An Asymmetric Synthesis of MK-0417. Observations on Oxazaborolidine-Catalyzed Reductions

Todd K. Jones,* Julie J. Mohan,† Lyndon C. Xavier, Thomas J. Blacklock,* David J. Mathre, Paul Sohar, E. Tracy Turner Jones, Robert A. Reamer, F. E. Roberts, and E. J. J. Grabowski

Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065-0900

Received April 20, 1990

Enantiomerically pure MK-0417 has been prepared in nine steps from thiophene. The key reactions in the sequence were an oxazaborolidine-catalyzed borane reduction followed by a tosylation/amine displacement. The borane reduction was studied in detail, and observations regarding substituents on the oxazaborolidine catalyst and the intricacies of the reaction are reported, as well as a mild method for recovering the enantiomerically pure amino alcohol derived from the catalyst.

Introduction

MK-0417[1] (the *S* enantiomer of MK-927, Scheme I) is a water-soluble carbonic anhydrase inhibitor (CAI). CAI's reduce intraocular pressure (IOP) and have been used therapeutically for treating glaucoma patients. Undesirable side effects that have been observed with oral administration of CAI's can be avoided by employing topical application,[2] an advantage the physical properties (binding ability, lipophilicity, water solubility)[1a] of MK-0417 offer. For developmental purposes, we required a practical multigram synthesis of MK-0417.

Our retrosynthesis of MK-0417 is shown in Scheme I. The cornerstone of this approach is the introduction of chirality: an asymmetric reduction of a ketone followed by activation and S_N2 displacement with isobutylamine. The sulfonamide is installed late in the synthesis because it presents solubility problems for intermediates in organic solvents. Our observations on the synthesis of MK-0417 by this route are detailed below.

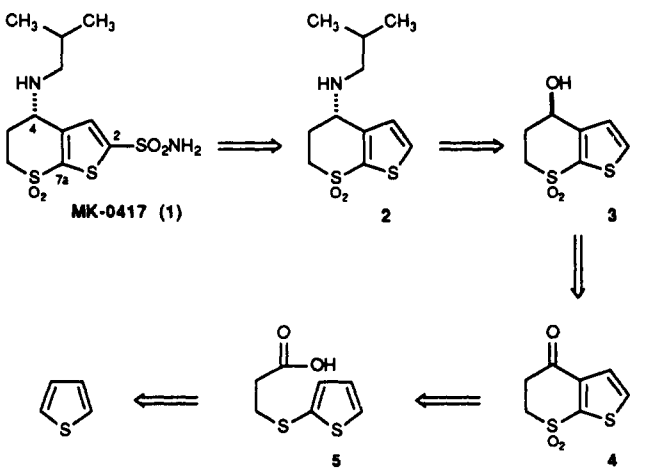
Ketosulfone Preparation. The ketosulfone was prepared as shown in Scheme II. Lithiation of thiophene[3] followed by addition of powdered sulfur resulted in formation of (lithiothio)thiophene (6). The reaction mixture was quenched by the addition of water and alkylated with the potassium salt of 3-bromopropionic acid resulting in formation of carboxylic acid 5. Lithiomercaptothiophene was not isolated; the lithiation/sulfurization was probably responsible for some of the impurities[4] isolated after cyclization (vide infra).

Cyclization was initially accomplished by preparing the acid chloride followed by treatment with tin tetrachloride. While this procedure worked reasonably well, the product (7) was always contaminated with several colored impurities. A superior cyclization protocol was therefore developed using trifluoroacetic anhydride (TFAA).[5] This method routinely provided 7 in good yield as a low-melting solid free from the intensely colored byproducts.

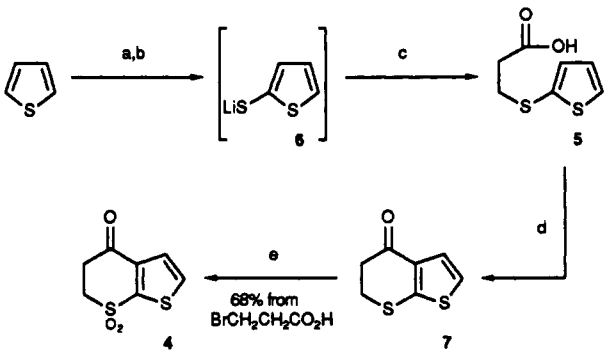
Oxidation of sulfide 7 to sulfone 4 was accomplished with hydrogen peroxide/sodium tungstate.[6] Ketosulfone 4 was chosen as a substrate for examination of asymmetric reductions because, if necessary, it could be readily purified by recrystallization from methanol.[7]

Asymmetric Reduction. Three common asymmetric reducing agents were screened for reducing 4 to alcohol 3: (−)-*B*-chlorodiisopinocampheylborane[8] (IPC_2BCl; 12:88, *R*:*S*),[9] yeast[10] (11:89, *R*:*S*), and borane-catalyzed by oxazaborolidine 8a[11] (10 mol%; eq 1, R = Ph, R′ = CH_3; 90:10, *R*:*S*). Since separation of IPC_2BCl reaction products from our substrate on large scale would be difficult and yeast gave the undesired enantiomer, we chose to optimize the oxazaborolidine-catalyzed borane reduction. This reduction offers two advantages: (1) the asymmetry is induced

Scheme I



Scheme II[a]



[a] (a) *n*-BuLi, THF, 0 °C; (b) S_8, THF, <20 °C; (c) $BrCH_2CH_2CO_2H$, K_2CO_3, H_2O, THF, 20 °C; (d) TFAA, toluene, 20 °C; (e) $NaWO_4 \cdot H_2O$, H_2O_2, EtOAc, 40 °C.

† Current address: Glaxo, Inc., 5 Moore Drive, Research Triangle Park, NC 27709.

(1) (a) Baldwin, J. J.; Ponticello, G. S.; Anderson, P. S.; Christy, M. E.; Murcko, M. A.; Randall, W. C.; Schwam, H.; Sugrue, M. F.; Springer, J. P.; Gautheron, P.; Grove J.; Mallorga, P.; Viader, M.-P.; McKeever, B. M.; Navia, M. A. *J. Med. Chem.* **1989**, *32*, 2510-2513. (b) Ponticello, G. S.; Freedman, M. B.; Habecker, C. N.; Lyle, P. A.; Schwam, H.; Varga, S. L.; Christy, M. E.; Randall, W. C.; Baldwin, J. J. *J. Med. Chem.* **1987**, *30*, 591-597.

(2) (a) Vogel, R. *Research and Clinical Forums* **1989**, *2*, 87-91. (b) Bron, A. M.; Lippa, E. A.; Feicht, B. I.; Hofmann, H. M.; Roger, J. G.; Brunner-Ferber, F. L.; Panebianco, D. L. *Archives of Ophthalmology* **1989**, *107*, 1143-1146. (c) Lippa, E. A.; von Denffer, H.; Hofmann, H. M.; Brunner-Ferber, F. L. *Archives of Ophthalmology* **1988**, *106*, 1694-1696.

(3) (a) Jones, E.; Moodie, I. M. *Organic Syntheses* **1970**, *50*, 104-106. (b) Wakefield, B. J. In *Organolithium Methods*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Academic Press: New York, 1988; pp 38-39.

