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ACAT Inhibitors Derived from Hetero-Diels–Alder Cycloadducts of Thioaldehydes

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Abstract—Acyl-CoA:cholesterol acyltransferase (ACAT) is the enzyme largely responsible for intracellular cholesterol esterification. A systemic inhibitor of ACAT is believed to be able to slow or even reverse the atherosclerotic process. Towards that goal, a series of cyclic sulfides, derived from the hetero-Diels–Alder reaction of thioaldehydes with 1,3-dienes, and bearing carboxamide substituents, were prepared and evaluated for in vitro (in several tissues and species) and ex vivo ACAT inhibition. Minor changes in subsequent structure were found to have a significant effect in optimization of the biological activity of this series of compounds. Copyright © 1996 The DuPont Merck Pharmaceutical Company. Published by Elsevier Science Ltd

Introduction

Agents which lower lipid levels in man are being sought as therapy against the onset of atherosclerosis, a major contributing factor to coronary artery disease. A recent approach involves the inhibition of the enzyme acyl-CoA:cholesterol acyltransferase (ACAT), which catalyses the intracellular esterification of cholesterol to cholesterol ester.[1] The enzyme is widely found in various tissues, and inhibition of intestinal,[2] hepatic,[3] and arterial macrophage[4] ACAT is believed to exert an antilipidemic/antiatherosclerotic effect by decreasing cholesterol absorption, apoB secretion, and foam cell formation, respectively. The results of a recent study by Parke–Davis have decoupled the dual effects of vessel wall ACAT inhibition and serum cholesterol lowering.[5] The conclusion is that a circulating ACAT inhibitor may have the dual affect of lipid lowering and direct antiatherosclerotic action. The trend in ACAT inhibitor research has therefore shifted somewhat in recent years from intestinally directed agents to more bioavailable compounds.[6]

The purpose of this work was to design a potent, systemically available series of ACAT inhibitors. Particular emphasis was to be given to the ability of the compound to inhibit hepatic and macrophage ACAT, as models for systemic activity in man. The database of current investigational compounds was to be employed as a guide in the psuedorational design process.[7]

Key words: acyl-CoA:cholesterol acyltransferase, atherosclerosis, thioaldehyde, cycloaddition.

Chemistry

In the design of a new series of ACAT inhibitors, we examined the lead compound structures from a number of groups, including Pfizer's CP-113,818,[8] Rhone-Poulenc Rorer's RP 70676,[9] and RP 64477,[10] and our own DuP 128[11] (Fig. 1). All of these molecules bear certain structural elements in common, including amide or urea groups, aromatic or heterocyclic head groups (such as substituted phenyl or pyridyl groups), and lipophilic hydrocarbon side chains. Many of these compounds also have sulfide groups. We believed this was no coincidence, and that these structural elements are important for high inhibitory potency. The hydrocarbon groups may be needed because of the location of the enzyme in cells (ACAT is primarily membrane-bound). The role of sulfur atoms in these various chemical series was unclear.

Armed with this information, we then began designing a new series. Such an entity (Fig. 2) would contain a carboxamide group bearing some heterocyclic system. The 'tail' portion of the molecule would contain a cyclic sulfide, which would act as a template to hold one or more hydrocarbon chains. Ring size, as well as chain attachment and stereochemistry, could be optimized for the best interaction in the lipid bilayer matrix. Six-membered ring systems were chosen first for investigation. The synthesis of such a compound (**1**, Scheme 1) was envisioned to employ as a starting material the unsaturated ring compound **2**. The dihydrothiopyran ring of compound **2** could be prepared from the hetero-Diels–Alder reaction[12] of a

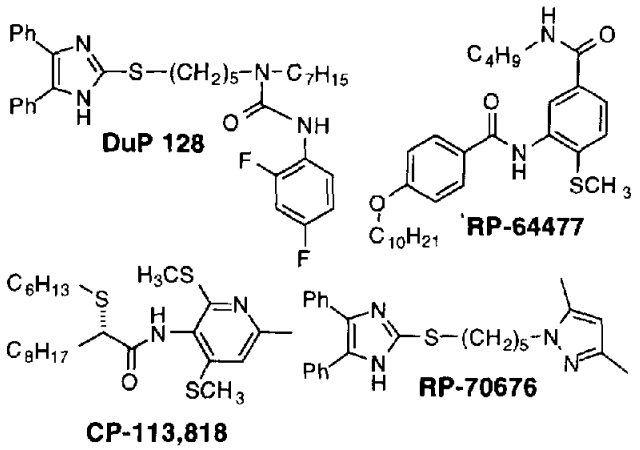


Figure 1. Recent ACAT inhibitors.

thioaldehyde (**3**) with an appropriately-substituted 1,3-butadiene. Thioaldehydes have traditionally been regarded in the organic chemistry literature as unstable compounds with very short lifetimes, and therefore not worthy of synthetic utility.[13] However, this was probably an artifact of the inadequate methods of preparation, because it was later demonstrated that the in situ presence of protic catalysts facilitated trimerization/polymerization.[14] Thioaldehydes have more recently achieved the status of a viable synthetic intermediate, as the increased volume of synthetic literature can attest.[15] The hetero-Diels–Alder reaction would allow control of the stereochemistry of the product by the stereospecificity and stereoselectivity of the cycloaddition, and (for unsymmetrical 1,3-dienes) the chain attachment would be controlled by the regioselectivity of the reaction. Issues of regioselectivity[16] and stereoselectivity[17] of thioaldehyde Diels–Alder reactions have been documented in the literature.

Synthesis of the substituted butadienes employed methods known in the literature for control of diene substitution and olefin stereochemistry (Scheme 2). The method of Butsugan et al.[18] was used for the preparation of the 2,3-disubstituted compounds **5**, which involves the Cu^{I}-catalysed double-S_N2' reaction of a Grignard reagent with butyne-1,4-diol diphosphonoester **4**. The 1,4-disubstituted dienes **7** were prepared by hydroalumination of alkynes **6**, followed by Cu^{I}-catalyzed head-to-head coupling of the resulting alkenylaluminum intermediate, according to the procedure of Zweifel and Miller.[19] Finally, the alkyne **6d** was allowed to react with catecholborane according to the method of Brown et al.,[20] the 2-alkenyl-1,3,2-benzodioxaborole

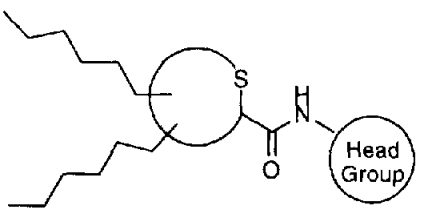
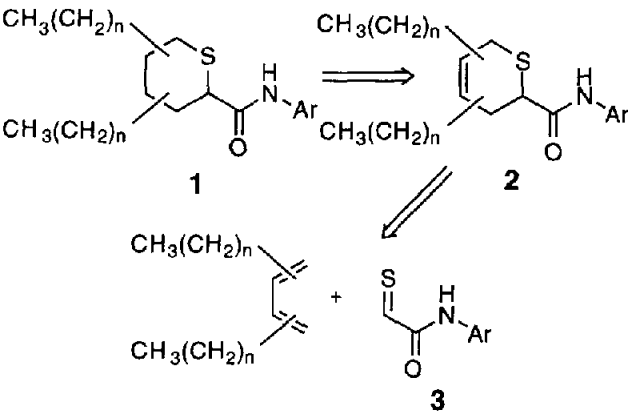


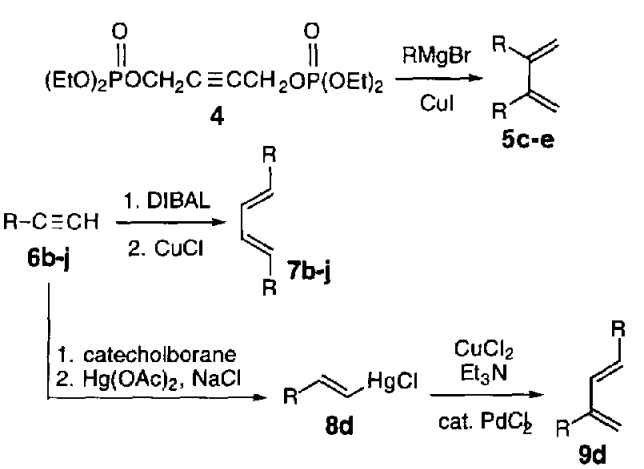
Figure 2. Design of cyclic inhibitors.



Scheme 1. Retrosynthesis of cyclic sulfides.

intermediate was converted into alkenyl mercuric salt **8d**,[21] and the Pd^{II}-catalyzed head-to-tail coupling procedure of Larock et al.[22] was employed to prepare the 1,3-disubstituted diene **9d**. Several other 1,3-dienes used in subsequent studies were obtained from commercial sources.

The initial preparation of the desired sulfur-containing cycloadducts employed the method of Hogeveen and Smit[23] for the transient generation of thioaldehydes. A phenacyl sulfide compound (such as **10** or **16**, Scheme 3) is irradiated in benzene solution with a simple sun-lamp (270 W). The phenacyl chromophore has a very low-lying n-to-π^* transition, which may be effected using such a low-power device. The modification by Vedejs[24] may be used, whereby a photochemical filter (such as aqueous $CuSO_4$ solution, used as the cooling bath medium) is placed in the beam in order to filter out radiation of wavelength below 310 nM, which results in fewer photolytically generated byproducts. The mechanism of the reaction, as investigated initially by Caserio[25] and Padwa,[26] and later by Wagner,[27] follows a Norrish-type-II path, involving γ-hydrogen abstraction by the excited carbonyl group. The resulting 1,4-diradical quickly fragments at the adjacent carbon–sulfur bond, giving the thioaldehyde and (transiently) the enol form of acetophenone.

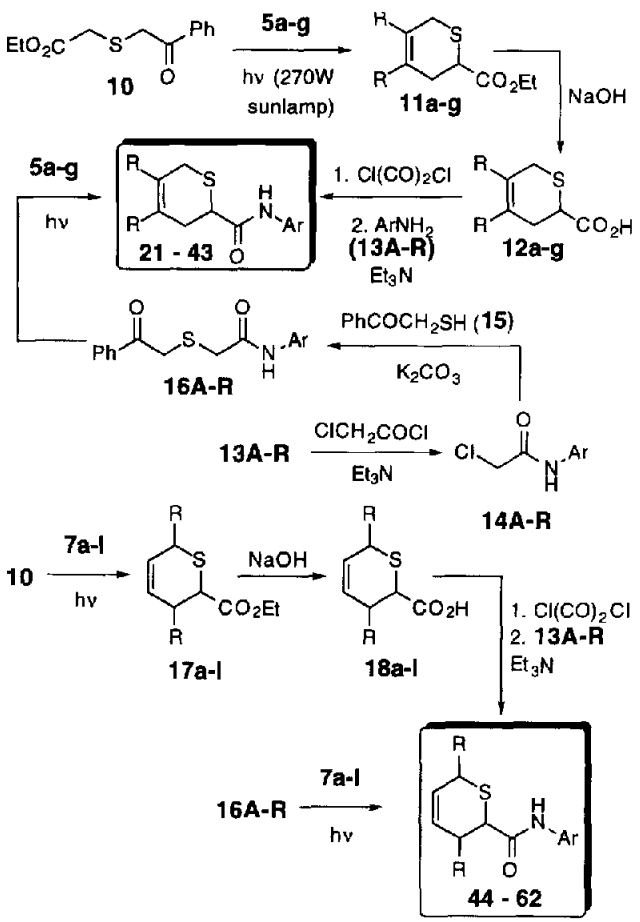


Scheme 2. Diene synthesis.

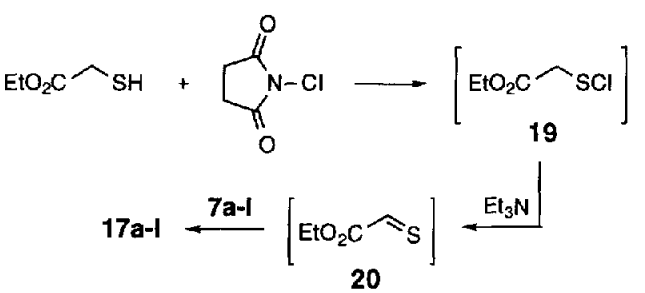
In the presence of an excess (usually 3 equiv or more) of a 1,3-diene, the thioaldehyde undergoes an uncatalysed hetero-Diels–Alder reaction at ambient temperature to afford the dihydrothiopyran products. In the case of the carboethoxy-substituted thial, ester-bearing products **11a–g** (from dienes **5a–g**) and **17a–l** (from dienes **7a–l**) were obtained. These compounds were converted to the amide final products by saponification to the acids **12** and **18**, conversion to the corresponding acid chlorides, and coupling with amines **13A–R**. A number of different amine-substituted substrates were investigated, including various substituted anilines, aminopyridines and amino-bearing five-membered heterocycles. This group included some amide substituents which had been demonstrated in previous series to impart ACAT inhibitory potency to the compounds in question. Alternatively, the final products could be prepared by photolysis and thial trapping of phenacyl sulfides **16A–R**. The amines **13A–R** were reacted with chloroacetyl chloride to give chloroacetamides **14A–R**, which were in turn coupled with thiol **15** to afford the sulfide photosubstrates. Irradiation and Diels–Alder trapping as before gave the cyclic sulfide amides directly.

The photolytic procedure has the advantage of thioaldehyde generation under completely neutral, aprotic conditions, which minimizes polymerization and trimerization, two processes that plagued thioaldehyde chemistry in the past. Also, one is allowed virtually any substituent group, not just carboalkoxy or carbonamide groups. However, one drawback to this method is that the physical limitation of the size of the photolysis apparatus (which is roughly the area of the sun-lamp bulb) requires that fairly small flasks (and therefore small amounts of substrate) be used in the reaction. An alternative procedure was therefore sought which would be amenable to scale-up. The method of Kirby et al.[28] generates carboalkoxymethyl sulfenyl chlorides (such as **19**, Scheme 4) from the corresponding thiols and *N*-chlorosuccinimide. The chloride is then added to a mixture of triethylamine and the trapping agent. Triethylamine-mediated dehydrochlorination generates the thioaldehyde **20**, which is trapped in situ in the above-described Diels–Alder reaction. The original Kirby papers described using only 1 equiv of cyclopentadiene as the trapping agent. For this work, 5 equiv of less-reactive dienes **5** and **7** were required for efficient trapping. Also, a fivefold excess of triethylamine was found to be necessary, since use of a smaller amount resulted in the formation of significant quantities of a sulfenyl chloride–diene addition product as an impurity. This modified procedure proved to be amenable to scale-up, so that the synthesis of multigram quantities of the intermediates became possible.

