t, 2H, J = 7.8 Hz), 1.60−1.55 (m, 2H), 1.29−1.26 (m, 10H), 0.89 (t, 3H, J = 7.0 Hz); IR (KBr) 3047, 1639 cm^{-1}; MS (EI) m/z 321 (M$^+$). Anal. ($C_{19}H_{31}NO_3$) C, H, N.

2-Amino-4-(4-heptyloxyphenyl)-2-methylbutanol Hydrochloride (30). To a solution of **63** (18.2 g, 46.3 mmol) in THF (300 mL) was slowly added $LiBH_4$ (2.01 g, 92.3 mmol). The mixture was refluxed for 3 h and cooled to 0 °C. The reaction mixture was acidified with 2 N HCl (45 mL), diluted with water, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. The residue was dissolved in THF (100 mL), MeOH (150 mL), and 5 N KOH (100 mL), and the solution was refluxed for 13 h. The reaction mixture was concentrated, diluted with water, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. The residue was converted to hydrochloride salt by treatment with EtOH (200 mL) and 1 N HCl solution in Et_2O (50 mL) and recrystallized from EtOH−EtOAc to give **30** (10.0 g, 66%) as a white solid: mp 162−163 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (brs, 3H), 7.09 (d, 2H, J = 8.5 Hz), 6.83 (d, 2H, J = 8.5 Hz), 5.51 (t, 1H, J = 4.9 Hz), 3.90 (t, 2H, J = 6.6 Hz), 3.47−3.36 (m, 2H), 2.52−2.49 (m, 2H), 1.78−1.64 (m, 4H), 1.38−1.26 (m, 8H), 1.18 (s, 3H), 0.86 (t, 3H, J = 6.8 Hz); IR (KBr) 3374, 3025, 2933, 1518, 1242, 1060 cm^{-1}; MS (EI) m/z 293 (M$^+$). Anal. ($C_{18}H_{31}NO_2$·HCl) C, H, N.

Similarly, compounds **31**−**35** were prepared from **50** and 2-substituted diethyl malonates.

2-Amino-2-ethyl-4-(4-heptyloxyphenyl)butanol hydrochloride (31): a white solid; mp 108−110 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.11 (d, 2H, J = 8.8 Hz), 6.83 (d, 2H, J = 8.8 Hz), 3.92 (t, 2H, J = 6.3 Hz), 3.60 (s, 2H), 2.59−2.53 (m, 2H), 1.88−1.83 (m, 2H), 1.81−1.72 (m, 4H), 1.48−1.44 (m, 2H), 1.40−1.31 (m, 6H), 1.00 (t, 3H, J = 7.3 Hz), 0.90 (t, 3H, J = 6.9 Hz); IR (KBr) 3359, 3183, 2928, 2871 cm^{-1}; MS (EI) m/z 307 (M$^+$). Anal. ($C_{19}H_{33}NO_2$·HCl) C, H, N.

2-Amino-2-[2-(4-heptyloxyphenyl)ethyl]-4-pentenol (32): not converted to hydrochloride salt; a brownish noncrystalline powder; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, 2H, J = 8.6 Hz), 6.81 (d, 2H, J = 8.6 Hz), 5.88−5.81 (m, 1H), 5.18−5.14 (m, 2H), 3.92 (t, 2H, J = 6.6 Hz), 3.39 (s, 2H), 2.60−2.55 (m, 2H), 2.26 (dd, 1H, J = 14.1 and 7.8 Hz), 2.19 (dd, 1H, J = 13.7 and 7.8 Hz), 1.80−1.72 (m, 2H), 1.72−1.27 (m, 10H), 0.89 (t, 3H, J = 6.9 Hz); IR (KBr) 3349, 3314, 3282, 3067, 2923, 2856, 2751 cm^{-1}; MS (EI) m/z 319 (M$^+$). Anal. ($C_{20}H_{33}NO_2$) C, H, N.

2-Amino-4-(4-heptyloxyphenyl)-2-isopropylbutanol hydrochloride (33): a yellow noncrystalline powder; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (brs, 3H), 7.11 (d, 2H, J = 8.6 Hz), 6.83 (d, 2H, J = 8.6 Hz), 5.39 (t, 1H, J = 4.9 Hz), 3.89 (t, 2H, J = 6.6 Hz), 3.57−3.52 (m, 2H), 2.53−2.49 (m, 2H), 2.11−2.08 (m, 1H), 1.75−1.70 (m, 2H), 1.70−1.63 (m, 2H), 1.38−1.26 (m, 8H), 0.92 (d, 6H, J = 6.8 Hz), 0.85 (t, 3H, J = 6.8 Hz); IR (KBr) 3349, 3185, 2923, 2852, 2616 cm^{-1}; MS (EI) m/z 321 (M$^+$). Anal. ($C_{20}H_{35}NO_2$·HCl·1/2H_2O) C, H, N.

2-Amino-2-[2-(4-heptyloxyphenyl)ethyl]pentanol (34): not converted to hydrochloride salt; a white solid; mp 48−50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, 2H, J = 8.3 Hz), 6.81 (d, 2H, J = 8.3 Hz), 3.92 (t, 2H, J = 6.6 Hz), 3.36 (s, 2H), 2.55−2.51 (m, 2H), 1.79−1.73 (m, 2H), 1.73−1.30 (m, 14H), 0.95 (t, 3H, J = 6.8 Hz), 0.89 (t, 3H, J = 6.8 Hz); IR (KBr) 3337, 3277, 3132, 2956, 2936, 2859 cm^{-1}; MS (EI) m/z 321 (M$^+$). Anal. ($C_{20}H_{35}NO_2$) C, H, N.

2-Amino-2-[2-(4-heptyloxyphenyl)ethyl]hexanol (35): not converted to hydrochloride salt; a white solid; mp 47−49 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.09 (d, 2H, J = 8.5 Hz), 6.79 (d, 2H, J = 8.5 Hz), 3.88 (t, 2H, J = 6.4 Hz), 3.29 (s, 2H), 2.48−2.42 (m, 2H), 1.67 (quint, 2H, J = 7.4 Hz), 1.45−1.25 (m, 16H), 0.87 (t, 3H, J = 5.4 Hz), 0.85 (t, 3H, J = 6.8 Hz); IR (KBr) 3328, 3280, 3124, 3031, 2956, 2933, 2858 cm^{-1}; MS (EI) m/z 335 (M$^+$). Anal. ($C_{21}H_{37}NO_2$·1/10H_2O) C, H, N.

2-Amino-2-[2-(4-heptyloxyphenyl)ethyl]butane-1,4-diol (36). To a solution of **66** (14.9 g, 31.9 mmol) in CH_2Cl_2 (250 mL) was added trimethylsilyl iodide (7.16 mL, 50.3 mmol). The solution was stirred for 7 h, diluted with MeOH (20 mL), and evaporated. The resultant residue was dissolved in pyridine (25 mL) and acetic anhydride (20 mL) and left for 13 h. The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with 1 N HCl, saturated $NaHCO_3$ and brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (1:1), gave 2-acetamido-2-[2-(4-heptyloxyphenyl)ethyl]butane-1,4-diol diacetate (10.1 g, 70%) as a colorless oil. To a solution of this intermediate (10.0 g, 22.2 mmol) in THF (50 mL) and MeOH (100 mL) was added 2 M LiOH (100 mL). The solution was refluxed for 2 h and concentrated. The mixture was diluted with water and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. Recrystallization from EtOAc−hexane gave **36** (6.71 g, 93%) as a white solid: mp 64−65 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.05 (d, 2H, J = 8.6 Hz), 6.79 (d, 2H, J = 8.6 Hz), 4.59 (brs, 1H), 3.88 (t, 2H, J = 6.8 Hz), 3.54 (t, 2H, J = 6.8 Hz), 3.19 (brs, 2H), 2.47−2.44 (m, 2H), 1.67 (quint, 2H, J = 6.8 Hz), 1.51−1.47 (m, 4H), 1.38−1.26 (m, 8H), 0.86 (t, 3H, J = 6.8 Hz); IR (KBr) 3360, 3268, 3068, 2927, 2858, 2673 cm^{-1}; MS (EI) m/z 323 (M$^+$). Anal. ($C_{19}H_{33}NO_3$) C, H, N.