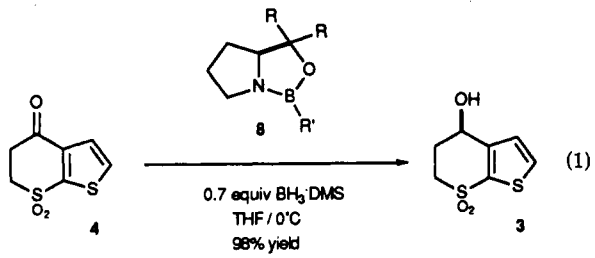
0022-3263/91/1956-0763$02.50/0

Table I. Effect of Water on the Oxazaborolidine-Catalyzed Reduction of 4[a]

H_2O (μg/mL THF)	R:S
41	97.5:2.5
103	78:22
396	75:25

[a] Ketone concentration 70 mg/mL.

catalytically and (2) the catalyst required for MK-0417 is derived from natural proline.



Initially, we obtained erratic results from the oxazaborolidine[12] catalyzed reduction: from 3:1 to 50:1 selectivity, regardless of order or time of addition of borane and ketone to the catalyst in tetrahydrofuran. Neat borane–methyl sulfide complex (BMS) was substituted for commercial solutions of BMS or borane–tetrahydrofuran complex (BH_3·THF) because we found commercial samples gave widely variable results (presumably due to decomposition from adventitious water, vide infra) with the same sample of ketone 4. After examining all of the possible modes of addition, we settled on adding the catalyst (solid or in toluene solution) to the ketone in tetrahydrofuran, cooling to −15 °C, and then adding BMS at a rate to maintain the temperature below −10 °C. This protocol *generally* provided >93% of the desired enantiomer; however, further investigation was mandatory for our needs.

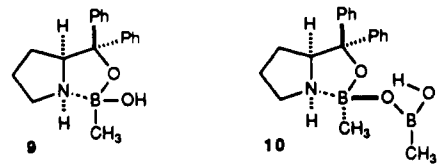


Figure 1.

As indicated in Table I, intentional addition of water to the rection with pure ketone 4 proved deleterious. Remarkably, the amount of water required to lower the enantiomeric excess from 95% to 50% is approximately 1 mg of water per 1 g of 4. With this information in hand, we routinely dried the ketone in tetrahydrofuran over 4- or 5-Å molecular sieves prior to reduction until a Karl-Fisher titration showed the water content to be less than 40 μg/mL (ketone concentration = 70 mg/mL). This drying procedure reproducibly provides ≥95:5 selectivity. However, the sieves must be removed prior to reduction or the enantioselectivity is low. After drying over molecular sieves and decantation, the catalyst was added and the reduction was carried out as previously described. Since small amounts of residual methanol from recrystallization do not affect the level of asymmetric induction, we postulate that boronic acid or anhydride species are responsible for the decay in selectivity rather than simple hydrolysis of the catalyst. Nevertheless, exactly how water or boronic acids/anhydrides affect the mechanism is not completely understood.[13,14]

Further, we were concerned that methylboronic acid, trimethylboroxine, diphenylprolinol, benzophenone, **9**, or **10** (Figure 1) could be in the catalyst we were using.[15] Separate addition of 2 mol % diphenylprolinol, 2 mol % methylboronic acid, 1 mol % triphenylboroxine, or 1 mol % benzophenone (based on ketone) to reaction mixtures prior to the addition of BMS resulted in diminished enantioselectivity: 85:15 for the first two reactions, 92:8 for the third and 96:4 for the fourth. Compounds **9** and **10** were screened as catalysts (10 mol %) and provided enantioselectivities of 79:21 and 86:14, respectively, with ketone 4.[16] With good catalyst and ketone there was limited variability in enantioselectivity (95–99% *R* isomer), and that has been attributed to the quality of the catalyst employed.[15]

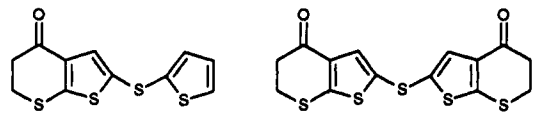
In order to test the generality of our reaction conditions and catalyst[15] we examined the reduction of several ketones as shown in Table II. All reactions in Table II were performed on 1 g of ketone (sieve dried until the residual water content was less than 25 μg/mL) in 14 mL of tetrahydrofuran with 10 mol % of catalyst and 0.7 equiv of BMS (~0.6 M in tetrahydrofuran, added at a rate to maintain the internal temperature at −15 °C). Once the reactions were complete, as judged by analytical thin layer

(4) For some interesting chemistry of mercaptothiophene, see: Ponticello, G. S.; Habecker, C. N.; Varga, S. L.; Pitzenberger, S. M. *J. Org. Chem.* **1989**, *54*, 3223–3224.

(5) Olah, G. A. *Friedel-Crafts and Related Reactions, Vol. III*; Interscience Publishers: New York, 1964; p 914.

(6) (a) Schultz, H. S.; Freyermuth, H. B.; Buc, S. R. *J. Org. Chem.* **1963**, *28*, 1140–1142. (b) Connon, N. W. *Eastman Organic Chemical Bulletin* **1972**, *44*, 1–4. (c) Giam, C. S.; Kikukawa, K.; Trujillo, D. A. *Org. Prep. and Proc. Int.* **1981**, *13*, 137–140. (d) Blacklock, T. J.; Butcher, J. W.; Sohar, P.; Lamanec, T. R.; Grabowski, E. J. J. *J. Org. Chem.* **1989**, *54*, 3907–3913.

(7) The following two impurities were isolated from 7 (<5%) and 4 (<2%), respectively, and identified by MS and NMR:



(8) Chandrasekharan, J.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 5448–5450.

(9) Enantiomeric purity was judged by preparation of an (*R*)-Mosher ester followed by GC analysis. The enantiomeric purity of the (*R*)-MTPA (Aldrich) used to prepare the acid chloride was determined to be 99.4% by derivatization with (4*S*)-4-(phenylmethyl)-2-oxazolidinone (>99.9% ee). The enantiomeric purity of the (*S*)-MTPA was found to be lower (97.4%). See the Experimental Section and the following: (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549. (b) Jeanneret-Gris, G.; Pousaz, P. *Tetrahedron Lett.* **1990**, *31*, 75–76.

(10) For a leading reference, see: Seebach, D.; Sutter, M. A.; Weber, R. H.; Züger, M. F. *Org. Synth.* **1984**, *63*, 1–9.

(11) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926. (b) Itsuno, S.; Sakurai, Y.; Ito, K.; Hirao, A.; Nakahama, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 395–396.

(12) All reactions for evaluating reaction conditions were run with 10 mol % catalyst. We found that for preparative purposes this could be reduced to 5 mol % with no deleterious effect. However, below 4 mol % uncatalyzed reduction became competitive.

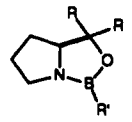
(13) Recrystallized **4** is 64% reduced by BMS (no catalyst) at 0 °C after 24 h under anhydrous conditions; recrystallized **4** plus 2 mol % water is 78% reduced by BMS (no catalyst) at 0 °C after 24 h. Following catalyzed reductions by capillary GC showed that, even in the presence of 100 μg/mL of water, the catalyst was still intact. This may be misleading due to reaction on the injector, however, since **9** is unstable in solution.[14]

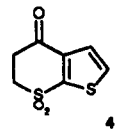
(14) Simple addition of methylboronic acid to **8a** to afford structure **10** could account for the diminished selectivity. However, **10** is a much less efficient catalyst (vide infra).

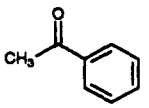
(15) A concurrent investigation into the nature of the catalyst was also undertaken; for preparation of the catalyst and a discussion of its quality and probable impurities, see: Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Jones, E. T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.*, preceding paper in this issue.

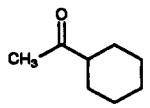
(16) Reaction with **9** and **10** as catalysts required hours for completion at 0 °C rather than the usual 30 min at −15 °C.

