Discovery of 1-(4-Fluorophenyl)-(3*R*)-[3-(4-fluorophenyl)-(3*S*)-hydroxypropyl]-(4*S*)-(4-hydroxyphenyl)-2-azetidinone (SCH 58235): A Designed, Potent, Orally Active Inhibitor of Cholesterol Absorption

Stuart B. Rosenblum,* Tram Huynh, Adriano Afonso, Harry R. Davis, Jr., Nathan Yumibe, John W. Clader, and Duane A. Burnett

Department of Discovery Research, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, New Jersey 07033-0539

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(3*R*)-(3-Phenylpropyl)-1,(4*S*)-bis(4-methoxyphenyl)-2-azetidinone (**2**, SCH 48461), a novel inhibitor of intestinal cholesterol absorption, has recently been described by Burnett et al. and has been demonstrated to lower total plasma cholesterol in man. The potential sites of metabolism of **2** were considered, and the most probable metabolites were prepared. The oral cholesterol-lowering efficacy of the putative metabolites was evaluated in a 7-day cholesterol-fed hamster model for the reduction of serum total cholesterol and liver cholesteryl esters versus control. On the basis of our analysis of the putative metabolite structure−activity relationship (SAR), SCH 58235 (**1**, 1-(4-fluorophenyl)-(3*R*)-[3-(4-fluorophenyl)-(3*S*)-hydroxypropyl]-(4*S*)-(4-hydroxyphenyl)-2-azetidinone) was designed to exploit activity enhancing oxidation and to block sites of potential detrimental metabolic oxidation. Additionally, a series of congeners of **2** were prepared incorporating strategically placed hydroxyl groups and fluorine atoms to further probe the SAR of 2-azetidinone cholesterol absorption inhibitors. Through the SAR analysis of a series of putative metabolites of **2**, compound **1** was targeted and found to exhibit remarkable efficacy with an ED_{50} of 0.04 mg/kg/day for the reduction of liver cholesteryl esters in a 7-day cholesterol-fed hamster model.

Introduction

Recent clinical trials and extensive epidemiological studies support the reduction of low-density plasma lipoproteins (LDL) as a major goal in the treatment and prevention of coronary heart disease (CHD).[1] The pharmacological reduction of LDL levels has been achieved in man by the use of cholesterol biosynthesis inhibitors (e.g., HMG-CoA reductase inhibitors, typified by the statins), bile acid sequestrates (e.g., resins, Cholestyramine, Colestipol), and HDL-elevating agents (e.g., fibrates, nicotinic acid analogues)[2] and with cholesterol absorption inhibitors (CAIs; e.g., Tiqueside (**6**, CP 88,818; Pfizer[3]), **2** (SCH 48461; Schering-Plough[4])) (Figure 1). Even with the current diverse repertoire of therapeutic agents and combinations thereof, a significant portion of the hypercholesterolemic population is unable to reach target serum cholesterol levels, or drug interaction and safety issues preclude the prolonged treatment regimen needed to reduce CHD risk.[5] Therefore, the discovery of more efficacious, well-tolerated agents and combinations of agents which regulate cholesterol homeostasis by complementary mechanisms of action remains of interest.

As part of an extensive synthetic effort to further explore the structure−activity relationship (SAR) of 2-azetidinone inhibitors of cholesterol absorption,[6,7] we wish to report a new, orally active cholesterol absorption inhibitor, 1-(4-fluorophenyl)-(3*R*)-[3-(4-fluorophenyl)-(3*S*)-hydroxypropyl]-(4*S*)-(4-hydroxyphenyl)-2-azetidinone (**1**, SCH 58235).[8] Azetidinone **1** exhibits remarkable reduction in liver cholesterol ester (LCE) potency in cholesterol-fed hamsters (LCE ED_{50} 0.04 mg/kg/day) and was designed to exhibit a simplified metabolic profile and an improved pharmacokinetic profile relative to our first-generation lead **2**.

The discovery of **2** and the structure−CAI activity relationship of related first-generation 2-azetidinone inhibitors of cholesterol absorption have been previously described.[6,10] Azetidinone **2** was found to reduce serum total cholesterol and liver cholesteryl ester levels in a dose-dependent fashion in the orally dosed 7-day cholesterol-fed hamster (LCE ED_{50} 2.2 mg/kg),[11] 7-day rat (LCE ED_{50} 2 mg/kg),[11] and 21-day monkey (LCE ED_{50} 0.2 mg/kg)[12] models by inhibiting lumenal cholesterol absorption. **2** was evaluated in a 8-week human trial after a 2-week American Heart Association step 1 diet lead-in regiment and reduced serum LDL levels by 15% at a 25 mg/day dose.[4]

Studies with [^{3}H]-**2** in a bile duct-diverted rat model indicated the rapid appearance of a complex metabolite mixture in the bile. Further studies confirmed that in rats, the metabolite mixture was a more potent inhibitor of [^{14}C]cholesterol absorption and had a greater localization in the intestinal lumen than **2**.[13] In light of the encouraging but modest activity in humans and the complex metabolic profile in rats of our first-generation lead (**2**), we speculated that a metabolite-like analogue with improved pharmacokinetic and pharmacodynamic profiles would have significantly increased CAI activity.

* Corresponding author: e-mail, stuart.rosenblum@spcorp.com.