2-Amino-2-[2-(4-octylphenyl)ethyl]butane-1,4-diol (37): mp 75−76 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.05 (s, 4H), 4.59 (brs, 1H), 3.54 (t, 2H, J = 6.9 Hz), 3.18 (brs, 2H), 2.55−2.49 (m, 4H), 1.53−1.45 (m, 6H), 1.25−1.23 (m, 10H), 0.84 (t, 3H, J = 6.9 Hz); IR (KBr) 3367, 3296, 2927, 2854 cm^{-1}; MS (EI) m/z 321 (M$^+$). Anal. ($C_{20}H_{35}NO_2$·1/10H_2O) C, H, N.

2-Amino-2-[2-(4-octylphenyl)ethyl]pentane-1,5-diol Hydrochloride (38). 68 (1.30 g, 2.50 mmol) was converted to 2-amino-2-[2-(4-octylphenyl)ethyl]-5-(tetrahydro-2*H*-pyran-2-yloxy)pentanol (820 mg, 78%) as described for **30**. This was purified by silica gel chromatography eluting with $CHCl_3$−MeOH (95:5): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, 2H, J = 8.5 Hz), 7.08 (d, 2H, J = 8.5 Hz), 4.58 (m, 1H), 3.87 (m, 1H),

3.76 (m, 1H), 3.52−3.46 (m, 4H), 2.62−2.53 (m, 4H), 1.80−1.54 (m, 14H), 1.30−1.26 (m, 10H), 0.88 (t, 3H, J = 7.1 Hz); IR (neat) 3348, 2924, 2856 cm^{-1}; MS (EI) m/z 419 (M^+).

To a solution of this intermediate (800 mg, 1.91 mmol) in MeOH (30 mL) was added a 1 N HCl solution in ether (3 mL). The mixture was stirred for 30 min, diluted with water, and washed with ether. The aqueous solution was alkalified with 1 N KOH and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. The residue was converted to hydrochloride salt by treatment with EtOH (30 mL) and 1 N HCl solution in ether (5 mL). This residue was suspended in ether (10 mL), and the sediment was collected to give **38** (230 mg, 32%) as a thick purple oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (brs, 3H), 7.09 (s, 4H), 5.48 (t, 1H, J = 4.9 Hz), 4.59 (t, 1H, J = 5.1 Hz), 3.47−3.45 (m, 2H), 3.42−3.39 (m, 2H), 2.55−2.51 (m, 4H), 1.75−1.71 (m, 2H), 1.63−1.58 (m, 2H), 1.52−1.46 (m, 4H), 1.25−1.23 (m, 10H), 0.84 (t, 3H, J = 6.9 Hz); IR (neat) 3346, 3009, 2924, 2854 cm^{-1}; MS (EI) m/z 335 (M^+). Anal. ($C_{21}H_{37}NO_2$·HCl·1/4H_2O) C, H, N.

3-Amino-3-methyl-5-(4-octylphenyl)pentanol Hydrochloride (39). Compound **71** (5.00 g, 18.0 mmol) was alkylated in two steps as described for **43** to give 3-acetamido-3-methyl-5-(4-octylphenyl)pentyl acetate (4.96 g, 87%) as a white solid. To a solution of this intermediate (4.95 g, 12.7 mmol) in THF (50 mL) and MeOH (50 mL) was added 2 N LiOH (50 mL). The solution was refluxed for 4 h, concentrated, diluted with water, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. The residue was converted to hydrochloride salt by treatment with EtOH (50 mL) and 1 N HCl solution in ether (20 mL) and recrystallized from EtOH−EtOAc to give **39** (4.12 g, 96%) as a white solid: mp 137−141 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (brs, 3H), 7.09 (s, 4H), 4.92 (brs, 1H), 3.59 (t, 2H, J = 6.1 Hz), 2.59−2.52 (m, 4H), 1.87−1.73 (m, 4H), 1.53−1.50 (m, 2H), 1.28 (s, 3H), 1.25−1.23 (m, 10H), 0.84 (t, 3H, J = 6.9 Hz); IR (KBr) 3120, 2956, 2854 cm^{-1}; MS (EI) m/z 305 (M^+). Anal. ($C_{20}H_{35}$NO·HCl) C, H, N.

Similarly, compound **40** was prepared from dimethyl 1,3-acetonedicarboxylate. Compound **40** was not converted to hydrochloride salt.

3-Amino-3-[2-(4-octylphenyl)ethyl]pentane-1,5-diol (40): a white solid; mp 57−59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (s, 4H), 3.88 (t, 4H, J = 5.9 Hz), 2.59−2.53 (m, 4H), 1.82−1.70 (m, 6H), 1.59−1.57 (m, 2H), 1.30−1.27 (m, 10H), 0.88 (t, 3H, J = 6.8 Hz); IR (KBr) 3375, 3326, 3267, 3061, 2922, 2849 cm^{-1}; MS (EI) m/z 335 (M^+). Anal. ($C_{21}H_{37}NO_2$·1/10H_2O) C, H, N.

4-Decylbenzyl Bromide (41). To a solution of decylbenzene (13.1 g, 60.0 mmol) in CH_2Cl_2 (40 mL) at 0 °C were added dropwise $TiCl_4$ (19.0 g, 100 mmol) and dichloromethyl methyl ether (5.75 g, 50.0 mmol). After stirring at room temperature for 1 h, the reaction mixture was poured into water and extracted with CH_2Cl_2. The extract was washed with brine, dried, and evaporated. To a solution of the residue in MeOH (30 mL) and 2-propanol (30 mL) was added $NaBH_4$ (1.13 g, 30.2 mmol). After stirring at room temperature for 10 min, the reaction mixture was evaporated, diluted with water, and extracted with isopropyl ether. The extract was washed with brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (9:1), gave 4-decylbenzyl alcohol (6.98 g, 56%) as a white solid. A mixture of this intermediate (4.48 g, 18.0 mmol), 48% HBr (50 mL), and toluene (40 mL) was stirred at 90 °C for 24 h. The organic layer was separated and washed with saturated $NaHCO_3$ and brine. The solution was dried and evaporated to provide **41** (5.50 g, 98%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, 2H, J = 8.1 Hz), 7.13 (d, 2H, J = 8.1 Hz), 4.47 (s, 2H), 2.57 (t, 2H, J = 7.6 Hz), 1.60−1.50 (m, 2H), 1.30−1.20 (m, 14H), 0.86 (t, 3H, J = 6.6 Hz); MS (EI) m/z 312 $(M + 1)^+$, 310 $(M - 1)^+$.

2-(4-Decylphenyl)-2-nitropropane-1,3-diol (42). To a suspension of $AgNO_2$ (4.15 g, 27.0 mmol) in Et_2O (20 mL) at 0 °C was added dropwise a solution of **41** (5.50 g, 17.7 mmol) in Et_2O (10 mL). After stirring at 0 °C for 4 h, the reaction mixture was filtered and evaporated. Crystallization in pentane gave 4-decylphenylnitromethane (2.32 g, 47%) as a yellow solid. A mixture of this intermediate (2.60 g, 9.37 mmol) in EtOH (15 mL) and 1,4-dioxane (6 mL), 1 N NaOH (0.05 mL), and 37% aqueous formaldehyde (1.70 mL) was stirred at room temperature for 15 h. After addition of 37% aqueous formaldehyde (0.50 mL), the mixture was stirred at 50 °C for 6 h. The reaction mixture was evaporated and diluted with EtOAc. The organic solution was washed with brine, dried, and evaporated. Crystallization from hexane gave **42** (1.75 g, 55%) as a white solid: mp 80−81 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.21 (d, 2H, J = 10 Hz), 7.17 (d, 2H, J = 10 Hz), 4.60 (m, 2H), 4.35 (m, 2H), 2.77 (m, 2H), 2.59 (t, 2H, J = 8 Hz), 1.60−1.50 (m, 2H), 1.30−1.20 (m, 14H), 0.88 (t, 3H, J = 6 Hz).

