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Enantioselective Synthesis of Brinzolamide (AL-4862), a New Topical Carbonic Anhydrase Inhibitor. The "DCAT Route" to Thiophenesulfonamides

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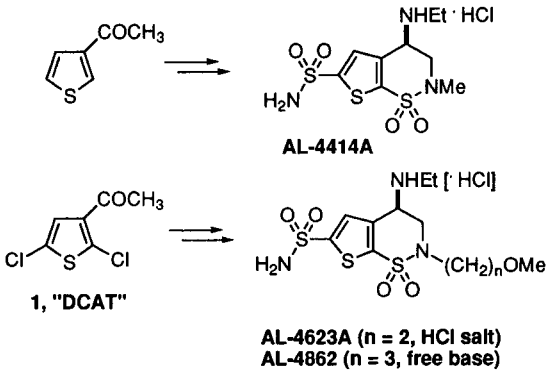
Abstract:

A large scale synthesis of the topical carbonic anhydrase inhibitors AL-4623A (13a·HCl) and AL-4862 (13b) from 3-acetyl-2,5-dichlorothiophene ("DCAT", 1) is described. Reaction of 1 with NaSBn gave thioether 2, which was converted via sulfenyl chloride 3 and sulfenamide 5 to sulfonamide 6. Bromination of 6 gave bromo ketone 7, which upon reduction with (+)-B-chlorodiisopinocampheylborane and cyclization of the resulting bromohydrin produced *S* thieno[3,2-*e*]-1,2-thiazine 8a (96% ee) after chromatography. Treatment of 8a in THF with *n*-BuLi at −70 °C resulted in Li−Cl exchange. Reaction of the thienyllithium with SO_2 and hydroxylamine O-sulfonic acid afforded bis-sulfonamide 11a. Protection of 11a as the acetimidate 12a, followed by tosylation and amination, gave *R* amine 13a. The synthesis of 13b proceeded via primary sulfonamide 16, which was brominated, reduced, and cyclized to give *S* thieno[3,2-*e*]-1,2-thiazine 18 (>98% ee). By virtue of the ionizable NH, 18 was separable from reduction byproducts by base extraction. Alkylation of 18 with 3-bromopropyl methyl ether afforded 8b, which was converted as above, via 11b, to AL-4862 (13b). These procedures provided multihundred gram lots of 13a and 13b.

We previously reported a large-scale synthesis of the water-soluble thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide carbonic anhydrase inhibitor (CAI) AL-4414A starting with 3-acetylthiophene.[1] The *N*-methyl sulfonamide, destined to form the thiazine ring, was formed by ketal-directed lithiation, addition of SO_2 to give the lithium sulfinate, chlorination to the sulfonyl chloride, and amination with methylamine. The primary sulfonamide arose by reaction of its lithium sulfinate precursor with hydroxylamine *O*-sulfonic acid (HOSA).[2] Early lots of a second clinical candidate, the *N*-methoxyethyl compound AL-4623A, were also prepared using this chemistry.

Herein we describe an improved synthesis of CAI's of this structural class. One goal of these studies was to evaluate alternatives to low-temperature lithiation for elaborating the sulfonamide groups. We have employed this new sequence to produce multihundred gram lots of both AL-4623A and the *N*-methoxypropyl homologue AL-4862. The latter compound, as the free base, was introduced by Alcon in April 1998 as Azopt ophthalmic suspension (brinzolamide) for the treatment of elevated intraocular pressure associated with glaucoma.[3]



3-Acetyl-2,5-dichlorothiophene ("DCAT", **1**), available in bulk, was selected as the starting material (Scheme 1). The sulfonamides were envisioned to arise from thioethers via oxidative chlorination[4] to the sulfonyl chloride (**2** → **4** → **6**). This would be an operationally simpler route to secondary sulfonamides than the lithium sulfinate method,[5] facilitating the option of installing the eventual primary sulfonamide in protected form, e.g., **9** → **10**. A key strategic feature was the sequential regioselective introduction of the thioethers by nucleophilic addition−elimination, controlled by the keto group (**1** → **2**) and later by the first-formed sulfonamide (**8a** → **9**).