Stereochemical control was a feature of interest, since it was believed that optimization of the stereochemical SAR would result in useful information as to the nature of the inhibitor–enzyme interaction. In the case of the dehydrochlorination of **19** (performed at 0 °C in the presence of base), compound **17d** was obtained as an inseparable 2:1 mixture of *endo/exo* isomers (Scheme 5). ^{1}H NMR clearly showed the two isomeric products whose structures could be assigned based on extrapolation of literature data for chemical shifts and coupling constants for compounds of this type.[24b] Ester hydrolysis, followed by conversion to the carbonyl chloride derivative and coupling with the pyridyl amine **13A** gave the isomers **50** and **51** in variable ratios (ranging from 2:1 to 10:1, depending on reaction conditions and temperature). The photolysis of sulfide **10** and diene trapping gave a product ratio of 4:1, and conversion of the mixture of esters thus obtained to the amides as above gave the same variable ratios of final products, seemingly independent of the diastereomeric ratio in the starting material. That a ketene intermediate was involved here could be demonstrated by



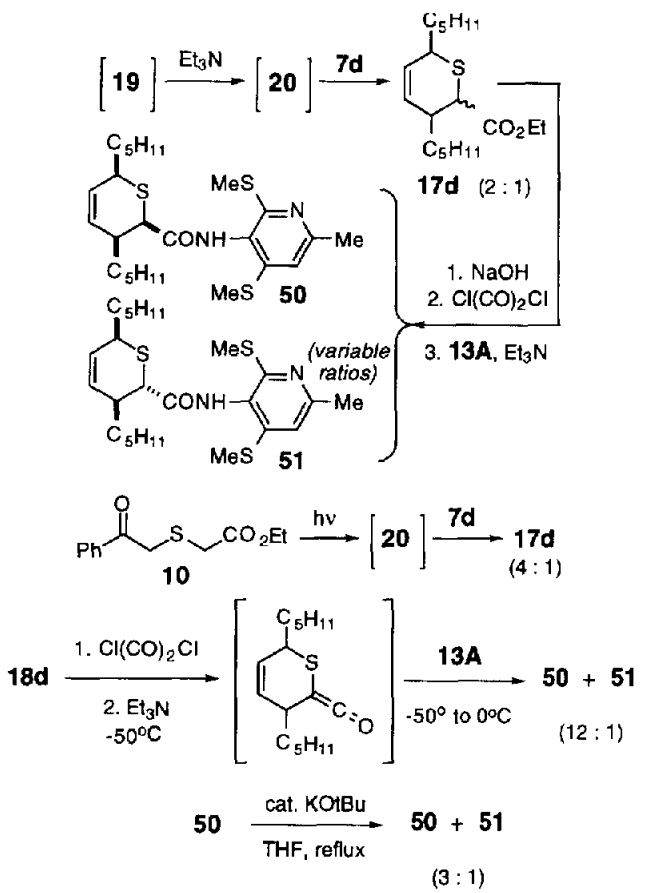
Scheme 3. Photolytic thioaldehyde generation and cycloaddition.



Scheme 4. Thioaldehyde generation via sulfenyl chlorides.

treatment of the chloride **18d** at low temperature with amine base, and subsequent addition of the pyridyl amine, to afford a 12:1 mixture of products. The presence of triethylamine (neat or in solvent) was not sufficient to equilibrate the mixture of amides, but catalytic potassium *tert*-butoxide in refluxing THF converted the single isomer **50** to a 3:1 mixture. Photolysis of sulfides such as **16A** with dienes **7** gave mixtures of products with low diasteriomeric ratios. For 1,4-disubstituted butadienes, ratios generally were lower as the steric bulk of the subsequent groups of the thioaldehyde increased.

The results of this stereochemical study can be understood by employing the reaction mechanisms involved. The *endo* selectivity of thioaldehydes bearing π-bond substituents has been explained by traditional secondary orbital overlap arguments using a transition state such as the one shown in Figure 3. This preference was diminished somewhat for dienes with bulky R^1 and R^2 groups, which interact with the thioaldehyde substituent X. The reason why the photolysis and dehydrochlorination experiments gave different product ratios is not clear but did not involve triethylamine-catalysed equilibration. Perhaps some of the cycloaddition in the dehydrochlorination method occurred from a bipolar intermediate. It is unlikely that any cycloaddition occurring in the photolysis experiment involved the reaction of the diene with an intermediate in the Norrish-type II process, since biradicals in such processes are thought to be very short-lived species. In any case, conversion of the ester groups to amides proceeding through ketene intermediates gave products with good selectivity. Thus, control of stereochemistry in the dihydrothiopyrancarboxamide series was achieved.



Scheme 5. Diastereoselectivity of thioaldehyde cycloaddition.

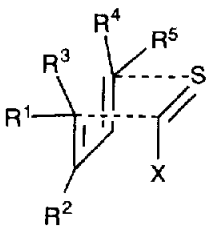


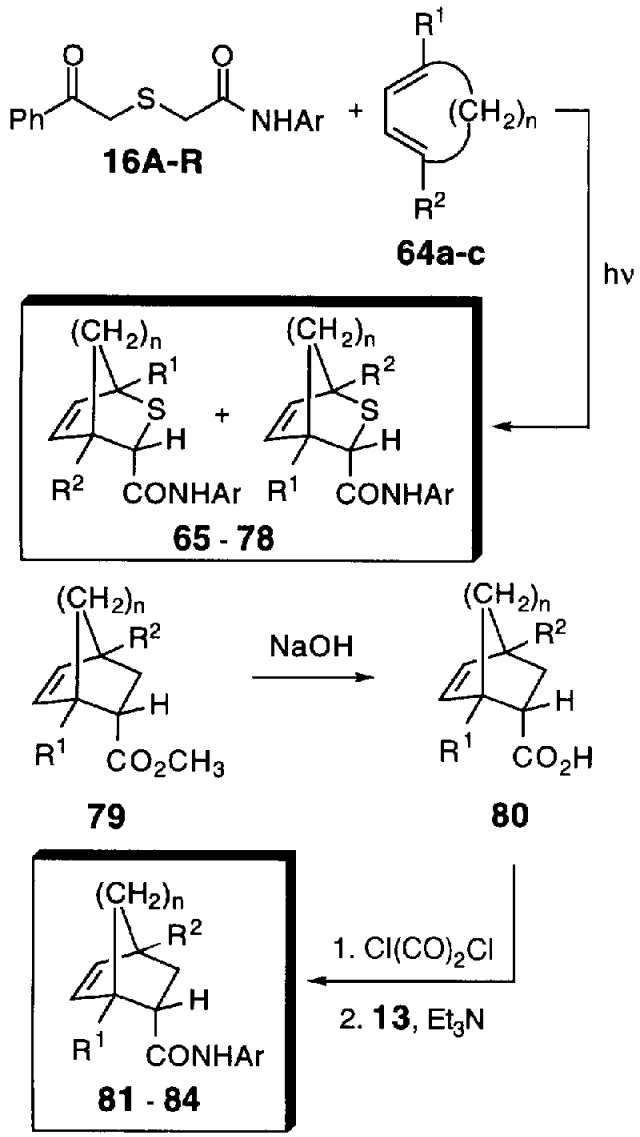
Figure 3. Cycloaddition transition state.

Cyclic dienes could also be used in this chemistry (Scheme 6), which produced amides **65–78**. In this case, particularly with cyclohexadienes, the cycloaddition proceeded with very high *endo* selectivity. This selectivity has been observed in previous studies,[17] and can be rationalized from the transition state in Figure 3, wherein R^3 and R^4 form a ring. Here, steric interactions and secondary orbital overlap work in tandem to favor *endo* products. With unsymmetrical substitution, cyclic dienes gave rise to regioisomeric mixtures of products. Bulkier aryl groups on the amide increasingly favored the isomer wherein the R^2 position was occupied by the sterically less demanding substituent, given that R^1 and R^2 were electronically similar (e.g., CH_3 and C_3H_7). For large differences in electronic properties (e.g., H and OCH_3), HOMO–LUMO interactions began to play a large role in the reaction regioselectivity, as has been demonstrated by Vedejs and Houk.[16]

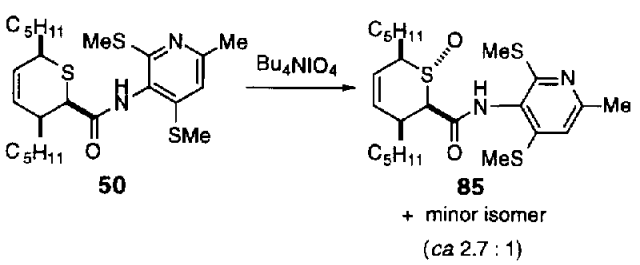
We next wanted to investigate the role of the sulfur atom in the ability for this class of compounds to inhibit the ACAT enzyme. The bicyclic series was used in this way, and some all-carbon bicyclic compounds (**81–84**, Scheme 6) were prepared. These were derived from acrylate Diels–Alder reactions, and employed the same amide-forming technology which was used for the thiabicycloalkanes. The oxidation state of the sulfur was also varied (Scheme 7) by oxidizing the single sulfide diastereomer **50** to a mixture of diastereomeric sulfoxides, the major one (**85**) of which was characterized. The sulfur atom was also replaced with oxygen, by preparing compounds **89–98** (Scheme 8). The starting point for this synthesis was the Diels–Alder cycloaddition of diethyl ketomalonate according to the method of Bonjouklian and Ruden.[29] The resulting diesters (**86a,b**) were saponified to diacids **87a,b**, which were then readily decarboxylated by heating with morpholine in pyridine solution to afford acids **88a,b**. Amides **89–98** were then prepared in the usual manner.

Our original design had tetrahydrothiopyrancarboxamides as the final products. They could be prepared from the dihydro compounds by olefin reduction

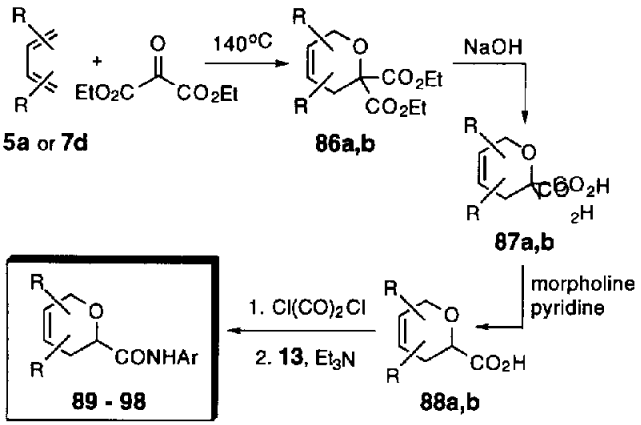
(Scheme 9). When compound **17d** (as a mixture of isomers) was present during the in situ generation of diimide (potassium diazodicarboxylate, acetic acid), the *exo* isomer was selectively reduced so that conversion of the ester to the *N*-substituted amide afforded *exo* compound **102**. The corresponding *endo* isomer **103**



Scheme 6. Use of cyclic dienes.



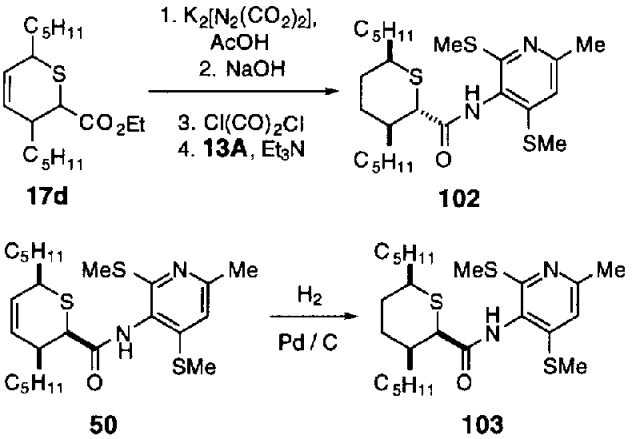
Scheme 7. Sulfide oxidation.



Scheme 8. Preparation of cyclic ethers.

could be produced by catalytic hydrogenation of the endo olefin **50**, although the reaction proceeded in very poor conversion, due probably to poisoning of the catalyst by the presence of sulfur-containing compounds.

The synthesis of a compound bearing a tertiary amide nitrogen atom could be accomplished by performing the cycloaddition sequence with a substituted amide group in place. Thus, 2,6-diisopropylaniline (**13B**) was acylated (acetyl chloride/triethylamine), and the resulting amide **104** was reduced (lithium aluminum hydride) to give the *N*-ethyl compound (**105**, Fig. 4). Chloroacetylation (to give **106**), coupling with **15** (to give **107**), and photolytic trapping with diene **5d** gave *N*-ethyl compound **108**.



Scheme 9. Saturation of dihydrothiopyran rings.

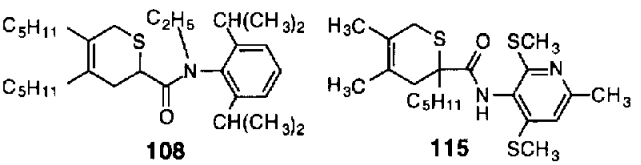


Figure 4. Alternate sites of substitution.

Many of the compounds discussed thus far were substituted with medium-length alkyl groups at the 3,6 or 4,5-positions. A compound bearing alkyl chain substitution at the 2-position was prepared by Diels–Alder cycloaddition of a thioketone. Ethyl 2-bromoheptanoate (**109**) was converted to thioacetate **110**, and then thiol **111**, by standard reactions. Coupling with chloroacetophenone gave sulfide **112**, which was photolysed in the usual manner with diene trapping to generate cycloadduct **113**. The yield of this thioketone cycloaddition was comparable to the thioaldehyde reactions, because the thioketone also bore activating substitution (carboethoxy). The remainder of the synthesis (saponification to acid **114** and amide-coupling to compound **115**, Fig. 4), proceeded without incident.

The next area of concern was absolute stereochemistry. Racemic acid **18d** was coupled to (*R*)- or (*S*)-2-amino-2-phenylethanol to give four compounds, one *endo* isomer in each case (compound **116**) being cleanly separable. The absolute assignment of all the stereocenters in (+)- and (−)-**116** could not be made with certainty at this point. Compound **116** could be subjected to methanolysis to give enantiomerically enriched methyl ester **117**, or acid hydrolysis to give (+)- or (−)-**18d**. Amide formation as before gave the enantiomers of **50**, which were measured with optical rotations of + or − 10.4±0.1° (*c* 0.60, ethanol, 25 °C). An alternative approach to (+)-**50** was investigated, which generated (+)-**116** from cycloaddition of the thioaldehyde derived from (*R*)-*N*-(2-hydroxy-1-phenylethyl)-2-phenacylthioacetamide (**119**, available from chloroacetamide **118** in the usual manner). The former route, starting from acid **18d**, proved more convenient.

