or without androstenedione and L-cysteine at 37 °C with the placental microsomes (1 mg of protein), 600 μM NADPH, and MeOH (50 μL) in 67 mM phosphate buffer, pH 7.5, in a total volume of 1 mL in air or N_2 atmosphere. Aliquots (50 μL), in duplicate, were removed at various time periods (0–12 min) and added to a solution of [1β-^{3}H]androstenedione (1 μM, 3.0×10^5 dpm), NADPH (180 μM) in 67 mM phosphate buffer, pH 7.5 (total volume, 0.5 mL), and the mixture was incubated at 37 °C for 20 min. ^3H_2O release was determined as described above.

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Syntheses of Tolrestat Analogues Containing Additional Substituents in the Ring and Their Evaluation as Aldose Reductase Inhibitors. Identification of Potent, Orally Active 2-Fluoro Derivatives

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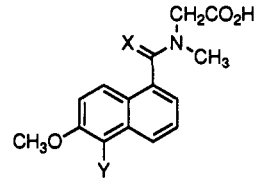
A series of aldose reductase inhibitors were prepared which were analogues of the potent, orally active inhibitor tolrestat (1). These compounds (**5**, **7**, **9**, and **10**) have an extra substituent on one of the unoccupied positions on the naphthalene ring of 1. Primary amide prodrugs of several members from the series **5** and **7**, namely **6** and **8**, respectively, were also prepared. These compounds were evaluated in two in vitro systems: an isolated enzyme preparation from bovine lens to assess their intrinsic inhibitory activity and an isolated sciatic nerve assay to determine their ability to penetrate membranes of nerve tissue. These compounds were also evaluated in vivo as inhibitors of galactitol accumulation in the lens, sciatic nerve, and diaphragm of galactose-fed rats. In general, compounds in series **5**, **7**, **9**, and **10** were potent inhibitors of bovine lens aldose reductase. 2-Halo-substituted analogues from the series **5**, **7**, and **9** exhibited high activity in the nerve of the 4-day-galactose-fed rat, and in several instances, the primary amide prodrug **8** enhanced the in vivo potency of the respective carboxylic acid **7**. Two 2-fluoro-derivatives, **8a** and **9a**, had especially high activity in vivo and were chosen for additional studies. These compounds were found to be approximately equipotent to tolrestat in the sciatic nerve of the galactose-fed rat and the STZ rat, as judged by their ED_{50}'s in these assays. Although primary amide analogue **8a** did not have intrinsic inhibitory activity toward aldose reductase, it was metabolized to an active form in vivo and also in vitro within the sciatic nerve.

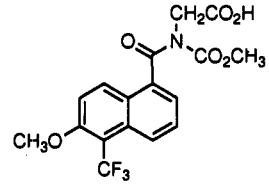
Introduction

Tolrestat[1] (1) is an orally effective aldose reductase inhibitor which is currently marketed under the tradename Alredase for the treatment of diabetic complications.[2,3] The naphthoylamide analogue of tolrestat, **2**,[3a] and the 5-bromo bioisostere, **3**,[3a] were also shown to be potent aldose reductase inhibitors, although both compounds were somewhat less active in vivo than tolrestat. In addition, the *N*-carbomethoxy derivative **4**,[4] was recently shown to have similar potency to **2**. Tolrestat and its analogues belong to the carboxylic acid class of aldose reductase inhibitors. The phthalazine acetic acids, ponalrestat[3d] and zopalrestat,[3e] are other members in this class reported to show good activity in vivo. Sorbinil[2] is the prototypical example for the other major structural class, the five-membered ring cyclic imides.

Our earlier studies demonstrated that the intrinsic and oral activities of analogues of **1** were strongly influenced by the nature and position of the substituents on the naphthalene ring. Optimal activity in vivo was associated with 6-methoxy-5-(trifluoromethyl) substitution. As one aspect of our program to identify new aldose reductase inhibitors, we further explored the scope of these substituent effects. In this regard, we synthesized derivatives of **1–4**, represented by **5**, **7**, **9**, and **10**, in which an extra substituent was added to one of the unoccupied positions on the naphthalene ring.

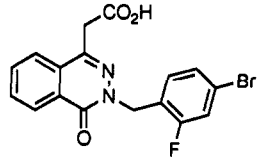
We had also previously shown that the carboxylic acid moiety in **1–4** was a key pharmacophore.[3a,4] Alteration of this group by, for instance, esterification or amidation resulted in intrinsically inactive compounds. However,



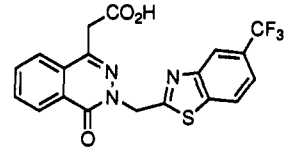


1, X = S, Y = CF_3, Tolrestat
2, X = O, Y = CF_3, "Oxo-tolrestat"
3, X = S, Y = Br

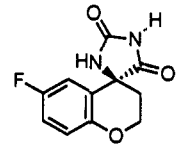
4



Ponalrestat



Zopalrestat



Sorbinil

† Current address: Department of Medicinal Chemistry and Natural Products, University of North Carolina, Chapel Hill, NC 27599-7360.

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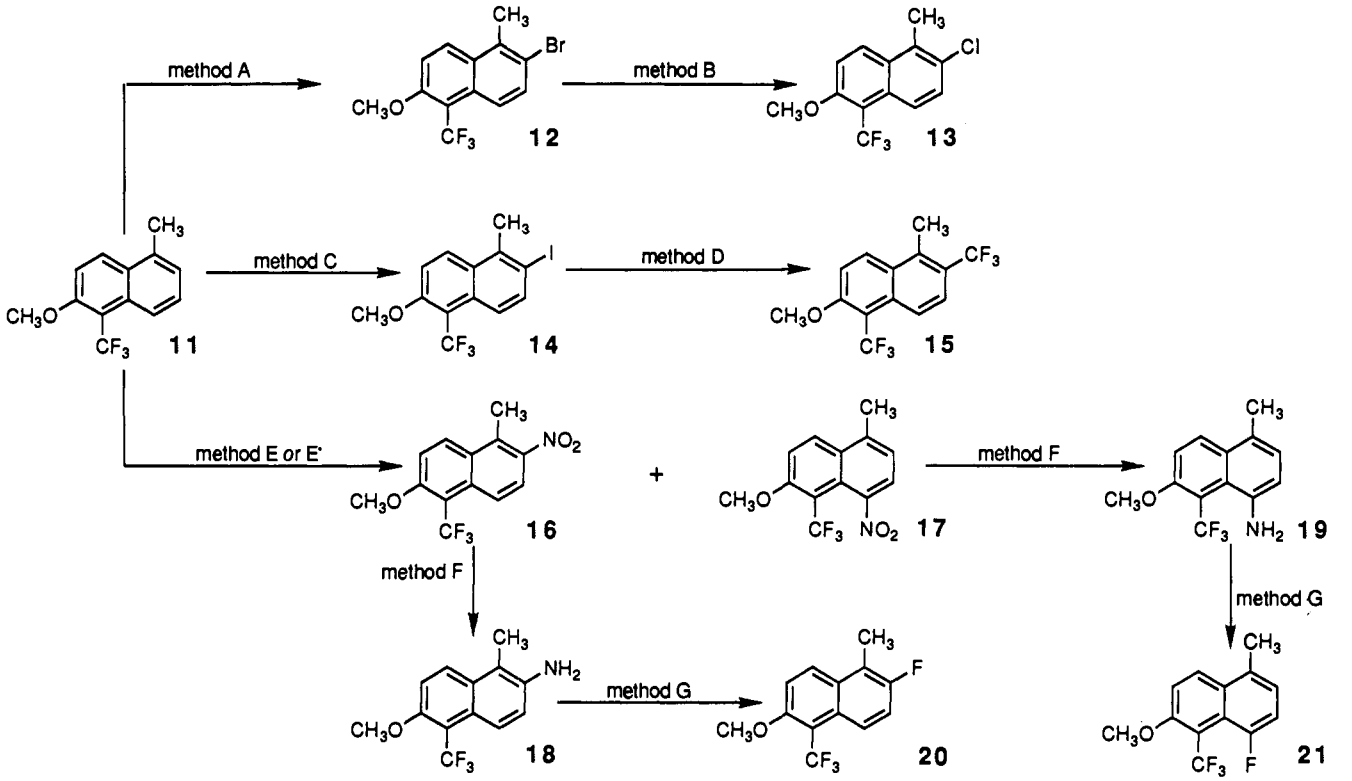
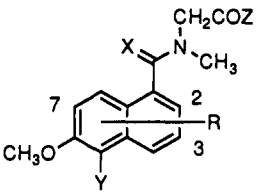
0022-2623/91/1834-2504$02.50/0

Scheme I[a]

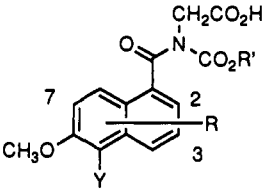


[a] Method A = Br_2/HOAc; method B = CuCl/DMSO/Δ; method C = $I_2/HIO_3/H_2SO_4$/HOAc/H_2O/60 °C; method D = CF_3CO_2Na/CuI/NMP/Δ; method E = fuming HNO_3/Ac_2O/5 °C; method E' = concentrated HNO_3; method F = H_2/Pd-C/EtOAc; method G = $NaNO_2$/HF-pyridine/−60 to 65 °C.

these ester and amide derivatives, particularly primary amides of compounds 1 and 2,[3b,c] showed appreciable oral activity and therefore were probably functioning as prodrugs. These findings encouraged us to prepare a number of primary amides of 5 and 7, namely 6 and 8 respectively.



5, X = S, Z = OH
6, X = S, Z = NH_2
7, X = O, Z = OH
8, X = O, Z = NH_2



9, R' = CH_3
10, R' = CH_2CH_3

Y = CF_3 or Br

Chemistry

Our target compounds were diversely substituted naphthoic acid derivatives that required different synthetic procedures for their preparation (Schemes I–IX). In general, these tolrestat analogues were prepared by amidation and amide side chain elaboration of the corresponding di- or trisubstituted naphthoic acids (Schemes VII and VIII). The naphthoic acids, in turn, were synthesized by several different methods (Schemes I–VI). For the preparation of several 2-alkyl-substituted analogues, Meyers' oxazoline chemistry[5] was utilized. In these instances, the required sarcosine side chain was constructed from the oxazoline ring (Scheme IX).

2-Halo, 2-(trifluoromethyl), 2-alkoxy, 2-(methylthio), and 4-fluoronaphthoic acids were prepared from the known naphthalene derivative 11[6] (Schemes I and II). Bromi-

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(3) (a) Humber, L. G. *Prog. Med. Chem.* **1987**, *24*, 299. (b) Bellini, F.; Sestanj, K.; Kraml, M. U.S. Patent 4 672 058, 1987. (c) Sestanj, K.; Ferdinandi, E. S. U.S. Patent 4 672 059, 1987. (d) Stribling, D.; Brittain, D. R. In *Approaches in Drug Research*: Harms, A. F., Ed.; Elsevier Science Publishers B. V.: Amsterdam, 1986; pp 297–313. (e) Mylari, B. L.; Larson, E. R.; Beyer, T. A.; Zembrowski, W. J.; Aldinger, C. E.; Dee, M. F.; Siegel, T. W.; Singleton, D. H. *J. Med. Chem.* **1991**, *34*, 108.

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(5) (a) Meyers, A. I.; Gabel, R.; Mehelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372. (b) Meyers, A. I.; Lutomski, K. A. *Synthesis* **1983**, 105.

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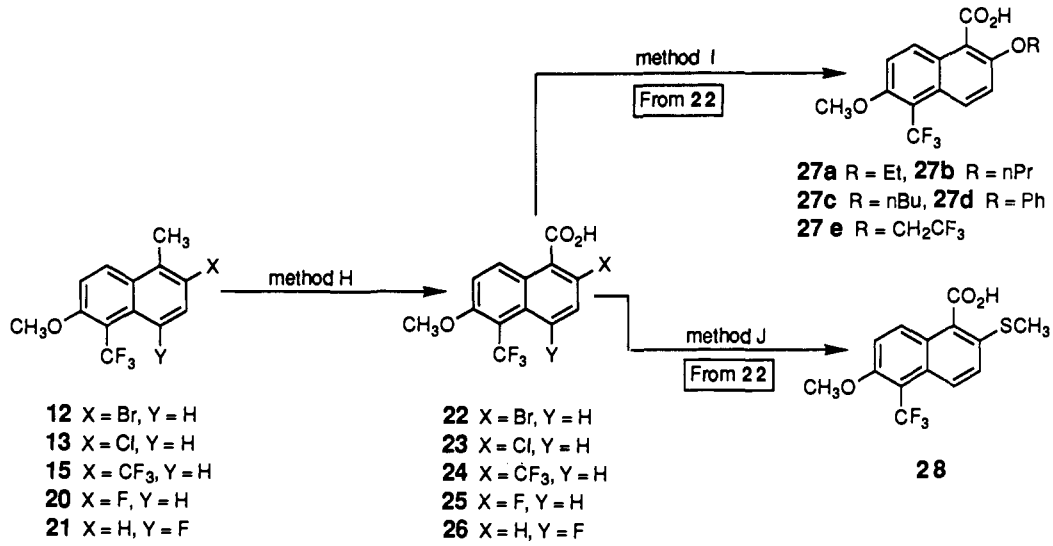
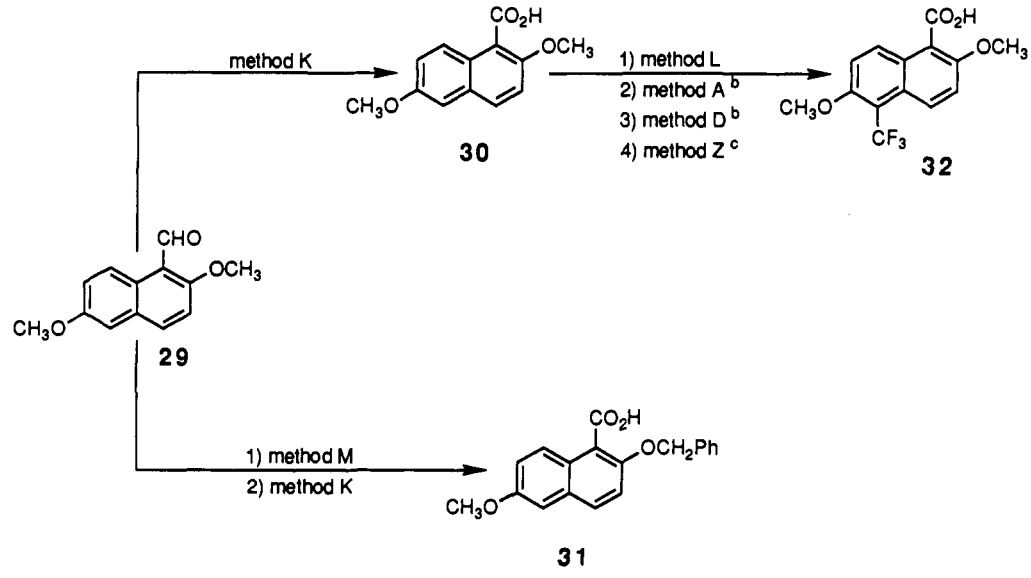
Scheme II[a]



[a] Method H = (1) NBS/$(PhCO_2)_2$/CCl_4, Δ, (2) HCO_2Na/EtOH/H_2O/Δ, (3) aq NaOH, (4) Jones oxidation; method I = NaH/ROH/CuI/THF/Δ; method J = KOtBu/CH_3SH/Cu_2O/DMF/Δ.

Scheme III[a]



[a] Method K = $NaClO_2$/resorcinol/tBuOH/dioxane/HOAc/Δ; method L = CH_3I/$EtiPr_2N$/CH_2Cl_2; method M = (1) nPrSH/NaH/DMF/60 °C; (2) $PhCH_2Br$/K_2CO_3/DMF. [b] See footnotes in Scheme I. [c] See footnotes in Scheme VI.

nation of **11** led to **12**[7] (method A, Scheme I, 98%), which underwent chlorine substitution to **13** upon reaction with CuCl in DMSO[8] (method B, 100%). A second trifluoromethyl substituent (compound **15**) was introduced by iodination of **11** (method C, 64%) followed by reaction of iodide **14** with sodium trifluoroacetate and CuI[7,9] (method D, 73%).

2- and 4-fluoro derivatives **20** and **21** were prepared from **11** via a three-step sequence. Reaction of **11** with concentrated HNO_3 (method E') provided a 45:55 mixture of nitro compounds **16** and **17** which were readily separated chromatographically. The selectivity for **16** (~5:1) could be greatly improved by treating **11** with fuming HNO_3 in acetic anhydride.[10] Compound **16** was selectively crystallized from the crude reaction mixture in 40–50% yields. Reduction of **16** or **17** using Pd–C-catalyzed hydrogenation afforded amines **18** and **19**, respectively (method F, 95%). One-pot diazotization and fluorine displacement could be effected in good yields with either amine by using the Olah procedure ($NaNO_2$ in HF–pyridine)[11] to provide fluorides **20** and **21** (method G, 60–80%).

The halo and (trifluoromethyl)naphthalenes **12**, **13**, **15**, **20**, and **21** were converted to their naphthoic acid derivatives (**22–26**, respectively, Scheme II) by oxidation of the 1-methyl moiety employing a four-step/three-pot sequence involving benzylic bromination with NBS, hydroxide displacement on the resultant bromide and Jones oxidation

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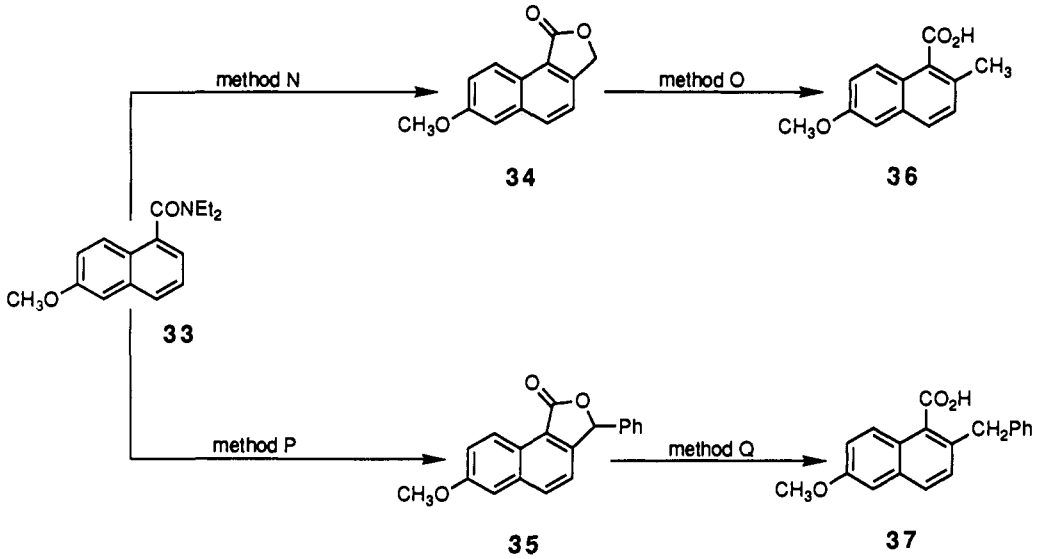
Scheme IV[a]



[a] Method N = (1) SBuLi/TMEDA/THF/−78 °C, (2) DMF/−78 to 25 °C, (3) $NaBH_4$/EtOH, (4) pTSA/$PhCH_3$/Δ; method O = (1) nPrSH/NaH/DMF/70 °C, (2) Raney Ni/EtOH/H_2O; method P = (1) sBuLi/TMEDA/THF/−78 °C, (2) PhCHO/−78 to 25 °C, (3) pTSA/$PhCH_3$/Δ; method Q = H_2/Pd–C/HOAc/95 °C.

