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Synthesis of C3 Heteroatom-Substituted Azetidinones That Display Potent Cholesterol Absorption Inhibitory Activity

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The C3 phenylpropyl side chain of *N*-phenylazetidinones related to SCH 56524 was modified by replacing the hydroxymethylene with various isoelectronic or isosteric groups. Modifications at the 3′ position led to less-active compounds; however, modifications at the 1′ position provided compounds with improved cholesterol absorption inhibitory activity. An enantioselective route for the synthesis of C3 1′-sulfur-substituted azetidinones and the development of structure−activity relationships for this series of compounds are presented.

Introduction

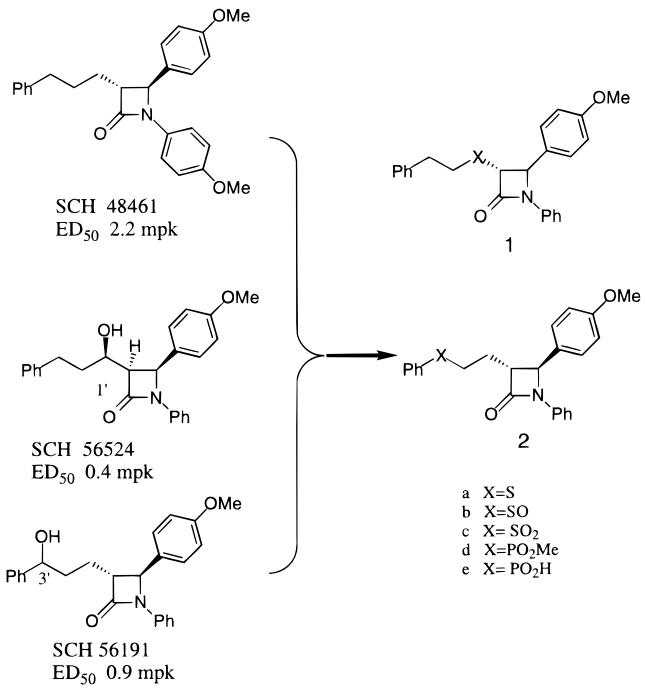
The reduction of serum cholesterol levels is an established therapeutic approach for the treatment and prevention of coronary heart disease. This has been effectively accomplished by inhibiting cholesterol biosynthesis, by increasing the rate of cholesterol clearance, or by blocking the absorption of dietary cholesterol.

SCH 48461 is a *trans*-azetidinone that was identified as a potent cholesterol absorption inhibitor (CAI) in the cholesterol-fed hamster[1] and monkey models.[2] Subsequently, SCH 48461 has been shown to reduce serum cholesterol in human clinical trials.[3] Although the specific mechanism of action for SCH 48461 has not been established, data suggest a unique mode of action that is unrelated to ACAT activity or the sequestration of bile acid.[2]

We recently reported that a structurally related *cis*-azetidinone, SCH 56524, which contains a 1′-hydroxyl group, had improved CAI activity relative to its deshydroxy analogue.[4] The improved activity of SCH 56524 was thought to be a result of either (i) preorganization of the C3 side chain in a biologically active conformation through the formation of an intramolecular H bond, (ii) the hydroxyl group acting as a H bond acceptor or donor with the biological receptor, or (iii) improved pharmacokinetics. Additionally, the 3′-hydroxyl derivative, SCH 56191, was identified as a metabolite that retained good CAI activity.[5] To further develop the structure−activity relationship (SAR) in this area and to address the role of the hydroxyl group, we have examined the effect of incorporating isosteric or isoelectronic replacements for the hydroxyl group at either the 1′ or 3′ position. Accordingly, the sulfoxide, sulfone, and phosphinic acid derivatives, **1** and **2** shown in Scheme 1, were selected for synthesis.

The sulfoxide and phosphinic acids were attractive targets since these polar groups could be expected to have a pronounced effect of the bioavailability of these molecules. Data suggested that the site of action for azetidinones such as SCH 48461 was the intestinal wall;[6] consequently, it was thought that compounds that were more poorly absorbed into the blood stream could exhibit improved CAI activity with an even better safety profile, due to lower blood levels and a longer residence in the intestine.

Scheme 1. Early SAR and Compounds Selected for Synthesis



Chemical Synthesis and Biological Results

We focused initially on preparing the trans-substituted azetidinones **1** and **2** in racemic form and planned to prepare the scalemic material and the corresponding cis isomers of those analogues that displayed good CAI activity. The incorporation of sulfur and phosphorus atoms at the 3′ position was readily accomplished from the chloroethyl-substituted azetidinone **5** which was

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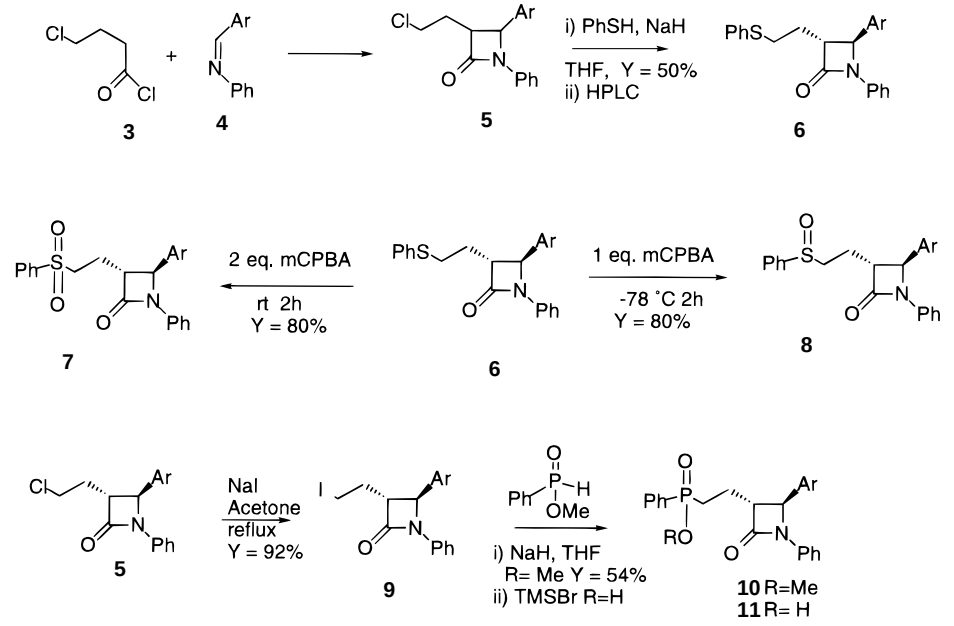
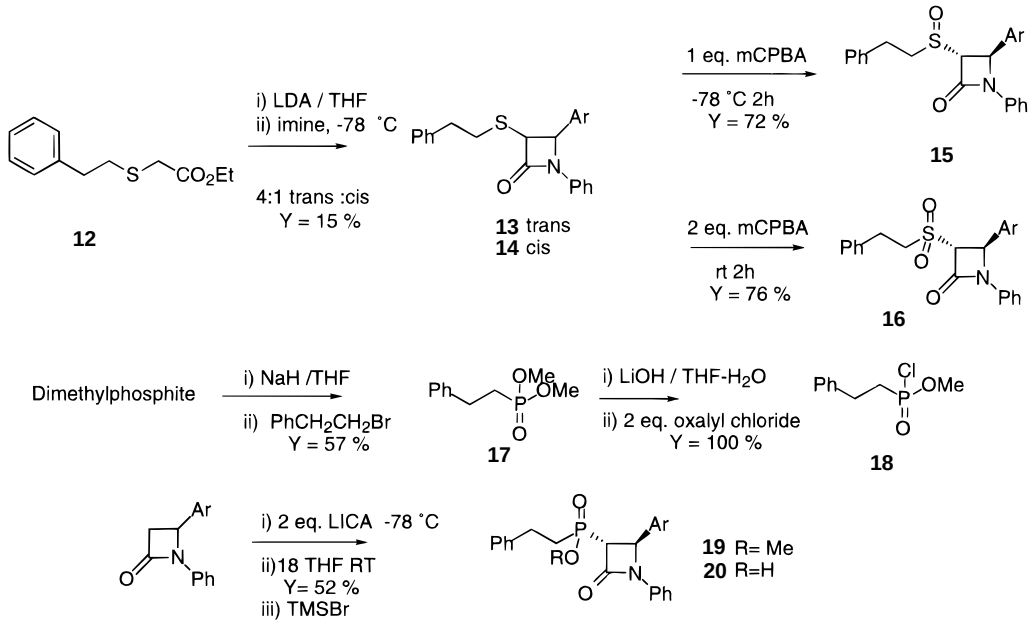
Scheme 2. Synthesis of 3′-Modified Azetidinones (Ar = 4-MeOPh)