Thioether **2** formed cleanly upon reaction of **1** with benzyl mercaptan and NaOH in refluxing aqueous ethanol or THF. For scale-up we used *S*-benzylisothiuronium chloride, prepared in situ from benzyl chloride and thiourea, as a convenient precursor of NaSBn.[4a,6] The product **2** precipitated

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(1) DuPriest, M. T.; Zinke, P. W.; Conrow, R. E.; Kuzmich, D.; Dantanarayana, A. P.; Sproull, S. J. *J. Org. Chem.* **1997**, *62*, 9372.

(2) Graham, S. L.; Scholz, T. H. *Synthesis* **1986**, 1031.

(3) (a) Clinical studies: Silver, L. H. and the Brinzolamide Primary Therapy Study Group. *Am. J. Ophthalmol.* **1998**, *126*, 400. (b) Crystallographic study of carbonic anhydrase isozymes complexed with brinzolamide: Stams, T.; Chen, Y.; Boriack-Sjodin, P. A.; Hurt, J. D.; Liao, J.; May, J. A.; Dean, T.; Laipis, P.; Silverman, D. N.; Christianson, D. W. *Protein Sci.* **1998**, *7*, 556. (c) The synthetic sequence proceeding via **18** is disclosed in Alcon Laboratories, Inc. U.S. patents 5,344,929 (6 Sept 1994), 5,424,448 (13 Jun 1995), and 5,473,067 (5 Dec 1995).

(4) (a) Baker, R. H.; Dodson, R. M.; Riegel, B. *J. Am. Chem. Soc.* **1946**, *68*, 2636. (b) Kwart, H.; Miller, R. K. *J. Am. Chem. Soc.* **1956**, *78*, 5008. (c) Langler, R. F. *Can. J. Chem.* **1976**, *54*, 498. (d) Barnette, W. E.; Dean, T. R.; Petersen, W. C.; Wexler, B. A. US Patent 4,789,465. (e) Kim, D.-W.; Ko, Y. K.; Kim, S. H. *Synthesis* **1992**, 1203.

(5) The method of ref 2 was not adaptable to direct synthesis of secondary sulfonamides: use of *N*-methylhydroxylamine *O*-sulfonic acid (Schmitz, E.; Ohme, R.; Murawski, D. *Chem. Ber.* **1965**, *98*, 2516) to quench lithium thiophenesulfinates gave the *N*-methylsulfonamide in poor yield (D. Kuzmich, unpublished observations).

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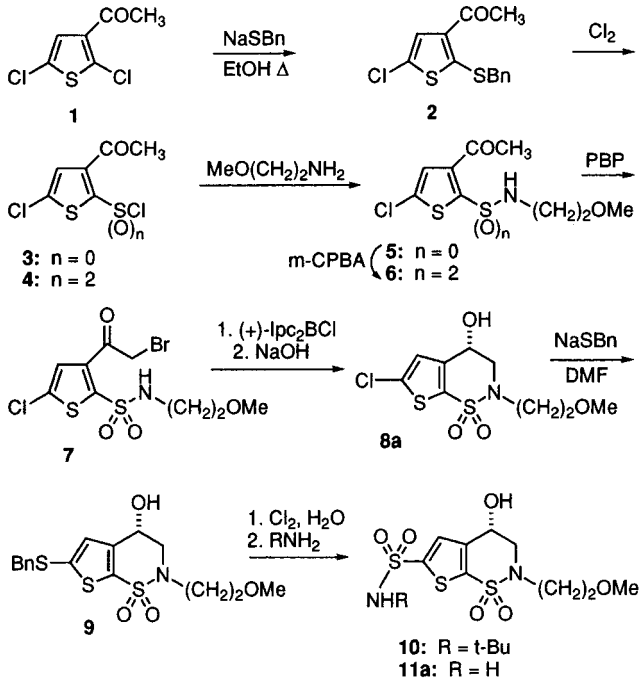
Scheme 1



upon quenching into water. Oxidation of excess thiol in solution with NaOCl was followed by filtration to afford **2** in 95−97% yield on a 15-mol scale.