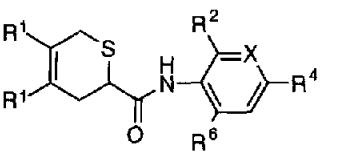
The compounds prepared by the methods described in the section above were evaluated by biological assays which are referred or described in the Experimental. The results from these assays are examined in the following section.

Results

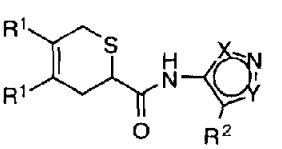
Table 1 presents inhibition data for 4,5-dialkyl-dihydrothiopyrancarboxamides wherein the aryl substituent on the amide nitrogen atom was varied, and some observations regarding the amide substituent can be made. Substituted phenyl groups, such as 2,4-difluorophenyl (found in DuP 128, our earlier lead compound[11]), provided limited potency to this series. The 2,6-disubstituted phenyl compounds, particularly 2,6-diisopropylphenyl analogues **22**, **23**, **27** and **34**, were hoped to strongly inhibit either liver or macrophage ACAT, but these routinely had only submicromolar IC_{50}s. Much more promising were the compounds bearing the 2,4-bis(methylthio)-6-methylpyridin-3-yl group (especially **21** and **26**, although for a compound bearing long-chain R groups such as **37**, potency dropped off considerably). This particular group was also used by Pfizer in their series of acyclic sulfide amides.[8] Changing the substitution pattern of the pyridine ring (i.e., **31**, **32**, and **33**) significantly lowered potency, as did substituting the pyridinyl group with five-membered heterocyclic groups as potential isosteres (**38**–**43**). The substitution of the remaining amide position with an ethyl group (**108**) had an adverse effect on ACAT inhibition. The IC_{50} for **108** was >50 μM, which represented a dramatic dropoff from the analogous N—H compound **27** (IC_{50} 600 nM).

A more limited survey of aryl substituents was performed for the 3,6-dialkyl-3,6-dihydro-2*H*-thiopyran-2-carboxamide series (Table 2). Again, the 2,4-bis(methylthio)-6-methylpyridin-3-yl group (in compound **50**, for example) proved most successful. We looked at the length and nature of the alkyl groups at the 3,6-positions. For the in vitro inhibition of rat liver ACAT, compounds with groups of 3 to 8 carbons were all sub-100 nM in IC_{50}, with C_3–C_7 (**50**, **52**, **53**, **54**, **55**, and **56**) all being virtually identical. Branching in

Table 1. ACAT in vitro data for 4,5-dialkyldihydrothiopyran compounds



Compd	R^1	R^2	R^5	R^6	X	AIV[a]
21	CH_3	CH_3S	CH_3	CH_3S	N	120
22	CH_3	$(CH_3)_2CH$	H	$(CH_3)_2CH$	CH	3300
23	C_4H_9	$(CH_3)_2CH$	H	$(CH_3)_2CH$	CH	600
24	C_4H_9	CH_3	H	CH_3	CH	1200
25	C_4H_9	Cl	H	Cl	CH	900
26	C_5H_{11}	CH_3S	CH_3	CH_3S	N	30
27	C_5H_{11}	$(CH_3)_2CH$	H	$(CH_3)_2CH$	CH	600
28	C_5H_{11}	CH_3	H	CH_3	CH	700
29	C_5H_{11}	Cl	H	Cl	CH	600
30	C_5H_{11}	F	F	H	CH	7000
31	C_5H_{11}	CH_3S	H	H	N	37,000
32	C_5H_{11}	H	CH_3S	H	N	49,000
33	C_5H_{11}	CH_3S	CH_3S	H	N	>50,000
34	C_6H_{13}	$(CH_3)_2CH$	H	$(CH_3)_2CH$	CH	600
35	C_6H_{13}	CH_3	H	CH_3	CH	900
36	C_6H_{13}	Cl	H	Cl	CH	5700
37	C_7H_{15}	CH_3S	CH_3	CH_3S	N	1720



Compd	R^1	R^2	X	Y	AIV[a]
38	CH_3	CH_3	COH	NCH_3	>50,000
39	C_5H_{11}	$CO_2C_2H_5$	NC_6H_5	CH	2400
40	C_5H_{11}	Br	NCH_3	CH	30,500
41	C_5H_{11}	CH_3	NCH_3	CCH_3	800
42	C_5H_{11}	SCH_3	CCH_3	NCH_3	1100
43	C_5H_{11}	H	NCH_3	CH	>50,000

[a]AIV designates ACAT in vitro IC_{50} in nM.

the chain (**59**), introduction of heteroatoms such as halogen (**60**) or sulfur (**61**), or introduction of unsaturation (**58** and **62**) all lowered in vitro potency from 2- to 20-fold. Thus, it appeared that straight-chain alkyl substituents on the dihydrothiopyran nucleus bearing an *N*-pyridyl carboxamide group were the superior combination in terms of in vitro ACAT inhibition.

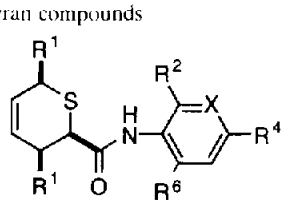
Since the positional isomers **26** and **50** were equipotent in in vitro inhibition of hepatic ACAT, substituent positioning on the dihydrothiopyran ring was studied (Table 3). For two alkyl substituents and either the 2,6-diisopropylphenyl or 2,4-bis(methylthio)-6-methylpyridin-3-yl groups on the amide nitrogen, the 4,5-, 3,6- and 3,5-substitutions were roughly equal in terms of in vitro inhibition (although positional isomerism clearly had an effect on other biological tests). However, substitution of a pentyl group at the 2-position (**115**) had the effect of lowering potency 20-fold. Thus, for in vitro ACAT inhibition, straight-chain alkyl group substitution at the 3-, 4-, 5-, or 6-positions of the dihydrothiopyran ring proved optimal. Compound **50** (DuPont Merck designation XP767) remained one of the most promising analogues in the series.

The results for bicyclic compounds are presented in Table 4. None of the bicyclic sulfides (**65–78**) were particularly potent, probably because substituent alkyl groups were insufficiently long. However, we were able to use these series to demonstrate a small dropoff in potency by replacement of sulfur with a methylene group. In all but one case (**77–83**), the inhibition IC_{50} increased without the sulfur atom.

When the sulfur atom was replaced with oxygen, a more dramatic dropoff in in vitro potency was observed (Table 5). Cyclic ether **89** was greater than 300-fold less potent than sulfide **21**, and ether **92** (bearing the less effective 2,6-diisopropylphenyl group) was threefold less potent than the corresponding sulfide **22**. A similar loss of potency was observed for all of the 3,6-disubstituted dihydropyrans from the corresponding dihydrothiopyrans. Oxidation of the sulfur atom to sulfoxide (compounds **50–85**) lowered inhibition activity threefold. At this point, the role of the sulfur atom is still unclear, but its presence does impart significant potency to these ACAT inhibitors. Perhaps the sulfur atom assists in stabilizing the hydrate of the amide, which might act as a transition state mimic for the acyl transfer reaction. Another hypothesis involves the sulfur atom mimicking the sulfur of the coenzyme A structure.

The effect of relative stereochemistry and ring saturation is shown in Table 6. The IC_{50} increased consistently by twofold by fully saturating the thiopyran ring for both the *endo* and *exo* isomers (**50–103**, **51–102**). There was little difference between *endo* isomer **50** and *exo* isomer **51**, a small preference for the *endo* compound **52** over the *exo* isomer **99**, but a more dramatic example of a stereochemistry difference between *endo* and *exo* isomers **57** and **101**, where only *endo* isomer **57** is active in vitro. In this case, perhaps the conformation of the exo compound prevents the

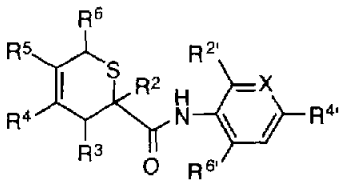
Table 2. ACAT in vitro data for 3,6-dialkyldihydrothiopyran compounds



Compd	R^1	R^2	R^4	R^6	X	AIV[a]
44	C_5H_{11}	$(CH_3)_2CH$	H	$(CH_3)_2CH$	CH	300
45	C_5H_{11}	CH_3	H	CH_3	CH	700
46	C_5H_{11}	Cl	H	Cl	CH	800
47	C_5H_{11}	F	F	H	CH	9000
48	C_5H_{11}	CH_3O	CH_3O	CH_3O	CH	1000
49	C_5H_{11}	C_2H_5O	CH_3	C_2H_5O	N	760
50	C_5H_{11}	CH_3S	CH_3	CH_3S	N	32
52	CH_3	CH_3S	CH_3	CH_3S	N	56
53	C_3H_7	CH_3S	CH_3	CH_3S	N	24
54	C_4H_9	CH_3S	CH_3	CH_3S	N	34
55	C_6H_{13}	CH_3S	CH_3	CH_3S	N	30
56	C_7H_{15}	CH_3S	CH_3	CH_3S	N	19
57	C_8H_{17}	CH_3S	CH_3	CH_3S	N	42
58	$C_3H_7CH{=}CH(CH_2)_3$	CH_3S	CH_3	CH_3S	N	410
59	$(CH_3)_2CH(CH_2)_3$	CH_3S	CH_3	CH_3S	N	107
60	$Cl(CH_2)_5$	CH_3S	CH_3	CH_3S	N	730
61	$c\text{-}C_6H_{11}S(CH_2)_3$	CH_3S	CH_3	CH_3S	N	63
62	C_6H_5	CH_3S	CH_3	CH_3S	N	94

[a]AIV designates ACAT in vitro IC_{50} in nM.

Table 3. ACAT in vitro data for positional isomers



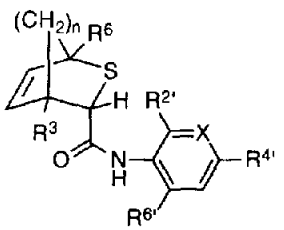
Compd	R^2	R^5	R^4	R^3	R^6	$R^{2'}$	$R^{4'}$	$R^{6'}$	X	AIV[a]
27	H	H	C_5H_{11}	C_5H_{11}	H	$(CH_3)_2CH$	H	$(CH_3)_2CH$	CH	600
44	H	C_5H_{11}	H	H	C_5H_{11}	$(CH_3)_2CH$	H	$(CH_3)_2CH$	CH	300
63	H	C_5H_{11}	H	C_5H_{11}	H	$(CH_3)_2CH$	H	$(CH_3)_2CH$	CH	600
21	H	H	CH_3	CH_3	H	CH_3S	CH_3	CH_3S	N	120
52	H	CH_3	H	H	CH_3	CH_3S	CH_3	CH_3S	N	56
26	H	H	C_5H_{11}	C_5H_{11}	H	CH_3S	CH_3	CH_3S	N	30
50	H	C_5H_{11}	H	H	C_5H_{11}	CH_3S	CH_3	CH_3S	N	32
115	C_5H_{11}	H	CH_3	CH_3	H	CH_3S	CH_3	CH_3S	N	2600

[a]AIV designates ACAT in vitro IC_{50} in nM.

key structures of the molecule from acting in the inhibition process. The difference in absolute stereochemistry for compound **50** is shown in Table 7. Most of the activity resides with the (+) enantiomer, which is the opposite rotation from that of Pfizer's CP-113,818.

Having identified XP767 and related compounds as the most potent examples in the series, these compounds were chosen to determine the hepatic bioavailability using a rat ex vivo model. Rats were dosed orally with the compounds for 3 days (see Experimental), livers were excised, and ACAT activity was determined using the standard in vitro assay. Decreased ACAT activity compared with that of the control animals would suggest that the compounds were absorbed and present in the liver in an active form. Compounds where the substituent alkyl groups were C_4 or longer showed

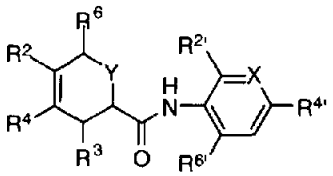
Table 4. ACAT in vitro data for bicyclic compounds



Compd	R^6	R^3	*n*	Y	$R^{2'}$	$R^{4'}$	$R^{6'}$	X	AIV[a]
65	CH_3	$(CH_3)_2CH$	2	S	CH_3S	CH_3	CH_3S	N	370
66	$(CH_3)_2CH$	CH_3	2	S	CH_3S	CH_3	CH_3S	N	1300
67	$(CH_3)_2CH$	CH_3	2	S	$(CH_3)_2CH$	H	$(CH_3)_2CH$	CH	1000
68	CH_3	$(CH_3)_2CH$	2	S	CH_3	H	CH_3	CH	8000
69	$(CH_3)_2CH$	CH_3	2	S	CH_3	H	CH_3	CH	9000
70	CH_3	$(CH_3)_2CH$	2	S	Cl	H	Cl	CH	5000
71	$(CH_3)_2CH$	CH_3	2	S	Cl	H	Cl	CH	7000
72	CH_3	$(CH_3)_2CH$	2	S	F	F	H	CH	6000
73	$(CH_3)_2CH$	CH_3	2	S	F	F	H	CH	15,000
74	CH_3O	H	2	S	CH_3S	CH_3	CH_3S	N	2600
75	H	CH_3O	2	S	CH_3S	CH_3	CH_3S	N	1400
81	H	CH_3O	2	CH_2	CH_3S	CH_3	CH_3S	N	6800
76	H	CH_3O	2	S	CH_3	H	CH_3	CH	16,500
82	H	CH_3O	2	CH_2	CH_3	H	CH_3	CH	68,000
77	H	H	1	S	CH_3S	CH_3	CH_3S	N	1170
83	H	H	1	CH_2	CH_3S	CH_3	CH_3S	N	780
78	H	H	1	S	CH_3	H	CH_3	CH	37,000
84	H	H	1	CH_2	CH_3	H	CH_3	CH	>50,000

[a]AIV designates ACAT in vitro IC_{50} in nM.