4-Octylphenethyl Alcohol (43, m = 2 and n = 8). To a suspension of $AlCl_3$ (14.7 g, 110 mmol) in 1,2-dichloroethane (200 mL) at 0 °C was added dropwise a solution of phenethyl acetate (12.1 g, 73.7 mmol) and octanoyl chloride (12.0 g, 73.8 mmol) in 1,2-dichloroethane (50 mL). After stirring at room temperature for 3 h, the mixture was poured into water, and extracted with Et_2O. The extract was washed with brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (8:1), gave 4-octanoylphenethyl acetate (9.20 g, 43%) as a colorless oil. To a solution of this acetate (4.20 g, 14.5 mmol) in trifluoroacetic acid (50 mL) was added triethylsilane (5.06 g, 28.9 mmol). After stirring at room temperature for 3 h, the mixture was concentrated and diluted with EtOAc. The solution was washed with 1 N NaOH and brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (8:1), gave 4-octylphenethyl acetate (4.94 g, crude) as a colorless oil. To a solution of this acetate (4.94 g) in MeOH (100 mL) was added sodium methoxide (2.05 g, 28.9 mmol). The mixture was refluxed for 2 h, evaporated, and partitioned between EtOAc and water. The organic layer was separated and washed with brine. The solution was dried over Na_2SO_4 and evaporated to provide **43** (3.40 g, 100%) as a brown oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.13 (brs, 4H), 3.84 (q, 2H, J = 6 Hz), 2.83 (t, 2H, J = 6 Hz), 2.58 (t, 2H, J = 6 Hz), 2.34 (t, 1H, J = 6 Hz), 1.81−1.45 (m, 2H), 1.45−1.10 (m, 10H), 0.86 (t, 3H, J = 6 Hz).

4-Octylphenethyl Iodide (44, m = 2 and n = 8). To a solution of **43** (15.9 g, 67.8 mmol) and triethylamine (12.2 mL, 88.1 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added methanesulfonyl chloride (9.32 g, 81.4 mmol). After stirring at room temperature for 1 h, the mixture was washed with brine, dried, and evaporated. A mixture of the residue and NaI (10.2 g, 67.8 mmol) in 2-butanone (400 mL) was refluxed for 2 h. The reaction mixture was concentrated and partitioned between EtOAc and water. The organic layer was separated and washed with 10% $Na_2S_2O_3$ and brine. The solution was dried and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (95:5), gave **44** (16.0 g, 69%) as a colorless oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.11 (s, 4H), 3.47−3.01 (m, 4H), 2.58 (t, 2H, J = 8 Hz), 1.79−1.46 (m, 2H), 1.43−1.08 (m, 10H), 0.87 (t, 3H, J = 6 Hz); MS (EI) m/z 344 (M^+).

Diethyl 2-Acetamido-2-[2-(4-octylphenyl)ethyl]malonate (45, m = 2 and n = 8). To a solution of diethyl acetamidomalonate (26.0 g, 120 mmol) in EtOH (300 mL) was added a solution of sodium ethoxide (8.20 g, 120 mmol) in EtOH (80 mL). After stirring at room temperature for 30 min, **44** (6.89 g, 20 mmol) was added. The mixture was stirred at 65 °C for 3 h, concentrated, and partitioned between EtOAc and water. The organic layer was separated and washed with brine. The solution was dried and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (3:1), gave **45** (10.6 g, 61%) as a white solid: mp 51−53 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.06 (s, 4H), 6.73 (brs, 1H), 4.20 (q, 4H, J = 6 Hz), 2.82−2.30 (m, 6H), 1.96 (s, 3H), 1.70−1.44 (m, 2H), 1.44−1.10 (m, 10H), 1.23 (t, 6H, J = 6 Hz), 0.86 (t, 3H, J = 6 Hz); IR (KBr) 3253, 2923, 1747, 1644 cm^{-1}; MS (EI) m/z 433 (M^+).

Methyl 8-(4-Ethylphenyl)octanoate (46). To a suspension of $AlCl_3$ (8.06 g, 60.5 mmol) in 1,2-dichloroethane (100 mL) at 0 °C was added dropwise a solution of ethylbenzene (6.16 g, 58.1 mmol) and methyl 8-chloro-8-oxooctanoate (10.0 g, 48.4 mmol) in 1,2-dichloroethane (50 mL). The mixture was stirred at room temperature for 3 h, poured into water, and

extracted with EtOAc. The extract was washed with 1 N NaOH and brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (5:1), gave methyl 8-(4-ethylphenyl)-8-oxooctanoate (8.80 g, 66%) as a colorless oil. This intermediate (8.80 g, 31.8 mmol) was reduced as described for **43** to give **46** (2.60 g, 31%) as a colorless oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.10 (s, 4H), 3.66 (s, 3H), 2.62 (q, 2H, J = 6 Hz), 2.56 (t, 2H, J = 6 Hz), 2.28 (t, 2H, J = 6 Hz), 1.81−1.18 (m, 10H), 1.21 (t, 3H, J = 6 Hz); IR (KBr) 2931, 2856, 1737 cm^{-1}; MS (EI) m/z 262 (M^+).

8-(4-Ethylphenyl)octyl Iodide (47). To a suspension of $LiAlH_4$ (560 mg, 14.8 mmol) in THF (100 mL) at 0 °C was added dropwise a solution of **46** (2.60 g, 9.91 mmol) in THF (25 mL). After stirring at room temperature for 1 h, the reaction was quenched with saturated Na_2SO_4 (20 mL). The reaction mixture was filtered through Celite and evaporated to provide 8-(4-ethylphenyl)octanol (2.32 g, 100%) as a colorless oil. This intermediate was converted to **47** as described for **44**. **47**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.11 (s, 4H), 3.18 (t, 2H, J = 7 Hz), 2.63 (q, 2H, J = 6 Hz), 2.58 (t, 2H, J = 7 Hz), 1.95−1.17 (m, 12H), 1.22 (t, 3H, J = 7 Hz); MS (EI) m/z 344 (M^+).

2-Acetamido-2-phenethylpropane-1,3-diol diacetate (48): synthesized as illustrated in Scheme 2 using phenethyl bromide; mp 116−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.15 (m, 5H), 5.64 (brs, 1H), 4.33 (s, 4H), 2.59 (m, 2H), 2.20 (m, 2H), 2.07 (s, 6H), 1.94 (s, 3H); IR (KBr) 3293, 3090, 1744, 1651 cm^{-1}; MS (EI) m/z 321 (M^+).

4-Heptyloxyphenethyl Alcohol (49). To a solution of 4-hydroxyphenethyl alcohol (30.9 g, 223 mmol) and sodium ethoxide (17.0 g, 250 mmol) in EtOH (1 L) was added heptyl bromide (40.0 g, 223 mmol). The reaction mixture was refluxed for 7 h and concentrated. The residue was diluted with water and extracted with EtOAc. The extract was washed with 1 N NaOH and brine, dried, and evaporated to give **49** (49.3 g, 94%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, 2H, J = 8.5 Hz), 6.85 (d, 2H, J = 8.5 Hz), 3.93 (t, 2H, J = 6.6 Hz), 3.82 (q, 2H, J = 6.3 Hz), 2.81 (t, 2H, J = 6.6 Hz), 1.77 (quint, 2H, J = 6.6 Hz), 1.46−1.43 (m, 2H), 1.39−1.24 (m, 7H), 0.89 (t, 3H, J = 6.9 Hz); IR (neat) 3355, 2931, 2859 cm^{-1}; MS (EI) m/z 236 (M^+).

4-Heptyloxyphenethyl iodide (50): compound **49** was converted to **50** as described for **44**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, 2H, J = 8.3 Hz), 6.84 (d, 2H, J = 8.3 Hz), 3.93 (t, 2H, J = 6.5 Hz), 3.31 (t, 2H, J = 7.8 Hz), 3.11 (t, 2H, J = 7.8 Hz), 1.77 (quint, 2H, J = 6.8 Hz), 1.46−1.41 (m, 2H), 1.39−1.24 (m, 6H), 0.89 (t, 3H, J = 6.9 Hz); IR (neat) 2928, 2854 cm^{-1}; MS (EI) m/z 346 (M^+).

