Thomboxane Receptor Antagonism Combined with Thromboxane Synthase Inhibition. 3. Pyridinylalkyl-Substituted 8-[(Arylsulfonyl)amino]octanoic Acids

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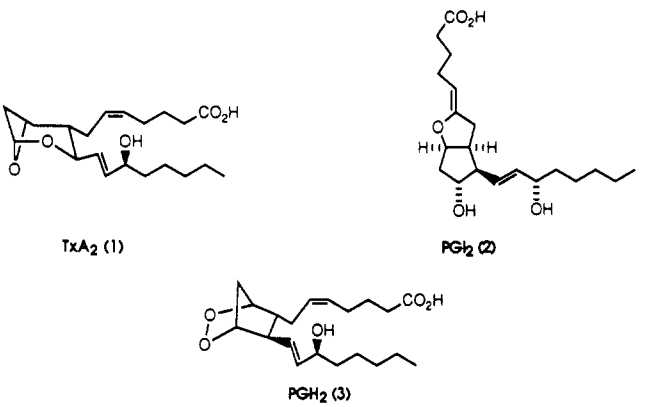
A series of 8-[(arylsulfonyl)amino]octanoic acids substituted with a pyridinylalkyl group along the chain were synthesized and tested in vitro for their ability to both antagonize the binding of thromboxane A_2 to its receptors and to inhibit the thromboxane synthase enzyme. This series of compounds were found to inhibit the U 46619-induced aggregation of human platelets and the U 46619-induced contraction of dog saphenous vein. The compounds also inhibited TxA_2 biosynthesis in a human microsomal platelet preparation. The relative position of the pyridinylalkyl and arylsulfonamido groups had significant effects on the thromboxane receptor antagonist (TxRA) activity and thromboxane synthase inhibitor (TxSI) activity. Compounds with the pyridine ring at the 7- or 8-position of the octanoic acid side chain were weakly active as TxSI but behaved as potent TxRA at the platelet receptor for TxA_2. However, these compounds were *agonists* at the vascular receptor. Substitution of the pyridinylalkyl group at the 2- or 3-position resulted in compounds with potent TxSI activity and weak TxRA activity. The activity profile of the compounds with the pyridinylalkyl substitution at the 4-, 5-, or 6-position was very desirable. Compound **22** with a pyridinylpropyl substituent at the 4-position was found to display extremely potent TxRA and TxSI properties.

A proper balance in the biosynthesis of thromboxane A_2 (TxA_2, 1) and prostacyclin (PGI_2, **2**), two extremely unstable metabolites of arachidonic acid with opposing activities, was postulated to be important for maintaining a normal hemodynamic status in the body.[1] Although this postulate may only be partially correct, it is well-documented that 1 plays an important role in the pathogenesis of certain circulatory disorders.[2] However, thromboxane synthase inhibitors (TxSIs) developed for treating such conditions have not proven to be very effective.[3] One of the reasons postulated for this lack of efficacy is that the endoperoxide PGH_2 (**3**), which is a substrate for thromboxane synthase, is itself a ligand at the receptor for TxA_2, causing platelet aggregation and vasoconstriction.[4] We therefore undertook a program to develop compounds which possess *both* TxA_2 receptor antagonist (TxRA) and TxSI properties (TxRA/TxSI).

In the preceding paper[5] we described the synthesis and



biological evaluation of a new class of pyridinyl-substituted arylsulfonamidoalkanoic acids of type **4**. While these compounds displayed potent dual activities as TxSIs and antagonized the TxA_2 receptor on platelets, they unfortunately showed agonist activity on vascular TxA_2 receptors. In this paper we describe our efforts to identify compounds that lack this undesired agonist activity.

We postulated in the preceding paper that the position of the pyridine group on the alkanoic acid side chain in compounds of type **4** was responsible for the observed agonist activity. To test this hypothesis, we set out to prepare compounds that fulfilled the structural criteria required for dual activity but where the position of the pyridine group on the alkanoic acid side chain was varied. Using the key SAR requirements for dual activity, i.e. seven methylenes distance between the arylsulfonamido

(1) Moncada, S.; Vane, J. R. Pharmacology and endogenous roles of prostaglandin endoperoxides, thromboxane A_2 and prostacyclin. *Pharmacol. Rev.* **1978**, *30*, 293-331.
(2) Majerus P. W. Arachidonate metabolism in vascular disorders. *J. Clin. Invest.* **1983**, *72*, 1521-1525.
(3) Fiddler, G. I.; Lumley, P. Preliminary clinical studies with thromboxane synthase inhibitors and thromboxane receptor blockers. *Circulation* **1990**, *81* (Suppl. 1), 169-180.
(4) FitzGerald, G. A.; Reilly, I. A. G.; Pedersen, A. K. The biochemical pharmacology of thromboxane synthase inhibition in man. *Circulation* **1985**, *72*, 1194-1201.
(5) Main, A. J.; Goldstein, R.; Cohen, D. S.; Furness, P.; Lee, W. Thromboxane receptor antagonism combined with thromboxane synthase inhibition. 2. Synthesis and biological activity of 8-[(phenylsulfonyl)-amino]-7-(3-pyridinyl)octanoic acid and related compounds. *J. Med. Chem.*, preceding paper in this issue.
(6) (a) Bhagwat, S. S.; Gude, C.; Cohen, D. S.; Lee, W.; Furness, P.; Clarke, F. H. Thromboxane receptor antagonism combined with thromboxane synthase inhibition. 1. (±)-3-(3-Pyridinylbicycloheptyl)alkanoic acids. *J. Med. Chem.* **1991**, *34*, 1790-1797. (b) Ford, N. F.; Browne, L. J.; Campbell, T.; Gemenden, C.; Goldstein, R.; Gude, C.; Wasley, J. W. F. Imidazo(1,5-*a*)pyridines: A new class of thromboxane A_2 synthetase inhibitors. *J. Med. Chem.* **1985**, *28*, 164-170.
(7) Halushka, P. V.; Mais, D. E.; Mayeux, P. R.; Morinelli, T. A.; Thromboxane, prostaglandin and leukotriene receptors. *Annu. Rev. Pharmacol. Toxicol.* **1989**, *29*, 213-239.
(8) Still, W. C.; Kahn, M.; Mitra, A. Rapid chromatographic technique for preparative separations with moderate resolution. *J. Org. Chem.* **1978**, *43*, 2923-2925.
(9) Bhagwat, S. S.; Gude, C.; Boswell, C.; Contardo, N.; Cohen, D. S.; Dotson, R.; Mathis, J.; Lee, W.; Furness, P.; Zoganas, H. Thromboxane receptor antagonism combined with thromboxane synthase inhibition. 4. 8-(4-Chlorophenylsulfonyl)amino-4-(3-(3-pyridinyl)propyl)octanoic acid and analogs. *J. Med. Chem.*, following paper in this issue.