(method H, ~70% overall). 2-Alkoxy- and 2-(methylthio)naphthoic acids **27** and **28** were then obtained by copper(I)-mediated reaction of 2-bromo acid **22** with sodium alkoxides or potassium methylmercaptide (methods I and J, respectively, 70–90%).[12]

2-Alkoxy-1-naphthoic acids were also be prepared from 2,5-dimethoxy-1-naphthaldehyde **29**[13] (Scheme III). Oxidation of **29** with sodium chlorite[14] provided 2,6-dimethoxy-1-naphthoic acid **30** in 82% yield (method K). Other oxidation methods ($KMnO_4$, Jones oxidation) caused extensive decomposition of **29**. The 2-(benzyloxy) substituent was introduced by selective demethylation of **29** at the 2-position using sodium propanethiolate in DMF,[15] followed by reaction of the 2-hydroxyaldehyde with benzylbromide and base (method M, 69%). Chlorite oxidation provided the corresponding 2-(benzyloxy)-1-naphthoic acid **31**.

2-Methyl and 2-benzyl analogues were prepared by employing ortho-lithiation technology[16,17] (Scheme IV). Reaction of 6-methoxy-1-naphthoic acid diethylamide (**33**)[17] with *sec*-butyllithium–TMEDA and quenching the resultant lithio species with DMF led to the 2-formyl derivative which was reduced with $NaBH_4$ to the alcohol and cyclized (catalytic pTSA in toluene) to γ-lactone **34** (method N, 70%). Similarly, reaction of the 2-lithio derivative of **33** with benzaldehyde, followed by cyclization, provided phenyl-substituted lactone **35** (method P, 85%). Sodium propanethiolate[15] opening of lactone **34**, then Raney nickel desulfurization led to 2-methyl-1-naphthoic acid **36** (method O, 47%). The 2-benzyl counterpart **37** was prepared via hydrogenolysis of the benzylic C–O bond of **35** (method Q, 92%).

3-, 4-, and 7-substituted naphthoic acids were most conveniently prepared from the appropriately substituted cinnamaldehydes **42**, **45**, and **47** according to the methods in Scheme VI. These cinnamaldehyde starting materials were prepared by a variety of methods shown in Scheme V. 3-Methoxybenzaldehyde **41** was condensed with an alkyl or aralkylaldehyde (**40c–f**) by using KOH in ethanol to afford **42c–f** (method T, 60–80%). Aldehyde **40f** was not commercially available but was readily prepared from the benzyl bromide **38** (methods R and S). α-Fluoro analogue **42a** was synthesized via a three-step sequence[18] involving condensation of ethyl fluoroacetate and **41**, followed by $LiAlH_4$ reduction of the resultant enoate to the allylic alcohol and oxidation of this alcohol to **42a** using MnO_2 (method T′, 40%). Bromination and dehydrobromination[19] of 3-(3-methoxyphenyl)propenal **43**[20] provided α-bromo derivative **42b** in 43% yield. 3-Methoxy-4-methylbenzaldehyde (**44**)[21] and phenylacetophenone **46** (the latter was prepared from aldehyde **41** and benzyl Grignard reagent, then Jones oxidation, method W) were converted to substituted cinnamaldehydes **45** and **47**, respectively, via standard Horner–Emmons conditions, followed by ester to aldehyde functional group conversion (method V, 60–70%).

Referring to Scheme VI, aldehydes **42**, **45**, and **47** were condensed with the sodium salt of triethyl 2-ethoxyphosphonoacetate[22] (method X[23]) and the resultant 2-ethoxy dienoate **48** was cyclized by action of catalytic *p*-toluenesulfonic acid to the naphthoic acid ethyl ester **49** (method Y,[23] ~60% from the corresponding cinnamaldehyde). Bromination, followed by saponification or, alternatively, bromination followed by trifluoromethylation and saponification, led to 3-, 4-, or 7-substituted-5-bromo or 5-(trifluoromethyl)-6-methoxynaphthoic acids **52a–i**.

The 1-naphthoic acids **22–28**, **30**, **31**, **36**, **37**, and **52a–i** were converted to tolrestat analogues in the following manner (Scheme VII). Reaction of **22–28** and **52** with sarcosine methyl ester under standard amidation conditions (methods AA, AA′, or AA″) afforded the naphthoylsarcosine methyl esters **53**. For compounds **30**, **31**,

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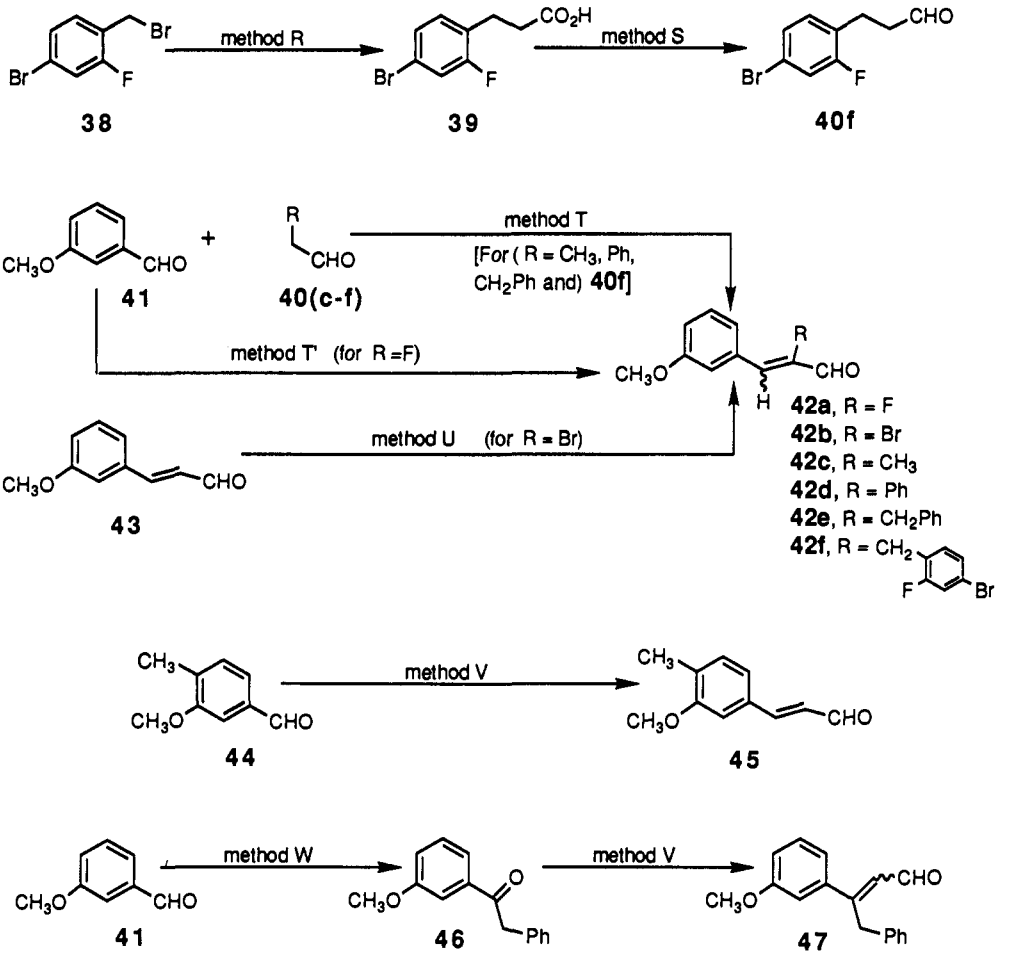
Scheme V[a]



[a] Method R = (1) $CH_2(CO_2Me)_2$/NaH/THF, (2) KOH/THF/H_2O/Δ, (3) HCl/H_2O, (4) xylenes/Δ; method S = (1) BH_3·THF, (2) PCC/CH_2Cl_2; method T = KOH/EtOH/0 °C; method T' = (1) FCH_2CO_2Et/NaH/EtOH/Et_2O, (2) $LiAlH_4$/Et_2O, (3) MnO_2/Et_2O; method U = (1) Br_2/HOAc/0 °C, (2) K_2CO_3/0 to 100 °C; method V = (1) $(Et_2O)_2POCH_2CO_2Et$/NaH/$PhCH_3$/THF, (2) DIBAL/Et_2O/−78 °C, (3) PCC/CH_2Cl_2; method W = (1) $PhCH_2MgCl$/THF/−78 °C, (2) Jones oxidation.

36, and **37**, the 5-trifluoromethyl substituent was introduced after the amidation (method AA) using previously mentioned procedures (methods A and D). Ester hydrolysis of **53** (method Z) led to targets **7**. Primary amide derivatives **8** were obtained from ester **53** or acid **7** by using standard methods (BB, CC, or CC'). Reaction of **7** with *N*-(ethoxycarbonyl)-*N*-*tert*-butylcarbodiimide[24] provided ethyl carbamate **54** (method DD, 50%).

Naphthoylthioamide methyl esters **55** were prepared from the corresponding naphthoylamides **53** with Lawesson's reagent[25] (method EE) or P_4S_{10}–pyridine (method EE'). Naphthoylamides with bulky, electron-withdrawing 2-substituents, i.e., 2-Br or 2-CF_3, did not react with either reagent. However the naphthoylamides with electron-releasing 2-substituents, even sterically demanding ones such as 2-OPh and 2-OCH_2Ph, were successfully converted to naphthoylthioamides **55**. Ester saponification (method Z) led to tolrestat analogues **5**. Primary amide derivatives **6** were synthesized from **5** or **55** by the methods described above.

N-Carbalkoxytolrestat analogues related to **4** were prepared as outlined in Scheme VIII from naphthoic acids **22**, **23**, **25**, **27e**, **33**, or **52b**. Reaction of these acids with the Mitsunobu carbodiimide[24] (method DD) led to *N*-naphthoylcarbamate **56**. Compounds **56** were also obtained via base-promoted acylation of the primary naphthamides with ethyl or methyl chloroformate (method DD, 50–60%) or by conversion of these amides to the acyl isocyanate using oxalyl chloride followed by treatment with ethanol or methanol (method DD'',[26] 50–60%). N-Alkylation of **56** with *tert*-butyl bromoacetate (method FF, 75–85%) provided **58**. Targets **9** and **10** were then obtained upon treatment of **58** with formic acid to removed the *tert*-butyl moiety (method II, 75–95%).

Alternatively, **58** was synthesized from naphthoylglycine ester **57** by N-acylation using ethyl or methyl chloroformate (methods HH, 70–80%). Precursor **57** was obtained from the corresponding naphthoic acid under standard amidation conditions (methods GG or GG'). Naphthoylglycine benzyl esters **59** were prepared from the naphthoic acid and glycine benzyl ester under standard amide-forming conditions followed by N-acylation of the resultant secondary amide with ethyl or methyl chloroformate (method JJ). Hydrogenolysis of **59** led to **9** or **10**. Primary amide **60** was made from **9a** in the usual manner (method CC') and alkylation of **9a** with chloro *N*,*N*-diethylacetamide provided glycolate diethylamide[27] **61** (method KK, 72%).

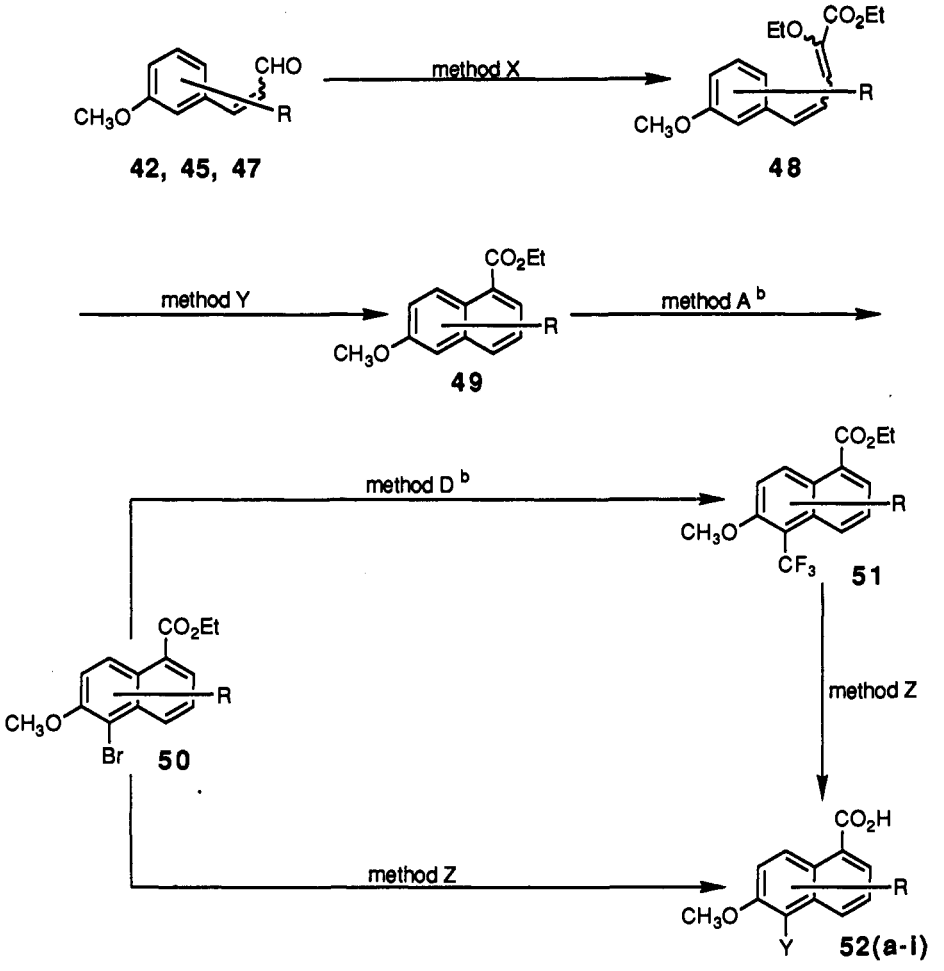
(24) Mitsunobu, O.; Tomani, M.; Morimoto, H.; Sato, T.; Sudo, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3607.

(25) (a) For a review on the thionation reaction with Lawesson's reagent, see: Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5087. (b) Mechanistic study: Rauchfuss, T. B.; Zank, G. A. *Tetrahedron Lett.* **1986**, 3445.

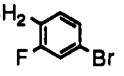
(26) Smith, L. R.; Sheziak, A. J. *U.S. Patent* 3 450 747, 1969; *Chem. Abstr.* **1969**, *71*, 49519*f*.

(27) Bundgaard, H.; Nielson, N. M. *J. Med. Chem.* **1987**, *30*, 454.

Scheme VI[a]



52a Y = Br, R = 3-F; **52b** Y = Br, R = 3-Br; **52c** Y = Br, R = 3-CH_3; **52d** Y = Br, R = 3-Ph **52e** Y = Br, R = 3-CH_2Ph; **52f** Y = CF_3, R = 3-Ph; **52g** Y = Br, R = 4-CH_2Ph, **52h** X = Br, R = 7-CH_3; **52i** Y = Br, R = 3-



[a] Method X = $(EtO)_2POCH(OEt)CO_2Et/NaH/DMF$; method Y = $I_2/pTSA/PhCH_3/\Delta$; method Z = $NaOH/H_2O/THF/EtOH$. [b] See footnotes for Scheme I.

In instances where the Meyers' oxazoline methods[5] were used to prepare 2-alkyl analogues (Scheme IX), hydrolysis of the resulting oxazolines to 2-alkylnaphthoic acids was difficult due to the hindered environment of the oxazoline moiety. Instead, the oxazoline, resulting from organolithium displacement of methoxide on **62**, was N-methylated[28] with methyl iodide and then the oxazoline ring was opened to the *N*-methyl-*N*-naphthoylethanolamine acetate upon treatment with Hunig's base and acetic acid.[29] Aromatic bromination provided **63** (method MM, 30% overall). Trifluoromethylation of **63**, followed by base-promoted acetate hydrolysis and Jones oxidation of the resultant primary alcohol (method NN) led to 2-alkyloxotolrestat analogues **7o** and **7n**. Chemical data and synthesis route information (by method letters) for the individual target compounds are compiled in Table I.