Ethyl 4-Methylthiophenylacetate (51). To a solution of 4-methylthiobenzaldehyde (7.61 g, 50.0 mmol) and methyl methylsulfinylmethyl sulfide (6.22 g, 50.0 mmol) in 1,4-dioxane (50 mL) was added Triton B (40% solution in MeOH, 4.18 g, 10.0 mmol). The mixture was stirred at 80 °C for 2 h, concentrated, and partitioned between EtOAc and water. The organic layer was separated, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (5:1), gave methyl 1-methylsulfinyl-2-(4-methylthiophenyl)vinyl sulfide (10.9 g, 84%) as a yellow oil. A solution of this intermediate (1.62 g, 6.27 mmol) in 26% HCl/EtOH was stirred at room temperature for 30 min and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (20:1), gave **51** (1.22 g, 93%) as a white solid: mp 30−32 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, 2H, J = 8.3 Hz), 7.20 (d, 2H, J = 8.3 Hz), 4.15 (q, 2H, J = 7.3 Hz), 3.65 (s, 2H), 2.45 (s, 3H), 1.24 (t, 3H, J = 7.3 Hz); MS (EI) m/z 210 (M^+).

4-(2-Iodoethyl)phenyl Methyl Sulfoxide (52). To a suspension of $LiAlH_4$ (2.30 g, 60.6 mmol) in THF (100 mL) at 0 °C was added dropwise a solution of **51** (12.2 g, 58.0 mmol) in THF (50 mL). After stirring at room temperature for 30 min, the reaction was quenched with saturated Na_2SO_4 (50 mL). The reaction mixture was filtered through Celite and evaporated. To a solution of the residue in $CHCl_3$ (100 mL) at 0 °C was added *m*-CPBA (10.0 g, 58.0 mmol). The mixture was stirred at room temperature for 2 h, washed with 1 N NaOH and brine, dried, and evaporated. The residue was converted to **52** (10.7 g, 63%) as described for **44**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, 2H, J = 8.3 Hz), 7.15 (d, 2H, J = 8.3 Hz), 3.30 (t, 2H, J = 7.8 Hz), 3.12 (t, 2H, J = 7.8 Hz), 2.70 (s, 3H); MS (EI) m/z 294 (M^+).

Diethyl 2-Acetamido-2-[2-(4-mercaptophenyl)ethyl]-malonate (53). Compound **52** (7.66 g, 26.0 mmol) was condensed with diethyl acetamidomalonate as described for **45** to give diethyl 2-acetamido-2-[2-(4-methylsulfinylphenyl)-ethyl]malonate (5.16 g, 62%) as a colorless oil. To a solution of this intermediate (4.00 g, 10.4 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added trifluoroacetic anhydride (3.00 mL, 21.2 mmol). After stirring at room temperature for 1 h, the mixture was evaporated. The residue was dissolved in EtOH (50 mL) and triethylamine (50 mL), and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated and partitioned between $CHCl_3$ and aqueous NH_4Cl. The organic layer was separated, dried, and evaporated. Silica gel chromatography, eluting with $CHCl_3$−MeOH (24:1), gave **53** (3.37 g, 92%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, 2H, J = 8.3 Hz), 7.00 (d, 2H, J = 8.3 Hz), 6.74 (s, 1H), 4.18 (m, 4H), 3.37 (s, 1H), 2.64 (t, 2H, J = 7.8 Hz), 2.43 (t, 2H, J = 7.8 Hz), 1.96 (s, 3H), 1.22 (t, 6H, J = 7.3 Hz); MS (EI) m/z 353 (M^+).

***N*-Methyl-*N*-[4-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]-phenyl]heptanamide (54).** To a solution of 4-aminophenethyl alcohol (13.8 g, 101 mmol) and triethylamine (10.8 g, 107 mmol) in THF (300 mL) at 0 °C was added dropwise heptanoyl chloride (15.0 g, 101 mmol). The mixture was stirred at room temperature for 3 h, poured into water, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. Recrystallization from EtOAc/isopropyl ether gave *N*-[4-(2-hydroxyethyl)phenyl]heptanamide (13.2 g, 52%) as a white solid. To a solution of this intermediate (4.45 g, 17.8 mmol) and *p*-toluenesulfonic acid monohydrate (95.0 mg, 0.499 mmol) in THF (50 mL) and CH_2Cl_2 (50 mL) was added 3,4-dihydro-2*H*-pyran (1.96 g, 23.3 mmol). After stirring at room temperature for 7 h, the mixture was evaporated and purified by silica gel chromatography, eluting with hexanes−EtOAc (1:1), to give *N*-[4-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]phenyl]-heptanamide. To a solution of this material in 1,2-dimethoxyethane (120 mL) were added potassium *tert*-butoxide (5.18 g, 46.2 mmol) and MeI (16.4 g, 116 mmol). The mixture was stirred at 60 °C for 1 h, concentrated and purified by silica gel chromatography, eluting with hexanes−EtOAc (7:1), to provide **54** (5.95 g, 96%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, 2H, J = 8.3 Hz), 7.19 (d, 2H, J = 8.3 Hz), 4.58 (t, 1H, J = 3.9 Hz), 3.92 (dt, 1H, J = 7.3 and 9.8 Hz), 3.79−3.76 (m, 1H), 3.47 (dt, 2H, J = 7.3 and 9.7 Hz), 3.47 (t, 2H, J = 6.4 Hz), 3.26 (s, 3H), 2.04 (t, 2H, J = 6.4 Hz), 1.90−1.63 (m, 4H), 1.60−1.42 (m, 4H), 1.26−1.17 (m, 6H), 0.83 (t, 3H, J = 6.8 Hz); IR (neat) 1655 cm^{-1}; MS (EI) m/z 347 (M^+).

4-(*N*-Methylheptylamino)phenethyl Iodide (55). To a solution of **54** (5.95 g, 17.1 mmol) in THF (90 mL) at 0 °C was added 1 M solution of BH_3·THF in THF (32.2 mL). After stirring at 0 °C for 3 h, MeOH (60 mL) was added. The reaction mixture was concentrated and purified by silica gel chromatography, eluting with hexanes−EtOAc (7:1). To a solution of this material in MeOH (60 mL) was added *p*-toluenesulfonic acid monohydrate (3.10 g, 16.3 mmol). After stirring at room temperature for 3 h, the mixture was concentrated and purified by silica gel chromatography, eluting with $CHCl_3$−MeOH (12:1), to provide 4-(*N*-methylheptylamino)phenethyl alcohol (3.22 g, 76%) as an oil. This intermediate alcohol (3.65 g, 14.6 mmol) was converted into the iodide as described for **44** to yield **55** (2.58 g, 49%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, 2H, J = 8.3 Hz), 6.62 (d, 2H, J = 8.3 Hz), 3.65 (t, 2H, J = 7.8 Hz), 3.63 (t, 2H, J = 5.9 Hz), 3.07 (t, 2H, J = 7.8 Hz), 2.90 (s, 3H), 1.40−1.22 (m, 10H), 0.88 (t, 3H, J = 7.3 Hz); MS (EI) m/z 359 (M^+).

(*E*)-2-(1-Octenyl)benzaldehyde (56). To a mixture of magnesium (6.56 g, 270 mmol) and I_2 (20 mg) in THF (10 mL) was added dropwise a solution of heptyl bromide (48.4 g, 270 mmol) in THF (200 mL). After the mixture had been stirred at 40 °C for 1 h, a solution of 2-bromobenzaldehyde (25.0 g,

135 mmol) was added dropwise at 0 °C. The solution was stirred at room temperature for 1 h, poured into saturated NH_4Cl, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (8:1), gave 1-(2-bromophenyl)-octanol (18.9 g, 49%) as a colorless oil. To a solution of this intermediate (15.6 g, 54.7 mmol) in benzene (300 mL) was added P_2O_5 (23.3 g, 164 mmol). The mixture was refluxed for 2 h, filtered, and diluted with EtOAc. The solution was washed with brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (20:1), gave (*E*)-1-(2-bromophenyl)-1-octene (12.0 g, 82%) as a yellowish oil. To a mixture of magnesium (3.74 g, 154 mmol) and I_2 (20 mg) in THF (10 mL) was added dropwise a solution of the intermediate (37.4 g, 140 mmol) in THF (100 mL). After the mixture had been stirred at 50 °C for 30 min, a solution of DMF (10.9 g, 149 mmol) in THF (100 mL) was added dropwise at room temperature. The solution was stirred at room temperature for 15 h, poured into saturated NH_4Cl, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (15:1), gave **56** (26.7 g, 88%) as a colorless oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 10.31 (s, 1H), 7.58 (d, 1H, J = 8 Hz), 7.53−7.48 (m, 2H), 7.37−7.33 (m, 1H), 7.15 (d, 1H, J = 16 Hz), 6.18−6.11 (m, 1H), 2.36−2.24 (m, 2H), 1.52−1.45 (m, 2H), 1.38−1.22 (m, 6H), 0.88 (t, 3H, J = 6 Hz); IR (neat) 2927, 2855, 1699 cm^{-1}; MS (EI) *m*/*z* 216 (M^+).

