An Enantioselective Synthesis of the Topically-Active Carbonic Anhydrase Inhibitor MK-0507: 5,6-Dihydro-(*S*)-4-(ethylamino)-(*S*)-6-methyl-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-Dioxide Hydrochloride

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The key feature in the synthesis of topically-active carbonic anhydrase inhibitor MK-0507 (**13b**) is a Ritter reaction that exhibits an unexpected tendency to proceed with retention of chirality. This phenomenon was further studied on model compounds free from potential diastereomeric effects. A mechanism involving transannular stabilization of the sp^2-hybridized center by sulfone oxygen is proposed with the net result of double inversion. A second key feature in the preferred sequence to MK-0507 involves the classic problem of how to maximize substitution over elimination. This problem manifests itself in the stereospecific alkylation of 2-mercaptothiophene with derivatized methyl (*R*)-3-hydroxybutyrate and is compounded by a subsequent Michael reaction leading to a loss of product chirality. Results are presented that eliminate this problem.

Introduction

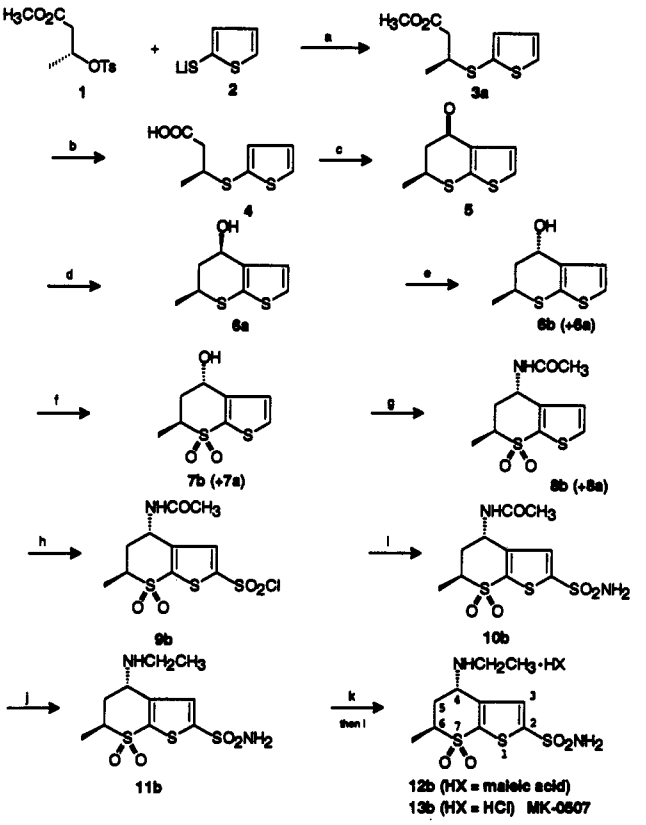
The current therapy for control of elevated intraocular pressure (IOP) associated with glaucoma is typically effected with a variety of topically-applied agents, all of which fall within the following four categories: β-blockers, sympathomimetics, parasympathomimetics, and anticholinesterase inhibitors.[1] The adjuvant oral administration of a carbonic anhydrase inhibitor (CAI) is generally added to the treatment when one of the above agent's side-effect profile limits its use and/or it fails to achieve adequate IOP control. The orally active CAI's, although extremely effective, can exhibit serious side-effects such an anorexia, gastrointestinal upset, and paresthesias. Therefore, an intense and ongoing search has been mounted for a topically-active CAI that would not exhibit such side effects due to the route of administration and inherent target organ specificity. The discovery of a new and novel class of H_2O-soluble CAI's by Ponticello et al. affords a major advancement toward the realization of this goal.[2] We report herein a practical total asymmetric synthesis of one leading topically-active CAI candidate, MK-0507, 5,6-dihydro-(*S*)-4-(ethylamino)-(*S*)-6-methyl-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-dioxide hydrochloride (**13b**) in >32% overall yield.[3] Key to the efficiency of the scheme was the order of introduction of the requisite two asymmetric centers, the first being introduced by S_N2 displacement in >97% ee and the second through diastereomeric control of a classic Ritter reaction and the latter being improved from 50% de to >78% de through the understanding and exploitation of sulfone stabilization of the Ritter-generated carbocation (Scheme I).

Discussion

MK-0507 (**13b**) was prepared in >32% overall yield from methyl (*R*)-3-hydroxybutyrate according to Scheme I. We envisioned tosylation of readily available methyl (*R*)-3-hydroxybutyrate followed by S_N2 displacement with 2-(lithiomercapto)thiophene (**2**) to prepare the requisite chiral intermediate for MK-0507. Initial attempts produced considerable elimination to methyl crotonate. Subsequent Michael addition then afforded racemic product (eq 1).

Evaluation of substituted benzenesulfonic acid leaving groups afforded the Hammett-type correlation shown in

Scheme I[a]



[a] (a) $HCONH_2$, 20 °C; (b) 12 N HCl, reflux; (c) TFAA, toluene; (d) LAH, toluene; (e) 1 N H_2SO_4, 0–5 °C; (f) H_2O_2, Na_2WO_4; (g) CH_3CN, H_2SO_4; (h) HSO_3Cl, $SOCl_2$; (i) NH_4OH, THF, 0–5 °C; (j) BH_3·DMS, THF; (k) maleic acid, acetone; (l) EtOAc, HCl.

(1) Kaufman, P. L.; Robin, A. L.; Weinreb, R. N.; Crawford, K.; Shaw, B. *Drugs 41*, 1991, 514.
(2) Baldwin, J. J.; Ponticello, G. S.; Sugrue, M. F. *Drugs of the Future* 1990, *15*, 351.
(3) (S)-Alkyl 3-Thien-(2-ylthio) Butyrate and Analogs and Synthesis Thereof. Blacklock, T. J.; Grabowski, E. J. J.; Sohar, P. U.S. Pat. 4 968 814; *Chem. Abstr.* 114(19):185253y.

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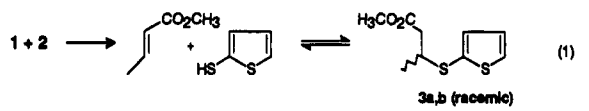


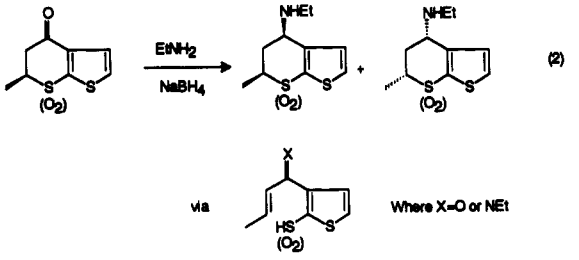
(1)

Figure 1 and Table I. Whereas displacement of tosylate 1 led to an 82% enantiomeric excess (ee) product mixture, the *m*-chlorobenzenesulfonate afforded a 97% ee mixture under identical conditions in THF. A dramatic solvent effect was also observed. With tosylate 1, H_2O, CH_3CN, and THF all produced product of relatively low % ee (89, 84, and 82%, respectively). However, when the displacement reaction was run in formamide, or in a 1:1 cosolvent system with THF, the product ee rose to >97%! Economy of scale thus suggested use of formamide and the much cheaper tosylate to be the preferred route.

Acid-catalyzed hydrolysis of methyl ester **3a** (HCl/H_2O) afforded carboxylic acid 4 in quantitative yield (saponification of **3a** was completely ineffective due to the reversible Michael reaction shown above). Subsequent intramolecular Friedel–Crafts acylation with trifluoroacetic anhydride in toluene afforded ketone **5**. The use of TFAA to promote intramolecular Friedel–Crafts acylation avoided a potential environmental problem. The traditional approach—acid chloride formation (oxalyl chloride/DMF) followed by Lewis acid addition ($SnCl_4$, $AlCl_3$, etc.)—invariably employed an environmentally disfavored solvent (CCl_4, CH_2Cl_2, CH_3NO_2, CS_2, and other chlorinated alkanes). Furthermore, the reaction workup with amphoteric salts caused isolation problems.

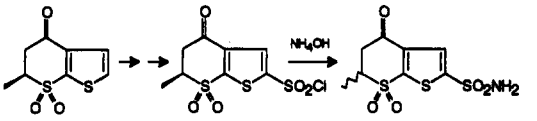
The reduction of this ketone fortuitously gives the *R*-enantiomer of the corresponding alcohol due to diastereomeric control in 98% ee, a transformation that requires asymmetric reduction in the synthesis of MK-0417, the 6-desmethyl analog.[4] Thus, similar methodology as previously described can be utilized to complete the synthesis. Unfortunately the process does not lend itself to industrial scale.[5]

At this stage a variety of options were considered for the installation of both the 6-ethylamino and the 2-sulfonamide moieties. Reductive amination of keto sulfide **5** or its corresponding sulfone with ethylamine/sodium borohydride in THF resulted in near-exclusive formation of the undesired cis adduct in >90% yield along with considerable racemization via the now-familiar reversible Michael reaction, through elimination of thiolate ion (eq 2). This demonstrated lability of keto sulfide **5** toward



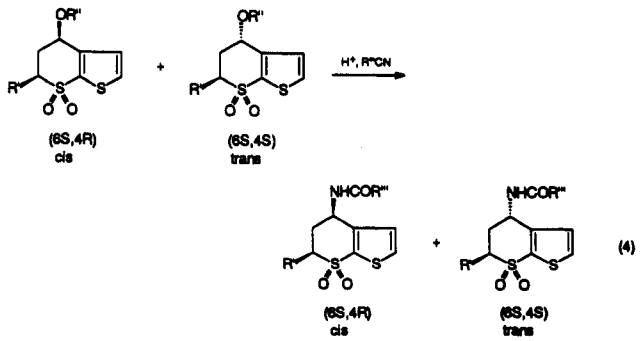
(2)

racemization via retro Michael addition also predominated during the installation of the 2-sulfonamide group. Amidation of the 2-sulfonyl chloride with aqueous ammonia/THF afforded racemic product in very high yield. Similar results were obtained on the keto sulfone of **5** (eq 3). Thus, these routes were rapidly abandoned.