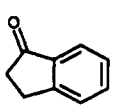
Table II. Enantiomeric Ratios of Alcohols Derived from Substituted Oxazaborolidine-Catalyzed Borane Reductions of Ketones[a-c]

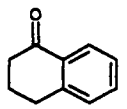

catalyst

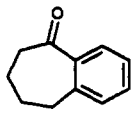

4


11


12


13


14


15

entry	cat. no.	R′	R	4	11	12	13	14	15
1	**8a**	Me	Ph	98:2	99:1	82:18	98:2	97:3	99:1
2	**16a**	Me	4-F	97:3	84:16	85:15	97:3	94:6	-
3	**17a**	Me	4-Cl	97:3	90:10	82:18	96:4	94:6	95:5
4	**18a**	Me	4-Me	96:4	86:14	83:17	95:5	95:5	88:12
5	**19a**	Me	4-CF_3	98:2	95:5	88:12	96:4	96:4	89:11
6	**20a**	Me	4-*t*-Bu	95:5	93:7	84:16	98:2	91:9	82:18
7	**21a**	Me	4-MeO	97:3	95:5	84:16	95:5	97:3	89:11
8	**22a**	Me	3-Cl	96:4	93:7	86:14	96:4	98:2	92:8
9	**23a**	Me	3,5-Cl	96:4	90:10	80:20	92:8	95:5	88:12
10	**24a**	Me	3,5-Me	96:4	97:3	86:14	96:4	97:3	95:5
11	**25a**	Me	2-naphth	96:4	89:11	82:18	96:4	96:4	89:11
12	**8b**	Bu	Ph	93:7	96:4	88:12	95:5	98:2	89:11
13	**8c**	Ph	Ph	98:2	86:14	77:23	91:9	97:3	95:5
14	**8d**	4-F	Ph	99:1	94:6	76:24	88:12	97:3	92:8
15	**8e**	4-Cl	Ph	98:2	87:13	72:38	86:14	94:6	96:4
16	**8f**	4-Me	Ph	99:1	94:6	81:19	92:8	97:3	94:6
17	**8g**	4-MeO	Ph	97:3	85:15	76:24	92:8	95:5	94:6
18	**8h**	mesityl	Ph	76:24	-	-	-	-	-

[a] All reactions were performed as described in the text. [b] R refers to aromatic groups substituted as described unless simply noted as phenyl; R′ refers to alkyl or substituted phenyl. [c] Enantiomeric ratios were determined by GC analysis of Mosher esters on column A for **4**, **12**, **13**, and **14** and on column B for **11** and **15** (see the Experimental Section).

chromatography, methanol was added and a sample was removed for analysis.[9]

As evidenced by the data in Table II, our conditions allow for the reproducible enantioselective reduction of a variety of ketones. Ketone **14** (α-tetralone, entry 1) is noteworthy for the direct comparison with ref 11 where a 91.6:8.4 ratio was reported for similar reaction conditions.[11a,17] Also notable is the lack of a significant electronic effect on substitution of the phenyl groups on diphenylprolinol. Interestingly, the cheaper and more readily available phenyl and substituted phenylboronic acids can be employed with tetralone and ketone **4** with good results. No significant electronic effect was observed with substitution on the boron-bearing phenyl. However, catalysts with phenyl groups attached to the boron were not as effective for the other ketones we screened.

Contrary to the hypothesis of the Harvard group,[18] our data indicate that the postulated transition-state assembly[11a,18] does not fully explain the observed results (Table II and the control experiments). Upon inspection of models of the proposed transition-state assembly, one would not predict that the larger *B*-phenyl group would fit endo to the 3.3.0 ring system as well as a *B*-methyl (1,3 interactions are encountered). Since the *B*-alkyl substituent can be as bulky as phenyl and still be an effective catalyst, one could argue that contact between the ketone and the weakly Lewis basic boron is minimized. Unfortunately, the studies required to thoroughly understand the nature of the asymmetric induction are beyond the scope of this investigation.

Once the reaction was complete, the problem of isolating alcohol **3** and separating diphenylprolinol remained. Simple aqueous acid extraction failed. Precipitation of the HCl salt of diphenylprolinol by addition of anhydrous HCl was ruled out because of the sensitivity of **4** to acid. We therefore developed an alternate nonaqueous isolation protocol. The excess borane was quenched with methanol and the volatile boron compounds were removed by distillation. Filtration through SuperCel removed the remaining boron species. We initially envisioned batch treatment of the resulting methanol solution with a sulfonic acid resin to complex diphenylprolinol. While this procedure effects separation, unfortunately even carboxylic acid resins racemize **3**. Fortunately, the ammonia form[19] of Amberlyst 15 did not racemize **3**. Eluting the alcohol/diphenylprolinol mixture in methanol through a column packed with the ammonia form of Amberlyst 15 resulted in clean separation with diphenylprolinol being retained. Diphenylprolinol was easily recovered by passing a solution of 6% concentrated aqueous ammonia in methanol through the column—reactivating the column for future use in the process. Employing this procedure (3 mL resin/g alcohol) we have separated reaction mixtures on kilogram scale and recovered 99% of **3** and 95% of diphenylprolinol. This protocol has three advantages: (1) acid-sensitive substrates are not affected, (2) the alcohol and diphenylprolinol are recovered in high yield, and (3) few manipulations are required.

The resulting purified alcohol could either be directly isolated or concentrated, diluted with tetrahydrofuran, and concentrated to provide a tetrahydrofuran solution for use in the next step. The latter is preferable for our purposes.

Activation/Displacement. The installation of the isobutylamine substituent was envisioned as a straightforward displacement of an activated alcohol. After initial attempts at preparing a mesylate or tosylate failed, the activation was studied in detail.

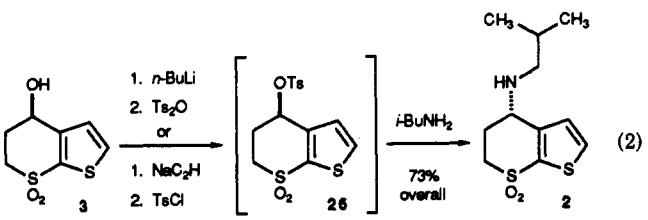
(17) We observed that neat α-tetralone (Aldrich) had a water content of ~1.2 mg/mL.

(18) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553. (b) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861–2863. (c) Corey, E. J.; Chen, C.-P.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5547–5550. (d) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1989**, *30*, 6275–6278. (e) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1990**, *31*, 601–604. (f) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611–614.

(19) For a discussion of ion exchange columns in general, see: Hale, D. K. In *Ion Exchangers in Organic and Biochemistry*; Calmon, C., Kressman, T. R. E., Eds.; Interscience Publishers, Inc.: New York, 1957; pp 173–174.

Tosylation of 3 under standard conditions (TsCl/pyridine) formed large amounts of chloride. Since pyridinium hydrochloride was responsible for chloride formation, we felt amine bases in general were undesirable. We therefore examined stoichiometric deprotonation of the alcohol followed by addition of toluenesulfonyl chloride (TsCl). Lithium and magnesium salts (prepared in tetrahydrofuran at 0 °C) with TsCl produced small (10–20%) and large (100%) amounts of chloride, respectively.

