Antihyperglycemic Activity of Novel Naphthalenyl 3*H*-1,2,3,5-Oxathiadiazole 2-Oxides

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A series of naphthalenyl 3*H*-1,2,3,5-oxathiadiazole 2-oxides was prepared and tested for antihyperglycemic activity in the db/db mouse, a model for type 2 (non-insulin dependent) diabetes mellitus. Substitution at the 1-, 5-, or 8-positions of the naphthalene ring with a halogen was found to be beneficial to antihyperglycemic activity. 4-[(5-Chloronaphthalen-2-yl)methyl]-3*H*-1,2,3,5-oxathiadiazole 2-oxide (**45**), one of the most potent compounds in this series, was selected for further pharmacological evaluation.

Drugs currently available for the control of the hyperglycemia associated with type 2 (non-insulin dependent) diabetes mellitus (sulfonylureas, biguanides, glucosidase inhibitors) possess significant liabilities or efficacy limitations. Thus, considerable effort has been directed recently toward the development of novel, orally active antihyperglycemic drugs. Many of these new compounds incorporate a relatively acidic heterocycle which serves as the pharmacophore responsible for antihyperglycemic activity. These heterocycles include the thiazolidine-2,4-dione,[1] tetrazole,[2] and oxazolidine-2,4-dione[3] rings. A series of structurally novel 3*H*-1,2,3,5-oxathiadiazole 2-oxides was also described recently.[4]

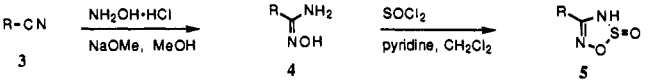
In this latter series, various heterocyclic (benzofuran, benzothiophene, and indole) as well as carbocyclic (indan, tetrahydronaphthalene, dihydronaphthalene, and naphthalene) groups were appended to the 3*H*-1,2,3,5-oxathiadiazole 2-oxide ring via a methylene bridge. The resultant compounds were examined in the genetically diabetic db/db mouse, an animal that exhibits many of the pathologies present in type 2 diabetes.[5] The compound with a 2-naphthalenyl substituent, 4-[(naphthalen-2-yl)methyl]-3*H*-1,2,3,5-oxathiadiazole 2-oxide (**1**) emerged as the most efficacious.

This result prompted the synthesis of a series of naphthalenyl oxathiadiazoles in which the effects of two structural factors on activity were examined: (1) variation of the tether linking the 2-position of the naphthalene ring to the oxathiadiazole ring; and (2) the addition of substituents on the naphthalene ring of naphthalen-2-ylmethyl compounds (e.g. compound **1**). From this group of compounds, 4-[(5-chloronaphthalen-2-yl)methyl]-3*H*-1,2,3,5-oxathiadiazole 2-oxide (**45**) (WAY-120,744) was selected for further evaluation and development. Reported in this paper are the synthesis of the series of naphthalenyl oxathiadiazoles, their effect on plasma glucose in the db/db mouse, and the characterization of compound **45** in additional animal models.

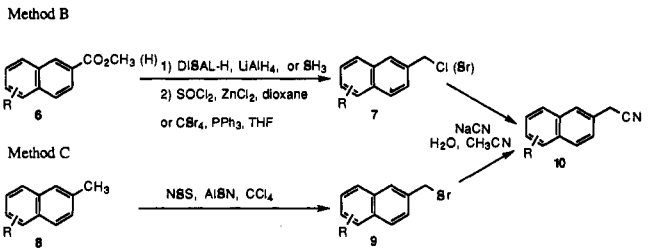
Chart I

1 **45**

Scheme I. 1,2,3,5-Oxathiadiazole 2-Oxides (Method A)



Scheme II. 2-Naphthaleneacetonitriles



Chemistry

The oxathiadiazoles **5** were prepared in two steps from a substituted nitrile **3** by (1) treatment with hydroxylamine to give an amidoxime (**4**), and (2) cyclization with thionyl chloride,[4] as illustrated in Scheme I (method A). The substituted nitriles were prepared as shown in Schemes II and III. 2-Naphthaleneacetonitriles **10** were derived from either a naphthoic acid or ester **6** via reduction, halogenation, and cyanide displacement (Scheme II, method B) or from a methylnaphthalene **8** by NBS bromination and cyanide displacement (Scheme II, method C).

The 2-naphthalenyl nitriles other than acetonitriles were prepared as shown in Scheme III. Thus 2-naphthalenebutanenitrile (**12**) was synthesized from 2-naphthaleneethanol (**11**) by oxidation to an aldehyde with Dess–Martin periodinane,[30] reaction with diethyl (cyanomethyl)phosphonate, and catalytic hydrogenation. The next higher homologue, 2-naphthalenepentanenitrile (**14**), was prepared from 2-naphthalenepropanenitrile (**13**) (synthesized according to Robertson et al.[6]) by DIBAL-H reduction of the nitrile to an aldehyde, reaction with diethyl

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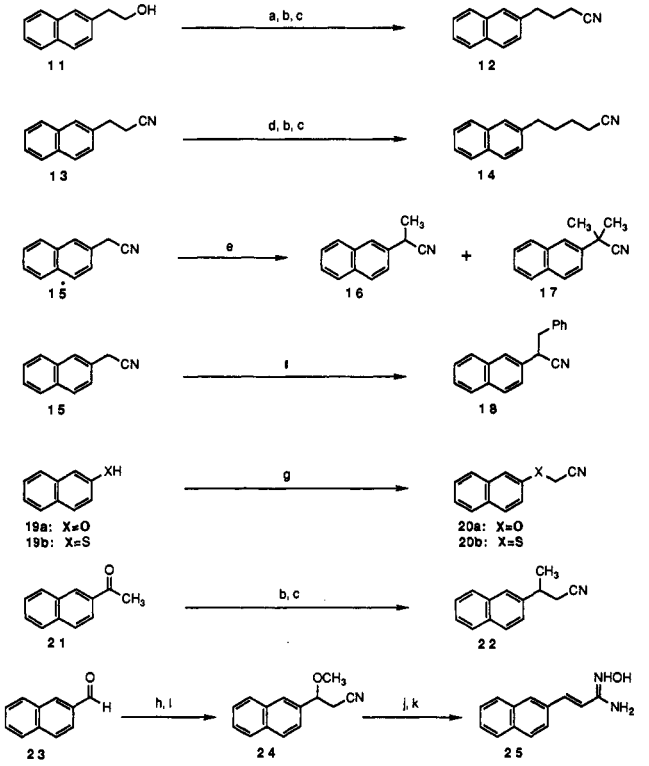
Scheme III. Other Nitriles[a]

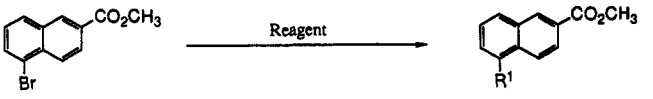


[a] (a) Dess–Martin periodinane, CH_2Cl_2; (b) $(EtO)_2P(O)CH_2CN$, NaH, THF; (c) H_2, 5% Pd/C, EtOH; (d) DIBAL-H, ether; (e) NaH, CH_3I, DME; (f) NaH, $PhCH_2Br$, DMR; (g) K_2CO_3, $ClCH_2CN$, acetone; (h) nBuLi, CH_3CN, THF; (i) NaH, $(CH_3)_2SO_4$, THF; (j) NHOH·HCl, $NaOCH_3$, CH_3OH; (k) CF_3CO_2H, 40 °C.

(cyanomethyl)phosphonate, and catalytic hydrogenation. Alkylation of 2-naphthaleneacetonitrile (**15**) according to a procedure of Hauser[7a] with sodium hydride and methyl iodide yielded the mono- and dimethyl compounds **16**[7b] and **17**.[7c] Alkylation of **15** with sodium hydride and benzyl bromide gave compound **18**.[8] The (2-naphthalenyloxy)- and (2-naphthalenylthio)acetonitriles **20a**[9] and **20b**[10] were prepared from 2-naphthol (**19a**) and 2-naphthalenethiol (**19b**), respectively, by alkylation with chloroacetonitrile and potassium carbonate. Treatment of 2-acetylnaphthalene (**21**) with diethyl (cyanomethyl)phosphonate and catalytic hydrogenation yielded 3-(2-naphthalenyl)butanenitrile (**22**). An aldol-type reaction of 2-naphthaldehyde (**23**) with lithioacetonitrile and subsequent methylation with sodium hydride and dimethyl sulfate gave 3-methoxy-3-(2-naphthalenyl)propanenitrile (**24**). The vinyl tether in compound **25** was introduced at a later stage by an elimination reaction on the amidoxime derived from compound **24**.

The mono- and disubstituted naphthoates **6** and methylnaphthalenes **8** used to prepare the substituted 2-naphthaleneacetonitriles were synthesized by a variety of methods. A number of 2-naphthoates were derived from the useful intermediate, methyl 5-bromo-2-naphthoate (**6a**)[11] (Table I). Thus, the 5-chloro group (**6b**)[12] was introduced with copper(I) chloride in DMSO;[13] the 5-methoxy group (**6c**) with sodium methoxide and copper(I) iodide in pyridine and methanol; the 5-methylthio group (**6d**) by reduction of the ester to an alcohol with DIBAL-H and treatment with sodium thiomethoxide and copper(I) oxide in *N*-methylpyrrolidinone;[14] the 5-vinyl group (**6e**) with vinyltributyltin and tetrakis(triphenylphosphine)palladium(0) in toluene;[15] the 5-ethynyl (**6f**) group with (trimethylsilyl)acetylene, bis(triphenylphosphine)palladium(II) chloride, and copper(I) iodide in

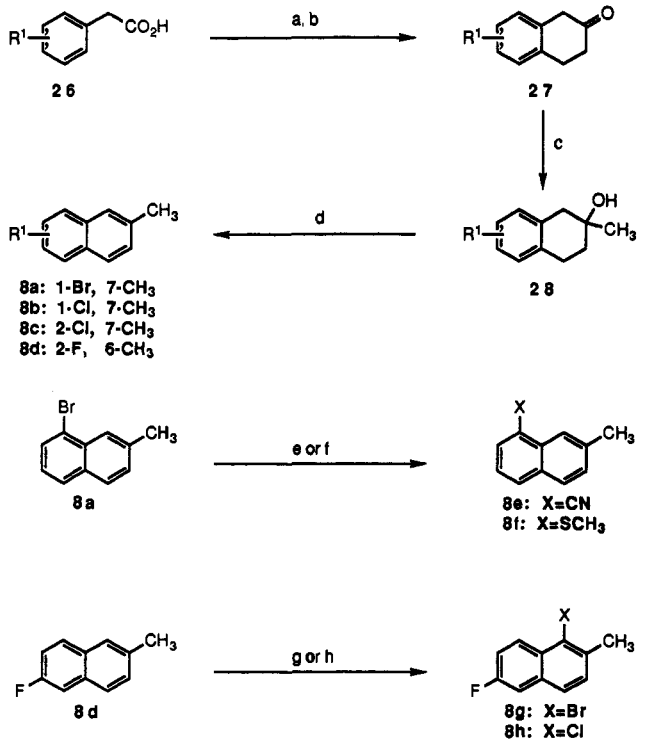
Table I. 5-Substituted 2-Naphthoates



compd	reagent	R^1	% yield
6b	CuCl, DMSO, 105–110 °C	Cl	100
6c	$NaOCH_3$, CuI, pyridine, CH_3OH, reflux; 2.5 N NaOH[a]	CH_3O	100
6d	$NaSCH_3$, Cu_2O, *N*-methylpyrrolidinone, reflux[b]	CH_3S	76
6e	CH_2=$CHSnBu_3$, $(Ph_3P)_4Pd$, toluene, reflux	CH_2=CH	92
6f	Me_3SiCCH, $(Ph_3P)_2PdCl_2$, CuI, Et_2NH, 20 °C; 1 N KOH, CH_3OH[a]	CHC	52
6g	CF_3CO_2Na, CuI, *N*-methylpyrrolidinone, reflux[c]	CF_3	48
6h	CH_3Li, CH_3I, THF, −78 °C to 20 °C[d]	CH_3	87

[a] Isolated as acid. [b] Ester reduced to alcohol prior to reaction. [c] Ethyl ester used. [d] Ester hydrolyzed to acid prior to reaction.