(3)

An interesting and viable alternative for the installation of the ethylamino moiety on hydroxy sulfones **7a,b** came via classic Ritter chemistry (Scheme I). Initially, treatment of the 95:5 mixture of diastereomeric alcohols **7a** and **7b** with H_2SO_4 in CH_3CN resulted in a 2:1 mixture of trans: cis acetamides **8b** and **8a**, respectively. However, during the course of evaluating/optimizing the process we had generated a variety of cis/trans alcohol mixtures and noticed that there was a linear correlation of product acetamide ratio relative to the ratio of starting diastereomeric alcohols (see eq 4, Tables II and III).



(4)

The implication was that the Ritter reaction was occurring mainly with retention of stereochemistry on trans starting material and with considerable inversion of stereochemistry on cis starting material. More to the point, factors other than diastereoselectivity due to the presence

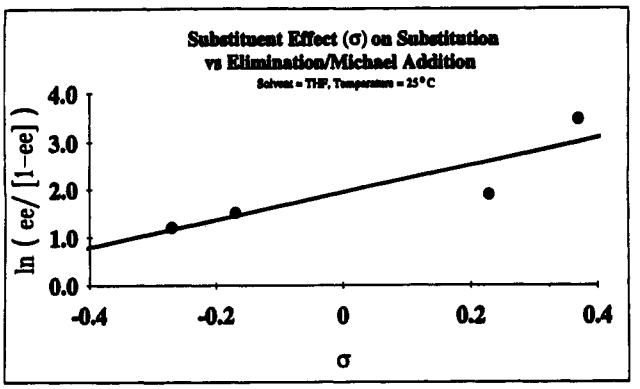


Figure 1. Enantiomeric excess (% ee) as a function of substituent effect.

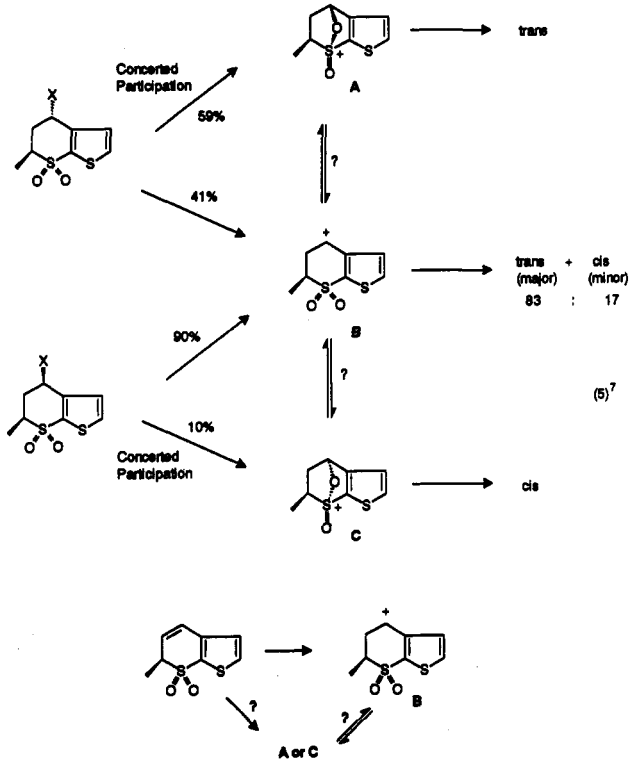
Table I. Solvent and Substituent Effect on Displacement Reaction of 1 (Scheme I) (A Measure of S_N2 vs E2/Michael Addition)

	reaction solvent			
R	% ee (THF)	% ee (H_2O)	% ee (CH_3CN)	% ee ($HCONH_2$)
p-OMe	77			
p-Me	82	89	84	>97
p-Cl	87			
m-Cl	97			

(4) Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock T. J.; Mathre, D. J.; Sohar, P.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 763–769.

(5) S_N2 displacement of the corresponding tosylate with ethylamine results in the desired *S*-enantiomer and trans diastereomer; the installation of the 2-sulfonamide is by direct quench of the total chlorosulfonylation mixture into a large excess of aqueous ammonia, highly energetic and environmentally unacceptable.

of the 6-methyl group were operative. This curious phenomenon was further investigated working with the desmethyl analogue of (*R*) hydroxy sulfone **7b** available from our earlier work on MK-0417.[4] With only one asymmetric center, this removed any diastereocontrol exerted by the 6-methyl group. To our surprise, the reaction occurred with significant retention (60% ee). Various nitriles were tried, both with and without a nonpolar cosolvent such as methylene chloride. The results summarized in Tables II and III and illustrated in eq 5, suggest an internally assisted reaction path involving transannular stabilization and partial trapping of the intermediate carbocation by sulfone oxygen. [Ritter-type reactions that proceed with high enantioselectivity have been reported; however, these reportedly proceed via episulfonium ion intermediates generated from β-hydroxy thiols.][6]



Substitution of nitrile at the least hindered face, thus, results in a net double inversion.[7] Consistent with our observations is that attack on the bridged structure would likely be favored by less bulky nucleophiles and low polarity solvent media. Conversely, bulky nucleophiles and higher polarity media favor the S_N1 mechanism.

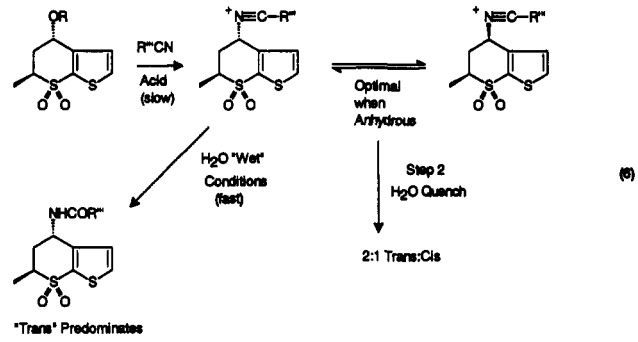
The tendency of this Ritter reaction to maintain the trans configuration contradicts not only its presumed racemic pathway (S_N1 mechanism) but also the well known racemization of the intermediate nitrilium species.[8] The nitrilium intermediate can equilibrate via a reversible reaction with the nitrile solvent (reagent) until it is trapped by reaction with another nucleophile, e.g., H_2O (eq 6).

Table II. Diastereomeric Ratio of Ritter Reaction Product (eq 4) Relative to Diastereomeric Ratio of Reactants (R′ and R‴ = Me)

R″	reactant ratio (6*S*,4*R*):(6*S*,4*S*) cis:trans	product ratio (6*S*,4*R*):(6*S*,4*S*) cis:trans
H	95:5	34:66
H	60:40	24:76
H	24:76	11:89
H	2:98	7:93
Ac	100:0	25:75
Ac	95:5	23:77
Ac	60:40	17:83
Ac	25:75	12:88
Ac	0:100	7:93
olefin (eq 6)	NA	17:83

Table III. Enantiomeric Excess of Ritter Reaction Product in the Desmethyl Series Relative to Enantiomeric Excess of Reactant (R′ and R″ = H) (eq 4)

R‴	reactant ee[4]	product % ee (neat)	product % ee (CH_2Cl_2 cosolvent)
Me (16)	100	45	60
Et (17)	100		50
i-Pr (18)	100	22	35



The standard reaction conditions for preparative Ritter reactions call for a nitrile solution containing 20% H_2SO_4. These conditions generally contain (or generate) enough H_2O to irreversibly quench the nitrilium ion and, thus, form amide. In an experiment to test this hypothesis of water involvement, trans hydroxy sulfone **7a** was subjected to rigorously dry Ritter reaction conditions (BF_3 etherate used as acid catalyst with sieve-dried CH_3CN).[9] A 2:1 trans:cis amide product ratio was obtained. Furthermore, on addition of dry propionitrile, a new set of HPLC peaks was observed corresponding to the propionamide derivatives. Product distribution was deemed to occur primarily from diastereocontrol of the 6(*S*)-methyl group. A control experiment run with CH_3CN and 98% H_2SO_4 gave the expected 10:1 trans:cis product ratio (and no reaction with propionitrile), thus giving credence to our hypothesis. Clearly, the adventitious presence of H_2O is necessary to maintain a reasonably high de. In a subsequent control experiment the chirality of the amide product was shown to be preserved under our standard Ritter reaction conditions, thus eliminating the hypothesis of subsequent rearrangement.