The sodium salt, generated with sodium hydride, provided the desired tosylate free from chloride, albeit with low conversion. The sodium salt prepared under these conditions formed an unstirrable gummy solid in tetrahydrofuran and dimethoxyethane.[20] If TsCl and 3 were added simultaneously to NaH, the tosylation would still not go to completion.[21] Two solutions to this problem were developed. The first was to use the lithium salt (generated either with lithium bis(trimethylsilyl)amide or *n*-butyllithium) and toluenesulfonic anhydride as shown in eq 2. This procedure cleanly provided the desired tosylate in >95% yield. While this is an acceptable solution, toluenesulfonic anhydride (Ts_2O) is not available in the quantities we desired.[22]

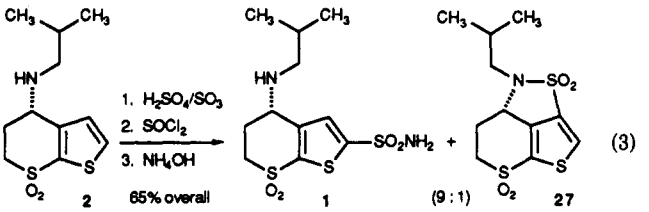


(2)

Several other sodium bases were examined,[23] including sodium bis(trimethylsilyl)amide and sodium acetylide. Although the sodium salts in both cases were easily stirred in tetrahydrofuran, sodium bis(trimethylsilyl)amide was ruled out because small amounts of chloride were formed upon addition of TsCl.[24] The best solution to this problem was sodium acetylide, commercially available as a slurry in xylenes/light mineral oil. The combination of sodium acetylide and TsCl cleanly provided tosylate in high yield. However, 26 should not be isolated since it readily undergoes solvolysis in water to form racemic 3.

The S_N2 displacement was effected by addition of 8–14 equiv of isobutylamine followed by stirring at room temperature for ~12 h. Considering the lability of the tosylate, it is noteworthy that this reaction underwent clean displacement with insignificant loss in stereochemical integrity (a 97:3 mixture of 3 provided a 4:96 mixture of 2).[25] After extractive isolation amine 2 was crystallized from 2-propanol to provide material with an enantiomeric purity of >99:1. The overall tosylation/displacement sequence using either *n*-BuLi/Ts_2O or sodium acetylide/TsCl (starting with a 95:5 mixture) provided a 73% yield of >99:1 (*S*:*R*) amine after recrystallization.

Sulfonamide Installation. The thiophene ring of amine 2 is sufficiently deactivated that forcing conditions are required for electrophilic substitution. Chlorosulfonic acid as solvent at 60 °C produced an 80:20 mixture of regioisomers. Fuming sulfuric acid (oleum) produced a 90:10 mixture of isomers at 5–8 °C over 2 h as shown in eq 3. Acid chloride formation was accomplished by addition of a large excess of thionyl chloride followed by reflux.[26] The excess thionyl chloride was removed by distillation, and the resulting solution was cautiously quenched into cold tetrahydrofuran/aqueous ammonia to provide MK-0417 and tricycle 27.



(3)

By monitoring this reaction with ^1H NMR,[26] we observed the formation of individual sulfonic acids (at C_2 and C_3) followed by sulfonyl chlorides. This suggests that 27 was produced via direct electrophilic aromatic substitution followed by cyclization, not prior sulfonylation of the nitrogen followed by aromatic substitution. Separation of 1 and 27 was accomplished by aqueous extraction and crystallization of the HCl salt of MK-0417. The HCl salt was recrystallized from water to provide the pure hemihydrate salt in 65% overall yield from amine 2.

This process provided MK-0417 (isolated as its hydrochloride salt hemihydrate) in nine steps, 30% overall yield from bromopropionic acid, with ≥95% enantioselectivity.

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 and by dipping in an aqueous ceric ammonium molybdate solution followed by heating. Analytical gas chromatography (GC) was performed on Hewlett-Packard 5890 chromatograph fitted with a flame ionization detector (He carrier gas). Columns: (A) 0.32 mm × 30 m DB-1 (15 lbs/in.^{2}, ~30:1 split); (B) 0.32 mm × 30 m DB-23 (15 lbs/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 Hewlett-Packard 1050 chromatograph. Columns: (A) 4.6 × 250 mm Zorbax RX; (B) 4.6 × 250 mm Chirasphere; (C) 4.1 × 250 mm Altex C-8, 5 μm ultrasphere. Solvents for extraction were reagent grade. Solvents for reactions were dried with 3- or 4-Å molecular sieves. Residual water content was determined by Karl-Fischer titration. All reactions were performed under an inert atmosphere of dry nitrogen in dry glassware, (*R*)-MTPA[9] (Aldrich) was converted to the acid chloride using oxalyl chloride (1.2 equiv) and catalytic *N*,*N*-dimethylformamide (0.05 equiv) in dichloromethane at room temperature for 4 h followed by filtration and distillation (80–83 °C, 0.50 Torr).

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*

(20) Use of other solvents was ruled out because they were detrimental to the S_N2 displacement.

(21) Deprotonation of 3 with NaH in THF is an unreliable reaction regardless of temperature or presence of TsCl. The presence of mineral oil or concentration of NaH (99%, 80% or 60%) had no effect. Because of the gumming problem, the reactions frequently would not go to completion.

(22) Methanesulfonic anhydride was not a satisfactory substitute in this reaction.

(23) Potassium bases, including potassium bis(trimethylsilyl)amide and potassium hydride, did not cleanly provide 25.

(24) The chloride is probably due to bis(trimethylsilyl)amine reacting with the small excess of TsCl employed.

(25) Enantiomeric purity was judged by preparation of a trifluoroacetamide followed by HPLC analysis on a ChiraSpher column, see the Experimental Section. The disparity in stereochemical integrity may well reflect the difference in analytical techniques, since enantiomeric purity of 3 was judged by a capillary GC assay (i.e. sharp peaks) and that of 4 by HPLC (broadened peaks).

(26) These reactions can be conveniently monitored by observing the aromatic protons in the ^1H NMR (concentric external D_2O lock) in either concentrated acid. *Caution*: The addition of thionyl chloride to fuming sulfuric acid and 2 causes slow gas evolution; the NMR tubes should not remain capped for protracted periods.

= 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 were also used: br (broadened), sh (shoulder). ^1H 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.

3-(2-Thienylthio)propanoic Acid (5). In a 2-L, three-neck round-bottom flask fitted with a thermometer, nitrogen inlet, mechanical stirrer, and addition funnel were placed thiophene (67 mL, 69.9 g, 831 mmol; *caution*: stench) and sieve-dried THF (400 mL, residual water ≤120 μg/mL). The solution was cooled to 0–5 °C, and 1.6 M *n*-butyllithium (490 mL, 784 mmol) was added at such a rate as to maintain the temperature at <20 °C. The reaction was stirred for 1 h at 0–5 °C and was used immediately in the next sequence. To the cooled reaction mixture (0–5 °C) was added sulfur (powdered sublimed, 25.1 g, 784 mmol) portionwise while maintaining the temperature at <20 °C. The reaction was stirred for an additional 2.0 h at 0–5 °C, after which nitrogen-purged water (160 mL) was added at such a rate as to maintain the temperature at <18 °C. The addition of sulfur was highly exothermic. (Note: the 2-mercaptothiophene and its anion (6) can air-oxidize to the correspondding disulfide. Therefore, solutions of 6 must be deoxygenated and stored under a nitrogen atmosphere.) Solids may form initially upon addition of water to the solution of 6 but eventually dissolve. The solution of 6 was titrated for total base. The yield of thiophene to 6 based on titration was 98%.