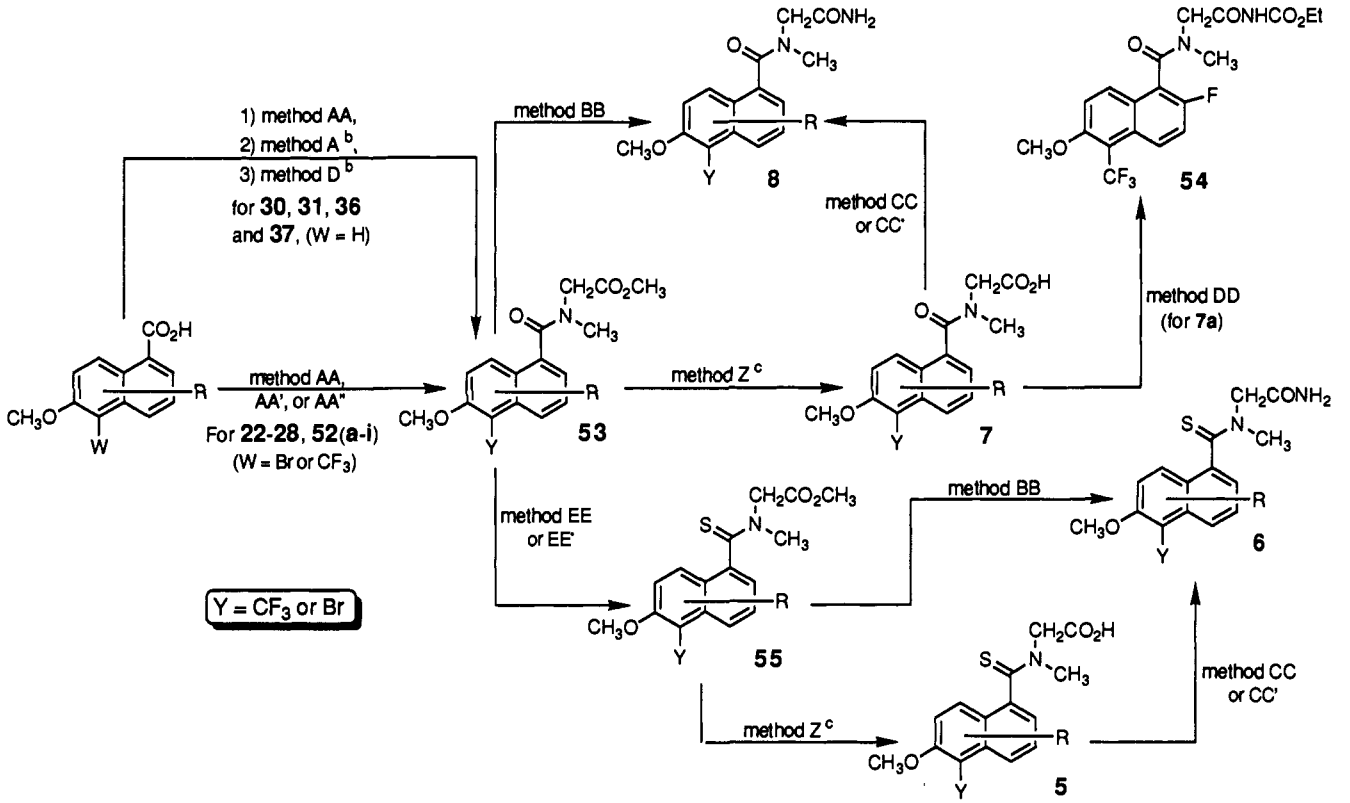
Biological Results and Discussion

Two in vitro systems were used to evaluate the target compounds as inhibitors of aldose reductase. The intrinsic activity of each compound was assessed by measuring the inhibition of enzymatic activity in a partially purified bovine lens preparation. Because aldose reductase is an intracellular enzyme, the ability of the inhibitor to penetrate the membranes of the target tissue is also an important component of its biological activity. This parameter was therefore evaluated by measuring the inhibition of sorbitol accumulation in rat sciatic nerves incubated in the presence of excess glucose. Finally, the compounds were evaluated in vivo as inhibitors of galactitol accumulation in the lens, sciatic nerve, and diaphragm of galactose-fed rats. The nerve and lens were evaluated because they are therapeutic targets. The diaphragm, although not a therapeutic target, was also evaluated because it accumulates polyol (3 μg of galactitol/mg wet weight) and is highly vascular, thus allowing the assessment of a compound in a tissue where there is optimal distribution. The results of the biological evaluations are given in Table II.

In general, analogues **5**, **7**, **9**, and **10** were potent inhibitors of aldose reductase, comparable to tolrestat (**1**) in the isolated enzyme preparation (≥60% at 10^{-7} M). Notable exceptions included 7-substituted compounds **5p** and **7w** and several analogues possessing sterically large or branched-chain 2-alkyl substituents (**7d**,**n**,**o**) or 2-alkoxy moieties (**7g**,**h**). The low activities exhibited by these compounds were probably due to a decreased ability to

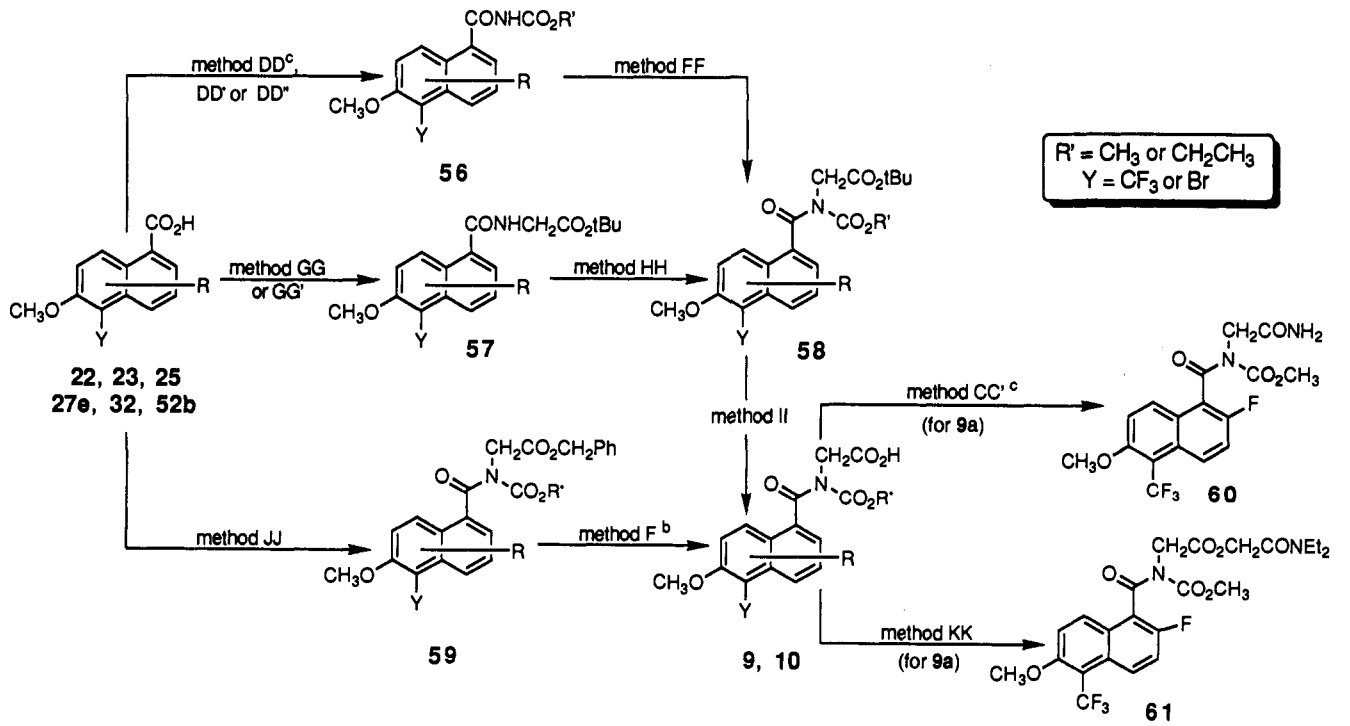
(28) Nordin, I. C. *J. Heterocycl. Chem.* **1966**, *3*, 531.
(29) For a similar ring opening reaction of oxazolines, see: Inaba, M.; Moriwake, T.; Saito, S. *Tetrahedron Lett.* **1985**, 3235.

Scheme VII[a]



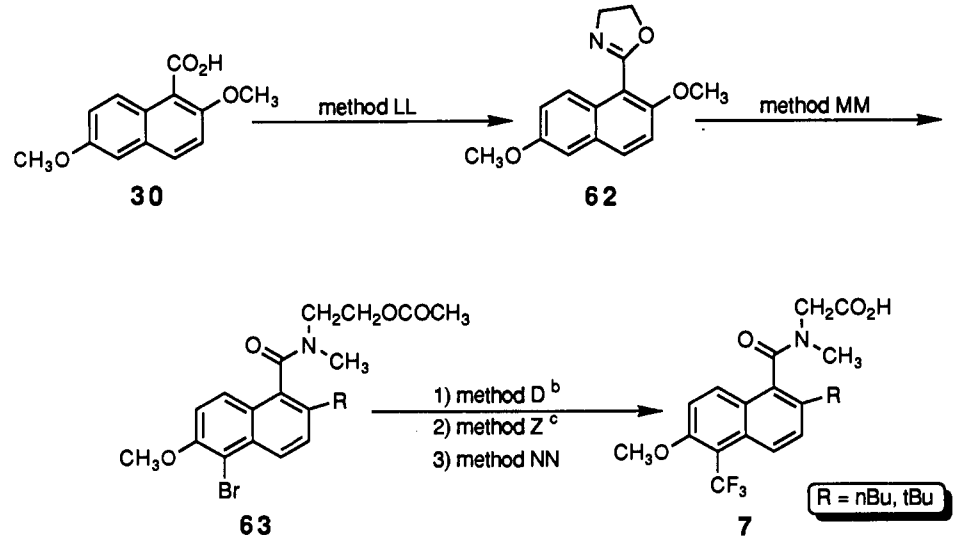
[a] Method AA = (1) $(COCl)_2$/DMF/CH_2Cl_2, (2) $CH_3NHCH_2CO_2CH_3$·HCl/TEA/THF; method AA′ = (1) $Me_2N(CH_2)_3N{=}C{=}NEt$·HCl/HOBT/DMF, (2) $CH_3NHCH_2CO_2CH_3$·HCl/TEA; method AA″ = (1) $SOCl_2$/DMF/CH_2Cl_2, (2) $CH_3NHCH_2CO_2CH_3$·HCl/TEA; method BB = NH_3/THF/MeOH; method CC = (1) $Me_2N(CH_2)_3N{=}C{=}NEt$·HCl/HOBT/DMF, (2) NH_3/THF; method CC′ = (1) $(COCl)_2$/DMF/THF, (2) NH_3/THF; method DD = tBuN=C=NCO_2Et/THF/D; method EE = Lawesson's reagent/$PhCH_3$/Δ; method EE′ = P_4S_{10}/pyridine/Δ. [b] See footnotes in Scheme I. [c] See footnotes in Scheme VI.

Scheme VIII[a]



[a] Method DD′ = (1) $SOCl_2$/DMF, (2) NH_4OH/THF/0 °C, (3) NaH/THF, (4) $ClCO_2R'$/THF; method DD″ = (1) $SOCl_2$/DMF, (2) NH_4OH/THF/0 °C, (3) $(COCl)_2$/$(CH_2Cl)_2$/Δ, (4) R′OH/PhH/Δ; method FF = (1) NaH/THF, (2) $BrCH_2CO_2tBu$·HCl/THF, 60 °C; method GG = (1) $(COCl)_2$/DMF/CH_2Cl_2, (2) $NH_2CH_2CO_2tBu$·HCl/TEA/THF; method GG′ = (1) $Me_2N(CH_2)_3N{=}C{=}NEt$·HCl/HOBT/DMF, (2) $NH_2CH_2CO_2tBu$·HCl/TEA; method HH = (1) NaH/THF/60 °C, (2) $ClCO_2R'$/THF; method II = HCO_2H; method JJ = (1) $(COCl)_2$/DMF/THF, (2) $NH_2CH_2CO_2CH_2Ph$, (3) LDA/THF/−78 °C, (4) $ClCO_2R'$/−78 to 25 °C; method KK = $ClCH_2CONEt_2/K_2CO_3$/DMF. [b] See footnotes in Scheme I. [c] See footnotes in Scheme VII.

Scheme IX[a]



[a] Method LL = (1) $(COCl)_2$/DMF/THF, (2) $NH_2CH_2CH_2OH$, (3) $SOCl_2$; method MM = RLi or RMgCl/THF/−40 °C, (2) CH_3I, (3) $EtiPr_2N$/HOAc/EtOAc, (4) Br_2/HOAc; method NN = Jones oxidation. [b] See footnotes in Scheme I. [c] See footnotes in Scheme VI.

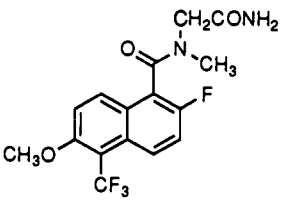
interact with the enzyme because of steric effects. Compounds in the thionaphthoylamide series (**5**) showed slightly higher inhibitory values than their naphthoylamide counterparts (**7**), a trend that has been observed previously.[4] The amide derivatives **6**, **8**, **54**, and **60** and ester analogues **53** and **61** were not active in this in vitro assay at 10^{-5} M, the highest dose tested, corraborating our previous in vitro findings.[3b] However, many of these compounds were active in vivo, and therefore, were probably functioning as prodrugs (vide infra).

Consistent with our previous studies,[4] we found that in vitro inhibitory activity of **5**, **7**, **9**, or **10** in the isolated sciatic nerve did not always predict oral activity in the galactose fed rat model. Although isolated nerve values ≥60% at 10^{-5} M and ≥30% at 10^{-6} M appeared to be necessary for good potency in vivo, there were many examples of analogues with strong activity in this assay that were devoid of any oral effects. For example **7t** caused a 63% decrease in in vitro sciatic nerve sorbitol accumulation at 10^{-6} M, which is similar to the value exhibited by tolrestat (**1**), yet this compound was inactive in vivo. While it is obvious that the inhibitor must possess some ability to cross biological membranes, high activity in this regard did not guarantee oral potency, and other factors including absorption, distribution, and metabolism also strongly influenced oral efficacy.

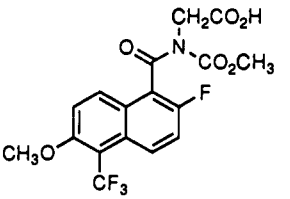
The target compounds (**5–10**) were most readily distinguished by their potency in vivo (galactose-fed rat model). In the thionaphthoylamide (**5**) and naphthoylamide (**7**) series, compounds with 2-halo substituents (i.e., **5a**, **7a**, **7b**) or 2-(lower)alkoxy moieties (i.e., **5d**,**g**, **7f**,**g**,**k**) showed the most promising results, exhibiting significant inhibition of galactitol accumulation in the sciatic nerve at reasonably low doses (≤50 mg/kg per day). Also, within these two series, naphthoylamide **7** was generally equally effective in the nerve when compared to the respective thionaphthoylamide congener **5**. For example, compare **5a** with **7a**, **5b** with **7b**, and **5g** with **7k**. These results differed from previous studies in which the thioamide analogue was always superior to the amide in vivo.[3,4] Another comparison demonstrated that 2-halo and 2-(lower)alkoxy derivatives of **7** had superior in vitro and in vivo profiles over the hydrogen substituted analogue oxotolrestat (**2**) (compare **2** with **7a**, **7b**, **7f**, and **7k**). Methyl naphthoylcarbamates **9** containing 2-halo substituents also showed significant activity in the nerve at doses ≤50 mg/kg per day. Also, these carbamates were superior in oral activity over their ethyl carbamate counterparts **10**, and over the hydrogen substituted congener **4**.

Several primary amide prodrugs of thionaphthoylamide series **5** and naphthoylamide series **7** were prepared. These were compounds in series **6** and **8**, respectively. In several instances oral activity in the nerve improved with the primary amide derivative (compare **7a** with **8a**, and **7b** with **8b**). Also, increased potency in vivo was observed in the one instance in which an ethyl carbamate prodrug was used (compare **7a** with **54**). On the other hand, ester prodrugs of **7a** (**53**) and **9a** (**61**) and the primary amide prodrug of **9a** (**60**) did not result in increased in vivo potency.

Oral activity was best demonstrated by the members of the series **5–10** that contained a 2-fluoro substituent (including **5a**, **6a**, **7a**, **8a**, **9a**, **10a**, and **54**). Two of these, primary amide prodrug **8a** and methyl carbamate **9a**, appeared to have potency equivalent to that of tolrestat (**1**) and were therefore evaluated more extensively.



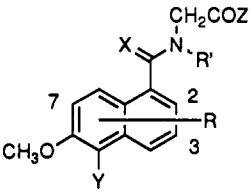
8a



9a

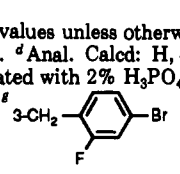
The comparative in vivo and in vitro data for **8a**, **9a**, and tolrestat are shown in Tables III and IV. ED_{50} values (Table III) for the inhibition of galactitol accumulation in the sciatic nerve and red blood cell (RBC) of the galactose-fed rat were determined. In addition, ED_{50} values in another in vivo model, the 2-week-streptozocin-diabetic rat (STZ), were also obtained. In this model the compound's ability to inhibit sorbitol accumulation in the sciatic nerve of the STZ rat was measured. IC_{50} values (Table IV) were also determined for **8a**, **9a**, and tolrestat in the bovine lens aldose reductase preparation and isolated sciatic nerve. Furthermore IC_{50} values for the inhibition of sorbitol accumulation in isolated lens cells and RBC were determined.