Conversion of **2** to sulfonamide **6** via sulfonyl chloride **4** proved erratic. Addition of gaseous chlorine to **2** in acetic acid−water,[4a−c] followed by removal of excess Cl_2 by air stream, resulted in clean formation of sulfonyl chloride **4** (TLC). Sulfenyl chloride **3** was the only intermediate observed. Quenching the reaction mixture into water invariably produced an oil (isolated **4** is a low-melting solid). Alternatively, removal of HOAc by rotary evaporation with moderate warming caused decomposition of **4**. Therefore, extractive workup (CH_2Cl_2−ice cold 2.5% NaOH)[4c] was used to provide an acid-free solution of **4**. Addition of 2-methoxyethylamine produced sulfonamide **6** in 75−78% yield on a 2−10-g scale, but on a 50-g scale the yield dropped to 30−50%. Oxidative chlorination conditions were varied—temperature, solvent (CH_2Cl_2,[4d] TFA, EtOAc, THF,[7] mixtures), aqueous component (water, HCl at different concentrations,[4d] buffers), chlorine source (NaOCl, NCS), and thioether substitution (*n*-Bu, *i*-Bu, *p*-methoxybenzyl)[8]—without improvement. The benzyl sulfoxide derived from **2** also afforded **4** upon oxidative chlorination; amination then delivered **6** in yields comparable to those observed above.

The crude amination mixtures contained numerous components, complicating the interpretation of these results. In contrast, a ketalized analogue of **4** had undergone amination with little difficulty.[1] The thiophene ring could have suffered oxidative degradation en route to **4**. Another pathway was suggested by our observation that the *N*-methylsulfonamide analogue of **6**, upon reaction with NaSBn (DMSO, room temperature), regenerated thioether **2** (87%) by elimination of $MeNHSO_2^-$. Given the greater electronegativity of the chlorosulfonyl group, an analogous addition−elimination might compete during the amination of **4**. Conversion of the carbonyl group to the acid-soluble imine was detected in small-scale trials; the ketone was regenerated on standing in the acidic aqueous extract.

In anhydrous media, chlorination of thioethers affords sulfenyl chlorides.[9] Thus **3** was obtained in high yield by reaction of **2** with Cl_2 in toluene, which served well as a replacement for the hazardous classical solvent CCl_4. Toluene also proved to be the solvent of choice for the subsequent amination and oxidation steps, enabling a one-flask process that proved reliable and easy to scale up. Addition of 2-methoxyethylamine to the toluene solution of **3**, removal of excess amine by acid extraction, and treatment of the resulting solution of sulfenamide **5** with *m*-CPBA and aqueous $NaHCO_3$[10] gave sulfonamide **6**. Trituration of the crude product with hexane dissolved the benzylic byproducts and precipitated **6** in 72−83% yield.

The bromination−reduction−cyclization sequence **6** → **7** → **8a** was accomplished as described for the *N*-methyl series.[1] Treatment of ketone **6** in THF with pyridinium bromide perbromide (PBP) and catalytic HBr produced bromo ketone **7**, typically accompanied by 10−15% of the dibromo ketone.[11] Crude **7** was reduced with (+)-B-chlorodiisopinocampheylborane ((+)-Ipc_2BCl)[12] in THF at ca. −30 °C, and the resulting bromohydrin was cyclized in situ to the thienothiazine **8a**. The dibromo ketone proved to be relatively innocuous, as it was found to undergo slow reductive debromination to **7** prior to carbonyl reduction.[13] Consistent with our earlier observations,[1] and those of others,[12d] workup using the recommended[12b,c] diethanolamine or acetaldehyde quenches did not adequately segregate the product **8a** from pinene, isopinocampheol, and other organic-soluble byproducts. A tedious chromatographic purification was necessary. Thienothiazine **8a** of 96% ee was thereby obtained in 55−60% yield from **6**. The *S* configuration follows from our previous work in the *N*-methyl series[1] and

(6) (a) Speziale, A. J. *Organic Syntheses*; Wiley: New York, 1963; Collect Vol. IV, p 401. (b) Kofod, H. *Organic Syntheses*; Wiley: New York, 1963; Collect Vol. IV, p 491.

(7) (a) CAUTION: THF and DME undergo delayed exothermic polymerization upon exposure to Cl_2 and are therefore not recommended as solvents for oxidative chlorinations. (b) Acetonitrile and DMF are useful water-miscible chlorination solvents; their utility was not assessed in the present studies.