Ethyl 2-Octylphenylacetate (57). A solution of **56** (26.7 g, 123 mmol) in EtOH (200 mL) was stirred under a hydrogen atmosphere in the presence of 5% Pd/C (1.0 g) for 4 h. The catalyst was removed by filtration and the filtrate was evaporated and purified by silica gel chromatography, eluting with hexanes−EtOAc (20:1), to provide 2-octylbenzaldehyde (22.0 g, 82%) as a colorless oil. This intermediate was converted into **57** as described for **51**. **57** was obtained as a yellowish oil (20.2 g, 72%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.35−7.10 (m, 4H), 4.13 (q, 2H, J = 6 Hz), 3.85 (s, 2H), 2.59 (t, 2H, J = 6 Hz), 1.62−1.49 (m, 2H), 1.38−1.19 (m, 10H), 1.24 (t, 3H, J = 6 Hz), 0.86 (t, 3H, J = 6 Hz); MS (EI) *m*/*z* 276 (M^+).

2-Octylphenethyl iodide (58): synthesized from **57** as described for **47**; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.25−7.10 (m, 4H), 3.28 (t, 2H, J = 6 Hz), 3.18 (t, 2H, J = 6 Hz), 2.57 (t, 2H, J = 6 Hz), 1.59−1.50 (m, 2H), 1.41−1.18 (m, 10H), 0.87 (t, 3H, J = 6 Hz); MS (EI) *m*/*z* 344 (M^+).

5-Octyl-2-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]thiophene (59). To a solution of 2-thiopheneethanol (12.8 g, 100 mmol) in CH_2Cl_2 (100 mL) were added 3,4-dihydro-2*H*-pyran (9.25 g, 110 mmol) and *p*-toluenesulfonic acid monohydrate (2.00 g, 10.5 mmol). The mixture was stirred at room temperature for 4 h and evaporated. Distillation (107−108 °C/1 mmHg) gave 2-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]thiophene (13.5 g, 64%) as an oil. To a solution of this intermediate (8.50 g, 40.0 mmol) in THF (100 mL) at −78 °C was added dropwise 1.6 M *n*-BuLi in hexanes (30 mL, 48.0 mmol). The mixture was stirred at 0 °C for 1 h; 1-bromooctane (10.0 g, 51.8 mmol) in THF (15 mL) was added. The mixture was stirred at room temperature for 7 h, poured into water, and extracted with EtOAc. The extract was washed with saturated NH_4Cl, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (20:1), gave **59** (6.59 g, 51%) as a yellowish oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (d, 1H, J = 3.4 Hz), 6.54 (d, 1H, J = 3.4 Hz), 4.61 (t, 1H, J = 3.5 Hz), 3.92 (dt, 1H, J = 10.2 and 7.3 Hz), 3.82−3.78 (m, 1H), 3.60 (dt, 1H, J = 10.2 and 7.3 Hz), 3.45−3.43 (m, 1H), 3.02 (t, 2H, J = 7.3 Hz), 2.71 (t, 2H, J = 7.2 Hz), 1.84−1.80 (m, 1H), 1.73−1.69 (m, 1H), 1.64−1.60 (m, 2H), 1.57−1.51 (m, 4H), 1.42−1.21 (m, 10H), 0.85 (t, 3H, J = 6.9 Hz).

2-(2-Iodoethyl)-5-octylthiophene (60): compound **59** was converted to **60** as described for **44**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (d, 1H, J = 3.4 Hz), 6.57 (d, 1H, J = 3.4 Hz), 3.34−3.27 (m, 4H), 2.72 (t, 2H, J = 7.4 Hz), 1.62 (quint, 2H, J = 7.4 Hz), 1.39−1.22 (m, 10H), 0.87 (t, 3H, J = 6.9 Hz); MS (EI) *m*/*z* 350 (M^+).

Ethyl 2-Acetamido-2-cyano-4-(4-octylphenyl)butyrate (61). 44 (21.3 g, 61.9 mmol) was condensed with ethyl acetamidocyanoacetate as described for **45** to give **61** (18.0 g, 75%) as a white solid: mp 83−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, 2H, J = 8.0 Hz), 7.10 (d, 2H, J = 8.0 Hz), 5.99 (brs, 1H), 4.30 (q, 2H, J = 8.0 Hz), 2.81 (t, 2H, J = 4.0 Hz), 2.57 (m, 4H), 1.94 (s, 3H), 1.58−1.55 (m, 2H), 1.37 (t, 3H, J = 8.0 Hz), 1.29−1.26 (m, 10H), 0.88 (t, 3H, J = 6.3 Hz); IR (KBr) 3281, 1755, 1660 cm^{-1}; MS (EI) *m*/*z* 387 (M^+).

Diethyl 2-[2-(4-Heptyloxyphenyl)ethyl]-2-methylmalonate (62, R = CH_3). To a suspension of NaH (60% dispersion in mineral oil, 5.12 g, 128 mmol) in DMF (110 mL) was added a solution of diethyl methylmalonate (20.6 g, 118 mmol) in DMF (50 mL). After the mixture had been stirred for 30 min, **50** (37.2 g, 107 mmol) was added. The suspension was stirred for 3 h, poured into water, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (9:1), gave **62** (33.3 g, 79%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, 2H, J = 8.6 Hz), 6.81 (d, 2H, J = 8.6 Hz), 4.19 (q, 4H, J = 7.3 Hz), 3.92 (t, 2H, J = 6.6 Hz), 2.51−2.46 (m, 2H), 2.15−2.10 (m, 2H), 1.78−1.70 (m, 2H), 1.48 (s, 3H), 1.48−1.27 (m, 8H), 1.26 (t, 6H, J = 7.3 Hz), 0.89 (t, 3H, J = 7.3 Hz); IR (neat) 2933, 2860, 1732 cm^{-1}; MS (EI) *m*/*z* 392 (M^+).

Ethyl 4-(4-Heptyloxyphenyl)-2-methoxycarbonylamino-2-methylbutyrate (63, R = CH_3). To a solution of **62** (33.3 g, 84.8 mmol) in EtOH (100 mL) was added KOH (85% pellets, 5.59 g, 84.8 mmol). The mixture was stirred for 6 h at 50 °C, evaporated, and diluted with water (600 mL). The aqueous solution was washed with hexane, acidified with 2 N HCl, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated to give 2-ethoxycarbonyl-4-(4-heptyloxyphenyl)-2-methylbutyric acid (22.7 g, 73%) as a yellow oil. To a solution of this intermediate (22.7 g, 62.0 mmol) and triethylamine (7.53 g, 74.4 mmol) in THF (300 mL) was added ethyl chloroformate (8.07 g, 74.4 mmol) at −5 °C. After the mixture had been stirred for 15 min, a solution of NaN_3 (8.06 g, 124 mmol) in water (20 mL) was added. The mixture was stirred for 1 h at 0 °C, poured into water, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. The residue was dissolved in benzene (250 mL), and the solution was refluxed for 1 h. After addition of MeOH (250 mL), the mixture was refluxed for 7 h and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (85:15), gave **63** (18.3 g, 75%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, 2H, J = 8.3 Hz), 6.80 (d, 2H, J = 8.3 Hz), 5.68 (brs, 1H), 4.17 (dq, 2H, J = 2.0 and 7.3 Hz), 3.91 (t, 2H, J = 6.6 Hz), 3.66 (s, 3H), 2.57−2.50 (m, 2H), 2.35−2.30 (m, 1H), 2.11−2.05 (m, 1H), 1.76 (quint, 2H, J = 6.9 Hz), 1.60 (s, 3H), 1.46−1.40 (m, 2H), 1.34−1.28 (m, 6H), 1.28 (t, 3H, J = 7.3 Hz), 0.89 (t, 3H, J = 6.8 Hz); IR (neat) 3421, 3363, 2933, 2859, 1725 cm^{-1}; MS (EI) *m*/*z* 393 (M^+).