Table 5. The effect of replacement or oxidation of the ring sulfur atom on ACAT in vitro inhibition

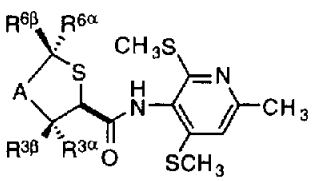


Compd	R^3	R^4	R^5	R^6	$R^{2'}$	$R^{4'}$	$R^{6'}$	X	Y	AIV[a]
21	H	CH_3	CH_3	H	CH_3S	CH_3	CH_3S	N	S	120
89	H	CH_3	CH_3	H	CH_3S	CH_3	CH_3S	N	O	41,000
50	C_5H_{11}	H	H	C_5H_{11}	CH_3S	CH_3	CH_3S	N	S	32
85	C_5H_{11}	H	H	C_5H_{11}	CH_3S	CH_3	CH_3S	N	S→O	100
90	C_5H_{11}	H	H	C_5H_{11}	CH_3S	CH_3	CH_3S	N	O	2100
22	H	CH_3	CH_3	H	$(CH_3)_2CH$	H	$(CH_3)_2CH$	CH	S	3300
92	H	CH_3	CH_3	H	$(CH_3)_2CH$	H	$(CH_3)_2CH$	CH	O	11,100
44	C_5H_{11}	H	H	C_5H_{11}	$(CH_3)_2CH$	H	$(CH_3)_2CH$	CH	S	300
94	C_5H_{11}	H	H	C_5H_{11}	$(CH_3)_2CH$	H	$(CH_3)_2CH$	CH	O	>50,000
48	C_5H_{11}	H	H	C_5H_{11}	CH_3O	CH_3O	CH_3O	CH	S	1000
96	C_5H_{11}	H	H	C_5H_{11}	CH_3O	CH_3O	CH_3O	CH	O	>50,000
49	C_5H_{11}	H	H	C_5H_{11}	C_2H_5O	CH_3	C_2H_5O	N	S	760
98	C_5H_{11}	H	H	C_5H_{11}	C_2H_5O	CH_3	C_2H_5O	N	O	>50,000

[a]AIV designates ACAT in vitro IC_{50} in nM.

greatly reduced ex vivo ACAT activity (Table 8). No inhibition was observed when the chains were C_3 or less. This absence of activity was not due to lack of absorption, because similar serum levels were observed for both **50** and **53**. Differences in tissue distribution or metabolism could explain the inactivity in C_3 versus C_4. An additional possibility is that the C_3-compound, but not C_4, was diluted during the preparation of the liver microsomes for the ACAT assay. However, since these two compounds differ by only one methylene group, one would not expect to observe such 'all-or-nothing' activity. There was a large stereochemical difference between *endo/exo* isomers **50** and **51**, and the (+) isomer of **50** appeared to have somewhat greater ex vivo activity than the (−) isomer.

Table 6. The effect of relative stereochemistry and ring saturation on ACAT in vitro inhibition



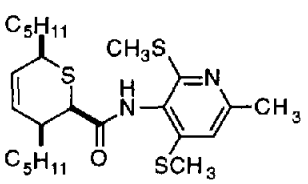
Compd	A	$R^{3\alpha}$	$R^{3\beta}$	$R^{6\alpha}$	$R^{6\beta}$	AIV[a]
52	CH=CH	H	CH_3	H	CH_3	56
99	CH=CH	CH_3	H	CH_3	H	99
50	CH=CH	H	C_5H_{11}	H	C_5H_{11}	32
51	CH=CH	C_5H_{11}	H	C_5H_{11}	H	43
103	CH_2CH_2	H	C_5H_{11}	H	C_5H_{11}	80
102	CH_2CH_2	C_5H_{11}	H	C_5H_{11}	H	85
57	CH=CH	H	C_8H_{17}	H	C_8H_{17}	42
101	CH=CH	C_8H_{17}	H	C_8H_{17}	H	>10,000

[a]AIV designates ACAT in vitro IC_{50} in nM.

It was clear that these compounds were sufficiently absorbed to work in the liver. A model for action at the arterial wall was obtained by measuring ACAT inhibition in human macrophage cells (Table 8, fourth column). Cultures of macrophages obtained from human monocytes were grown, and the cholesterol esterification in the presence of these inhibitors was measured in the cell culture upon addition of labeled oleic acid. The IC_{50} in nM was obtained for each compound as shown for **50** (XP767) in Figure 5 and as presented in Table 8.

The hepatic ACAT inhibition by the compounds with substituents of varying chain lengths was of comparable magnitude. In constrast, inhibition of macrophage ACAT activity was 20–35 times less potent with a substituent chain length of C_7 or C_8 than corresponding compounds with shorter chains. This decrease is not thought to be due to decreased solubility of the more

Table 7. The effect of absolute stereochemistry on ACAT in vitro inhibition



Compd	$[\alpha]_{25}$[a] (°)	AIV[b]
rac-**50**	0	32
(−)-**50**	−10.30	160
(+)-**50**	+10.50	56

[a]Optical rotation, *c* 0.60, ethanol.
[b]AIV designates ACAT in vitro IC_{50} in nM.

Table 8. The effect of structure on various biological results

Compd	Comment	AIV[a]	Ex vivo[b]	Serum levels[c]	HFC[d]
99	All *endo*; side-chain = CH_3	99	20	[e]	[e]
53	C_3H_7	24	0	1293	19
54	C_4H_9	34	76	[e]	[e]
50	C_5H_{11}	32	64[f]	896	12
55	C_6H_{13}	30	[e]	[e]	[e]
56	C_7H_{15}	19	91	2302	363
57	C_8H_{17}	42	86	584	708
51	All C_5H_{11}; stereochem. = *exo*	43	0	[e]	46
(−)-**50**	*endo*, absolute	160	33	[e]	24
(+)-**50**	*endo*, absolute	56	86	[e]	1.4
103	Reduced double bond	80	68	2110	[e]
—	CP-113,818	20	60	958	58

[a]AIV designates ACAT in vitro IC_{50} in nM.
[b]ACAT ex vivo: % inhibition in in vitro assay by liver microsomes compared with control.
[c]Serum levels by HPLC, in ng/mL.
[d]Inhibition of ACAT in human foam cells, IC_{50}, in nM.
[e]Not recorded.
[f]Standard deviation = ± 15, SEM = ± 4. **50** used as positive standard for each compound.

lipophilic analogues because the same vehicle (DMSO) was used in both the in vitro hepatic and macrophage assays. This is not dissimilar from data obtained from the diarylthioimidazole ACAT inhibitor series, where it was demonstrated that two similar compounds had quite different potencies with respect to hepatic and macrophage ACAT,[30] and suggests either the presence of isozymes or that a different microenvironment surrounds the enzyme in the two tissues. A twofold increase in potency was measured for *endo* isomer **50** over exo **51**. Again, (+)-**50** was preferred, being 17 times more potent than the other enantiomer. Taken together, the data suggest that to obtain optimal hepatic and arterial wall (macrophage) ACAT inhibition, the substituent chain length should be between four and six carbons.

The pharmacokinetics of **50** was then studied. The compound was dosed in rats at 5 mg/kg (iv) and 10 mg/kg (po). The graph in Figure 6 shows the serum levels versus time. At the T_{max} of 4 h, the C_{max} was 1.0 μg/mL. The bioavailability (F) was found to be 71%.

Finally, compounds **50** and **57** were taken into safety assessment to look for adverse effects on adrenal tissue, which has been observed for other systemic ACAT inhibitors (such as Warner–Lambert's PD-132301, in dogs[31]). The compounds were dosed orally to rabbits at three different doses for 7 days, after which the animals were sacrificed and adrenals removed for further study. The effects of the drugs are presented in Table 9 as the percent ratio of the weight of the adrenals to that of the brain. Significant damage to the adrenals was observed with XP767 (**50**), as adrenal weight loss was recorded at dosing as low as 10

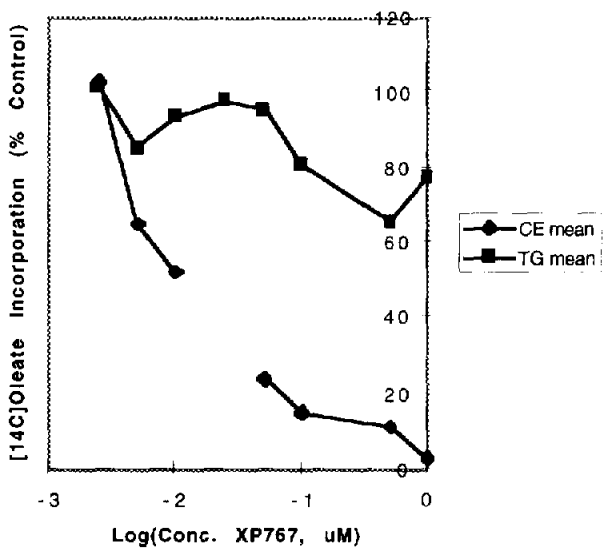


Figure 5. The effect of XP767 (**50**) on cholesterol esterification and triglyceride formation in human macrophages.

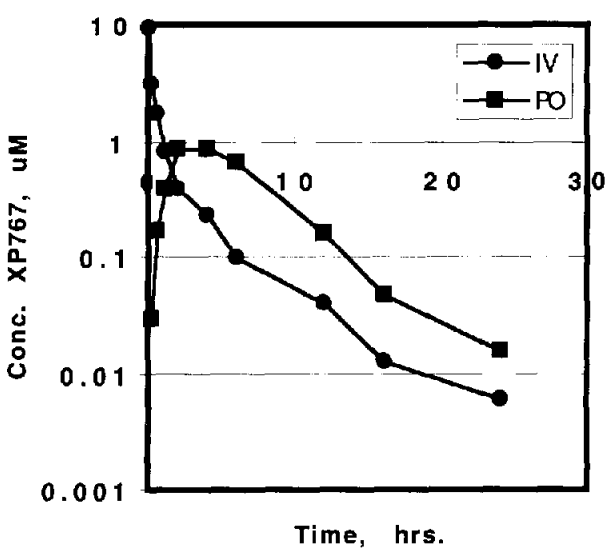


Figure 6. Pharmacokinetic profile of XP767.

mg/kg. Histology slides revealed severe cellular damage. The thickness of the zona fasiculata and reticularis portions of the cells was markedly reduced compared with controls (roughly one-half the normal thickness). Close examination revealed multifocal vacuolar degeneration of epithelial cells and a mild inflammatory cell infiltrate. On the other hand, the higher homologue **57** (DuPont Merck designation XR920), which was equipotent in terms of liver ACAT and even slightly more effective at liver ex vivo inhibition than **50**, was not significantly toxic toward adrenal tissue. Organ weight loss was significantly lower, and cellular damage was noticeably less. Hepatic activity was measured in this study, and both **50** and **57** significantly affected ACAT activity in the livers of the rabbits. Since there appeared to be some difference in tissue selectivity, inhibition of ACAT in adrenal cells was determined for **50** (IC_{50} 13 nM) and **57** (IC_{50} 84 nM). Therefore, the potency of ACAT inhibition varied somewhat between tissue types, with little difference seen in the liver for **50** and **57**, more in the adrenals (sixfold), and a large difference seen in human foam cells (60-fold).

Discussion and Conclusions

A new series of compounds derived from cycloaddition products of in situ-generated thioaldehydes were shown to be a source of potent ACAT inhibitors. The most promising compound in terms of inhibiting ACAT (in rat liver, human foam cells and rabbit adrenals) and absorption was XP767 (**50**). However, XP767 was shown to be toxic toward adrenal tissue in rabbits. A similar compound, XR920 (**57**), did not exhibit significant toxicity, but compounds **50** and **57** had similar potency of inhibiting ACAT in adrenal tissue. Although other groups have observed adrenal toxicity for other ACAT inhibitors, the above results indicate that inhibition of ACAT in any tissue and adrenal toxicity are not inherently linked by mechanism. A low-toxicity, well-absorbed compound such as XR920 would make a fine candidate for further study, save for the fact that the potency of XR920 for inhibition of ACAT in human foam cells, which should be a good model for antiatherogenesis, was observed to be quite low. Therefore, future efforts in this field need to focus on finding potent inhibitors without adverse side-effects in adrenal tissue.

Table 9. Safety assessment data for compounds **50** and **57**

Compd	Dose[a]	Plasma[b]	Wt %[c]	Hepatic activity[d]
Vehicle	—	—	2.5 ± 0.3	100
50	100	513 ± 76	0.6 ± 0.2	10 ± 2
50	30	420 ± 117	0.9 ± 0.9	12 ± 2
50	10	41 ± 4	1.1 ± 0.3	51 ± 17
57	100	306 ± 80	2.2 ± 0.2	5 ± 2
57	30	261 ± 45	2.1 ± 0.2	22 ± 16
57	10	197 ± 43	2.1 ± 0.1	13 ± 5

[a]Dose of compound to rabbits ($n = 3$), mg/kg. [b]Concentration of drug in plasma, ng/mL. [c]Weight ratio of adrenals to brain, in percent. [d]Activity of hepatic ACAT, percent of control.

Experimental

All reactions detailed below were performed using reagent-grade materials and solvents, and were performed under dry nitrogen atmosphere. Starting materials were purchased from Aldrich, Lancaster Synthesis, or Janssen (Spectrum). The phrase 'flash chromatography' and related phrases refer to the separation method reported by Still et al.[32] Melting points are uncorrected, and were obtained in an open capillary tube in an Electrothermal 9100 apparatus. ^1H and ^{13}C NMR spectra were obtained on a Unity 300 MHz spectrometer, and chemical shifts are reported in ppm δ using tetramethylsilane as reference. IR spectra were obtained on a Perkin–Elmer 1600 FTIR spectrometer. Mass spectra were obtained on a Hewlett Packard 5988A MS spectrometer, employing NH_3 CI detection. Elemental analyses were performed by Quantitative Technologies, Inc., Bound Brook, NJ. Selected physical and spectral data for the compounds of interest are collected in Table 10.

Assay of the inhibition of ACAT

The ability of the compounds to inhibit ACAT in rat hepatic microsomes was determined by measuring the formation of labeled cholesteryl oleate (pmol/min/mg) from [^{14}C] oleyl-CoA as described in the literature.[33] The data are expressed as the concentration at which ACAT activity is inhibited by 50% (IC_{50}). IC_{50}s were obtained from assays performed in duplicate containing a minimum of four inhibitor concentrations which bracket the IC_{50}. The average range of replicates was ±17%.