(8) The *tert*-butyl thioether did not form efficiently from DCAT and *t*-BuSH in THF−aq NaOH.

(9) (a) Drabowicz, J.; Kielbasinski, P.; Mikolajczyk, M. In *The Chemistry of Sulfenic Acids and Their Derivatives*; Patai, S., Ed.; Wiley: Chichester, UK, 1990; p 221. (b) Capozzi, G.; Modena, G.; Pasquato, L. ref 9a, p 403. (c) Kühle, E. *Synthesis* **1970**, 561; **1971**, 563, 617. (d) Kurzer, F.; Powell, J. R. *Organic Syntheses*; Wiley: New York, 1963; Collect Vol. IV, p 934.

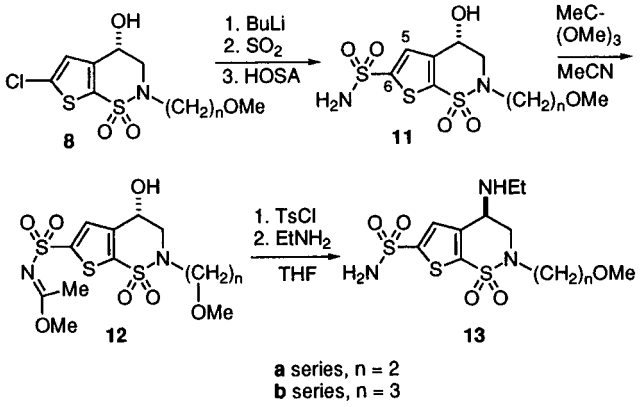
(10) The presence of aqueous bicarbonate was required for good yields in this *m*-CPBA oxidation. Chlorine in aqueous HOAc, while effective for oxidizing **3** to **4**, was unsatisfactory for oxidizing **5** to **6**. Oxone or H_2O_2 in aqueous HOAc converted **5** to **6** but too slowly to be preparatively useful.

(11) (a) Use of methanol as solvent decreased dibromination, but concomitant ketalization proved troublesome: Gaudry, M.; Marquet, A. *Organic Syntheses*; Wiley: New York, 1988; Collect Vol. VI, p 193. (b) Phenyltrimethylammonium tribromide in THF also converted **6** to **7**, plus dibromo ketone, at a slower rate than PBP: Jacques, J.; Marquet, A. *Organic Syntheses*; Wiley: New York, 1988; Collect Vol. VI, p 175.

(12) (a) Chandrasekharan, J.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 5446. (b) Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*, 16. (c) Dhar, R. K. *Aldrichim. Acta* **1994**, *27(2)*, 43. (d) Simpson, P.; Tschaen, D.; Verhoeven, T. R. *Synth. Commun.* **1991**, *21*, 1705.

(13) This pathway was confirmed using isolated dibromo ketone, best prepared by condensing **6** with DMF dimethyl acetal (1.2 equiv, MeCN, 60 °C, 70−80%) and reacting the resulting enaminone with 2 equiv of Br_2 in wet THF.

Scheme 2



from the results obtained by Brown for phenacyl halide reductions.[12a−c]

Reaction of **8a** with NaSBn in DMF at 40−50 °C gave thioether **9** in 64−72% yield. Oxidative chlorination of **9** (Cl_2 or NaOCl, HOAc, H_2O) followed by extractive workup[4c] and amination with *t*-$BuNH_2$ provided bis-sulfonamide **10** in about 50% yield on a gram scale. Use of two-phase mixtures[4d] for oxidative chlorination gave inferior results.[7b] Upon scale-up, the yield of **10** declined markedly, and much water-soluble material was formed. When the sulfonyl chloride was quenched with ammonia, primary sulfonamide **11a** was obtained in poor yield. The sulfenyl chloride to sulfenamide alternative gave no useful results. Substitution of NHEt for OH (see below) in **9**, not surprisingly, led to decomposition upon subsequent chlorination. Hydroxyl protection was not considered an attractive tactic due to increasing step count.