Scheme 3. Synthesis of 1′-Modified Azetidinones (Ar = 4-MeOPh)



obtained from the ketene imine reaction with 4-chlorobutyryl chloride (**3**)[7] (Scheme 2). Reaction of **5** with thiophenol gave **6** which could be selectively oxidized to either the sulfoxide **8** or the sulfone **7**. Finkelstein reaction with **5** gave the iodo compound **9**. This was reacted with methylphosphinic acid to give **10** followed by deprotection to give the acid **11**.

The 1′-thioether **13** and 1′-phosphinic acid **20** were obtained as shown in Scheme 3. An ester enolate reaction with **12** and the imine derived from *p*-anisaldehyde and aniline give a mixture of *trans*- and *cis*-azetidinones **13** and **14**. Reaction of the *trans*-thioether **13** with 1 equiv of mCPBA gave a 3:2 mixture of sulfoxides **15.** The sulfone **16** was cleanly obtained by treatment of **13** with 2 equiv of mCPBA. The phosphinic ester **19** was obtained from reaction of the Li enolate of the C3 unsubstituted azetidinone with methyl phenethylphosphonoyl chloride **18**. Subsequent deprotection with TMSBr gave the desired phosphinic acid **20**.

Compounds were evaluated for in vivo activity using a 7-day cholesterol-fed hamster model.[1] Table 1 contains the biological results for the racemic compounds modified at the 1′ or 3′ position. All of the changes at the 3′ position led to compounds that were less active than SCH 56191 despite the wide range of functionalities introduced. The results for the 1′-phosphinic acid **20**, phosphinic ester **19**, and sulfone **16** were equally disappointing. In contrast, the thioether **13** and the sulfoxide **15** showed very significant CAI activity.

Since earlier studies have demonstrated that the absolute configuration at C4 is a critical determinant of CAI activity, an enantioselective synthesis of **13** and **15** was needed in order to more thoroughly evaluate the CAI activity of these compounds. We focused on modifying the Thiruvengadam route to SCH 48461, whereby

Scheme 4. Enantioselective Synthesis of 1′-Sulfur-Substituted Azetidinones

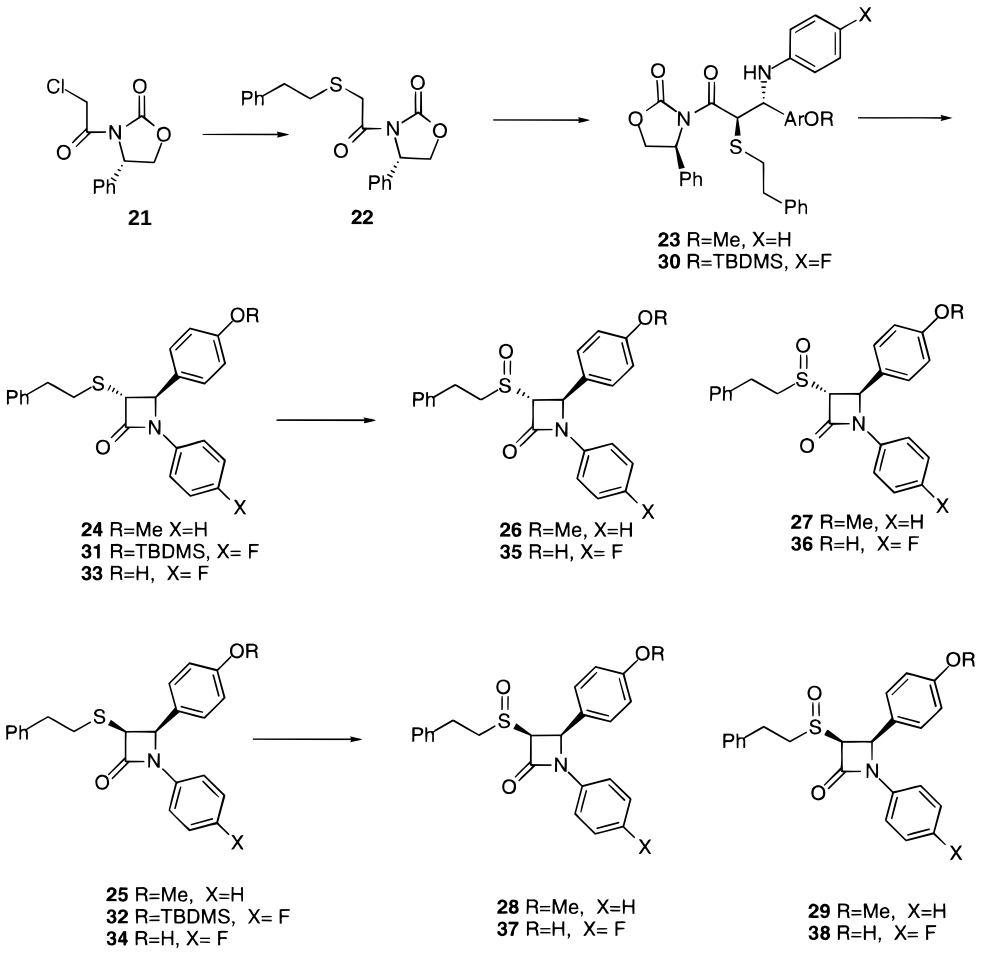


Table 1. Percent Reduction of Liver Cholesterol Ester Levels after po Administration of Compounds for 7 days in Cholesterol-Fed Hamsters[a]

compd	% reduction of CE[b]	compd	% reduction of CE[b]
SCH 48461	(2.2)	SCH 56524	(0.4)
SCH 56191	(0.9)	**13**	97% @ 25
6	0% @ 10	**14**	−31% @ 10
7	23% @ 10	**15**	97% @ 25 (0.59)
8	21% @ 10	**16**	54% @ 25
10	0% @ 25	**19**	0% @ 25
11	0% @ 25	**20**	0% @ 25

[a] Dose given in mg/kg/day. [b] % *I* @ dose or (ED_{50}) in mpk/day, n = 4/compound.

the reaction of a titanium enolate, derived from an Evans chiral acyloxazolidinone, and an imine was used for the diastereoselective synthesis of β-amino acid derivatives.[8] Condensation of the titanium enolate of **22** with the imine derived from *p*-anisaldehyde and aniline provided **23** (Scheme 4) as a single diastereomer in 25−30% yield (50−60% based on recovered starting material). Despite the poor yield of this reaction, the desired compound was readily obtained in pure form by a single crystallization. A subsequent silylation−desilylation−cyclization sequence provided the *trans*- and *cis*-azetidinones **24** and **25** in good yield as a 5:1 mixture (97% enantiomeric purity by chiral HPLC). In control experiments, the purified trans azetidinone **24** was subjected to these reaction conditions and gave a similar 5:1 ratio of *trans*- and *cis*-azetidinones, suggesting that the cis isomer resulted from TBAF-catalyzed epimerization of the C3 substituent. After separation of **24** and **25**, these were individually oxidized with mCPBA to provide the sulfoxides **26** and **27**, and **28** and **29**, respectively, as diastereomeric mixtures which were separated by chromatography and crystallization.