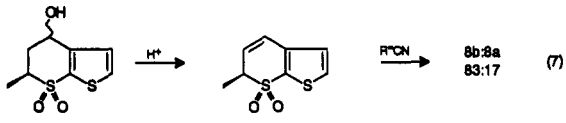
(6) Toshimitsu, A.; Hirosawa, C.; Tanimoto, S. *Tetrahedron Lett.* **1991**, *32*(34), 4317–20.

(7) Simple mathematics lend support to eq 5. From Table II, assuming olefin proceeds only through carbocation B to products, and for X = OAc, trans starting material **7b** gives 93:7 trans:cis amide products **8b** and **8a**, respectively; **7b** must give 41% B and 59% A. Similarly, the cis starting material **7a** gives 75:25 trans:cis amide products **8b** and **8a**, respectively, arising from 90% B and 10% C. A is, therefore, considerably more stable than C, or is more easily formed in a concerted manner from its precursor. The 59% participation via species A also approaches the maximum transannular participation (60%) observed in the simpler desmethyl case, thus lending additional support to this interpretation.

(8) Barton, D. H. R.; Magnus, P. D.; Young, R. N. *J. Chem. Soc., Chem. Commun.* 1973, 331–332. Barton, D. H. R.; Magnus, P. D.; Garbarino, J. A.; Young, R. N. *J. Chem. Soc., Perkin Trans. I* **1974**, 2101–2107.

(9) The presence of nitrilium ion was also demonstrated by nitrile interchange. Addition of CH_3CN to a propionitrile Ritter reaction with **7a–OAc** afforded a corresponding mixture of amides. Addition of CH_3CN was made after no starting material could be detected by HPLC.

In light of the above, the difficulty of inducing and demonstrating the proposed bridged carbocation becomes clear. Classical S_N1 reactions, such as solvolyses, prove to be reversible under strongly acidic conditions and are, therefore, useless for preservation of chirality. Thus, an independent confirmation of the proposed sulfone participation in our Ritter reactions might only be provided by subsequent irreversible reaction, or an irreversible capture, of the initial adduct. Simple S_N1-type solvolysis reactions on alcohol sulfones **7a** or **7b** and their derivatives such as methoxy, acetate, and tosylate (in alcohols or acetic acid catalyzed by H_2SO_4) all provided alkoxy or acetate products with a 2:1 trans:cis ratio. Additionally, these reactions rapidly afforded completely racemic products when run on the desmethyl analog. At present it is only the "wet" Ritter-type reactions that offer the unique set of circumstances that lead to relatively high preservation of chirality. Thus far, attempted observation of the stabilized carbocation by NMR has resulted only in formation of the olefin dehydration product (shown in eq 7). This was a mixed blessing, for although we were unable



(7)

to observe the suspected bridged intermediate we, nevertheless, had a lead on improving the Ritter reaction for MK-0507. When the olefin shown in eq 7 was subjected to our standard Ritter reaction conditions, wherein H_2SO_4 was added to a mixture of substrate in CH_3CN, a favorable 83:17 ratio (66% de) of diastereomers was obtained. The immediate result was an 8% increase in Ritter yield over an already improved version utilizing acetate derivatives as precursors (the acetates had curiously offered an 8% advantage in de over the corresponding alcohols). The isolation efficiency also improved dramatically to near 85% (up from 70%), resulting in a net increase of about 15% over these two steps (dehydration/Ritter vs acylation/Ritter). The problem, thus, was to devise a way of generating the precursor olefin in situ before trapping of the carbocation with CH_3CN occurred. One procedure considered from our NMR experiments was to dissolve alcohols **7a** and **7b** (any ratio) in cold H_2SO_4, allowing them to convert to olefin, and then proceeding with the Ritter reaction by adding the appropriate nitrile. With use of this strategy the Ritter reaction proceeded through olefin to consistently afford the expected 83:17 ratio of acetamides, the ratio due predominantly to diastereomeric control.

This formally raised the yield of MK-0507 to >15% overall from methyl (*R*)-3-hydroxybutyrate. However, the challenge to take advantage of the unusual and unsuspected tendency of the Ritter reaction to retain chirality turned our attention to the reduction of the keto sulfone and the variables that might influence the diastereomeric purity of the alcohol product. Various reducing agents (LAH, Red-Al, $NaBH_4$, H_2/Raney nickel) were tried under a variety of conditions (molar ratio and mode of addition) on the likely candidates, sulfide **5** and its sulfone analogue. In all cases the reductions afforded 95–98% cis product (90–96% de). Higher proportions of the trans product were only obtained after a strongly acidic workup of the LAH reduction. This observation led us to suspect acid-catalyzed epimerization, and suspicion confirmed after demonstrating that a 95:5 cis:trans mixture of alcohols **6a** and **6b**, respectively, was easily equilibrated to a 24:76 cis:trans mixture, and with negligible decomposition, in aqueous THF over 24 h at 0–5 °C with a catalytic amount of HCl. Thus, to avoid the potential for chloride formation during epimerization we ultimately switched to H_2SO_4. Noteworthy is that the equilibration could also be effected in a well-agitated biphasic medium such as toluene/H_2O. This facilitated the use of toluene as the solvent for the two prior steps, obviating the need for any intermediary isolations. [Interestingly, hydroxy sulfones **7a** and **7b** required more highly acidic conditions to effect essentially the same degree of epimerization. The reaction was more difficult to control.]

The higher trans:cis ratio (76:24 **6b**:**6a**) achieved via the above epimerization translated into an 89:11 trans:cis ratio of Ritter product acetamides without the need for intermediate acetate formation which had previously improved the ratio from 2:1 to 3:1. The yield advantage thus exceeded that offered by the olefin method, improving the Ritter reaction by 14% and increasing the isolation efficiency to 92%; a net increase of nearly 25% over these steps.

Oxidation of **6a,b** to sulfone **7a,b** was effected catalytically in near quantitative yield with sodium tungstate[10] and 30% aqueous H_2O_2 in aqueous ethyl acetate (EtOAc) (the oxidizing species is likely sodium pertungstate). The solvent of choice, EtOAc, was key to obtaining a high yield of sulfone. The above oxidation was based on a report by Schultz et al.[11] for the oxidation of H_2O-soluble sulfides to sulfones (less H_2O-soluble sulfides could be run, however, in aqueous alcohols or with dioxane present). Workup in these H_2O-miscible solvents became tedious. Our EtOAc biphasic modification removed this constraint and made the reaction more manageable. The heat of reaction has been measured at 54 kcal/mol[12] which is moderately exothermic for large-scale work. The reaction can be easily controlled, however, via the rate of addition of peroxide. After oxidation is complete, excess H_2O_2 is decomposed with sodium sulfite, the layers are cut, and the EtOAc product layer is concentrated to crystallize the sulfone. In our estimation this catalytic procedure is clearly superior to the alternatives such as *m*-chloroperbenzoic acid, peracetic acid, or Oxone. One need not deal with the enormous bulk of solids (peculiar to oxone oxidations) that need be efficiently stirred and filtered. This S-oxidation has since been applied to a variety of thienothiopyran derivatives. In each case yields of sulfone of >95% were obtained.

The 89:11 mixture of acetamides obtained from our optimized Ritter reaction was sulfonamidated (chlorosulfonic acid/thionyl chloride followed by amidation of the sulfonyl chloride with ammonia) and reduced with BH_3/DMS to an identical 89:11 mixture of ethylamine sulfonamides **11b** and **11a**. A 5-mol excess was required to complete the reduction within 4–10 h and hydrogen evolution was rapid since both sulfonamide protons reacted. The resultant amine–borane and complexes were then decomposed in 1.8 M H_2SO_4. After neutralization to pH 7.3 the product was extracted into EtOAc and

(10) Connon, N. W. *Eastman Organic Chemical Bulletin* **1972**, *44*, 1–4.
(11) Schultz, H. S.; Freyermuth, H. B.; Buc, S. R. *J. Org. Chem.* **1963**, *28*, 1140–1142.
(12) In-house determination by L. Williams and R. Cutro of Merck Manufacturing Division Process Safety Laboratory.

separation of the desired trans diastereomer was accomplished in 90% isolation efficiency by formation of the maleate salt. Subsequent neutralization and formation of the hydrochloride salt afforded MK-0507 in 90% yield after recrystallization from H_2O.

Experimental Section

General. Melting points were determined on a Haake-Buchler capillary melting point apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on EM Reagents 0.25-mm silica gel 60-F plates. Visualization was accomplished with UV light or by dipping in an aqueous ceric ammonium molybdate solution followed by heating. Analytical gas chromatography (GC) was performed on a Hewlett-Packard 5890 chromatograph fitted with a flame ionization detector (He carrier gas) on columns (A) 0.32 mm × 30 m DB-1 (15 lb/in.^{2}, ≈30:1 split); (B) 0.32 mm × 30 m DB-23 (15 lb/in.^{2}, ≈30:1 split). Retention times (t_R) and integrals were obtained from a Hewlett-Packard 3396A integrator. High-performance liquid chromatography (HPLC) was performed on a Spectra Physics chromatograph utilizing a C-8 Altex Ultrasphere 5 μm (4.1 mm × 25 cm) column unless otherwise noted. General conditions employed a binary mixture of eluants A and B; A = H_2O (0.1% H_3PO_4 v/v), B = CH_3CN at a combined flow rate of 2.0 mL/min and UV detection at 254 nm. Three methods were commonly used: method A, eluant 50:50 A:B isocratic; method B, gradient 97:3 A:B to 35:65 over 21 min; method C, eluant 90:10 A:B isocratic. Solvents for extraction were reagent grade. Solvents for reactions were dried with 3- or 4-Å molecular sieves. Residual H_2O content "K.F." was determined by Karl-Fischer titration. All reactions were performed under an inert atmosphere of dry N_2 in dry glassware.