Table I. Chemical Data



no.	R	R'	X	Y	Z	formula[a]	synthesis route[b]	mp, °C	purification method[c] (solvent)
5a	2-F	CH_3	S	CF_3	OH	$C_{16}H_{13}F_4NO_3S$	E, F, G, H, AA, EE, Z	179–190 dec	I ($EtOH/H_2O$)
5b	2-Cl	CH_3	S	CF_3	OH	$C_{16}H_{13}ClF_3NO_3S$	A, B, H, AA′, EE, Z	164–166	II (hexane)
5c	2-OMe	CH_3	S	CF_3	OH	$C_{17}H_{16}F_3NO_4S$	K, AA, A, D, EE, Z	162–164	I (hexane/toluene)
5d	2-OEt	CH_3	S	CF_3	OH	$C_{18}H_{18}F_3NO_4S$	A, H, I, AA′, EE, Z	180–182	I (petroleum ether/$CHCl_3$)
5e	2-OPh	CH_3	S	CF_3	OH	$C_{22}H_{18}F_3NO_4S$	A, H, I, AA′, EE, Z	112–132 dec	I (hexane/$CHCl_3$)
5f	2-OCH_2Ph	CH_3	S	CF_3	OH	$C_{23}H_{20}F_3NO_4S$	M, K, AA, A, D, EE, Z	190–195	I (EtOH)
5g	2-OCH_2CF_3	CH_3	S	CF_3	OH	$C_{18}H_{15}F_6NO_4S$	A, H, I, AA′, EE, Z	194–196	I ($CHCl_3$)
5h	2-CH_3	CH_3	S	CF_3	OH	$C_{17}H_{18}F_3NO_3S$[d]	N, O, AA, A, D, EE, Z	176–179	I (hexane/toluene)
5i	3-F	CH_3	S	Br	OH	$C_{15}H_{13}BrFNO_3S$	T′, X, Y, A, Z, AA″, EE, Z	190–191	I ($iPrOH/H_2O$)
5j	3-Br	CH_3	S	Br	OH	$C_{15}H_{13}Br_2NO_3S$	U, X, Y, A, Z, AA′, EE, Z	205–207	III (4:1 hexane/EtOAc)[e] then II (hexanes)
5k	3-CH_3	CH_3	S	Br	OH	$C_{16}H_{16}BrNO_3S$	T, X, Y, A, Z, AA″, EE, Z	219–221	I ($Et_2O/CHCl_3$)
5l	3-Ph	CH_3	S	Br	OH	$C_{21}H_{16}BrNO_3S$	T, X, Y, A, Z, AA″, EE′, Z	142–144	III (99:1 CH_2Cl_2/MeOH)[e]
5m	3-Ph	CH_3	S	CF_3	OH	$C_{22}H_{16}F_3NO_3S$	T, X, Y, A, D, Z, AA″, EE′, Z	186–188.5	III (9:1 CH_2Cl_2/CH_3CN)[e]
5n	3-CH_2Ph	CH_3	S	Br	OH	$C_{22}H_{20}BrNO_3S$	T, X, Y, A, Z, AA″, EE, Z	156–158	I (acetone/Et_2O/hexane/−20 °C)
5o	4-F	CH_3	S	CF_3	OH	$C_{16}H_{13}F_4NO_3S$	E′, F, G, H, AA, EE, Z	174–176	I ($EtOH/H_2O$)
5p	7-CH_3	CH_3	S	Br	OH	$C_{16}H_{16}BrNO_3S$	V, X, Y, A, Z, AA′, EE, Z	215 dec	I (Et_2O/hexane/0 °C)
6a	2-F	CH_3	S	CF_3	NH_2	$C_{16}H_{14}F_4N_2O_2S$	E, F, G, H, AA, EE, Z, CC	222–224	III (98:2 $CHCl_3$/MeOH)
6b	3-CH_3	CH_3	S	Br	NH_2	$C_{16}H_{17}BrN_2O_2S$	T, X, Y, A, Z, AA″, EE, Z	113–115	III (1:4 hexane/CH_2Cl_2)[e] then II (hexanes)
7a	2-F	CH_3	O	CF_3	OH	$C_{16}H_{13}F_4NO_4$	E, F, G, H, AA, Z	160–161	I (EtOH)
7b	2-Cl	CH_3	O	CF_3	OH	$C_{16}H_{13}ClF_3NO_4$	A, B, H, AA′, Z	157–159	I (petroleum ether/$CHCl_3$)
7c	2-Br	CH_3	O	CF_3	OH	$C_{16}H_{13}BrF_3NO_4$	A, H, AA′, Z	163.5–165	I (1:1 hexane/$CHCl_3$)
7d	2-CF_3	CH_3	O	CF_3	OH	$C_{17}H_{13}F_6NO_4$	C, D, H, AA″, Z	189–191	I (hexane/$CHCl_3$)
7e	2-OMe	CH_3	O	CF_3	OH	$C_{17}H_{16}F_3NO_5$[f]	K, AA, A, D, Z	195–197	I (hexane/CH_2Cl_2)
7f	2-OEt	CH_3	O	CF_3	OH	$C_{18}H_{18}F_3NO_5$	A, H, I, AA′, Z	168–170	I ($EtOH/H_2O$)
7g	2-OnPr	CH_3	O	CF_3	OH	$C_{19}H_{20}F_3NO_5$	A, H, I, AA′, Z	70–73	II (petroleum ether)
7h	2-OnBu	CH_3	O	CF_3	OH	$C_{20}H_{22}F_3NO_5$	A, H, I, AA′, Z	150–155	II (petroleum ether)
7i	2-OPh	CH_3	O	CF_3	OH	$C_{22}H_{18}F_3NO_5$	A, H, I, AA′, Z	180–182	I ($EtOH/H_2O$)
7j	2-OCH_2Ph	CH_3	O	CF_3	OH	$C_{23}H_{20}F_3NO_5$	M, K, AA, A, D, Z	174–175	I (EtOH)
7k	2-OCH_2CF_3	CH_3	O	CF_3	OH	$C_{18}H_{15}F_6NO_5$	A, H, I, AA′, Z	158–160	I (hexane/$CHCl_3$)
7l	2-SMe	CH_3	O	CF_3	OH	$C_{17}H_{16}F_3NO_4S$	A, H, J, AA″, Z	190–191	I (2:1 hexane/$CHCl_3$)
7m	2-CH_2Ph	CH_3	O	CF_3	OH	$C_{23}H_{20}F_3NO_4$	P, Q, AA, A, D, Z	202–203	I ($EtOH/H_2O$)
7n	2-nBu	CH_3	O	CF_3	OH	$C_{20}H_{22}F_3NO_4$	K, LL, MM, D, Z, NN	148–152	I (hexane/EtOAc)
7o	2-tBu	CH_3	O	CF_3	OH	$C_{20}H_{22}F_3NO_4$	K, LL, MM, D, Z, NN	188–194	III (5:1 CH_2Cl_2/EtOAc)[e] then II (hexane/EtOAc)
7p	3-CH_3	CH_3	O	Br	OH	$C_{16}H_{16}BrNO_4$	T, X, Y, A, Z, AA″, Z	195–196	I ($MeOH/H_2O$)
7q	3-Ph	CH_3	O	Br	OH	$C_{21}H_{16}BrNO_4$	T, X, Y, A, Z, AA″, Z	208–210	I ($MeOH/H_2O$)
7r	3-Ph	CH_3	O	CF_3	OH	$C_{22}H_{16}F_3NO_4$	T, X, Y, A, D, Z, AA″, Z	175–177	II (petroleum ether)
7s	3-CH_2Ph	CH_3	O	Br	OH	$C_{22}H_{20}BrNO_4$	T, X, Y, A, Z, AA′, Z	160–162	I ($CHCl_3/Et_2O$/−20 °C)
7t	g	CH_3	O	Br	OH	$C_{22}H_{16}Br_2FNO_4$	R, S, T, X, Y, A, Z, AA″, Z	183–185	I (acetone/H_2O)
7u	4-F	CH_3	O	CF_3	OH	$C_{16}H_{13}F_4NO_4$	E′, F, G, H, AA′, Z	201–203	I ($EtOH/H_2O$)
7v	4-CH_2Ph	CH_3	O	Br	OH	$C_{22}H_{20}BrNO_4$	W, V, X, Y, A, Z, AA′, Z	93–95	I ($CHCl_3/Et_2O$/hexane/−20 °C)
7w	7-CH_3	CH_3	O	Br	OH	$C_{16}H_{16}BrNO_4$	V, X, Y, A, Z, AA′, Z	141–143	I (Et_2O −20 °C)
8a	2-F	CH_3	O	CF_3	NH_2	$C_{16}H_{14}F_4N_2O_3$	E, F, G, H, AA, BB	171–173	II (petroleum ether/Et_2O) then I (toluene)
8b	2-Cl	CH_3	O	CF_3	NH_2	$C_{16}H_{14}ClF_3N_2O_3$	A, B, H, AA′, BB	196–198	III (19:1 $CHCl_3$/MeOH)
8c	2-OCH_2CF_3	CH_3	O	CF_3	NH_2	$C_{18}H_{16}F_6N_2O_4$	A, H, I, AA′, BB	162–164	III (19:1 $CHCl_3$/MeOH) then I (hexane/$CHCl_3$)
8d	2-nBu	CH_3	O	CF_3	NH_2	$C_{20}H_{23}F_3N_2O_3$	K, LL, MM, D, Z, NN, CC	156–158	I (3:2 hexane/EtOAc)
8e	2-tBu	CH_3	O	CF_3	NH_2	$C_{20}H_{23}F_3N_2O_3$	K, LL, MM, D, Z, NN, CC	115–120	III (EtOAc) then II (hexane)
8f	4-F	CH_3	O	CF_3	NH_2	$C_{16}H_{14}F_4N_2O_3$	E′, F, G, H, AA, BB	180–183	III (9:1 $CHCl_3$/MeOH)
9a	2-F	CO_2Me	O	CF_3	OH	$C_{17}H_{13}F_4NO_6$	E, F, G, H, GG, HH, II	158.5–160	II (petroleum ether/Et_2O) then I (toluene/hexane)
9b	2-Cl	CO_2Me	O	CF_3	OH	$C_{17}H_{13}ClF_3NO_6$	A, B, H, GG′, HH, II	162–165	I (benzene)
9c	2-Br	CO_2Me	O	CF_3	OH	$C_{17}H_{13}BrF_3NO_6$	A, H, DD′, FF, II	164–166	I (petroleum ether/$CHCl_3$)
9d	2-OMe	CO_2Me	O	CF_3	OH	$C_{16}H_{16}F_3NO_7$	K, L, A, D, Z, JJ, F	175–177	II (hexane/EtOAc)
9e	2-OCH_2CF_3	CO_2Me	O	CF_3	OH	$C_{19}H_{15}F_6NO_7$	A, H, I, GG′, HH, II	186–187	I ($CHCl_3$)
10a	2-F	CO_2Et	O	CF_3	OH	$C_{18}H_{15}F_4NO_6$	E, F, G, H, DD, FF, II	135.5–138	I (petroleum ether/benzene)
10b	2-Cl	CO_2Et	O	CF_3	OH	$C_{18}H_{15}ClF_3NO_6$	A, B, H, DD, FF, II	144–146	I (petroleum ether/benzene)
10c	2-Br	CO_2Et	O	CF_3	OH	$C_{18}H_{15}BrF_3NO_6$	A, H, DD, FF, II	167–168.5	I (hexane/$CHCl_3$)
10d	2-OCH_2CF_3	CO_2Et	O	CF_3	OH	$C_{20}H_{17}F_6NO_7$	A, H, I, BB, FF, II	165.5–167	I (petroleum ether/$CHCl_3$)
10e	3-Br	CO_2Et	O	Br	OH	$C_{17}H_{15}Br_2NO_6$	U, X, Y, A, Z, DD″, FF, II	164–165	III (7:3 hexanes/EtOAc)[e] then II (hexanes)
53	2-F	CH_3	O	CF_3	OMe	$C_{17}H_{15}F_4NO_4$	E, F, G, H, AA	112.5–114	I (petroleum ether/$CHCl_3$)
54	2-F	CH_3	O	CF_3	$NHCO_2Et$	$C_{19}H_{18}F_4N_2O_5$	E, F, G, H, AA, Z, DD	130–132	III (1:1 petroleum ether/Et_2O) then II (petroleum ether)
60	2-F	CO_2Me	O	CF_3	NH_2	$C_{17}H_{14}F_4N_2O_5$	E, F, G, H, GG, HH, II, CC	199–202	I (petroleum ether/$CHCl_3$)
61	2-F	CO_2Me	O	CF_3	OCH_2CONEt_2	$C_{23}H_{24}F_4N_2O_7$	E, F, G, H, GG, HH, II, KK	104–107	II (hexane)

Footnotes to Table I

[a] Analyses (C, H, N) were within ±0.4% of theoretical values unless otherwise indicated. [b] Sequential order of methods from Schemes I–IX. [c] I, Recrystallization; II, trituration; III, flash chromatography. [d] Anal. Calcd: H, 4.34. Found: H, 5.41. Exact mass (M + H) 372.08812, found 372.0879. [e] Flash chromatography performed with silica gel first treated with 2% H_3PO_4 in MeOH then dried in an oven. [f] Anal. Calcd: C, 54.99. Found: C, 54.58. Exact mass (M + H) 372.10587, found 372.10550. [g] 

Inhibitors **8a** and **9a** were equipotent to **1** in the sciatic nerve of the 4-day-galactose-fed rat; however **8a** appeared to be slightly more potent in the nerve of the 2-week-streptozotocin-diabetic rat than the other two compounds. Tolrestat, however had greater activity in the RBC than either **8a** or **9a**. The in vitro analyses (Table IV) revealed some interesting observations. While **9a** was roughly similar to tolrestat in the various in vitro assays, compound **8a**, because it is a prodrug, was expected to be inactive or very weakly active in all in vitro screens. Although this was the case for the partially purified enzyme preparation and the isolated lens and RBC assays, **8a** had relatively good potency in the isolated sciatic nerve, comparable to that of **9a**. Presumably **8a** was metabolized to an active form, possibly the parent acid **7a**, in this tissue.

Conclusions

Analogues, represented by **5**, **7**, **9**, and **10**, of aldose reductase inhibitors **1–4** were prepared. These new compounds have an extra substituent on one of the unoccupied positions on the naphthalene ring. Primary amide prodrugs of several members from the series **5** and **7**, namely **6** and **8**, respectively, were also prepared. With only a few exceptions, all compounds in series **5**, **7**, **9**, and **10** were highly active as inhibitors of bovine lens aldose reductase. 2-Halo-, especially 2-fluoro-, substituted analogues from the series **5**, **7**, and **9** exhibited strong activity in the nerve of the 4-day-galactose-fed rat, and, as a departure to what was observed previously, the 2-halothionaphthoylamides (**5a**, **5b**) were not superior in in vivo potency in the nerve relative to their naphthoylamide counterparts **7a** and **7b**. In several instances, the primary amide prodrug **8** enhanced the in vivo potency of the respective carboxylic acid **7**. The best compounds in this study, **8a** and **9a**, were approximately equipotent to tolrestat in the sciatic nerve of the galactose-fed rat and the STZ rat, as judged by their ED_{50}'s in these assays. Compound **8a**, although not an inhibitor of aldose reductase in vitro, can be metabolized to an active form in vivo and also within the sciatic nerve. The data presented here demonstrate that analogues **8a**, **9a**, and tolrestat, to date, remain among the most orally potent, carboxylic acid based aldose reductase inhibitors known.

Experimental Section

Partially Purified Enzyme Preparation. Previously described procedure was used.[4]

Isolated Tissues. Sciatic nerves, lenses, and erythrocytes (RBCs) were isolated from rats (Sprague–Dawley male, 200–250 g) and incubated with 5 or 50 mM glucose as previously described.[4] All incubations were performed in triplicate.

Galactose Fed Rat Model. As previously described[4] with the addition of RBC collection and analysis for polyol.

Streptozocin (STZ) Diabetic Rat Model. Sprague–Dawley male rats (Charles River, NY) weighing 200–250 g were used. Diabetes was induced by the iv injection of STZ (60 mg/kg, Sigma Chemical Co., St. Louis, MO) into the tail vein. STZ was dissolved in cold 0.03 M citrate buffer, pH 4.5. Plasma glucose concentrations were determined 2 days after STZ administration and at the termination of the study. Blood samples were drawn from the tail after a 4-h fast. Glucose was quantitated with a hexokinase procedure on an Abbott automated analyzer. Only animals which had plasma glucose levels >300 mg/dL at both time points were included in the study. Test compounds were suspended in 2% Tween 80 in saline and administered to individual groups of rats (n = 8–15) daily by gavage beginning on the day of STZ administration. Control diabetic rats (n = 8) received vehicle. All rats were maintained on normal rodent diet (Purina rodent chow 5001) with free access to food and water. After 2 weeks the rats were killed by decapitation and the sciatic nerves were removed and immediately frozen on porcelain plates on dry ice. Frozen tissues were homogenized in 5% trichloroacetic acid (TCA) and the deproteinized extracts were analyzed for sorbitol and as their aldonitrile acetate or acetate derivatives as previously described.[30]

Statistical Analyses. In the in vitro tissue incubations and the in vivo studies (galactose fed and STZ diabetic rat models) all data are reported as mean values for three to eight drug-treated tissues samples. The Dunnett's multiple comparison test was used to assess the statistical significance between means of compound-treated tissues compared to the nontreated group. $P < 0.05$ was statistically significant. Thus all percentage inhibition values given in the tables for each compound are statistically significant unless otherwise indicated.

Chemistry. Melting points were determined on an Electrothermal capillary melting point apparatus and are not corrected. Proton magnetic resonance (^{1}H NMR) spectra were recorded at 200 MHz (Varian XL-200), 400 MHz (Bruker AM-400), or 80 MHz (Varian CFT-20). Infrared spectra were obtained on either a Beckman Accu Lab 2 or a Perkin-Elmer Model 781 spectrophotometer as KBr pellets, thin films on sodium chloride plates, or solutions in chloroform and are reported in reciprocal centimeters (cm^{-1}). Mass spectra were recorded on either a Finnigan Model 8230 or a Hewlett-Packard Model 5995A spectrometer. Analyses (C, H, N) were carried out on a modified Perkin-Elmer Model 240 CHN analyzer. Analytical results for elements were within ±0.4% of the theoretical values. Flash chromatography was carried out according to the procedure of Still.[30] Thin-layer analyses were done on E. Merck silica gel 60 F-254 plates of 2.5-mm thickness.

Method B. 2-Chloro-6-methoxy-1-methyl-5-(trifluoromethyl)naphthalene (13). Copper(I) chloride (35.78 g, 0.361 mol) was added to a solution of 2-bromo-6-methoxy-1-methyl-5-(trifluoromethyl)naphthalene (**12**)[7] (19.22 g, 0.0602 mol) in dry DMSO (194 mL) at room temperature under a dry N_2 atmosphere. The reaction mixture was heated at ~188 °C for 3 h, then cooled to room temperature and diluted with water (3 L). The resultant solids were collected and triturated well with EtOAc (2 L total). The triturates were combined, dried ($MgSO_4$), and filtered, and the solvent was removed to give **13** as a white solid (16.7 g, 100%). A small sample was purified by flash chromatography (9:1 petroleum ether/$CHCl_3$) to give an analytically pure product: mp 102–103 °C; NMR ($CDCl_3$, 200 MHz) δ 2.72 (s, 3 H, CH_3), 3.99 (s, 3 H, OCH_3), 7.34 (d, 1 H, J = 10 Hz, ArH), 7.48 (d, 1 H, J = 10 Hz, ArH), 7.98 (d, 1 H, J = 9 Hz, ArH), 8.17 (d, 1 H, J = 10 Hz, ArH); IR ($CHCl_3$) 2950, 2858. Anal. ($C_{13}H_{10}ClF_3O$) C, H.