Table 2. Percent Reduction of Liver Cholesterol Ester Levels after po Administration of Compounds for 7 days in Cholesterol-Fed Hamsters[a]

	thio-ether	activity[b]	sulfoxide	activity[b]	sulfoxide	activity[b]
R = Me trans	**24**	89% @ 1 (0.13)	**26**	58% @ 1 (0.90)	**27**	82% @ 1 (0.21)
R = Me cis	**25**	31% @ 10	**28**	78% @ 3	**29**	58% @ 1 (0.58)
R = H trans	**33**	83% @ 1	**35**	56% @ 10	**36**	82% @ 1
R = H cis	**34**	0% @ 1	**37**	40% @ 1	**38**	42% @ 1

[a] Dose given in mg/kg/day. [b] % *I* @ dose or (ED_{50}) in mpk/day, n = 4/compound.

Biological results for the enantiomerically pure series of 1′-thioethers and sulfoxides are given in Table 2. In the *trans*-azetidinone series with R = Me, both the thioether **24** and the sulfoxide **27** showed improved CAI activity relative to their corresponding carbon analogues or the analogues that contained a hydroxyl group at the 1′ position. Surprisingly, in the cis series with R = Me, the thioether **25** displayed only weak CAI activity and was approximately 100-fold less active than the *trans*-thioether, even though the *cis*-sulfoxide **29** still displayed very good CAI activity.

The encouraging biological results for compounds **24**, **27**, and **29** led us to further modify this series. Since the C4 arylmethoxyl group of SCH 48461 is known to be demethylated in vivo,[6] we chose to prepare the corresponding phenols of the most active compounds. In addition, we replaced the *N*-phenyl group with a 4-fluorophenyl substituent in order to prevent metabolic hydroxylation at this position.

Accordingly, the reaction sequence in Scheme 4 was repeated using the TBDMS-protected imine prepared from *p*-hydroxybenzaldehyde and 4-fluoroaniline. However, in this case, the Evans chemistry gave the desired compound **30** in only 8−14% yield, along with 70−80% of recovered starting material. It seemed likely that the poor yield was due to incomplete enolate formation and/or a facile retro-aldol reaction. Two important modifications of the reaction conditions improved the yield. The use of *i*-PrOTiCl$_3$ instead of TiCl$_4$ improved the yield to 40%, presumably as a result of the more reversible nature of the complexation of DIPEA and *i*-PrOTiCl$_3$.[9] Furthermore,, the nature of the quenching agent was found to have a pronounced effect on the yield: quenching the reaction at −78 °C with IPA (instead of AcOH) further improved the yield to 55−60%, to give **30** as a 5:1 mixture of diastereomers. The crude reaction mixture was readily purified by crystallization from MeOH to give the single diastereomer **30** in 40% yield. Compound **30** was cyclized as before to give **31** and **32**. After chromatographic separation, **31** was treated with aqueous HF and the resultant phenol **33** oxidized using mCPBA to give sulfoxides **35** and **36** as a 2:1 mixture. Using (*S*)-camphorsulfonyloxaziridine to oxidize **33**, however, allowed us to reverse the selectivity of oxidation and gave **35** and **36** as a 1:2.5 mixture. For the large-scale preparation of **36**, the sulfoxide **35** was efficiently recycled by a reduction with NaI and TsOH which proceeded in quantitative yield.[10] To complete the preparation of the *cis*-sulfoxides, compound **34** was oxidized with mCPBA to give **37** and **38**.

The relative and absolute configuration of **36** was established by X-ray analysis to be 1′(*R*),3(*R*),4(*R*). The X-ray structure of the sulfoxide **36** contained a H bond from the OH of IPA, that cocrystallized with **36**, to the sulfoxide oxygen. This result was particularly interesting, since one of our initial rationales for preparing the sulfoxides was to introduce a group that was a potential H bond acceptor.

The biological data for the phenolic compounds, Table 2 (R = H), paralleled the results for the methoxyl series (R = Me) in that the *trans*-thioether **33** and one of the diastereomeric *trans*-sulfoxides **36** both displayed very potent CAI activity and were equipotent to each other. In the cis series the thioether **34** was again much less active than the corresponding trans isomer **33**, but the *cis*-sulfoxides **37** and **38** still retained CAI activity. A possible explanation for this could be that, in both the trans and cis series, the sulfoxide is actually the more biologically active species and the *trans*-thioether is oxidized, in vivo, to the sulfoxide more rapidly than the more sterically crowded *cis*-thioether. To investigate this possibility, the thioether **33** and sulfoxide **36** were individually dosed 50 mpk po in the cynomolgus monkey. Bile concentrations of these compounds were analyzed by HPLC 6 and 24 h postdosing. These experiments showed that only a small amount (<5%) of thioether is metabolized to the sulfoxides **35** and **36**. Furthermore, treatment with sulfoxide **36** did not lead to detectable levels of the thioether **33** (data not shown). These results indicate that there is little in vivo interconversion between the thioether and the sulfoxide and suggest that neither compound is a prodrug for the other.

Discussion

In this report we have focused on the preparation and evaluation of a series of azetidinones as inhibitors of cholesterol absorption. We previously observed that a hydroxyl group at either the 1′ or 3′ position of the C3 side chain was well-tolerated or in some cases improved the CAI activity approximately 10-fold relative to the compounds that lacked a hydroxyl group. In addition, we speculated that the 1′-hydroxyl-containing compound, SCH 56524, had improved CAI activity due to either an intramolecular H bond between the hydroxyl and the azetidinone carbonyl or the hydroxyl group acting as an H bond donor or acceptor to the receptor. This led us to replace the hydroxymethylene group at the 1′ or 3′ position with various isosteric or isoelectronic groups. Intially the targeted compounds were prepared in racemic form. Although all of the modifications that were made at the 3′ position gave less active compounds, incorporating the same modifications at the 1′ position, however, was more successful as the thioether **13** and sulfoxides **15** showed improved CAI activity.

Earlier work in this area had demonstrated the importance of the absolute configuration at C4 for CAI activity. Accordingly, we developed an enantioselective route to further evaluate the SAR in this series. This enantioselective route allowed a complete analysis of both the optically pure trans and cis compounds which led to the identification of some particularly potent compounds: the *trans*-azetidinone thioethers **24** and **33**, the *trans*-sulfoxides **27** and **36**, and the *cis*-sulfoxide **29**, all of which are orally active inhibitors of cholesterol absorption with approximately a 4−15-fold improvement in CAI activity over SCH 48461.

The identification and elucidation of the biological receptor for these molecules remains an area of active research. Among other things this will enable us to establish whether the improved biological activity of this series of compounds is a result of increased binding affinities or whether it is due to altered pharmacokinetics. Even in the absence of an in vitro binding assay, by pursuing a hypothesis on the potential role of the 1′-hydroxyl group, a series of 1′-sulfur-substituted azetidinones was discovered which had improved CAI activity. Furthermore, this work uncovered some intriguing structure−activity relationships and importantly indicates that although SAR trends for the *trans*- and *cis*-azetidinones can be quite different, potent compounds can be obtained in both series. Additional efforts to further modify the C3 side chain in this series are in progress and will be reported shortly.