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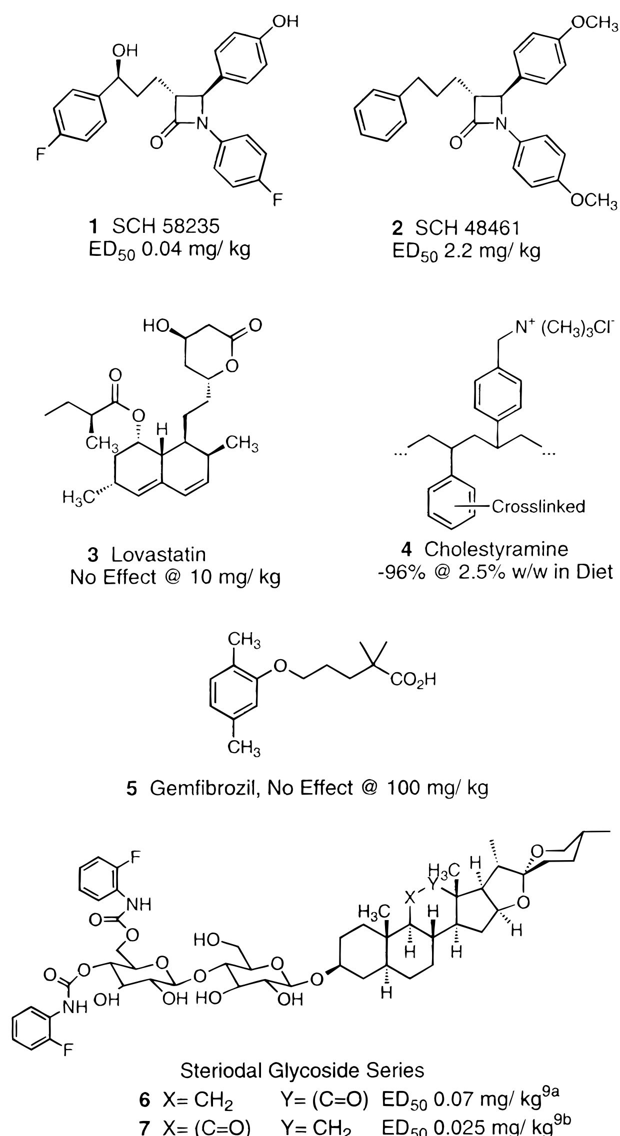
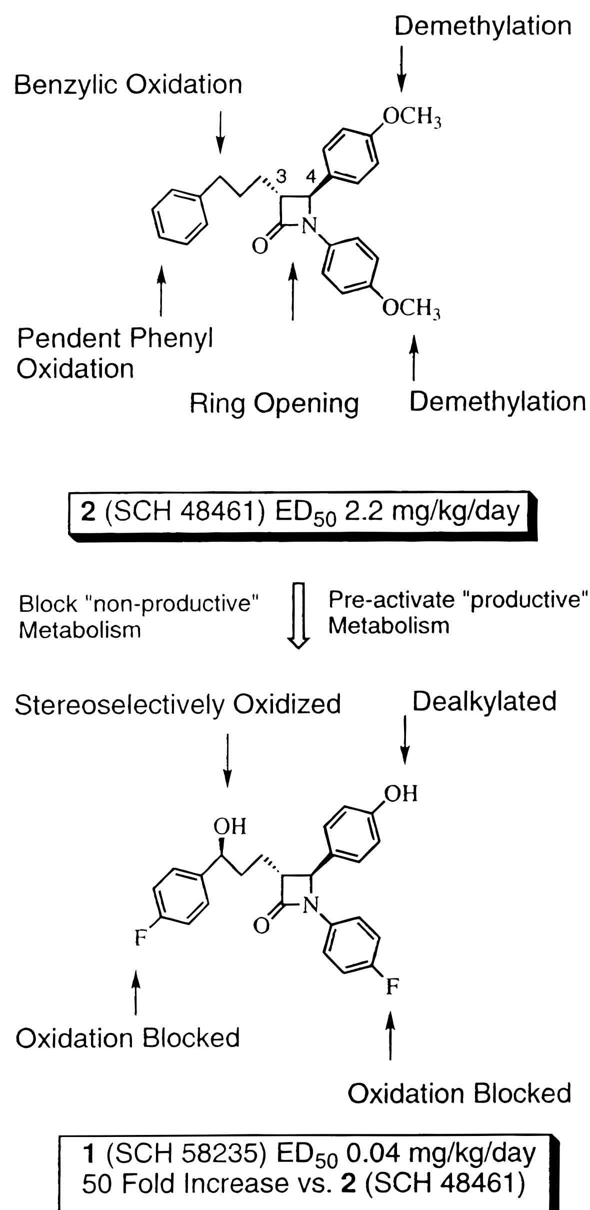


Figure 1. Potency comparison of various agents for the reduction of liver cholesterol ester levels in cholesterol-fed hamsters.

Scheme 1. Putative Sites of Metabolism of **2**: Design of **1** (SCH 58235)[a]



[a] ED_{50} of reduction of liver cholesterol esters in hamsters.

Results and Discussion

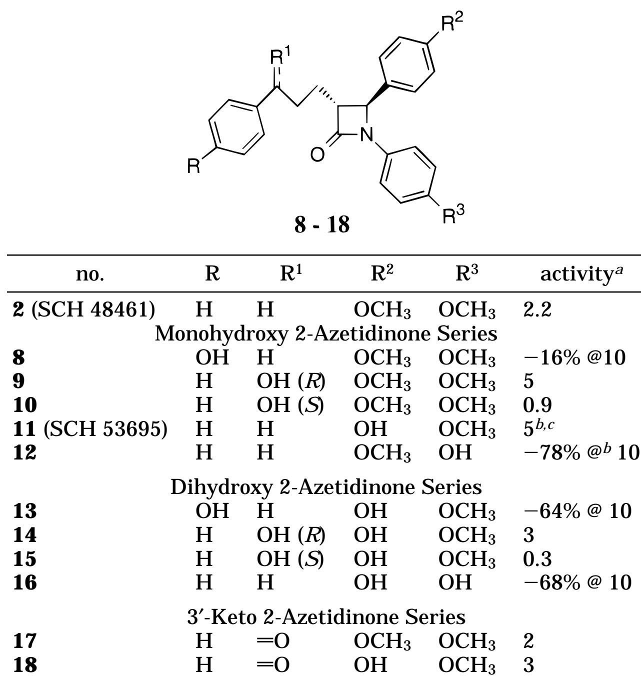
The expected modes of primary metabolism of **2** are dealkylation of the N1- and C4-methoxyphenyl groups (Scheme 1), para hydroxylation of the pendent C3-side chain phenyl group, benzylic oxidation (hydroxylation potentially followed by ketone formation), and 2-azetidinone ring opening.[14] Limiting the analysis to these five sites of metabolism, greater than 40 constitutively different potential metabolites are predicted. Additional consideration of the stereochemical consequences of benzylic hydroxylation and potential intramolecular cyclization/lactone formation from the benzylic hydroxyl metabolites[15] would make preparation of all possible metabolites a formidable task. A directed synthetic effort toward the most probable metabolites was undertaken using the 7-day cholesterol-fed hamster model as the primary assay to evaluate activity. The CAI activity of these putative metabolites is summarized in Table 1.

Previous work[6] has shown that the key structural elements for CAI activity of 2-azetidinones are an N1-aryl-substituted 2-azetidinone backbone, a (4*S*)-alkoxyaryl substituent, and a C3-arylalkyl substituent (either 3*R* or 3*S*). It has also been previously shown that CAI activity is maintained with a wide variety of para substituents (H, halogen, OH, OCH_3) on the N1-phenyl but that the C4-phenyl requires a hydroxyl or alkoxyl residue for activity.[6]

The current work focuses on the effect of C3-pendent aryl ring hydroxylation, C3-side chain benzylic oxidation, and strategic incorporation of fluorine on the CAI activity of 2-azetidinones in the cholesterol-fed hamster model. The effect of para hydroxylation of the C3-pendent aryl ring in both **8** (monohydroxy series) and **13** (dihydroxy series) was deleterious with only marginal CAI activity (i.e., LCE reduction) at 10 mg/kg. This may partly be due to the poor solubility of these compounds in the oral gavage vehicle (i.e., corn oil).