Optical rotations were determined on a Perkin-Elmer 241 polarimeter using the sodium D line (λ = 589) at the temperature indicated and are reported as follows: $[\alpha]^{temp}_D$, concentration (c g/100 mL), and solvent. Infrared spectra were recorded on a Perkin-Elmer 281B spectrophotometer. Peaks are reported in cm^{-1} with the following relative intensities: s (strong, 67–100%), m (medium, 34–66%), w (10–33%). The following abbreviations also are used: br (broadened), sh (shoulder). ^{1}H NMR spectra were recorded in deuteriochloroform on a Bruker AM-250 (250 MHz) spectrometer. Chemical shifts are reported in ppm from an internal standard of residual chloroform (7.27 ppm). Selected data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broadened, obs = obscured), coupling constants (hertz), and assignments. ^{13}C NMR spectra were recorded in deuteriochloroform on a Bruker AM-250 (62.9 MHz) spectrometer. Chemical shifts are reported in ppm from the center peak of deuteriochloroform (77.0 ppm). Data are reported as follows: chemical shift, assignment. Grouped shifts and assignments are provided where an ambiguity has not been resolved. Proton and carbon NMR assignments were made with the aid of COSY-45 and HETCOR data. Mass spectra were obtained on a Finnigan-MAT TSQ 70B mass spectrometer. Low-resolution spectra using electron impact (EI) were obtained at 70 eV. Combustion analyses were obtained in-house from our Analytical Research Department.

Methyl (*R*)-3-(*p*-Toluenesulfonyloxy)butyrate (1).[13] At a temperature ≤−5 °C, *p*-toluenesulfonyl chloride (2.35 kg, 98% technical grade, 12.4 mol) was added to dry pyridine (3.0 L, K.F. <0.005%) and methyl (*R*)-3-hydroxybutyrate (1.14 assay kg, 9.67 mol, K.F. <0.005 wt %). The reaction mixture was stirred for 24 h at 0 °C or until judged complete by HPLC. Workup was commenced by cooling the batch to −16 °C and subsequently adding H_2O (200 mL), dropwise, while maintaining the temperature at <2 °C. (It is essential that all tosyl chloride be decomposed with the addition of H_2O while the batch is still homogeneous. If too much H_2O is added initially, the reaction becomes biphasic and the rate of hydrolysis slows dramatically. Tosyl chloride then co-crystallizes with the product.) After vigorous agitation for 30 min at 0–2 °C an additional 400 mL of H_2O was then added dropwise. When HPLC analysis (see below) showed no remaining tosyl chloride the batch was diluted with the slow addition of H_2O (9 L) at 0–5 °C. Product crystallized spontaneously. After 2 h at 0–5 °C the crystalline product was filtered, slurry-washed with H_2O *at least 5 times* to remove *p*-toluenesulfonic acid and pyridine, and sucked dry. The yield of methyl (*R*)-3-(*p*-toluenesulfonyloxy)butyrate (1) was 2.57 kg (98%), mp 46–47.5 °C. HPLC conditions: method A [Sample preparation: A quantity of 0.1 mL of the above reaction mixture was shaken with 5 mL of H_2O, 5 mL of EtOAc, and 1.0 mL of concentrated HCl to neutralize and remove the pyridine solvent. The mixture was then separated and the upper EtOAc layer was diluted 1:10 with CH_3CN for injection. At 254 nm, an area ratio of 1:2 product tosylate:tosyl chloride signifies a complete reaction. t_R(tosylate 1) 3.5 min, t_R(tosyl choride) 5.5 min]. 1: ^{1}H NMR ($CDCl_3$) 7.79 (d, 2 H, J = 8.36 Hz), 7.34 (d, 2 H, J = 8.36 Hz), 4.97 (m, 1 H), 3.59 (s, 3 H), 2.74 (dd, 1 H, J = 15.8, J = 6.5 Hz), 2.52 (dd, 1 H, J = 15.8, J = 6.8 Hz), 2.45 (s, 3 H), 1.36 (d, 3 H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$) 169.7 (s), 144.8 (s), 133.9 (s), 129.8 (s), 127.7 (s), 75.8 (s), 51.8 (s), 41.2 (s), 21.6 (s), 20.9 (s); $[\alpha]^{25}_{405}$ = −16.3° (c = 2, toluene). Anal. Calcd for $C_{12}H_{16}O_5S$: C, 52.94; H, 5.88; S, 11.76. Found: C, 52.98; H, 5.93; S, 11.76.

The following substituted benzenesulfonates were also prepared in similar fashion and characterized by NMR and HRMS.

Methyl (*R*)-3-[(*p*-Chlorobenzenesulfonyl)oxy]butyrate: ^{1}H NMR ($CDCl_3$) δ 7.85 (d, 2 H, J = 8.7), 7.52 (d, 2 H, J = 8.7), 5.02 (septet, 1 H, J = 6.3), 3.58 (s, 3 H), 2.74 (dd, 1 H, J = 6.6, J = 16.1), 2.53 (dd, 1 H, J = 6.1, J = 16.1), 1.38 (d, 3 H, 6.3); HRMS calcd for $C_{11}H_{14}O_5ClS$ (MH^+) 293.0250, found 293.0290.

Methyl (*R*)-3-[(*p*-Methoxybenzenesulfonyl)oxy]butyrate: ^{1}H NMR ($CDCl_3$) δ 7.85 (d, 2 H, J = 8.9), 7.01 (d, 2 H, J = 8.9), 4.95 (septet, 1 H, J = 6.5), 3.89 (s, 3 H), 3.61 (s, 3 H), 2.75 (dd, 1 H, J = 6.5, J = 15.8), 2.52 (dd, 1 H, J = 6.8, J = 15.8), 1.36 (d, 3 H, J = 6.5); HRMS calcd for $C_{12}H_{17}O_6S$ (MH^+) 289.0746, found 289.0753.

Methyl (*R*)-3-[(*m*-Chlorobenzenesulfonyl)oxy]butyrate: ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1 H), 7.82 (d, 1 H, J = 8.7), 7.63 (d, 1 H, J = 8.7), 7.50 (d, 1 H, J = 8.7), 5.06 (septet, 1 H, J = 6.4), 3.60 (s, 3 H), 2.78 (dd, 1 H, J = 6.6, J = 16.1), 2.54 (dd, 1 H, J = 6.1, J = 16.1), 1.41 (d, 3 H, J = 6.4); HRMS calcd for $C_{11}H_{14}O_5ClS$ (MH^+) 293.0250, found 293.0281.

Methyl (*S*)-3-(2-Thienylthio)butyrate (3a). To a solution of thiophene (18.1 mL, 19.0 g, 226 mmol) and dry THF (200 mL, K.F. <0.05%) at <−5 °C was added *n*-butyllithium (137 mL of 1.6 M in hexane, 219 mmol), maintaining the temperature at <0 °C. The reaction was stirred for 1 h at 0–5 °C and powdered sulfur (7 g, 219 mmol) was added portionwise, at <5 °C. The reaction mixtures was stirred for 2.5 h at 0–5 °C and diluted with formamide (200 mL of technical grade) that had been thoroughly purged with N_2. To this biphasic mixture was then added solid methyl (*R*)-3-(*p*-toluenesulfonyloxy)butyrate (1, 57.0 g, 209 mmol), and the mixture was stirred at 25 °C for 3 days. (The progress of the alkylation was conveniently monitored by HPLC: method A, t_R(methyl crotonate) 4.25 min, t_R(thiophene) 6.82 min, t_R(tosylate 1) 10.17 min, t_R(2-mercaptothiophene) 11.50 min, t_R(methyl (*S*)-3-(2-thienylthio)butyrate (3)) 12.50 min, t_R(disulfide) 14.89 min, t_R(methyl (*S*)-3-[[5-(2-thienylthio)-2-thienyl]thio]butyrate) 19.54 min. The entire reaction mixture was then poured into a stirred vessel containing H_2O (400 mL) and EtOAc (200 mL) at 25 °C.) The organic layer was separated and the aqueous layer was back-extracted once with 1:1 EtOAc:hexanes (100 mL). The organic layers were combined and washed with brine (200 mL). Concentration of the EtOAc solution from H_2O under vacuum removed residual EtOAc and afforded a viscous oil/H_2O mixture (ca. 100 mL H_2O/60 mL oil) which was hydrolyzed directly in the next step. A small sample of the oil was chromatographed on silica gel (10% EtOAc in hexanes) for byproduct identification and product characterization and chirality determination.

The first eluted component, R_f = 0.82, was identified as 2-thiophene disulfide on the basis of its spectral characteristics: ^{1}H NMR ($CDCl_3$) 7.35 (m, 2 H), 7.23 (m, 2 H), 6.97 (m, 2 H); ^{13}C NMR ($CDCl_3$) 135.5 (s), 132.8 (s), 129.7 (s), 127.5 (s); HRMS calcd for $C_8H_6S_4$ (M^+) 229.9352, 229.9353.