Scheme IV. Tetralone Route (Method D)[a]



[a] (a) $SOCl_2$, DMF, CH_2Cl_2; (b) $AlCl_3$, ethylene, CH_2Cl_2, −20 °C to −10 °C; (c) $TiCl_4$, CH_3MgCl, THF, CH_2Cl_2, −40 °C to 0 °C; (d) Ph_3COH, CF_3CO_2H; (e) CuCN, *N*-methylpyrrolidinone; (f) $NaSCH_3$, Cu_2O, *N*-methylpyrrolidinone; (g) Br_2, HOAc; (h) SO_2Cl_2, CH_2Cl_2.

diethylamine;[16] the 5-trifluoromethyl group (**6g**) with sodium trifluoroacetate and copper(I) iodide in *N*-methylpyrrolidinone;[17] and the 5-methyl group (**6h**) by hydrolysis of the ester and treatment of the resultant naphthoic acid with methyllithium and methyl iodide in THF. Bromination of compound **6c** with bromine yielded 8-bromo-5-methoxy-2-naphthoic acid (**6i**).

The preparation of 7- or 6-methylnaphthalenes **8** with a substituent in the 1, 2, or 3-position was most readily achieved by the synthesis of a 2-tetralone **27** (Scheme IV, method D). The 2-tetralones **27** were prepared from a substituted phenylacetic acid **26** by formation of the acid chloride and cyclization by treatment with aluminum chloride and ethylene.[18] The resultant 2-tetralones **27** were

methylated with titanium(IV) chloride/methylmagnesium chloride.[19] It is necessary to use this nonbasic methylating reagent because of the facile enolization of 2-tetralones. Cerium(III) chloride/methyllithium[20] was also used for the methylation reaction, but the yields were generally lower than with the titanium reagent. Aromatization of the alcohols **28** with triphenylmethanol in trifluoroacetic acid[21] gave the 7- or 6-methylnaphthalenes **8**. The tetralone route was used to prepare the 1-bromo, 1-chloro, and 2-chloro-7-methylnaphthalenes (**8a–c**) and 2-fluoro-6-methylnaphthalene (**8d**). Compound **8a** was converted to the 1-cyano compound (**8e**) by treatment with copper(I) cyanide and to the 1-methylthio compound (**8f**) with sodium thiomethoxide and copper(I) oxide in *N*-methylpyrrolidinone. Upon NBS bromination (method C) of **8f**, the product resulting from bromination of the naphthalene ring at the 5-position and a lesser amount of the 2-(bromomethyl)-5-bromo compound were produced. None of the desired monobrominated compound, 7-(bromomethyl)-1-(methylthio)naphthalene, was obtained. Compound **8d** was converted to 1-bromo-6-fluoro-2-methylnaphthalene (**8g**) with bromine in acetic acid and to 1-chloro-6-fluoro-2-methylnaphthalene (**8h**) with sulfuryl chloride in dichloromethane.

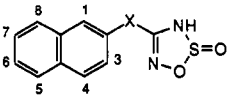
Additional naphthoic acids (or derivatives) and methylnaphthalenes were prepared by literature methods or as described below: 1-chloro-2-naphthoic acid (**6j**),[22] 3-chloro-2-naphthoic acid (**6k**),[22] 3-bromo-2-naphthoic acid (**6l**),[23] 4-bromo-2-naphthoic acid (**6m**),[11] 6-bromo-2-naphthoic acid (**6n**),[24,11] 7-bromo-2-naphthoic acid (**6o**),[11] 1-methoxy-2-naphthoic acid (**6p**)[25] by methylation of 1-hydroxy-2-naphthoic acid, 3-methoxy-2-naphthoic acid (**6q**)[25] by methylation of 3-hydroxy-2-naphthoic acid, 6-methoxy-2-naphthaldehyde (**6r**),[26] 7-methoxy-2-naphthoic acid (**6s**),[11] 1-methyl-2-naphthoic acid (**6t**),[27] 7-methyl-2-naphthoic acid (**6u**),[11] 1-ethyl-2-naphthoic acid (**6v**) by the same procedure as for **6t**, 1-methoxy-4-chloro-2-naphthoic acid (**6w**),[28] 1,3-dimethyl-2-naphthoic acid (**6x**) by the same procedure as for **6t**, 8-bromo-7-methyl-2-naphthoic acid (**6y**) by bromination of **6u**, 1-fluoro-2-methylnaphthalene (**8i**),[29] 1-bromo-2-methylnaphthalene (**8j**),[27] 3-methyl-2-(trifluoromethyl)naphthalene (**8k**) by trifluoromethylation[17] of 2-bromo-3-methylnaphthalene, and 1-bromo-2,3-dimethylnaphthalene (**8l**) by bromination of 2,3-dimethylnaphthalene. Also, the 5-ethyl group was introduced at a later stage by catalytic hydrogenation of 5-ethynyl-2-naphthaleneacetonitrile (**10c**).

Results and Discussion

The compounds were tested in a postprandial assay in the db/db mouse (see Experimental Section). Reported in Tables II–IV are the % changes in plasma glucose after 4 days of drug treatment (po). A reduction of 50–60% represents a normalization of plasma glucose levels in the db/db mouse.

In Table II, the results of an examination of the tether portion of this series of compounds are outlined. As reported earlier,[4] compound 1 lowered plasma glucose by 37% at a dose of 20 mg/kg. In compound **29**, removal of the methylene linker between the naphthalene and the oxathiadiazole groups decreased the activity (less than −15% change in plasma glucose vs control). An increase in the length of the linker by one methylene to give compound **30** did not affect activity, but any further increase in chain length yielded less potent compounds (**31** and **32**). Also, replacement of the ethylene tether of compound **30** with an alkenyl group (**33**) or ether linkage (**34**) resulted in a less than −15% change in plasma glucose. However, with the sulfide linker of compound **35**, plasma glucose was lowered by 40%. Monomethylation of the tether of compound 1 to give compound **36** improved activity whereas dimethylation to give compound **37** decreased activity (−49% and less than −15%, respectively). Also, benzylation (**38**) lowered the activity. In the case of compound **30**, monomethylation (**39**) or methoxylation (**40**) of the ethylene linker lowered the glucose decrease to −27% and less than −15%, respectively. Thus, in the linker region of this series of compounds, only a small degree of variation in chain length, lipophilicity, and steric volume is tolerated: a chain length of one or two carbons (1 and **30**), replacement of a carbon with a sulfur (**35**), and monomethylation of the methylene linker (**36**).

Table II. Variations of Tether

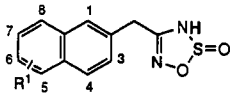


compd	X	mp, °C	formula[a]	% change in plasma glucose, 20 mg/kg[b]
29	bond	137–138	$C_{11}H_8N_2O_2S$	*c*
1	CH_2	145–147	$C_{12}H_{10}N_2O_2S$	−37 ± 2[d]
30	$(CH_2)_2$	114–115	$C_{13}H_{12}N_2O_2S$	−38 ± 2[d]
31	$(CH_2)_3$	139–140	$C_{14}H_{14}N_2O_2S$	*c*
32	$(CH_2)_4$	94–95	$C_{15}H_{16}N_2O_2S$	*e*
33	CH=CH	146–147	$C_{13}H_{10}N_2O_2S$	*c*
34	OCH_2	101–103	$C_{12}H_{10}N_2O_3S$	*c*
35	SCH_2	102–103	$C_{12}H_{10}N_2O_2S_2$	−40 ± 3[d]
36	$CH(CH_3)$	oil	$C_{13}H_{12}N_2O_2S$	−49 ± 1[d]
37	$C(CH_3)_2$	146–147	$C_{14}H_{14}N_2O_2S$	*c*
38	$CH(CH_2Ph)$	61–62	$C_{19}H_{16}N_2O_2S$	*c*
39	$CH(CH_3)CH_2$	99–101	$C_{14}H_{14}N_2O_2S$	−27 ± 3[d]
40	$CH(OCH_3)CH_2$	137–138	$C_{14}H_{14}N_2O_3S$	*c*

[a] Satisfactory C, H, and N elemental analyses (±0.4%) were obtained. [b] Values (mean ± SE) are percent changes relative to vehicle-treated group with use of 4–6 mice per group. [c] Less than −15% change. [d] $p < 0.05$. [e] −28 ± 5%[d] at 100 mg/kg.