Next, the effect of C3-side chain benzylic hydroxylation was examined and found to be stereochemistry-dependent. The 3′*S* alcohol analogue **10** was found to

Table 1. CAI Activity of **2** and Putative Metabolites **8**−**18**



no.	R	R^1	R^2	R^3	activity[a]
2 (SCH 48461)	H	H	OCH_3	OCH_3	2.2
Monohydroxy 2-Azetidinone Series					
8	OH	H	OCH_3	OCH_3	−16% @10
9	H	OH (*R*)	OCH_3	OCH_3	5
10	H	OH (*S*)	OCH_3	OCH_3	0.9
11 (SCH 53695)	H	H	OH	OCH_3	5[b,c]
12	H	H	OCH_3	OH	−78% @[b] 10
Dihydroxy 2-Azetidinone Series					
13	OH	H	OH	OCH_3	−64% @ 10
14	H	OH (*R*)	OH	OCH_3	3
15	H	OH (*S*)	OH	OCH_3	0.3
16	H	H	OH	OH	−68% @ 10
3′-Keto 2-Azetidinone Series					
17	H	=O	OCH_3	OCH_3	2
18	H	=O	OH	OCH_3	3

[a] Activity reported as ED_{50} (mg/kg/day) or percent reduction of liver cholesterol esters (LCE) in cholesterol-fed hamsters. [b] Synthesis described in ref 6. [c] Isolation of **11** (SCH 53695) from the bile of **2** (SCH 48461)-dosed rats described in ref 13.

be 5-fold more potent than the 3′*R* alcohol isomer **9** (LCE ED_{50} 0.9 vs 5 mg/kg) in the monohydroxy series. More dramatically, in the dihydroxy series (side chain-3′-OH and C4-phenyl-4-OH) the 3′*S* alcohol **15** was found to be 1 order of magnitude more potent than the 3′*R* alcohol isomer **14** and at least 7-fold more potent than **2**. Attempts to prepare the pendent 4-hydroxyphenyl benzyl alcohol ($R = R^1 = OH$; $R^2 = R^3 = OCH_3$) analogue were unsuccessful and highlighted the instability of this potential metabolite. The CAI profiles of C3-side chain ketone congeners **17** and **18** were not significantly different than that of **2**. The clear stereochemical preference at the C3-side chain benzylic position and at the C4-azetidinone position for CAI activity suggests a well-defined molecular interaction with an as yet undiscovered target.

The highlight of our SAR investigation based on putative metabolites of **2** was the activity enhancement of a 3′*S*-hydroxylated C3-side chain substituent. Coupling this discovery with previous SAR results[6] led us to incorporate in our synthetic targets "productive" (i.e., enhanced activity) functional groups and also to block sites of potential "nonproductive" metabolism. We postulated that strategically hydroxylated and metabolically blocked analogues would have simpler metabolic and pharmacokinetic profiles and thus increased CAI potency. The use of a halogen to block sites of metabolism is well-known,[16] and fluorine was chosen due to its small steric demand and its deactivating effect to deter P_{450}-mediated aromatic hydroxylation at other sites on a phenyl ring. *This reasoning led directly to the targeted synthesis of compound **1**, a compound whose structure has been optimized at the putative metabolic sites for CAI activity as outlined in Scheme 1.*

1 was found to have a dose−responsive effect (Table 2) on serum cholesterol and liver cholesterol esters with

Table 2. CAI Dose−Response of **1** (SCH 58235) and **2**

	1 (SCH 58235)		**2** (SCH 48461)	
dose (mg/kg/day)	liver CE[a] (%)	serum TC[b] (%)	liver CE[a] (%)	serum TC[b] (%)
3	−100	−100	−68	−76
1	−100	−100	−14	NS
0.3	−96	−72	NS	NS
0.1	−87	−37		
0.03	−39	−23		

[a] Percent negation of rise in liver cholesterol esters relative to control-fed 0.5% cholesterol for 7 days. [b] Percent negation of rise in total serum cholesterol relative to control-fed 0.5% cholesterol for 7 days. NS, percent reduction was not statistically significant; all percent values ±10%; see Experimental Section for details.

an LCE ED_{50} of 0.04 mg/kg/day in the 7-day cholesterol-fed hamster model, a 50-fold (50×) increase in potency relative to **2**. The dramatic increase in in vivo potency is probably due to both an increased intrinsic binding interaction with the (3′*S*)-hydroxyl side chain substituent and a greatly improved ADME (absorption, distribution, metabolism, and excretion) profile which increased lumenal retention time (i.e., the site of biological action).

A series of congeners of **2** were prepared incorporating various desirable metabolic transformations into their structure, while undesired metabolic transformations were blocked by strategic substitution with fluorine. Significant increases in CAI activity relative to **2** were observed in most analogues (Figure 2) which incorporated *p*-fluorine substitution on the N1-phenyl and C3-pendent phenyl rings (compounds **19**−**27**). Dramatic activity improvements relative to **2** were also observed with a variety of C4-(4-alkoxyphenyl) substituents (e.g., **20**, **21**) and with 3′-acetoxy side chain substitution (e.g., **25**, **26**). The SAR in this series confirmed the importance and stereochemical preference of a C3−(3′*S*)-hydroxyl substituent.

Chemistry. Our initial approach to the preparation of the putative **2** metabolites described above (Table 1) is outlined in Scheme 2. Multigram quantities of enantiomerically pure **2**[17] were available and served as the starting material for our initial targets. Treatment of **2** with *N*-bromosuccinimide afforded a diastereomeric mixture of C3-side chain benzylic bromides **28** and **29**. Repeated attempts to prepare C3-side chain benzylic hydroxyl analogues by direct solvolysis of the corresponding bromides (**28**, **29**) afforded only trace amounts of **9** and **10** within a complex mixture of non-2-azetidinone products.[15] Benzylic bromide displacement with tetra-*n*-butylammonium trifluoroacetate followed by mild trifluoroacetate deprotection with ethanolic ammonia provided the desired putative metabolites **9** and **10**. Manganese oxide oxidation of both **9** and **10** afforded ketone **17** in 80% yield.

Access to nonhydroxylated **2** congeners was accomplished in good yield by the previously disclosed method B (Scheme 3).[6] Compound **1** and a series of fluorinated analogues (Figure 2) were prepared as summarized in Scheme 4. Using the trans-stereoselective conditions developed by Vaccaro et al.,[18] racemic ester **35** was assembled by the cycloaddition of a suitably protected imine (**34**) with the ketene derived from methyl 4-(chloroformyl)butyrate (**33**). Chiral chromatographic separation of **35** provided enantiomerically pure (>98% ee)