Experimental Section

General. All reagents were used as received with the exception of mCBPA which was purified by washing with phosphate buffer according to the procedure of Schwartz.[12] All melting points were taken on a Thomas-Hoover or Mel-Temp

II melting point apparatus and are uncorrected. Chromatography was performed over Universal Scientific or Selecto Scientific flash silica gel, 32−63 μM. ^{1}H NMR spectra were determined with a Varian VXR 200, Gemini 300, or Gemini 400 MHz instrument using residual solvent signal as internal standards. *J* values are given in hertz (Hz). IR spectra were obtained on a Perkin-Elmer 727B series IR spectrophotometer or on a Nicolet 10 MX-FTIR instrument. Rotations were determined on a Rudolph Autopol III or Perkin-Elmer 243B polarimeter. Mass spectra were obtained on VG-ZAB-SE, Extrel-401, HP-MS Engine, or JEOL HX-110 mass spectrometers. Elemental analyses were determined by the Physical-Analytical Department of Schering-Plough Research Institute using either CEC 240-HA, CEC CE-440, or Fisons EA 1108 CHNS elemental analyzers and are within 0.4% of the theoretical value unless otherwise noted.

In Vivo Metabolism Studies. A 5.7-kg adult male cynomolgus monkey from the Schering-Plough Research Institute (Lafayette, NJ) was fasted for at least 18 h prior to being anesthetized with halothane. The gall bladder was removed, and the bile duct was cannulated at two ends with a single piece of Tygon Microbore tubing (Formulation S-54-HL). This closed-loop cannula allowed for normal bile flow into the GI tract prior to sample collection. The monkey was fitted with a jacket to minimize damage to the exposed cannula, and after the animal regained consciousness, blood clinical chemistry data and urinary and fecal output were evaluated to ensure that the animal was suitable for the study. To initiate the experiment, the exposed cannula was cut and both ends were placed in a 50-mL plastic centrifuge tube to collect bile. The monkey was dosed orally by gavage with either 50 mg of **33** or **36**/kg, and bile was collected for 24 h. Approximately 2 mL of bile was hydrolyzed with Glusulase (Sigma Chemicals; 3500 units for 16 h at 37 °C) since glucuronide conjugates of several SCH 48461 metabolites have previously been identified in monkey bile. The biliary metabolites were initially isolated from endogenous components using a Waters C-18 Sep-Pak solid-phase extraction cartridge (Waters Corp.). The material which eluted from the Sep-Pak cartridge with methanol was concentrated in vacuo; the residue was reconstituted in the mobile phase and analyzed using a Waters HPLC system with on-line UV detection at 260 nm. Separation was achieved on a Jones chromatography Hypersil C-18 column (4.6 × 250 mm) using a water/methanol gradient system starting at 50% methanol/50% water, held isocratic for 10 min, followed by a 5-min gradient to 70% methanol/30% water, which was then held isocratic for 10 min, followed by a 5-min gradient to 80% methanol/20% water. This gradient separated all available putative metabolite standards, including the diastereoisomeric sulfoxides **35** and **36**. Metabolites were identified by comparison of retention times with authentic standards and by particle beam LC/MS (Hewlett-Packard Instruments).

Chemical Synthesis. (4-Methoxybenzylidene)anisidine 4. A mixture of *p*-anisaldehyde (60 g, 0.44 mol) and aniline (41 mL, 0.44 mol) in toluene (1 L) was evaporated to dryness on a rotorary evaporator and dried under high vacuum to give **4** as a solid, 93.31 g, *Y* = 100%.

3-(2-Chloroethyl)-4-(4-methoxyphenyl)-*N*-phenyl-2-azetidinone, 5. A solution of 4-chlorobutyryl chloride (8.35 g, 59.25 mmol) in toluene (20 mL) was added dropwise to a refluxing solution of **4** (12.5 g, 59.25 mmol) and DIPEA (10.3 mL, 59.2 mmol). After refluxing for 14 h the cooled reaction was quenched with the addition of 1 N HCl (50 mL) and the mixture partitioned with EtOAc (200 mL). The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography on silica gel using EtOAc/Hex (1:6) afforded **5** (18.11 g, 96% yield): NMR δ 2.32 (m, 1H, CH_2), 2.46 (m, 1H, CH_2), 3.25 (m, 1H, C3H), 3.67−3.79 (m, 2H, CH_2Cl), 3.80 (s, 3H, OMe), 4.74 (d, *J* = 2.4, 1H, C4H), 6.90 (d, 2H, ArH), 7.03 (dd, 1H, ArH), 7.25−7.33 (m, 6H, ArH).

3-[2-(Phenylthio)ethyl]-4-(4-methoxyphenyl)-*N*-phenyl-2-azetidinone, 6. NaH (245 mg, 10.2 mmol) was added to a solution of thiophenol (1.05 mL, 10.2 mmol) in THF (15 mL) at 0 °C under N_2. After 5 min a solution of **5** (2.15 g, 6.81 mmol) in THF (5 mL) was added dropwise and the resultant mixture stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (100 mL), washed with $NaHCO_3$ and brine, and then dried ($MgSO_4$) and evaporated. Flash chromatography on silica gel using EtOAc/Hex (1:6) afforded **6** (2.32 g, 50% yield): NMR δ 2.15 (m, 1H, CH_2), 2.28 (m, 1H, CH_2), 3.07 (m, 1H, SCH_2), 3.17 (m, 1H, SCH_2), 3.25 (m, 1H, C3H), 3.80 (s, 3H, OMe), 4.67 (d, *J* = 2.3, 1H, C4H), 6.9 (d, 2H, ArH), 7.03 (dd, 1H, ArH), 7.17−7.36 (m, 11H, ArH); MS (CI) 390 (M^+ H), 418 (M^+ C_2H_5). Anal. ($C_{24}H_{23}NO_2S$) C, H, N.

3-[2-(Phenylsulfonyl)ethyl]-4-(4-methoxyphenyl)-*N*-phenyl-2-azetidinone, 7. To a solution of **6** (0.185 g, 0.48 mmol) in DCM (20 mL) was added mCPBA (0.205 g) at room temperature. After 3 h, a saturated solution of $NaHSO_3$ (10 mL) and $NaHCO_3$ (20 mL) was added, and the mixture was extracted with EtOAc. The organic layer was purified by flash chromatography on silica gel using EtOAc/Hex (1:4) to give **7** as a colorless solid (0.154 g, 76.4% yield): NMR δ 2.21−2.40 (m, 2H, CH_2), 3.08 (m, 1H, C3H), 3.25 (ddd, 1H, SO_2CH), 3.42 (m, 1H, SO_2CH), 3.80 (s, 3H, OMe), 4.62 (d, *J* = 2.3, 1H, C4H), 6.88 (d, 2H, ArH), 7.04 (m, 1H, ArH), 7.22−7.29 (m, 6H, ArH), 7.58 (m, 2H, ArH), 7.67 (m, 1H, ArH), 7.90 (d, 2H, ArH); MS (FAB) 422 (M^+ H). Anal. ($C_{24}H_{23}NO_4S$) C, H, N.