An examination of substitutions on the naphthalene ring is reported in Table III. The compounds listed in this table all have the methylene linker found in compound 1. Only results for the lower doses of 5 and 1 mg/kg are included. At 5 mg/kg, compound 1 lowered plasma glucose by less than 15% and was therefore not tested at 1 mg/kg. The introduction of a substituent on the naphthalene ring of 1 led, in many cases, to an improvement in activity. However, the degree of improvement was influenced by the electronic and steric character of the substituent and especially by the position of substitution on the naphthalene ring. Substitution at positions 1, 5, or 8 was found to give the best activity. This trend is best illustrated by compounds **48–54**, in which a bromine has been placed at each position of the naphthalene ring. Compounds **48** (1-Br), **51** (5-Br), and **54** (8-Br) lowered plasma glucose by 40, 47, and 59%, respectively, at a dose of 5 mg/kg. The remaining bromo compounds (**49**, **50**, **52**, and **53**) lowered glucose by less than 30%. At the lower dose of 1 mg/kg, only the 1-, 5-, and 8-bromo compounds produced a significant drop in plasma glucose (−21, −35, and −48%, respectively). In some cases, 3-substituted compounds were comparable to 1-, 5-, or 8-substituted compounds. For example compounds **61** (1-CH_3), **62** (3-CH_3), and **63** (5-CH_3) lowered plasma glucose at 5 mg/kg by 36, 36, and 37%, respectively, and compounds **44** (3-Cl), **45** (5-Cl),

Table III. 2-Naphthalenylmethyl Oxathiadiazoles



compd	R^1	synthesis method (of 10)	mp, °C	formula[a]	% change in plasma glucose[b] 1 mg/kg	% change in plasma glucose[b] 5 mg/kg
1	H		145–147	$C_{12}H_{10}N_2O_2S$	*d*	*c*
41	6-F	D, C	168–169	$C_{13}H_9FN_2O_2S$	*d*	*e*
42	1-F	C	158–159	$C_{12}H_9FN_2O_2S$	*c*	−39 ± 4[f]
43	1-Cl	C	130–132	$C_{12}H_9ClN_2O_2S$	*c*	−27 ± 7[f]
44	3-Cl	B	161–162	$C_{12}H_9ClN_2O_2S$	*c*	−44 ± 2[f]
45	5-Cl	B	169–170	$C_{12}H_9ClN_2O_2S$	−21 ± 5[f]	−44 ± 3[f]
46	7-Cl	D, C	185–186	$C_{12}H_9ClN_2O_2S$	*d*	*c*
47	8-Cl	D, C	149–150	$C_{12}H_9ClN_2O_2S$	*c*	−55 ± 2[f]
48	1-Br	C	140–142	$C_{12}H_9BrN_2O_2S$	−21 ± 6[f]	−40 ± 2[f]
49	3-Br	B	153–154	$C_{12}H_9BrN_2O_2S$	*c*	−28 ± 11
50	4-Br	B	164–165	$C_{12}H_9BrN_2O_2S$	*c*	−21 ± 6
51	5-Br	B	159–160	$C_{12}H_9BrN_2O_2S$	−35 ± 2[f]	−47 ± 9[f]
52	6-Br	B	164–165	$C_{12}H_9BrN_2O_2S$	*c*	−25 ± 4
53	7-Br	B	145 (dec)	$C_{12}H_9BrN_2O_2S$	*d*	*c*
54	8-Br	D, C	159–160	$C_{12}H_9BrN_2O_2S$	−48 ± 8[f]	−59 ± 2[f]
55	1-OCH_3	B	143–144	$C_{13}H_{12}N_2O_3S$	*c*	−43 ± 4[f]
56	3-OCH_3	B	143–145	$C_{13}H_{12}N_2O_3S$	−16 ± 4	*g*
57	5-OCH_3	B	137–138	$C_{13}H_{12}N_2O_3S$	*c*	*c*
58	6-OCH_3	B	146–147	$C_{13}H_{12}N_2O_3S$	*d*	*h*
59	7-OCH_3	B	147–148	$C_{13}H_{12}N_2O_3S$	*d*	−19 ± 4
60	5-SCH_3	B	151–152	$C_{13}H_{12}N_2O_2S_2$	*d*	*c*
61	1-CH_3	B	118–119	$C_{13}H_{12}N_2O_2S$	−20 ± 2[f]	−36 ± 3[f]
62	3-CH_3	B	146–147	$C_{13}H_{12}N_2O_2S$	−20 ± 2[f]	−36 ± 7[f]
63	5-CH_3	B	156–157	$C_{13}H_{12}N_2O_2S$	*c*	−37 ± 2[f]
64	7-CH_3	B	165–166	$C_{13}H_{12}N_2O_2S$	*d*	*i*
65	1-CH_3CH_2	B	106–107	$C_{14}H_{14}N_2O_2S$	*c*	−24 ± 7[f]
66	5-CH_3CH_2	B	145–147	$C_{14}H_{14}N_2O_2S$	*c*	−23 ± 3[f]
67	3-CF_3	C	145–146	$C_{13}H_9F_3N_2O_2S$	*c*	−30 ± 4[f]
68	5-CF_3	B	175–176	$C_{13}H_9F_6N_2O_2S$[j]	*c*	−30 ± 6[f]
69	5-CH_2=CH	B	166–168	$C_{14}H_{12}N_2O_2S$	*d*	−17 ± 7
70	5-CH≡C	B	175–176	$C_{14}H_{10}N_2O_2S$[k]	−19 ± 3	−45 ± 3[f]
71	8-CN	D, C	177–179	$C_{13}H_8N_3O_2S$	*c*	*c*

[a] Satisfactory C, H, and N elemental analyses (±0.4%) were obtained, except as noted. [b] Values (mean ± SE) are percent changes relative to vehicle-treated group with use of 4–6 mice per group. [c] Less than −15% change. [d] Not tested. [e] −26 ± 2% [f] at 100 mg/kg. [f] $p < 0.05$. [g] −50 ± 3% [f] at 20 mg/kg. [h] Less than −15% at 20 mg/kg. [i] −36 ± 2% [f] at 20 mg/kg. [j] C: calcd, 49.68; found, 49.11. [k] C: calcd, 62.21; found, 60.70.

and **47** (8-Cl) lowered glucose by 44, 44, and 55%, respectively.

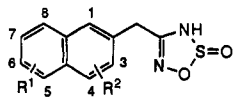
In addition to the position of substitution, the steric and electronic nature of the substituent was found to be important. An example of a possible steric effect can be seen in the decrease in activity on replacing a methyl group with an ethyl group. As mentioned above, the 1-CH_3 and 5-CH_3 compounds (**61** and **63**) lowered plasma glucose by about 36% at 5 mg/kg. The corresponding ethyl compounds (**65** and **66**) brought about only 24 and 23% decreases. Changing the degree of saturation of the 5-ethyl group to yield a 5-vinyl substituent (**69**) did not improve activity (−17%). In contrast, the 5-ethynyl group (**70**) lowered plasma glucose by 45% at 5 mg/kg. This significant improvement in activity may result from the difference in electronic character of the substituent.

Electronic effects are further illustrated by the following series of 5-substituted compounds, with test results at a dose of 5 mg/kg: **45** (5-Cl, −44%), **51** (5-Br, −47%), **57** (5-OCH_3, <−15%), and **68** (5-CF_3, −30%). Thus, an electron-donating group (OCH_3) is detrimental and the strong electron-withdrawing trifluoromethyl group is inferior to both the chloro and bromo groups, the optimal substituents in this series. The 1-methoxy compound **55** stands out as an exception since it lowered plasma glucose by 43%. In this case the methoxy group may participate in an intramolecular hydrogen bond with the proton of the oxathiadiazole, thus stabilizing a bioactive conformation. However, the results for the remaining methoxy compounds (**56–59**) are consistent with those for **57**. Therefore, some electron-withdrawing character, such as that associated with a chloro or bromo group, appears to be optimal for antihyperglycemic activity.

Listed in Table IV are some disubstituted naphthalen-2-ylmethyl compounds and testing results in the db/db mouse at 5 and 1 mg/kg. Additional substituents on the naphthalene ring did not generally improve activity. For example, compounds **73** (1-Br, 6-F) and **78** (1-Br, 3-CH_3) lowered plasma glucose by 16 and 34%, respectively, at 5 mg/kg. However, the monosubstituted 1-Br compound **48** brought about a 40% decrease at the same dose. The other disubstituted compounds were less active than the analogous monosubstituted compounds, except for **77**, which lowered plasma glucose by 45% at 5 mg/kg. Compound **77** is a 1,3-dimethyl analog, and is superior to both **61** (1-CH_3) and **62** (3-CH_3).

Compound **45**, the 5-chloro substituted (naphthalen-2-ylmethyl)oxathiadiazole, was selected for further pharmacological evaluation. Although compounds **51** and **54** had greater potency than **45** in preliminary studies, both **51** and **54** caused emesis in dogs. In db/db mice, compound **45** caused a dose-dependent reduction of hyperglycemia (Figure 1). The minimal effective dose ($p < 0.05$) of compound **45** in this animal model of diabetes was 0.5 mg/kg. Compound **45** also significantly reduced the mild hyperglycemia of obese ob/ob mice (Table V). Although compound **45** was ineffective at lowering the plasma glucose of nondiabetic rats (Table VI), the compound was able to

Table IV. Disubstituted 2-Naphthalenyl Oxathiadiazoles



compd	R^1	R^2	synthesis method (of 10)	mp, °C	formula[a]	% change in plasma glucose[b] 1 mg/kg	5 mg/kg
72	1-Cl	6-F	D, C	153–154	$C_{12}H_8ClFN_2O_2S$	*d*	*c*
73	1-Br	6-F	D, C	150–151	$C_{12}H_8BrFN_2O_2S$	*d*	−16 ± 5[e]
74	1-OCH_3	4-Cl	B	148–149	$C_{13}H_{11}ClN_2O_3S$[f]	−17 ± 4	−31 ± 4[e]
75	5-OCH_3	8-Br	B	164–165	$C_{13}H_{11}BrN_2O_3S$	*c*	*d*
76	5-Br	8-SCH_3	C	173–174	$C_{13}H_{11}BrN_2O_2S_2$	*c*	−19 ± 7
77	1-CH_3	3-CH_3	C	152–154	$C_{14}H_{14}N_2O_2S$	*c*	−45 ± 2[e]
78	1-Br	3-CH_3	C	175–176	$C_{13}H_{11}BrN_2O_2S$	*c*	−34 ± 3[e]
79	7-CH_3	8-Br	B	175–176	$C_{13}H_{11}BrN_2O_2S$	*d*	−21 ± 4[e]

[a] Satisfactory C, H, and N elemental analyses (±0.4%) were obtained, except as noted. [b] Values (mean ± SE) are percent changes relative to vehicle-treated group with use of 4–6 mice per group. [c] Less than −15% change. [d] Not tested. [e] $p < 0.05$. [f] C: calcd, 50.25; found, 50.74.

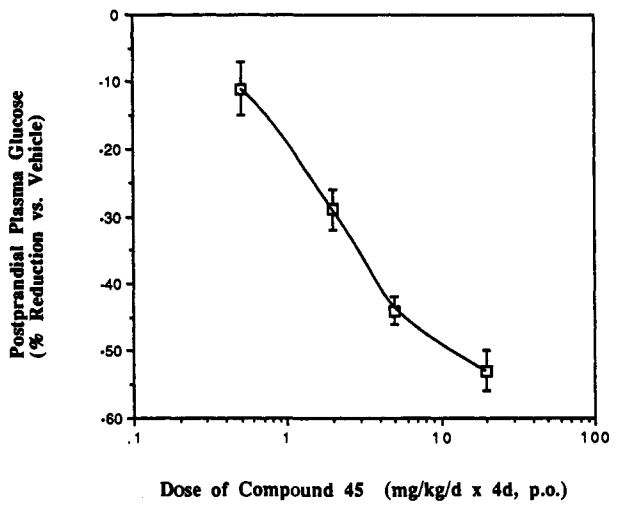


Figure 1.

Table V. Plasma Glucose Levels of Fed ob/ob Mice

drug	dose (mg/kg, po)[a]	plasma glucose (mg/dL)[b]
vehicle		289 ± 16
ciglitazone	20	189 ± 5[c]
45	5	223 ± 7[c]
	20	199 ± 6[c]
metformin	50	253 ± 10
	200	208 ± 8[c]
glyburide	5	297 ± 16
	20	311 ± 16

[a] Mice were treated once daily for 10 days. [b] Data are expressed as mean ± SEM, $n = 36$ per group. [c] $p < 0.05$ versus vehicle-treated mice.