Method C. 2-Iodo-6-methoxy-1-methyl-5-(trifluoromethyl)naphthalene (14). A suspension of I_2 (22.28 g, 87.5 mmol), HIO_3 (5.74 g, 32.5 mmol), and 2-methoxy-5-methyl-1-(trifluoromethyl)naphthalene (**11**)[6] (30.0 g, 125 mmol) in 80% HOAc (250 mL) and concentrated H_2SO_4 (1.5 mL) was heated to 60 °C under a dry N_2 atmosphere. After 5 h, more I_2 (9.52 g, 37.5 mmol) and HIO_3 (2.20 g, 12.5 mmol) were added. After 6 h, the reaction was cooled to room temperature and diluted with aqueous $NaHSO_3$ (2.5 L). The solid was collected by suction filtration and washed with aqueous $NaHSO_3$ (2 × 100 mL) and water (4 × 100 mL). The crude product was recyrstallized (ethanol) to provide **14** as a light pink solid (29.13 g, 64%): mp 129–130 °C; NMR ($CDCl_3$, 200 MHz) δ 2.85 (s, 3 H, ArCH_3), 3.99 (s, 3 H, ArOCH_3), 7.29 (d, 1 H, J = 9.9 Hz, ArH), 7.75 (d, 1 H,

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Table II. Biological Data

compd	% aldose reductase inhibn in vitro: isolated enzyme prepn:[a] 10^{-7} M	% aldose reductase inhibn in vitro: isolated sciatic nerve[b] 10^{-5} M	% aldose reductase inhibn in vitro: isolated sciatic nerve[b] 10^{-6} M	aldose reductase inhibition in vivo: dose, mg/kg per day	aldose reductase inhibition in vivo: % inhibn sciatic nerve[c]	aldose reductase inhibition in vivo: % inhibn diaphragm[c]
5a	86	NT		25	92	93
				5	NS	86
5b	81	NT		24	NS	90
5c	91	NT		26	NS	71
5d	87	NT		28	46	85
5e	89	NT		24	NS	83
5f	84	NT		26	NS	80
5g	86	NT		26	33	88
5h	70	NT		26	NS	91
5i	86	NT		26	NS	86
5j	94	NT		26	NS	86
5k	85	86	43	123	86	91
				11	NS	48
5l	81	68	30	133	58	85
5m	93	87	36	53	NS	82
5n	84	78	48	144	46	84
5o	84	NT		25	94	90
5p	8	NT		105	NS	34
	(53% at 10^{-6} M)					
				10	54	87
6a	NA	NT		5	33	80
				2	NS	53
6b	NA	NT		20	NS	NS
				24	68	70
7a	80	66	41	20	62	72
				16	45	46
7b	63	67	39	49	83	80
				26	43	63
7c	63	67	37	97	44	84
7d	32	65	35	48	NS	52
7e	62	48	33	53	NS	NS
7f	65	55	30	49	45	57
7g	46	NT		50	48	57
7h	42	NT		49	NS	55
7i	83	78	45	48	32	67
7j	73	NT		65	NS	23
7k	67	57	31	50	79	82
				24	37	65
7l	69	60	41	50	NS	NS
7m	52	NT		50	NS	NS
7n	23	NT		94	NS	37
7o	6	NT		47	NS	NS
	(23% at 10^{-6} M)					
7p	63	52	20	114	NS	NS
7q	83	71	28	132	24	33
7r	63	77	32	50	NS	17
7s	74	72	44	144	NS	24
7t	66	92	63	52	NS	NS
7u	64	NT		26	NS	15
7v	80	NT		52	NS	34
7w	20% at 10^{-5} M	NT		112	NS	NS
				19	77	63
8a	NA	80	17	10	59	41
				5	39	32
8b	NA	NT		24	62	53
8c	NA	NT		25	NS	NS
8d	NA	NT		48	30	NS
8e	NA	NT		48	NS	NS
8f	NA	NT		27	56	31
				14	72	74
9a	86	61	36	10	61	62
				5	50	52
9b	85	75	49	26	53	68
9c	77	68	29	51	69	62
9d	83	NT		49	36	33
9e	83	64	36	27	NS	49
10a	87	75	51	25	70	65
				15	55	59
10b	79	79	54	50	NS	47
10c	76	73	52	43	NS	24
10d	78	72	42	27	NS	39
10e	84	NT		47	NS	NS
53	NA	NT		27	48	48

Table II (Continued)

compd	% aldose reductase inhibn in vitro: isolated enzyme prepn:[a] 10^{-7} M	% aldose reductase inhibn in vitro: isolated sciatic nerve[b] 10^{-5} M	% aldose reductase inhibn in vitro: isolated sciatic nerve[b] 10^{-6} M	aldose reductase inhibition in vivo: dose, mg/kg per day	% inhibn: sciatic nerve[c]	% inhibn: diaphragm[c]
				11	29	34
				22	80	55
54	NA	NT		10	59	41
				5	36	22
60	NA	34	4	16	NS	33
				11	NS	28
61	NA	NT		32	75	75
				11	39	36
1 (tolrestat)	65	82	61	6	53	80
2	57	74	27	75	56	27
				25	33	NS
				53	93	94
3	72	NT		25	64	90
				18	39	88
4	82	58	NS	48	70	54
				10	86	76
ponalrestat	$IC_{50} = 3.7 \times 10^{-8}$ M	100	35	5	61	63
		($IC_{50} = 1.4 \times 10^{-6}$ M)			(ED_{50} = 4.0 mg/kg nerve)	
zopalrestat	89	NT		10	70	80
				5	NS	88
sorbinil	10	96	27	4	55	69
	($IC_{50} = 1.1 \times 10^{-6}$ M)	($IC_{50} = 2.2 \times 10^{-6}$ M)			(ED_{50} = 4.2 mg/kg nerve)	

[a] Inhibition of enzymatic activity in partially purified bovine lens preparation (mean of two determinations). [b] Inhibition of sorbitol accumulation in rat sciatic nerves incubated in the presence of 50 mM glucose ($n = 3$). [c] Inhibition of galactitol accumulation in the sciatic nerves or diaphragms of rats ($n = 6$) fed 20% galactose for 4 days; compounds were administered in the diet. All compounds were inactive or very weakly active in the lens at the given doses. NA = not active, no inhibitory activity at 10^{-5} M. NT = not tested. NS = no significant inhibition of polyol accumulation ($p > 0.05$).

Table III. Inhibition of Aldose Reductase in Vivo by 8a and 9a

compd	ED_{50}, mg/kg: galactose-fed rat[a] sciatic nerve	galactose-fed rat[a] RBC	STZ rat[b] sciatic nerve
8a	5.5	8.5	<3[c]
9a	4.8	3.5	4.0
tolrestat	6.4	<2[c]	4.8

[a] Inhibition of galactitol accumulation in the sciatic nerves or RBC of rats fed 20% galactose for 4 days; compounds were administered in the diet. All compounds had ED_{50}'s >100 mg/kg in the lens. [b] Inhibition of sorbitol accumulation in the sciatic nerves of two week streptozotocin diabetic rat; compounds were administered daily by gavage. [c] Lowest dose level examined.

Table IV. Inhibition of Aldose Reductase in Vitro by 8a and 9a

compd	$IC_{50} \times 10^8$ M: bovine lens AR[a]	isolated tissue[b]: sciatic nerve	lens	RBC
8a	inactive	310	>1000	1200
9a	2.5	280	34	1.9
tolrestat	3.4	54	100	1.5

[a] Inhibition of activity in a partially purified bovine lens preparation. [b] Inhibition of sorbitol accumulation in rat sciatic nerves, lens, or RBC incubated in the presence of 50 mM glucose.

J = 9.8 Hz, Ar*H*), 7.87 (d, 1 H, J = 9.6 Hz, Ar*H*), 8.22 (d, 1 H, J = 9.5 Hz, Ar*H*); MS (*m/e*) 366 (43), 129 (40), 82 (52), 69 (100). Anal. ($C_{13}H_{10}F_3IO$) C, H.

Method D. 2-Methoxy-5-methyl-1,6-bis(trifluoromethyl)naphthalene (15). A suspension of NaO_2CCF_3 (43.08 g, 0.317 mol), CuI (30.17 g, 0.158 mol), and 14 (14.5 g, 39.6 mmol) in anhydrous 1-methyl-2-pyrrolidinone (145 mL) was heated at 180 °C under a dry N_2 atmosphere for 2.5 h. The reaction was cooled to room temperature and diluted with water (1.4 L). The resultant solid was collected by suction filtration, washed with water (2 × 100 mL), and triturated with Et_2O (5 × 100 mL). The ether phase was washed with water (3 × 100 mL), brine (1 × 50 mL), dried ($MgSO_4$), and concentrated. The crude product was flash chromatographed (19:1 petroleum ether/EtOAc) to provide 15 as a white solid (5.94 g, 73%): mp 124–125.5 °C; NMR ($CDCl_3$, 200 MHz) δ 2.80 (s, 3 H, ArCH_3), 4.02 (s, 3 H, ArOCH_3), 7.41 (d, 1 H, J = 9.9 Hz, Ar*H*), 7.71 (d, 1 H, J = 9.5 Hz, Ar*H*), 8.13 (d, 1 H, J = 8.9 Hz, Ar*H*), 8.35 (d, 1 H, J = 9.5 Hz, Ar*H*); MS (*m/e*) 308 (51), 239 (27), 196 (32), 146 (28), 69 (100). Anal. ($C_{14}H_{10}F_6O$) C, H.

Method E. 2-Methoxy-5-methyl-6-nitro-1-(trifluoromethyl)naphthalene (16). To a cooled solution (0–5 °C) of Ac_2O (1.28 L) was added fuming HNO_3 (90%, specific gravity = 1.5 g/cm^3, 320 mL) dropwise via an addition funnel at such a rate as to keep the internal temperature at or below 8 °C (1.3 h total addition time). After the internal temperature had again cooled to 3–4 °C, 11[6] (400 g, 1.77 mol) was added portionwise such that the internal temperature did not rise above 10 °C and each portion was added after the temperature had recooled to 5 °C (addition time 1.25 h). After an additional 15 min the reaction mixture was added to water (3 L). The resulting solid was filtered, washed with water, and dried in vacuo. The dry solid (450 g, 5:1 mixture of 16/17) was recrystallized from EtOH (4.5 L) to provide 16 as long yellow needles (201 g, 40%): mp 141–142 °C; NMR ($CDCl_3$, 200 MHz) δ 2.84 (s, 3 H, CH_3), 4.05 (s, 3 H, OCH_3), 7.47 (d, 1 H, J = 10.0 Hz, Ar*H*), 7.87 (d, 1 H, J = 9.9 Hz, Ar*H*), 8.16 (dm, 1 H, Ar*H*), 8.39 (d, 1 H, J = 10.0 Hz, Ar*H*); MS (*m/e*) 285 (67), 268 (80), 266 (13), 248 (48), 240 (42), 196 (100), 146 (100). Anal. ($C_{13}H_{10}F_3NO_3$) C, H, N.

Method E′. 2-Methoxy-5-methyl-8-nitro-1-(trifluoromethyl)naphthalene (17). Powdered 11[6] (40.0 g, 0.167 mol) was added to mechanically stirred concentrated HNO_3 at 0–10 °C. This suspension was stirred at room temperature for 30 min and then added to water (80 mL) and filtered to provide a yellow solid. This solid was flash chromatographed (4:1 to 2:3 petroleum ether/EtOAc). Product 16 (18.8 g, 40%, R_f = 0.22, 4:1 petroleum ether/EtOAc) eluted first followed by 17 (21.83 g, 46%, R_f 0.12, 4:1 petroleum ether/EtOAc, yellow solid). A small portion of 17 was recrystallized from petroleum ether/EtOAc: mp 158–151 °C; NMR ($CDCl_3$, 200 MHz) δ 2.73 (s, 3 H, CH_3), 4.08 (s, 3 H, OCH_3), 7.25 (d, 1 H, J = 8.1 Hz, Ar*H*), 7.47 (d, 1 H, J = 9.6 Hz, Ar*H*), 8.04 (d, 1 H, J = 8.1 Hz, Ar*H*), 8.22 (d, 1 H, J = 9.6 Hz, Ar*H*); MS (*m/e*) 285 (71), 266 (8), 216 (70), 201 (48), 200 (32), 195 (100). Anal. ($C_{13}H_{10}F_3NO_3$) C, H, N.

Method F. 6-Amino-2-methoxy-5-methyl-1-(trifluoromethyl)naphthalene (18). Compound 16 (125 g, 0.438 mol),

EtOAc (100 mL), and 10% Pd–C (2.0 g) was hydrogenated at 20 psi. Due to the exothermic nature of the reduction, the shaker was shut off periodically to keep the temperature below 60 °C. After hydrogen uptake was completed, the reaction was filtered through Sulka Floc. The filtrate was concentrated and dried in vacuo to provide 18 as a yellow solid (107 g, 96%): mp 108–110 °C; NMR ($CDCl_3$, 200 MHz) δ 2.40 (s, 3 H, CH_3), 3.77 (br s, 2 H, NH_2), 3.95 (s, 3 H, OCH_3), 7.04 (d, 1 H, J = 9.7 Hz, ArH), 7.26 (d, 1 H, J = 9.5 Hz, ArH), 7.92 (dm, 1 H, ArH), 8.05 (d, 1 H, J = 9.5 Hz, ArH); IR ($CHCl_3$) 3510, 3420; MS (m/e) 255 (100), 234 (79), 212 (75). Anal. ($C_{13}H_{12}F_3NO$) C, H, N.

Method G. 2-Fluoro-6-methoxy-1-methyl-5-(trifluoromethyl)naphthalene (20). Pyridine (184 mL) was slowly added to HF–pyridine (558 mL) contained in a 4-L nalgene bottle at –60 °C under a dry N_2 atmosphere. Powdered 18 (152 g, 0.59 mol) was added followed by powdered $NaNO_2$ (68.8 g, 0.997 mol). The cooling bath was removed and the reaction was allowed to warm to room temperature. The reaction slurry was placed in an oil bath (65 °C) and heated until N_2 evolution ceased (2 h). The reaction was cooled to 10 °C and water (4 L) was added. The solid was filtered, washed with water, and dried in vacuo. The crude product (125 g) was recrystallized from ethanol to afford a light orange solid (96 g, 62%): mp 98–99 °C; NMR ($CDCl_3$, 200 MHz) δ 2.56 (d, 3 H, J = 2.2 Hz, CH_3), 3.99 (s, 3 H, OCH_3), 7.28 (d, 1 H, J = 9.3 Hz, ArH), 7.34 (t, 1 H, J = 9.3 Hz, ArH), 8.04 (m, 1 H, ArH), 8.13 (d, 1 H, J = 9.3 Hz, ArH); MS (m/e) 258 (96). Anal. ($C_{13}H_{10}F_4O$) C, H.

Method H. 2-Fluoro-6-methoxy-5-(trifluoromethyl)-1-naphthoic Acid (25). A suspension of **20** (200 g, 0.77 mol), CCl_4 (3.1 L), NBS (151 g, 0.85 mol), and $(PhCO_2)_2$ (1.2 g) was heated at reflux for 4 h. The reaction slurry was cooled to 30 °C and filtered through silica gel, and the silica gel was washed with CH_2Cl_2. The organic phase was concentrated and dried in vacuo to afford 1-(bromomethyl)-2-fluoro-6-methoxy-5-(trifluoromethyl)naphthalene (266 g, 100%): mp 96–98 °C. Anal. ($C_{13}H_9BrF_4O$) C, H.

This bromide (329 g, 0.87 mol), EtOH (3.3 L), HCO_2Na (145 g, 2.10 mol), and water (847 mL) were heated to reflux for 2 h. Upon cooling 2.5 N NaOH (250 mL) was added and the reaction mixture was then concentrated to a slurry. After the addition of water the solid was filtered, washed thoroughly with water, and dried in vacuo to afford 2-fluoro-1-(hydroxymethyl)-6-methoxy-5-(trifluoromethyl)naphthalene as a white solid (236 g, 99%): mp 110–113 °C (toluene/hexane). Anal. ($C_{13}H_8F_4O_3$) C, H.

Jones reagent (518 mL) was added dropwise over 45 min to a stirred solution of the alcohol (211 g, 0.77 mol) in acetone (2.4 L) at 10–15 °C. Stirring was continued for 2 h at ambient temperatures. The reaction slurry was cooled to 10 °C and treated with *i*PrOH (400 mL). The reaction was then filtered through Celite and the cake was washed with acetone. The filtrate was concentrated to a green solid. Water was added and the solid was mechanically stirred for 1 h. The tan solid was collected and washed thoroughly with water. The crude compound (204 g) was recrystallized from toluene/hexane to afford **25** as white crystals (158 g, 71%): mp 177–178 °C; NMR ($CDCl_3$, 200 MHz) δ 4.02 (s, 3 H, OCH_3), 7.40 (t, 1 H, J = 9.5 Hz, ArH), 7.46 (d, 1 H, J = 9.6 Hz, ArH), 8.37 (m, 1 H, ArH), 8.53 (d, 1 H, J = 9.6 Hz, ArH); IR (KBr) 3600–2500, 1695; M_r 288.0380 (calcd for $C_{13}H_8F_4O_3$, 288.0409).

Method I. 2-Ethoxy-6-methoxy-5-(trifluoromethyl)-naphthoic Acid (27a). Absolute EtOH (8.1 mL, 139 mmol) was added over a 5-min period to a stirred, room temperature suspension of NaH (7.3 g, 151 mmol, 50% dispersion in mineral oil) in dry THF (30 mL). After gas evolution ceased, CuI (13.2 g, 151 mmol) and a solution of 2-bromo-6-methoxy-5-(trifluoromethyl)-1-naphthoic acid (**22**)[7] (4.05 g, 11.6 mmol) in dry THF (20 mL) were added slowly to avoid excessive foaming. The dark green reaction mixture was heated to reflux for 2.5 h, cooled to room temperature, and added to water (1 L). Ether (600 mL) was added and the reaction mixture was acidified with concentrated HCl and stirred for 10 min. The biphasic mixture was filtered through Celite and the Celite was washed with Et_2O (100 mL) and EtOAc (100 mL). The layers were separated, and the organic layer was washed with brine and dried ($MgSO_4$). The solvent was removed and the gummy solid was triturated with petroleum ether. The resulting solid was dried in vacuo (2.66 g, 74%). A small portion was recrystallized from EtOH/water to give **27a** as an off white solid: mp 178–180 °C; NMR ($CDCl_3$, 200 MHz) δ 1.52 (t, 3 H, J = 4.8 Hz, OCH_2CH_3), 3.99 (s, 3 H, OCH_3), 4.35 (q, 2 H, J = 4.8 Hz, OCH_2CH_3), 7.39 (m, 2 H, ArH), 8.34 (dm, 1 H, ArH), 8.77 (d, 1 H, ArH); IR (KBr) 3400–2700, 1710. Anal. ($C_{15}H_{13}F_3O_4$) C, H.