The inhibition of esterification of cholesterol in the human foam cell model was determined as follows: human blood was obtained in heparin by venipuncture. Mononuclear cells were isolated using LeucoPREP™ tubes. The cells were resuspended in growth media, then seeded at 75,000 cells/cm^2. They were incubated 3 h at 37 °C, 5% CO_2. Nonadherent cells were removed by washing three times with 10% FBS-PBS, and the cells were re-fed with growth media with 10% human serum added. The cells were grown for 7–10 days, and re-fed every 2–3 days. They were cholesterol loaded with ac-LDL (100 μg/mL) 17 h prior to use in the experiments. After loading, cholesterol esterification was determined in the presence or absence of inhibitors. Compounds of interest were dissolved in DMSO and incubated with the cells for 4 h. Cells were incubated with [^{14}C] oleic acid (100 mM) for the last 2 h of drug incubation, and quantitation of cholesterol ester formation was performed as described by Maduskuie et al.[30]

The inhibition of esterification of cholesterol ex vivo from liver cells was determined as follows: male Sprague–Dawley rats were dosed (oral gavage) with

Table 10. Selected physical and spectral data for new compounds

Compd	Mp (°C)	^{1}H NMR δ^a	^{1}H NMR J^b	^{13}C NMR[c]	IR[d]	MS[e]	Analysis
21	188–190	3.73	4.8	169.8	1658	355	f
22	189–191	3.77	5.1	170.3	1650	332	f
23	111–113	3.79	5.3	170.5	1650	416	f
24	115–117	3.77	5.5	169.4	1654	360	f
25	105–107	3.78	5.0	169.5	1666	400	f
26	80–82	3.73	5.3	169.9	g	467	h
27	88–89	3.79	5.1	170.5	1652	444	f
28	75–77	3.77	5.3	169.4	1652	388	f
29	93–94	3.78	5.1	169.5	1666	428	f
30	i	3.80	5.0	169.8	1690	396	f
31	i	3.80	5.0	170.2	1688	407	h
32	99–100	3.78	5.1	170.0	1698	407	j
33	96–97	3.78	4.9	170.0	1686	453	f
34	60–63	3.79	5.1	170.5	1652	472	f
35	79–81	3.76	5.3	169.5	1682	416	f
36	91–93	3.75	5.1	169.4	1666	456	p
37	77–79	3.73	5.3	169.9	1658	551	f
38	186–188	3.69	4.9	g	1696	358	f
39	i	3.54	5.3	169.7	g	498	h
40	84–86	3.76	5.0	169.5	1686	442	h
41	94–96	3.75	5.1	170.5	1654	392	f
42	94–95	3.76	5.1	170.5	1668	424	f
43	i	3.70	5.5	168.9	1688	364	f
44	99–101	4.02	4.4	169.5	1650	444	f
45	125–127	4.01	4.0	168.5	1650	388	f
46	110–112	4.02	4.0	168.7	1662	428	h
47	i	3.44	2.2	g	g	396	h
48	55–57	3.48	1.8	169.7	1686	450	h
49	83–85	3.45	1.1	169.2	1662	463	f
50	88–89	3.46	2.2	169.1	1656	467	f
51	150–151	4.03	4.4	168.9	1656	467	f
52	138–139	3.38	3.0	169.5	1658	355	f
53	97–98	3.46	3.0	169.8	1670	411	f
54	117–118	3.46	2.2	169.8	1656	439	f
55	i	3.45	2.6	169.8	g	495	f
56	i	3.45	2.2	169.8	1689	523	f
57	i	3.45	2.6	g	1658	551	f
58	52–54	3.46	2.2	169.8	g	467	f
59	87–89	3.47	2.5	169.2	1692	479	f
60	i	3.46	2.2	g	g	547	h
61	i	3.46	2.0	g	g	639	h
62	185–186	3.68	1.8	168.9	g	479	f
63	85–86	3.82	4.8	169.8	g	444	f
65	i	4.29	k	175.4	1664	409	h
66	149–150	3.89	k	169.8	1664	409	f
67	177–178	3.89	k	170.3	1660	386	f
68	155–156	4.27	k	169.0	1654	330	f
69	159–160	3.88	k	169.2	1654	330	p
70	i	4.28	k	g	1660	370	h
71	140–141	3.86	k	169.1	1668	370	f
72	i	4.22	k	169.1	g	338	h
73	i	3.81	k	169.2	g	338	h
74	72–74	4.24	3.3	169.4	1680	383	h
75	75–77	4.36	k	168.2	1680	383	h
76	147–148	4.33	k	167.9	1656	304	f
77	158–159	4.51	4.0	169.1	1662	339	f
78	139–140	4.52	4.0	168.4	1652	260	j
81	140–141	2.92	9.9, 3.6 m	171.9	1666	365	f
82	152–153	2.92	10.0, 4.2 m	171.7	1648	286	f
83	189–190	2.98	k	172.9	1662	305	f
84	190–191	2.98	k	171.9	1652	242	f
89	149–150	4.21	9.9, 4.7 m	170.5	1698	339	f
90	i	4.31	3.3	169.6	g	451	f

Table 10. Selected physical and spectral data for new compounds (continued)

Compd	Mp (°C)	^{1}H NMR δ[a]	^{1}H NMR J[b]	^{13}C NMR[c]	IR[d]	MS[e]	Analysis
91	i	4.14	6.6	170.5	g	451	f
92	150–151	4.21	11.0, 4.0 [m]	171.0	1664	316	f
93	126–127	4.33	7.0	171.0	g	428	f
94	i	4.32	3.3	170.1	g	428	f
95	i	4.17	5.5	170.5	g	434	h
96	i	4.26	3.3	169.7	g	434	h
97	74–76	4.15	5.5	170.0	1698	447	h
98	i	4.25	3.3	169.1	g	447	h
99	147–149	4.08	4.0	168.4	1558	355	h
100	i	4.03	4.0	g	1670	411	h
101	116–117	4.03	4.0	169.0	1658	551	h
102	i	3.35	2.2	170.2	g	469	h
103	i	3.35	[k]	170.2	g	469	h
108	i	[n]	[n]	173.0	1652	427	h
115	i	—	—	171.9	1670	425	f

[a]Chemical shift of methine proton adjacent to sulfur atom and amide group (H^2), in ppm δ.
[b]Coupling constant of H^2 doublet in Hz.
[c]Chemical shift of carbonyl carbon in ppm δ.
[d]IR stretch of carbonyl group in cm^{-1}.
[e]MS, CI detection, $M+H^+$, m/z.
[f]Elemental analysis ±0.4% with calculated values for C, H, and N.
[g]Not taken.
[h]High-resolution MS ±5 ppm with calcd values, and compound homogeneous by TLC and ^{1}H NMR.
[i]Viscous oil or waxy solid.
[j]Elemental analysis ±0.4% on C and H.
[k]Singlet in ^{1}H NMR; [m] doublet of doublets in ^{1}H NMR; [n] signal obscurred; [o] elemental analysis ±0.6% on C, ±0.4% on H, N.

the compound at 10 mg/kg for 2 days. The animals were euthanized, and the livers were perfused and homogenized. Postnuclear microsomes were obtained by centrifugation, and assayed for ACAT activity as described above. The data are expressed as the degree of ACAT activity lowering compared with the control. In a few cases, serum samples were obtained immediately prior to euthanasia, samples were extracted, and the amount of inhibitor was determined by HPLC; serum levels are expressed in ng/mL. This data is not intended as a formal pharmacokinetic study, but rather as a general indication that the compounds are being absorbed.

Pharmacokinetic data for **50** was obtained by administering the compound to fed, male Sprague–Dawley rats ($n=4$ each) at 5 mg/kg (iv) and 10 mg/kg (po). Work up and analysis proceeded according to standard protocols.

Safety assessment data for **50** and **57** were obtained by the following: the compounds were dosed orally in methocel to male, drug-naive normal-diet rabbits ($n=3$) at 10, 30, and 100 mg/kg/day for 7 days. The animals were sacrificed and dissected for necropsy.

Preparation of 2,3-dipentyl-1,3-butadiene (5d). A solution of pentylmagnesium bromide (200 mmol) in THF (270 mL) was cooled to 0 °C, and CuI (3.81 g, 20.0 mmol) was added slowly over 10 min. After an additional 5 min, a solution of dipropargyl ester **4**[18] (23.9 g, 66.7 mmol) in THF (135 mL) was added dropwise. The mixture was stirred overnight, then cooled to 0 °C, and quenched by the slow addition of isopropanol (35 mL). The resulting mixture was filtered through a short column of Celite™, and the filtrate was evaporated. The resulting oil was eluted through a short column of silica gel (hexane), and the filtrate was evaporated to afford **5d** as an oil (11.7 g, 60.0 mmol, 90%).

Using this procedure and the appropriate starting materials, the following compounds were prepared: **5c** from butylmagnesium chloride (79%), **5e** from hexylmagnesium bromide (69%), **5g** from octylmagnesium chloride (93%).

Preparation of 6,8-tetradecadiene (7d). A modification of the method of Zweifel and Miller[19] was used here. Thus, a commercial solution of DIBAL (400 mL, 1 M, 400 mmol) was treated dropwise with neat heptyne (**6d**) (52.0 mL, 396 mmol). This solution was heated to gentle reflux for 4 h, then cooled and evaporated. The flask was purged with nitrogen off the rotary evaporator, and rapidly cooled to 0 °C. THF (400 mL) was carefully added, and the solution was stirred while CuCl (47.3 g, 478 mmol) was added in small portions over 20 min. The mixture was allowed to stir overnight, then was cooled to 0 °C and quenched by the addition of a solution of water (20 mL) and THF (200 mL). The resulting mixture was filtered through a short column of Celite™, with THF washing. The filtrate was poured into an ice-cooled flask containing an equal volume of 5% aq H_2SO_4. The resulting biphasic mixture was

separated, and the aq layer was extracted with hexane (2 × 1 L). The organic phases were washed in portions with brine (500 mL), then combined, dried over $MgSO_4$, filtered and evaporated. The resulting oil was distilled (70–75 °C, 0.5 mm) to afford **7d** (26.1 g, 134 mmol, 68%).

Using the same procedure, the following compounds were prepared: **7b** from 1-pentyne, **6b** (46%), **7c** from 1-hexyne, **6c** (56%), **7e** from 1-octyne, **6e** (75%), **7f** from 1-nonyne, **6f** (100%), **7g** from 1-decyne, **6g** (92%), **7h** from 5-methyl-1-hexyne, **6h** (63%), and **7i** from 5-chloro-1-pentyne, **6i** (49%). Compound **6j** was prepared from 5-hexynal[34] from Wittig coupling with butyltriphenylphosphonium bromide. Copper-mediated coupling of the DIBAL adduct as above gave **7j** (64%). The reaction of **7i** with cyclohexyl mercaptan (2 equiv; 2 equiv K_2CO_3, 0.3 equiv Bu_4NI, THF, 67 °C) gave **7k** in 51% yield, after work up and chromatography.

Preparation of 2-pentyl-1,3-nonadiene (9d). A solution of catecholborane (77.0 mL, 1.00 M, 77.0 mmol) in THF was treated dropwise at ambient temperature with 1-heptyne, **6d** (10.0 mL, 76.2 mmol). The mixture was heated to reflux for 4 h, then cooled to 0 °C, and treated with $Hg(OAc)_2$ (24.2 g, 76.0 mmol). The mixture was stirred for 1 h, then treated with NaCl (45 g, 77 mmol) in H_2O (300 mL). This was stirred at ambient temperature for 1 h, then the biphasic mixture was separated. The organic phase was evaporated to afford an organomercurial intermediate as a gum, which was dissolved in benzene (500 mL). The solution was treated in sequence with $PdCl_2$ (0.81 g, 7.61 mmol), $CuCl_2$ (22.0 g, 164 mmol) and Et_3N (22.0 mL, 158 mmol). After stirring for 10 h, the mixture was filtered through a short column of celite, and the filtrate was evaporated. The resulting oil was eluted through a short column of silica gel (hexane), and the filtrate was evaporated to afford **9d** as a liquid (1.01 g, 5.20 mmol, 7%).

Preparation of ethyl 2-phenacylthioacetate (10). A solution of 2-chloroacetophenone (14.1 g, 91.2 mmol), ethyl 2-mercaptoacetate (10.0 mL, 91.2 mmol), and K_2CO_3 (13.9 g, 100 mmol) in THF (200 mL) was stirred at ambient temperature for 10 h. The mixture was poured into H_2O (400 mL), and extracted with CH_2Cl_2 (2 × 400 mL). The extracts were combined, dried over $MgSO_4$, filtered and evaporated. The residual oil was separated by flash chromatography (1:4 EtOAc:hexane) to afford the product, **10**, as an oil (16.1 g, 67.7 mmol, 74%). ^1H NMR ($CDCl_3$): δ 7.97 (2H, dd, J = 8.0, 1.5 Hz), 7.62 (1H, tt, J = 5.1, 1.4 Hz), 7.48 (2H, t, J = 7.7 Hz), 4.19 (2H, q, J = 7.3 Hz), 4.04 (2H, s), 3.33 (2H, s), 1.27 (3H, t, J = 7.3 Hz). MS (NH_3-CI/DDIP): *m/z* 256 (100%), 240 (6), 239 (42), 210 (1), 193 (1).

Preparation of ethyl 3,6-dipentyl-3,6-dihydro-2*H*-thiopyran-2-carboxylate (standard photolysis procedure). The preparation of compound **17d** is representative of this type of reaction. A solution of the sulfide **10** (4.00 g, 16.8 mmol) and **7d** (15.61 g, 80.3 mmol) in benzene (180 mL) was partitioned to 12 100-mL Pyrex round-bottom flasks. The flasks (four per run; this reaction was performed in three runs) were suspended in a Pyrex cooling bath (with a tapwater line for cooling), the bath was filled with 5% aq $CuSO_4$ soln (to filter out light wavelengths lower than 310 nm), and the bath was supported above a 270 W sunlamp. The reaction flasks were irradiated for 7 h (each run); at the end of the three runs, the contents of the flasks were combined and evaporated. The oily residue was separated by flash chromatography (3:97 EtOAc:hexane) to afford the product, **17d**, as an oil (4.53 g, 14.5 mmol, 86%). The material was determined to be a mixture of diastereomers, with one favored to the extent of about 5:1. ^1H NMR (major isomer, $CDCl_3$): δ 5.80–5.68 (2H, m), 4.19 (2H, q, J = 7.0 Hz), 3.41 (1H, br t, J = 5.9 Hz), 3.33 (1H, d, J = 4.4 Hz), 2.55–2.46 (1H, m), 1.70–1.27 (16H, m), 1.29 (3H, t, J = 7.0 Hz), 0.89 (6H, t, J = 6.8 Hz). MS (NH_3-CI/DDIP): *m/z* 330 (30%), 314 (18), 313 (100), 279 (2), 239 (4).

The following compounds were prepared by treatment of **10** with the appropriate diene and sun lamp photolysis: **11a** from 5a (89%), **11d** from 5d (88%), **11g** from 5g (99%), **17f** from **7f** (85%), **17i** from **7i** (18%), **17j** from **7j** (31%), **17k** from **7k** (12%), and **17l** from **7l** (20%).