3-[2-(Phenylsulfinyl)ethyl]-4-(4-methoxyphenyl)-*N*-phenyl-2-azetidinone, 8. To a solution of **6** (0.25 g, 0.64 mmol) in DCM (20 mL) at −78 °C was added mCPBA (0.13 g, 0.64 mmol). After 2 h, a saturated solution of $NaHSO_3$ (10 mL) was added, and the mixture was allowed to warm to room temperature and then extracted with EtOAc. The organic layer was purified by flash chromatography on silica gel using EtOAc/Hex (1:1) to give **8** as a colorless solid (0.19 g, 73% yield), as a 1:1 mixture of diastereomers by NMR: NMR δ 2.04−2.48 (m, 2H, CH_2), 2.85 (m, 1H, C3H), 2.98−3.21 (m, 2H, $SOCH_2$), 3.80 (s, 3H, OMe), 4.62, 4.64 (d, *J* = 2.4, 1H, C4H), 6.89 (d, 2H, ArH), 7.03 (m, 1H, ArH), 7.21−7.30 (m, 6H, ArH), 7.52 (m, 3H, ArH), 7.60 (m, 2H, ArH); HRMS (FAB) calcd 406.1477, found 406.1466. Anal. ($C_{24}H_{23}NO_3S$) H, N; C: calcd, 71.09; found, 70.11.

3-[2-(Methoxyphenylphosphinyl)ethyl]-4-(4-methoxyphenyl)-*N*-phenyl-2-azetidinone, 10. Step 1: To a solution of **5** (1.0 g, 3.17 mmol) in acetone (30 mL) was added NaI (0.95 g, 6.34 mmol). The mixture was heated to reflux for 4 h, then additional NaI (0.95 g) was added, and the reaction mixture refluxed overnight. Water was added to the cooled mixture, and it was partitioned with Et_2O, washed with brine, dried ($MgSO_4$), and evaporated to give compound **9** which was used without further purification.

Step 2: To a solution of methyl phenylphosphinic acid (0.109 g, 0.7 mmol) in THF (5 mL) was added NaH (17 mg, 0.7 mmol) at 0 °C. The mixture was warmed to room temperature and stirred for 10 min. To this was added dropwise a solution of **9** (0.19 g, 0.47 mmol) in THF (3 mL). After stirring at room temperature overnight the mixture was concentrated in vacuo, and the residue was purified by flash chromatography on silica gel using EtOAc/Hex (1:4) to give a 1:1 mixture of diastereomers **10** as a solid (0.11 g, 54% yield): NMR δ 1.92−2.30 (m, 4H, CH_2CH_2), 3.08 (bt, 1H, C3H), 3.61, 3.65 (d, 3H, POMe), 3.78, 3.80 (s, 3H, OMe), 4.58, 4.61 (d, *J* = 2.4, 1H, C4H), 6.88 (dd, 2H, ArH), 7.03 (m, 1H, ArH), 7.20−7.28 (m, 6H, ArH), 7.50 (m, 2H, ArH), 7.76 (dd, 2H, ArH); MS (FAB) 436 (M^+ H). Anal. ($C_{25}H_{26}NO_4P\cdot 0.33H_2O$) C, H, N.

3-[2-(Phenylphosphinyl)ethyl]-4-(4-methoxyphenyl)-*N*-phenyl-2-azetidinone, 11. TMSBr (0.37 mL, 0.27 mmol) was added at 0 °C to a solution of **10** (0.103 g, 0.24 mmol) in DCM (10 mL). The mixture was warmed to room temperature and stirred overnight. The mixture was concentrated in vacuo, and the residue was treated with 95% acetone (3 mL). Evaporation of the solvent gave **11** as a solid (0.045 g, 45% yield): NMR δ 1.92−2.12 (m, 4H, CH_2CH_2), 2.96 (bt, 1H, C3H), 3.78 (s, 3H, OMe), 4.53 (d, *J* = 2.4, 1H, C4H), 6.84 (d, 2H, ArH), 7.03 (m, 1H, ArH), 7.21−7.25 (m, 6H, ArH), 7.38 (m, 2H, ArH), 7.47 (m, 1H, ArH), 7.73 (m, 2H, ArH); MS (FAB) 422 (M^+ H). Anal. ($C_{24}H_{24}NO_4P\cdot 0.2H_2O$) C, H, N.

3-(2-Phenethylthio)-4-(4-methoxyphenyl)-*N*-phenyl-2-azetidinone, 13 and 14. To a solution of diisopropylamine (2.16 mL, 15.4 mmol) in THF at 0 °C was added *n*-BuLi in hexane (1.6 M, 10.2 mL, 16.08 mmol). After 15 min, the mixture was cooled to −78 °C, and a solution of **12** (3.0 g, 13.4 mmol) in THF (15 mL) was added over 5 min followed 60 min later by the slow addition of a solution of the imine (3.15 g, 13.4 mmol) in THF. After 1 h, the mixture was warmed to room temperature, stirred for 2 h, and then partitioned with EtOAc and 1 N HCl. The organic layers were washed with brine, dried ($MgSO_4$), and evaporated. The residue was dissolved in MeOH, and $NaBH_4$ was added (to reduce unreacted imine). After 1 h, the solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel using EtOAc/Hex (1:9) to give **13** (0.67 g, 12% yield) and **14** (0.15 g, 3% yield). **13**: NMR δ 2.95 (m, 4H, CH_2CH_2), 3.82 (s, 3H, OMe), 3.95 (d, J = 2.2, 1H, C3H), 4.72 (d, J = 2.2, 1H, C4H), 6.9 (m, 2H, ArH), 7.04 (m, 1H, ArH), 7.18−7.29 (m, 11H, ArH); MS (FAB) 390 (M^+ H). Anal. ($C_{24}H_{23}NO_2S$) C, H, N. **14:** NMR δ 2.80 (m, 4H, CH_2CH_2), 3.81 (s, 3H, OMe), 4.53 (d, 1H, J = 5.6, C3H), 5.27 (d, 1H, J = 5.72, C4H), 6.9 (m, 2H, ArH), 7.04 (m, 1H, ArH), 7.13−7.26 (m, 11H, ArH); HRMS (FAB) calcd 390.1528, found 390.1520.

3-(2-Phenethylsulfinyl)-4-(4-methoxyphenyl)-*N*-phenyl-2-azetidinone, 15. To a solution of **13** (0.25 g, 0.64 mmol) in DCM (20 mL) at −78 °C was added mCPBA (0.13 g, 0.64 mmol). After 2 h, a saturated solution of $NaHSO_3$ (10 mL) was added and the mixture allowed to warm to room temperature, then extracted with EtOAc. The organic layer was purified by flash chromatography on silica gel using EtOAc/Hex (1:1) to give **15**, a colorless solid (0.19 g, 72% yield), as a 3:2 mixture of diastereomers (a and b) by NMR: NMR δ 3.15 (m, 3H, CH_2CH_2), 3.82 (s, 3H, OMe), 3.90 (m, 1H, $SOCH_2$), 3.94 (d, J = 2.5, 0.6H, $C3H_a$), 4.11 (d, J = 2.1, 0.4H, $C3H_b$), 5.32 (d, J = 2.6, 0.6, $C4H_a$), 5.51 (d, J = 2, 0.4H, $C4H_b$), 6.9 (m, 2H, ArH), 7.04 (m, 1H, ArH), 7.21−7.36 (m, 11H, ArH); MS (EI) 405 (M^+), 251 (100). Anal. ($C_{24}H_{23}NO_3S$) C, H, N.

3-(2-Phenethylsulfonyl)-4-(4-methoxyphenyl)-*N*-phenyl-2-azetidinone, 16. mCPBA (0.205 g, 1.2 mmol) was added to a solution of **13** (0.185 g, 0.48 mmol) in DCM (20 mL). After 3 h, sodium bisulfite and sodium bicarbonate were added, the mixture and stirred for 10 min and then was partitioned with ethyl acetate. The organic fraction was purified by flash chromatography on silica gel using hexane/ethyl acetate (4:1) to give **16** as a white solid (0.15 g, 76%): MS (EI) 421 (M^+); NMR δ 3.2 (m, 2H, CH_2), 3.55 (m, 2H, SO_2CH_2), 3.80 (s, 3H, OMe), 4.23 (d, J = 2.4, 1H, C4H), 5.53 (d, J = 2.4, 1H, C3H), 6.9 (d, 2H, ArH), 7.1 (m, 1H, ArH), 7.28 (m, 11H, ArH). Anal. ($C_{24}H_{23}NO_4S$) C, H, N.