Table VI. Plasma Glucose Levels of Nondiabetic Rats

drug (mg/kg/d, po)	glucose (mg/dL)[a] at time (h) after drug 0	1	2	4
vehicle	110 ± 4	123 ± 3	124 ± 3	114 ± 5
glyburide (25)	110 ± 5	71 ± 5[b]	51 ± 3[b]	55 ± 2[b]
45 (25)	111 ± 6	120 ± 6	122 ± 3	118 ± 4

[a] Values are mean ± SE, $n = 5$ per group. [b] $p < 0.05$ versus respective vehicle group.

significantly reduce the severe hyperglycemia of streptozocin-diabetic rats, an animal model of Type 1 diabetes (Table VII). Surprisingly, repetitive administration of compound **45** to nondiabetic rats resulted in a dose-dependent increase in urinary glucose excretion (Table VIII). The mechanism for the induction of glucosuria, as well as possible relevance to the antihyperglycemic efficacy in diabetic animals, is not known.

Table VII. Plasma Glucose Levels of Streptozocin-Diabetic Rats

drug	dose (mg/kg, po)	plasma glucose (mg/dL)[a]
vehicle		423 ± 20
45	5	329 ± 20
45	25	255 ± 16[b]

[a] Values are mean ± SE, $n = 9$–12 per group. [b] $p < 0.05$.

Table VIII. Urinary Glucose of Nondiabetic Rats

drug	dose[a] (mg/kg)	urine[b] glucose (g/dL)	glucose (g/d)	volume (mL/d)	consumption[b] water (mL/d)	food (g/d)
vehicle		0.03 ± 0.0	0.01 ± 0	20 ± 2	41 ± 2	24 ± 1
45	5	0.1 ± 0.1	0.03 ± 0	29 ± 5	49 ± 6	25 ± 1
45	10	2.9 ± 0.8	0.70 ± 0.2	23 ± 2	45 ± 2	25 ± 1
45	25	5.7 ± 0.7	2.10 ± 0.3	37 ± 2	59 ± 5	25 ± 4

[a] Rats were treated for 11 days. [b] Values are mean ± SE, $n = 6$ per group.

In summary, compound **45**, the 5-chloro-substituted (naphthalen-2-ylmethyl)oxathiadiazole, was found to be a potent antihyperglycemic agent in a variety of diabetic animal models. The in vivo pharmacological properties of the naphthalenyl oxathiadiazoles appear to be unique; however, the cellular mechanism of action has yet to be determined.

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. The NMR spectra were recorded on a Varian VXR200, Varian VXR300, or a Bruker AM-400 instrument. The infrared spectra were recorded on a Perkin-Elmer diffraction grating or a Perkin-Elmer 784 spectrophotometer. The mass spectra were recorded on a Hewlett-Packard 5995A or a Finigan 8230 mass spectrometer. Analyses (C, H, N) were carried out on a modified Perkin-Elmer Model 240 CHN analyzer. Merck silica gel (70–230 mesh) was used for flash chromatography. Preparative HPLC was performed on a Waters Prep 500. Organic extracts were dried over $MgSO_4$ unless otherwise noted.

Method A. 4-[(5-Chloronaphthalen-2-yl)methyl]-3*H*-1,2,3,5-oxathiadiazole 2-Oxide (45). To a stirred solution of 5-chloro-2-naphthaleneacetonitrile (**10a**) (5.00 g, 0.0248 mol) and hydroxylamine hydrochloride (3.45 g, 0.0496 mol) in DMSO (50 mL) was added NaOMe (25 wt% in MeOH; 11.3 mL, 0.0496 mol). The mixture was heated at 80 °C for 1.5 h and the MeOH was removed under reduced pressure. H_2O (150 mL) was added and the mixture was stirred for 30 min. The precipitate was collected by filtration and recrystallized from toluene to give 5.04 g (87%) of 5-chloro-*N*-hydroxy-2-naphthaleneethanimidamide (**80**) as a white solid: mp 133–134 °C; ^1H NMR (DMSO-d_6) δ 3.47 (s, 2 H), 5.50 (br s, 2 H), 7.47 (m, 1 H), 7.62 (m, 2 H), 7.86

(d, J = 7.1 Hz, 1 H), 7.87 (s, 1 H), 8.09 (d, J = 8.7 Hz, 1 H), 8.95 (s, 1 H); IR (KBr, cm^{-1}) 3490, 3380 (NH, OH), 1660 (C=N); MS m/e 234 (M^+). Anal. ($C_{12}H_{11}ClN_2O$) C, H, N.

To a cooled (0 °C) stirred suspension of **80** (4.8 g, 0.0205 mol) in CH_2Cl_2 (75 mL) was added pyridine (3.2 g, 0.0409 mol) all at once. A solution of thionyl chloride (2.7 g, 0.0225 mol) in CH_2Cl_2 (10 mL) was added over 5 min. After 25 min, H_2O (150 mL) was added and the precipitate was collected by filtration. Recrystallization from *i*-PrOH (35 mL) gave 3.5 g (61%) of **45** as an off-white solid: mp 169–170 °C; ^1H NMR (DMSO-d_6) δ 4.16 (s, 2 H), 7.52 (m, 1 H) 7.61 (dd, J = 8.7 Hz, 1.7 Hz, 1 H), 7.69 (dd, J = 7.5 Hz, 1.0 Hz, 1 H), 7.90 (d, J = 8.3 Hz, 1 H), 7.94 (s, 1 H), 8.16 (d, J = 8.7 Hz, 1 H), 11.52 (s, 1 H); IR (KBr, cm^{-1}) 3400 (NH); MS m/e 280 (M^+). Anal. ($C_{12}H_9ClN_2O_2S$) C, H, N.

Method B. 5-Chloro-2-naphthaleneacetonitrile (10a). To a cooled (0 °C) stirred solution of methyl 5-chloro-2-naphthoate (26.7 g, 0.121 mol) in THF (100 mL) was added 1 M DIBAL in THF (266 mL, 0.266 mol) over 1.5 h. The cooling bath was removed and stirring was continued for 18 h. The mixture was recooled to 0 °C and 1 N NaOH (275 mL) was added. Ether (200 mL) and H_2O (100 mL) were added, and the mixture was stirred at room temperature for 1 h. The layers were separated, and the aqueous phase was extracted with ether. The combined extracts were dried and concentrated to give 23.2 g (99%) of 5-chloro-2-naphthalenemethanol (**81**) as a white solid. This material was sufficiently pure for the next reaction. An analytical sample was recrystallized from toluene/hexane: mp 85–87 °C; ^1H NMR (DMSO-d_6) δ 4.70 (d, J = 5.7 Hz, 2 H), 5.42 (t, J = 5.7 Hz, 1 H), 7.48 (m, 1 H), 7.63 (m, 2 H), 7.91 (d, J = 7.8 Hz, 1 H), 7.92 (s, 1 H), 8.12 (d, J = 8.6 Hz, 1 H); IR (KBr, cm^{-1}) 3300 (OH); MS m/e 192 (M^+ – OH). Anal. ($C_{11}H_9ClO$) C, H.

To a stirred solution of **81** (17.0 g, 0.0882 mol) in dioxane (100 mL) was added $ZnCl_2$ (360 mg, 2.65 mmol) and thionyl chloride (21.0 g, 0.176 mol). After 40 min, the mixture was concentrated, taken up in ether, and washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried and concentrated to give 18.2 g (98%) of **7a** as a white solid. An analytical sample was recrystallized from hexane: mp 86–88 °C; ^1H NMR ($CDCl_3$) δ 4.76 (s, 2 H), 7.40 (m, 1 H), 7.57 (d, J = 7.4 Hz, 1 H), 7.61 (d, J = 8.8 Hz, 1 H), 7.75 (d, J = 8.2 Hz, 1 H), 7.84 (s, 1 H), 8.27 (d, J = 8.8 Hz, 1 H); MS m/e 210 (M^+). Anal. ($C_{11}H_8Cl_2$) C, H.

A mixture of **7a** (24.5 g, 0.116 mol), sodium cyanide (6.8 g, 0.139 mol), H_2O (25 mL), and acetonitrile (225 mL) was heated under reflux for 19 h. The mixture was concentrated and suspended in H_2O. The white solid was collected by filtration to give 22.4 g (96%) of **10a**. An analytical sample was recrystallized from toluene/hexane: mp 110–111 °C; ^1H NMR (DMSO-d_6) δ 4.27 (s, 2 H), 7.54 (m, 1 H), 7.64 (dd, J = 8.7 Hz, 1.9 Hz, 1 H), 7.71 (dd, J = 7.4 Hz, 0.8 Hz, 1 H), 7.97 (d, J = 8.2 Hz, 1 H), 7.99 (s, 1 H), 8.20 (d, J = 8.7 Hz, 1 H); IR (KBr, cm^{-1}) 2240 (CN); MS m/e 201 (M^+). Anal. ($C_{12}H_8ClN$) C, H, N.

Method C. 8-Bromo-2-naphthaleneacetonitrile (10b). To boiling CCl_4 (250 mL) was added *N*-bromosuccinimide (20.4 g, 0.114 mol) and AIBN (1.4 g, 0.009 mol). After 1 min, a solution of 1-bromo-7-methylnaphthalene (**8a**) (24.1 g, 0.109 mol) in CCl_4 (15 mL) was added all at once. The heating mantle was removed for several min and then heating was resumed for 30 min. The mixture was cooled and filtered, and the filtrate was concentrated to give 32.7 g of an off-white solid. This material was combined with 32.6 g of similarly prepared material and recrystallized from EtOAc/hexane to give 29.6 g (45%) of 8-bromo-2-(bromomethyl)naphthalene (**9a**) as an off-white solid: mp 103–105 °C; ^1H NMR (DMSO-d_6) δ 4.99 (s, 2 H), 7.48 (m, 1 H), 7.68 (dd, J = 8.7 Hz, 1.8 Hz, 1 H), 7.93 (dd, J = 7.5 Hz, 0.9 Hz, 1 H), 8.00 (d, J = 7.8 Hz, 1 H), 8.03 (d, 8.7 Hz, 1 H), 8.23 (s, 1 H).

Compound **9a** was converted to 8-bromo-2-naphthaleneacetonitrile (**10b**) by the procedure described in the third step of method **B** to give 24.1 g (99%) of product. An analytical sample was recrystallized from toluene/hexane: mp 56–57 °C; ^1H NMR (DMSO-d_6) δ 4.32 (s, 2 H), 7.46 (m, 1 H), 7.58 (dd, J = 8.4 Hz, 1.7 Hz, 1 H), 7.92 (dd, J = 7.5 Hz, 1.0 Hz, 1 H), 8.00 (d, J = 8.4 Hz, 1 H), 8.04 (d, J = 8.4 Hz, 1 H) 8.14 (s, 1 H); IR (KBr, cm^{-1}) 2250 (CN); MS m/e 245 (M^+). Anal. ($C_{11}H_8BrN$) C, H, N.