These results were not taken as an abrogation of the original plan. However, the necessity of delivering material in quantity within a practical time frame occasioned a speculative return to organolithium chemistry (Scheme 2). To our delight, **8a** underwent efficient lithium−chlorine exchange,[14] ascertained by quenching with MeSSMe, upon reaction with *n*-butyllithium (2 equiv) in THF at −65 to −70 °C. Addition of SO_2 to this dianion solution, followed by reaction of the resulting lithium sulfinate with an aqueous solution of HOSA and NaOAc[2] produced sulfonamide **11a** in 65−67% yield on a kilo scale. Conversion of the alkoxy group to the sulfite or sulfamate could account for some of the material loss, although this was not confirmed. Proton transfer from OH to the thienyllithium rather than to BuLi, a likely side reaction dependent upon mixing rate,[15] would be of no practical consequence since further reaction of the resulting dechloro compound with BuLi is regioselective for C-6 (α) thienyllithium formation.[1] Butyllithium treatment of **8a** at higher temperature (−40 to −20 °C) led to the appearance of the 6-chloro-5-sulfonamide, arising from deprotonation[16] in competition with Li−Cl exchange. Higher temperature also favored protonation of the lithiated intermediates, presumably by THF: 2.3 equiv of BuLi was added to a solution of **8b** in THF at −10 °C, followed by stirring at this temperature for 4 h, simulating a process delay. Quenching with SO_2 and HOSA as above gave a 1:1 mixture of **8b** and dechloro-**8b** in >90% yield, and little sulfonamide.

This "hybrid" approach to bis-sulfonamides exploits the best features of both sulfonamide-forming methods. The thioether route was advantageous early in the synthesis where the scale was greatest and the properties of the keto group could be utilized, in contrast with the cumbersome ketalization required previously.[1] The organolithium chemistry was deployed at a more advanced stage, saved one step compared to the route via **9**, and was the preferred route to primary sulfonamides **11** which turned out to be the intermediates of choice. The low temperature required for efficient Li−Cl exchange was not viewed as a serious drawback, as −80 °C capability is becoming increasingly common in manufacturing facilities.

There remained a tosylation−amination sequence to convert **11a** to **13a**. In the *N*-methyl series, we had observed tosylation of the primary sulfonamide concurrent with O-tosylation.[1] A *tert*-butyl group, as in compound **10**, effectively suppressed this side reaction and could be cleaved with TFA (45 °C, 18 h) after amination. Access to **10** via the thienyllithium, however, required a chlorination step and was low-yielding and inconvenient. Better results were realized via acetimidate **12a**, readily prepared[17] by condensing **11a** with trimethyl orthoacetate. This protecting group survived tosylation, then cleaved during amination to furnish **13a** in about 55% yield from **11a**.[18] Acetonitrile proved superior to THF as a solvent for the protection step, while the converse was true of the tosylation and amination; hence a solvent exchange was required. Treatment of **13a** with gaseous HCl gave the target compound AL-4623A. Single-crystal X-ray crystallographic analysis of AL-4623A confirmed the *R* configuration, consistent with inversion of the assigned *S* configuration of alcohol **8a**.[19]

The synthesis of the homologue AL-4862 was first accomplished essentially as described above. As in the case of **8a**, chromatographic purification of the reduction−cyclization product **8b** constituted a troublesome bottleneck. We therefore developed a modified sequence proceeding via the unsubstituted thienothiazine **18** (Scheme 3), which by virtue of the ionizable NH was isolable from neutral organic materials by extraction into aqueous hydroxide.[20] Oxidative chlorination of **2** to **4** followed by introduction of ammonia

(14) Li−Cl exchange is a rarely reported event, in comparison with Li−Br and Li−I exchange: (a) Slocum, D. W. *FMC Lithium Link*, No. 5, Winter 1993, pp 1−12. (b) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: New York, 1992; pp 625−6.

(15) Gallagher, D. J.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 7984.

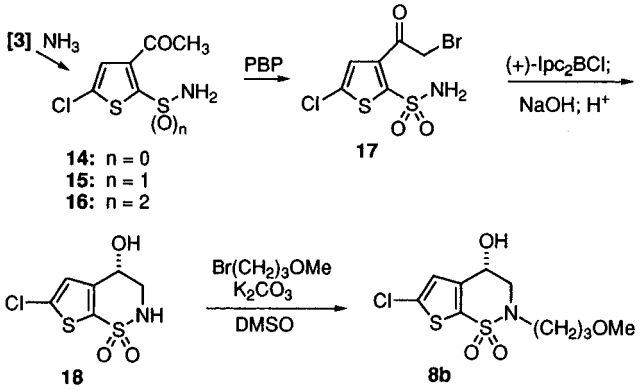
(16) (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) *FMC Lithium Link*, No. 3, Spring 1992, pp 1−14; No. 4, Spring 1993, pp 1−17.