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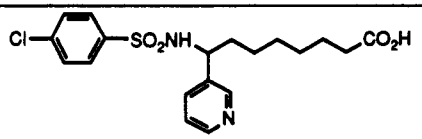
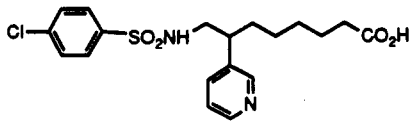
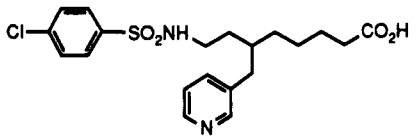
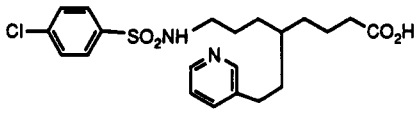
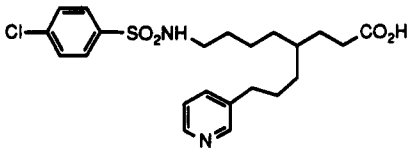
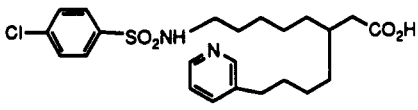
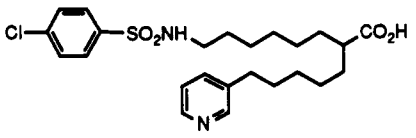
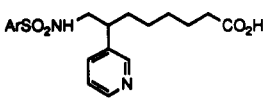
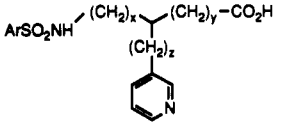
Table I. Pyridinylalkyl Substitution on the Octanoic Acid Backbone

compd	structure	x	y	z
7		0	6	0
8		1	5	0
13		2	4	1
18		3	3	2
22		4	2	3
26		5	1	4
29		6	0	5

and carboxylic acid groups for TxRA activity and five or six methylenes distance between the 3-pyridinyl group and the carboxylic acid, we were able to construct a family of compounds as shown in structure 5.



4



5

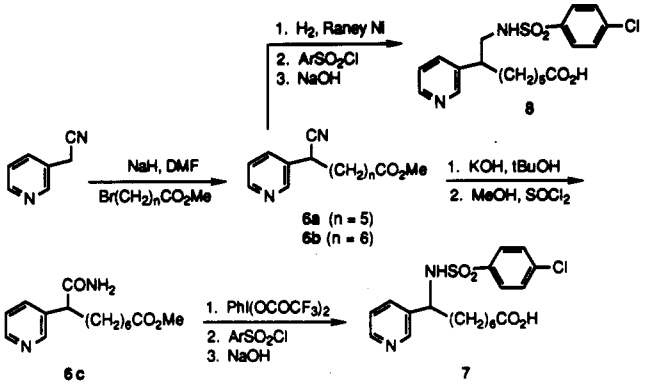
The key SAR requirements for dual activity are fulfilled when $x + y = 6$ and $y + z = 5$ or 6. For example, it can be seen that compound 4 represents one member of this series where $x = 1$, $y = 5$, and $z = 0$. Using this algorithm we constructed a series of seven target structures shown in Table I, all of which fulfill the above criteria.

Chemistry

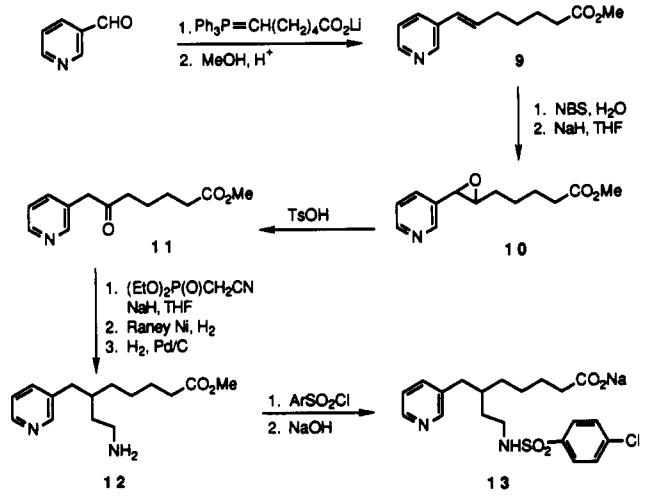
All of the target molecules described here were synthesized by essentially separate routes (shown in Schemes I–VI) because of the variations in the substitution pattern and chain length.

Alkylation of 3-pyridinylacetonitrile with either methyl 7-bromoheptanoate or 6-bromohexanoate gave 6. Hydrolysis of **6b** to the primary amide followed by esterification gave **6c**. Conversion of **6c** to the corresponding amine followed by sulfonylation of the amine and hydrolysis gave 7 with the pyridine ring at the 8-position of

Scheme I



Scheme II



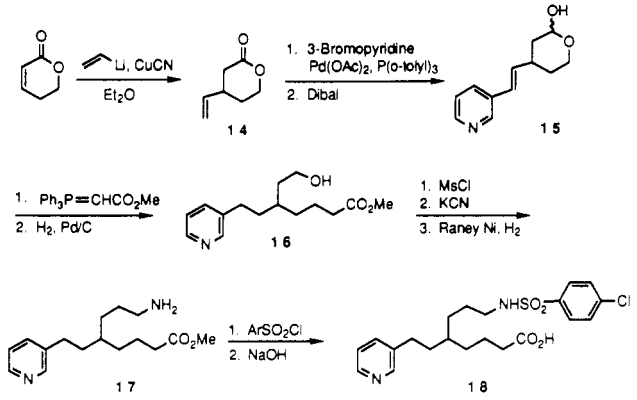
the sulfonamidooctanoic acid backbone (Scheme I). Reduction of **6a** with Raney nickel followed by sulfonylation of the resulting amine and hydrolysis of the ester gave 8 which has the 3-pyridine ring at the 7-position.

Compound 13 with a 3-pyridinylmethyl group at the 6-position was prepared as shown in Scheme II. The Wittig reagent obtained by the treatment of (5-carboxypentyl)-triphenylphosphonium bromide with 2 equiv of *n*-butyllithium was condensed with nicotinaldehyde and the resulting product was esterified to give the olefin 9. Treatment with N-bromosuccinimide and water followed by cyclization of the resulting bromohydrin with sodium hydride gave the epoxide 10, which was rearranged to the ketone 11 by treatment with *p*-toluenesulfonic acid. Horner–Emmons reaction of (diethylphosphono)acetonitrile with 11 followed by Raney nickel reduction of the nitrile and hydrogenation of the olefin gave 12. Sulfonylation of the amine followed by ester hydrolysis and sodium salt formation gave 13.