In a 1-L, three-neck, round-bottom flask fitted with an addition funnel, thermometer, nitrogen sweep, and mechanical overhead stirrer was prepared a solution of potassium carbonate (48.0 g, 347 mmol) in nitrogen-purged water (160 mL). To this solution was added solid 3-bromopropionic acid (109.4 g of 97% pure material (Aldrich), 694 mmol) at such a rate as to control foaming (CO_2 evolution). The mixture was stirred until a clear solution was obtained. The temperature increased from 23 °C to 50 °C during the dissolution of potassium carbonate (*caution*: foaming occurs during the addition). The solution of 6 was cooled to 10 °C, and the aqueous solution of potassium 3-bromopropionate was added at such a rate as to maintain the temperature at 0–5 °C. The reaction was stirred for 24 h at ambient temperature. The reaction was monitored by HPLC: column C (2 mL/min, 65:35 0.1% M phosphoric acid in H_2O–CH_3CN; 240 nm), 50 °C; t_R (6) 10.5 min, (5) 5.4 min, and (thiophene), 7.1 min. The layers were separated, and the aqueous layer was washed with toluene (2 × 100-mL portions) to remove neutral organic impurities. The aqueous layer was then cooled to 10 °C and stirred with toluene (175 mL) as aqueous HCl (160 mL, 6 N) was added, maintaining the temperature at <14 °C (pH <1). The organic layer was separated, and the aqueous layer was extracted with additional toluene (190 mL). The organic layers were combined and dried azeotropically under vacuum to a volume of 250 mL and residual water of ≤2.5 mg/mL. The solution was stored at 0–5 °C overnight. A small amount of the carboxylic acid was isolated and characterized as its *tert*-butylammonium salt (1.2 equiv of amine added to acid in diethyl ether at 20 °C): mp 110–112 °C (recrystallized from isopropyl acetate); IR ($CHCl_3$) 3400–2300 br s (OH), 2980 m, 2630 m, 2200 w, 1635 m, 1580 br s (C=O), 1480 w, 1390 s, 1300 m, 1270 m, 990 w, 930 w, 850 w; ^1H NMR δ 8.36 (br s, NH_3^+), 7.29 (d, J = 5.4, $H_{5'}$), 7.07 (d, J = 3.5, $H_{3'}$), 6.93 (dd, J = 5.4, 3.5, $H_{4'}$), 2.99 (m, C_2H_2), 2.43 (m, C_3H_2), 1.27 (s, $C(CH_3)_3$); ^{13}C NMR δ_C 177.9 (C_1), 134.5 ($C_{2'}$), 133.5, 129.0, 127.4 ($C_{3'}$, $C_{4'}$, $C_{5'}$), 50.6 ($C(CH_3)_3$), 38.4, 35.6 (C_2, C_3), 27.8 ($C(CH_3)_3$); MS (EI, 70 eV) 188 (M^+, acid, 100), 129 (12), 116 (27), 115 (22), 71 (39), 45 (17). Anal. Calcd for $C_{11}H_{19}NO_2S_2$: C, 50.54; H, 7.33; N, 5.36. Found: C, 50.53; H, 7.12; N, 5.27.

5,6-Dihydro-4*H*-thieno[2,3-*b*]thiopyran-4-one (7). In a 2-L three-neck round-bottom flask fitted with an overhead mechanical stirrer, thermometer, addition funnel, reflux condenser, and nitrogen bubbler vented through an acid-vapor scrubber was placed the toluene solution of 5 (130.7 g, 694 mmol). The reaction mixture was brought to an initial temperature of 20 °C, and trifluoroacetic anhydride (161 g, 767 mmol) was added over 5 min to the stirred solution of 5. The reaction was then heated to 35–38 °C and stirred until judged complete by HPLC (~1.5 h). The progress of the acylation was monitored by HPLC: column A, (1 mL/min, 50:50 0.01 M H_3PO_4 in H_2O–CH_3CN, 240 nm) t_R (5) 5.51 min, (7) 6.18 min. The reaction was then slowly added to water (500 mL), maintaining the temperature at <25 °C. A pH probe was placed in the vessel, and the mixture was titrated to pH 7.0 with 50% sodium hydroxide (123 g, 1.53 mol). The layers were separated, and the aqueous phase was extracted once with toluene (200 mL). The combined organic extracts were then concentrated under vacuum (43 mbar) to a volume of 200 mL and then diluted to 1.2 L with ethyl acetate for the next step (oxidation). A small sample was chromatographed to obtain the following data: R_f = 0.29 (85:15 hexane–ethyl acetate); mp 61–62 °C; IR ($CHCl_3$) 3120 w, 3090 w, 3010 m, 2930 w, 1660 s (C=O), 1500 m, 1390 s, 1315 w, 1280 w, 1265 m, 1190 w, 1035 w, 890 w; ^1H NMR δ 7.42 (d, J = 5.4, H_2), 6.98 (d, J = 5.4, H_3), 3.33 (m, C_5H_2), 2.82 (m, C_6H_2); ^{13}C NMR δ_C 188.9 (C_4), 150.9, 135.0 (C_{3a}, C_{7a}), 126.1, 121.8 (C_2, C_3), 38.1 (C_5), 30.0 (C_6); MS (EI, 70 eV) 170 (M^+, 79), 142 (100), 114 (27), 60 (21). Anal. Calcd for $C_7H_7OS_2$: C, 49.39; H, 3.55; S, 37.66. Found: C, 49.56; H, 3.58; S, 37.68.

5,6-Dihydro-4*H*-thieno[2,3-*b*]thiopyran-4-one 7,7-Dioxide (4). The ethyl acetate/toluene solution of ketone 7 (118 g, 693 mmol in 1.2 L of 5:1 v:v EtOAc–toluene) was charged to a 5-L three-neck round-bottom flask equipped with an overhead mechanical stirrer 250-mL pressure-equalizing dropping funnel, and thermocouple temperature probe. The mixture was stirred, and water (35 mL) was added to saturate the organic phase. A solution of sodium tungstate dihydrate (11.7 g, 35.5 mmol) dissolved in water (35 mL) was then added. The mixture was heated to 35 °C, and hydrogen peroxide (30%, 250 mL, 2.45 mole) was added over 45 min (*caution*: there is an induction period of several minutes before an exotherm). The temperature of the reaction was allowed to rise to 55–58 °C and was maintained there, initially with cooling and subsequently with heating. The reaction temperature was maintained at 55–58 °C until judged complete by HPLC: column A, (1 mL/min, 50:50 0.01 M H_3PO_4 in H_2O–CH_3CN, 240 nm) t_R (7) 6.18 min, (4) 4.07 min. On completion the mixture was cooled to 0–5 °C, and excess hydrogen proxide was decomposed by the slow addition of aqueous sodium sulfite (205 g, 1.63 mol dissolved in 700 mL of water). The temperature of the reaction mixture was maintained at <20 °C. When the reaction mixture tested negative to acidified starch–iodide paper, the layers were separated. The upper organic layer was concentrated under vacuum at 45 °C bath temperature to a volume of 400 mL. Hexanes (400 mL) were then added over ~10 min, and the batch was aged for 1 h. The product was filtered, washed with hexanes, and dried under vacuum at 60 °C with a nitrogen sweep to constant weight. The yield of crude keto sulfone 4 was 107 g (76% from 3-bromopropionic acid). Crude keto sulfone was then recrystallized from methanol using the following procedure. Crude keto sulfone (107 g) was dissolved in anhydrous methanol (3 L) at 55–60 °C. The solution was cooled to 40 °C, and 10 g of Calgon ADP carbon was added. The mixture was aged at 40 °C for a minimum of 4 h with stirring. The batch was then filtered warm at 40 °C through a well-washed pad of SuperCel. The filter cake was washed with methanol (2 × 500 mL) at 40 °C, and the filtrates were combined. The batch was then concentrated under vacuum to a volume of 500 mL and aged at 0–5 °C for 4 h. Crystallization ensued during concentration. The batch was filtered, washed with 75 mL of cold methanol, sucked dry under nitrogen, and dried under vacuum (100 Torr) at 80 °C with a nitrogen sweep for 12 h. The recovery yield was 94.7 g (89%, 99.6

wt % by HPLC, see above, against an external standard): R_f = 0.30 (dichloromethane); mp 121–121.5 °C; IR ($CHCl_3$) 3120 w, 3100 w, 3020 m, 1690 s (C=O), 1500 w, 1410 m, 1390 m, 1330 s (SO_2), 1310 m, 1285 m, 1260 m, 1190 s, 1155 s (SO_2), 1130 m, 1090 m, 860 s, 820 w; ^1H NMR δ 7.60 (d, J = 5.1, H_2), 7.50 (d, J = 5.1, H_3), 3.76 (m, C_6H_2), 3.36 (m, C_5H_2); ^{13}C NMR δ_C 186.3 (C_4), 147.2 (C_{3a}), 139.3 (C_{7a}), 130.2 (C_2), 126.3 (C_3), 52.8 (C_6), 37.0 (C_5); MS (EI 70 eV) 202 (M^+, 35), 174 (38), 138 (15), 110 (100), 84 (30), 82 (25). Anal. Calcd for $C_7H_6O_3S_2$: C, 41.57; H, 2.99; S, 31.70. Found: C, 41.49; H, 3.02; S, 31.60.