Method D. 1-Bromo-7-methylnaphthalene (8a). To a stirred solution of 2-bromophenylacetic acid (**26a**) (150 g, 0.698 mol) in CH_2Cl_2 (500 mL) was added DMF (1 mL) and thionyl chloride (102 mL, 1.395 mol). The mixture was left standing for 18 h and then concentrated. Azeotropic distillation with CCl_4 (3 × 100 mL) gave 163 g (100%) of 2-bromophenylacetyl chloride (**82**). The material was used directly in the next reaction.

To a cooled (–20 °C) mechanically stirred suspension of $AlCl_3$ (186 g, 1.395 mol) in CH_2Cl_2 (1 L) was added a solution of **82** (163 g, 0.698 mol) in CH_2Cl_2 (350 mL) over 30 min. Ethylene was bubbled into the mixture for 1 h (at –15 °C for 45 min and then at –10 °C for 15 min; total ethylene used: 69.2 g, 2.47 mol). Stirring at –10 °C was continued for 15 min and the mixture was poured onto ice (1.2 kg). The layers were separated, and the organic phase was washed with H_2O, saturated aqueous $NaHCO_3$, and brine, dried, and concentrated. The resultant yellow solid was taken up in acetonitrile (1 L), washed with pentane to remove polyethylene, and concentrated to give 146.2 g (93%) of 8-bromo-2-tetralone (**27a**) as a yellow solid. An analytical sample was recrystallized from ether/hexane: mp 75–77 °C; ^1H NMR (DMSO-d_6) δ 2.48 (t, J = 6.6 Hz, 2 H), 3.06 (t, J = 6.6 Hz, 2 H), 3.60 (s, 2 H), 7.15 (dd, J = 7.6 Hz, 7.6 Hz, 1 H), 7.29 (d, J = 7.6 Hz, 1 H), 7.50 (d, J = 7.6 Hz, 1 H); IR (KBr, cm^{-1}) 1710 (C=O); MS m/e 224 (M^+). Anal. ($C_{10}H_9BrO$) C, H.

To a cooled (–39 °C) stirred solution of $TiCl_4$ (109.9 g, 0.580 mol) in CH_2Cl_2 (580 mL) was added 3.0 M CH_3MgCl in THF (193 mL, 0.580 mol) over 35 min. To the resultant mixture was added a solution of **27a** (108.7 g, 0.483 mol) in CH_2Cl_2 (150 mL) over 30 min. The mixture was then warmed to 0 °C. After 2 h, the mixture was poured onto ice (1 kg). The layers were separated and the organic phase was washed with 2 N HCl and brine, dried, and concentrated to give 117.0 g (100%) of 8-bromo-2-hydroxy-2-methyl-1,2,3,4-tetrahydronaphthalene (**28a**) as a brown solid. This material was used directly in the next reaction without further purification. An analytical sample was recrystallized from hexane: mp 73–74 °C; ^1H NMR (DMSO-d_6) δ 1.24 (s, 3 H), 1.58 (m, 1 H), 1.70 (m, 1 H), 2.57 (d, J = 17.0 Hz, 1 H), 2.64 (m, 1 H), 2.70 (d, J = 17.0 Hz, 1 H), 2.95 (m, 1 H), 4.48 (s, 1 H), 7.03 (dd, J = 7.6 Hz, 7.6 Hz, 1 H), 7.11 (d, J = 7.6 Hz, 1 H), 7.39 (d, J = 7.6 Hz, 1 H); IR (KBr, cm^{-1}) 3350 (OH); MS m/e 240 (M^+). Anal. ($C_{11}H_{13}BrO$) C, H.

A mixture of triphenylmethanol (138.2 g, 0.531 mol), **28a** (116.4 g, 0.483 mol), and trifluoroacetic acid (338 mL) was stirred at room temperature for 2 days. The mixture was extracted with hexane, and the combined extracts were washed with H_2O, saturated aqueous $NaHCO_3$, and brine. The hexane solution was dried, concentrated to about 200 mL, and left standing until the triphenylmethane crystallized. The mixture was filtered and the filtrate was concentrated to give a brown oil. Purification by flash chromatography (hexane) gave 72.2 g (70%) of **8a** as a colorless oil. An analytical sample was prepared by Kugelrohr distillation: ^1H NMR (DMSO-d_6) δ 2.53 (s, 3 H), 7.36 (m, 1 H), 7.46 (dd, J = 8.6 Hz, 1.0 Hz, 1 H), 7.83 (dd, J = 7.4 Hz, 1.0 Hz, 1 H), 7.91 (m, 3 H); MS m/e 220 (M^+). Anal. ($C_{11}H_9Br$) C, H.

1-Cyano-7-methylnaphthalene (8e). A mixture of **8a** (25.9 g, 0.117 mol), CuCN (18.3 g, 0.204 mol), and *N*-methylpyrrolidinone (120 mL) was heated under reflux for 3.5 h. The mixture was cooled and a 2:3 mixture of 30% NH_4OH/NH_4Cl (300 mL) was added. The mixture was stirred for 3 h and extracted with ether. The combined extracts were washed with H_2O and brine, dried, and concentrated to give 19.4 g (98%) of **8e** as a brown oil: ^1H NMR (DMSO-d_6) δ 2.54 (s, 3 H), 7.57 (m, 2 H), 7.85 (s, 1 H), 8.00 (d, J = 8.5 Hz, 1 H), 8.09 (dd, J = 1.2 Hz, 7.2 Hz, 1 H), 8.23 (d, J = 8.2 Hz, 1 H).

1-(Methylthio)-7-methylnaphthalene (8f). A mixture of **8a** (7.50 g, 0.034 mol), $NaSCH_3$ (2.61 g, 0.037 mol), Cu_2O (2.67 g, 0.019 mol), and *N*-methylpyrrolidinone (35 mL) was heated at 180–190 °C for 17 h. The mixture was cooled, diluted with ether (150 mL) and H_2O (150 mL), and filtered through Celite. The layers were separated, and the organic phase was washed with H_2O and brine, dried, and concentrated to give 6.30 g (98%) of **8f** as a brown oil: ^1H NMR (DMSO-d_6) δ 2.54 (s, 3 H), 2.60 (s, 3 H), 7.44 (m, 3 H), 7.71 (dd, J = 7.8 Hz, 0.9 Hz, 1 H), 7.86 (d, J = 8.3 Hz, 1 H), 7.94 (d, J = 0.9 Hz, 1 H).

1-Bromo-6-fluoro-2-methylnaphthalene (8g). To a warmed (50 °C) solution of **8d** (5.20 g, 0.032 mol) in HOAc (25 mL) was added a solution of Br_2 (5.20 g, 0.032 mol) in HOAc (10 mL). Heating was continued for 3 h. The mixture was cooled and diluted with H_2O (200 mL), and the precipitate was collected by filtration. The crude product (5.7 g) was combined with 2.0 g of similarly prepared material and recrystallized from hexane to

2.8 g (28%) of **8g** as a white solid: mp 65–66 °C; ^{1}H NMR (DMSO-d_6) δ 2.55 (s, 3 H), 7.53 (d, J = 8.4 Hz, 1 H), 7.54 (m, 1 H), 7.77 (dd, J = 9.9 Hz, 2.7 Hz, 1 H), 7.86 (d, J = 8.4 Hz, 1 H), 8.22 (dd, J = 9.4 Hz, 5.5 Hz, 1 H).

1-Chloro-6-fluoro-2-methylnaphthalene (8h). To a stirred solution of **8d** (10.0 g, 0.062 mol) in CH_2Cl_2 (30 mL) was added a solution of sulfuryl chloride (5.3 mL, 0.066 mol) in CH_2Cl_2 (5 mL) over 15 min. The resultant solution was stirred at room temperature for 18 h. CH_2Cl_2 (100 mL) was added and the mixture was washed with H_2O, saturated aqueous $NaHCO_3$, and brine, dried, and concentrated to give 12.0 g (99%) of **8h** as an oil: ^{1}H NMR (DMSO-d_6) δ 2.55 (s, 3 H), 7.36 (m, 1 H), 7.56 (d, J = 8.4 Hz, 1 H), 7.81 (dd, J = 10.2 Hz, 2.4 Hz, 1 H), 7.86 (d, J = 8.4 Hz, 1 H), 8.25 (dd, J = 9.3 Hz, 5.7 Hz, 1 H).

2-Naphthalenebutanenitrile (12). To a cooled (0 °C) stirred solution of 2-naphthaleneethanol (11) (8.60 g, 0.050 mol) in CH_2Cl_2 (400 mL) was added Dess–Martin periodinane[30] (21.2 g, 0.050 mol) in one portion. After 10 min, the mixture was warmed to room temperature and stirring was continued for 45 min. The reaction mixture was diluted with CH_2Cl_2 (400 mL) and poured into saturated aqueous $NaHCO_3$ (1000 mL) containing $Na_2S_2O_3$ (55 g). The mixture was shaken for 5 min, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (800 mL), and the combined organic phases were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated to give 8.50 g (100%) of 2-naphthalenylacetaldehyde (**83**) as a yellow oil. Due to the instability of the aldehyde, this material was used without purification in the next reaction. ^{1}H NMR ($CDCl_3$) δ 3.84 (d, J = 2.0 Hz, 2 H), 7.33 (d, J = 8.0 Hz, 1 H), 7.50 (m, 2 H), 7.70 (s, 1 H), 7.84 (m, 3 H), 9.85 (t, J = 2.0 Hz, 1 H).

To a cooled (0 °C) stirred suspension of NaH (60% dispersion; 3.00 g, 0.075 mmol) in THF was added a solution of diethyl (cyanomethyl)phosphonate (9.74 g, 0.055 mol) in THF (75 mL) dropwise over 40 min. After an additional 10 min, a solution of **83** (8.50 g, 0.050 mol) in THF (75 mL) was added dropwise over 70 min. The resultant solution was stirred for 30 min and H_2O (100 mL) was added. The mixture was concentrated, and the residue was diluted with H_2O (400 mL) and extracted with ether (2 × 400 mL). The combined extracts were dried and concentrated to give a brown oil. Purification by preparative HPLC (hexane/CH_2Cl_2 gradient) gave 1.36 g (14%) of 4-(2-naphthalenyl)-2-butenenitrile (**84**) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 3.33 (dd, 2 H), 6.19 (dt, 1 H), 6.91 (dt, 1 H), 7.08 (m, 2 H), 7.57 (dd, 1 H), 7.77 (s, 1 H), 7.83 (m, 3 H).

A mixture of **84** (1.35 g, 7.00 mmol) and 5% Pd/C (135 mG) in EtOH (70 mL) was shaken under 50 psig of H_2 for 45 min. The catalyst was removed by filtration and the filtrate was concentrated to give 1.34 g (99%) of **12** as a white solid: ^{1}H NMR ($CDCl_3$) δ 2.07 (m, 2 H), 2.32 (t, J = 7.0 Hz, 2 H), 2.95 (t, J = 7.0 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 1 H), 7.45 (m, 2 H), 7.65 (s, 1 H), 7.80 (m, 3 H).