2-Ethoxycarbonyl-2-[2-(4-heptyloxyphenyl)ethyl]-4-butanolide (64). Diethyl malonate (33.5 g, 209 mmol) was alkylated with 2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl iodide (56.1 g, 219 mmol) as described for **62** to give diethyl 2-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]malonate (45.1 g, 75%) as a colorless oil. This intermediate (44.9 g, 156 mmol) was alkylated with **50** (64.7 g, 187 mmol) as described for **62** to give diethyl 2-[2-(4-heptyloxyphenyl)ethyl]-2-[2-(tetrahydro-2*H*-pyran-2-yloxy)ethyl]malonate (67.9 g, 86%) as a yellow oil. To a solution of this intermediate (66.9 g, 132 mmol) in MeOH (400 mL) was added 1 N HCl solution in ether (5 mL). The solution was stirred for 5 h, concentrated, and diluted with EtOAc. The solution was washed with brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (9:1), gave **64** (43.0 g, 86%) as a yellowish oil: ^{1}H NMR ($CDCl_3$) δ 7.07 (d, 2H, J = 8.8 Hz), 6.80 (d, 2H, J = 8.8 Hz), 4.33 (dd, 2H, J = 8.8 and 5.3 Hz), 4.22 (dq, 2H, J = 2.2 and 7.1 Hz), 3.90 (t, 2H, J = 6.8 Hz), 2.76 (dt, 1H, J = 12.9 and 5.3 Hz), 2.65 (ddd, 1H, J = 13.7, 11.7 and 4.9 Hz), 2.51 (ddd, 1H, J = 13.7, 11.7 and 4.9 Hz), 2.37 (ddd, 1H, J = 13.7, 11.7 and 4.9 Hz), 2.24 (dt, 1H, J = 12.9 and 8.8 Hz), 2.02 (ddd, 1H, J = 13.7, 11.7 and 4.9 Hz), 1.74 (quint, 2H, J = 6.8 Hz), 1.44−

1.38 (m, 2H), 1.34−1.26 (m, 6H), 1.28 (t, 3H, J = 7.1 Hz), 0.87 (t, 3H, J = 6.9 Hz); IR (neat) 2929, 2859, 1774, 1735 cm^{-1}; MS (EI) m/z 376 (M^+).

2-[2-(4-Heptyloxyphenyl)ethyl]-2-methoxycarbonylamino-4-butanolide (65). To a solution of **64** (42.6 g, 113 mmol) in acetone (350 mL) was added 0.25 N NaOH (500 mL) at 0 °C. After the solution had been stirred for 1.5 h at room temperature, the acetone was removed. The aqueous solution was acidified with 2 N HCl (100 mL) and extracted with EtOAc. The extract was washed with brine, dried, and evaporated to give the intermediate, 2-[2-(4-heptyloxyphenyl)-ethyl]-4-butanolide-2-carboxylic acid (39.9 g, 100%), as a white solid. This intermediate (39.9 g, 115 mmol) underwent Curtius rearrangement to give **65** as described for **63**. **65** (26.9 g, 62%) was obtained as a white solid: mp 86−88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, 2H, J = 8.8 Hz), 6.80 (d, 2H, J = 8.8 Hz), 5.22 (brs, 1H), 4.47 (t, 1H, J = 9.3 Hz), 4.25 (dt, 1H, J = 9.3 and 7.1 Hz), 3.90 (t, 2H, J = 6.9 Hz), 3.65 (s, 3H), 2.75−2.67 (m, 1H), 2.64 (t, 2H, J = 8.6 Hz), 2.54−2.50 (m, 1H), 2.22−2.14 (m, 1H), 2.02−1.94 (m, 1H), 1.74 (quint, 2H, J = 6.9 Hz), 1.44−1.38 (m, 2H), 1.34−1.28 (m, 6H), 0.87 (t, 3H, J = 6.8 Hz); IR (neat) 3531, 3346, 2932, 2859, 1771, 1733 cm^{-1}; MS (FAB, NBA) m/z 378 $(M + H)^+$.

2-[2-(4-Heptyloxyphenyl)ethyl]-2-methoxycarbonylaminobutane-1,4-diol Diacetate (66). To a solution of **65** (17.3 g, 45.7 mmol) in THF (400 mL) was added $LiBH_4$ (1.99 g, 91.4 mmol). The mixture was refluxed for 30 min, acidified with 2 N HCl (20 mL) at 0 °C, diluted with water, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. The resultant oil was dissolved in pyridine (40 mL) and acetic anhydride (35 mL) and left for 13 h at room temperature. The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with 1 N HCl, saturated $NaHCO_3$ and brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (7:3), gave **66** (14.9 g, 70%) as a white solid: mp 75−76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, 2H, J = 8.3 Hz), 6.79 (d, 2H, J = 8.3 Hz), 4.83 (brs, 1H), 4.25 (s, 2H), 4.16 (t, 2H, J = 6.8 Hz), 3.90 (t, 2H, J = 6.8 Hz), 3.62 (s, 3H), 2.52 (dd, 2H, J = 10.7 and 6.4 Hz), 2.13 (t, 2H, J = 6.8 Hz), 2.08 (s, 3H), 2.02 (s, 3H), 2.00−1.96 (m, 2H), 1.74 (quint, 2H, J = 6.8 Hz), 1.44−1.38 (m, 2H), 1.34−1.28 (m, 6H), 0.87 (t, 3H, J = 6.8 Hz); IR (neat) 3359, 2933, 2859, 1733, 1717, 1699 cm^{-1}; MS (EI) m/z 465 (M^+).

Diethyl 2-[2-(4-Octylphenyl)ethyl]-2-[3-(tetrahydro-2*H*-pyran-2-yloxy)propyl]malonate (67). Diethyl malonate (28.7 g, 179 mmol) was condensed with 3-(tetrahydro-2*H*-pyran-2-yloxy)propyl bromide (40.0 g, 179 mmol) as described for **62** to give diethyl 2-[3-(tetrahydro-2*H*-pyran-2-yloxy)propyl]-malonate (30.3 g, 56%) as a colorless oil. This intermediate (10.0 g, 33.1 mmol) was condensed with **44** (13.7 g, 39.7 mmol) as described for **62** to give **67** (13.1 g, 76%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 4H), 4.59−4.57 (m, 1H), 4.19 (q, 4H, J = 7.3 Hz), 3.88−3.83 (m, 1H), 3.77−3.72 (m, 1H), 3.52−3.47 (m, 1H), 3.42−3.36 (m, 1H), 2.58−2.54 (m, 2H), 2.50−2.46 (m, 2H), 2.21−2.16 (m, 2H), 2.06−2.02 (m, 2H), 1.84−1.81 (m, 1H), 1.73−1.68 (m, 1H), 1.58−1.50 (m, 8H), 1.29−1.27 (m, 10H), 1.26 (t, 6H, J = 7.1 Hz), 0.88 (t, 3H, J = 6.8 Hz); IR (neat) 2927, 2856, 1732 cm^{-1}.

Ethyl 2-methoxycarbonylamino-2-[2-(4-octylphenyl)-ethyl]-5-(tetrahydro-2*H*-pyran-2-yloxy)valerate (68): synthesized according to the procedure described for **63**; a yellow oil (11%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, 2H, J = 8.3 Hz), 7.03 (d, 2H, J = 8.3 Hz), 5.87 (brs, 1H), 4.54 (m, 1H), 4.21−4.10 (m, 2H), 3.85−3.81 (m, 1H), 3.72−3.67 (m, 1H), 3.64 (s, 3H), 3.49−3.47 (m, 1H), 3.39−3.31 (m, 1H), 2.70−2.56 (m, 2H), 2.56−2.52 (m, 2H), 2.36−2.25 (m, 2H), 2.12−2.05 (m, 1H), 1.88−1.78 (m, 2H), 1.72−1.67 (m, 1H), 1.64−1.50 (m, 6H), 1.30−1.24 (m, 12H), 1.28 (t, 3H, J = 7.3 Hz), 0.88 (t, 3H, J = 6.8 Hz); IR (neat) 3423, 3381, 2928, 2856, 1721 cm^{-1}; MS (EI) m/z 519 (M^+).