Alternate preparation of ethyl 3,6-dipentyl-3,6-dihydro-2*H*-thiopyran-2-carboxylate (standard dehydrochlorination procedure). The preparation of compound **17d** is representative of this type of reaction, a modification of the method of Kirby et al.[28] A slurry of *N*-chlorosuccinimide (5.85 g, 43.8 mmol) in benzene (60 mL) was cooled to 5 °C, and ethyl mercaptoacetate (4.00 mL, 36.5 mmol) was added by syringe. The reaction was observed to be colorless for about 20 min, at which time a yellow color evolved, signaling the formation of the sulfenyl chloride intermediate. The mixture was allowed to stir for 2 h, then settle. The supernatant was delivered dropwise by cannula to an ice-cooled solution of diene **7d** (35.1 g, 181 mmol) and triethylamine (25.0 mL, 179 mmol) in (1:1) benzene:methanol (120 mL). After stirring for 10 h, the mixture was poured into H_2O (400 mL), and was extracted with EtOAc (200 mL). The aqueous phase was extracted again with EtOAc (400 mL), and the extracts were washed in sequence with brine (400 mL), then combined, dried over $MgSO_4$, filtered and evaporated. The residual oil was separated by flash chromatography (3:97 EtOAc:hexane) to afford the product **17d** (8.63 g, 27.6 mmol, 76%) as a 2:1 mixture of diastereomers.

The dehydrochlorination procedure was used in the preparation of the following compounds: **17b** from **7b** (74%), **17c** from **7c** (90%), **17e** from **7e** (90%), **17g** from **7g** (86%), **17h** from **7h** (83%), and **17l** from **7l** (12%).

Preparation of 3,6-dipentyl-3,6-dihydro-2*H*-thiopyran-2-carboxylic acid (18d). A solution of the ester **17d** (4.53 g, 14.5 mmol) and NaOH (0.25 N solution) in 95% EtOH (120 mL, 30.0 mmol NaOH) was stirred for

12 h at ambient temperature. The reaction mixture was evaporated, and the residue acidified with HCl (1 N, 150 mL). This was saturated with NaCl and extracted with CH_2Cl_2 (2 × 200 mL). The extracts were combined, dried over $MgSO_4$, filtered, and evaporated to afford the product, **18d**, as an oily mixture of diastereomeric products (5:1 by NMR: 4.01 g, 14.1 mmol, 97%). ^1H NMR (major isomer; $CDCl_3$): δ 5.73 (2H, s), 3.48 (1H, br t, J = 7 Hz), 3.40 (1H, d, J = 3.7 Hz), 2.60–2.52 (1H, m), 1.71–1.24 (16H, m), 0.89 (6H, t, J = 3.7 Hz). MS (NH_3-CI/DDIP): *m/z* 287 (6%), 286 (18), 285 (100), 239 (25), 211 (2).

Using the same hydrolysis procedure, the following compounds were prepared: **12d** from **11d** (96%), **12g** from **11g** (93%), **18b** from **17b** (98%), **18c** from **17c** (95%), **18e** from **17e** (97%), **18f** from **17f** (95%), **18g** from **17g** (97%), **18h** from **17h** (95%), **18i** from **17i** (86%), **18j** from **17j** (95%), **18k** from **17k** (83%), and **114** from **113** (76%).

Preparation of *endo* and *exo* isomers of *N*-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-3,6-dipentyl-2,3-dihydro-2*H*-thiopyran-2-carboxamide (50 and 51) (standard amide formation procedure). A solution of the acid **18d** (4.01 g, 14.1 mmol) in benzene (30 mL) was treated with DMF (0.15 mL), and then oxalyl chloride (4.00 mL, 45.8 mmol). The mixture was stirred for 10 h, then evaporated. The residue was taken up in THF (30 mL), and delivered dropwise by cannula to an ice-cooled, stirred solution of 3-amino-2,4-bis(methylthio)-6-methylpyridine (**13A**, prepared according to the methods of Wang,[35] Albert et al.[36] and McCarthy et al.,[37] 2.80 g, 14.0 mmol) in THF (30 mL). After being stirred for 14 h, the mixture was poured into H_2O (200 mL), and extracted with EtOAc (2 × 200 mL). The extracts were washed with saturated brine (200 mL), then combined, dried over Na_2SO_4, filtered and evaporated. The residue was separated by flash chromatography (3:17 ethyl acetate:hexane) to afford the title product as a waxy solid mixture of two diastereomers (6.46 g, 13.8 mmol, 98%). A portion of the mixture (5 g) was separated by HPLC (column: preparative Pirkle DNBPG, 20 × 250 mm; temperature: 20 °C; solvent: 0.1% triethylamine/20% isopropanol/80% hexane; flow:10.0 mL/min; detection: 265 nm UV) to afford the two isomeric products [major (**50**): t_R 34 min, weight 3.80 g; minor (**51**): t_R 40 min, weight 0.85 g). **50**: mp 88–89 °C. ^1H NMR ($CDCl_3$): δ 8.31 (1H, br s), 6.65 (1H, s), 5.81 (1H, ddd, J = 11.0, 5.1, 1.8 Hz), 5.69 (1H, br d, J = 11.0 Hz), 3.90–3.81 (1H, m), 3.46 (1H, d, J = 2.2 Hz), 3.08–2.99 (1H, m), 2.50 (3H, s), 2.49 (3H, s), 2.40 (3H, s), 1.75–1.25 (16H, m), 0.89 (6H, t, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$): δ 169.1, 156.8, 148.7, 133.0, 130.4, 128.1, 123.3, 113.6, 49.5, 41.0, 37.6, 35.3, 32.4, 32.0, 31.7, 27.2, 24.5, 22.7, 22.6, 14.1, 14.0, 13.0, 12.9. IR (KBr): 3440, 3226, 2954, 2922, 2854, 1656, 1564, 1514, 1466, 1432, 1334, 1310, 806 cm^{-1}. MS (NH_3-CI/DDIP): *m/z* 469 (17%), 468 (29), 467 (100). Analysis: HRMS. **51**: mp 150–151 °C. ^1H NMR ($CDCl_3$): δ 7.33 (1H, br s), 6.64 (1H, s), 5.99 (1H, ddd, J = 10.3, 5.2, 2.6 Hz), 5.82 (1H, dt, J = 10.3, 2.0 Hz), 4.03 (1H, d, J = 4.4 Hz), 3.69–3.60 (1H, m), 2.69–2.59 (1H, m), 2.50 (3H, s), 2.48 (3H, s), 2.40 (3H, s), 1.89–1.60 (4H, m), 1.56–1.22 (12H, m), 0.90 (3H, t, J = 7.0 Hz), 0.87 (3H, t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$): δ 168.9, 157.3, 156.7, 148.5, 146.1, 133.1, 130.4, 113.7, 49.5, 41.0, 37.6, 35.3, 32.4, 32.0, 31.7, 27.1, 26.7, 24.4, 22.6, 22.5, 14.1 (2C), 14.0, 12.9. MS (NH_3-CI/DDIP): *m/z* 469 (19%), 468 (29), 467 (100). Elemental analysis: C, H, N.

Using this amide-forming procedure, the following compounds were prepared: **37** from **18g** and **13A** (52%), **53** and **100** from **18b** and **13A** (65%), **54** from **18c** and **13A** (68%), **44** from **18d** and **13B** (72% total), **49** from **18d** and **13F** (18%), **48** from **18d** and **13G** (73%), **55** from **18e** and **13A** (78%), **56** from **18f** and **13A** (32%), **57** and **101** from **18g** and **13A** (64%), **58** from **18h** and **13A** (64%), **59** from **18i** and **13A** (39%), **60** from **18j** and **13A** (42%), **61** from **18k** and **13A** (19%), **62** from **18l** and **13A** (45%), **89** from **88a** and **13A** (79%), **92** from **88a** and **13B** (36%), **90** and **91** from **88b** and **13A** (95%), **93** and **94** from **88b** and **13B** (59%), **97** and **98** from **88b** and **13F** (92%), **95** and **96** from **88b** and **13G** (93%), and **115** from **114** and **13A** (17%).

Preparation of *N*-[2,4-bis(methylthio)-6-methyl-pyridin-3-yl]-2-chloroacetamide (14A). A solution of 3-amino-2,4-bis(methylthio)-6-methylpyridine, **13A** (0.38 g, 1.88 mmol), and triethylamine (0.30 mL, 2.07 mmol) in THF (8 mL) was cooled to 0 °C, and treated with a solution of chloroacetyl chloride (0.18 mL, 2.26 mmol) in THF (4 mL). After being stirred for 10 h, the mixture was poured into H_2O (100 mL), and this was extracted with EtOAc (2 × 100 mL). The extracts were combined, dried over Na_2SO_4, filtered and evaporated. The resulting solid was recrystallized to purity from ether, mp 190–192 °C, to afford **14A** (0.39 g, 1.41 mmol, 75%). ^1H NMR ($CDCl_3$): δ 7.69 (1H, br s), 6.68 (1H, s), 4.26 (2H, s), 2.53 (3H, s), 2.51 (3H, s), 2.43 (3H, s). MS (NH_3-CI/DDIP): *m/z* 279 (42%), 278 (17), 277 (100), 227 (4).

Using this same procedure, the following compounds were prepared: **14B** from **13B** (79%), **14E** from **13E** (99%), **14H** from **13H** (83%), **14J** from **13J** (57%), **14K** from **13K** (52%), **14L** from **13L** (80%), **14M** from **13M** (80%), **14N** from **13N** (71%), and **14P** from **13P** (83%), **14Q** from **13Q** (80%), and **14R** from **13R** (63%).

Preparation of 2-mercaptoacetophenone (15). A modified version of the procedure of Vedejs et al.[24] was used here. K_2CO_3 (19.4 g, 140 mmol) was suspended in THF (500 mL), and thiolacetic acid (10.0 mL, 140 mmol) was added dropwise. Then, a solution of 2-chloroacetophenone (16.6 g, 108 mmol) in THF (100 mL) was added dropwise, and the mixture was allowed to stir for 10 h. It was poured into H_2O (700 mL), and the resulting mixture was extracted with EtOAc (700 mL), then CH_2Cl_2 (700 mL). The extracts were combined, dried over $MgSO_4$, filtered, and evaporated. The residual oil was purified by filtration through a short plug of silica gel (1:1, EtOAc:hexane) to afford 2-thioacetylacetophenone (20.0 g, 103 mmol, 96%) as

an oil. ^{1}H NMR ($CDCl_3$): δ 7.99 (2H, d, J=8.4 Hz), 7.60 (1H, t, J=7.7 Hz), 7.48 (2H, t, J=8.1 Hz), 4.41 (2H, s), 2.41 (3H, s). MS (NH_3-CI/DDIP): m/z 212 (100%), 197 (2), 196 (4), 195 (19), 153 (1).

A solution of 2-thioacetylacetophenone (8.70 g, 44.8 mmol) in ether (50 mL) was stirred vigorously while aq NaOH soln (50 mL, 2 N, 100 mmol) was added. This mixture was stirred for 2 h, then separated. The aqueous layer was cooled to 0 °C, and acidified. This was extracted with CH_2Cl_2 (2 × 100 mL), and the extracts were combined, dried over $MgSO_4$, filtered, and evaporated. The residual liquid was distilled (110–120 °C, 1 mm Hg, bulb-to-bulb) to afford the pure product, **15** (6.00 g, 39.4 mmol, 88%). ^{1}H NMR ($CDCl_3$): δ 7.97 (2H, dd, J=8.2, 1.2 Hz), 7.63–7.57 (1H, m), 7.52–7.45 (2H, m), 3.97 (2H, d, J=7.3 Hz), 2.14 (1H, t, J=7.3 Hz). MS (NH_3-CI/DDIP): m/z 172 (5%), 171 (10), 170 (100), 153 (20), 138 (15).

Preparation of *N*-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-2-phenacylthioacetamide (16A). A solution of compound **14A** (0.49 g, 1.77 mmol), **15** (0.49 g, 3.22 mmol), and K_2CO_3 (0.27 g, 1.95 mmol) in THF (20 mL) was heated to 50 °C for 6 h. The mixture was then cooled, and poured into H_2O (100 mL). This was extracted with CH_2Cl_2 (2 × 100 mL). The extracts were combined, dried over $MgSO_4$, filtered, and evaporated. The resulting solid was recrystallized from ether (mp 140–142 °C) to afford pure **16A** (0.433 g, 1.10 mmol, 62%). ^{1}H NMR ($CDCl_3$): δ 8.11 (1H, br s), 8.02–7.96 (2H, m), 7.65–7.45 (3H, m), 6.66 (1H, s), 4.31 (2H, s), 3.46 (2H, s), 2.49 (3H, s), 2.48 (3H, s), 2.39 (3H, s). MS (NH_3-CI/DDIP): m/z 395 (17%), 394 (25), 393 (100), 285 (1), 275 (5).

Using the same procedure described above, the following compounds were prepared: **16B** from **14B** (81%), **16C** from **14C** (90%), **16D** from **14D** (73%), **16E** from **14E** (88%), **16H** from **14H** (11%), **16J** from **14J** (84%), **16K** from **14K** (82%), **16L** from **14L** (56%), **16M** from **14M** (80%), **16N** from **14N** (55%), **16P** from **14P** (87%), **16Q** from **14Q** (65%), and **16R** from **14R** (73%).

Alternate photolytic preparation of 50 and 51. The standard photolysis procedure was employed for the sulfide **16A** (280 mg, 0.71 mmol) and **7d** (1.11 g, 5.71 mmol) in 1:5 DMF:benzene soln in a single 100-mL Pyrex round-bottom flask. Evaporation and flash chromatography gave the product mixture **50**+**51**, which was separated by HPLC exactly as above and recrystallized to purity from ether (100 mg total, 0.21 mmol, 30%), and which showed identical spectral characteristics to the samples prepared from the other method.

Using the same procedure as above, the following compounds were prepared: **21** from **5a** and **16A** (85%), **22** from **5a** and **16B** (67%), **38** from **5a** and **16R** (47%), **23** from **5c** and **16B** (57%), **24** from **5c** and **16C** (50%), **25** from **5c** and **16D** (55%), **26** from **5d** and **16A** (71%), **27** from **5d** and **16B** (72%), **28** from **5d** and **16C** (57%), **29** from **5d** and **16D** (54%), **30** from **5d** and **16E** (51%), **39** from **5d** and **16H** (42%), **40** from **5d** and **16J** (53%), **41** from **5d** and **16K** (56%), **31** from **5d** and **16L** (20%), **32** from **5d** and **16M** (23%), **33** from **5d** and **16N** (21%), **42** from **5d** and **16P** (59%), **43** from **5d** and **16Q** (45%), **34** from **5e** and **16B** (51%), **35** from **5e** and **16C** (53%), **36** from **5e** and **16D** (56%), **52** and **99** from **7a** and **16A** (86%), **53** and **100** from **7b** and **16A** (78%), **44** from **7d** and **16B** (55%), **45** from **7d** and **16C** (36%), **46** from **7d** and **16D** (37%), **47** from **7d** and **16E** (47%), **57** and **101** from **7g** and **16A** (71%), **63** from **9d** and **16B** (64%), **65** and **66** from α-terpinene and **16A** (58%), **67** from α-terpinene and **16B** (47%), **68** and **69** from α-terpinene and **16C** (52%), **70** and **71** from α-terpinene and **16D** (61%), **72** and **73** from α-terpinene and **16E** (28%), **74** and **75** from 1-methoxy-1,3-cyclohexadiene and **16A** (31%), **76** from 1-methoxy-1,3-cyclohexadiene and **16C** (27%), **77** from cyclopentadiene and **16A** (52%), **78** from cyclopentadiene and **16C** (48%), **77** from cyclopentadiene and **16A** (52%), and **108** from **5d** and **107** (60%).