2-Naphthalenepentanenitrile (14). To a cooled (0 °C) stirred solution of 2-naphthalenepropanenitrile (**13**)[6] (2.72 g, 15.0 mmol) in ether (150 mL) was added DIBAL-H (1.0 M in toluene; 18.0 mL, 18.0 mmol) dropwise over 15 min. The resultant solution was stirred at 0 °C for 30 min and poured into 5% H_2SO_4 (200 mL). The layers were separated, and the aqueous phase was extracted with ether. The combined organic layers were dried and concentrated to give 2.00 g (72%) of 2-naphthalenepropionaldehyde (**85**) as an oil: ^{1}H NMR ($CDCl_3$) δ 2.86 (t, J = 7.0 Hz, 2 H), 3.16 (t, J = 7.0 Hz, 2 H), 7.34 (d, J = 8.0 Hz, 1 H), 7.46 (m, 2 H), 7.64 (s, 1 H), 7.82 (m, 3 H), 9.86 (s, 1 H).

Compound **85** (2.00 g, 10.8 mmol) was converted to 5-(2-naphthalenyl)-2-pentenenitrile (**86**) according to the procedure described in the second step for compound **12** above. Purification by flash chromatography (25% CH_2Cl_2/hexane) gave 1.97 g (88%) of **86** as a colorless oil (1:1 *cis–trans*): ^{1}H NMR ($CDCl_3$) δ 2.64 (m, 0.5 H), 2.92 (m, 3.5 H), 5.32 (m, 1 H), 6.50 (dt, 0.5 H), 6.76 (dt, 0.5 H), 7.29 (dd, J = 8.2 Hz, 0.5 H), 7.35 (dd, J = 8.2 Hz, 0.5 H), 7.47 (m, 3 H), 7.60 (s, 0.5 H), 7.64 (s, 0.5 H), 7.81 (m, 3 H).

A mixture of **86** (1.97 g, 9.50 mmol) and 5% Pd/C (197 mg) in EtOH (75 mL) was shaken under 50 psig of H_2 for 25 min. The catalyst was removed by filtration and the filtrate was concentrated to give 1.82 g (92%) of **14** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.74 (m, 2 H), 1.90 (m, 2 H), 2.37 (t, J = 7.0 Hz, 2 H), 2.84 (t, J = 7.0 Hz, 2 H), 7.34 (dd, 1 H), 7.47 (m, 2 H), 7.62 (s, 1 H), 7.80 (m, 3 H).

2-(2-Naphthalenyl)propanenitrile (16) and 2-Methyl-2-(2-naphthalenyl)propanenitrile (17). According to a procedure of Hauser,[7a] to a refluxing suspension of NaH (60% dispersion; 3.0 g, 0.075 mol) in DME (150 mL) was added a solution of 2-naphthaleneacetonitrile (**15**) (12.5 g, 0.075 mol) and iodomethane (10.7 g, 0.075 mol) in DME (75 mL) dropwise over 1 h. The resultant solution was heated under reflux for 3 h, cooled, and concentrated. The residue was partitioned between H_2O (150 mL) and ether (200 mL), the layers were separated, and the aqueous phase was extracted with ether. The combined organic layers were dried and concentrated to give a dark oil. Purification by preparative HPLC (EtOAc/hexane gradient) gave 5.68 g (42%) of **16** as a white solid and 2.28 g (20%) of **17** as a yellow oil. Compound **16**: ^{1}H NMR ($CDCl_3$) δ 1.75 (d, J = 7.0 Hz, 3 H), 4.03 (q, J = 7.0 Hz,1 H), 7.49 (m, 3 H), 7.87 (m, 4 H). Compound **17**: ^{1}H NMR ($CDCl_3$) δ 1.80 (s, 6 H), 7.55 (m, 3 H), 7.85 (m, 3 H), 7.95 (s, 1 H).

2-(2-Naphthalenyl)-3-phenylpropanenitrile (18). According to the procedure described above for **16**, alkylation with benzyl bromide gave 7.7 g (40%) of **18** as a white solid: ^{1}H NMR ($CDCl_3$) δ 3.25 (m, 2 H), 4.18 (t, J = 7.0 Hz, 1 H), 7.21 (m, 6 H), 7.55 (m, 2 H), 7.75 (s, 1 H), 7.82 (m, 3 H).

2-(Naphthalenyloxy)acetonitrile (20a). To a refluxing suspension of 2-naphthol (**19a**) (5.04 g, 0.035 mol) and K_2CO_3 (5.38 g, 0.039 mol) in acetone (250 mL) was added a solution of chloroacetonitrile (2.94 g, 0.039 mol) in acetone (50 mL) dropwise over 30 min. The resultant mixture was heated under reflux for 18 h, cooled, and concentrated. The residue was partitioned between EtOAc (200 mL) and H_2O (200 mL), the layers were separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were dried (Na_2SO_4) and concentrated to give a brown solid. Purification by flash chromatography (40% CH_2Cl_2/hexane) gave 5.44 g (85%) of **20a** as a white solid: ^{1}H NMR ($CDCl_3$) δ 4.68 (s, 2 H), 7.08 (m, 2 H), 7.35 (m, 2 H), 7.68 (m, 3 H).

2-(Naphthalenylthio)acetonitrile (20b). According to the procedure described for **20a** above, 2-naphthalenethiol (**19b**) was alkylated to give 5.86 g (65%) of **20b** as an off-white solid: ^{1}H NMR ($CDCl_3$) δ 3.61 (s, 2 H), 7.54 (m, 3 H), 7.81 (m, 3 H), 8.05 (s, 1 H).

3-(2-Naphthalenyl)butanenitrile (22). According to steps 2 and 3 of the procedure for **12** described above, 2-acetylnaphthalene (**21**) (6.80 g, 0.040 mol) was converted to 6.60 g (85%) of **22** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.59 (d, 3 H), 2.70 (m, 2 H), 3.35 (m, 1 H), 7.38 (d, 1 H), 7.50 (m, 2 H), 7.70 (s, 1 H), 7.85 (m, 3 H).

3-Methoxy-3-(2-naphthalenyl)propanenitrile (24). To a cooled (−78 °C) stirred solution of acetonitrile (2.46 g, 0.060 mol) in THF (300 mL) was added *n*-BuLi (1.6 M in hexane; 37.5 mL, 0.060 mol) dropwise over 30 min. After an additional 15 min, a solution of 2-naphthaldehyde (**23**) (6.24 g, 0.040 mol) in THF (50 mL) was added dropwise over 45 min. The mixture was stirred at −78 °C for 20 min and saturated aqueous NH_4Cl (60 mL) was added. The mixture was warmed to room temperature and concentrated. The residue was partitioned between CH_2Cl_2 (250 mL) and H_2O (200 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, dried (Na_2SO_4), and concentrated to give 7.88 g (100%) of 3-hydroxy-3-(2-naphthalenyl)propanenitrile (**87**) as an off-white solid: ^{1}H NMR ($CDCl_3$) δ 2.75 (d, J = 7.0 Hz, 2 H), 3.05 (d, J = 2.0 Hz, 1 H), 5.08 (m, 1 H), 7.45 (m, 3 H), 7.80 (m, 4 H).

To a cooled (0 °C) stirred suspension of NaH (60% dispersion; 1.50 g, 0.038 mol) in THF (200 mL) was added a solution of **87** (4.92 g, 0.025 mol) in THF (50 mL) dropwise over 20 min. The resultant solution was stirred at 0 °C for 5 min and dimethyl sulfate (4.72 g, 0.038 mol) was added in one portion. After 20 min, the mixture was warmed to room temperature and stirred for 1.5 h, H_2O (50 mL) was added, and the mixture was concentrated. The residue was partitioned between CH_2Cl_2 (250 mL) and H_2O (200 mL), the layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated to give a yellow oil. Purification by preparative HPLC (EtOAc/hexane gradient) gave 4.58 g (87%) of **24** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.80 (m, 2 H), 3.32 (s, 3 H), 4.62 (t, J = 7.0 Hz, 1 H), 7.51 (m, 3 H), 7.88 (m, 4 H).

N-Hydroxy-3-(2-naphthalenyl)propenimidamide (25). 3-Methoxy-3-(2-naphthalenyl)propanenitrile (**24**) (4.15 g, 0.020 mol) was converted to 3.60 g (75%) of *N*-hydroxy-3-methoxy-3-(2-naphthalenyl)propanimidamide (**88**) (yellow oil) according to part 1 of method A: ^{1}H NMR ($CDCl_3$) δ 2.50 (dd, 1 H), 2.71 (dd, 1 H), 3.28 (s, 3 H), 4.60 (dd, 1 H), 5.13 (br s, 2 H), 7.47 (m, 3 H), 7.77 (s, 1 H), 7.85 (m, 3 H), 9.13 (br s, 1 H).

A solution of **88** (1.95 g, 8.00 mmol) in trifluoroacetic acid (80 mL) was heated at 40 °C for 6 h. The solution was concentrated and the residue was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were dried and concentrated to give a yellow solid. Trituration with CH_2Cl_2 afforded 1.15 g (68%) of **25** as a white solid: ^{1}H NMR (DMSO-d_6) δ 5.62 (br s, 2 H), 6.58 (d, 1 H), 7.23 (d, J = 16.0 Hz, 1 H), 7.48 (m, 2 H), 7.70 (d, 1 H), 7.90 (m, 4 H), 9.75 (s, 1 H).

Methyl 5-Chloro-2-naphthoate (6b). According to a procedure of Bacon and Hill,[13] a mixture of methyl 5-bromo-2-naphthoate (**6a**)[11] (35.0 g, 0.132 mol), copper(I) chloride (43.1 g, 0.436 mol), and dry DMSO (400 mL) was heated at 105–110 °C for 6 h. The mixture was cooled, diluted with H_2O (250 mL) and ether (250 mL), and filtered through Celite. The layers were separated, and the organic phase was washed with H_2O/brine (1:1), 1 N HCl, and saturated aqueous $NaHCO_3$, dried, and concentrated to give 28.7 g (99%) of **6b**[12] as a white solid: mp 70–75 °C; ^{1}H NMR (DMSO-d_6) δ 3.93 (s, 3 H), 7.60 (m, 1 H), 7.84 (dd, J = 7.5 Hz, 0.9 Hz, 1 H), 8.10 (dd, J = 8.7 Hz, 1.8 Hz, 1 H), 8.15 (d, J = 8.4 Hz, 1 H), 8.24 (d, J = 9.0 Hz, 1 H), 8.69 (d, J = 1.8 Hz, 1 H).