Method J. 6-Methoxy-2-(methylthio)-5-(trifluoromethyl)naphthoic Acid (28). Copper(I) oxide (0.82 g, 5.72 mmol) and KOtBu (1.28 g, 11.44 mmol) were added to a stirred solution of **22**[7] (1.00 g, 2.86 mmol) in anhydrous DMF at room temperature under an Ar atmosphere. Methyl mercaptan was condensed into the reaction vessel. The reaction was heated to reflux for 3.25 h. The reaction was cooled to room temperature and diluted with 1 N HCL (200 mL) and ether (100 mL). The two-phase system was stirred rapidly for 10 min then filtered through Celite. The Celite was washed with Et_2O (4 × 30 mL). The two layers of the filtrate were separated; the aqueous phase was extracted with Et_2O (2 × 30 mL). The combined organic phase was washed with brine (2 × 50 mL), dried ($MgSO_4$), and concentrated to provide **28** as a yellow solid (0.86 g, 95%). A small sample was recrystallized from $CHCl_3$/hexane for analysis: mp 208–209 °C; NMR (DMSO-d_6, 200 MHz) δ 2.55 (s, 3 H, SCH_3), 4.00 (s, 3 H, OCH_3), 7.73 (t, 2 H, J = 9.8 Hz, ArH), 8.01 (d, 1 H, J = 9.5 Hz, ArH), 8.08 (d, 1 H, J = 10.0 Hz, ArH); IR (KBr) 1680. Anal. ($C_{14}H_{11}F_3O_3S$) C, H.

Method K. 2,6-Dimethoxy-1-naphthalenecarboxylic Acid (30). A mixture of 2,6-dimethoxy-1-naphthaldehyde (**29**)[13] (21.6 g, 95.3 mmol), resorcinol (14.71 g, 134 mmol, technical), *p*-dioxane (95 mL), *tert*-butyl alcohol (95 mL), and a catalytic amount of acetic acid (10 drops) was heated gently until it became homogeneous (~70 °C). Then a solution of sodium chlorite (80%, 12.94 g, 114 mmol, Aldrich technical grade), dissolved in water (38 mL) was added. The solution was stirred and allowed to cool to room temperature over 30 min. The mixture was concentrated and the residue was partitioned between CH_2Cl_2 and 1 M KOH. The KOH phase was washed with CH_2Cl_2 and acidified with 6 N HCl. The acidified aqueous phase was extracted with CH_2Cl_2. The extracts were combined, washed with brine, dried (Na_2SO_4), and concentrated to provide **30** (18.0 g, 82%) as an off white solid: mp 153–155 °C; NMR ($CDCl_3$, 200 MHz) δ 3.91 (s, 3 H), 4.09 (s, 3 H), 7.10 (m, 1 H), 7.24–7.35 (m, 2 H), 7.89 (d, 1 H), 8.61 (d, 1 H); IR (KBr) 3300–2900, 1690. Anal. ($C_{13}H_{12}O_4$) C, H.

Method M. 6-Methoxy-2-(phenylmethoxy)-1-naphthalenecarboxaldehyde. 1-Propanethiol (12.8 mL, 0.141 mol) was added over a 20-min period to a suspension of NaH (97%, 2.92 g, 0.122 mol) in DMF (50 mL) at 0 °C under a dry N_2 atmosphere. To the resulting solution was added a solution of 2,6-dimethoxy-1-naphthaldehyde (**29**)[13] (21.6 g, 0.100 mol) in DMF (100 mL) and the mixture was heated at 50–60 °C for 3 h. Anhydrous K_2CO_3 (28 g, 0.20 mol) and benzyl bromide (28.6 mL, 0.24 mol) were added, and heating was continued for 2 h. The reaction mixture was cooled to room temperature overnight. The mixture was concentrated and the residue was dissolved in water (800 mL) and EtOAc (1 L). The organic phase was collected, washed successively with 1 M KOH (400 mL), water (200 mL), and brine, and dried (Na_2SO_4). The residue was recrystallized from absolute EtOH to provide the title compound as a yellow solid (19.6 g, 67%): mp 115–117 °C; NMR ($CDCl_3$, 200 MHz) δ 3.91 (s, 3 H), 5.31 (s, 2 H), 7.08 (d, 1 H, J = 2 Hz) 7.2–7.5 (m, 7 H), 7.95 (d, 1 H, J = 7 Hz), 9.21 (d, 1 H, J = 8 Hz), 10.94 (s, 1 H); IR (KBr) 1650. Anal. ($C_{18}H_{16}O_3$) C, H.

Method N. 7-Methoxynaphthol[1,2-*c*]furan-1(3*H*)-one (34). *sec*-Butyllithium (1.3 M in hexane, 15.06 mL, 19.58 mmol) was added over a period of 10 min to a stirred solution of 6-methoxy-1-naphthoic acid diethylamide (**33**)[17] (5.0 g, 19.0 mmol) and TMEDA (2.96 mL, 19.58 mmol) in THF (100 mL) at –78 °C under a dry N_2 atmosphere. After an additional 1 h, DMF (3.75 mL, 47.50 mmol) was added over a 10-min period. The reaction mixture was warmed to room temperature, stirred for 1 h, and quenched with 3 M HCl (29 mL). The reaction mixture was concentrated and partitioned between ether (200 mL) and water (200 mL). The ether layer was dried (brine, Na_2SO_4) and concentrated to provide *N*,*N*-diethyl-2-formyl-6-methoxy-1-naphthalenecarboxamide as a colorless oil (5.10 g, 94%): NMR ($CDCl_3$, 400 MHz) δ 0.94 (t, 3 H, J = 7.2 Hz, CH_2CH_3), 1.41 (t, 3 H, J = 7.2 Hz, CH_2CH_3), 3.06 (dq, 2 H, J = 3.2, 7.1 Hz, CH_2),

3.76 (dq, 2 H, J = 3.6, 7.1 Hz, CH_2), 3.95 (s, 3 H, OCH_3), 7.17 (d, 1 H, J = 2.5 Hz, ArH), 7.23 (dd, 1 H, J = 2.5, 9.2 Hz, ArH), 7.78 (d, 1 H, J = 9.2 Hz, ArH), 7.79 (d, 1 H, J = 8.6 Hz, ArH), 10.14 (s, 1 H, CHO).

The amide aldehyde (5.06 g, 17.73 mmol) was dissolved in absolute EtOH (87 mL) and $NaBH_4$ (0.216 g, 5.7 mmol) was cautiously added at ambient temperature. After 3 h the reaction mixture was concentrated and added to a mixture of CH_2Cl_2 (650 ml) and water (430 mL). HCl (1 M) was added until the aqueous layer had acidic pH, and the layers were separated. The CH_2Cl_2 layer was dried (brine, Na_2SO_4) and concentrated to provide *N,N*-diethyl-2-(hydroxymethyl)-6-methoxy-1-naphthalenecarboxamide as an oil (5.10 g, 100%): NMR ($CDCl_3$, 200 MHz) δ 0.92 (t, 3 H, J = 7.2 Hz, CH_3), 1.36 (t, 3 H, J = 7.2 Hz, CH_3), 3.05 (q, 2 H, J = 7.2 Hz, NCH_2), 3.72 (m, 2 H, NCH_2), 3.90 (s, 3 H, OCH_3), 4.54 (d, 1 H, J = 12 Hz, CH_2OH), 4.72 (d, 1 H, J = 12 Hz, CH_2OH), 7.12 (m, 2 H, ArH), 7.48 (d, 1 H, J = 9.0 Hz, ArH), 7.60 (d, 1 H, J = 9.0 Hz, ArH), 7.72 (d, 1 H, J = 9.0 Hz, ArH).

A solution of the alcohol (5.10 g, 17.73 mmol), *p*-toluenesulfonic acid hydrate (5.10 g, 26.81 mmol), and toluene (187 mL) were heated at reflux overnight. The solvent was removed and the residue was flash chromatographed (1:1 hexane/EtOAc) to provide **34** (2.83 g, 74%) as a white solid: mp 164–166 °C (EtOH); NMR ($CDCl_3$, 200 MHz) δ 3.95 (s, 3 H, OCH_3), 5.35 (s, 2 H, OCH_2), 7.25 (d, 1 H, J = 3.0 Hz, ArH), 7.37 (dd, 1 H, J = 3.0, 9.2 Hz, ArH), 7.47 (d, 1 H, J = 8.4 Hz, ArH), 8.02 (d, 1 H, J = 8.4 Hz), 8.89 (d, 1 H, J = 9.2 Hz); IR (KBr) 1740; M_r 214.0623 (calcd for $C_{13}H_{10}O_3$, 214.0630).

Method O. 6-Methoxy-2-methyl-1-naphthalenecarboxylic Acid (36). Propanethiol (8.64 mL, 95.3 mmol) was added dropwise to a stirred suspension of NaH (97%, 1.95 g, 78.8 mmol) in DMF (80 mL) at room temperature under a dry N_2 atmosphere. A solution of **34** (6.80 g, 31.8 mmol) in DMF (80 mL) was added and the solution was heated at 70 °C for 4.5 h. The reaction mixture was cooled to room temperature and added to 1 N HCl (400 mL). The oil that separated was extracted with toluene (400 mL). The toluene extract was washed with water (200 mL) and saturated aqueous $NaHCO_3$ (2 × 200 mL). The $NaHCO_3$ layer was acidified with 6 N HCl and then extracted with toluene (400 mL). The toluene layer was dried (brine, $MgSO_4$) and concentrated. The resulting oil was triturated with hexane and the solid was filtered and dried in vacuo to provide 6-methoxy-2-[(propylthio)methyl]-1-naphthalenecarboxylic acid as an off-white solid (4.60 g, 50%): mp 80–83 °C; NMR ($CDCl_3$, 200 MHz) δ 0.92 (t, 3 H, J = 7.0 Hz, CH_2CH_3), 1.57 (quin, 2 H, J = 7.0 Hz, CH_2CH_3), 2.45 (t, 2 H, J = 7.0 Hz, SCH_2), 3.92 (s, 3 H, OCH_3), 4.02 (s, 2 H, $ArCH_2S$), 7.14 (d, 1 H, J = 3.0 Hz, ArH), 7.23 (m, 2 H, ArH), 7.52 (d, 1 H, J = 9.0 Hz, ArH), 7.80 (d, 1 H, J = 9.0 Hz, ArH), 8.05 (d, 1 H, J = 9.0 Hz, ArH); IR (KBr) 3300–2300, 1680. Anal. ($C_{16}H_{18}O_3S$) C, H.

A solution of the thioether (4.0 g, 13.8 mmol) in absolute EtOH (150 mL) was treated with Raney nickel (50% suspension in water, 88.8 g) and the suspension was stirred overnight under a dry N_2 atmosphere. The reaction mixture was filtered through Sulka Floc and the cake was washed with 9:1 EtOH/1 N NaOH (1 L). The filtrate was concentrated, acidified with 1 N HCl, and extracted with EtOAc (3 × 500 mL). The EtOAc phase was dried (brine, Na_2SO_4) and concentrated to provide **34** as a tan solid (2.79 g, 93%): mp 160–162 °C (6:1 MeOH/H_2O); NMR ($CDCl_3$, 200 MHz) δ 2.62 (s, 3 H, CH_3), 3.91 (s, 3 H, OCH_3), 7.2–7.4 (m, 3 H, ArH), 7.75 (d, 1 H, J = 9.0 Hz, ArH), 8.03 (d, 1 H, J = 9.0 Hz); IR (KBr) 3300–2300, 1685. Anal. ($C_{13}H_{12}O_3$) C, H.

Method P. 7-Methoxy-3-phenylnaphtho[1,2-*c*]furan-1(3*H*)-one (35). The 2-lithio analogue of 6-methoxy-1-naphthoic acid diethylamide **33**[17] (19.0 mmol) was prepared according to method N. Benzaldehyde (2.89 mL, 28.5 mmol) was added over a 10-min period at −78 °C and the reaction mixture was warmed to room temperature for 2 h. *p*-Toluenesulfonic acid hydrate (9.09 g, 45.5 mmol) was added and the reaction mixture was concentrated. Toluene (150 mL) was added and the solution was heated at reflux for 3 h. The cooled reaction mixture was concentrated and flash chromatographed (gradient 3:1 to 1:1 hexane/EtOAc) to provide a solid (4.66 g, 85%) which was recrystallized from ethanol to provide **35** as a white solid (3.62 g, 66%): mp 146–148 °C; NMR ($CDCl_3$, 200 MHz) δ 3.97 (s, 3 H, OCH_3), 6.45 (s, 1 H, OCHPh), 7.2–7.5 (m, 8 H, ArH, PhH), 8.01 (d, 1 H, J = 8.1 Hz, ArH), 9.00 (d, 1 H, J = 9.6 Hz, ArH); IR (KBr) 1745. Anal. ($C_{19}H_{14}O_3$) C, H.

Method Q. 6-Methoxy-2-(phenylmethyl)-1-naphthalenecarboxylic Acid (37). A suspension of **35** (3.6 g, 12.4 mmol), 5% Pd–C (0.8 g), and glacial HOAc (45 mL) were stirred in a 95 °C oil bath under 1 atm of H_2 pressure for 4 h. The cooled reaction mixture was filtered through Sulka Floc and the cake was washed with EtOAc (400 mL). The filtrate was concentrated and dried in vacuo to provide **37** as a white solid (3.33 g, 92%): mp 145–147 °C (EtOH); NMR ($CDCl_3$, 200 MHz) δ 3.92 (s, 3 H, OCH_3), 4.23 (s, 2 H, CH_2), 7.2–7.5 (m, 8 H, PhH, ArH), 7.74 (d, 1 H, J = 8.7 Hz, ArH), 8.00 (d, 1 H, J = 9.2 Hz, ArH); IR (KBr) 3300–2300, 1690. Anal. ($C_{19}H_{16}O_3$) C, H.

Method T. α-[(3-Methoxyphenyl)methylene]benzeneacetaldehyde (42e). To a solution of anhydrous EtOH (30 mL) and KOH (2.53 g, 46.3 mmol), at 10 °C, was added 3-methoxybenzaldehyde (41) (70.0 g, 514 mmol) and the mixture was stirred for 10 min. hydrocinnamaldehyde (**40e**) (61.9 g, 427 mmol) was added dropwise over a 4-h period. The mixture was stirred for 2 h and placed in a refrigerator overnight, poured into H_2O, and extracted with Et_2O. The crude product was distilled (0.5 mmHg, 170–176 °C) to provide **42e** as a light yellow oil (75 g, 65%): NMR (DMSO-d_6, 200 MHz) δ 3.63 (s, 3 H, OCH_3), 3.85 (s, 2 H, $ArCH_2$), 6.9–7.3 (m, 9 H, ArH, olefinic), 7.4 (s, 1 H, ArH), 9.7 (s, 1 H, CHO); IR (film) 1685; MS (m/e) 252 (62), 161 (15). Anal. ($C_{17}H_{16}O_2$) C, H.

Method T′. 2-Fluoro-3-(3-methoxyphenyl)-2-propenal (42a). 3-Methoxybenzaldehyde (41) (60 mL, 0.50 mol) and ethyl fluoroacetate (48 mL, 0.50 mol) were simultaneously added to a 0–5 °C cooled suspension of NaH (10.0 g, 0.5 mol), Et_2O (600 mL), and EtOH (2 mL) over a 1-h period. The resulting suspension was stirred overnight at room temperature and then added to water (300 mL). The layers were separated, and the organic phase was dried and concentrated to provide an oil which was flash chromatographed (85:15 hexanes/EtOAc) to provide 2-fluoro-3-(3-methoxyphenyl)-2-propenoic acid ethyl ester as an oil. The aqueous phase was acidified to pH 1 with concentrated HCl and extracted with ether (300 mL). The ether phase was dried ($MgSO_4$) and concentrated to provide the corresponding acid. This acid was esterified under Fisher conditions (concentrated H_2SO_4/EtOH) to provide more of the desired ethyl ester. The combined amount of the ethyl ester was distilled to provide pure product (63.4 g, 57%): bp 122 °C (0.1 mm); NMR ($CDCl_3$, 200 MHz) δ 1.65 (t, 3 H, J = 8 Hz, CH_2CH_3), 4.09 (s, 3 H, OCH_3), 4.63 (q, 2 H, CH_2CH_3), 7.1–7.3 (m, 2 H, vinyl H, ArH), 7.45–7.65 (m, 3 H, ArH); IR ($CHCl_3$) 1720.

A solution of this ester (63.4 g, 0.288 mol) in Et_2O (600 mL) was added dropwise over 2 h to a stirred suspension of $LiAlH_4$ (7.50 g, 0.2 mol) in Et_2O (200 mL) at 0–5 °C under a dry N_2 atmosphere. This suspension was stirred overnight at room temperature and the $LiAlH_4$ was destroyed by careful addition of water at 0 °C. The organic layer was separated, dried (brine, $MgSO_4$), and concentrated. The crude reaction product was flash chromatographed (4:1 hexanes/EtOAc) to provide 2-fluoro-3-(3-methoxyphenyl)-2-propenol as an oil (50.4 g, 96%): NMR ($CDCl_3$, 200 MHz) δ 4.12 (s, 3 H, OCH_3), 4.60 (d, 2 H, CH_2OH), 6.60–7.70 (m, 5 H, vinyl H, ArH); IR ($CHCl_3$) 3620 (sharp), 3460 (br).

A mixture of this allylic alcohol (50.0 g, 0.274 mol), MnO_2 (150 g), and ether (1 L) was stirred at room temperature for 24 h. The reaction mixture was filtered through Celite and the Celite cake was washed with ether. The combined ether extracts were concentrated, and the crude product was flash chromatographed (9:1 petroleum ether/EtOAc) to provide **42a** as an oil (36.7 g, 73%): NMR ($CDCl_3$, 200 MHz) δ 4.04 (s, 3 H, OCH_3), 6.89 (m, 1 H, vinyl H), 7.25 (m, 2 H, ArH), 7.54 (m, 2 H, ArH), 9.89 (d, 1 H, J = 8 Hz, CHO); IR ($CHCl_3$) 2840, 2740, 1680.

Method U. 2-Bromo-3-(3-methoxyphenyl)-2-propenal (42b). A solution of Br_2 (13.0 g, 81.3 mmol) in glacial HOAc (80 mL) was added over a 1-h period to a stirred, cold (10 °C) solution of 3-(3-methoxyphenyl)-2-propenal **43**[20] in HOAc (80 mL). Anhydrous K_2CO_3 (13.0 g, 101 mmol) was added and the reaction mixture was slowly warmed to 100 °C for 1 h. After cooling to room temperature, the reaction mixture was poured into ice (800 g). The separated oil was extracted with Et_2O (600 mL), washed with saturated aqueous $NaHCO_3$ (200 mL) and dried (brine,

$MgSO_4$). The extracts were concentrated and flash chromatographed (95:5 petroleum ether/EtOAc) to provide **42b** as an oil (8.4 g, 43%): NMR ($CDCl_3$, 200 MHz) δ 3.82 (s, 3 H, OCH_3), 7.04 (dd, 1 H, J = 2, 8.5 Hz, ArH), 7.40 (t, 1 H, J = 8.5 Hz, ArH), 7.53 (dd, 1 H, J = 2, 8.5 Hz, ArH), 7.64 (d, 1 H, J = 2 Hz, ArH), 7.84 (s, 1 H, olefinic), 9.30 (s, 1 H, CHO); IR ($CHCl_3$) 2860, 1695; MS (m/e) 242 (43), 240 (45), 214 (43), 212 (45), 133 (100). Anal. ($C_{10}H_9BrO_2$) C, H.