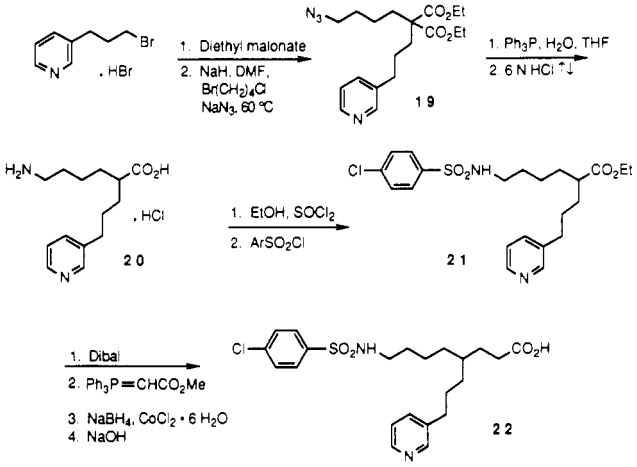
Copper-catalyzed 1,4-addition of vinyllithium to 5,6-dihydro-2*H*-pyran-2-one gave 14. Heck reaction[10] of 14 with 3-bromopyridine followed by Dibal reduction gave the lactol 15. Wittig reaction with (triphenylphosphoranylidene)acetate followed by hydrogenation gave 16. Conversion of 16 to the corresponding nitrile using standard procedures followed by reduction gave the primary amine 17. Sulfonylation of the amine followed by saponification gave 18 with a 3-pyridinylethyl group at the 5-position (Scheme III).

(10) Heck, R. F. Palladium catalyzed vinylation of organic halides. *Org. React.* **1982**, *27*, 345–390.

Scheme III



Scheme IV



Compound **22** with a 3-pyridinylpropyl group at the 4-position was prepared as shown in Scheme IV. Successive alkylation of diethyl malonate with 3-(3-pyridinyl)-propyl bromide hydrobromide and bromochlorobutane followed by displacement by azide anion in the same reaction pot gave **19**. Conversion of **19** to the amino compound followed by decarboxylation gave the amino acid hydrochloride salt **20**. Esterification followed by sulfonylation gave **21**. Chain extension by conversion to the aldehyde, Wittig reaction, and reduction of the double bond followed by saponification gave **22**.

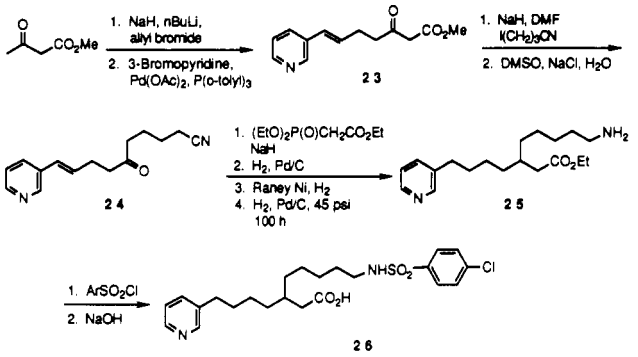
Monoalkylation of the dianion of methyl acetoacetate with allyl bromide followed by a Heck reaction with 3-bromopyridine gave **23**. Alkylation of **23** using 4-iodobutyronitrile followed by decarboxylation gave **24**. Horner–Emmons reaction of **24** with ethyl (diethylphosphono)acetate followed by consecutive hydrogenations gave the amine **25**. Sulfonylation of the amine followed by hydrolysis gave **26** with a pyridinylbutyl group at the 3-position (Scheme V).

Finally, compound **29** with a pyridinylphenyl group at the 2-position was prepared as shown in Scheme VI. Intermediates **27** and **28** were prepared from diethyl malonate by employing a similar sequence of reactions as in Scheme V. Reduction of the nitrile **28** to the corresponding amine followed by sulfonylation and saponification gave **29**.

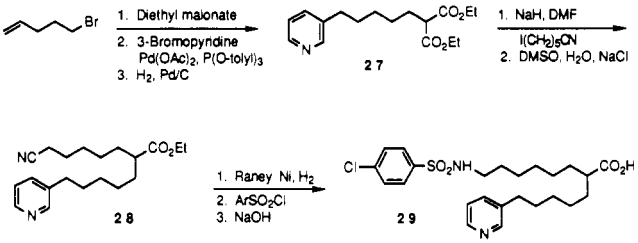
In Vitro Pharmacology and Discussion

The final compounds (all racemic) were tested for their in vitro potency for inhibiting the formation of TxB_2 from (^{14}C)arachidonic acid and platelet aggregation induced by

Scheme V



Scheme VI



U 46619 according to the procedures previously described.[6a,b] Table II lists the IC_{50} values for thromboxane synthase inhibition and thromboxane receptor antagonism.

The two compounds, **7** and **8**, with the pyridine ring close to the sulfonamide nitrogen (positions 8 and 7, respectively) are only moderately active as TxSIs (IC_{50} > 0.2 μM), but they potently inhibit the U 46619-induced aggregation of human washed platelets (WP). It appears therefore that placing a polar group like a sulfonamide or sulfonamidomethyl group next to the pyridine ring in these compounds significantly affects the TxSI activity because the parent, unsubstituted compound 7-(3-pyridinyl)-heptanoic acid (not shown), is much more potent as a TxSI (IC_{50} of 0.03 μM). Moving the pyridinylalkyl group away from the sulfonamide nitrogen atom and into the middle of the chain, improves the TxSI activity by more than 10-fold (**13** and **18**). These two compounds are moderately active as TxRAs in washed platelets. Compound **22** with a pyridinylpropyl group at the 4-position was found to be the most potent compound both as a TxSI and TxRA in this series. One could infer that the pyridinylpropyl group at the 4-position is optimally disposed to allow the molecule to bind to the receptor. Additionally, the arylsulfonamido chain presumably does not interfere with the binding of the molecule to the enzyme. Placement of the pyridinylalkyl group proximal to the carboxylic acid (**26** and **29**) seems to affect the TxRA activity to a greater extent than the TxSI activity. In fact, **29** has an extremely potent TxSI activity and only moderate TxRA activity.

The compounds which showed good TxRA activity in washed platelets were tested further in human platelet-rich plasma (PRP) and in dog saphenous vein preparations (Table III). The difference in TxRA activity in WP (protein free) vs PRP (protein rich) is probably an indication of the extent of protein binding of the compounds in PRP. The TxRA activity in dog saphenous vein was measured, as it has been suggested that the vascular receptor of TxA_2 may be different from the platelet receptor.[7]

The compounds shown in Table III were less active in human PRP (as compared to human WP) by 3–22-fold.

Table II. TxRA and TxSI Activity of Compounds

compound	formula[a]	mp, °C	IC_{50}, μM: thromboxane synthease inhibn[b]	IC_{50}, μM: inhibition of U 46619-induced aggregation of washed human platelets[c]
7	$C_{19}H_{23}ClN_2O_4S$	127–128	>0.5	0.027
8	$C_{19}H_{24}Cl_2N_2O_4S \cdot H_2O$	107–110	0.22	0.02
13	$C_{20}H_{25}ClN_2NaO_4S \cdot 0.5H_2O$	82–84	0.014	0.117
18	$C_{21}H_{27}ClN_2O_4S$	83–85	0.02	0.22
22	$C_{22}H_{29}ClN_2O_4S$	114–115	0.002	0.019[d]
26	$C_{23}H_{31}ClN_2O_4S \cdot 0.5H_2O$	oil	0.1	1.39
29	$C_{24}H_{37}ClN_2O_4S \cdot 0.5H_2O$	oil	0.004	0.3

[a] C, H, and N analyses were within ±0.4% of the calculated values. [b] Values represent an average of two determinations. [c] Values represent a single determination unless otherwise indicated. [d] n = 10, SEM = ±0.003.