(*R*)-(+)-5,6-Dihydro-4*H*-thieno[2,3-*b*]thiopyran-4-ol 7,7-Dioxide (3). Ketosulfone 4 (50.0 g, 0.247 mol) was dissolved in tetrahydrofuran (700 mL) over 4-Å molecular sieves (50 g) and occasionally swirled until the residual water content was <40 μg/mL (~2 h). A 2-L three-neck round-bottom flask fitted with a mechanical stirrer, nitrogen inlet tube, 500-mL addition funnel, and Teflon-coated thermocouple probe was charged with 4 (decanted from the sieves). To the solution was added oxazaborole catalyst (14.4 mL of a 0.86 M solution in toluene, 12.4 mmol, 0.05 equiv).[15] The resulting solution was cooled to −15 °C. In a separate vessel borane–methyl sulfide (17.3 mL, 173 mmol, 0.70 equiv) was dissolved in dry tetrahydrofuran (297 mL; residual water < 40 μg/mL). The borane–methyl sulfide solution was placed in the addition funnel and added to the keto sulfone/catalyst solution at a rate to maintain the internal temperature at −15 °C (~30 min). After all of the borane was added, the reaction was aged for 30 min. An easily stirred precipitate usually formed during the age. This reaction can be conveniently monitored by GC. An aliquot (0.10 mL) was quenched into methanol (0.9 mL), aged 5 min, and then injected on column A; (15 psi, 200 °C, isothermal) t_R (4) 2.55 min, (oxazaborole 8a) 5.21 min, (3) 3.64 min, (diphenylprolinol) 5.97 min. The reaction was quenched by the cautious addition of 10 mL of methanol (*caution*: there was a significant induction period (1–2 min) before hydrogen was evolved after the initial methanol was added), maintaining the temperature at −10 °C. After hydrogen evolution subsided, methanol (365 mL) was added. The reaction became homogeneous during the quench. After complete addition of methanol, the reaction mixture was warmed to 20 °C and stirred for 12 h. The resulting solution was concentrated at atmospheric pressure to ~125 mL (*caution*: the distillate contains malodorous methyl sulfide). Methanol (375 mL) was added, and the resulting solution was concentrated at atmospheric pressure to 125 mL to remove any remaining volatile boron species.

Amberlyst 15 (56 g, 100 mL dry) was suspended in methanol (100 mL). (*Caution*: the slurry exotherms to ~40 °C without external cooling and expands on wetting to ~1.5 times its initial volume.) The slurry was poured into a 2.5 × 30 cm column and eluted with 1 L of ammonium hydroxide (15 M) in methanol (6 vol %, ~1 M) until the eluate was basic (pH ~11 when diluted 1:1 with water). The initial brown eluate was discarded. (*Caution*: *The resin must be treated with ammonium hydroxide in methanol prior to elution of the hydroxy sulfone or the hydroxy sulfone will racemize.*) The column was eluted with methanol (~500 mL) until the eluate was neutral. The methanol solution of (*R*)-hydroxy sulfone (~50 g) and (*S*)-diphenylprolinol (3.13 g) was filtered through a pad of SuperCel. The cake was washed with methanol (2 × 50 mL), and the combined filtrates were brought to a volume of 500 mL (10 mL/g) with methanol. The filtered methanol solution was eluted through the column containing Amberlyst 15 (NH_4^+) at 3.8 mL/min, collecting 38-mL fractions. The column was rinsed with methanol (380 mL) to remove all of the product hydroxy sulfone. The column was then eluted with 94:6 (v/v) methanol/15 M aqueous ammonia (400 mL) to elute diphenylprolinol. Fractions 3–21 containing (*R*)-hydroxy sulfone (95:5 *R*:S, 49 g (98%), contaminated with less than 0.4% diphenylprolinol) were combined and concentrated (recrystallization of this material from hexane/ethyl acetate only serves to lower enantiomeric purity). Addition of tetrahydrofuran (500 mL) followed by concentration to 250 mL was repeated twice. Tetrahydrofuran was added to generate a solution of 3 in a total volume of 500 mL for use in the next reaction. Fractions 29–33 containing (*S*)-diphenylprolinol (<1:99 *R*:*S*, 3.0 g) were combined and concentrated to afford a crystalline solid. The progress of the column can be monitored by HPLC: column A (1 mL/min, 60:40 0.01 M KH_2PO_4 in H_2O–CH_3CN) t_R (4) 4.78 min (240 nm), (3) 3.30 min (240 nm), (diphenylprolinol) 5.60 min (210 nm).

Mosher Ester Preparation. To alcohol 3 (20 mg) in dry dichloromethane (2 mL) was added (dimethylamino)pyridine (12 mg, 1.0 equiv), triethylamine (14 μL, 10 mg, 3.0 equiv), and (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride (Mosher acid chloride, 27 mg, 21 μL, 1.1 equiv, see General of the Experimental Section). The mixture was stirred for 1–5 h, as judged by TLC (EM Si-60, 1:1 hexane–EtOAc, R_f alcohol 3 = 0.10, R_f ester = 0.60). The reaction mixture was diluted with hexane (8 mL) and centrifuged (5 min). The resulting clear yellow solution was eluted through a Baker Silica SPE (1 g) column (previously washed with 5 mL of hexane). The initial eluate was discarded, and 6:4 hexane–EtOAc (10 mL) was eluted and collected. The latter eluate was then analyzed by capillary GC on column A (15 psi, 200 °C, isothermal): t_R (*R*,*R*)-Mosher ester (major), 10.0 min; (*R*,*S*)-Mosher ester (minor), 10.4 min. Enantiomeric purity: >95.5.

A small sample of 3 was chromatographed to obtain characterization data: R_f = 0.07 (60:40 hexane–ethyl acetate). $[\alpha]^{21}_D$ = +16.4° (*c* 0.210, MeOH); mp 89–90 °C; IR ($CHCl_3$) 3600 w (OH), 3550–3400 br w (OH), 3110 w, 3010 m, 2940 w, 1520 w, 1400 m, 1305 s (SO_2), 1285 s, 1180 w, 1145 s (SO_2), 1125 s, 1000 w, 1060 m, 1040 m, 970 w, 915 w, 890 w, 845 w, 825 m; ^1H NMR δ 7.59 (d, J = 5.1, H_2), 7.12 (d, J = 5.1, H_3), 4.91 (ddd, J = 10.0, 5.9, 1.5, H_4), 3.62 (m, H_6), 3.31 (m, H_6), 2.75 (m, H_5), 2.55 (m, H_5, OH); ^{13}C NMR δ_C 144.9 (C_{3a}), 135.9 (C_{7a}), 130.5 (C_2), 127.0 (C_3), 63.5 (C_4), 49.1 (C_6), 31.0 (C_5); MS (EI, 70 eV) 204 (M^+, 64), 176 (16), 158 (20), 140 (11), 128 (22), 112 (58), 111 (100). Anal. Calcd for $C_7H_8O_3S_2$: C, 41.16; H, 3.95; S, 31.39. Found: C, 41.23; H, 3.93; S, 31.24.