(17) (a) Loev, B.; Kormendy, M. F. *Can. J. Chem.* **1964**, *42*, 176. (b) This condensation was later found to be markedly accelerated, and to proceed more cleanly, in the presence of powdered $NaHCO_3$.

(18) (a) The formamidine $Me_2NCH{=}NSO_2R$, formed by condensation of **11a** with DMF dimethyl acetal, was also examined as a primary sulfonamide masking group. Tosylation/amination ($EtNH_2$) then gave the expected amine, plus an isomer having a substituted protecting group $EtN{=}CHNHSO_2R$ (^{13}C and ^1H NMR, MS). The former product was cleaved to **13a** by dilute acid, but the latter material resisted 2 M HCl treatment for several days at room temperature (D. Pierce, unpublished observations). (b) Variations tried on the tosylation-amination reaction included the use of DMAP; MsCl, Ms_2O, and Ts_2O in place of TsCl; gaseous vs aqueous $EtNH_2$; and Mitsunobu conditions: Edwards, M. L.; Stemerick, D. M.; McCarthy, J. R. *Tetrahedron Lett.* **1990**, *31*, 3417.

(19) May, J. A. *J. Med. Chem.* Manuscript in preparation for submission.

Scheme 3



gave primary sulfonamide **16** in up to 80% yield on a 10−20-g scale. Once again, scale-up (>50 g) resulted in a dropoff in yield. The preferred route to **16** proceeded via sulfenyl chloride **3** and primary sulfenamide **14**. Oxidation of **14** with *m*-CPBA/$NaHCO_3$ produced sulfinamide **15** rapidly, but further oxidation of **15** to **16** was sluggish unless a large excess of reagents was used. This contrasted with the oxidation of **5** to **6**, in which the sulfinamide was observed by TLC as a minor, transitory component. Sulfinamide **15** was poorly soluble in most common solvents, and once precipitated could not be oxidized to **16** effectively.

The combination of H_2O_2 (20 equiv) and sodium tungstate (0.5 equiv) in ethyl acetate−water[21] gave superior results for the oxidation of **14** to **16**. This reaction was characterized by an accelerating exotherm from ambient to reflux temperature, requiring careful monitoring. A workable modification involved adding the H_2O_2 to a preheated reaction mixture to allow better control over the oxidation rate.[22] The prior chlorination and amination steps also proceeded well in ethyl acetate, so a one-flask procedure for the conversion of thioether **2** to sulfonamide **16** was possible. A series of eleven 1-kg runs delivered **16** in 64−79% yield and 98−99% purity.

Reaction of **16** with PBP and H_2SO_4 in ethyl acetate gave more reliable initiation and cleaner conversion than the earlier (HBr, THF) method. The use of freshly opened PBP in slight deficiency (0.9 equiv), plus a generous amount of acid, minimized dibromination; dibromo ketone in small amounts (<5%) was acceptable (see above), but in larger amounts was detrimental to the subsequent reduction. Bromo ketone **17** of >90% purity, containing ≤3% each of **16** and dibromo ketone, was obtained in 72−80% yield after trituration of the crude product with CH_2Cl_2.

For the (+)-Ipc_2BCl reduction of **17**, the water-immiscible, relatively nonhygroscopic solvent methyl *tert*-butyl ether (MTBE) proved superior to THF.[23] After complete reduction (3.5 h at −25 to −20 °C), aqueous NaOH was added to the crude mixture to cyclize the bromohydrin and partition the product **18** into the aqueous phase. Acidification and extraction into EtOAc was followed by dilution with toluene to effect crystallization, affording **18** in 70−77% yield and assaying at >98% for both HPLC chemical purity and ee.