Method V. 3-(3-Methoxy-4-methylphenyl)-2-propenal (45). To a cold (0 °C) suspension of NaH (80% in mineral oil, 6.3 g, 210 mmol) in toluene (500 mL) was added triethyl phosphonoacetate (41.62 mL, 210 mmol) dropwise over a 1-h period, and the mixture was stirred for 1 h. Aldehyde **44**[21] (21.0 g, 140.0 mmol) in THF (50 mL) was added dropwise and the solution was stirred at room temperature for 20 h, quenched with H_2O, poured into H_2O, extracted with EtOAc, and dried ($MgSO_4$). Evaporation and purification by flash chromatography (4:1 hexane/EtOAc) gave 3-(3-methoxy-4-methylphenyl)-2-propenoic acid ethyl ester (25.0 g, 81%): mp 60–61 °C; MS (m/e) 220 (87), 175 (100). Anal. ($C_{13}H_{16}O_3$) C, H.

To a cold (−78 °C) solution of the ester (25.0 g, 113 mmol) in Et_2O (500 mL) was added DIBAL (1.0 M, 227.6 mL) dropwise over a 30-min period. The mixture was stirred for 1 h, quenched with MeOH, EtOAc, H_2O, acidified with HCl (6 N), extracted with EtOAc, and dried over $MgSO_4$. Evaporation gave an oil (18.9 g). This oil was dissolved in CH_2Cl_2 (300 mL) and to it was added PCC (27.46 g, 127.4 mmol) portionwise. After stirring for 2 h, ether (800 mL) was added and the dark suspension was filtered through a Florisil pad. Evaporation gave **45** as a yellow oil (13.9 g, 72%) which was carried to the next step without any further purification. A small sample was purified by flash chromatography (10:1 hexane/EtOAc). NMR (DMSO-d_6, 200 MHz) δ 2.18 (s, 3 H, $ArCH_3$), 3.85 (s, 3 H, OCH_3), 6.87 (dd, 1 H, J = 15.2 Hz, 7.8 Hz, CHCHO), 7.23 (m, 2 H, ArH), 7.32 (s, 1 H, ArH), 7.72 (d, 1 H, J = 15.2 Hz, CH=CHCHO), 9.68 (d, 1 H, J = 7.8 Hz, CHO); IR (film) 1680; MS (m/e) 176 (69), 161 (100). Anal. ($C_{15}H_6O_2$) C, H.

Method X. 2-Ethoxy-5-(3-methoxyphenyl)-4-(phenylmethyl)-2,4-pentadienoic Acid Ethyl Ester (48, R = 4-CH_2Ph). To a suspension of NaH (80% in oil, 3.57 g, 119 mmol) in DMF (500 mL) at 0 °C was added dropwise triethyl 2-ethoxyphosphonoacetate[22] (35.09 g, 130.9 mmol) over a 1-h period. After stirring for 2 h, aldehyde **42e** (30.0 g, 119 mmol) was added dropwise over a 30-min period. The whole mixture was stirred at room temperature for 15 h, poured into H_2O, and extracted with 1:1 EtOAc/Et_2O. The crude product (52 g) was used without further purification. A small sample was purified by flash chromatography (4:1 hexane/EtOAc) to give a yellow oil. NMR (DMSO-d_6, 200 MHz) δ 0.94 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 1.22 (t, 3 H, J = 7.8 Hz, OCH_2CH_3), 3.56 (m, 5 H, OCH_3, OCH_2CH_3), 4.0 (s, 2 H, $ArCH_2$), 4.16 (q, 2 H, J = 7.0 Hz, OCH_2CH_3), 6.65 (s, 1 H, olefinic), 6.85 (m, 3 H, 1 olefinic, 2 ArH), 7.1–7.4 (m, 8 H, ArH); IR (film) 1720; MS (EI) (m/e) 366 (3), 320 (21). Anal. ($C_{23}H_{26}O_4$) C, H.

Method Y. 6-Methoxy-3-(phenylmethyl)-1-naphthalenecarboxylic Acid Ethyl Ester (49, R = 3-CH_2Ph). To a solution of the ester 48 (R = 4-CH_2Ph, 50 g, 136 mmol) in toluene (500 mL) were added *p*-toluenesulfonic acid hydrate (50.0 g, 262 mmol) and I_2 (0.5 g, 1.97 mmol). The mixture was refluxed for 1 h, poured into H_2O, and extracted with Et_2O. The organic layer was washed with aqueous $NaHSO_3$ and brine and dried ($MgSO_4$). The crude product was purified by flash chromatography (10:1 hexanes/EtOAc) to provide the title compound as a light yellow solid (25.0 g, 66%): mp 86–87 °C; NMR (DMSO-d_6, 200 MHz) δ 1.4 (t, 3 H, J = 7.8 Hz, $CH_2CH_2CH_3$), 3.94 (s, 3 H, OCH_3), 4.13 (s, 2 H, $ArCH_2$), 4.4 (q, 2 H, J = 7.8 Hz, $CH_2CH_2CH_3$), 7.07 (d, 1 H, J = 1.6 Hz, ArH), 7.2–7.35 (m, 6 H, ArH), 7.64 (s, 1 H, ArH), 7.9 (d, 1 H, J = 1.6 Hz, ArH), 8.77 (d, 1 H, J = 9.4 Hz, ArH); IR (KBr) 1710; MS (EI) (m/e) 320 (100). Anal. ($C_{21}H_{20}O_3$) C, H.

Method Z. *N*-[[2-Fluoro-6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]-*N*-methylglycine (7a). Aqueous sodium hydroxide (2.5 N, 43 mL, 1.3 equiv) was added to a stirred solution of **53** (Y = CF_3, R = 2-F, 0.1 g, 8.3 mmol) in 4:1 THF/methanol (50 mL) at room temperature. After 25 min the THF/methanol was removed. Water (200 mL) was added and the aqueous solution was extracted with ether (150 mL). This ether extract was discarded. The aqueous phase was acidified to pH 1–3 with 10% aqueous HCl. The resulting white solid was collected, washed with water, and then recrystallized from ethanol/water to provide the title compound (2.48 g, 83%): mp 160–161 °C; NMR (DMSO-d_6, 400 MHz; mixture of rotamers) δ 2.81, 3.16 (2 s, 3 H, NCH_3), 3.99, 4.02 (2 s, 3 H, OCH_3), 4.08 (d, 1 H, J = 17.2 Hz, NCH_2), 4.56 (d, 1 H, J = 17.2 Hz, CH_2), 7.62, 7.66 (2 t, 1 H, J = 8.7 Hz, ArH), 7.73, 7.77 (2 d, 1 H, J = 9.5 Hz, ArH), 8.17 (m, 1 H, ArH), 7.94, 8.22 (2 d, 1 H, J = 9.5 Hz, ArH); IR (KBr) 3600–2700, 1750, 1740; MS (m/e) 359 (19), 314 (17), 271 (100). Anal. ($C_{16}H_{13}F_4NO_4$) C, H, N.

Method AA. *N*-[[2-Fluoro-6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]-*N*-methylglycine Methyl Ester (53, Y = CF_3, R = 2-F). DMF (1.6 mL) was added over a 1-min period to a stirred, room temperature suspension of **25** (125.0 g, 0.434 mol) and $(COCl)_2$ (42 mL, 0.477 mol) in CH_2Cl_2 (600 mL) under a dry N_2 atmosphere. Dissolution occurred and after 1 h the reaction mixture was concentrated and the brown solid was dried in vacuo.

In a separate flask, triethylamine (170 mL, 1.22 mol) was added to a 0 °C, stirred suspension of sarcosine methyl ester hydrochloride (91.0 g, 0.651 mol) in dry THF (600 mL) under a dry N_2 atmosphere. A solution of the above acid chloride in dry THF (350 mL) was immediately added and the resulting suspension was warmed to room temperature and stirred for 30 min. The THF was removed and the reaction mixture was added to water (1.5 L) and scratched until it solidified. The solid was collected, washed well with water (4 × 300 mL) and triturated with petroleum ether (2 × 300 mL) and then ethanol (3 × 100 mL) to provide the title compound as a tan solid (126.0 g, 78%). A small portion (1.57 g) was recrystallized with hot filtration from petroleum ether/$CHCl_3$: mp 112.5–114 °C; NMR ($CDCl_3$, 200 MHz; mixture of rotamers) δ 2.90, 3.27 (2 s, 3 H, NCH_3), 3.56, 3.82 (2 s, 3 H, CO_2CH_3), 3.85 (d, 1 H, NCH_2), 3.97 (s, 3 H, OCH_3), 4.95 (d, 1 H, NCH_2), 7.3–7.5 (m, 2 H, ArH), 8.0, 8.25 (2 m, 2 H, ArH); IR ($CHCl_3$) 1745, 1645; MS (m/e) 373 (17), 271 (100). Anal. ($C_{17}H_{15}F_4NO_4$) C, H, N.

Method BB. *N*-[(Aminocarbonyl)methyl]-2-fluoro-6-methoxy-5-(trifluoromethyl)-1-naphthalenecarboxamide (8a). A solution of **53** (Y = CF_3, R = 2-F, 126.0 g, 0.338 mol) in THF (410 mL)/methanol (350 mL) contained in a pressure apparatus at 0 °C was purged with ammonia gas for 1.5 h. This solution was warmed to room temperature with shaking where the internal pressure rose to 20 psi. After 3 days the reaction mixture was concentrated and the resulting brown solid was triturated with petroleum ether (3 × 300 mL), 1:1 petroleum ether/ether (300 mL), and ether (3 × 200 mL) and dried in vacuo to give the crude product (113 g, 94%). This tan solid was recrystallized from toluene (2.25 L) and dried at 90 °C under high vacuum to provide **8a** as an off-white solid (98 g, 82%): mp 171–173 °C; NMR ($CDCl_3$, 400 MHz; product is a 7:1 mixture of rotamers, major rotamer reported first) δ 2.98, 3.32 (2 s, 3 H, NCH_3), 4.01, 4.00 (2 s, 3 H, $ArOCH_3$), 4.22 (d, 1 H, J = 15.5 Hz, NCH_2CO_2), 4.47 (d, 1 H, J = 15.5 Hz, NCH_2CO_2), 5.54 (br s, 1 H, $CONH_2$), 6.19 (br s, 1 H, $CONH_2$), 7.38 (t, 1 H, J = 9.7 Hz, ArH), 7.45 (d, 1 H, J = 9.4 Hz, ArH), 8.01, 7.90 (2 d, 1 H, J = 9.4 Hz, ArH), 8.29 (q, 1 H, J = 3.2 Hz, ArH); IR (KBr) 3405, 1678, 1655; MS (m/e) 358 (6), 341 (6), 271 (100), 200 (34), 195 (30). Anal. ($C_{16}H_{14}F_4N_2O_3$) C, H, N.

Method DD. *N*-[2-[(Ethoxycarbonyl)amino]-2-oxoethyl]-2-fluoro-6-methoxy-*N*-methyl-5-(trifluoromethyl)-1-naphthalenecarboxamide (54). A solution of (ethoxycarbonyl)-*tert*-butylcarbodiimide[24] (0.436, 1.10 equiv) and **7a** (0.838 g, 2.38 mmol) in anhydrous THF (13.5 mL) was heated to reflux under a dry N_2 atmosphere for 10 h. The reaction was cooled to room temperature and the organic solvent was removed. The solid was flash chromatographed (1:1 petroleum ether/ethyl acetate). The resultant foam was triturated with petroleum ether and dried to provide **54** as a white solid (0.567 g, 50%): mp 130–132 °C; NMR (DMSO-d_6, 400 MHz; product is a mixture of rotamers, major rotamer reported first) δ 1.25, 1.08 (2 t, 3 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 2.79, 3.13 (2 s, 3 H, NCH_3), 4.17, 3.96 (2 q, 2 H, J = 7.1 Hz, $CO_2CH_2CH_3$), 4.02, 3.99 (2 s, 3 H, $ArOCH_3$), 4.26 (d, 1 H, J = 17.5 Hz, NCH_2CO_2), 4.86 (d, 1 H, J = 17.6 Hz, NCH_2CO_2), 7.66, 7.62 (2 t, 1 H, J = 9.4 Hz, ArH), 7.80, 7.72 (2 d, 1 H, J = 9.5 Hz, ArH), 8.17 (m, 1 H, ArH), 8.31, 7.94 (2 d, 1

H, J = 9.5 Hz, ArH), 10.95, 10.51 (2 s, 1 H, NH); IR (KBr) 1760, 1718, 1647; MS (CI) m/e 431 (M + H, 100), 411 (32), 342 (53). Anal. ($C_{19}H_{18}F_4N_2O_5$) C, H, N.

Method DD′. N-[[2-Bromo-6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]carbamic Acid Methyl Ester (56, Y = CF_3, R = 2-Br, R′ = Me). A suspension of **22** (2.0 g, 5.73 mmol), $SOCl_2$ (11 mL), and DMF (40 μL) was heated with stirring at 60 °C under a dry N_2 atmosphere for 35 min. The reaction mixture was cooled to room temperature and the $SOCl_2$ was removed. The solid was dissolved in THF (20 mL) and this solution was added dropwise to stirred, cold (0–5 °C) NH_4OH over a 5-min period. After 15 min, water (100 mL) was added and the suspension was filtered. The solid was washed with water and dried in vacuo: NMR (DMSO-d_6, 200 MHz) δ 3.99 (s, 3 H, OCH_3), 7.88 (m, 2 H, ArH), 7.90–8.25 (m, 4 H, NH_2, 2 ArH).

This carboxamide (4.18 g, 12.01 mmol) was added to a stirred, cold (0–5 °C) suspension of NaH (50% dispersion in mineral oil, 632 mg, 13.2 mmol) in anhydrous THF (110 mL) precooled in an ice bath under a dry N_2 atmosphere. The ice bath was removed and the suspension was stirred at ambient temperatures for 30 min, warmed to 40 °C, and stirred an additional 20 min. The reaction mixture was cooled to room temperature and $ClCO_2CH_3$ (0.93 mL, 12.01 mmol) in THF (25 mL) was added dropwise over a 10-min period. After an additional 20 min, saturated aqueous NH_4Cl (35 mL) was added. The reaction mixture was added to water (400 mL) and extracted with Et_2O (2 × 300 mL). The combined extracts were washed with saturated aqueous NaCl (300 mL). Silica gel (25 mL) was added to the Et_2O solution and the solvent was removed. The silica gel absorbate was flash chromatographed (3:2 petroleum ether/EtOAc) to provide the title compound as a white solid (2.71 g, 56%): mp 180–182 °C; NMR ($CDCl_3$, 200 MHz) δ 3.75 (s, 3 H, CO_2CH_3), 4.01 (s, 3 H, OCH_3), 7.38 (d, 1 H, ArH), 7.68 (d, 1 H, ArH), 7.92 (d, 1 H, ArH), 8.17 (d, 1 H, ArH); IR ($CDCl_3$) 3400, 1770, 1700. Anal. ($C_{15}H_{11}BrF_3NO_4$) C, H, N.

Method DD″. N-[[3-Bromo-6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]carbamic Acid Ethyl Ester (56, Y = CF_3, R = 3-Br, R′ = Et). 3-Bromo-6-methoxy-5-(trifluoromethyl)-1-naphthalenecarboxylic acid amide was prepared from carboxylic acid **52b**, thionyl chloride, and ammonium hydroxide according to the procedure in method DD′: mp 255 °C. Anal. ($C_{12}H_9BrNO_2$) C, H, N.

A solution of this amide (3.0 g, 8.36 mmol) and oxalyl chloride (3.0 mL, 34.4 mmol) in 1,2-dichloroethane (50 mL) was heated at reflux temperature for 24 h. The cooled reaction mixture was concentrated and redissolved in benzene (50 mL). This benzene solution was added to a solution of absolute EtOH (10 mL) in benzene (10 mL) and the reaction mixture was heated at reflux temperature for 3 h and filtered hot. Crystals were collected from the cooled reaction mixture and triturated with hexane to provide the product (2.3 g, 64%): mp 230 °C dec; NMR (DMSO-d_6, 200 MHz) δ 1.21 (t, 3 H, J = 8 Hz, CH_2CH_3), 4.01 (s, 3 H, OCH_3), 4.13 (q, 2 H, J = 8 Hz, CH_2CH_3), 7.66 (d, 1 H, J = 9 Hz, ArH), 7.78 (s, 1 H, ArH), 8.05 (d, 1 H, J = 9 Hz, ArH), 8.36 (s, 1 H, ArH), 11.37 (s, 1 H, NH). Anal. ($C_{15}H_{13}BrNO_4$) C, H, N.

Method EE. N-[[2-Fluoro-6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]thioxomethyl]-N-methylglycine Methyl Ester (55, Y = CF_3, R = 2-F). A stirred suspension of **53** (CF_3, R = 2-F, 4.54 g, 12.16 mmol), Lawesson's reagent (3.0 g, 0.6 equiv), and toluene (45 mL) was heated to reflux under a dry N_2 atmosphere. Dissolution occurred. After 3 h, more Lawesson's reagent (1.83 g, 0.37 equiv) was added. After 19 h, the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2. Silica gel was then added, and the solvents were removed. The silica gel absorbate was flash chromatographed (3:2 dichloromethane/petroleum ether) to provide the product (4.6 g, 97%). A small portion was triturated with hexane to provide an off white solid: mp 108.5–111 °C; NMR ($CDCl_3$, 200 MHz; mixture of rotamers) δ 3.12 and 3.60 (2 s, 3 H, NCH_3), 3.72 and 3.88 (2 s, 3 H, CO_2CH_3), 3.99 (s, 3 H, OCH_3), 4.29 (d, 1 H, J = 16.8 Hz, NCH_2), 5.64 (d, 1 H, J = 16.8 Hz, NCH_2), 7.34 (t, 1 H, J = 9.3 Hz, ArH), 7.47 (d, 1 H, J = 9.9 Hz, ArH), 8.20 (m, 1 H, ArH), 8.27 (d, 1 H, J = 9.9 Hz, ArH); IR ($CHCl_3$) 1745. Anal. ($C_{17}H_{15}F_4NO_3S$) C, H, N.