Dimethyl Phenethylphosphonate, 17. Dimethyl phosphite (2.0 g, 18.2 mmol) was added slowly to a suspension of NaH (0.44 g, 18.2 mmol) in DMF at 0 °C. The mixture was stirred for 15 min, and then (2-bromoethyl)benzene (3.72 mL, 27 mmol) was added slowly at 0 °C, and the mixture warmed to room temperature for 3 h. The reaction mixture was diluted with EtOAc (200 mL), washed with 1 N HCl (100 mL), 1 N NaOH (3 × 50 mL), and brine, and then dried ($MgSO_4$). After concentration, the organic soluble fraction was purified by flash chromatography on silica gel using DCM/EtOAc (24:1) to give **17** as a colorless oil (2.21 g, 57%): NMR δ 2.07 (m, 2H, CH_2P), 2.91 (m, 2H, CH_2Ar), 3.74 (d, 6H, $P(OMe)_2$), 7.20 (m, 3H, ArH), 7.28 (m, 2H, ArH).

3-(Methoxyphenethylphosphinyl)-4-(4-methoxyphenyl)-*N*-phenyl-2-azetidinone, 19. To a solution of **17** (2.2 g, 10.3 mmol) in THF (10 mL) was added a solution of $LiOH-H_2O$ (0.52 g, 12 mmol) in H_2O (5 mL). The mixture was stirred at room temperature overnight and then acidified with 1 N HCl and extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated to give the acid (2.03 g, 100%). A portion of this (0.525 g, 2.62 mmol) was dissolved in DCM (40 mL) and a few drops of DMF added followed by dropwise addition of oxalyl chloride (0.46 mL) at 0 °C. After 10 min, the solution was warmed to room temperature for 2 h and concentrated to dryness. Without further purification, **18** was dissolved in THF (7 mL) and added to a preformed solution of the Li enolate of 4-(4-methoxyphenyl)-*N*-phenyl-2-azetidinone at − 78 °C. [Prepared as follows: *n*-BuLi (3.5 mL of 1.6 M in hexane) was added to a stirring solution of *N*-isopropylcyclohexylamine (0.93 mL, 5.46 mmol) in THF (5 mL) at 0 °C. After 15 min this was cooled to −78 °C for 30 min followed by addition of a solution of *N*-phenyl-4-(4-methoxyphenyl)-2-azetidinone (1.33 g, 5.25 mmol) in THF (5 mL) and stirred 30 min before the solution of **18** was added.] After stirring at − 78 °C for a further 2 h, the reaction was quenched with 20% $KHSO_4$ (20 mL), the mixture was extracted into EtOAc, and the organic layer was passed through silica gel using DCM/EtOAc (99:1) to yield **19** (0.60 g, 52%) as a 3:1 mixture of diastereomers by NMR: NMR (diastereomer A) δ 2.21 (m, 2H, CH_2P), 2.98 (m, 2H, CH_2Ar), 3.42 (m, 1H, C3H), 3.80 (s, 3H, OMe), 3.84 (d, J = 10, 3H, POMe), 5.32 (dd, J = 2.4, 8, C4H), 6.9 (m, 2H, ArH), 7.06 (m, 1H, ArH), 7.18−7.37 (m, 11H, ArH); NMR (diastereomer B) δ 2.33 (m, 2H, CH_2P), 2.98 (m, 2H, CH_2Ar), 3.51 (m, 1H, C3H), 3.72 (d, J = 11, 3H, POMe), 3.81 (s, 3H, OMe), 5.36 (dd, J = 2.5, 8, C4H), 6.9 (m, 2H, ArH), 7.06 (m, 1H, ArH), 7.18−7.37 (m, 11H, ArH); MS (FAB) 436 (M^+). Anal. ($C_{25}H_{26}NO_4P$) C, H, N.

3-(Phenethylphosphinyl)-4-(4-methoxyphenyl)-*N*-phenyl-2-azetidinone, 20. TMSBr (1.1 equiv) was added to a solution of **19** (244 mg, 0.56 mmol) in DCM (10 mL) at 0 °C. After stirring for 14 h at room temperature, the mixture was evaporated to dryness. The residue was dissolved in 95% acetone (5 mL), stirred briefly, and then evaporated to dryness and dried under vacuum to give **20** (235 mg, Y = 99%): NMR δ 2.28 (m, 2H, CH_2P), 2.97 (m, 2H, CH_2Ar), 3.45 (dd, J = 3, 8, 1H, C3H), 3.78 (s, 3H, OMe), 5.40 (dd, J = 2.5, 8, C4H), 6.84 (d, 2H, ArH), 7.03 (t, 1H, ArH), 7.20 (m, 4H, ArH), 7.27 (m, 5H, ArH), 7.33 (d, 2H, ArH), 7.33 (d, 2H, ArH), 8.48 (bs, 1H, POH). MS (FAB) 444 (M^+ Na). Anal. ($C_{24}H_{24}NO_4P$) C, H, N.

[4-(*tert*-Butyldimethylsiloxy)benzylidene]-4-fluoroanisidine. A mixture of 4-fluoroaniline (128 mL, 1.35 mol) and 4-(*tert*-butyldimethylsiloxy) benzaldehyde (290 g, 1.23 mmol) was heated in toluene (1.2 L) to reflux under a Dean−Stark trap. After 24 h, the solution was concentrated in vacuo, and the residue was dissolved in warm hexane (0.2 L) and cooled to −20 °C to collect the title compound (378 g, 94% yield) by filtration: mp 51.4−52.2 °C; NMR δ 0.22 (s, 6H, Me_2Si), 1.05 (s, 9H, *t*-BuSi), 6.95 (d, 2H, ArH), 7.12 (m, 2H, ArH), 7.19 (m, 2H, ArH),7.80 (d, 2H, ArH), 8.18 (s, 1H, NCH).

4-Phenyl-*N*-(chloroacetyl)-2-oxazolidinone, 21. Method A: A solution of chloroacetyl chloride (9.76 mL, 122 mmol) in DCM (110 mL) was added dropwise to a solution of 4-phenyloxazolidinone (10 g, 61 mmol), Et_3N (35 mL, 244 mmol), and DMAP (9.5 g, 4 mmol) in DCM (0.15 L). After 30 min at 0 °C additional chloroacetyl chloride was added (0.2 equiv), and the mixture was allowed to warm to room temperature. After 1 h, silica gel was added, and the reaction mixture was concentrated in vacuo and then loaded onto a silica gel flash column. Elution with EtOAc/Hex (1:4) gave **21** (11.29 g, 77%).

Method B: Prepared using the general procedure described by Pridgen[12] for the synthesis of the bromoacetyl analogue using in this case chloroacetyl chloride to yield a colorless solid: NMR δ 4.38 (dd, 1H, J = 3.8, 9), 4.68 (d, 1H, J = 15.8), 4.75 (d, 1H, J = 15.8), 4.78 (t, 1H, J = 9), 5.45 (dd, 1H, J = 3.7, 9), 7.32−7.46 (m, 5H).