Preparation of 1-methoxybicyclo[2.2.2]oct-5-ene-2-carboxylic acid (80). A solution of methyl 1-methoxybicyclo[2.2.2]oct-5-ene-2-carboxylate (Aldrich, 5.00 mL, 24.9 mmol) in 95% ethanol (200 mL) was treated with sodium hydroxide (50 mmol). The mixture was stirred for 20 h at ambient temperature, then evaporated. The residual material was taken up in 20 mL 1 N aq sodium hydroxide, and washed with ether (40 mL). The aqueous phase was adjusted to pH 5 with 6 N HCl, then extracted with ethyl acetate (2 × 100 mL). The extracts were combined, dried over $MgSO_4$, filtered, and evaporated to afford **80** as an oil. ^{1}H NMR ($CDCl_3$): δ 6.42–6.20 (2H, m), 4.20–4.05 (1H, m), 3.51 (3H, s), 2.94–2.53 (2H, m), 2.03–1.20 (5H, m). MS (CI): m/z 200 (100%), 184 (5), 183 (43), 165 (22), 137 (2).

Preparation of *N*-[2,4-bis(methylthio)-6-methylpyridin-3-yl]-1-methoxybicyclo-[2.2.2]oct-5-ene-2-carboxamide (81). A solution of the acid **80** (3 mmol) in CH_2Cl_2 (10 mL) containing 1 drop DMF was treated with oxalyl chloride (10 mmol) in CH_2Cl_2 (5 mL). The solution was stirred for 2 h, then evaporated. The crude acid chloride thus produced was taken up in THF (5 mL), and added slowly to an ice-cooled solution of 3-amino-2,4-bis(methylthio)-6-methylpyridine (**13A**, 443 mg, 2.21 mmol) and triethylamine (1.00 mL, 7.17 mmol) in THF (10 mL). The mixture was allowed to stir for 12 h, then poured into water (100 mL). This was extracted with ethyl acetate (2 × 100 mL), and the extracts were combined, dried over Na_2SO_4, filtered, and evaporated. The resulting solid was triturated with warm ether, filtered and dried to afford **81**, mp 140–141 °C. ^{1}H NMR ($CDCl_3$): δ 8.52 (1H, br s), 6.62 (1H, s), 6.45 (1H, d, J=8.8 Hz), 6.35 (1H, dd, J=8.8, 6.4 Hz), 3.53 (3H, s), 2.92 (1H, dd, J=9.9, 3.6 Hz), 2.65–2.59 (1H, m), 2.49 (3H, s), 2.47 (3H, s), 2.38 (3H, s), 2.28–2.18 (1H, m), 1.89–1.61 (4H, m), 1.49–1.37 (1H, m); ^{13}C NMR ($CDCl_3$): δ 171.9, 156.4, 156.2, 148.4, 134.8, 131.4, 124.3, 113.4, 79.4, 50.9,

47.5, 29.5, 29.3, 27.4, 26.7, 24.4, 14.0, 12.9. IR (KBr): 3262, 2940, 1666, 1562, 1500, 1434, 1340, 810, 698 cm^{-1}. MS (CI): *m/z* 367 (13%), 366 (25), 365 (100), 349 (2), 201 (1). Elemental anal. C, H, N.

In a similar manner, compounds **82**, **83**, and **84** were prepared from the appropriate starting materials.

Preparation of racemic (1*S*,2*R*,3*S*,6*R*)-*N*-[2,4-bis-(methylthio)-6-methylpyridin-3-yl]-3,6-dipentyl-1-oxo-3,6-dihydro-2*H*-thiopyran-2-carboxamide (85). A mixture of sulfides **50** and **51** (650 mg, 1.39 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C, and treated with tetra-*n*-butylammonium periodate (602 mg, 1.39 mmol). The mixture was stirred for 10 h at ambient temperature, then heated to 45 °C for and additional 20 h. The mixture was cooled and evaporated, and the residue was separated by flash chromatography (3:7 EtOAc:hexane to 1:1 EtOAc:hexane) to afford, first, a solid identified as compound **85** (28 mg, 58 mmol, 4%), then a fraction corresponding to other stereoisomers of the title product (18 mg, 37 mmol, 3%). For **85**: ^{1}H NMR ($CDCl_3$): δ 8.74 (1H, br s), 6.65 (1H, s), 5.88 (1H, br d, J=11 Hz), 5.49 (1H, br d, J=11 Hz), 4.09–4.00 (1H, m), 3.74 (1H, d, J=5 Hz), 3.39–3.30 (1H, m), 2.51 (3H, s), 2.49 (3H, s), 2.41 (3H, s), 1.80–1.25 (16H, m), 0.91 (3H, t, J=6 Hz), 0.90 (3H, t, J=6 Hz); ^{13}C NMR ($CDCl_3$): δ 166.0, 156.7, 156.6, 148.4, 132.2, 123.4, 121.5, 113.6, 59.0, 56.4, 35.8, 34.3, 31.8, 31.7, 30.0, 26.7, 25.9, 24.4, 22.6, 22.4, 14.1, 14.0, 13.9, 13.0. MS (CI): *m/z* 485 (19%), 484 (29), 483 (100). Anal. HRMS.

Preparation of diethyl 4,5-dimethyl-3,6-dihydro-2*H*-pyran-2,2-dicarboxylate (86a). A modification of the method of Bonjouklian and Ruden[29] was employed here. Thus, a solution of diethyl ketomalonate (10.0 mL, 65.6 mmol) and 2,3-dimethyl-1,3-butadiene (16.3 mL, 144 mmol) in acetonitrile (22 mL) was divided into two portions, and delivered to two scalable tubes. The tubes were degassed under vacuum and sealed, then heated to 140 °C for 4 h. After being cooled, the contents of the tubes were evaporated, and the oily residue was separated by flash chromatography (1:4, ethyl acetate:hexane) to afford **86a** as an oil (13.6 g, 53.1 mmol, 81%). ^{1}H NMR ($CDCl_3$): δ 4.26 (4H, q, J=7.0 Hz), 4.15 (2H, br s), 2.57 (2H, br s), 1.69 (3H, s), 1.51 (3H, s), 1.28 (6H, t, J=7.0 Hz). MS (CI) *m/z* 275 (14%), 274 (100), 257 (23), 183 (1).

A similar procedure was used to prepare **86b** from **7d** (66%).

Preparation of 4,5-dimethyl-3,6-dihydro-2*H*-pyran-2,2-dicarboxylic acid (87a). A modification of the method of Bonjouklian and Ruden[29] was employed here. Thus, a solution of **86a** (9.63 g, 37.6 mmol) in THF (150 mL) was treated with aq KOH (150 mL, 10 N, 1.5 mol). The mixture was stirred vigorously for 10 h, then filtered. The resulting solid was taken up in a small amount of water, and neutralized to pH 5 with 1 N HCl. The aqueous mixture was extracted with ethyl acetate (2 × 100 mL). The extracts were washed with brine, combined, dried over Na_2SO_4, filtered, and evaporated to afford **87a** as a solid (7.46 g, 37.3 mmol, 99%). ^{1}H NMR ($CDCl_3$): δ 4.16 (2H, br s), 2.57 (2H, br s), 1.68 (3H, br s), 1.51 (3H, br s).

A similar procedure was used to prepare **87b** from **86b**.

Preparation of 4,5-dimethyl-3,6-dihydro-2*H*-pyran-2-carboxylic acid (88a). A solution of **87a** (7.46 g, 37.3 mmol) in dry pyridine (50 mL) was treated with morpholine (5.00 mL, 57.2 mmol). The mixture was heated to reflux for 12 h, then cooled and partially evaporated. The residue was taken up in CH_2Cl_2 (200 mL), and washed with 1 N aq HCl (3 × 150 mL). The organic phase was dried over $MgSO_4$, filtered, and evaporated. The resulting solid was recrystallized from ether:hexane to afford pure **88a**, mp 82–84 °C (3.32 g, 21.3 mmol, 57%). ^{1}H NMR ($CDCl_3$): δ 10.45 (1H, br s), 4.24 (1H, dd, J=9.5, 4.8 Hz), 4.12 (2H, br s), 2.40–2.20 (2H, m), 1.69 (3H, br s), 1.55 (3H, br s). MS (CI): *m/z* 175 (10%), 174 (100).

The same procedure was used to convert **87b** to **88b** (96%).

Preparation of racemic (2*R*,3*R*,6*S*)-*N*-[2,4-bis-(methylthio)-6-methylpyridin-3-yl]-3,6-dipentyl-3,4,5,6-tetrahydro-2*H*-thiopyran-2-carboxamide (102). A solution of **17d** (1.95 g, 6.24 mmol) in methanol (15 mL) was treated with potassium diazadicarboxylate[38] (3.64 g, 18.7 mmol). Then, a solution of acetic acid (2.25 mL, 39.3 mmol) in methanol (5 mL) was added by syringe pump over 4 h. After stirring for an additional 8 h, the reaction mixture was evaporated, and the residue was taken up between water and ethyl acetate (100 mL each). The aqueous phase was extracted with ethyl acetate (100 mL), and the extracts were washed in sequence with brine (100 mL), combined, dried over $MgSO_4$, filtered, and evaporated. The residual oil was dissolved in 95% ethanol (48 mL), and treated with aq NaOH (3.00 mL, 4 M, 12.0 mmol). The mixture was stirred for 12 h, then evaporated. The residue was neutralized to pH 5 with 1 N HCl, then diluted to 100 mL with water. This mixture was extracted with ethyl acetate (2 × 100 mL). The extracts were washed with brine, combined, dried over $MgSO_4$, filtered, and evaporated. The residual oil was dissolved in CH_2Cl_2 (10 mL), and treated with 1 drop DMF, then oxalyl chloride (10.0 mmol) in CH_2Cl_2 solution (5.00 mL). After stirring for 2 h, the solution was evaporated, and the residue was taken up in THF (5 mL), which was added slowly to an ice-cooled solution of **13A** (510 mg, 2.55 mmol) and triethylamine (0.50 mL, 3.58 mmol) in THF (10 mL). The mixture was allowed to stir for 10 h, then was poured into water (100 mL). This was extracted with ethyl acetate (2 × 100 mL). The extracts were washed with brine (100 mL), combined, dried over Na_2SO_4, filtered, and evaporated. The residue was separated by flash chromatography (1:4, ethyl acetate: hexane) to afford first, **102** (220 mg, 0.47 mmol, 15%), then, **50** (650 mg, 1.39 mmol, 45%), both as low-melting solids. For **102**: ^{1}H NMR ($CDCl_3$): δ 8.84 (1H, br s), 6.67 (1H, s), 3.35 (1H, d, J=2.2 Hz),

3.20–3.10 (1H, m), 2.74–2.64 (1H, m), 2.52 (3H, s), 2.50 (3H, s), 2.42 (3H, s), 1.80–1.24 (20H, m), 0.90 (3H, t, $J=7$ Hz), 0.88 (3H, t, $J=7.0$ Hz); ^{13}C NMR ($CDCl_3$): δ 170.2, 156.7, 156.5, 148.5, 124.0, 113.7, 49.7, 41.5, 36.1, 32.3, 32.0, 31.8, 31.6, 27.9, 27.0, 26.5, 26.2, 24.4, 22.7, 22.5, 14.1, 14.0 (2C), 12.9. MS (CI): *m/z* 471 (18%), 470 (30), 469 (100), 312 (10). Anal. HRMS.

Preparation of racemic (2*R*,3*S*,6*R*)-*N*-[2,4-bis-(methylthio)-6-methylpyridin-3-yl]-3,6-dipentyl-3,4,5,6-tetrahydro-2*H*-thiopyran-2-carboxamide (103). A solution of **50** (600 mg, 1.29 mmol) in ethyl acetate (20 mL) was treated with 5% Pd on carbon (2.00 g) in a Parr shaker bottle. This was subjected to hydrogenation (50 psi) for 12 h. The vessel was purged with N_2, and the contents were filtered through Celite™ and evaporated. The residue was separated by flash chromatography (1:3 ethyl acetate:hexane) to afford first the product **103** (60 mg, 0.13 mmol, 10%), then unreacted **50** (150 mg, 25%). The product was a viscous oil: ^{1}H NMR ($CDCl_3$): δ 8.85 (1H, br s), 6.68 (1H, s), 3.35 (1H, br s), 3.20–3.10 (1H, m), 2.74–2.64 (1H, m), 2.55 (3H, s), 2.53 (3H, s), 2.42 (3H, s), 1.79–1.25 (20H, m), 0.89 (3H, t, $J=6$ Hz), 0.88 (3H, t, $J=6$ Hz); ^{13}C NMR ($CDCl_3$): δ 170.2, 156.6, 156.4, 149.1, 124.1, 113.8, 49.7, 41.5, 36.1, 32.2, 32.0, 31.8, 31.6, 27.8, 27.0, 26.4, 26.3, 24.3, 22.7, 22.5, 14.1, 14.0 (2C), 13.2. MS (CI): *m/z* 471 (18%), 470 (3), 469 (100).

Preparation of 50 through a ketene intermediate. A solution of **18d** (600 mg, 2.11 mmol) in 10 mL CH_2Cl_2 was treated with 1 drop DMF, then oxalyl chloride (0.60 mL, 6.88 mmol) in CH_2Cl_2 (5 mL) was added. The mixture was allowed to stir for 2 h, then was evaporated. The acid chloride was taken up in THF (10 mL), and cooled to −50 °C. Triethylamine (0.35 mL, 2.51 mmol) was slowly added by syringe, and the mixture was allowed to stir for 10 min. Then, amine **13A** was added in THF solution (5 mL), and the mixture was allowed to warm to ambient temperature. Work up as before gave a mixture of **50** and **51**, measured to be 12:1 by ^{1}H NMR.

Equilibration of 51. A solution of **51** (120 mg) in THF (2 mL) was treated with *tert*-butanol (100 mL) and potassium *tert*-butoxide (40 mL of a 1 M THF solution, 40 mmol). The solution was allowed to heat at reflux for 14 h, then cooled. The mixture was poured into water (30 mL), and was extracted with ethyl acetate (2 × 30 mL). The extracts were washed with brine (30 mL), combined, dried over Na_2SO_4, filtered and evaporated. Analysis by ^{1}H NMR showed a mixture of **50** and **51** (3:1).