Table III. TxRA Activity on the Platelet and Vascular Receptors

compd	IC_{50},[a] μM: inhibn of U 46619-induced aggregation of washed human platelets	IC_{50},[a] μM: inhibn of U 46619-induced aggregation of human PRP	inhibn of U 46619-induced contraction of dog saphenous vein, pA_2[b]
7	0.027	0.6	agonist[c]
8	0.02	0.28	agonist[c]
13	0.117	0.37	7.93 (19)
18	0.22	4.6	8.76 (12)
22	0.019[d]	0.39[e]	8.9 (27)

[a] Values represent a single determinations unless otherwise indicated. [b] Number of experiments is in parentheses. [c] Marked agonist activity was observed at 10^{-6}–10^{-7} M. [d] n = 7, SEM = ±0.023. [e] n = 10, SEM = ±0.003.

This loss of activity is probably due to protein binding of the compounds in PRP. Despite a high level of protein binding, 22 shows good TxRA activity in PRP because of its potent intrinsic activity. Compound 29 was inactive as a TxRA in PRP (not shown). Compound 26 was not tested because of its weak TxRA activity in WP.

The TxRA activity of this series of compounds at the vascular receptor (dog saphenous vein) changes dramatically as the pyridinylalkyl group is moved away from the sulfonamide functionality. As described in the preceeding paper and here, compound 8 showed potent *agonist* activity at the vascular TxA_2 receptor. The closely related compound 7 also showed this activity, giving further support to the original hypothesis proposed, that the proximity of the pyridine ring (or any bulk?) to the sulfonamide group is responsible for the agonist activity of 7 and 8 on the vascular receptor. When the pyridine ring is moved by one position, as in 13, the agonist property is not observed. In fact, 13 is moderately active as a TxRA in dog saphenous vein. Moreover, moving the pyridinylalkyl group further into the middle of the chain produces 18 and 22, which are extremely potent as TxRA on the vascular receptor. Compounds 26 and 29 were not tested in dog saphenous vein because of their weak TxRA activity on the platelet receptor. Further evaluation of 22 and its analogs in vitro, ex vivo, and in vivo models are published in the following paper.[9]

Conclusion

The series of compounds described here, with a pyridinylalkyl group substituted along the arylsulfonamidooctanoic acid backbone, were found to exhibit both thromboxane receptor antagonist and thromboxane synthase inhibitory activities. The position of the pyridinylalkyl group had a significant effect on the TxRA activity and, similarly, the position of the arylsulfonamidoalkyl group had a significant effect on the TxSI activity. Compounds 7 and 8 with the pyridine ring at the α- and β-position of the sulfonamide nitrogen were weakly active as TxSI and behaved as *antagonists* on the platelet receptor and *agonists* on the vascular receptor for 1. Moving the pyridinylalkyl group away from the sulfonamide substituent improved, in general, both synthase inhibitory activity and the antagonist properties on platelet and vascular receptors. Compound 22 was found to be the most potent TxRA/TxSI, presumably because the three side chains are optimally disposed for binding to the thromboxane receptor and thromboxane synthase enzyme.

Experimental Section

Infrared (IR) spectra were recorded on a Nicolet 55SCFT spectrometer. Proton NMR spectra were recorded on a Varian EM-390, Varian XL-300, or Varian XL-400 spectrometer. Chemical shifts are reported in ppm (δ) using tetramethylsilane, $CDCl_3$, or CD_3OD as internal standard. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Tetrahydrofuran (THF) was distilled from sodium benzophenone. Methylene chloride (CH_2Cl_2) was dried over 4-Å molecular sieves for 72 h before use. Organic solutions during workup were dried using anhydrous $MgSO_4$ or Na_2SO_4. Flash chromatography[8] was performed using silica gel 60 (0.04–0.06 mm) (Merck).

The procedure for the preparation of compound 8 can be found in the preceeding paper and for compound 22 in the following paper.[9]

Methyl 8-Cyano-8-(3-pyridinyl)octanoate (6b). To a suspension of 1.8 g (44.3 mmol, 60% dispersion in oil) of NaH in 40 mL of DMF was added dropwise 4.5 mL (42.2 mmol) of 3-pyridinylacetonitrile. The reaction was allowed to stir for 1 h and 10.3 g (46 mmol) of methyl 7-bromoheptanoate was added dropwise. The mixture was allowed to stir for 18 h and then quenched using 20 mL of saturated aqueous NH_4Cl and extracted with EtOAc (3 × 100 mL). The EtOAc extract was washed with brine, dried, and evaporated to give 15.0 g of a brown oil. Purification by flash chromatography on silica gel using 1:1 EtOAc/hexane as eluent gave 4.0 g (35%) of methyl 8-cyano-8-(3-pyridinyl)octanoate: IR (CH_2Cl_2) 2941, 2861, 2245, 1732, 1426, 1201, 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.56 (m, 2 H), 7.68 (br d, J = 8 Hz, 1 H), 7.32 (dd, J = 8, 4 Hz, 1 H), 3.8 (t, J = 7 Hz, 1 H), 3.65 (s, 3 H), 2.28 (t, J = 7 Hz, 2 H), 1.9 (m, 2 H), 0.8–1.65 (m, 8 H).

Methyl 8-Carbamoyl-8-(3-pyridinyl)octanoate (6c). To a solution of 10.6 g (40.8 mmol) of methyl 8-cyano-8-(3-pyridinyl)-octanoate in 50 mL of tBuOH was added 8 g (143 mmol) of finely powdered KOH. The mixture was allowed to stir for 1 h and then cooled to 10 °C and neutralized with 6 N HCl to pH = 6.5. The mixture was extracted with EtOAc (3 × 50 mL) and the combined extracts were washed with brine, dried, and concentrated in vacuo. The residue was taken up in 100 mL of MeOH and 1.5 mL (20.5 mmol) of $SOCl_2$ was added slowly, the temperature being maintained below 40 °C. The reaction mixture was allowed to stir at room temperature for 18 h and then neutralized to pH = 6.5 using 2 N NaOH. The mixture was extracted with EtOAc (3 × 50 mL) and the combined EtOAc

extract washed with brine, dried, and concentrated in vacuo. The residue was purified by flash chromatography using 95:5 EtOAc/MeOH to obtain 7.25 g (64%) of methyl 8-carbamoyl-8-(3-pyridinyl)octanoate as a white solid melting at 99–100 °C: IR (KBr) 3300 (br), 3109 (br), 2935, 2851, 1735, 1668, 1406, 1168 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.52 (br s, 2 H), 7.78 (br d, J = 8 Hz, 1 H) 7.3 (dd, J = 8, 4 Hz, 1 H), 5.69 (br s, 1 H), 5.48 (br s, 1 H), 3.65 (s, 3 H), 3.4 (t, J = 7 Hz, 1 H), 2.27 (t, J = 7 Hz, 2 H), 1.2–2.2 (m, 10 H).