5-Methoxy-2-naphthoic Acid (6c). A mixture of **6a** (14.2 g, 0.054 mol), $NaOCH_3$ (25 wt% in MeOH; 73.3 g, 0.321 mol), CuI (5.4 g, 0.027 mol), pyridine (200 mL), and MeOH (200 mL) was heated under reflux for 36 h. The mixture was cooled and concentrated, and H_2O was added. The mixture was acidified with 2 N HCl and extracted with EtOAc. The combined extracts were dried and concentrated to give a brown solid. This material was taken up in 2.5 N NaOH (50 mL) and stirred for 3 h. The mixture was acidified and the white precipitate was collected by filtration to give 10.8 g (100%) of **6c** as a white solid: ^{1}H NMR (DMSO-d_6) δ 3.97 (s, 3 H), 7.09 (d, J = 7.8 Hz, 1 H), 7.50 (m, 1 H), 7.64 (d, J = 8.3 Hz, 1 H), 7.95 (d, J = 7.5 Hz, 1 H), 8.21 (d, J = 8.3 Hz, 1 H), 8.52 (s, 1 H).

5-(Methylthio)-2-naphthalenemethanol (6d). A stirred mixture of 5-bromo-2-naphthalenemethanol (**89**) (7.20 g, 0.030 mol), $NaSCH_3$ (2.77 g, 0.039 mol), Cu_2O (2.61 g, 0.018 mol), and *N*-methylpyrrolidinone (50 mL) was heated at 180–190 °C for 18 h. The mixture was cooled, diluted with water, and filtered through Celite. The filtrate was extracted with ether, and the combined extracts were washed with brine, dried, and concentrated to give an orange solid, which was a 70:30 mixture of product and starting material (^{1}H NMR). The mixture was resubjected to the above reaction conditions to give 2.10 g (34%) of **6d** as an orange solid: ^{1}H NMR (DMSO-d_6) δ 2.58 (s, 3 H), 4.68 (d, J = 5.8 Hz, 2 H), 5.36 (t, J = 5.8 Hz, 1 H), 7.37 (d, J = 7.3 Hz, 1 H), 7.49 (m, 2 H), 7.71 (d, J = 7.9 Hz, 1 H), 8.08 (d, J = 9.0 Hz, 1 H).

Methyl 5-Vinyl-2-naphthoate (6e). According to a procedure of Stille,[12] a stirred mixture of **6a** (1.00 g, 3.77 mmol), vinyltributyltin (1.32 g, 4.15 mmol), $(Ph_3P)_4Pd$ (87 mg, 0.075 mmol), and toluene (15 mL) was heated under reflux for 4 h. The mixture was cooled, pyridine (1.6 mL) and 1.4 N hydrogen fluoride–pyridine in THF (3.3 mL) were added, and the mixture was stirred at room temperature for 18 h. Ether was added and the mixture was washed with H_2O, 10% HCl, H_2O, and saturated aqueous $NaHCO_3$, dried, and concentrated. Purification by flash chromatography (10% EtOAc/hexane) gave 0.59 g (73%) of **6e** as a colorless oil: ^{1}H NMR (DMSO-d_6) δ 3.91 (s, 3 H), 5.54 (dd, J = 11.1 Hz, 1.5 Hz, 1 H), 5.90 (dd, J = 17.2 Hz, 1.5 Hz, 1 H), 7.61 (m, 2 H), 7.85 (d, J = 7.5 Hz, 1 H), 8.01 (dd, J = 9.0 Hz, 2.0 Hz, 1 H), 8.10 (d, J = 9.0 Hz, 1 H), 8.31 (d, J = 9.0 Hz, 1 H), 8.64 (d, J = 2.0 Hz, 1 H).

5-Ethynyl-2-naphthoic Acid (6f). According to a procedure of Takahashi et al.,[13] to a solution of **6a** (11.25 g, 0.0424 mol) and (trimethylsilyl)acetylene (5.00 g, 0.0509 mol) in diethylamine (170 mL) were added $(Ph_3P)_2PdCl_2$ (595 mg, 0.848 mmol) and CuI (81 mg, 0.424 mmol). The mixture was stirred at room temperature for 18 h and concentrated, and the crude product was purified by flash chromatography (5% EtOAc/hexane) to give 8.80 g (73%) of methyl 5-[(trimethylsilyl)ethynyl]-2-naphthoate (**90**) as a yellow oil: ^{1}H NMR (DMSO-d_6) δ 0.31 (s, 9 H), 3.92 (s, 3 H), 7.59 (dd, J = 8.1 Hz, 7.2 Hz, 1 H), 7.84 (dd, J = 7.2 Hz, 0.9 Hz, 1 H), 8.10 (dd, J = 8.7 Hz, 1.8 Hz, 1 H), 8.19 (d, J = 8.1 Hz, 1 H), 8.67 (d, J = 1.8 Hz, 1 H).

To a solution of **90** (8.8 g, 0.031 mol) in MeOH (65 mL) was added 1 N KOH (68 mL, 0.068 mol). After the MeOH was removed under reduced pressure and the aqueous phase was extracted with ether (discarded). Acidification with 2 N HCl yielded a white precipitate. Trituration with hot acetone gave 4.8 g (79%) of **6f** as a white solid: mp 247–248 °C; ^{1}H NMR (DMSO-d_6) δ 4.69 (s, 1 H), 7.60 (dd, J = 8.1 Hz, 7.5 Hz, 1 H), 7.87 (dd, J = 7.5 Hz, 0.9 Hz, 1 H), 8.11 (dd, J = 9.8 Hz, 1.8 Hz, 1 H), 8.19 (d, J = 8.1 Hz,1 H), 8.30 (d, J = 9.0 Hz, 1 H), 8.66 (d, J = 1.8 Hz, 1 H); MS *m/e* 196 (M^+).

Ethyl 5-(Trifluoromethyl)-2-naphthoate (6g). According to a procedure of Matsui et al.,[17] a mixture of ethyl 5-bromo-2-naphthoate (5.00 g, 0.018 mol), CuI (6.84 g, 0.036 mol), sodium trifluoroacetate (9.80 g, 0.072 mol), and *N*-methylpyrrolidinone (55 mL) was heated under reflux for 27 h. The mixture was cooled, poured into H_2O/brine (1:1), filtered through Celite, and extracted with EtOAc. The combined extracts were dried and concentrated. Purification by preparative HPLC (EtOAc/hexane gradient) gave 2.3 g (48%) of **6g** as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.43 (t, 3 H), 4.48 (q, 2 H), 7.58 (m, 1 H), 7.80–8.30 (m, 4 H), 8.7 (s, 1 H).

5-Methyl-2-naphthoic Acid (6h). To a cooled (−78 °C) stirred solution of 5-bromo-2-naphthoic acid (20.0 g, 0.080 mol) in THF (400 mL) was added MeLi (1.3 M in THF; 123 mL, 0.159 mol) dropwise over 1 h. The resultant solution was stirred for 40 min and CH_3I (22.6 g, 0.159 mol) was added in one portion. After 2 h, the mixture was warmed to room temperature and stirred for 18 h. H_2O was added and the mixture was extracted with ether. The combined extracts were washed with H_2O and extracted with 10% NaOH. The combined aqueous layers were acidified to pH 1 with concentrated HCl, and the precipitate was collected by filtration. The filtrate was extracted with ether, and the combined extracts were dried, concentrated, and combined with the precipitate to give 12.8 g (87%) of **6h** as a white solid: ^{1}H NMR (DMSO-d_6) δ 2.64 (s, 3 H), 7.50 (s, 1 H), 8.00 (m, 4 H), 8.63 (d, J = 8.0 Hz, 1 H).

8-Bromo-5-methoxy-2-naphthoic Acid (6i). To a cooled (−78 °C), stirred suspension of **6c** (5.00 g, 0.025 mol) in CH_2Cl_2 (100 mL) was added a solution of Br_2 (3.95 g, 0.026 mol) in CH_2Cl_2 (40 mL) dropwise over 30 min. The mixture was warmed to room temperature, stirred for 2.5 h, and concentrated. The residue was taken up in H_2O and extracted with EtOAc. The combined extracts were washed with brine, dried, and concentrated to give 6.31 g (91%) of **6i** as a yellow solid: ^{1}H NMR (DMSO-d_6) δ 3.99 (s, 3 H), 7.05 (d, J = 8.4 Hz, 1 H), 7.86 (d, J = 8.4 Hz, 1 H), 8.03 (d, J = 8.7 Hz, 1 H), 8.26 (d, J = 8.7 Hz, 1 H), 8.71 (s, 1 H).

8-Bromo-7-methyl-2-naphthoic Acid (6y). According to the procedure for **8g** above, 7-methyl-2-naphthoic acid (**6u**) was brominated to give **6y** as a white solid: mp 274–276 °C; ^{1}H NMR (DMSO-d_6) δ 2.57 (s, 3 H), 7.59 (d, J = 8.4 Hz, 1 H), 7.92 (d, J = 8.4 Hz, 1 H), 7.98 (m, 2 H), 8.82 (s, 1 H). Anal. ($C_{12}H_9BrO_2$) C, H.

3-Methyl-2-(trifluoromethyl)naphthalene (8k). According to the procedure for **6h** above, 3-methyl-2-bromonaphthalene (2.20 g, 0.010 mol) was converted to 1.60 g (62%) of **8k** as a white solid: ^{1}H NMR ($CDCl_3$) δ 2.62 (s, 3 H), 7.54 (m, 2 H), 7.80 (m, 3 H), 8.15 (s, 1 H).

1-Bromo-2,3-dimethylnaphthalene (8l). To a heated (50 °C) mixture of 2,3-dimethylnaphthalene (15.7 g, 0.10 mol), catalytic iodine, and acetic acid (350 mL) was added bromine (19.2 g, 0.12 mol) dropwise. Heating was continued for 1.5 h, and the mixture was cooled and diluted with H_2O (350 mL). The precipitate was collected by filtration, taken up in ether, washed with water, dried, and concentrated. The 1,4-dibromo-2,3-dimethylnaphthalene was removed by crystallization from hexane. The filtrate was concentrated to give 18.2 g (77%) of **8l** as a yellow solid: ^{1}H NMR (DMSO-d_6) δ 2.47 (s, 3 H), 2.54 (s, 3 H), 7.50 (dd, J = 7.3 Hz, 8.0 Hz, 1 H), 7.56 (dd, J = 7.3 Hz, 8.0 Hz, 1 H), 7.73 (s, 1 H), 7.82 (d, J = 8.0 Hz, 1 H), 8.11 (d, J = 8.0 Hz, 1 H); MS *m/e* 234 (M^+).

5-Ethyl-2-naphthaleneacetonitrile (10d). A mixture of 5-ethynyl-2-naphthaleneacetonitrile (**10c**) (1.10 g, 5.75 mmol), 5% Pd/$BaSO_4$ (0.10 g), quinoline (0.1 mL), and acetone (8 mL) was stirred under H_2 (1 atm) for 21 h. The mixture was diluted with ether and the catalyst was removed by filtration. The filtrate was washed with 1 N HCl and saturated aqueous $NaHCO_3$, dried, and concentrated. Purification by flash chromatography (10% EtOAc/hexane) gave 1.00 g (76%) of **10d** as a yellow oil (none of the desired 5-vinyl-2-naphthaleneacetonitrile was obtained): ^1H NMR ($CDCl_3$) δ 1.37 (t, J = 7.6 Hz, 3 H), 3.10 (q, J = 7.6 Hz, 2 H), 3.91 (s, 2 H), 7.41 (m, 3 H), 7.68 (d, J = 7.9 Hz, 1 H), 7.82 (d, J = 1.0 Hz, 1 H), 8.06 (d, J = 9.0 Hz, 1 H).