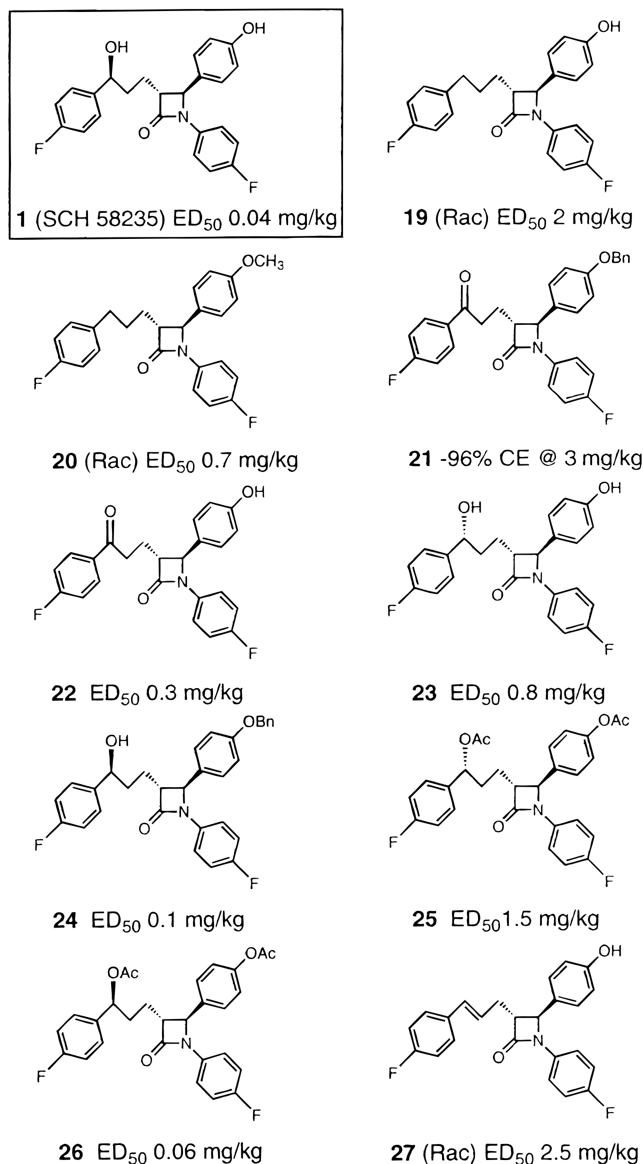


Figure 2. CAI activity of SCH 58235 (**1**) and analogues. Unless otherwise noted, absolute stereochemistry is shown and compounds were determined to be >98% ee by chiral chromatography (Chiracel OD). Activity reported as ED_{50} of reduction in liver cholesterol esters in 7-day hamster model.

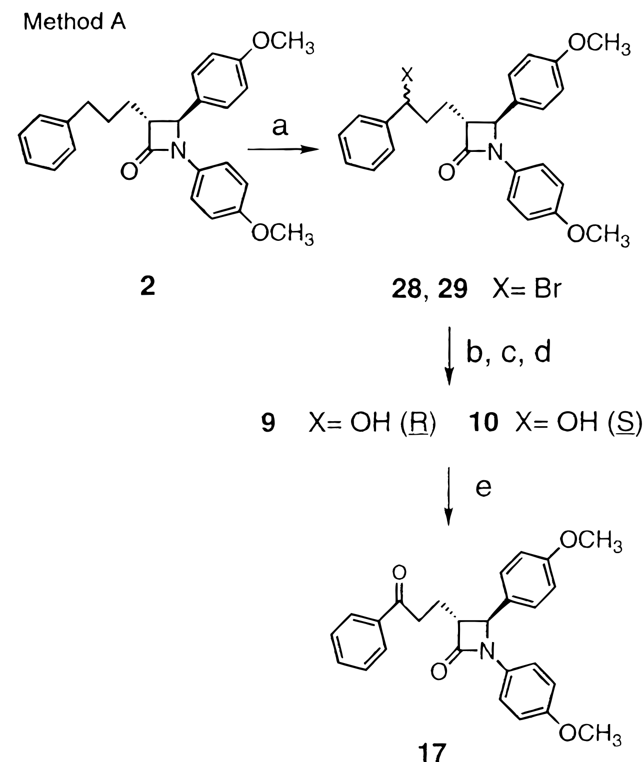
2-azetidinone **36** (3*R*,4*S*). Chemoselective ester hydrolysis with lithium hydroxide followed by acid chloride formation afforded acid chloride **38**. Introduction of the C3-pendent 4-fluorophenyl moiety was accomplished efficiently by application of palladium-mediated arylzinc acid chloride coupling methodology pioneered by Negeshi.[19] Stereorandom borane reduction of the benzylic ketone followed by chromatographic separation affords the benzylic hydroxy isomers (**1**, **23**, **24**) in high enantiomeric purity. A scalable stereospecific synthesis of azetidinone **1** has been accomplished which will be reported elsewhere.

Summary

The impressive CAI activity of **1** in the cholesterol-fed hamster (LCE ED_{50} 0.04 mg/kg/day) has been additionally confirmed in a cholesterol-fed rhesus monkey model (LCE ED_{50} 0.0005 mg/kg/day, 400 times more potent than **2**).[13] The truly remarkable activity in animal models suggests a mechanism that interferes with a fundamental cholesterol-trafficking process. Further biological evaluation of **1** has found its CAI activity to be synergistically potentiated by the HMG-CoA reductase inhibitor Lovastatin in dogs.[20]

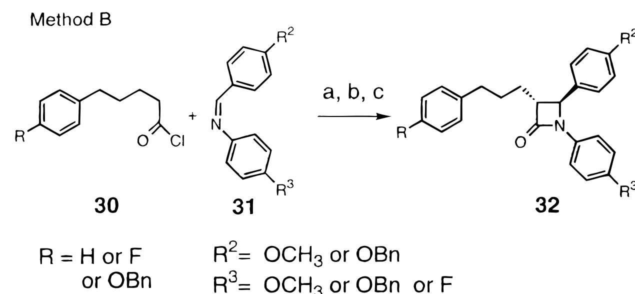
The integration of synthetic and medicinal chemistry with metabolic and pharmacological data led to the design of azetidinone **1**, which is being progressed for the treatment of hypercholesterolemia in humans and as a mechanistic tool in the study of cholesterol trafficking.

Scheme 2. Preparation of Putative Metabolites of **2**[a]



[a] Reagents: (a) *N*-bromosuccinimide, CCl_4; (b) $(n\text{-}Bu)_4NTFA$, CH_2Cl_2, H_2O; (c) $NH_3(s)$ in EtOH; (d) chiral chromatography (Chiracel OD column); (e) MnO_2, dioxane.

Scheme 3. Preparation of Analogues of **2**[a]



R = H or F or OBn

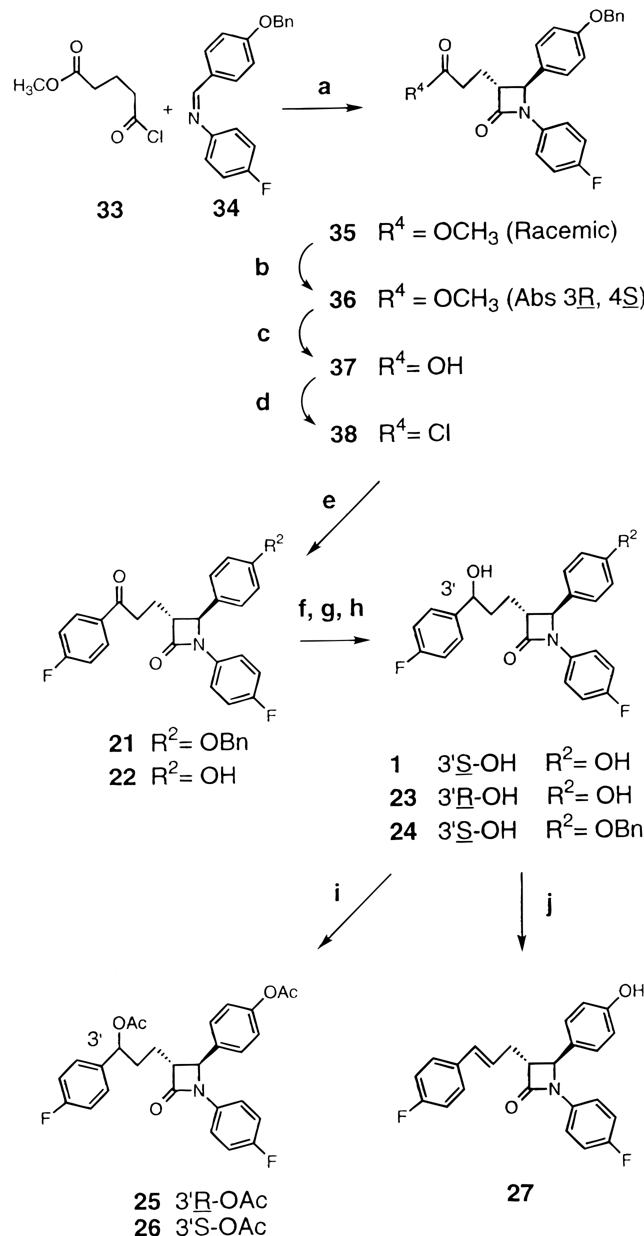
R^2 = OCH_3 or OBn

R^3 = OCH_3 or OBn or F

	R	R^2	R^3	
8	OH	OCH_3	OCH_3	racemic
11	H	OH	OCH_3	abs 3R, 4S
12	H	OCH_3	OH	abs 3R, 4S
13	OH	OH	OCH_3	racemic
16	H	OH	OH	abs 3R, 4S
19	F	OH	F	racemic
20	F	OCH_3	F	racemic