(*S*)-(−)-5,6-Dihydro-*N*-(2-methylpropyl)-4*H*-thieno[2,3-*b*]thiopyran-4-amine 7,7-Dioxide (2). A 3-L three-neck flask fitted with a mechanical stirrer, nitrogen inlet tube, 500-mL addition funnel, and Teflon-coated thermocouple probe was charged with a slurry of sodium acetylide in xylene/light mineral oil (Aldrich, 71.8 g, 0.269 mol of an 18% slurry) and was well mixed with 400 mL of tetrahydrofuran. Hydroxy sulfone 3 (50.0 g, 0.245 mol) was dissolved in dry tetrahydrofuran (500 mL, see above; residual water content should be <100 μg/mL)[27] and placed in the addition funnel. The solution was cooled to 15 °C, and the solution of 3 was added to the sodium acetylide over 5 min. (*Caution*: sodium acetylide is moisture sensitive and generates acetylene upon addition of water.) The resulting suspension was stirred at 20 °C for 2 h. During the age, the fine slurry of sodium acetylide was converted to the easily stirred, coarse, crystalline sodium salt of the hydroxy sulfone. (The deprotonation can be monitoried by removing a 1-mL aliquot and adding it to excess toluenesulfonyl chloride (45 mg, 0.24 mmol) in 1 mL of tetrahydrofuran and monitoring by TLC: 60:40 hexane–ethyl acetate; R_f hydroxy sulfone 3, 0.07, tosylate 25, 0.37.) The resulting slurry was cooled to −15 °C. Toluenesulfonyl chloride (51.3 g, 0.269 mol) was dissolved in 250 mL of tetrahydrofuran and placed in the addition funnel. The toluenesulfonyl chloride/tetrahydrofuran solution was added to the sodium salt at a rate to maintain the internal temperature below −10 °C (~10 min). The cold bath was removed, and the resulting mixture was aged for 2 h. The tosylation can be followed by TLC (60:40 hexane–ethyl acetate; R_f tosylate = 0.37, R_f alcohol = 0.07). The sodium salt of the hydroxy sulfone dissolved during the age and the reaction usually turned dark green. (Note: tosylate 26 should not be isolated since it readily hydrolyzes to racemic 3 in water.) The resulting solution was cooled to 0 °C and dry (residual water <100 μg/mL) isobutylamine (250 g, 340 mL, 3.43 mol) was added over 5 min. The resulting mixture was warmed to 20 °C and aged for 14 h. (This reaction was monitored by TLC analysis: 60:40 hexane–ethyl acetate; R_f tosylate = 0.37, R_f amine = 0.25). The resulting mixture was cooled to −15 °C, and aqueous hydrochloric acid (1.54 L, 2 N) was added at a rate to maintain the internal temperature at or below 5 °C (~30 min). The resulting pH was ~2.5. The solution was concentrated to ~1.6 L to remove most (90%) of the tetrahydrofuran and extracted with isopropyl acetate (2 × 600 mL). The aqueous phase was cooled to 0 °C, and sodium hydroxide (120 mL, 5 N) was added at a rate to maintain the

(27) The water content can be lowered either by drying with 3- or 4-Å molecular sieves or by atmospheric distillaton and addition of dry tetrahydrofuran.

internal temperature below 5 °C (~5 min). The resulting pH was ~10 and the reaction mixture became cloudy upon addition of sodium hydroxide. The resulting mixture was extracted with isopropyl acetate (2 × 600 mL). The organic layers were combined and concentrated to ~120 mL. 2-Propanol (600 mL) was added, and the mixture was concentrated to 100 mL. A second flush was performed to remove the isopropyl acetate. (Solubility of amine **2** in 2-propanol: 2.5 mg/mL at -20 °C; 7.3 mg/mL at 0 °C; 28.3 mg/mL at 20 °C; 151 mg/mL at 45 °C). 2-Propanol was added to bring the volume to ~1 L, the resulting solution was warmed to 55–60 °C, and Calgon ADP (5 g) decolorizing carbon was added. The mixture was stirred at 50 °C for 4 h. The resulting mixture was filtered at 50 °C through prewashed SuperCel. The filtered solution was concentrated to 0.61 L (10 mL/g amine) and allowed to cool slowly to room temperature. The resulting suspension was cooled to 0 °C and aged for 2 h. The suspension was filtered, washed twice with 150 mL of 0 °C 2-propanol, and dried in vacuo at 45 °C for 12 h to yield 47 g (73%) of amine **2** as off white crystals. Amine **2** can be analyzed by HPLC (240 nm): column A (1 mL/min, 60:40 0.01 M KH_2PO_4 in H_2O–CH_3CN, isocratic) t_R (**2**) 4.78 min.

Assay for enantiomeric purity: To amine **2** (10 mg) in dry ethyl acetate (1 mL) was added trifluoroacetic anhydride (20 μL). The mixture was stirred for 1–5 min, as judged by TLC (EM Si-60, 60:40 hexane–EtOAc, R_f amine **2** = 0.30, R_f amide = 0.50). The reaction mixture was concentrated to dryness and then diluted with tetrahydrofuran (2 mL). The resulting clear yellow solution was eluted through a Baker quaternary amine SPE (1 g) column (previously washed with 5 mL of 2-propanol). The eluate was collected, and 88:11:1 hexane–tetrahydrofuran–2-propanol (20 mL) was eluted and collected. The eluate was then analyzed by normal-phase HPLC (250 nm): column B (2.0 mL/min, 88:11:1 hexane–tetrahydrofuran–2-propanol, isocratic) t_R ((*R*)-TFA-**2**) 10.65 min, ((*S*)-TFA-**2**) 12.82 min. Enantiomeric purity >99:1.

Data for **2**: R_f = 0.25 (60:40 hexane–ethyl acetate); $[\alpha]^{22}_D$ = -8.68° (*c* 0.316, MeOH); mp 86–86.5 °C; IR ($CHCl_3$) 3110 w, 3010 m, 2960 m, 2950 sh, 2900 w, 2870 w, 2830 w, 1520 w, 1460 m, 1400 m, 1365 w, 1305 s (SO_2), 1280 m, 1140 s (SO_2), 1090 m, 1055 w, 890 w, 850 w, 830 w; ^{1}H NMR δ 7.53 (d, *J* = 5.0, H_2), 7.08 (d, *J* = 5.0, H_3), 3.91 (dd, *J* = 6.3, 4.1, H_4), 3.68 (ddd, *J* = 13.6, 9.8, 2.8, H_6), 3.27 (ddd, *J* = 13.6, 8.8, 2.6, H_6), 2.55 (m, C_5H_2, $C_{1'}H_2$), 1.68 (m, $H_{2'}$), 0.92 (d, *J* = 6.8, 2 CH_3); ^{13}C NMR δ_C 146.0 (C_{3a}), 135.6 (C_{7a}), 129.7 (C_2), 127.1 (C_3), 55.0 ($C_{1'}$), 52.6 (C_4), 49.6 (C_6), 28.8 ($C_{2'}$), 27.8 (C_5), 20.6, 20.5 (2 CH_3); MS (EI, 70 eV) 260 ($[M + H]^+$, 16), 231 (35), 216 (98), 187 (62), 167 (15), 125 (15), 124 (42), 123 (41), 122 (100), 97 (17). Anal. Calcd for $C_{11}H_{17}NO_2S_2$: C, 50.94; H, 6.61; N, 5.40; S, 24.72. Found: C, 51.00; H, 6.64; N, 5.30; S, 24.50.