Pharmacological Procedures. The effect of drugs on plasma glucose levels of diabetic mice (male, db/db (C57BL/KsJ), Jackson Laboratories) was determined as previously described.[4]

Female obese ob/ob (C57BL/6J, Jackson Laboratories) mice of 3–5 months of age were used. Drugs were administered daily for 10 days by oral gavage to the ad libitum fed mice. Four hours after the last administration of drug or vehicle (0.2 mL of 2% Tween 80/saline, w/v) the mice were decapitated, and the blood was collected for assay of glucose and insulin.

Streptozocin-treated (100 mg/kg, ip) diabetic rats (male, Sprague-Dawley, Charles River) received daily administration of drug or vehicle for 3 weeks. Blood samples were collected from the tail tip 90 min after the last dosage and assayed for plasma glucose levels.

Nondiabetic rats (male, Sprague-Dawley, Charles River) received a single administration of drug or vehicle and blood samples were collected from the tail tip at 1, 2, and 4 h after dosing. Plasma glucose levels were determined. Alternatively, drug or vehicle was administered daily for 11 days and urine was collected for 24 h and assayed for glucose. Food and water consumption were also measured.

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References

(1) (a) Colca, J. R.; Morton, D. R. Antihyperglycaemic Thiazolidinediones: Ciglitazone and Its Analogues. In *New Antidiabetic Drugs*; Bailey, C. J., Flatt, P. R., Eds.; Smith-Gordon: London, 1990; pp 255–261. (b) Sohda, T.; Momose, Y.; Meguro, K.; Kawamatsu, Y.; Sugiyama, Y.; Ikeda, H. Studies on Antidiabetic Agents. Synthesis and Hypoglycemic Activity of 5-[4-(pyridylalkoxy)benzyl]-2,4-thiazolidinediones. *Arzneim.-Forsch.* **1990**, *40*, 37–42. (c) Larson, E. R.; Clark, D. A.; Stevenson, R. W. New Approaches to Diabetes. *Annu. Rep. Med. Chem.* **1989**, *25*, 205–213. (d) Zask, A.; Jirkovsky, I.; Nowicki, J. W.; McCaleb, M. L. Synthesis and Antihyperglycemic Activity of Novel 5-(Naphthalenylsulfonyl)-2,4-thiazolidinediones. *J. Med. Chem.* **1990**, *33*, 1418–1423. (e) Hulin, B.; Clark, D. A.; Goldstein, S. W.; McDermott, R. E.; Dambek, P. J.; Kappeler, W. H.; Lamphere, C. H.; Lewis, D. M.; Rizzi, J. P. Novel Thiazolidine-2,4-diones as Potent Euglycemic Agents. *J. Med. Chem.* **1992**, *35*, 1853–1864. (f) Sohda, T.; Mizuno, K.; Momose, Y.; Ikeda, H.; Fujita, T.; Meguro, K. Studies on Antidiabetic Agents. 11. Novel Thiazolidinedione Derivatives as Potent Hypoglycemic and Hypolipidemic Agents. *J. Med. Chem.* **1992**, *35*, 2617–2626.

(2) Kees, K. L.; Smith, T. M.; McCaleb, M. L.; Prozialeck, D. H.; Cheeseman, R. S.; Christos, T. E.; Patt, W. C.; Steiner, K. E. Perfluorocarbon-Based Antidiabetic Agents. *J. Med. Chem.* **1992**, *35*, 944–953.

(3) Dow, R. L.; Bechle, B. M.; Chou, T. T.; Clark, D. A.; Hulin, B.; Stevenson, R. W. Benzyloxazolidine-2,4-diones as Potent Hypoglycemic Agents. *J. Med. Chem.* **1991**, *34*, 1538–1544.

(4) Ellingboe, J. W.; Alessi, T. R.; Dolak, T. M.; Nguyen, T. T.; Tomer, J. D.; Guzzo, F.; Bagli, J. F.; McCaleb, M. L. Antihyperglycemic Activity of Novel Substituted 3*H*-1,2,3,5-Oxathiadiazole 2-Oxides. *J. Med. Chem.* **1992**, *35*, 1176–1183.

(5) Coleman, D. L.; Hummel, K. P. Studies with the Mutation, Diabetes, in the Mouse. *Diabetologia* **1967**, *3*, 238–248.

(6) Robertson, D. W.; Krushinski, J. H.; Beedle, E. E.; Leander, J. D.; Wong, D. T.; Rathbun, R. C. Structure-Activity Relationships of (Arylalkyl)imidazole Anticonvulsants: Comparison of the (Fluorenylalkyl)imidazoles with Nafimidone and Denzimol. *J. Med. Chem.* **1986**, *29*, 1577–1586.

(7) (a) Kenyon, W. G.; Kaiser, E. M.; Hauser, C. R. Alkylations of Phenylacetic, α-Alkylphenylacetic, and Diphenylacetic Esters by Means of Sodamide and Sodium Hydride. *J. Org. Chem.* **1965**, *30*, 2937–2942. (b) Harusawa, S.; Nakamura, S.; Yagi, S.; Kurihara, T.; Hamada, Y.; Shioiri, T. A New Synthesis of Some Non-Steroidal Anti-Inflammatory Agents Via Cyanophosphates. *Synth. Commun.* **1984**, *14*, 1365–1371. (c) Kuendig, E. P.; Desobry, V.; Simmons, D. P.; Wenger, E. Thermodynamic Control of Regioselectivity in the Addition of Carbanions to (Arene)tricarbonylchromium Complexes. *J. Am. Chem. Soc.* **1989**, *111*, 1804–1114.

(8) Miyano, S.; Abe, N. The Facile Benzylation of Aromatic Nitriles by Means of Benzyl Alcohol and Sodium. *Tetrahedron Lett.* **1966**, 1509–1511.

(9) Julia, M. Growth Factors in Plants. X. α-Amino-β-(2,4-dichlorophenoxy)propionic Acid. *Bull. Soc. Chim. Fr.* **1956**, 1363–1365.

(10) Cervena, I.; Hrubantova, M.; Bartosova, M.; Protiva, M. Neurotropic and Psychotropic Agents. CXLIX. Synthesis of Arylthioacetamidoximes as Potential Antidepressants. *Collect. Czech. Chem. Commun.* **1981**, *46*, 1188–1198.

(11) Adcock, W.; Wells, P. R. Substituent Effects in Naphthalene I. The Syntheses of 4, 5, 6, 7, and 8-Substituted 2-Naphthoic Acids. *Aust. J. Chem.* **1965**, *18*, 1351–1364.

(12) Goldstein, H.; Matthey, R. Contribution à l'étude des acides 5-bromo- et 5-chloro-2-naphthoïques. *Helv. Chim. Acta* **1938**, *21*, 62–66.

(13) Bacon, R. G. R.; Hill, H. A. O. Metal Ions and Complexes in Organic Reactions. Part I. Substitution Reactions between Aryl Halides and Cuprous Salts in Organic Solvents. *J. Chem. Soc.* **1964**, 1097–1107.

(14) Jones, E.; Moodie, I. M. In *Organic Syntheses*; Breslow, R., Ed.; John Wiley and Sons: New York, 1970; Vol. 50, p 75.

(15) McKean, D. R.; Parrinello, G.; Renaldo, A. F.; Stille, J. K. Synthesis of Functionalized Styrenes via Palladium-Catalyzed Coupling of Aryl Bromides with Vinyl Tin Reagents. *J. Org. Chem.* **1987**, *52*, 422–424.

(16) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. A Convenient Synthesis of Ethynylarenes and Diethynylarenes. *Synthesis* **1980**, 627–630.

(17) Matsui, K.; Tobita, E.; Ando, M.; Kondo, K. A Convenient Trifluoromethylation of Aromatic Halides with Sodium Trifluoroacetate. *Chem. Lett.* **1981**, 1719–1720.

(18) Rosowsky, A.; Battaglia, J.; Chen, K. K. N.; Modest, E. J. Synthesis of New Chlorine-Substituted Derivatives of 2-Tetralone. *J. Org. Chem.* **1968**, *33*, 4288–4290.

(19) Reetz, M. T.; Kyung, S. H.; Hüllman, M. $CH_3Li/TiCl_4$: A Non-Basic and Highly Selective Grignard Analogue. *Tetrahedron* **1986**, *42*, 2931–2935.

(20) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. Carbon-Carbon Bond-Forming Reactions Using Cerium Metal or Organocerium(III) Reagents. *J. Org. Chem.* **1984**, *49*, 3904–3912.

(21) Fu, H,; Harvey, R. A Convenient Dehydrogenation Reagent: Trityl Trifluoroacetate Generated *In Situ*. *Tetrahedron L.tt.* **1974**, 3217–3220.

(22) Bergmann, E.; Hirshberg, J. Remarks on the Structure of Naphthalene. *J. Chem. Soc.* **1936**, 331–336.

(23) Kenner, J.; Ritchie, W. H.; Wain, R. L. A Relationship between β-Naphthylamine and Ethyl β-Aminocrotonate. *J. Chem. Soc.* **1937**, 1526–1529.

(24) Girdler, R. B.; Gore, P. H.; Hoskins, J. A. A Re-examination of the Friedel-Crafts Acetylation of 2-Bromonaphthalene. *J. Chem. Soc. (C)* **1966**, 518–520.

(25) Bretscher, E.; Rule, H. G.; Spence, J. Optical Activity and the Polarity of Substituent Groups. Part IX. Menthyl Esters of Methoxynaphthoic and of Diphenyl-2-carboxylic Acids. *J. Chem. Soc.* **1928**, 1493–1504.

(26) Eriguchi, A.; Takegoshi, T. Studies on Hypolipidemic Agents. I. Synthesis of 1,3-Dioxolanes and 1,3-Dioxanes. *Chem. Pharm. Bull.* **1982**, *30*, 428–439.

(27) Cornejo, J. J.; Ghodsi, S.; Johnson, R. D.; Woodling, R.; Rickborn, B. Benzo[*e*]isobenzofuran. Formation and Reactions of the Parent and Alkoxy-Substituted Derivatives. *J. Org. Chem.* **1983**, *48*, 3869–3876.

(28) Jadhav, G. V.; Rao, S. N. 4-Halo-1-methoxy-2-naphthoic Acids and their Derivatives. *J. Indian Chem. Soc.* **1936**, *13*, 645–648.

(29) Newman, M. S.; Dhawan, B.; Kumar, S. Abnormal Products in the Siegrist Reaction Involving Ortho-Fluorinated Intermediates. *J. Org. Chem.* **1978**, *43*, 524–525.

(30) Dess, D. B.; Martin, J. C. A Useful 12-I-5 Triacetoxyperiodinane (the Dess-Martin Periodinane) for the Selective Oxidation of Primary or Secondary Alcohols and a Variety of Related 12-I-5 Species. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.