4-Benzyloxy-2-butanone Ethylene Acetal (69, R = CH₃). A solution of ethyl acetoacetate (50.0 g, 384 mmol), ethylene glycol (64.1 mL, 1.15 mol), and *p*-toluenesulfonic acid monohydrate (570 mg, 3.00 mmol) in benzene (500 mL) was refluxed for 17 h using a Dean−Stark apparatus. The reaction mixture was diluted with EtOAc, washed with brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (9:1), gave ethyl acetoacetate ethylene acetal (63.8 g, 95%) as a colorless oil. To a suspension of $LiAlH_4$ (13.9 g, 365 mmol) in THF (400 mL) was slowly added a solution of this intermediate (63.5 g, 365 mmol) in THF (200 mL) at 0 °C. After the mixture had been stirred for 30 min at 0 °C, the reaction was quenched with saturated Na_2SO_4 (250 mL). The reaction mixture was filtered through Celite and evaporated. A solution of the residue in DMF (50 mL) was added to a suspension of NaH (60% dispersion in mineral oil, 16.1 g, 402 mmol) in DMF (250 mL). After the mixture had been stirred for 15 min, a solution of benzyl bromide (65.5 g, 383 mmol) in DMF (50 mL) was added at 0 °C. The mixture was stirred for 30 min at room temperature, evaporated, diluted with water, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (9:1), gave **69** (34.5 g, 43%) as a yellowish oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.26 (m, 5H), 4.51 (s, 2H), 3.97−3.88 (m, 4H), 3.60 (t, 2H, J = 7.1 Hz), 2.02 (t, 2H, J = 7.1 Hz), 1.35 (s, 3H); IR (neat) 3030, 2983, 2957, 2878 cm^{-1}.

1-Benzyloxy-3-methyl-5-phenyl-3-pentanol (70, R = CH₃). A solution of **69** (34.4 g, 155 mmol) in THF (200 mL), acetone (200 mL), and 2 N HCl (200 mL) was stirred for 2 h. The reaction mixture was concentrated, diluted with water, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (9:1), gave 4-benzyloxy-2-butanone (23.7 g, 86%) as a colorless oil. To a mixture of magnesium (3.45 g, 142 mmol) and I_2 (10 mg) in THF (20 mL) was added dropwise over 15 min a solution of phenethyl bromide (26.3 g, 142 mmol) in THF (70 mL). After the mixture had been stirred for 30 min, a solution of 4-benzyloxy-2-butanone (23.0 g, 129 mmol) in THF (150 mL) was added at 0 °C dropwise to the reaction mixture. The solution was stirred for 1 h at 0 °C, poured into saturated NH_4Cl, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (9:1), gave **70** (25.1 g, 68%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.16 (m, 10H), 4.52 (s, 2H), 3.76−3.69 (m, 2H), 3.27 (s, 1H), 2.76−2.62 (m, 2H), 1.94−1.71 (m, 4H), 1.26 (s, 3H); IR (neat) 3434, 3028, 2937, 2866 cm^{-1}.

3-Acetamido-3-methyl-5-phenylpentyl Acetate (71, R = CH₃). To a solution of **70** (24.8 g, 87.2 mmol) in CH_3CN (150 mL) was added dropwise concentrated H_2SO_4 (9.27 mL, 174 mmol) at 0 °C. After being stirred for 5 h at room temperature, the reaction mixture was diluted with water (500 mL), concentrated, and extracted with EtOAc. The extract was washed with saturated $NaHCO_3$ and brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (85:15), gave *N*-[3-benzyloxy-1-methyl-1-(2-phenethyl)propyl]-acetamide (17.0 g, 60%) as a white solid. A solution of this intermediate (16.8 g, 51.6 mmol) in AcOH (150 mL) was stirred under a hydrogen atmosphere in the presence of 10% Pd-$(OH)_2$/C (1.7 g) until the starting material was converted to a single more polar compound. The catalyst was removed by filtration and the filtrate was evaporated. The resultant oil was dissolved in pyridine (25 mL) and acetic anhydride (25 mL), and left for 15 h at room temperature. The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with 1 N HCl, saturated $NaHCO_3$ and brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (2:3), gave **71** (13.1 g, 92%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.25 (m, 2H), 7.19−7.16 (m, 3H), 5.37 (s, 1H), 4.18−4.09 (m, 2H), 2.63−2.53 (m, 2H), 2.34−2.17 (m, 2H), 2.04 (s, 3H), 2.03−1.92 (m, 2H), 1.90 (s, 3H), 1.36 (s, 3H); IR (neat) 3308, 3064, 3028, 2974, 2935, 1733, 1652 cm^{-1}; MS (EI) m/z 277 (M^+).

3,5-Dinitro-*N*-[3-(4-heptyloxyphenyl)-1-hydroxymethyl-1-methylpropyl]benzamide (72a). To a mixture of **30** (562 mg, 1.70 mmol) and $KHCO_3$ (512 mg, 5.11 mmol) in EtOAc (40 mL) and water (40 mL) was added 3,5-dinitrobenzoyl

chloride (412 mg, 1.79 mmol). The mixture was stirred for 15 min at room temperature and diluted with EtOAc (100 mL). The organic layer was washed with brine, dried, and evaporated. Recrystallization from EtOAc−hexane gave **72a** (670 mg, 81%) as a white solid: mp 132−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (t, 1H, J = 1.9 Hz), 8.64 (d, 2H, J = 1.9 Hz), 7.11 (d, 2H, J = 8.7 Hz), 6.70 (d, 2H, J = 8.7 Hz), 6.11 (brs, 1H), 3.88 (dd, 1H, J = 11.2 and 6.3 Hz), 3.79−3.71 (m, 2H), 3.76 (dd, 1H, J = 11.2 and 6.3 Hz), 3.49 (t, 1H, J = 6.3 Hz), 2.80−2.75 (m, 1H), 2.72−2.65 (m, 1H), 2.37−2.29 (m, 1H), 2.09−2.02 (m, 1H), 1.69 (quint, 2H, J = 7.3 Hz), 1.50 (s, 3H), 1.37−1.31 (m, 8H), 0.90 (t, 3H, J = 6.8 Hz); IR (KBr) 3250, 3102, 2928, 2857, 1642 cm^{-1}; MS (EI) m/z 487 (M^+).

(*R*)- and (*S*)-3,5-Dinitro-*N*-[3-(4-heptyloxyphenyl)-1-hydroxymethyl-1-methylpropyl]benzamide [(*R*)-72a and (*S*)-72a]. The racemic **72a** was separated by HPLC using a CHIRALCEL OD column [20 mm × 500 mm, hexanes−EtOH (55:45), 4.6 mL/min] into the enantiomers. The optical purity for both enantiomers was estimated to be >99% ee by HPLC analyses. **(*R*)-72a:** retention time 56 min; mp 150−151 °C; $[\alpha]^{24}_D$ −18.0° (*c* 0.83, $CHCl_3$). **(*S*)-72a:** retention time 68 min; mp 150−151 °C; $[\alpha]^{24}_D$ +17.2° (*c* 1.15, $CHCl_3$).

Similarly, racemic **72b** and **72c** were separated into the enantiomers.

(*R*)- and (*S*)-3,5-Dinitro-*N*-[1-[2-(4-heptyloxyphenyl)-ethyl]-1-hydroxymethylbutyl]benzamide [(*R*)-72b and (*S*)-72b]. **(*R*)-72b**: retention time 56 min (hexanes−EtOH 6:4); mp 115−116 °C; $[\alpha]^{24}_D$ −20.7° (*c* 0.98, $CHCl_3$). **(*S*)-72b**: retention time 68 min (hexanes−EtOH 6:4); mp 114−115 °C; $[\alpha]^{24}_D$ +18.2° (*c* 0.71, $CHCl_3$).

(*R*)- and (*S*)-3,5-Dinitro-*N*-[1-[2-(4-heptyloxyphenyl)-ethyl]-3-hydroxy-1-hydroxymethylpropyl]benzamide [(*R*)-72c and (*S*)-72c]. **(*R*)-72c**: retention time 61 min (hexanes−EtOH 4:6); mp 115−116 °C; $[\alpha]^{26}_D$ −13.8° (*c* 0.46, $CHCl_3$). **(*S*)-72c**: retention time 47 min (hexanes−EtOH 4:6); mp 115−116 °C; $[\alpha]^{23}_D$ +15.2° (*c* 0.46, $CHCl_3$).