(*S*)-(+)-5,6-Dihydro-4-[(2-methylpropyl)amino]-4*H*-thieno[2,3-*b*]thiopyran-2-sulfonamide 7,7-Dioxide Monohydrochloride Hemihydrate (MK-0417, 1). A 5-L round-bottom flask fitted with a mechanical stirrer, nitrogen inlet, and septum was charged with fuming sulfuric acid (12–20% SO_3 in H_2SO_4, 250 mL). (*Caution*: fuming sulfuric acid (oleum) is extremely corrosive.) The solution was cooled to -10 °C, and amine **2** (50 g, 193 mmol) was added portionwise at a rate to maintain the temperature ≤0 °C. (*Caution*: the addition is exothermic.) After the resultant solution was stirred for 2 h at 5–8 °C,[26] thionyl chloride (1 L, 1631 g, 13.7 mol) was added and the mixture was refluxed for 3 h.[26] The thionyl chloride was removed by distillation, and the resulting oil was cooled to 0 °C. A 12-L round-bottom flask fitted with a mechanical stirrer, 500-mL pressure equalizing addition funnel (with a Teflon tube attached to the bottom that reached below the surface of the contained liquid), and nitrogen inlet was charged with concentrated aqueous ammonia (1.6 L) and tetrahydrofuran (2.0 L) and cooled to -15 °C. The addition funnel was charged with the sulfuric acid solution of the sulfonyl chloride. The sulfuric acid solution was slowly added (subsurface) to the ammonia/tetrahydrofuran mixture at a rate to maintain the temperature below 0 °C (~1 h). (*Caution*: addition of strong acid to strong base is exothermic and spattering may occur. The pH of the aqueous layer was monitored and should remain above 9.5 during the quench.) After complete addition, the resulting mixture was stirred at 0 °C for 30 min. The resulting pH was 10. The resulting suspension was filtered, and the filter cake washed with tetrahydrofuran (2 × 600 mL). The filtrate was concentrated to remove tetrahydrofuran and extracted with ethyl acetate (2 × 1.2 L). The organic layers were combined, concentrated to 700 mL, and stirred well as concentrated hydrochloric acid (20 mL, 241 mmol) was slowly added. The mixture was concentrated under vacuum at 45 °C (bath temperature) to remove water, replacing ethyl acetate twice, until a solution with a water content of <0.1 mg/mL was attained at a volume of ~600 mL. The crystallized mixture was aged at 20 °C for 1 h, cooled, and stirred at 0 °C for 1 h. The slurry was filtered and washed with two bed volumes of ethyl acetate. The white solid was dried under vacuum at 45 °C to afford 51.2 g (69%) of MK-0417·HCl. The salt could be recrystallized from water as follows. MK-0417·HCl (51.2 g, 133 mmol) was dissolved in water (100 mL) at 80–90 °C. The mixture was well stirred, and activated carbon (Darco KB, 5 g) was added to the hot mixture. After being stirred for 2 h, the mixture was filtered hot (85–90 °C) through a washed bed of SuperCel, and the filter cake was washed with 25 mL of boiling water. The combined filtrate and wash was allowed to slowly cool to 40–50 °C and held at 40–50 °C until crystallization occurred. After stirring for 1 h at 55 °C after crystallization occurred, the mixture was cooled to 3 °C and aged for 1 h. The resulting mixture was filtered, and the filter cake was washed with cold water (one bed volume). The product was dried under vacuum at 45 °C with a nitrogen sweep to afford 48.0 g (65%) of MK-0417·HCl. This sequence can be monitored by HPLC: column A (1 mL/min, 55:45 0.01 M K_2HPO_4 in H_2O–CH_3CN, 240 nm) t_R (sulfonic acid) 2.37 min, (**1**) 6.34 min, (**2**) 8.54 min, (**27**) 10.17 min; $[\alpha]^{25}_D$ = +49° (*c* 0.50, MeOH); mp 222 °C dec; IR (KBr) 3350 w (NH), 2950 s, 2800–2300 w (NH_2^+), 1620 w, 1590 w, 1540 m, 1466 w, 1420 w, 1400 w, 1350 s (SO_2), 1340 s (SO_2), 1300 s (SO_2), 1160 s (SO_2), 1145 s (SO_2), 1050 m, 1020 m, 910 w, 880 m, 740 m, 700 w; ^{1}H NMR (DMSO-d_6) δ 9.82 (br s, $C_4NH_2^+$), 8.20 (s, SO_2NH_2), 8.16 (s, H_3), 4.80 (br s, H_4), 3.94 (m, C_6H_2), 2.82 (m, C_5H_2, $C_{1'}H_2$), 2.15 (septet, *J* = 6.6, $H_{2'}$), 0.98 (d, *J* = 6.6, CH_3), 0.96 (d, *J* = 6.6, CH_3); ^{13}C NMR (DMSO-d_6) δ_C 149.4 (C_2), 141.8 (C_{7a}), 137.5 (C_{3a}), 129.8 (C_3), 51.2 (C_6), 50.9 (C_4), 48.3 ($C_{1'}$), 25.5 ($C_{2'}$), 23.7 (C_5), 20.3, 20.0 (2 CH_3): HRMS (free base EI, 90 eV) calcd for $C_{11}H_{18}N_2O_4S_2$ 338.0429, found 338.0430. Anal. Calcd for $C_{11}H_{19}ClN_2O_4S_3 \cdot 0.5H_2O$: C, 34.41; H, 5.25; N, 7.30; S, 25.05; Cl, 9.23. Found: C, 34.55; H, 5.20; N, 7.21; S, 24.89; Cl, 9.50.

Data for 1,6,7,7a-tetrahydro-1-(2-methylpropyl)-2,4,5-trithia-1-azacyclopent[*cd*]indene 2,2,5,5-tetraoxide (27): IR ($CHCl_3$) 3110 w, 3020 m, 2960 w, 2870 w, 1460 w, 1325 s (SO_2), 1285 w, 1150 m, 1135 s (SO_2), 1055 w, 930 w; ^{1}H NMR δ 8.07 (s, H_3), 4.20 (dd, *J* = 11.2, 4.7, H_{7a}), 3.63 (m, C_6H_2), 3.37 (dd, *J* = 13.9, 7.0, $H_{1'}$), 2.65 (m, $H_{1'}$, H_7), 2.49 (m, H_7), 2.04 (m, $H_{2'}$), 1.01 (d, *J* = 6.8, CH_3), 0.99 (d, *J* = 6.8, CH_3). ^{13}C NMR: δ_C 144.5, 135.2, 132.8 (C_{2a}, C_{2b}, C_{4a}), 128.0 (C_3), 56.8 (C_{7a}), 54.3, 53.1 (C_6, $C_{1'}$), 30.0 (C_7), 28.0 ($C_{2'}$), 20.38, 20.37 (2 CH_3); MS (CI, NH_3) 339 ($[M + NH_4]^+$, 100), 322 ($[M + H]^+$, 15). Anal. Calcd for $C_{11}H_{15}NO_4S_3$: C, 41.10; H, 4.70; N, 4.36; S, 29.92. Found: C, 40.74; H, 4.83; N, 4.61; S, 29.63.

Acknowledgment. We thank J. Wu and her associates J. Perkins and M. Valenciano for microanalytical data. We also thank S. E. Denmark, S. G. Mills, and D. Tschaen for useful suggestions.