[a] Reagents: (a) $(n\text{-}Bu)_3N$, toluene; (b) optional chiral chromatography (Chiracel OD column); (c) 10% Pd–C, EtOH, $H_2(g)$ (60 psi).

Scheme 4. Synthesis of **1** (SCH 58235) and Analogues[a]



[a] Reagents: (a) (n-Bu)$_3$N, toluene; (b) chiral chromatography (Chiracel OD column); (c) LiOH, THF; (d) oxalyl chloride, CH_2Cl_2; (e) F-4-PhZnBr, $(Ph_3P)_4Pd$, THF; (f) $BH_3-S(CH_3)_2$; (g) chiral chromatography (Chiracel OD column); (h) 10% Pd/C, EtOH, H_2(g) (60 psi); (i) acetyl chloride, pyridine; (j) $pTolSO_3H$, toluene.

Experimental Section

All reactions were performed under argon with magnetic stirring unless otherwise stated. Air- and moisture-sensitive reagents were transferred with disposable all-polypropylene syringes available from Aldrich Chemical Co. Anhydrous ether, tetrahydrofuran, toluene, and methylene chloride were obtained from Aldrich Chemical Co. and used without further drying. All commercially available compounds were used without further purification unless otherwise noted. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Analytical TLC was performed using Analtech glass-coated plates with fluorescent indicator (silica gel GF, 250 μm), and visualization was accomplished with a UV lamp (254 nm). Preparative flash chromatography utilized Selecto Scientific flash silica gel (32−63 μm) under medium pressure with compound-to-silica gel weight ratios of 1:10−30. Analytical HPLC was performed on a Rainin HPXL pump system using either Rainin Dynamax 60A columns (achiral) or Chiracel columns (chiral) with UV detection (254 nm) as detailed. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in deuterated chloroform (Cambridge Isotope Laboratories) unless otherwise noted on a Varian Gemini 300 spectrometer. Chemical shifts are reported in ppm (δ) relative to TMS, and coupling constants *(J)* are reported in Hz. Elemental analyses were within 0.4% of theory, unless otherwise noted. Specific rotation $[\alpha]_D$ is reported in degree/dm at the specified temperature and the concentration (c) expressed in g/100 mL of specified solvent. Chemical ionization (CI; CH_4 carrier) and electron ionization (EI; ~70 eV) mass spectra were recorded on a Hewlett-Packard 5989A spectrometer. Tandem liquid chromatography−electrospray mass spectra were recorded on a SCIEX API-100 spectrometer. Typical gradient chromatography conditions were acetonitrile/water (5:95 to 95:5) over 10 min on a Suplecosil LC-18DB (3.3-cm × 4.6-mm i.d.) column with ion-current detection. High-resolution mass spectra were recorded on a peak matching JEOL JMS-HX110A spectrometer.

Method A: **1,(4*S*)-Bis(4-methoxyphenyl)-(3*R*)-((3*R*)-hydroxy-3-phenylpropyl)-2-azetidinone (9).** To a solution of 1,(4*S*)-bis(4-methoxyphenyl)-(3*R*)-(3-phenylpropyl)-2-azetidinone[17] (**2**; 5.04 g, 12.6 mmol) in 20 mL of CCl_4 at 80 °C were added *N*-bromosuccinimide (2.76 g, 15.5 mmol) and benzoyl peroxide (0.24 g, 1.0 mmol) in three equal portions over 1 h. After 4 h, the reaction mixture was cooled to 22 °C, and 1 N $NaHSO_4$ was added. The organic layer was separated, washed thrice with water, and dried over $MgSO_4$. Purification by chromatography afforded **28** and **29** as a diastereomeric mixture (3.6 g): ^{1}H NMR (300 MHz) δ 5.05 (m, 1H, PhC*H*Br (isomers a and b)), 4.70 (d, 1H, $J = 2.2$ Hz, NCH−Ar (isomer a)), 4.68 (d, 1H, $J = 2.2$ Hz, NCH−Ar (isomer b)); $R_f = 0.4$, 4:1 hexane/ethyl acetate; MS (CI) *m*/*e* 480 (M^+H). Anal. ($C_{26}H_{26}NO_3Br$) C, H, N.

An equal mixture of isomers **28** and **29** (0.423 g) was dissolved in 5 mL of CH_2Cl_2, and 40% aqueous (n-BuN)$_4$TFA (0.25 mL) was added. The biphasic reaction mixture was refluxed for 12 h and cooled, water and ethyl ether were added, and the layers were separated. The organic layer was concentrated to dryness, immediately redissolved in ethanol saturated with ammonia (10 mL), and stirred at room temperature. After 1 h the reaction mixture was concentrated to dryness and the residue applied to a Chiralcel OD chromatography column, eluting with hexane/ethanol (9:1) to obtain enantiomerically pure (>98% ee) diastereomers **9** and **10**. **9**: $[\alpha]^{22}_D$ +8.3° (c 3, MeOH); MS (CI) *m*/*e* 418 (M^+H, 63), 400 (M − 18, 100); ^{1}H NMR (300 MHz) δ 4.82 (dd, 1H, PhC*H*OH), 4.67 (d, 1H, $J = 2.2$ Hz, NCH−Ar). Anal. ($C_{26}H_{27}NO_4$) C, H, N.

1,(4*S*)-Bis(4-methoxyphenyl)-(3*R*)-((3*S*)-hydroxy-3-phenylpropyl)-2-azetidinone (10): see experimental for compound **9**; oil; $[\alpha]^{22}_D$ +33.1° (c 3, MeOH); MS (CI) *m*/*e* 418 (M^+H, 52), 400 (M − 18, 100); ^{1}H NMR (300 MHz) δ 4.70 (dd, 1H, PhC*H*OH), 4.57 (d, 1H, $J = 2.2$ Hz, NCH−Ar). Anal. ($C_{26}H_{27}NO_4$) C, H, N.