8-[[(4-Chlorophenyl)sulfonyl]amino]-8-(3-pyridinyl)octanoic Acid (7). To a solution of 0.5 g (1.8 mmol) of methyl 8-carbamoyl-8-(3-pyridinyl)octanoate in 3 mL of CH_2CN was added 1.16 g (2.7 mmol) of 1,1-bis(trifluoroacetoxy)-4-iodobenzene and allowed to stir for 2 h. The reaction mixture was quenched using 20 mL of 2 N HCl. The aqueous layer was washed with 25 mL of Et_2O and then neutralized to pH = 6.5 with 2 N NaOH. The resulting solution was extracted with EtOAc (3 × 75 mL) and the combined EtOAc extract was washed with brine, dried, and concentrated in vacuo. The residue was taken up in CH_2Cl_2 and passed through a plug of silica gel using 9:1:5 EtOAc/MeOH/Et_3N as eluent to obtain 0.335 g (74%) of methyl 8-amino-8-(3-pyridinyl)octanoate: IR (CH_2Cl_2) 3100–2500 (br), 2937, 2862, 1732, 1666, 1194 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.65 (br s, 1 H), 8.53 (d, J = 4 Hz, 1 H), 7.91 (br d, J = 8 Hz, 1 H), 1.9–2.2 (m, 2 H), 1.54 (m, 2 H), 0.9–1.35 (m, 6 H).

To a solution of 0.32 g (1.28 mmol) of methyl 8-amino-8-(3-pyridinyl)octanoate in 5 mL of CH_2Cl_2 and 0.54 mL of Et_3N (3.85 mmol) was added a catalytic amount of 4-(dimethylamino)-pyridine followed by 0.24 g (1.15 mmol) of 4-chlorobenzenesulfonyl chloride. After 1 h, the reaction mixture was diluted with 50 mL of CH_2Cl_2 and washed with saturated $NaHCO_3$ followed by brine. The organic layer was dried and concentrated to obtain 0.47 g of a residue which was purified by flash chromatography using 3:2 EtOAc/hexane as eluent to obtain 0.38 g (70%) of methyl 8-[[(4-chlorophenyl)sulfonyl]amino]-8-(3-pyridinyl)octanoate: ^1H NMR ($CDCl_3$) δ 8.49 (br s, 2 H), 7.6 (d, J = 8 Hz, 2 H), 7.56 (m, 2 H), 7.32 (d, J = 8 Hz, 2 H), 7.24 (m, 1 H), 5.81 (m, 1 H), 4.37 (q, J = 7 Hz, 1 H), 3.67 (s, 3 H), 2.28 (t, J = 7 Hz, 2 H), 1.1–1.9 (m, 10 H).

A solution of 0.38 g (0.9 mmol) methyl 8-[[(4-chlorophenyl)-sulfonyl]amino]-8-(3-pyridinyl)octanoate in 1.8 mL of dioxane and 1.8 mL of 1 N NaOH was allowed to stir for 18 h at room temperature. The mixture was neutralized to pH = 6.5 using 1 N HCl and then extracted with EtOAc (3 × 35 mL). The organic phase was dried, filtered, and evaporated in vacuo. The residue was crystallized from CH_2Cl_2, and the crystals were filtered and washed with Et_2O. The product after drying at 50 °C weighed 0.19 g (51%) with mp 127–128 °C: IR (KBr) 3336, 3241, 2938, 2857, 1713, 1331, 1161, 752, 625 cm^{-1}; ^1H NMR (CD_3OD) δ 8.3 (br s, 2 H), 7.61 (d, J = 8 Hz, 2 H), 7.59 (m, 1 H), 7.38 (d, J = 8 Hz, 2 H), 7.24 (dd, J = 8, 4 Hz, 1 H), 4.35 (t, J = 7 Hz, 1 H), 2.24 (t, J = 7 Hz, 2 H), 1.1–1.8 (m, 10 H). Anal. ($C_{19}H_{23}ClN_2O_4S$) C, H, N.

Methyl 7-(3-Pyridinyl)hept-6-enoate (9). To a suspension of (5-carboxypentyl)triphenylphosphonium bromide (69 g, 0.15 mol) in a mixture of DMSO (125 mL) and THF (250 mL) cooled to 20 °C was added a solution of n-butyllithium (130 mL of a 2.4 M solution in hexane) dropwise over a period of 0.5 h. After stirring for a further 1 h, a solution of 3-pyridinecarboxaldehyde (10.7 g, 0.1 mol) in THF (25 mL) was added dropwise. The reaction was stirred for a further 1 h before adding water and acidifying to pH 6 with 1 N HCl. The solution was extracted with EtOAc and the organic phase was dried, filtered, and evaporated to give 7-(3-pyridyl)hept-6-enoic acid. The crude acid was dissolved in MeOH (100 mL), saturated with HCl gas, and heated to reflux for 4 h. The solvent was removed under reduced pressure and the residue flash chromatographed over silica gel using EtOAc to elute the product (9) as a colorless oil (11 g, 50% overall yield from 3-pyridinecarboxaldehyde): IR (CH_2Cl_2) 1732, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.5 (m, 2 H), 7.5 (m, 1 H), 7.2 (m, 1 H), 6.3 (m, 1 H), 5.8 (m, 1 H), 3.7 (s, 3 H), 2.2 (m, 4 H), 1.5 (m, 4 H).

2-(3-Pyridinyl)-3-[4-(methoxycarbonyl)butyl]oxirane (10). The above olefin (11 g, 50 mmol) was dissolved in a mixture of acetone (100 mL) and water (50 mL) and cooled to 0 °C and N-bromosuccinimide (13.5 g, 75 mmol) added in portions over 0.5 h. The reaction mixture was allowed to warm up to room temperature, stirred for 2 h, and then quenched with water and extracted with EtOAc. The organic layer was dried, filtered, and concentrated to give the crude bromohydrin (16.3 g), which was directly used in the next reaction without further purification.

Bromohydrin (16.3 g) was dissolved in THF (200 mL) and NaH (4.5 g of a 50% dispersion in oil) was added in portions. After stirring at room temperature for 3 h, the reaction mixture was poured into water and extracted with EtOAc. The organic phase was dried, filtered, and concentrated to give an amber oil which was further purified by flash chromatography using EtOAc to elute the product (10) as a colorless oil (5.0 g, 43% overall yield from 9): IR (CH_2Cl_2) 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.6 (m, 2 H), 7.6 (m, 1 H), 7.4 (m, 1 H), 4.0 (d, J = 5 Hz, 1 H), 3.6 (m, 4 H), 2.2 (m, 4 H), 1.5 (m, 4 H).