Method FF. N-[[2-Fluoro-6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]-N-(ethoxycarbonyl)-glycine 1,1-Dimethylethyl Ester (58, Y = CF_3, R = 2-F, R′ = Et). Sodium hydride (80% by weight dispersion in mineral oil, 0.208 g, 6.92 mmol) was added to a stirred solution of **56** (CF_3, R = 2-F, R′ = Et, 2.26 g, 6.29 mmol) in anhydrous THF (75 mL) at room temperature under a dry N_2 atmosphere. After 45 min, *tert*-butyl bromoacetate (1.52 mL, 9.43 mmol) was added and the reaction was heated to 60 °C. After 1.25 h of heating, the reaction was cooled to room temperature and the THF was removed. The residue was suspended in Et_2O (150 mL), washed with water (2 × 75 mL) and saturated aqueous NaCl (50 mL), and dried ($MgSO_4$) and the Et_2O was removed. The crude oil was flash chromatographed (4:1 petroleum ether/EtOAc) then triturated with petroleum ether (3 × 30 mL) to provide a white powder (2.40 g, 81%): mp 81–83 °C; NMR ($CDCl_3$, 200 MHz) δ 0.81 (t, 3 H, J = 7.4 Hz, $CO_2CH_2CH_3$), 1.53 (s, 9 H, $CO_2C(CH_3)_3$), 3.98 (m, 5 H, $ArOCH_3$ and $CO_2CH_2CH_3$), 4.65 (br d, 2 H, NCH_2CO_2), 7.31 (t, 1 H, J = 9.5 Hz, ArH), 7.40 (d, 1 H, J = 9.5 Hz, ArH), 8.14 (d, 1 H, J = 9.2 Hz, ArH), 8.23 (m, 1 H, ArH); IR ($CHCl_3$) 2990, 1740, 1675. Anal. ($C_{22}H_{23}F_4NO_6$) C, H, N.

Method GG. N-[[2-Fluoro-6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]glycine 1,1-Dimethyl Ester (57, Y = CF_3, R = 2-F). Triethylamine (112 mL, 0.806 mol) was added to a stirred, 0 °C suspension of glycine, *tert*-butyl ester hydrochloride (60.4 g, 0.432 mol) in dry THF (35 mL) under a dry N_2 atmosphere. After 2 min, a solution of the acid chloride of **25** (0.288 mol, prepared by method AA from 83.0 g of **25**) in dry THF (175 mL) was then added rapidly. After 10 min at 0 °C and 20 min at room temperature the THF was removed. Water (1 L) was added and the resulting solid was filtered, washed well with water, and dried in vacuo to provide **57** (R = 2-F) as a tan solid (111.4 g, 96%). A small portion was flash chromatographed (99:1 $CHCl_3/CH_3CN$) for analysis: mp 144–146 °C; NMR ($CDCl_3$, 400 MHz) δ 1.50 (s, 9 H, $OC(CH_3)_3$), 3.98 (s, 3 H, OCH_3), 4.22 (d, 2 H, J = 5.5 Hz, $NHCH_2$), 6.50 (m, 1 H, $NHCH_2$), 7.35 (m, 2 H, ArH), 8.25 (m, 1 H, ArH), 8.35 (d, 1 H, ArH); IR ($CHCl_3$) 3450, 3430, 1735, 1665. Anal. ($C_{19}H_{19}F_4NO_4$) C, H, N.

Method HH. N-[[2-Fluoro-6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]-N-(methoxycarbonyl)-glycine 1,1-Dimethyl Ester (58, Y = CF_3, R = 2-F, R′ = Me). Sodium hydride (6.63 g, 0.221 mol, 80% dispersion in mineral oil) was added to a solution of **57** (R = 2-F, 73.7 g, 0.184 mol) in dry THF (495 mL) at room temperature under a dry N_2 atmosphere. The solution was heated to 55–60 °C for 45 min and then cooled to 0 °C. A solution of $ClCO_2CH_3$ (20.0 mL, 0.259 mmol) in dry THF (120 mL) was then added dropwise over a 30-min period. After an additional 30 min at room temperature saturated aqueous NH_4Cl (13 mL) was added, and the solvents were removed. The remaining oil was then triturated with water (1 L) followed by EtOH (100 mL) whereupon it solidified with scratching. The solid was filtered, triturated further with EtOH (100 mL, then 2 × 50 mL), washed with water (3 × 200 mL), and dried in vacuo to provide the title compound as a tan solid (69.0 g, 82%). A small portion was recrystallized from petroleum ether for analysis: mp 111–114 °C; NMR ($CDCl_3$, 200 MHz) δ 1.54 (s, 9 H, $OC(CH_3)_3$), 3.57 (s, 3 H, CO_2CH_3), 3.99 (s, 3 H, OCH_3), 4.65 (m, 2 H, NCH_2), 7.35 (m, 2 H, ArH), 8.12 (d, 1 H, ArH), 8.28 (m, 1 H, ArH); IR (neat) 1755, 1740, 1690. Anal. ($C_{21}H_{21}F_4NO_6$) C, H, N.

Method II. N-[[2-Fluoro-6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]-N-(methoxycarbonyl)-glycine (9a). Compound **58** (Y = CF_3, R = 2-F, R′ = Me, 208 g, 0.453 mol) was suspended in HCO_2H (1.9 L) and stirred at room temperature under a dry N_2 atmosphere. Dissolution occurred within 45 min. After 1.5 h the HCO_2H was removed and water (4.5 L) was added. The tan solid was filtered, washed well with water, and dried in vacuo to provide material of good purity (179.8 g, 98%). The material was further purified by dissolution in toluene (600 mL) followed by precipitation by the addition of hexane (300 mL). The resulting off white solid was collected and dried at 90 °C under high vacuum: mp 159.5–162 °C; NMR (DMSO-d_6, 400 MHz) δ 3.53 (s, 3 H, CO_2CH_3), 4.01 (s, 3 H, OCH_3), 4.62 (m, 1 H, NCH_2), 4.71 (m, 1 H, NCH_2), 7.63 (t, 1 H, ArH), 7.72 (d, 1 H, ArH), 8.15 (m, 2 H, ArH); IR (KBr) 3600–2450, 1765, 1695; MS (m/e) 403 (48), 271 (100). Anal. ($C_{17}H_{13}F_4NO_6$) C, H, N.

Method JJ. N-[[2,6-Dimethoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]-N-(methoxycarbonyl)glycine Phenylmethyl Ester (59, R = 2-OMe, R′ = Me). The acid chloride of 2,6-dimethoxy-5-(trifluoromethyl)-1-naphthalene carboxylic acid **32** (3.16 g, 10.53 mL) was prepared as in method AA and reacted with glycine benzyl ester to provide *N*-[[2,6-dimethoxy-5-(trifluoromethyl)-1-naphthalenyl]carbonyl]glycine phenylmethyl ester (3.27 g, 69%). A solution of this amide ester (2.55 g, 5.70 mmol) in THF (115 mL) was cooled to −78 °C and treated with LDA (1.96 M in hexane, 3.49 mL, 6.84 mmol). After 10 min, $ClCO_2CH_3$ (0.66 mL, 8.55 mmol) was added over a 5-min period and the mixture was allowed to warm to room temperature. After 1.25 h the solvent was removed and the residue was dissolved in EtOAc (250 mL) and washed with 0.1 M H_3PO_4 (2 × 50 mL), water (50 mL), dried (brine, Na_2SO_4), and concentrated. The residue was flash chromatographed (CH_2Cl_2) to provide the title compound as a white solid (1.68 g, 58%): mp 167–168 °C; NMR ($CDCl_3$, 200 MHz) δ 3.50 (s, 3 H, CO_2CH_3) 3.89 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 4.6–5.1 (m, 2 H, NCH_2), 5.29 (s, 2 H, OCH_2), 7.15–7.45 (m, 7 H, ArH), 7.95 (d, 1 H, J = 9 Hz, ArH), 8.25 (m, 1 H, ArH). Anal. ($C_{25}H_{22}F_3NO_7$) C, H, N.

Method LL. 4,5-Dihydro-2-(2,6-dimethoxy-1-naphthalenyl)oxazole (62). The acid chloride of **30** (19.0 g, 51.8 mmol) was prepared according to the procedure in method AA and reacted with ethanolamine to provide 2,6-dimethoxy-*N*-(2-hydroxyethyl)-1-naphthalenecarboxamide (21.38 g, 95%). This amide was added to $SOCl_2$ (64 mL) at room temperature and the solution was stirred for 1 h. The reaction mixture was concentrated and the residue was dissolved in Et_2O (2.5 L) and washed with 10% NaOH (2 × 1 L). The Et_2O phase was dried (brine, K_2CO_3) and concentrated to provide **62** as an off-white solid (15.30 g, 77%): mp 117.5–120 °C; NMR ($CDCl_3$, 200 MHz) δ 3.90 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 4.23 (t, 2 H, J = 8 Hz, CH_2), 4.52 (t, 2 H, J = 8 Hz, CH_2), 7.09 (d, 1 H, J = 3 Hz, ArH), 7.17 (dd, 1 H, J = 3, 9 Hz, ArH), 7.25 (d, 1 H, J = 9 Hz, ArH), 7.80 (dd, 1 H, J = 3, 9 Hz, ArH); IR (KBr) 1665; MS (m/e) 257 (100), 228 (35), 213 (40), 198 (27), 185 (30); M_r 257.10534 (calcd for $C_{15}H_{15}NO_3$, 257.10519).

Method MM. N-(2-Acetoxyethyl)-5-bromo-2-butyl-6-methoxy-1-naphthalenecarboxamide (63). *n*-Butyllithium (2.6 N in hexane, 10.4 mL, 27 mmol) was added dropwise over 15 min to a solution of **62** (5.79 g, 22.5 mmol) in THF (200 mL) at −42 °C (CH_3CN/dry ice) under an argon atmosphere. After 1.25 h the reaction mixture was quenched with a solution of CH_3OH (5 mL) in THF (20 mL). The reaction mixture was concentrated and the residue was dissolved in Et_2O (200 mL), washed with water (100 mL), dried (brine, K_2CO_3), and concentrated to provide an oil (6.19 g) that contained 4,5-dihydro-2-(2-butyl-6-methoxy-1-naphthalenyl)oxazole and was used in the next step without further purification. This oil (6.14 g, 21.7 mmol) was dissolved in a solution of CH_2Cl_2 (20 mL) and CH_3I (10 mL, 160 mmol) and stirred 40 h at room temperature. The reaction was concentrated and a mixture containing $EtiPr_2N$ (11.34 mL, 65.1 mmol), and HOAc (3.73 mL, 65.1 mmol) in EtOAc (130 mL) was added to it. After stirring for 3 h at room temperature this mixture was added to 1 M H_3PO_4 (100 mL) and EtOAc (100 mL). The layers were separated, and the organic phase was washed with 1 M H_3PO_4 (50 mL), H_2O (25 mL), and saturated aqueous $NaHCO_3$ (25 mL), dried (brine, Na_2SO_4), and concentrated. The crude product (7.7 g) was flash chromatographed (gradient 20:1 to 10:1 CH_2Cl_2/EtOAc) to provide *N*-(2-acetoxyethyl)-*N*-methyl-2-butyl-6-methoxy-1-naphthalenecarboxamide (3.62 g, 45% from **62**) as a pale yellow oil: NMR ($CDCl_3$, 200 MHz, mixture of rotomers) δ 0.94 (t, 3 H, J = 7.5 Hz, CH_2CH_3), 1.2–1.8 (m, 4 H, $CH_2(CH_2)_2CH_3$), 1.91, 2.14 (2 s, 3 H, $COCH_3$), 2.63 (m, 2 H, $CH_2(CH_2)_2CH_3$), 2.79, 3.28 (2 s, 3 H, NCH_3), 3.92 (s, 3 H, OCH_3), 3.95 (m, 2 H, NCH_2), 4.47 (m, 2 H, OCH_2), 7.15 (m, 2 H, ArH), 7.36 (d, 1 H, J = 9 Hz, ArH), 7.56 (m, 1 H, ArH), 7.70 (d, 1 H, J = 9 Hz, ArH).

This compound was brominated with Br_2 in HOAc according to the procedure in method A to provide a light yellow solid (4.31 g) which was recrystallized from hexane/toluene to provide **63** as a tan solid (2.78 g, 64%): mp 103–105 °C; NMR ($CDCl_3$, 200 MHz) δ 0.92 (t, 3 H, J = 7.0 Hz, CH_2CH_3), 1.40 (m, 2 H, $CH_2(CH_2)_2CH_3$), 1.65 (m, 2 H, $CH_2(CH_2)_2CH_3$), 2.11 (s, 3 H, $COCH_3$), 2.67 (m, 2 H, $CH_2(CH_2)_2CH_3$), 2.75 (s, 3 H, NCH_3), 3.95 (m, 2 H, NCH_2), 4.01 (s, 3 H, OCH_3), 4.46 (m, 2 H, CH_2O), 7.25 (m, 2 H, ArH), 7.46 (d, 1 H, J = 9 Hz, ArH), 7.67 (d, 1 H, J = 9 Hz, ArH), 8.19 (d, 1 H, J = 9 Hz, ArH); IR (KBr) 1735, 1630. Anal. ($C_{21}H_{26}BrNO_4$) C, H, N.

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Registry No. **2**, 84533-47-1; **3**, 84533-26-6; **4**, 121731-13-3; **5a**, 124323-53-1; **5b**, 124323-64-4; **5c**, 134057-50-4; **5d**, 124323-58-6; **5e**, 134057-51-5; **5f**, 124323-67-7; **5g**, 124323-59-7; **5h**, 134057-52-6; **5i**, 134057-53-7; **5j**, 134057-54-8; **5k**, 134057-55-9; **5l**, 134057-56-0; **5m**, 134057-57-1; **5n**, 134057-58-2; **5o**, 134057-59-3; **5p**, 134057-60-6; **6a**, 124323-51-9; **6b**, 134057-61-7; **7a**, 124323-52-0; **7b**, 124323-55-3; **7c**, 124323-63-3; **7d**, 134057-62-8; **7e**, 124323-66-6; **7f**, 124323-60-0; **7g**, 124323-61-1; **7h**, 124323-65-5; **7i**, 124323-62-2; **7j**, 134057-63-9; **7k**, 124323-56-4; **7l**, 134057-64-0; **7m**, 134057-65-1; **7n**, 134057-66-2; **7o**, 134057-67-3; **7p**, 134057-68-4; **7q**, 134057-69-5; **7r**, 134057-70-8; **7s**, 134057-71-9; **7t**, 134057-72-0; **7u**, 134057-73-1; **7v**, 134057-74-2; **7w**, 134057-75-3; **8a**, 124323-49-5; **8b**, 124323-54-2; **8c**, 124323-57-5; **8d**, 134057-76-4; **8e**, 134057-77-5; **8f**, 134057-78-6; **9a**, 122670-49-9; **9b**, 122670-52-4; **9c**, 122670-53-5; **9d**, 134057-79-7; **9e**, 122670-54-6; **10a**, 122670-51-3; **10b**, 122670-56-8; **10c**, 122670-87-5; **10d**, 122670-55-7; **10e**, 134057-80-0; **11**, 85674-78-8; **12**, 122670-67-1; **13**, 122670-68-2; **14**, 134057-81-1; **15**, 134057-82-2; **16**, 122670-70-6; **17**, 134057-83-3; **18**, 122670-71-7; **19**, 134057-84-4; **20**, 122670-69-3; **21**, 134057-85-5; **22**, 122670-62-6; **22** carboxamide derivative, 122670-76-2; **23**, 122670-65-9; **24**, 134057-86-6; **25**, 122670-89-7; **26**, 134057-87-7; **27a**, 124323-74-6; **27b**, 124323-75-7; **27c**, 124323-82-6; **27d**, 124323-77-9; **27e**, 122670-60-4; **28**, 134057-88-8; **29**, 55218-08-1; **30**, 125342-90-7; **31**, 134057-89-9; **32**, 134057-90-2; **33**, 114326-25-9; **34**, 134057-91-3; **35**, 134057-92-4; **36**, 134057-93-5; **37**, 134057-94-6; **38**, 76283-09-5; **39**, 134057-95-7; **40e**, 104-53-0; **40f**, 134057-96-8; **41**, 591-31-1; **42a**, 134057-97-9; **42b**, 134057-98-0; **43**, 39677-52-6; **44**, 24973-22-6; **45**, 134057-99-1; **48** (R = 4-CH_2Ph), 134058-00-7; **49** (R = 3-CH_2Ph), 134058-01-8; **53**, 124323-68-8; **54**, 124323-50-8; **55** (Y = CF_3, R = 2-F), 124323-69-9; **56** (Y = CF_3, R = 2-Br, R′ = Me), 122670-77-3; **56** (Y = CF_3, R = 3-Br, R′ = Et), 134058-02-9; **56** (Y = CF_3, R = 2-F, R′ = Et), 122670-72-8; **57** (Y = CF_3, R = 2-F), 122670-88-6; **58** (Y = CF_3, R = 2-F, R′ = Et), 122670-73-9; **58** (Y = CF_3, R = 2-F, R′ = Me), 122670-57-9; **59** (Y = CF_3, R = 2-OMe, R′ = Me), 134058-03-0; **60**, 122670-50-2; **61**, 134058-04-1; $(EtO)_2POCH(OEt)CO_2Et$, 13676-06-7; $(EtO)_2POCH_2CO_2Et$, 867-13-0; methyl mercaptan, 74-93-1; 6-methoxy-2-(phenylmethoxy)-1-naphthalenecarboraldehyde, 125342-95-2; 1-propanethiol, 107-03-9; *N*,*N*-diethyl-2-formyl-6-methoxy-1-naphthalenecarbonamide, 134058-05-2; *N*,*N*-diethyl-2-(hydroxymethyl)-6-methoxy-1-naphthalenecarbonamide, 134058-06-3; 6-methoxy-2-[(propylthio)methyl]-1-naphthalenecarboxylic acid, 134077-95-5; ethyl fluoroacetate, 459-72-3; 2-fluoro-3-(3-methoxyphenyl)-2-propenoic acid ethyl ester, 120781-19-3; 2-fluoro-3-(3-methoxyphenyl)-2-propenol, 134058-07-4; 3-(3-methoxy-4-methylphenyl)-2-propenoic acid ethyl ester, 134058-08-5; 3-bromo-6-methoxy-5-(trifluoromethyl)-1-naphthalenecarboxylic acid amide, 134058-09-6; aldose reductase, 9028-31-3; galactinol, 3687-64-7.