1,(4*S*)-Bis(4-methoxyphenyl)-(3*R*)-(3-oxo-3-phenylpropyl)-2-azetidinone (17). An equal mixture of alcohols **9** and **10** (0.130 g) was dissolved in 1.8 mL of acetone, and manganese dioxide (0.374 g) was added. The mixture was heated at reflux for 20 h, cooled, and filtered through silica gel (acetone wash). Further purification by column chromatography eluting with ethyl acetate/hexane (1:1) afforded **17** (0.102 g): oil; ^{1}H NMR (300 MHz) δ 8.1 (d, 2H, Ar), 7.7−7.3 (m, 7H, Ar), 6.95 (d, 2H, Ar), 6.85 (d, 2H, Ar), 4.78 (d, 1H, $J = 2.1$ Hz, NCH−Ar), 3.9 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.5−3.2 (m, 2H, $COCH_2$), 2.5−2.3 (m, 2H, CH_2CH); MS (CI) *m*/*e* 416 (M^+H, 100), 266 (93). Anal. ($C_{26}H_{25}NO_4$) C, H, N.

(4*S*)-(4-Hydroxyphenyl)-(3*R*)-((3*R*)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone (14): prepared by method A to obtain an equal mixture of compounds **14** and **15**, can be further purified on a Chiracel OD column to obtain **14**; mp 87−90 °C; ^{1}H NMR (300 MHz) δ 4.82 (d, 1H, PhC*H*OH); HRMS calcd for $C_{25}H_{25}NO_4$ 403.1783, found 403.1797.

(4*S*)-(4-Hydroxyphenyl)-(3*R*)-((3*S*)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone (15): see experimental for compound **14**; ^{1}H NMR (300 MHz) δ 4.78 (d, 1H, PhC*H*OH); HRMS calcd for $C_{25}H_{25}NO_4$ 403.1783, found 403.1787.

(4*S*)-(4-Hydroxyphenyl)-(3*R*)-(3-oxo-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone (18): prepared by method A; ^{1}H NMR (300 MHz) δ 8.05 (d, 2H, Ar), 7.65 (t, 1H, Ar), 7.55 (t, 2H, Ar), 7.3 (m, 3H, Ar), 6.95 (d, 2H, Ar), 6.85 (d, 2H, Ar), 4.75 (d, 1H, *J* = 1.98 Hz, CHAr), 3.82 (s, 3H, OCH_3), 3.4 (m, 1H) 3.3 (m, 1H), 3.2 (m, 1H), 2.5 (m, 1H), 2.35 (m, 1H); HRMS calcd for $C_{25}H_{23}NO_4$ 401.1627, found 401.1610.

General Method B: 1-(4-Fluorophenyl)-(3*R*)-[3-(4-fluorophenyl)propyl]-(4*S*)-(4-methoxyphenyl)-2-azetidinone (19). A round-bottomed flask was charged with 4-fluoroiodobenzene (8.63 mL, 75 mmol), palladium acetate (2.24 g, 10 mmol), triphenylphosphine (2.53 g, 10 mmol), potassium acetate (29.4 g, 300 mmol), tetrabutylammonium chloride (20.9 g, 75 mmol), 50 mL of dimethylformamide, and 4-pentenoic acid (5.1 mL, 50 mmol). The reaction mixture was heated at 80 °C for 24 h, cooled, and poured into 1 N NaOH. Ethyl acetate was added, and the layers were separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated to afford 5-(4-fluorophenyl)-(3*E*)-pentenoic acid (4.5 g).

A Parr hydrogenation vessel was charged with 5-(4-fluorophenyl)-(3*E*)-pentenoic acid (4.2 g, 21 mmol) and 30 mL of ethanol, and 10% palladium on carbon (0.5 g) was added. The mixture was shaken under hydrogen pressure (50 psi) for 3 h at room temperature and filtered through Celite and the filtrate concentrated to afford 5-(4-fluorophenyl)pentanoic acid (4.1 g).

To a solution of 5-(4-fluorophenyl)pentanoic acid (1.2 g, 6.3 mmol) in 10 mL of CH_2Cl_2 was added oxalyl chloride (1.0 mL, 12 mmol), and the solution was heated to mild reflux. After 2 h the reaction mixture was concentrated in vacuo to afford the acid chloride as an oil (1.3 g).

In a separate flask containing the imine (1.75 g, 5.73 mmol) derived from 4-(benzyloxy)benzaldehyde and 4-fluoroaniline were added 10 mL of toluene and tributylamine (2.75 mL, 12 mmol), and the solution was heated to 80 °C. A solution of the acid chloride above (1.3 g, 6 mmol) was dissolved in 10 mL of toluene and added dropwise over 0.5 h to the hot solution of imine. After 30 h the reaction mixture was cooled, acidified with 1 N HCl (20 mL), and diluted with ethyl acetate. The organic layer was separated, washed twice with 1 N HCl and twice with water, dried over magnesium sulfate, and concentrated to afford crude azetidinone (2.7 g). Purification by flash chromatography using hexane/ethyl acetate (4:1) eluent afforded analytically pure rel-(4*S*)-[4-(benzyloxy)phenyl]-1-(4-fluorophenyl)-(3*R*)-[(4-fluorophenyl)propyl]-2-azetidinone (1.8 g). Optional chiral chromatographic separation on a Chiralcel OD column using 9:1 hexane/ethanol eluent afforded the abs-3*R*,4*S* isomer (later eluting peak) in >98% ee (0.8 g).

The benzyl-protected phenol (0.166 g) was charged in a Parr hydrogenation vessel with 10% palladium on carbon (16 mg) and shaken under hydrogen (60 psi) for 4 h at room temperature. Filtration through Celite followed by concentration afforded the desired pure C4-phenol analogue **19** (0.130 g): ^{1}H NMR (300 MHz) δ 7.4–6.9 (m, 12H, Ar), 5.73 (br s, 1H, OH), 4.70 (d, 1H, *J* = 2.1 Hz, NCHAr), 3.22 (m, 1H, C(O)CH), 2.75 (t, 2H, CH_2Ar), 2.1–1.85 (m, 4H, CH_2CH_2); MS (CI) *m*/*e* 394 (M^+H, 5), 257 (16), 138 (100); IR ($CHCl_3$, cm^{-1}) 1738. Anal. Calcd for $C_{24}H_{21}F_2NO_2$: C, 73.27; H, 5.38; N, 3.56. Found: C, 72.59; H, 5.78; N, 3.47.

1,(4S)-Bis(4-methoxyphenyl)-(3*R*)-[3-(4-hydroxyphenyl)propyl]-2-azetidinone (8): prepared by method B starting with 4-(benzyloxy)phenyl iodide; ^{1}H NMR (300 MHz) δ 7.5–6.9 (m, 12H, Ar), 4.75 (d, 1H, *J* = 2.1 Hz, NCHAr), 3.3 (m, 1H, C(O)CH), 2.75 (t, 2H, CH_2Ar), 2.1–1.85 (m, 4H, CH_2CH_2); MS (EI) *m*/*e* 417 (M^+, 48), 268 (100); IR ($CHCl_3$, cm^{-1}) 3381 (br, OH), 1730 (C=O). Anal. ($C_{26}H_{27}NO_4$) C, H, N.