(13) Liu, H.; Auchus, R.; Walsh, C. T. *J. Am. Chem. Soc.* **1984**, *106*, 5335–5348.

The product **3a** was eluted as the major second fraction, R_f = 0.52, and was identified as methyl (*S*)-3-(2-thienylthio)butyrate on the basis of its spectral characteristics: ^{1}H NMR ($CDCl_3$) 7.41 (m, 1 H), 7.17 (m, 1 H), 7.02 (m, 1 H), 3.69 (s, 3 H), 3.39 (m, 1 H), 2.67 (dd, 1 H, J = 15.7, J = 6.4 Hz), 2.42 (dd, 1 H, J = 15.7, J = 8.2 Hz), 1.32 (d, 3 H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) 171.6 (s), 136.2 (s), 130.9 (s), 130.7 (s), 127.7 (s), 51.7 (s), 41.8 (s), 41.4 (s), 20.7 (s). Anal. Calcd for $C_9H_{12}O_2S_2$: C, 50.00; H, 5.56. Found: C, 50.08; H, 5.65. Chirality: >98:2 *S*:*R* by NMR using (+)-Eu(hfc)$_3$ chiral shift reagent and monitoring the methyl doublet at 1.32 ppm.

The third eluted component, R_f = 0.42, was identified as methyl (*S*)-3-[[5-(2-thienylthio)-2-thienyl]thio]butyrate on the basis of its spectral characteristics: ^{1}H NMR ($CDCl_3$) δ 7.39 (m, 1 H), 7.25 (m, 1 H), 6.99 (m, 1 H), 3.67 (s, 3 H), 3.39 (m, 1 H), 2.65 (dd, 1 H, J = 15.7, J = 6.5 Hz), 2.43 (dd, 1 H, J = 15.7, J = 8.0 Hz), 1.31 (d, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) 171.5 (s), 140.7 (s), 136.3 (s), 134.5 (s), 133.8 (s), 133.8 (s), 131.7 (s), 130.4 (s), 127.6 (s), 51.8 (s), 42.0 (s), 41.4 (s), 20.8 (s); HRMS calcd for $C_{13}H_{14}O_2S_4$ (M^+) 329.9877, found 329.9872.

For comparative purposes the substituted *p*-Me, *p*-Cl, *m*-Cl, and *p*-OMe benzenesulfonates were subjected to identical displacement reactions in THF as described above and the product analyzed for ee. Reactions were allowed to go to completion (>95%) as determined by HPLC. The % ees obtained are presented in Table I. Solvent effect of H_2O and CH_3CN was determined by the addition of these solvents in place of formamide.

(*S*)-3-(2-Thienylthio)butyric Acid (4). The viscous oil/H_2O mixture of methyl ester **3a** above and concentrated HCl (100 mL, 12 N) was brought to reflux with vigorous agitation for 3 h, or until complete, as judged by HPLC. [HPLC method A, t_R(butyric acid (**4**)), 7.11 min.] The product was extracted 2× into toluene (160 mL for the first extraction and 50 mL for the second extraction). The combined toluene extracts were washed with brine and dried azeotropically under vacuum to 200 mL containing approximately 45 g of product at K.F. <0.05%. A small portion of the product was chromatographed on silica gel for product characterization: ^{1}H NMR ($CDCl_3$) δ 7.43 (dd, 1 H, J = 1.2, J = 5.3), 7.19 (dd, 1 H, J = 1.2, J = 3.4), 7.03 (dd, 1 H, J = 3.4, J = 5.3), 3.43–3.34 (m, 1 H), 2.72 (dd, 1 H, J = 6.4, J = 16.1), 2.48 (dd, 1 H, J = 8.0, J = 16.1), 1.35 (d, 3 H, J = 6.9); HRMS calcd for $C_8H_{10}O_2S_2$ (M^+) 202.0122, found 202.0123.

(*S*)-5,6-Dihydro-6-methylthieno[2,3-*b*]thiopyran-4-one (5). To the solution of butyric acid **4** in toluene from above (approximately 38.5 g, 209 mmol in 209 mL of toluene) at 0 °C was added trifluoroacetic anhydride (43.6 g, 29.3 mL, 209 mmol) at 0–5 °C. The mixture was warmed to 25 °C and monitored by HPLC or TLC until ring closure was complete (ca. 1 h). [HPLC, same conditions as for methyl ester above: t_R(acid **4**), 6.89 min; t_R(ketone **5**), 7.7 min]. The reaction mixture was cooled to 0–5 °C and quenched into cold H_2O (200 mL, 5 °C) keeping the temperature at <25 °C. The mixture was stirred for 30 min and the layers were separated. The organic layer was washed with brine (200 mL) and then concentrated to approximately 200 mL at K.F. <0.05%. A small portion of the product was chromatographed on silica gel for product characterization: ^{1}H NMR ($CDCl_3$) δ 7.45 (d, 1 H, J = 5.5), 7.02 (d, 1 H, J = 5.5), 3.80 (ddq, 1 H, J = 11.4, J = 3.2, J = 6.9), 2.89 (dd, 1 H, J = 3.2, J = 16.8), 2.69 (dd, 1 H, J = 11.4, J = 16.8), 1.49 (d, 3 H, J = 6.9). Anal. Calcd for $C_8H_8OS_2$: C, 52.14; H, 4.34; S, 34.79. Found: C, 52.27; H, 4.42; S, 34.65.

Evidence for Retro-Michael/Michael Racemization of (*S*)-5,6-Dihydro-6-methylthieno[2,3-*b*]thiopyran-4-one (5). Upon treatment of **5** with catalytic triethylamine in CD_3OD both protons at C-5 rapidly exchanged, giving rise to a clean quartet for the methine proton at C-6. Complete and concurrent loss of optical rotation was also observed. No deuterium exchange could be detected at C-6 by NMR. This led us to conclude that the mechanism proposed in eq 3 is operative. Clearly imine formation is not a prerequisite to racemization. It is also reasonable to assume that racemization would similarly occur from the imine.

5,6-Dihydro-(*R*)-4-hydroxy-(*S*)-6-methyl-4*H*-thieno[2,3-*b*]thiopyran (6a). Lithium aluminum hydride·2THF (53 mL, 1 M in toluene, 53 mmol) was added to ketone **5** (39 g, 209 mmol) in toluene (200 mL, K.F. <0.05%) at 0 °C. The reaction was stirred at 0–5 °C until complete by HPLC. [HPLC, same conditions as for methyl ester above: t_R(ketone **5**), 7.7 min; t_R(alcohols **6a** and **6b**), 5.6 min]. The mixture was warmed to 25 °C and stirred for 30 min, and the layers were separated. The aqueous layer was extracted with toluene (2 × 50 mL) and the combined toluene layers were concentrated to 60 mL and diluted 5:1 with EtOAc (300 mL) for use in the oxidation step. A small portion was further concentrated and crystallized for analysis: ^{1}H NMR ($CDCl_3$) δ 7.10 (d, 1 H, J = 5.3), 7.05 (d, 1 H, J = 5.3), 4.87 (dd, 1 H, J = 5.9, J = 9.9), 364–3.51 (m, 1 H), 2.45 (ddd, 1 H, J = 2.0, J = 5.9, J = 9.5), 2.17–1.82 (m, 2 H), 1.42 (d, 3 H, J = 6.9). Anal. Calcd for $C_8H_{10}OS_2$: C, 51.57; H, 5.41; S, 34.42. Found: C, 51.32; H, 5.47; S, 34.30.

Reduction with Epimerization (6b + 6a). The above reaction was repeated at the 53-mmol scale, and after reduction was judged complete the mixture was quenched into 50 mL of 1 M H_2SO_4 at 0–5 °C. The mixture was stirred for 30 min and separated. The aqueous layer was extracted once with toluene (10 mL) and the combined toluene liquors were stirred vigorously with 100 mL of 1 M H_2SO_4 for 27 h. The cis:trans ratio of alcohols changed from 95:5 to 24:76 as determined by HPLC analysis of small aliquots oxidized to sulfone (we were unable to effect separation of the diastereomeric hydroxy sulfides by HPLC). The layers were separated and the aqueous layer was washed with toluene (20 mL). The combined organic extracts were then treated as above for the oxidation step. See assay procedure in **7b**.