(*R*)-2-Amino-4-(4-heptyloxyphenyl)-2-methylbutanol Hydrochloride [(*R*)-30]. To a solution of **(*R*)-72a** (400 mg, 0.820 mmol) in MeOH (20 mL) and THF (15 mL) was added 2 N LiOH (3 mL). The mixture was stirred for 30 min at room temperature, concentrated, diluted with water, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. The residue was converted to hydrochloride salt by treatment with MeOH (10 mL) and 1 N HCl solution in ether (2 mL) and solidified from EtOH/ether to give **(*R*)-30** (70 mg, 26%) as a yellowish noncrystalline powder: $[\alpha]^{25}_D$ +3.30° (*c* 0.42, $CHCl_3$). Anal. ($C_{18}H_{31}NO_2 \cdot HCl \cdot 1/2H_2O$) C, H, N.

Similarly, compounds **(*S*)-30**, **(*R*)-34**, **(*S*)-34**, **(*R*)-36** and **(*S*)-36** were prepared from **(*S*)-72a**, **(*R*)-72b**, **(*S*)-72b**, **(*R*)-72c** and **(*S*)-72c**, respectively.

(*S*)-2-Amino-4-(4-heptyloxyphenyl)-2-methylbutanol hydrochloride [(*S*)-30]: $[\alpha]^{25}_D$ −3.61° (*c* 0.31, $CHCl_3$). Anal. ($C_{18}H_{31}NO_2 \cdot HCl \cdot 1/2H_2O$) C, H, N.

(*R*)-2-Amino-2-[2-(4-heptyloxyphenyl)ethyl]pentanol hydrochloride [(*R*)-34]: mp 89−90 °C; $[\alpha]^{24}_D$ +1.68° (*c* 0.51, EtOH). Anal. ($C_{20}H_{35}NO_2 \cdot HCl$) C, H, N.

(*S*)-2-Amino-2-[2-(4-heptyloxyphenyl)ethyl]pentanol hydrochloride [(*S*)-34]: mp 90−91 °C; $[\alpha]^{26}_D$ −0.45° (*c* 0.51, EtOH). Anal. ($C_{20}H_{35}NO_2 \cdot HCl$) C, H, N.

(*R*)-2-Amino-2-[2-(4-heptyloxyphenyl)ethyl]butane-1,4-diol [(*R*)-36]: not converted to hydrochloride salt; mp 77−79 °C; $[\alpha]^{27}_D$ −4.08° (*c* 0.40, $CHCl_3$). Anal. ($C_{19}H_{33}NO_3 \cdot 1/5H_2O$) C, H, N.

(*S*)-2-Amino-2-[2-(4-heptyloxyphenyl)ethyl]butane-1,4-diol [(*S*)-36]: not converted to hydrochloride salt; mp 78−79 °C; $[\alpha]^{27}_D$ +4.01° (*c* 0.49, $CHCl_3$). Anal. ($C_{19}H_{33}NO_3 \cdot 1/5H_2O$) C, H, N.

4-[2-(4-Heptyloxyphenyl)ethyl]-4-(2-hydroxyethyl)-2-methyl-2-oxazoline (73). To a solution of **(+)-36** (290 mg, 0.897 mmol) and *N*,*N*-diisopropylethylamine (0.173 mL, 0.987 mmol) in DMF (10 mL) was added triethyl orthoacetate (0.181 mL, 0.987 mmol). The solution was stirred for 2.5 h at 115 °C, diluted with H_2O, and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. Silica gel chromatography, eluting with $CHCl_3$−MeOH (97:3), gave **73** (215 mg, 69%) as an oil: $[\alpha]^{27}_D$ +60.8° (*c* 0.60, $CHCl_3$); MS (EI) m/z 347 (M^+).

4-[2-(4-Heptyloxyphenyl)ethyl]-2-methyl-4-propyl-2-oxazoline (74). To a solution of oxalyl chloride (157 mL, 1.79 mmol) in CH_2Cl_2 (10 mL) was added DMSO (191 mL, 2.69 mmol) at −70 °C. After the solution had been stirred for 30 min at −70 °C, a solution of **73** (210 mg, 0.604 mmol) in CH_2Cl_2 (5 mL) was added dropwise to the solution. The mixture was stirred for 2 h at −55 °C, and triethylamine (933 mL, 6.73 mmol) was added. The reaction mixture was poured into saturated NH_4Cl and extracted with CH_2Cl_2. The extract was washed with brine, dried, and evaporated to give an aldehyde as a yellow oil. To a mixture of zinc powder (528 mg, 8.07 mmol) and CH_2I_2 (217 mL, 2.69 mmol) in THF (7 mL) was added a 2 M trimethylalminium solution in hexane (269 mL, 0.538 mmol). After the solution was stirred for 20 min at room temperature, a solution of the aldehyde described above in THF (5 mL) was added at −15 °C. The mixture was stirred for 16 h at 0 °C and diluted with EtOAc. The solution was washed with saturated $NaHCO_3$ and brine, dried, and evaporated. Silica gel chromatography, eluting with hexanes−EtOAc (8:2), gave 4-[2-(4-heptyloxyphenyl)ethyl]-2-methyl-4-(2-propenyl)-2-oxazoline (19.1 mg, 8.7%). A solution of this intermediate (19 mg, 0.055 mmol) in EtOH (10 mL) was stirred under a hydrogen atmosphere in the presence of 10% Pd/C (20 mg) for 4 h. The catalyst was removed by filtration and the filtrate was evaporated to give **74** (19 mg, 99%) as an oil: MS (EI) m/z 345 (M^+).

3,5-Dinitro-*N*-[1-[2-(4-heptyloxyphenyl)ethyl]-1-hydroxymethylbutyl]benzamide (75). A solution of **74** (19 mg, 0.055 mmol) in EtOH (6 mL) and concentrated HCl (2 mL) was refluxed for 1 h and evaporated. The residue was acylated as described for **72a** to give **75** (22.1 mg, 77%) as a yellow oil. Its optical rotation and retention time on HPLC were identical to those of **(*R*)-72b**: retention time 56 min (hexanes−EtOH 6:4); $[\alpha]^{24}_D$ −17.3° (*c* 0.30, $CHCl_3$).

Biological Procedures. 1. Lymphocyte-Decreasing Effect. F344 rats were purchased from Japan Charles River and used at 5 weeks of age. Compounds were dissolved in 20% hydroxypropyl-β-cyclodextrin and administered intraperitoneally. Peripheral blood was collected 24 h later, and the number of total lymphocytes was determined by lymphocyte-gating method. Flow cytometry analysis was performed by using EPICS XL-MCL (Coulter). The numbers of T-cells and B-cells were determined by two-color flow cytometry using fluorescein isothiocyanate-conjugated mouse anti-rat CD3 monoclonal antibody (MAb) (clone: 1F4) and phycoerythrin-conjugated mouse anti-rat CD45RA or A/B MAb (clone: OX-33).

2. Rat Skin Allograft. Major histocompatibility complex-compatible rat skin allograft was performed using LEW rats ($RT1^l$) as donors and F344 rats ($RT1^{lv1}$) as recipients. F344 rats and LEW rats were purchased from Japan Charles River. All rats were used at 4−6 weeks of age. Full-thickness skin grafts (square pieces 2.0 × 2.0 cm) from donor rats were transplanted to the lateral thorax of the recipient rats and covered with sterile bactericidal gauze. The entire chest was then wrapped with an elastic bandage. The dressings were removed on day 5, and the grafts were inspected daily until rejection, which was defined as more than 90% necrosis of the graft epithelium. Compounds were dissolved in 20% hydroxypropyl-β-cyclodextrin and administered intraperitoneally to the allografted recipients daily for 10 days from the day of transplantation.

3. Popliteal Lymph Node Gain Assay and T-Cell-Decreasing Effect. Spleen cells (5×10^6 cells) of WKAH rats ($RT1^k$) were injected into the footpad of LEW rats ($RT1^l$) to induce an enlargement of the draining popliteal lymph node. Compounds were administered orally for 4 days from the day of the injection of spleen cells, and the weight of the popliteal lymph node was then measured. The number of T-cells in peripheral blood was determined by flow cytometry using

fluorescein isothiocyanate-conjugated mouse anti-rat CD3 monoclonal antibody (clone: 1F4). The results are expressed as ID_{50} versus vehicle-treated group.

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