(3*R*)-[3-(4-Hydroxyphenyl)propyl]-1-(4-methoxyphenyl)-(4*S*)-(4-hydroxyphenyl)-2-azetidinone (13): prepared by method B starting with 4-(benzyloxy)phenyl iodide; ^{1}H NMR (300 MHz) δ 7.4–7.2 (m, 8H, Ar), 6.92 (d, 2H, Ar), 6.85 (d, 2H, Ar), 5.8 (br s, 1H, OH), 4.65 (d, 1H, *J* = 2.1 Hz, NCHAr), 3.82 (s, 3H, OCH_3), 3.15 (m, 1H, C(O)CH), 2.65 (t, 2H, CH_2-Ar), 2.1–1.85 (m, 4H, CH_2CH_2); MS (CI) *m*/*e* 404 (M^+H, 2), 388 (100); IR ($CHCl_3$, cm^{-1}) 3942 (br, OH), 1734 (C=O). Anal. ($C_{25}H_{25}NO_4$) C, H, N.

1,(4*S*)-Bis(4-hydroxyphenyl)-(3*R*)-(3-phenylpropyl)-2-azetidinone (16): prepared by method B using the imine derived from 4-(benzyloxy)benzaldehyde and 4-(benzyloxy)-aniline; ^{1}H NMR (300 MHz) δ 7.4–7.2 (m, 4H, Ar), 7.0–6.8 (4d, 8H, Ar), 5.7 (br s, 2H, OH), 4.65 (d, 1H, *J* = 2.1 Hz, NCHAr), 3.15 (m, 1H, C(O)CH), 2.63 (t, 2H, CH_2Ar), 2.1–1.85 (m, 4H, CH_2CH_2); MS (CI) *m*/*e* 374 (M^+H). Anal. ($C_{24}H_{23}NO_3$) C, H, N.

1-(4-Fluorophenyl)-(3*R*)-[3-(4-fluorophenyl)propyl]-(4*S*)-(4-methoxyphenyl)-2-azetidinone (20): prepared by method B using 4-fluorophenyl iodide; ^{1}H NMR (300 MHz) δ 7.4–7.0 (m, 12H, Ar), 4.60 (d, 1H, *J* = 2.2 Hz, NCHAr), 3.9 (s, 3H, OCH_3), 3.2 (m, 1H, C(O)CH), 2.70 (t, 2H, CH_2Ar), 2.1–1.85 (m, 4H, CH_2CH_2); IR ($CHCl_3$, cm^{-1}) 1741 (C=O); MS (CI) *m*/*e* 408 (M^+H, 100). Anal. ($C_{25}H_{23}F_2NO_2$) C, H, N.

General Method C: Ketene–Imine General Procedure. A solution of an appropriate imine (prepared from the corresponding benzaldehyde and an aniline)[18] (100 mol %) in heptane and tributylamine (220 mol %) was heated to 80 °C under argon. A solution of an acid chloride (110 mol %) in toluene was added dropwise to the reaction solution over 0.5 h. The solution was stirred at 80–90 °C for 18–30 h. The reaction mixture was then cooled, ethyl acetate was added, and the layers were separated. The organic layer was washed successively with 1 N HCl (3×), H_2O, and saturated NH_4Cl, then dried with $MgSO_4$, and concentrated in vacuo. The crude product mixture was purified by flash chromatography, eluting with hexane/ethyl acetate (ca. 9:1) to afford 2-azetidinones.

1-(4-Fluorophenyl)-(3*R*)-[3-(4-fluorophenyl)-3-oxopropyl]-(4*S*)-[4-(phenylmethoxy)phenyl]-2-azetidinone (21). Using the general ketene–imine procedure above, 4-(benzyloxy)benzylidine 4-fluoroanisidine (10.5 g, 34.4 mmol), tributylamine (18 mL, 75.5 mmol), and methyl 4-(chloroformyl)-butyrate (5 mL, 36.1 mmol) were reacted to prepare racemic methyl ester **35** (9.7 g, 64%). Chromatographic resolution on a Chiralcel OD column using hexane/2-propanol (83:17) eluent afforded optically pure **36** (>98% ee).

To a solution of methyl ester **36** (1.6 g, 3.7 mmol) in 3.5 mL of CH_3OH were added 1.5 mL of water and $LiOH{\cdot}H_2O$ (0.155 g, 3.7 mmol). After 1 h additional $LiOH{\cdot}H_2O$ (54 mg, 1.3 mmol) was added. After a total of 2 h, 1 N HCl and ethyl acetate were added, and the organic layer was separated and dried. Concentration in vacuo afforded carboxylic acid **37** (1.5 g, 97% yield) which was used without purification.

To a solution of the **37** (1.03 g, 2.46 mmol) in CH_2Cl_2 at 22 °C, oxalyl chloride (0.32 mL, 3.67 mmol) was added and the reaction mixture stirred at 22 °C. After 16 h the reaction mixture was concentrated to dryness in vacuo to afford acid chloride **38** (1.08 g, 100%) which was used without further purification.

To suspension of 4-fluorophenylzinc bromide (2.1 mmol) prepared fresh from flamed zinc chloride and 4-fluorophenylmagnesium bromide in THF (4 mL) at 10 °C was added tetrakis(triphenylphosphonium)palladium (118 mg, 0.1 mmol). After 5 min a solution of acid chloride **38** (0.9 g, 2.0 mmol) in 2 mL of THF was added, and the ice bath was removed. After 1 h, 1 N HCl and ethyl acetate were added, and the organic layer was separated and dried. Concentration followed by flash chromatography afforded ketone **21** (0.79 g, 80%): ^{1}H NMR (300 MHz) δ 8.0 (2d, 2H, Ar), 7.4–7.1 (m, 11H, Ar), 6.95 (2d, 4H, Ar), 5.1 (s, 2H, CH_2Ph), 4.70 (d, 1H, *J* = 2.2 Hz, NCHAr), 3.3 (m, 1H, C(O)CH), 3.2 (m, 2H, CH_2CO), 2.4–2.2 (m, 2H, CH_2); HRMS calcd for $C_{31}H_{25}F_2NO_3$ 498.1880, found 498.1877.

1-(4-Fluorophenyl)-(3*R*)-[3-(4-fluorophenyl)-3-oxopropyl]-(4*S*)-(4-hydroxyphenyl)-2-azetidinone (22). To a solution of **21** (0.5 g, 1.0 mmol) in 10 mL of ethanol was added 10% Pd/C (0.05 g), and the reaction mixture stirred under a

pressure of hydrogen gas (60 psi) for 12 h. The reaction mixture was filtered and concentrated to obtain compound **22**: ^{1}H NMR (300 MHz) δ 7.4–6.8 (m, 12H, Ar), 6.05 (br s, 1H, OH), 4.75 (d, 1H, J = 2.2 Hz, NCHAr), 4.60 (m, 1H C*H*OH), 3.15 (m, 1H, C(O)CH), 2.6 (br s, 1H, OH), 2.1–1.9 (m, 4H, CH_2CH_2). Anal. ($C_{24}H_{19}F_2NO_3$) C, H, N.