(*S*)-4-Phenyl-*N*-(2-phenethylthio)acetyl-2-oxazolidinone, 22. Phenethyl mercaptan(5.1 mL, 37.5 mmol) was added to a solution of **21** (6.0 g, 25 mmol) and triethylamine (5.2 mL, 37.5 mmol) in DCM (0.1 L). After stirring at room temperature for 16 h, silica gel (approx 50 g) was added and the mixture was concentrated in vacuo. The residue was purified by flash chromatography on silica using ethyl acetate: hexane 1:4 to give a colorless solid (7.81 g, 92%) which was crystallized from ethyl acetate:hexane 1:4. NMR δ 2.65 (m, 2H), 2.80, (m, 2H), 3.68 (d, 1H, J = 13.7, CHS), 3.97(d, 1H, J = 13.7 CHS), 4.29 (dd, 1H, J = 4, 9.5), 4.53 (dd, 1H, J = 4, 8.8), 4.72 (t, 1H, J = 8.8), 7.12−7.43 (m, 10H, ArH); Anal. ($C_{19}H_{19}NO_3S$) C, H, N; MS (FAB) 342.1 (M^+H).

(*S*)-4-Phenyl-*N*-[2-(2-phenethylthio)-3-(phenylamino)-3-(4-methoxyphenyl) propionyl]-2-oxazolidinone, 23. $TiCl_4$ (1.0 mL of 1 N in DCM, 1 mmol) was added to a solution of **22** (0.34 g, 1 mmol) in DCM (5 mL) at −30 °C. The mixture was stirred for 10 min and then DIPEA added (0.35 mL, 2 mmol). After 1 h, the imine **4** (422 mg, 2 mmol) was added, and the mixture was warmed to 0 °C for 3 h and then recooled to −25 °C. The reaction was quenched by the addition of AcOH (0.5 mL) in DCM (2 mL). After 10 min the mixture was poured into 2 N H_2SO_4 (15 mL), partitioned with EtOAc, washed with $NaHCO_3$, H_2O, brine, and dried over $MgSO_4$. The solid obtained after filtration and concentration was crystallized from EtOAc/Hex (1:2) to yield **23** (150 mg, 27%): NMR δ 2.77 (s, 4H), 3.80 (s, 3H, OMe), 4.18 (dd, 1H, J = 9, 3), 4.65 (t, 1H, J = 8), 4.76 (d, 1H, J = 7), 5.16 (bs, 1H), 5.40 (dd, 1H, J = 9, 3), 5.52 (d, 1H, J = 7), 6.50 (d, 2H, J = 8), 6.64 (dd, 1H, J = 8, 8), 6.78 (d, 2H, J = 8), 6.93 (d, 2H, J = 8), 7.02−7.31 (m, 7H).

(3*R*,4*R*)-3-(2-Phenethylthio)-4-(4-methoxyphenyl)-*N*-phenyl-2-azetidinone, 24, and (3*S*,4*R*)-3-(2-Phenethylthio)-4-(4-methoxyphenyl)-*N*-phenyl-2-azetidinone, 25. Bis-(trimethylsilyl)acetamide (BSA) (1.2 mL, 2.45 mmol) was added to a solution of **23** (1.35 g, 2.45 mmol) in toluene (50 mL) at 90 °C under N_2. After 2 h, the reaction mixture was cooled to 50 °C and TBAF (90 mg, 0.28 mmol) added. After 1.5 h, the solvent was evaporated, and the residue was purified by flash chromatography on silica gel using EtOAc/Hex (1:7) to elute first the *trans*-azetidinone **24** (560 mg, y = 59%): [θ] 232 nM = $+3.4 \times 10^4$, [θ] 248 nM = -3.07×10^4; NMR δ 2.95 (m, 4H, CH_2CH_2), 3.82 (s, 3H, OMe), 3.95 (d, J = 2.2, 1H, C3H), 4.72 (d, J = 2.2, 1H, C4H), 6.9−7.3 (14H, ArH); MS (FAB) 390 (M + H), 252 (100). Anal. ($C_{24}H_{23}NO_2S$) C, H, N, S. Continued elution gave the *cis*-azetidinone **25** (145 mg, 15%): NMR δ 2.78 (m, 4H, CH_2CH_2), 3.8 (s, 3H, OMe), 4.53 (d, J = 2.2, 1H, C3H), 5.27 (d, J = 2.2, 1H, C4H), 6.9−7.3 (14H, ArH); HRMS (FAB) calcd 390.1528, found 390.1512).

3(*R*)-[2(*S*)-Phenethylsulfinyl]-4(*R*)-(4-methoxyphenyl)-*N*-phenyl-2-azetidinone, 26, and 3(*R*)-[2(*R*)-Phenethylsulfinyl]-4(*R*)-(4-methoxyphenyl)-*N*-phenyl-2-azetidinone, 27. To a solution of **24** (0.36 g, 0.92 mmol) in dichloromethane (15 mL) at −78 °C wa added *m*-chloroperbenzoic acid (0.16 g, 0.92 mmol). After 2 h, dilute sodium bisulfite was added, and the mixture was warmed to room temperature and partitioned with EtOAc. The organic layer was sequentially washed with 10% sodium bicarbonate and brine, then dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by HPLC on silica gel using ethyl acetate/hexane (1:2) to elute **26** (0.185 g, Y = 46%): [θ] 220 nM = -5.36×10^4, [θ] 257 nM = $+5.46 \times 10^4$; NMR δ 3.15 (m, 3H, CH_2CH_2), 3.81 (s, 3H, OMe), 3.9 (m, 1H, CH_2), 3.94 (d, J = 2.5, 1H, C4H), 5.33 (d, J = 2.2, 1H, C3H), 6.9−7.35 (14H, ArH). Anal. ($C_{24}H_{23}NO_3S$) C, H, N. Continued elution gave **27** (0.10 g, Y = 25%): [θ] 220 nM = -4.8×10^3, [θ] 233 nM = $+7.4 \times 10^4$, [θ] 250 nM = -4.0×10^4; NMR δ 3.18 (m, 4H, CH_2CH_2), 3.80 (s, 3H, OMe), 4.12 (d, J = 2, 1H, C4H), 5.5 (d, J = 2, 1H, C3H), 6.9−7.35 (m, 14H, ArH). Anal. ($C_{24}H_{23}NO_3S$) C, H, N.

3(*S*)-[2(*S*)-Phenethylsulfinyl]-4(*R*)-(4-methoxyphenyl)-*N*-phenyl-2-azetidinone, 28, and 3(*S*)-[2(*R*)-Phenethylsulfinyl]-4(*R*)-(4-methoxyphenyl)-*N*-phenyl-2-azetidinone, 29. Treatment of **25** (60 mg, 0.15 mmol) with mCPBA (27 mg, 0.15 mmol) according to the procedure for the preparation of **26** and **27** gave **28** (17 mg, Y = 28%): NMR δ 2.85 (m, 1H, CH_2), 2.95 (m, 1H, CH_2), 3.12 (m, 1H, CH_2), 3.62 (m, 1H, CH_2), 3.8 (s, 3H, OMe), 4.4 (d, J = 5.6, 1H, C4H), 5.35 (d, J = 5.6, 1H, C3H), 6.9−7.35 (14H, ArH). Anal. ($C_{24}H_{23}NO_3S \cdot 0.2H_2O$) C, H, N. It also gave **29** (37 mg, y = 61%): NMR δ 3.17 (m, 3H, CH_2CH_2), 3.4 (m, 1H, CH_2), 3.83 (s, 3H, OMe), 4.69 (d, J = 5.2, 1H, C4H), 5.55 (d, J = 5.2, 1H, C3H), 6.95−7.4 (14H, ArH); $[\alpha]^{25}_D$ = −136° (2 mg/2 mL MeOH). Anal. ($C_{24}H_{23}NO_3S \cdot 0.2\ H_2O$) C, H, N.