5,6-Dihydro-(*R*,*S*)-4-hydroxy-(*S*)-6-methyl-4*H*-thieno[2,3-*b*]thiopyran 7,7-Dioxide (7b). Water (28 mL) was added to the EtOAc/toluene mixture of alcohols **6b** and **6a** above (360 mL containing 39 g, 209 mmol) followed by sodium tungstate dihydrate (6.93 g, 21 mmol). Hydrogen peroxide (30% aqueous, 65 mL, 627 mmol) was added slowly at 0–15 °C. The reaction was stirred for 30 min, warmed to 25 °C, and monitored until complete by HPLC or TLC (approximately 2 h). [HPLC method B, t_R(hydroxy sulfides **6a** and **6b**) 16.0 min, t_R(hydroxy sulfones **7a** and **7b**) 8.58 and 9.03 min, respectively; TLC (1:1 EtOAc: hexanes R_f(hydroxy sulfoxides) 0.14, R_f(hydroxy sulfides **6a** and **6b**) 0.64, R_f(hydroxy sulfones **7a** and **7b**) 0.39)] (NOTE! The reaction is initially exothermic and is preceded by an induction period while the pertungstic acid oxidant forms. After approximately 50% of the H_2O_2 has been added the reaction will require heat to maintain the temperature.) The mixture was cooled to 0 °C and excess H_2O_2 was decomposed by the controlled addition of saturated sodium sulfide (500 mL of H_2O/60 g of Na_2SO_3). The layers were separated and the organic layer was concentrated under vacuum at 50 °C to a volume of 200 mL. The crystallizing mixture was cooled to 25 °C and diluted with hexanes (800 mL) to afford 24 g of a 93:7 mixture of alcohols **7a** and **7b** (68% from tosylate **1**): ^{1}H NMR (DMSO-d_6) δ 7.94 (d, 1 H, J = 5.1), 7.17 (d, 1 H, J = 5.1), 5.89 (d, 1 H, J = 7.2), 4.82 (ddd, 1 H, J = 7.2, J = 5.4, J = 10.5), 3.73 (m, 1 H), 3.35 (s, 1 H), 2.34 (ddd, 1 H, J = 2.3, J = 5.4, J = 14.0), 2.13 (ddd, 1 H, J = 10.5, J = 14.0), 1.34 (d, 3 H, J = 6.8). Anal. Calcd for $C_8H_{10}O_3S_2$: C, 44.02; H, 4.62; S, 29.37. Found: C, 44.10; H, 4.65; S, 29.15.

The oxidation products of the epimerized hydroxy sulfide at 24:76 cis:trans ratio did not readily crystallize and, therefore, were taken without isolation into the Ritter reaction. HPLC assay showed a 67% overall yield from tosylate **1**.

5,6-Dihydro-(*R*,*S*)-4-acetoxy-(*S*)-6-methyl-4*H*-thieno[2,3-*b*]thiopyran 7,7-Dioxide (7a,b-OAc). Hydroxy sulfone **7a,b** (24 g, 110 mmol) in THF (240 mL) was combined with acetic anhydride (23 mL, 243 mmol) and pyridine (20 mL, 247 mmol). The mixture was stirred at 25–30 °C until complete by HPLC (ca. 2 days). [HPLC method B, t_R(cis alcohol **7b**) 9.95 min, t_R(trans alcohol **7a**) 10.2 min, t_R(trans acetate **7b-OAc**) 15.7 min, t_R(cis acetate **7a-OAc**) 15.9 min; TLC (1:1 EtOAc:hexanes R_f(alcohols **6a** and **6b**) 0.24, R_f(acetates **7a-OAc** and **7b-OAc**) 0.79, R_f(pyridine 0.36]. The reaction mixture was quenched with H_2O at −10 °C, extracted with EtOAc, concentrated to dryness, and dissolved in CH_3CN (325 mL) for the next step (Ritter reaction). The yield of acetates **7a-OAc** and **7b-OAc** was 27.2 g (95%) based on a solution assay by HPLC against an external standard. As an alternative workup, the acetates were crystallized directly from EtOAc/hexane in 90% yield. Silica gel chromatography (10% EtOAc in hexanes) separated the diasteromers

for characterization. **7a-OAc**: ^{1}H NMR ($CDCl_3$) δ 7.59 (d, 1 H, J = 5.0), 6.95 (d, 1 H, J = 5.0), 6.04 (dd, 1 H, J = 5.7, J = 9.2), 3.59–3.45 (m, 1 H), 2.70–2.42 (m, 2 H), 2.16 (s, 3 H), 1.55 (d, 3 H, J = 6.9). **7b-OAc**: ^{1}H NMR ($CDCl_3$) δ 7.57 (d, 1 H, J = 5.0), 7.07 (d, 1 H, J = 5.0), 6.04 (dd, 1 H, J = 3.3, J = 3.3), 3.80 (dqd, 1 H, J = 3.5, J = 2.7, J = 6.9), 2.69 (ddd, 1 H, J = 15.7, J = 12.2, J = 3.5), 2.38 (ddd, 1 H, J = 15.7, J = 2.8), 2.09 (s, 3 H), 1.55 (d, 3 H, J = 6.9). Anal. Calcd for $C_{10}H_{12}O_4S_2$: C, 46.14; H, 4.65; S, 24.63. Found: C, 46.19; H, 4.78; S, 24.63.

***N*-(5,6-Dihydro-(*S*)-6-methyl-4*H*-thieno[2,3-*b*]thiopyran-4-yl)acetamide 7,7-Dioxide (8b) (Ritter Reaction).** Sulfuric acid (92.5 mL, 18 M, 1.67 mol) was added slowly to the acetates of **7a** and **7b** from above (27.2 g, 0.105 mol) in CH_3CN (325 mL) at −5 °C. The reaction was allowed to warm to 20–25 °C and stirred overnight [HPLC method B, t_R(acetamides **8a** and **8b**) 16.2 and 14.0 min, respectively, t_R(acetates **7a-OAc** and **7b-OAc**) 24.6 and 24.3 min, respectively]. The mixture was quenched into 1:1 ice/EtOAc (550 mL) and the pH of the mixture adjusted to 5 with NaOH. The phases were separated and the lower aqueous layer was extracted with EtOAc (100 mL). The combined organic layers were concentrated under vacuum at 50 °C to 100 mL. The acetamides crystallized spontaneously. Hexanes (300 mL) was added and the product was filtered, washed with hexanes, and dried. The yield of acetamides **8a** and **8b** was 24.4 g (89.6%) in a ratio of 75:25, respectively. **8a** + **8b**: ^{1}H NMR (DMSO) δ 8.57 (br d, 1 H, J = 8.5), 8.53 (br d, 1 H, J = 11.7), 7.96 (d, 1 H, J = 5.0), 7.94 (d, 1 H, J = 5.0), 7.03 (d, 1 H, J = 5.0), 6.95 (d, 1 H, J = 5.0), 5.21–5.14 (m, 2 H), 3.84–3.76 (m, 2 H), 2.51–2.36 (m, 2 H), 2.29–2.21 (m, 2 H), 1.84 (s, 3 H), 1.75 (s, 3 H), 1.35 (d, 3 H, J = 6.8), 1.32 (d, 3 H, J = 6.2). Anal. Calcd for $C_{10}H_{13}O_3NS_2$: C, 46.32; H, 5.05; N, 5.40; S, 24.73. Found: C, 46.41; H, 4.94; N, 5.34; S, 24.55.

The same procedure as directly above was followed for the Ritter reaction on the unisolated hydroxy sulfones **7b** and **7a** resulting from the acid-catalyzed epimerization route. After a solvent exchange from EtOAc to CH_3CN (100 mL), the cooled reaction mixture (33.5 mmol by HPLC assay) was combined with 26 mL of H_2SO_4 and treated identically to above. The yield of acetamido sulfones **8b** and **8a** (89:11 trans:cis) was 7.5 g (86%), $[\alpha]^{25}_{589}$ = −403° (*c* 1, MeOH).

Acid-Catalyzed Epimerization of Sulfones 7a and 7b Followed by Ritter Reaction. To a stirred and cooled solution of 1 g of **7a** and **7b** in THF (10 mL) was added concd H_2SO_4 (5 mL), dropwise, maintaining the temperature below 25 °C. The mixture was allowed to stand at room temperature and analyzed periodically for **7a**:**7b** ratio by HPLC. After 48 h the ratio had stabilized at 25:75 **7a**:**7b**. CH_3CN (10 mL) was added to the mixture and the reaction mass was concentrated under vacuum at 22 °C to remove approximately 5 mL of distillate (presumably THF). The concentrated reaction mixture was allowed to stand overnight and then worked up in the manner described above to afford 92% **8a** and **8b** in an 11:89 ratio.

Ritter Reaction via Olefin. With vigorous stirring, hydroxy sulfones **7a** and **7b** (1 g, 4.6 mmol) were added to 10 mL of H_2SO_4 under N_2 at −5 °C. The resulting dark solution was stirred at −5 °C until formation of the olefin (cf. eq 7) was complete by HPLC [method B, t_R(olefin) 11.0 min]. [The olefin could be isolated by quenching the solution into ice and extracting it into methylene chloride.] [A sample (oil) was chromatographed on silica gel (5% EtOAc/hexanes) for analysis: ^{1}H NMR ($CDCl_3$) δ 7.60 (d, 1 H, J = 5.0), 7.03 (d, 1 H, J = 5.0), 6.70 (dd, 1 H, J = 2.2, J = 10.1), 6.06 (dd, 1 H, J = 4.0, J = 10.1), 3.98 (dqd, 1 H, J = 2.2, J = 4.0, J = 7.4); 1.60 (d, 3 H, J = 7.4); HRMS calcd for $C_8H_9O_2S_2$ (MH^+) 201.0044, found 201.0054.] Acetonitrile (2 mL) was added slowly at −5–0 °C and the dark reaction mixture was held overnight at −5 °C followed by workup (quench and extraction) as described above. The yield of crude acetamides **8b** and **8a** (83:17 trans:cis) was 0.9 g (76%).