Preparation of 2,6-diisopropylacetanilide (104). An ice-cooled solution of 2,6-diisopropylaniline (5.00 mL, 26.5 mmol) and triethylamine (4.10 mL, 29.2 mmol) in THF (30 mL) was treated with a solution of acetyl chloride (2.30 mL, 31.8 mmol) in THF (20 mL). The mixture was allowed to stir for 10 h, then was poured into water. The mixture was extracted with ethyl acetate (2 × 100 mL), and the extracts were combined, dried over Na_2SO_4, filtered, and evaporated. The resulting solid was recrystallized from ether:hexane (mp 189–190 °C) to afford **104** (5.06 g, 23.1 mmol, 87%). The ^{1}H NMR showed rotational isomerism. MS (CI): *m/z* 237 (26%), 221 (17), 220 (100), 176 (1).

Preparation of *N*-ethyl-2,6-diisopropylaniline (105). A solution of **104** (5.00 g, 22.8 mmol) in THF (10 mL) was added to an ice-cooled solution of $LiAlH_4$ (50.2 mL, 1.0 M, 50.2 mmol) in THF. The ice bath was removed after 1 h, and the solution was heated to reflux for 10 h. The solution was again cooled in an ice bath, and quenched by the careful addition of 2 mL water in 20 mL THF, followed by 6 mL of 15% aq NaOH, followed by 6 mL water. The resulting mixture was filtered through celite with THF washing, and the filtrate was dried over K_2CO_3, filtered, and evaporated. The residue was separated by flash chromatogaphy (1:4 ethyl acetate:hexane) to afford, first, **105** (3.01 g, 14.7 mmol, 64%), then unreacted **104** (1.66 g, 33%). Amine **105** was an oil: ^{1}H NMR ($CDCl_3$): δ 7.12–7.00 (3H, m), 3.26 (2H, heptet, $J=7.0$ Hz), 2.91 (2H, q, $J=7.3$ Hz), 2.86 (1H, br s), 1.26 (3H, t, $J=7.3$ Hz), 1.24 (12H, d, $J=7.0$ Hz). MS (CI): *m/z* 207 (18%), 206 (100), 178 (2), 106 (4).

Preparation of ethyl 2-thioacetylheptanoate (110). A solution of ethyl 2-bromoheptanoate (10.0 mL, 51.1 mmol) in THF (50 mL) was treated with K_2CO_3 (8.47 g, 61.3 mmol), and cooled to 0 °C. Thioacetic acid (4.10 mL, 56.2 mmol) was added dropwise in THF solution (15 mL), and the mixture was warmed to 60 °C and stirred for 10 h. An additional 1 mL thioacetic acid was added, and the mixture was stirred for 6 h. It was cooled, poured into water (200 mL), and extracted with CH_2Cl_2 (2 × 200 mL). The extracts were combined, dried over $MgSO_4$, filtered, and evaporated. The oily residue was separated by flash chromatography (3:97 ethyl acetate:hexane) to afford **110** as an oil (11.5 g, 49.4 mmol, 97%). ^{1}H NMR ($CDCl_3$): δ 4.24–4.11 (3H, m), 2.35 (3H, s), 1.95–1.81 (1H, m), 1.79–1.65 (1H, m), 1.40–1.21 (9H, m), 0.88 (3H, t, $J=6.6$ Hz).

Preparation of ethyl 2-mercaptoheptanoate (111). A solution of the thiolacetate **110** (5.00 g, 21.5 mmol) in 95% ethanol (30 mL) was cooled to −10 °C, and a solution of sodium hydroxide (1.76 g, 44.1 mmol) in 95% ethanol (45 mL) was added dropwise. The mixture was allowed to stir for 4 h, then was brought to 0 °C and neutralized to pH 4 with 6 N aq HCl. The solution was evaporated, and the residual material was partitioned between water and CH_2Cl_2 (100 mL each). The organic phase was dried over $MgSO_4$, filtered, and evaporated to afford sufficiently pure thiol **111** as an oil (3.68 g, 19.3 mmol, 90%). ^{1}H NMR ($CDCl_3$): δ 4.20 (2H, g, $J=7.3$ Hz), 3.29 (1H, dt, $J=9.1$, 7.7 Hz), 2.03 (1H, d, $J=9.1$ Hz), 1.97–1.84 (1H, m), 1.78–1.63 (1H, m), 1.50–1.25 (6H, m), 1.29 (3H, t, $J=7.3$ Hz), 0.89 (3H, t, $J=7.0$ Hz).

Preparation of ethyl 2-phenacylthioheptanoate (112). A solution of **111** (3.68 g, 19.3 mmol), 2-chloroaceto-

phenone (2.72 g, 17.6 mmol) and K_2CO_3 (2.92 g, 21.1 mmol) in THF (40 mL) was heated to 60 °C for 12 h, then cooled and poured into water (200 mL). This was extracted with CH_2Cl_2 (2 × 200 mL), and the extracts were combined, dried over $MgSO_4$, filtered, and evaporated. The oily residue was separated by flash chromatography (1:19, ethyl acetate:hexane) to afford sulfide **112** as an oil (5.10 g, 16.5 mmol, 85%). ^{1}H NMR ($CDCl_3$): δ 7.99–7.94 (2H, m), 7.62–7.56 (1H, m), 7.50–7.44 (2H, m), 4.18 (2H, q, J = 7.3 Hz), 4.03 (2H, s), 3.37 (1H, dd, J = 8.2, 6.8 Hz), 1.94–1.81 (1H, m), 1.76–1.60 (1H, m), 1.49–1.25 (6H, m), 1.26 (3H, t, J = 7.3 Hz), 0.86 (3H, t, J = 7.0 Hz). MS (CI): *m/z* 326 (49%), 310 (19), 309 (100), 280 (4).

Preparation of ethyl 4,5-dimethyl-2-pentyl-3,6-dihydro-2*H*-thiopyran-2-carboxylate (113). The standard photolysis procedure as described for the synthesis of compound **17d** was performed here. Thus, sulfide **112** (1.00 g, 3.24 mmol) and diene **5a** (3.70 mL, 32.4 mmol) afforded, after 7 h sun lamp photolysis, evaporation and chromatography, the product **113** as an oil (560 mg, 2.07 mmol, 64%). ^{1}H NMR ($CDCl_3$): δ 4.21 (1H, dq, J = 10.5, 7.0 Hz), 4.14 (1H, dq, J = 10.5, 7.0 Hz), 3.20 (1H, dd, J = 16.7, 1.0 Hz), 2.88 (1H, dd, J = 16.7, 0.8 Hz), 2.62 (1H, d, J = 16.8 Hz), 2.25 (1H, dd, J = 16.8, 1.1 Hz), 1.89–1.70 (2H, m), 1.70 (6H, br s), 1.40–1.22 (6H, m), 1.26 (3H, t, J = 7.0 Hz), 0.88 (3H, t, J = 6.9 Hz). MS (CI): *m/z* 288 (8%), 272 (19), 271 (100), 197 (9).

Preparation of the isomers of *N*-(2-hydroxy-1-phenylethyl)-3,6-dipentyl-3,6-dihydro-2*H*-thiopyran-2-carboxamide. The acid **18d** (as a racemic mixture of diastereomers, 26 mmol) was converted to the corresponding acid chloride exactly as above (3 equiv oxalyl chloride, cat. DMF, in CH_2Cl_2). After evaporation, the acid chloride was taken up in THF (20 mL), and added dropwise to a solution of (*S*)-2-amino-2-phenylethanol (2.81 g, 20.5 mmol) and triethylamine (3.50 mL, 25.1 mmol) in THF (40 mL) at 0 °C. After stirring for 10 h, the mixture was poured into water (200 mL), and extracted with ethyl acetate (2 × 200 mL). The extracts were combined, dried over $MgSO_4$, filtered, and evaporated. The residual material was separated by flash chromatography (1:3 ethyl acetate:hexane) to afford the four possible isomers of the product as first, one clean *endo* isomer (2.64 g), then an inseparable mixture of an *endo* and an *exo* isomer, then finally the other *exo* isomer (total yield 7.04 g, 17.4 mmol, 85%). The fraction with the highest R_f on TLC was assigned as compound **116**, and was a waxy solid. ^{1}H NMR ($CDCl_3$): δ 7.75 (1H, br d, J = 7.0 Hz), 7.40–7.23 (5H, m), 5.78 (1H, ddd, J = 10.9, 5.2, 2.0 Hz), 5.65 (1H, dd, J = 10.9, 1.6 Hz), 5.06 (1H, q, J = 5.9 Hz), 3.90 (2H, t, J = 5.3 Hz), 3.49 (1H, ddd, J = 9.4, 4.5, 2.1 Hz), 3.30 (1H, d, J = 2.6 Hz), 2.99–2.90 (1H, m), 2.43 (1H, t, J = 5.8 Hz), 1.69–1.20 (16H, m), 0.90 (3H, t, J = 6.6 Hz), 0.88 (3H, t, J = 6.6 Hz).

The same procedure was performed using (*R*)-2-amino-2-phenylethanol to obtain a similar mixture, containing the enatiomer of **116**.

Preparation of (−)-methyl 3,6-dipentyl-3,6-dihydro-2*H*-thiopyran-2-carboxylate (117). A solution of amide **116** (308 mg, 763 mmol) in methanol (20 mL) was treated with 6 N aq H_2SO_4 (10 mL). The mixture was heated to gentle reflux for 10 h, then cooled and partially evaporated. The residual material was poured into water (100 mL), and extracted with ethyl acetate (2 × 100 mL). The extracts were washed in sequence with brine (100 mL), then combined, dried over $MgSO_4$, filtered, and evaporated. The product ester **117** was purified by filtration through a short column of silica gel with (1:4) ethyl acetate:hexane, and was obtained as an oil upon evaporation of the filtrate (190 mg, 637 mmol, 83%). ^{1}H NMR ($CDCl_3$): δ 5.79–5.69 (2H, m), 3.74 (3H, s), 3.42 (1H, br t, J = 6.6 Hz), 3.36 (1H, d, J = 4.0 Hz), 2.55–2.45 (1H, m), 1.68–1.22 (16H, m), 0.89 (6H, t, J = 6.8 Hz). MS (CI): *m/z* 316 (20%), 300 (20), 299 (100), 239 (6).

Preparation of (−)-50. A solution of **116** (2.33 g, 5.77 mmol) in dioxane (100 mL) was treated with 6 N H_2SO_4 (100 mL), and the mixture was heated to reflux overnight. The solution was cooled, and poured into water (200 mL). This mixture was extracted with ethyl acetate (2 × 200 mL). The extracts were combined, dried over $MgSO_4$, filtered, and evaporated to afford (−)-**18d** as a single diastereomer by ^{1}H NMR, identical to the spectrum of the *endo* isomer.

This material (1.57 g, 5.52 mmol) was treated with oxalyl chloride (2.00 mL, 22.9 mmol) in CH_2Cl_2 solution, containing 1 drop DMF. After stirring for 2 h, the solution was evaporated, and the residue was taken up in THF and added to a solution of amine **13A** (1.10 g, 5.49 mmol) and triethylamine (1.00 mL, 7.17 mmol) in THF (10 mL) at 0 °C. After stirring for 12 h, the mixture was poured into water, and extracted twice with ethyl acetate. The extracts were washed with brine, combined, dried over Na_2SO_4, filtered, and evaporated. Chromatography as before gave the title product as a waxy solid. Optical rotation: $[\alpha]_{25}$ −10.30° (*c* 0.602, ethanol).

The same procedure was repeated for the enantiomeric system to afford (+)-**50**. Optical rotation: $[\alpha]_{25}$ +10.50° (*c* 0.600, ethanol). Elemental analysis: C, H, N.

Preparation of (*R*)-*N*-(2-hydroxy-1-phenylethyl)-2-chloroacetamide (118). A solution of (*R*)-2-amino-2-phenylethanol (2.50 g, 18.2 mmol) and triethylamine (3.00 mL, 21.5 mmol) in THF (40 mL) was cooled to 0 °C, and treated dropwise with a solution of chloroacetyl chloride (1.60 mL, 20.1 mmol) in THF (10 mL). The solution was stirred for 10 h, then poured into water (100 mL) and extracted with ethyl acetate (2 × 100 mL). The extracts were washed with brine (100 mL), then combined, dried over $MgSO_4$, filtered, and evaporated. The residual material was triturated with ether and filtered, and the solid dried (mp 94–96 °C) to afford pure **118** (2.48 g, 11.6 mmol, 64%). ^{1}H NMR ($CDCl_3$): δ 7.43–7.28 (6H, m), 5.10 (1H, dt, J = 7.7, 4.8 Hz), 4.15 (1H, d, J = 15.4 Hz), 4.07 (1H, d, J = 15.4 Hz),

3.94 (2H, d, $J=4.4$ Hz), 1.60 (1H, br s). MS (CI): *m/z* 216 (34%), 215 (14), 214 (100).

Preparation of (*R*)-*N*-(2-hydroxy-1-phenylethyl)-2-phenacylthioacetamide (119). A solution of chloride **118** (2.48 g, 11.6 mmol), thiol **15** (1.95 g, 12.8 mmol), and K_2CO_3 (1.77 g, 12.8 mmol) in THF (30 mL) was heated to reflux for 6 h, then cooled and poured into water (100 mL). This mixture was extracted with CH_2Cl_2 (2×100 mL), and the extracts were combined, dried over $MgSO_4$, filtered, and evaporated. The residual material was separated by flash chromatography (1:4 acetone:hexane) to afford sulfide **119** as a solid, mp 97–98 °C (1.62 g, 4.92 mmol, 42%). ^1H NMR ($CDCl_3$): δ 7.99–7.93 (2H, m), 7.65–7.26 (9H, m), 5.11 (1H, ddd, $J=7.7$, 6.2, 4.4 Hz), 4.01 (1H, d, $J=15.4$ Hz), 3.96 (1H, d, $J=15.4$ Hz), 3.94–3.81 (2H, m), 3.30 (2H, s), 2.81 (1H, dd, $J=6.9$, 5.8 Hz). MS (CI): *m/z* 332 (8%), 331 (23), 330 (100), 296 (2), 212 (1).

Alternate preparation of (+)-50. The standard photolysis procedure was employed for sulfide **119** (330 mg, 1.00 mmol) and diene **7d** (1.95 g, 10.0 mmol) to afford the enantiomer of **116** (100 mg, 0.25 mmol, 25%), which showed identical spectral properties to the other enantiomer. H_2SO_4 hydrolysis as before gave (+)-**18d** (95%), then coupling with **13A** exactly as before gave (+)-**50** (36%).

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