(*S*)-4-Phenyl-*N*-[2-(2-phenethylthio)-3-[(4-fluorophenyl)amino]-3-[4-(*tert*-butyldimethylsiloxy)phenyl]-propionyl]-2-oxazolidinone, 30. Titanium tetraisoproxide (7.5 mL, 25 mmol) was added to a stirring solution of titanium tetrachloride (75 mL of 1 N $TiCl_4$ in methylene chloride) in methylene chloride (200 mL) at 0 °C. After 15 min **22** (34.1 g) was added followed 5 min later by the addition of the imine (66 g, 200 mmol) derived from 4-(*tert*-butyldimethylsiloxy)-benzaldehyde and 4-fluoroaniline. The reaction mixture was cooled to −40 °C internal temperature and stirred for 20 min, and then diisopropylethylamine (35 mL) was added. After stirring for 15 h at −40 °C, the reaction mixture was cooled to −70 °C and isopropyl alcohol (250 mL) added. The reaction mixture was slowly allowed to warm to room temperature over 6 h, then 0.1 N HCl (500 mL) was added, and the mixture was partitioned with Et_2O; the organic layers were washed (H_2O), dried ($MgSO_4$), concentrated, and purified by crystallization from MeOH to give **30** as a colorless solid (30.9 g, 46%): NMR δ 0.18 (s, 6H, $SiMe_2$), 0.97 (s, 9H, Me_3Si), 2.68 (m, 4H, CH_2CH_2), 4.20 (dd, J = 3, 8.7, 1H, CHO), 4.65 (m, 2H, CHO, CHS), 5.40 (dd, J = 3, 8.5, 1H, ArCHN), 5.46 (d, J = 8, 1H, CHN), 6.44 (m, 2H, ArH), 6.74 (m, 4H, ArH), 7.02 (m, 2H, ArH), 7.1−7.3 (m, 10H, ArH); $[\alpha]^{20}_D$ = −63.3° (1.3 mg/mL MeOH).

(3*R*,4*R*)-3-(2-Phenethylthio)-4-(4-hydroxyphenyl)-*N*-(4-fluorophenyl)-2-azetidinone, 33, and (3*S*,4*R*)-3-(2-Phenethylthio)-4-(4-hydroxyphenyl)-*N*-(4-fluorophenyl)-2-azetidinone, 34. Step 1: Bis(trimethylsilyl)acetamide (7.4 mL, 30 mmol) was added to a solution of **30** (10 g, 15 mmol) in toluene (0.5 L) at 90 °C. After 1 h, the reaction mixture was cooled to 45 °C and tetrabutylammonium fluoride (0.47 g, 1.5 mmol) added. Periodically over the next 18 h, additional bis(trimethylsilyl)acetamide (a total of 3 mol equiv) was added with continued stirring at 45 °C. After a total time of 24 h, the reaction mixture was diluted with MeOH (150 mL) and stirred at room temperature for 1 h. The mixture was concentrated in vacuo and purified by flash chromatography on silica gel using hexane/ethyl acetate (10:1) to elute the trans isomer **31** (4.80 g, Y = 63%). Continued elution with hexane/ethyl acetate (5:1) gave the cis isomer **32** (11.14 g, Y = 15%).

Step 2A: Aqueous HF (2.5 mL of 48%) was added to a solution of **31** (0.215 g, 0.42 mmol) in acetonitrile (21 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The mixture was partitioned with Et_2O and cold water. The organic layers were washed with 10% sodium bicarbonate and water. The dried ($MgSO_4$) and concentrated organic layer was purified by flash chromatography on silica gel using hexane/ethyl acetate (5:1) to collect compound **33** as a colorless solid (0.16 g, 97%): MS (FAB) 394 (M + H), 256 (100); $[\alpha]^{25}_D$ = +44.8° (1.25 mg/mL MeOH); NMR δ 2.95 (m, 4H, CH_2CH_2), 3.93 (d, J = 2.4, 1H, C_3H), 4.67 (d, J = 2.4, 1H, C_4H), 5.06 (s, 1H, OH), 6.85 (d, 2H, ArH), 6.92 (dd, 2H, ArH), 7.15−7.3 (9H, ArH). Anal. ($C_{23}H_{20}NO_2SF$) C, H, N.

Step 2B: Aqueous HF (9 mL of 48%) was added to a solution of **32** (0.85 g, 1.68 mmol) in acetonitrile (80 mL) at 0 °C as described in step 2A to give **34** (0.63 g, Y = 95%): MS (CI) 394 (M + H) (100); NMR δ 2.78 (m, 4H, CH_2CH_2), 4.52 (d, J = 5, 1H, C4H), 5.23 (d, J = 5, 1H, C3H), 6.82−7.3 (13H, ArH); $[\alpha]^{21}_D$ = −41.3° (1.9 mg/mL MeOH). Anal. ($C_{23}H_{20}NO_2SF$) C, H, N, S.

(3*R*,4*R*)-3-[2(*S*)-Phenethylsulfinyl]-4-(4-hydroxyphenyl)-*N*-(4-fluorophenyl)-2-azetidinone, 35, and (3*R*,4*R*)-3-[2(*R*)-Phenethylsulfinyl]-4-(4-hydroxyphenyl)-*N*-(4-fluorophenyl)-2-azetidinone, 36. A solution of **33** (2.3 g, 5.85 mmol) and (1*S*)-(+)-(10-camphorsulfonyl)oxaziridine (1.48 g, 6.45 mmol) in THF (40 mL) was heated to reflux. After 14 h, the reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography on silica gel using dichloromethane/isopropyl alcohol (100:1) to elute first the diastereomer **35** (0.6 g, 25%): [θ] 219 nM = -5.49×10^4, [θ] 254 nM = $+5.2 \times 10^4$; $[\alpha]^{25}_D$ = +214.4° (1.25 mg/mL MeOH); NMR δ 3.15 (m, 3H, CH_2CH_2), 3.92 (m, 2H, CH_2, C4H), 5.25 (d, J = 2.5, 1H, C3H), 6.01 (bs, 1H, OH), 6.8−6.9 (4H, ArH); 7.15−7.35 (9H, ArH) MS (CI) 410 (M + H). Anal. ($C_{23}H_{20}NO_3SF$) C, N, N. Then diastereomer **36** eluted, which was crystallized from isopropyl alcohol to give a colorless solid (1.48 g, 62%): [θ] 233 nM = $+5.56 \times 10^4$, [θ] 251 nM = − 2.79

$\times 10^4$; $[\alpha]^{25}_D = -16°$ (1.25 mg/mL MeOH); NMR δ 3.1−3.4 (m, 4H, CH_2CH_2), 4.2 (d, $J = 2$, 1H, C4H), 5.39 (d, $J = 2$, 1H, C3H), 6.7 (d, 2H, ArH), 6.95 (m, 2H, ArH), 7.15−7.35 (m, 9H, ArH); CIMS 410 (M + H). Anal. ($C_{23}H_{20}NO_3SF$) C, H, N.

(3*S*,4*R*)-3-(2-Phenethylsulfinyl)-4-(4-hydroxyphenyl)-*N*-(4-fluorophenyl)-2-azetidinone, 37, and (3*S*,4*R*)-3-(2-Phenethylsulfinyl)-4-(4-hydroxyphenyl)-*N*-(4-fluorophenyl)-2-azetidinone, 38. Treatment of **34** (0.52 g, 1.32 mmol) according to the procedure for the preparation of **35** and **36** and elution from a flash column using EtOAc/Hex (1:1) gave **37** (0.19 g, $Y = 35\%$) [Anal. $C_{23}H_{20}NO_3SF$) C, H, N, S] and **38** (0.27 g, $Y = 50\%$) [Anal. ($C_{23}H_{20}NO_3SF$) C, H, N, S].

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