4-(Acetylamino)-5,6-dihydro-(*S*)-6-methyl-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonyl Chloride 7,7-Dioxide (9b). Solid acetamides **8a** and **8b** (5.3 g, 20.46 mmol) were added slowly to chlorosulfonic acid (11 mL, 166 mmol) at 0 °C. The dark solution was heated to 50 °C for 12 h to complete the initial sulfonylation. The reaction mixture was cooled to 20 °C and thionyl chloride (11 mL, 151 mmol) was added slowly at such a rate as to control the evolution of HCl gas. The mixture was heated to 50 °C until judged completed by HPLC (ca. 6 H) [method B, t_R(acetamides **8a** and **8b**) 13.6 and 14.4 min, respectively, t_R(sulfonic acids) 5.6 and 5.3 min, respectively, t_R(sulfonyl chlorides **9a** and **9b**) 14.5 and 14.4 min, respectively]. The reaction mixture was cooled to 15–20 °C and metered slowly into H_2O (330 mL) at 0–5 °C with vigorous agitation. The slurry of sulfonyl chloride was stirred for 1 h at 0–5 °C, filtered, slurry-washed with H_2O (400 mL), and sucked well to afford ca. 10 g of **9a,b** as a moist solid (ca. 40 wt % H_2O) which was used immediately in the next step: ^{1}H NMR ($CDCl_3$) δ 7.74 (s, 1 H), 8.07 (br d, 1 H, J = 8.1), 5.45–5.35 (m, 1 H), 3.63–3.56 (m, 1 H), 2.64–2.56 (m, 2 H), 2.09 (s, 3 H), 1.57 (d, 1 H, J = 6.9).

4-(Acetylamino)-5,6-dihydro-(*S*)-6-methyl-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-Dioxide (10b). Sulfonyl chlorides **9a** and **9b** were added to concentrated ammonium hydroxide (6.5 mL, 15 M, 97.5 mmol) and THF (11 mL) at −12 °C with agitation. The reaction was stirred for 1 h at 0–5 °C or until complete by HPLC [method B, t_R(sulfonamides **10a** and **10b**) 12.8 and 11.7 min, respectively]. The reaction mixture was diluted with H_2O and concentrated to remove excess ammonia and THF. Crystalline product was filtered, slurry-washed with H_2O (30 mL), and dried to afford 5.4 g (78% from acetamide sulfones **8a** and **8b**) of an 90:10 mixture of sulfonamides **10a** and **10b**: ^{1}H NMR (DMSO-d_6) δ 8.65 (br d, 1 H, J = 9.5), 8.60 (br d, 1 H, J = 9.5), 8.05 (br s, 4 H), 7.42 (s, 1 H), 7.31 (s, 1 H), 5.32–5.15 (m, 2 H), 4.10–3.80 (m, 2 H), 2.53–2.41 (m, 2 H), 2.34–2.18 (m, 2 H), 1.91 (s, 3 H), 1.87 (s, 3 H), 1.37 (d, 3 H, J = 7.0), 1.34 (d, 3 H, J = 7.6). Anal. Calcd for $C_{10}H_{14}O_5N_2S_3$: C, 35.49; H, 4.17; N, 8.28; S, 28.42. Found: C, 35.60; H, 4.04; N, 8.21; S, 28.40.

5,6-Dihydro-(*S*)-4-(ethylamino)-(*S*)-6-methyl-4*H*-thieno-[2,3-*b*]thiopyran-2-sulfonamide 7,7-Dioxide (11b) (Reduction). Acetamides **10a** and **10b** (4.0 g, 11.8 mmol) were added to a borane–dimethyl sulfide (4.8 mL, 10 M, 48 mmol) solution in THF (42 mL, K.F. <0.1 mg/mL) at <15 °C. (CAUTION! Rapid hydrogen evolution occurs as the sulfonamide protons react.) The reaction was stirred at room temperature until complete by HPLC (4–10 h) as signified by the complete disappearance of starting material [method B, t_R(cis amine **11a**) 9.95 min, t_R(trans amine **11b**) 10.2 min, t_R(trans acetamide **10b**) 15.7 min, t_R(cis acetamide **10a**) 15.9 min, t_R(presumed amine–borane complex) 20 min]. Upon completion, the reaction mixture was added to well-stirred H_2SO_4 (1.1 M, 70 mL), cooled to 0–5 °C (CAUTION! Hydrogen Evolution), and then concentrated at atmospheric pressure to remove THF (60–65 °C) until a volume of 70 mL was attained. Hydrolysis of the borate esters and amine–borane complex(s) was monitored by HPLC using the above conditions and judged complete when the later-eluting borane complex(s) had disappeared. The mixture was neutralized to pH 7.5 with NaOH, extracted with EtOAc (2 × 100 mL), and concentrated under vacuum at 35 °C to dryness. The residue was dissolved in acetone (22 mL). HPLC wt % assay showed the reaction to be quantitative: HRMS calcd for $C_{10}H_{16}N_2O_4S_3$ (M^+) 324.0272, found 324.0773. The product was then isolated as its maleate salt as shown in the following procedure.

5,6-Dihydro-(*S*)-4-(ethylamino)-(*S*)-6-methyl-4*H*-thieno-[2,3-*b*]thiopyran-2-sulfonamide 7,7-Dioxide Maleate Salt (12b). Maleic acid (1.3 g, 11.2 mmol) was added to the acetone solution of amine sulfonamides **11a** and **11b** from above at 20 °C. The crystallizing mixture was stirred overnight at 20 °C; the product was filtered, washed with fresh acetone (10 mL), and dried. HPLC analysis showed the product to contain a mixture of 98:2 trans:cis isomers **11b** and **11a** [method C, t_R(sulfonamides **11a** and **11b**) 12.8 and 11.7 min, respectively]. The yield of product was 4.3 g (92%) based on HPLC analysis which showed <2% cis isomer **11a**: $[\alpha]^{25}_{405}$ = −36.2° (*c* 1, MeOH); ^{1}H NMR (DMSO-d_6) δ 8.17 (br s, 2 H), 7.81 (s, 1 H), 6.05 (s, 2 H), 4.61 (br s, 1 H), 4.08–4.00 (m, 1 H), 3.24–3.14 (m, 1 H), 3.06–2.93 (m, 1 H), 2.7–2.45 (m, 2 H), 1.39 (d, 3 H, J = 6.7), 1.20 (t, 3 H, J = 7.1). Anal. Calcd for $C_{14}H_{20}N_2O_8S_3$: C, 38.17; H, 4.58; N, 6.39; S, 21.83. Found: C, 38.19; H, 4.58; N, 6.29; S, 21.60.

5,6-Dihydro-(*S*)-4-(ethylamino)-(*S*)-6-methyl-4*H*-thieno-[2,3-*b*]thiopyran-2-sulfonamide 7,7-Dioxide Hydrochloride Salt (13b) (MK-0507). Crude maleate from above containing <2% cis isomer (3.7 g, 7.6 mmol) and ca. 10 wt % acetone solvate was stirred with EtOAc (50 mL) and and saturated $NaHCO_3$ (16 mL) at 25 °C until both phases became clear. The aqueous layer

was separated and back extracted with EtOAc (50 mL), and the combined organic layers were stirred with concentrated HCl (0.63 mL, 12 N, 7.6 mmol). The mixture was concentrated under vacuum at a 45 °C bath temperature to remove H_2O to a volume of 30 mL. The thick slurry was filtered and washed with fresh EtOAc to afford 2.6 g of MK-0507 (**13b**) in 95% yield (32% overall from methyl (*R*)-3-hydroxybutyrate). Recrystallization from H_2O (7 mL) afforded pharmaceutically acceptable product free of the minor cis contaminant as a hemihydrate: HPLC area % 99.9 at 254 nm; 99.6 wt % against an external standard; chirality 99.96% *S*:0.04% *R* [Pirkle (*S*)-phenylglycine column, eluent 9:1 water (0.1% H_3PO_4 v/v):MeOH]; $[\alpha]^{25}_{589} = -17.1°$ (*c* 1, H_2O); IR (cm^{-1}) 3372, 3046, 2691, 2455, 2372, 1590, 1535, 1345, 1306, 1159, 1133; UV A 1% 1 cm – 339 at 254 nm (0.1 N HCl/MeOH); TG 2.3% single step wt loss to 130 °C; mp DSC 238 °C dec at 2 °C/min ramp; ^1H NMR (DMSO-d_6) δ 9.91 (br s, 1 H), 9.63 (br s, 1 H), 8.21 (s, 2 H), 8.02 (s, 1 H), 4.68 (br s, 1 H), 4.37 (m, 2 H), 3.19 (br s, 1 H), 3.04 (br s, 1 H), 2.80 (d, 1 H), 2.55 (m, 1 H), 1.39 (d, 3 H), 1.29 (d, 3 H); ^{13}C NMR (DMSO-d_6) 149.7 (s), 141.9 (s), 137.4 (s), 130.7 (s), 51.6 (s), 49.2 (s), 40.8 (s), 30.7 (s), 11.1 (s), 10.0 (s). Anal. Calcd for $C_{10}H_{17}ClN_2O_4S_3$: C, 33.28; H, 4.75; N, 7.76; S, 26.66; Cl 9.84. Found: C, 33.33; H, 4.70; N, 7.67; S, 26.60; Cl, 9.77.