1-(4-Fluorophenyl)-(3*R*)-[(3*S*)-(4-fluorophenyl)-3-hydroxypropyl]-(4*S*)-[4-(phenylmethoxy)phenyl]-2-azetidinone (24). To a solution of ketone **21** (0.35 g, 0.71 mmol) in 3 mL of THF was added borane–dimethyl sulfide complex (2 M, 0.4 mL, 0.8 mmol). The reaction mixture was stirred for 3 h at 22 °C and the reaction quenched by the addition of 2 mL of methanol. The resulting solution was filtered through Celite to afford an equal mixture of diastereomeric alcohols. Chromatographic purification on a Chiracel OD column using hexane/2-propanol (9:1) eluent afforded the desired 3*S* alcohol isomer **24** (>98% ee, 0.141 g) as the slower eluting peak: MS (CI) *m*/*e* 500 (M^+H, 9), 482 (100); ^{1}H NMR (300 MHz) δ 7.5–6.8 (m, 17H, Ar), 5.1 (s, 2H, CH_2Ph), 4.75 (m, 1H, C*H*OH), 4.60 (d, 1H, J = 2.2 Hz, NCHAr), 3.15 (m, 1H, C(O)CH), 2.4 (br s, 1H, OH), 2.1–1.8 (m, 4H, CH_2CH_2). Anal. ($C_{31}H_{27}F_2NO_3$) C, H, N.

1-(4-Fluorophenyl)-(3*R*)-[(3*S*)-(4-fluorophenyl)-3-hydroxypropyl]-(4*S*)-(4-hydroxyphenyl)-2-azetidinone (1). To a solution of **24** (0.4 g, 0.8 mmol) in 10 mL of ethanol was added 10% Pd/C (0.03 g), and the reaction mixture stirred under a pressure of hydrogen gas (60 psi) for 16 h. The reaction mixture was filtered and concentrated to obtain compound **1** as a white solid: mp 164–166 °C; MS (CI) *m*/*e* 410 (M^+H); IR ($CHCl_3$) 1739 (C=O); $[\alpha]^{22}_D$ −33.9° (*c* 3, MeOH); ^{1}H NMR (300 MHz) δ 7.5–7.2 (m, 6H, Ar), 7.1–6.80 (m, 6H, Ar), 5.2 (s, 1H, OH), 4.80 (m, 1H, C*H*OH), 4.65 (d, 1H, J = 2.2 Hz, NCHAr), 3.15 (m, 1H, C(O)CH), 2.1–1.9 (m, 2H, CH_2). Anal. ($C_{24}H_{21}F_2NO_3$) C, H, N.

1-(4-Fluorophenyl)-(3*R*)-[(3*R*)-(4-fluorophenyl)-3-hydroxypropyl)]-4*S*-(4-hydroxyphenyl)-2-azetidinone (23): prepared from **21** by borane reduction, chiral chromatographic separation, and debenzylation; MS (CI) *m*/*e* 410 (M^+H, 7), 392 (7), 133 (100); IR ($CHCl_3$, cm^{-1}) 1739 (C=O); ^{1}H NMR (300 MHz) δ 7.5–7.2 (m, 6H, Ar), 7.1–6.80 (m, 6H, Ar), 5.3 (s, 1H, OH), 4.80 (m, 1H, C*H*OH), 4.65 (d, 1H, J = 2.2 Hz, NCHAr), 3.15 (m, 1H, C(O)CH), 2.5 (br s, 1H, OH), 2.1–1.9 (m, 2H, CH_2). Anal. ($C_{24}H_{21}F_2NO_3$) C, H, N.

(4*S*)-[4-(Acetyloxy)phenyl]-(3*R*)-[(3*R*)-(acetyloxy)-3-(4-fluorophenyl)propyl)]-1-(4-fluorophenyl)-2-azetidinone (25). To a solution of the compound **23** (0.09 g, 0.2 mmol) in CH_2Cl_2 were added acetyl chloride (0.08 g, 1.0 mmol) and pyridine (8 mg, 0.1 mmol) at 22 °C. After 1 h water was added and the organic layer separated, concentrated, and applied to a silica gel column to afford diacetoxy analogue **25**: ^{1}H NMR (300 MHz) δ 7.5–7.0 (m, 12H, Ar), 5.84 (dd, 1H, J = 5.4, 9 Hz, CHOAc), 4.70 (d, 1H, J = 2.2 Hz, NCHAr), 3.15 (m, 1H, C(O)CH), 2.4 (s, 3H, OCH_3), 2.25 (m, 1H, C*H*CH_2), 2.15 (s, 3H, OCH_3), 2.10–1.8 (m, 3H, CHCH2); MS (FAB) 493.4; HRMS calcd for $C_{28}H_{25}F_2NO_5$ 493.1701, found 493.1695.

(4*S*)-[4-(Acetyloxy)phenyl]-(3*R*)[(3*S*)-(acetyloxy)-3-(4-fluorophenyl]propyl)-1-(4-fluorophenyl)-2-azetidinone (26). **1** (0.25 g, 0.6 mmol) was reacted with acetyl chloride as above to obtain **26** (0.260 g): ^{1}H NMR (300 MHz) δ 7.5–7.0 (m, 12H, Ar), 5.80 (dd, 1H, J = 5.4, 9 Hz, CHOAc), 4.70 (d, 1H, J = 2.2 Hz, NCHAr), 3.15 (m, 1H, C(O)CH), 2.4 (s, 3H, OCH_3), 2.15 (s, 3H, OCH_3), 2.20–1.8 (m, 4H, $CHCH_2$); MS (FAB) *m*/*e* 493.4; HRMS calcd for $C_{28}H_{25}F_2NO_5$ 493.1701, found 493.1694.

1-(4-Fluorophenyl)-(3*R*)-[(4-fluorophenyl)-(2*E*)-propenyl]-(4*S*)-(4-hydroxyphenyl)-2-azetidinone (27). A solution of **1** (0.1 g, 0.24 mmol) in 5 mL of toluene and *p*-toluenesulfonic acid monohydrate (0.01 g, 0.05 mmol) was heated for 6 h at 80 °C. The reaction mixture was then concentrated to dryness and **27** isolated by column chromatography with hexane/ethyl acetate (1:1): ^{1}H NMR (300 MHz) δ 7.4–7.2 (m, 6H, Ar), 7.2–7.0 (m, 6H, Ar), 6.7 (d, 1H, J = 15.9, C*H*=CHCH_2), 6.3 (m, 1H, CH=C*H*CH_2), 5.8 (s, 1H, OH), 4.75 (d, 1H, J = 2.0 Hz, NCHAr), 3.4 (m, 1H, C(O)CH), 3.0–2.75 (m, 2H, CH_2); MS (CI) *m*/*e* 392 (M^+H). Anal. ($C_{24}H_{19}F_2NO_2$) C, H, N.

Cholesterol-Fed Hamster Assay. All animals were housed, treated, and cared for according to NIH guidelines for humane treatment of laboratory animals and the Animal Welfare Act in a program accredited by the American Association for Accreditation of Laboratory Animal Care. Male golden Syrian hamsters (Charles River Labs, Wilmington, MA), weighing between 100 and 125 g, were fed rodent chow and provided water ad libitum. Treatment protocols consisted of feeding chow which had been supplemented with 0.5% cholesterol for 7 days. During this period the animals were gavaged once daily with test compounds dissolved in 0.2 mL of corn oil. On day 7, liver samples were taken for lipid analyses. Samples of liver were extracted for neutral lipid analysis. Hepatic neutral lipid composition was determined subsequently using a HPLC method which has been described previously.[6] Data are reported as percent change in hepatic cholesterol ester content versus control animals receiving the high-cholesterol diet (oral gavaged in 0.2 mL of corn oil/day) without drug.

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