Reactions of **18** with 3-bromopropyl methyl ether in the presence of a variety of bases and solvents were discouraging at first. Slow or incomplete conversion to multiple products, including both N- and O-alkylated materials, was observed. The combination of solid potassium carbonate and DMSO was then found to promote N-alkylation with excellent selectivity, affording the product **8b** in 94% yield. The remaining steps of the synthesis of **13b** (AL-4862) were performed according to Scheme 2 and proceeded in comparable yields to those observed in the **a** series.

Compound **18** also proved to be a versatile intermediate for preparation of diversely substituted experimental carbonic anhydrase inhibitors. Notably, alkylation of **18** with 1-bromo-3-chloropropane (K_2CO_3, DMSO) provided the *N*-(3-chloropropyl) derivative in 94% yield. Subsequent Li−Cl exchange selectively engaged the thienyl chloride and gave after SO_2/HOSA treatment the 3-chloropropyl analogue of **11b** (65%, mp 135−137 °C). The primary chloride could then be displaced with various nucleophiles, for example cyanide which provided an entry to carboxylic ester-bearing compounds.

These studies resulted in practical preparative routes to AL-4623A and AL-4862. The stepwise thioetherification strategy proved sound, but difficulties were encountered in subsequent processing to form the sulfonamide groups. Consequently, the original goal of replacing both low-temperature lithiations was realized only in part. Lithium−chlorine exchange provided an efficient alternative entry to the primary sulfonamide functionality. Use of the base-soluble thienothiazine **18**, in concert with a highly selective method for N-alkylation, proved to be a critical advance for high material throughput. The procedures described have been successfully adapted, with further refinements, to manufacturing scale.

Experimental Section

General Methods. 3-Acetyl-2,5-dichlorothiophene ("DCAT") was obtained from Lancaster Synthesis. Anhydrous THF and (+)-Ipc_2BCl were used as received from Aldrich Chemical Co. Pyridinium bromide perbromide (PBP, manufacturer's assay 91−98%) was used as received from Aldrich or Lancaster. Temperatures recorded are those of the reaction mixture. Concentration refers to removal of volatile components by rotary evaporation *in vacuo.* Melting points are uncorrected. Coupling constants (*J*) are reported

(20) The base solubility of secondary sulfonamides was also used to advantage for isolating the waxy methoxypropyl homologue of keto sulfonamide **6**, which could not be separated from the crude reaction mixture by trituration as done for **6**.

(21) Blacklock, T. J.; Butcher, J. W.; Sohar, P.; Lamanec, T. R.; Grabowski, E. J. J. *J. Org. Chem.* **1989**, *54*, 3907.

(22) CAUTION: Addition of brine to the oxidation mixture resulted in an exothermic reaction and eruption of the flask contents. Blank experiments verified that brine reacts exothermically with a combination of hydrogen peroxide and sodium tungstate. Separation of the aqueous oxidant phase, followed by thorough washing of the organic phase with bisulfite until a peroxide test was negative, remedied this problem. Sulfite is more effective than bisulfite for reducing organic peroxy compounds: Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12(4)*, 63−74: see p 64 and footnotes 17 and 18 therein.

(23) Solutions of (+)-Ipc_2BCl in MTBE could be prepared in advance and stored refrigerated for several days; however, upon longer storage (>1 month), several bottles burst from pressure buildup.

in hertz. Elemental analyses were performed by Atlantic Microlab (Norcross, GA). Reactions were monitored by TLC on E. Merck Silica Gel 60 F_{254} plates, with visualization by UV light and phosphomolybdic acid staining. Purity of reaction products was assayed by reverse-phase HPLC on C_{18} columns with UV detection at 255 nm. Enantiomeric excesses (ee) were determined using a Daicel OF analytical HPLC column with a mobile phase consisting of hexane/*i*-PrOH mixtures, containing 0.0−0.1% Et_3N.