Methyl 7-(3-Pyridinyl)-6-oxoheptanoate (11). The oxirane (5.0 g, 21 mmol) prepared above was dissolved in toluene (100 mL), p-toluenesulfonic acid monohydrate (190 mg, 1 mmol) added, and the reaction heated to reflux for 8 h. The reaction mixture was then partitioned between water and EtOAc. The organic phase was dried, filtered, and concentrated to give the crude product which was then flash chromatographed over silica gel using EtOAc as eluent. The product was obtained as a colorless oil (3.7 g, 74% yield): IR (CH_2Cl_2) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.6 (m, 2 H), 7.6 (m, 1 H), 7.4 (m, 1 H), 3.7 (s, 3 H), 3.6 (s, 2 H), 2.5 (t, 2 H), 2.2 (t, 2 H), 1.6 (m, 4 H).

Methyl 8-Amino-6-(3-pyridinylmethyl)octanoate (12). To a suspension of NaH (0.68 g of a 60% dispersion in oil, 17 mmol) in THF (45 mL), cooled to 0 °C under nitrogen, was added dropwise a solution of diethyl (cyanomethyl)phosphonate (3.0 g, 17 mmol), in THF (15 mL) at such a rate that the reaction temperature did not exceed 5 °C. To the resulting solution was added the above ketone (4.28 g, 17 mmol) in THF (15 mL) at such a rate that the temperature of the solution did not exceed 8 °C. The reaction mixture was then allowed to warm up to 25 °C and stirred overnight. The solution was diluted with H_2O (50 mL) and extracted with EtOAc (3 × 50 mL) and the resulting organic phase was dried, filtered, and concentrated to give crude product as an amber oil (4.86 g). This material was purified by flash chromatography over silica gel using EtOAc as eluent. The α,β-unsaturated nitrile was obtained as a colorless oil (3.97 g, 86% yield): IR (CH_2Cl_2) 2982, 2940, 2218, 1732, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.5 (m, 2 H), 7.5 (m, 1 H), 7.2 (m, 1 H), 5.25 (s, 2 H), 3.7 (s, 3 H), 2.2 (t, 2 H), 2.1 (t, 2 H), 1.5 (m, 4 H).

The above α,β-unsaturated nitrile (0.6 g, 2.3 mmol) was dissolved in MeOH (70 mL) that had previously been saturated with ammonia gas. Activated Raney nickel catalyst (2 mL) was added and the mixture hydrogenated for 6 h at a pressure of 3 atm. The catalyst was filtered off, the MeOH removed under reduced pressure to give the crude product which was directly dissolved in MeOH (50 mL), 10% Pd/C (0.7 g) added, and the mixture further hydrogenated at a pressure of 3 atm for 8 h. The catalyst was filtered off and the solvent removed under reduced pressure to give the saturated amine (12).

8-[[(4-Chlorophenyl)sulfonyl]amino]-6-[(3-pyridinyl)-methyl]octanoic Acid Sodium Salt (13). The above crude amine (0.5 g) was then dissolved in CH_2Cl_2 (50 mL) and excess Et_3N (3 mL) and a solution of 4-chlorobenzenesulfonyl chloride (0.5 g, 2.4 mmol) in CH_2Cl_2 (10 mL) added. The reaction mixture was stirred at room temperature for 1 h, the solvent removed under reduced pressure, and the residue thus obtained directly purified by flash chromatography over silica gel using CH_2Cl_2 as eluent to obtain the sulfonamide as a colorless oil (0.3 g).

The above material (0.3 g) was hydrolyzed by dissolving in MeOH (10 mL), adding 1 N aqueous NaOH (20 mL), and stirring at room temperature for 18 h. The MeOH was removed under reduced pressure and the aqueous phase extracted with EtOAc. The aqueous layer was then acidifed to pH = 6.1 and extracted with EtOAc. The organic extract was dried, filtered, and concentrated to give the product as an oil (270 mg, 30% overall yield from α,β-unsaturated nitrile). To obtain a satisfactory microanalysis, the acid was converted to the sodium salt by dissolving in 0.1 N NaOH. The solution was concentrated in vacuo and the resulting foam triturated with ether to give a solid which was further dried under high vacuum at 60 °C for 2 days to give a powder: IR (KBr) 3620–3070 (br), 2931, 2860, 1653,

1568, 1477, 1423, 1328, 1161 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.4 (m, 1 H), 8.3 (m, 1 H), 7.8 (d, J = 8 Hz, 2 H), 7.6 (d, J = 7 Hz, 2 H), 1.6 (m, 1 H), 1.4–1.0 (m, 8 H). Anal. ($C_{24}H_{24}ClN_2NaO_4S \cdot 0.5H_2O$) C, H, N.

4-Vinyltetrahydro-2*H*-pyran-2-one (14). A steam of nitrogen gas was passed through a mixture of 19.6 mL (41.2 mmol) of 2.1 M vinyllithium in THF and 21 mL of toluene to evaporate THF. The resulting pale yellow suspension was diluted with 21 mL of Et_2O and cooled to −78 °C. To this solution was added 1.87 g (20.9 mmol) of CuCN and then the reaction was warmed to 0 °C for 2 min. The resulting gray precipitate was cooled to −78 °C and 0.9 mL (10.4 mmol) of 5,6-dihydro-2*H*-pyran-2-one was added. The reaction mixture was stirred at −78 °C for 30 min and at −20 °C for 15 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl and stirred for 1 h at room temperature. The insoluble salts were filtered off and washed with H_2O (20 mL) and Et_2O (2 × 20 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (2 × 30 mL). The combined organic extracts were dried, filtered, and evaporated to give 1.37 g of a yellow oil which was purified by flash chromatography using 1:1 Et_2O/hexane as eluent to obtain 0.39 g (30%) of 4-vinyltetrahydro-2*H*-pyran-2-one: IR (CH_2Cl_2) 3090, 2963, 2910, 1732, 1224 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.88 (m, 1 H), 5.2 (m, 2 H), 4.42 (m, 2 H), 1.5–2.9 (m, 2 H).

4-[2-(3-Pyridinyl)ethenyl]-2-hydroxytetrahydro-2*H*-pyran (15). To a solution of 0.88 g (7 mmol) of 4-vinyltetrahydro-2*H*-pyran-2-one in 5 mL of Et_3N and 5 mL of CH_3CN was added 0.081 g (0.36 mmol) of palladium(II) acetate followed by 0.66 g (2.5 mmol) tri-*o*-tolylphosphine and 0.76 mL (7.9 mmol) 3-bromopyridine and then heated at 125 °C for 20 h in a sealed tube. It was then cooled, diluted with CH_2Cl_2, and washed with H_2O. The organic phase was dried, filtered, and evaporated in vacuo to give 3.66 g of reddish oil which was purified by flash chromatography using EtOAc as eluent to obtain 0.914 g (64%) of 4-[2-(3-pyridinyl)ethenyl]tetrahydro-2*H*-pyran-2-one: ^1H NMR ($CDCl_3$) δ 8.7 (m, 2 H), 7.8 (br d, J = 8 Hz, 1 H), 7.38 (dd, J = 8, 4 Hz, 1 H), 5.9–6.3 (m, 2 H, *E*- and *Z*-mixture), 4.58 (m, 2 H), 1.75–3.1 (m, 5 H).