Ritter Reactions and Reductions on Desmethyl Analogues. (*R*)-(+)-5,6-Dihydro-4-(ethylamino)-4*H*-thieno[2,3-*b*]thiopyran 7,7-Dioxide (16R). [Enantiomeric excesses of the resulting acetamido products described below were determined by reducing the entire crude product mixtures to the corresponding amines. The amines were then converted quantitatively to their trifluoroacetamides and assayed by chiral HPLC.] Results are presented in Table III. To a stirred solution of (*R*)-(+)-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-4-ol 7,7-dioxide[5] (0.5 g, 2.5 mmol) in 20 mL of CH_3CN and 10 mL of methylene chloride at 0–2 °C under an N_2 atmosphere was added 5 mL of 98% H_2SO_4. The resulting solution was allowed to warm to room temperature, stirred overnight, and then poured (quenched) into 75 mL of a 1:1 ice:EtOAc mixture. The aqueous layer was separated and exhaustively extracted with EtOAc. The combined organic extracts were washed with saturated sodium bicarbonate solution containing 5% sodium chloride, dried over dry sodium sulfate, and concentrated to dryness. The residual solid acetamido Ritter product was flush concentrated with dry THF to 10 mL and K.F. <0.1 mg/mL. The solution was then treated with borane–dimethyl sulfide complex (1 mL, 10 M, 10 mmol) with cooling. The mixture was allowed to warm to room temperature and stirred. [HPLC method B, t_R(ethylamine derivative) 6.0 min, t_R(acetamido derivative) 7.2 min, t_R(hydroxy derivative) 6.3 min, t_R(trifluoroacetyl derivative) 15 min]. The reduction mixture was slowly poured (quenched) into 1 M H_2SO_4 with cooling and stirring. After an atmospheric distillation of THF and adjustment of the mixture to pH 8 with NaOH, the mixture was extracted with EtOAc. The layers were separated and the aqueous layer was further extracted with additional EtOAc. The combined organic extracts were concentrated to an oil and the residue flush was concentrated with EtOAc until a small volume of dry solution was obtained which was then treated with trifluoroacetic anhydride (0.5 mL, 3 mmol). The formation of the trifluoroacetamide was confirmed by TLC [EtOAc/hexane 1:1, R_f(hydroxy sulfone) 0.3, R_f(ethylamino sulfone) 0.2, R_f(trifluoroacetamido derivative) 0.7, R_f(tosyl sulfone) 0.8]. An aliquot was evaporated to dryness and diluted with 1:1 THF:IPA for chirality assessment by HPLC [HPLC conditions: Chirosphere column (1.5 mL/min, hexane:THF:IPA 88:11:1; t_R((*R*)-ethylamide) 15.6 min and t_R((*S*)-ethylamide) 17.7 min at 4:1 *R*:*S* ratio, respectively.] The intermediate Ritter product and ethylamine compounds were isolated in near quantitative yields in subsequent experiments.

Acetamide 16R: ^1H NMR (DMSO-d_6) δ 8.54 (br d, 1 H, J = 8.7), 7.95 (d, 1 H, J = 5.1), 7.00 (d, 1 H, J = 5.1), 5.20 (m, 1 H), 3.80–3.55 (m, 1 H), 2.57–2.22 (m, 2 H), 1.88 (s 3 H); HRMS calcd for $C_9H_{12}NO_3S_2$ (MH^+) 246.0259, found 246.0221.

Ethylamino sulfone (recrystallized as HCl salt): ^1H NMR (DMSO-d_6) δ 7.91 (d, 1 H, J = 5.0), 7.21 (d, 1 H, J = 5.0), 3.95 (dd, 1 H, J = 6.2, J = 4.7), 3.78–3.60 (m, 2 H), 3.60–3.42 (m, 2 H), 2.69–2.25 (m, 4 H), 1.03 (t, 3 H, J = 7.0). Anal. Calcd for $C_9H_{14}NClO_2S_2$: C, 40.36; H, 5.27; N, 45.23. Found: C, 40.01; H, 5.39; N, 5.14.

(*S*)-(–)-5,6-Dihydro-4-(ethylamino)-4*H*-thieno[2,3-*b*]thiopyran 7,7-Dioxide (16S). In order to confirm assignment of optical configuration, the (*S*)-enantiomer was prepared by an independent route of inversion. To a cooled solution of (*R*)-(+)-5,6-dihydro-4*H*-thieno[2,3-*b*]thiopyran-4-ol 7,7-dioxide[4] (1 g, 4.9 mmol) in THF (25 mL) was added 5 mL of a solution of 1.0 M lithium bis(trimethylsilyl)amide in THF. After a 30-min age *p*-toluenesulfonic anhydride (1.77 g, 5.4 mmol) was added at 0 °C. After 2 h at 22 °C, complete conversion was observed by TLC (EtOAc:hexane 1:1, R_f 0.7). Ethylamine (5 mL, 3.4 g, 76.6 mmol) was added at 0–5 °C and the solution was warmed to room temperature and stirred overnight. The mixture was partitioned between H_2O and EtOAc at pH 3 to remove a neutral impurity (*N*-ethyl-*p*-toluenesulfonamide). The aqueous layer was neutralized with solid bicarbonate and extracted with EtOAc (2 × 50 mL), and the combined organic extracts were concentrated to dryness. Derivatization with trifluoroacetic anhydride (see above) afforded the corresponding trifluoroacetamides for enantiomeric comparison with the previous experiment. The major product peak assigned as the (*S*)-trifluoroacetamide enantiomer 16 (98%) at 17.7 min was shown to be coincidental with the minor peak from the Ritter procedure described above. The EtOAc derivatization solutions from the above two experiments were also adjusted to the same molar concentrations by quantitative HPLC assay and evaluated in a polarimeter, the Ritter product showing a 60% positive (+) rotation of the negative (–) rotation magnitude shown by the inversion product, thus confirming the chiral assay of 60% ee.

(*R*)-(+)-5,6-Dihydro-*N*-(2-methylpropyl)-4*H*-thieno[2,3-*b*]thiopyran-4-amine 7,7-Dioxide (18). This opposite enantiomer of the key intermediate in the synthesis of MK-417[4] was prepared by the same Ritter procedure as above. (*R*)-(+)-5,6-Dihydro-4*H*-thieno[2,3-*b*]thiopyran-4-ol 7,7-dioxide[4] (0.3 g, 1.47 mmol) was combined with 10 mL of isobutyronitrile, 5 mL of methylene chloride, and 2.5 mL of H_2SO_4 as described above. After reaction completion and the usual workup, 10% of the crude product was set aside for characterization (HPLC assay, NMR), the remainder being reduced to the corresponding amino compound with borane–dimethyl sulfide by the aforementioned procedure. Prior to isolation of the isobutylamino sulfone (98% by HPLC), a 10% aliquot of this reaction mixture was sequestered for product chirality assessment. Trifluoroacetamide derivatization and ee determination HPLC (Chirasphere column) showed a 2:1 mixture of *R*:*S* enantiomers as compared to an authentic sample of the *S* enantiomer similarly prepared by the inverstion route.

Amide 18: ^1H NMR (DMSO-d_6) δ 8.41 (br d, 1 H, J = 8.7), 7.94 (d, 1 H, J = 5.1), 6.92 (d, 1 H, J = 5.1), 5.27–5.12 (m, 1 H), 3.80–3.58 (m, 2 H), 2.52–2.22 (m, 4 H), 1.05 (d, 3 H, J = 6.9), 1.00 (d, 3 H, J = 6.9); HRMS calcd for $C_{11}H_{16}NO_3S_2$ (MH^+) 274.0572, found 274.0579.

Amine 18: ^1H NMR (DMSO-d_6) δ 7.91 (d, 1 H, J = 5.1), 7.22 (d, 1 H, J = 5.1), 3.99 (br s, 1 H), 3.78–3.60 (m, 2 H), 3.60–3.42 (m, 2 H), 2.52–2.23 (m, 4 H), 1.72–1.55 (m, 1 H), 0.90 (d, 6 H, J = 6.8).

The *n*-propylamino analogue 17 was prepared via the same method, affording a 3:1 *R*:*S* ratio from *n*-propionitrile. **Amide 17**: ^1H NMR ($CDCl_3$) δ 7.54 (d, 1 H, J = 5.1), 6.95 (d, 1 H, J = 5.1), 6.44–6.31 (m, 1 H), 5.40–5.24 (m, 1 H), 3.52–3.30 (m, 1 H), 2.78–2.61 (m, 1 H), 2.60–2.40 (m, 1 H), 2.27 (q, 2 H, J = 7.6), 1.19 (t, 3 H, J = 7.6); HRMS calcd for $C_{10}H_{13}NO_3S_2$ (MH^+) 260.0415, found 260.0431.

Amine hydrochloride 17: ^1H NMR (D_2O) δ 8.01 (d, 1 H, J = 5.1), 7.36 (d, 1 H, J = 5.1), 4.90–4.75 (m, 1 H), 3.94–3.68 (m, 2 H), 3.14 (t, 2 H, J = 7.6), 3.09–2.78 (m, 1 H), 1.74 (septet, 2 H, J = 7.6), 0.98 (t, 3 H). Anal. Calcd for $C_{10}H_{16}NClO_2S_2$: C, 42.62; H, 5.72; N, 4.97. Found: C, 42.59; H, 5.58; N, 4.67.

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