A solution of 1.01 g (5 mmol) of 4-[2-(3-pyridinyl)ethenyl]-tetrahydro-2*H*-pyran-2-one in CH_2Cl_2 (23 mL) was cooled to −78 °C and 3.3 mL(5 mmol) of a 1.53 M solution of diisobutylaluminum hydride in toluene was added. The solution was warmed to 0 °C and allowed to stir for 2 h. The reaction was quenched with 2.5 mL of MeOH and filtered through a short plug of silica gel and washed with MeOH (10 × 10 mL). The filtrate was evaporated in vacuo to give 0.99 g (99%) of 4-[2-(3-pyridinyl)-ethenyl]-2-hydroxytetrahydro-2*H*-pyran which was used without further purification: ^1H NMR ($CDCl_3$) δ 8.65 (m, 2 H), 7.7 (m, 1 H), 7.27 (dd, J = 8, 4 Hz, 1 H), 6.42 (m, 1 H), 5.53 (m, 1 H), 4.95 (m, 1 H), 4.24 (dd, J = 10, 3 Hz, 1 H), 3.82 (m, 1 H), 1.3–3.2 (m, 5 H).

Methyl 7-Hydroxy-5-[2-(3-pyridinyl)ethyl]heptanoate (16). To a solution of 4-[2-(3-pyridinyl)ethenyl]-2-hydroxytetrahydro-2*H*-pyran (0.99 g, 4.8 mmol) in 12 mL of CH_2Cl_2 was added 1.86 g (5.4 mmol) of methyl (triphenylphosphoranylidene)acetate and then allowed to stir at room temperature for 16 h. The solvent was evaporated and the residue taken up in Et_2O and filtered to remove the precipitated triphenylphosphine oxide. The filtrate was extracted with 1 N HCl (1 × 10 mL, 2 × 5 mL). The combined aqueous extracts were washed with Et_2O and then adjusted to pH = 8 and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo to give 1.53 g (100%) of methyl 7-hydroxy-5-[2-(3-pyridinyl)-ethenyl]hept-2-enoate which was used without further purification: ^1H NMR ($CDCl_3$) δ 8.58 (m, 2 H), 5.8–7.9 (m, 6 H), 3.7 (q, 3 H), 3.65 (t, J = 8 Hz, 2 H), 2.6 (m, 1 H), 1.72 (m, 2 H).

A solution of unpurified methyl 7-hydroxy-5-[2-(3-pyridinyl)-ethenyl]hept-2-enoate (1.75 g, 0.48 mmol) prepared above in 50 mL of EtOH was hydrogenated with 0.35 g of 10% Pd/C at 45 psi of H_2 at room temperature for 21 h. The catalyst was filtered off and washed with EtOH (4 × 10 mL). The filtrate was concentrated in vacuo to give 1.7 g of a yellow oil which was purified by flash chromatography using EtOAc as eluent to give 0.8 g (62%) of methyl 7-hydroxy-5-[2-(3-pyridinyl)ethyl]heptanoate: ^1H NMR ($CDCl_3$) δ 8.65 (m, 2 H), 7.62 (br d, J = 8 hz, 1 H), 7.3 (dd, J = 8, 4 Hz, 1 H), 4.2 (br s, 1 H), 3.67 (s, 3 H), 3.6–3.8 (m, 2 H), 2.6 (br t, J = 7 Hz, 2 H), 2.3 (t, J = 7 Hz, 2 H), 1.2–1.8 (m, 9 H).

Methyl 8-Amino-5-[2-(3-pyridinyl)ethyl]octanoate (17). A solution of 0.8 g (3 mmol) of methyl 7-hydroxy-5-[2-(3-pyridinyl)ethyl]heptanoate in 3 mL of CH_2Cl_2 was cooled to 0 °C and 0.52 mL (3.7 mmol) of Et_3N was added followed by 0.26 mL (3.3 mmol) of methanesulfonyl chloride. The reaction mixture was allowed to stir at 0 °C for 30 min and then 1.65 g (25 mmol) of finely powdered KCN was added followed by 15 mL of DMSO. The ice bath was removed after the reaction was allowed to stir for 30 min and then stirring was continued for 18 h at room temperature. The reaction mixture was poured into saturated aqueous NH_4Cl (20 mL) and then extracted with EtOAc (3 × 70 mL). The combined organic phase was washed with H_2O (4 × 60 mL) and brine (60 mL), dried, filtered, and evaporated in vacuo to give 0.8 g of an amber oil. Purification by flash chromatography using 7:3 EtOAc/Et_2O as eluent gave 0.3 g of methyl 7-cyano-5-[2-(3-pyridinyl)ethyl]heptanoate and 0.3 g of the mesylate of the starting alcohol. The mesylate was resubjected to the cyanide displacement conditions described above to produce a further 0.32 g of an oil which was combined with the nitrile prepared above and purified by flash chromatography to give 0.47 g (57%) of methyl 7-cyano-5-[2-(3-pyridinyl)-ethyl]heptanoate: ^1H NMR ($CDCl_3$) δ 8.62 (m, 2 H), 7.68 (br d, J = 8 Hz, 1 H), 7.37 (dd, J = 8, 4 Hz, 1 H), 3.77 (s, 3 H), 2.72 (br t, J = 7 Hz, 2 H), 2.41 (m, 4 H), 1.7 (m, 9 H).

To a solution of 0.1 g (0.37 mmol) of methyl 7-cyano-5-[2-(3-pyridinyl)ethyl]heptanoate in 20 mL of MeOH saturated with ammonia was added 0.15 mL of Raney nickel suspended in H_2O and the mixture was hydrogenated at 50 psi of H_2 at room temperature for 4 h. The catalyst was filtered off and washed with MeOH (4 × 20 mL). The filtrate was evaporated to give 0.13 g (100%) of methyl 8-amino-5-[2-(3-pyridinyl)ethyl]octanoate which was used immediately for the next step.

8-[[(4-Chlorophenyl)sulfonyl]amino]-5-[2-(3-pyridinyl)-ethyl]octanoic Acid (18). To a solution of 0.13 g (0.45 mmol) of methyl 8-amino-5-[2-(3-pyridinyl)ethyl]octanoate in 5 mL of CH_2Cl_2 was added a few crystals of 4-(dimethylamino)pyridine followed by 0.1 mL (0.7 mmol) of Et_3N and 0.112 g (0.51 mmol) of 4-chlorobenzenesulfonyl chloride. The reaction mixture was allowed to stir at room temperature for 16 h and then diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous $NaHCO_3$ solution. The organic phase was dried, filtered, and evaporated in vacuo to give 0.2 g of an amber oil which upon preparative thin-layer chromatography using 3:2 EtOAc/hexane gave 0.083 g (41%) of methyl-8-[[(4-chlorophenyl)sulfonyl]amino]-5-[2--(3-pyridinyl)ethyl]octanoate: IR (CH_2Cl_2) 3373, 2938, 1734, 1421, 1278, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.57 (m, 2 H), 7.93 (d, J = 8 Hz, 2 H), 7.58 (d, J = 8 Hz, 2 H), 7.2–7.7 (m, 2 H), 5.85 (br t, J = 6 Hz, 1 H), 3.71 (s, 3 H), 2.98 (q, J = 7 Hz, 2 H), 2.57 (br t, J = 7 Hz, 2 H), 2.3 (t, J = 7 Hz, 2 H), 1.1–1.8 (m, 11 H).

A mixture of 0.83 g (0.18 mmol) of methyl-8-[[(4-chlorophenyl)-sulfonyl]amino]-5-[2-(3-pyridinyl)ethyl]octanoate, 2 mL of dioxane, and 0.4 mL (0.4 mmol) of 1 N NaOH was allowed to stir at room temperature for 16 h. The solvent was evaporated and the residue taken up in water and then adjusted to pH = 5.0. The mixture was extracted with CH_2Cl_2 (4 × 10 mL) and the combined organic extracts were dried, filtered, and evaporated in vacuo to give 0.08 g of an oil which was crystallized from Et_2O to give 0.064 g (81%) of **18** as an off-white powder, mp 83–85 °C: IR ($CDCl_3$) 2929, 2858, 1710, 1478, 1334, 1163, 1097 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.58 (m, 2 H), 7.83 (d, J = 8 Hz, 2 H), 7.47 (d, J = 8 Hz, 2 H), 7.4–7.9 (m, 2 H), 5.59 (br s, 1 H), 2.88 (m, 2 H), 2.68 (t, J = 7 Hz, 2 H), 2.32 (t, J = 7 Hz, 2 H), 1.25–1.65 (m, 11 H). Anal. ($C_{21}H_{27}ClN_2O_4S$) C, H, N.

Methyl 7-(3-Pyridinyl)-3-oxohept-6-enoate (23). Methyl acetoacetate (34.8 g, 0.3 mol) was added dropwise to a suspension of NaH (16.2 g of a 50% dispersion in oil) in THF (750 mL) cooled to 0 °C. To this solution was then added dropwise a solution of *n*-butyllithium in hexane (141 mL of 2.3 M solution) and the temperature of the THF solution was kept at 0–5 °C. To the reaction mixture was then added a solution of allyl bromide (36 g, 0.3 mol) in THF (150 mL). After stirring for 0.5 h, the reaction was poured into a mixture of concentrated HCl (60 mL), H_2O (150 mL), and Et_2O (500 mL). The ether layer was separated

and washed with H_2O and the organic phase dried, filtered, and concentrated to give the crude product as an oil (36 g). The above olefin (36 g) was combined with 3-bromopyridine (40 g, 0.25 mol), tri-o-tolylphosphine (1.8 g, 6 mmol), palladium acetate (0.67 g, 3 mmol), Et_3N (150 mL), and CH_3CN (300 mL) and the resulting mixture heated to reflux for 20 h. After cooling to room temperature, the solvents were removed under reduced pressure, and the residue was partioned between EtOAc and H_2O. The organic phase was dried, filtered, and evaporated to give the crude product which was further purified by flash chromatography over silica gel using ether to elute the pure product (**23**) as an oil (23.3 g, 33% overall yield from methyl acetoacetate): ^1H NMR ($CDCl_3$) δ 8.6 (m, 2 H), 7.6 (m, 1 H), 7.2 (m, 1 H), 6.3 (m, 2 H), 3.7 (s, 3 H), 3.4 (s, 2 H), 2.5 (m, 4 H).

10-(3-Pyridinyl)-6-oxo-9-decenenitrile (24). To a solution of the above β-keto ester (23.3 g, 0.1 mol) in DMF (50 mL) was added dropwise a mixture of NaH (5.5 g of a 50% dispersion in oil) in DMF (500 mL) and the temperature was kept below 25 °C. After 0.5 h, 4-iodobutyronitrile (19.5 g, 0.1 mol) in DMF (50 mL) was added over a period of 0.5 h and the reaction mixture stirred at room temperature for 18 h. The mixture was then poured into cold dilute brine solution (2 L) and extracted with EtOAc. The organic phase was dried, filtered, and concentrated to give crude product which was further purified by chromatography over silica gel using Et_2O as eluent to yield the desired product (8.1 g) as a colorless oil.

The above ester (8.1 g) was decarboxylated by dissolving in a mixture of DMSO (75 mL) and water containing NaCl (5 g) and heating to reflux for 14 h. The reaction was allowed to cool to room temperature, water (200 mL) added, and the mixture extracted with EtOAc. The organic phase was dried, filtered, and concentrated to give crude product which was further purified by chromatography over silica gel using EtOAc/hexane (7:3) to elute the product (**24**) as an oil (6.05 g, 25% overall yield from **22**): ^1H NMR ($CDCl_3$) δ 8.6 (m, 2 H), 7.7 (m, 1 H), 7.3 (m, 1 H), 6.3 (m, 2 H), 2.4 (m, 8 H), 1.7 (m, 4 H).

8-[[-(p-Chlorophenyl)sulfonyl]amino]-3-[4-(3-pyridyl)-butyl]octanoic Acid (26). This compound was prepared from intermediate **24** by a sequence analogous to that described above for the conversion of intermediate **11** to the product **13**. Compound **26** was obtained as a colorless oil: IR (CH_2Cl_2) 2936, 2860, 1741 (sh), 1707, 1478, 1336, 1280, 1164, 1095, 1086 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.5 (bs, 2 H), 7.8 (d, J = 8 Hz, 2 H), 7.55 (d, J = 7 Hz, 1 H), 7.45 (d, J = 8 Hz, 2 H), 7.25 (m, 1 H), 5.3 (bs, 1 H), 2.9 (t, J = 7 Hz, 2 H), 2.6 (t, J = 7 Hz, 2 H), 1.8 (m, 1 H), 1.6 (m, 2 H), 1.45 (m, 2 H), 1.45 (m, 2 H), 1.4–1.2 (m, 10 H). Anal. ($C_{23}H_{31}ClN_2O_4S \cdot 0.5H_2O$) C, H, N.

8-(p-Chlorobenzenesulfonamido)-2-[5-(3-pyridyl)pentyl]-octanoic Acid (29). This compound was prepared as shown in Scheme VI using experimental procedures essentially analogous to those used to prepare compound **26**. The product was obtained as a colorless oil: IR (CH_2Cl_2) 2937, 2860, 1742 (sh), 1705, 1478, 1421, 1336, 1280, 1164, 1095, 1086 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.6 (br s, 2 H), 7.8 (d, J = 8 Hz, 2 H), 7.55 (d, J = 7 Hz, 1 H), 7.45 (d, J = 8 Hz, 2 H), 7.25 (m, 1 H), 5.2 (br s, 1 H), 2.9 (t, J = 7 Hz, 2 H), 2.6 (t, J = 7 Hz, 2 H), 2.3 (m, 1 H), 1.6 (m, 4 H), 1.5–1.2 (m, 14 H). Anal. ($C_{24}H_{33}ClN_2O_4S \cdot 0.5H_2O$) C, H, N.

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