3-Acetyl-5-chloro-2-(benzylthio)thiophene (2). A mixture of thiourea (1.29 kg, 16.9 mol), benzyl chloride (1.86 L, 2.04 kg, 16.1 mol), EtOH (13.5 L), and water (4.5 L) was heated to reflux over 2 h, then allowed to cool to 74 °C over 20 min. 3-Acetyl-2,5-dichlorothiophene (**1**) (3.00 kg, 15.4 mol) was added, followed by 4 M NaOH (10 L). The mixture was refluxed for 3 h, cooled to room temperature, diluted with water (10 L), stirred for 30 min, and treated with bleach (3 L of 5.25% NaOCl). After the mixture was stirred for 30 min, the solid was collected by filtration, washed with water (4 × 2.5 L) and 2-propanol (3 × 2 L), and dried in air at room temperature to give 4.22 kg (97%) of **2**. A sample was recrystallized from EtOH: mp 86−88 °C; ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 4.15 (s, 2H), 7.17 (s, 1H), 7.25−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.7, 40.5, 125.9, 127.3, 127.9, 128.7, 129.1, 134.9, 135.1, 147.2, 191.6. Anal. Calcd for $C_{13}H_{11}OS_2Cl$: C, 55.21; H, 3.92. Found: C, 55.34; H, 3.96.

***N*-(2-Methoxyethyl)-3-acetyl-5-chloro-2-thiophenesulfonamide (6).** Chlorine was bubbled into a stirred, ice-cooled solution of **2** (1.24 kg, 4.38 mol) in toluene (14 L) for 25 min, keeping the temperature below 8 °C, to form sulfenyl chloride **3**. Dry air was then bubbled through the solution for 1.2 h. 2-Methoxyethylamine (1.13 L, 13.2 mol) was added dropwise over 40 min, keeping the temperature below 12 °C. The resulting solution of sulfenamide **5** was washed with 1 M HCl (2 × 3L), and the combined washes were back-extracted with CH_2Cl_2 (2 × 2L). The combined organic solutions were washed with brine. Water (15 L) and $NaHCO_3$ (1.48 kg, 17.6 mol) were added to the organic solution, and the two-phase mixture was stirred vigorously and cooled to 8 °C. *m*-CPBA (84%, 2.85 kg, 13.8 mol) was added in portions over 1 h, taking care to avoid excessive foaming. The temperature was allowed to rise to 20 °C over 15.5 h. $NaHSO_3$ (1.5 kg) was added over 30 min and the phases were separated. The organic solution was washed with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated. The residual solid was triturated with hexane (4 L), collected by filtration, washed with hexane, and dried in air at room temperature to give 1.01 kg (77.5%) of **6**. A sample was recrystallized from MTBE: mp 92−93 °C; ^{1}H NMR ($CDCl_3$) δ 2.57 (s, 3H), 3.17−3.22 (m, 2H), 3.26 (s, 3H), 3.41−3.46 (m, 2H), 6.46 (br t, 1H), 7.33 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.4, 43.6, 58.7, 70.4, 128.9, 134.9, 138.4, 143.9, 192.5. Anal. Calcd for $C_9H_{11}NO_3S_2Cl$: C, 36.30; H, 4.06; N, 4.70. Found: C, 36.38; H, 4.02; N, 4.79.

***N*-(2-Methoxyethyl)-3-bromoacetyl-5-chloro-2-thiophenesulfonamide (7).** A 30% solution of HBr in HOAc (231 mL) was added to a stirred, 0 °C solution of **6** (3.43 kg, 11.6 mol) in THF (28 L). PBP ("90%", 3.69 kg, 10.4 mol) was added in 0.5-kg portions over 10 min, and the mixture was stirred at 0 °C until TLC showed consumption of **6**. Water (15 L) was added and the mixture was extracted with EtOAc (2 × 4L). The combined organic solution was washed with brine, dried ($MgSO_4$), filtered, and concentrated. 2-Propanol (4 L) was added to the residue to initiate crystallization. The mixture was chilled in an ice bath and the solid was collected by filtration, washed with 2-propanol (3 × 1.3 L) and hexane (2 × 2 L), and dried in air at room temperature to give 3.02 kg (70%) of **7**. This material contained 9.6% of the dibromo ketone by HPLC. A sample was recrystallized from EtOH: mp 84−86 °C; ^{1}H NMR ($CDCl_3$) δ 3.20−3.28 (m, 2H), 3.26 (s, 3H), 3.39−3.44 (m, 2H), 4.28 (s, 2H), 6.27 (br t, 1H), 7.40 (s, 1H).

(*S*)-3,4-Dihydro-6-chloro-4-hydroxy-2-(2-methoxyethyl)-4*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-Dioxide (8a). Under N_2, a precooled solution of (+)-Ipc_2BCl (1.96 kg, 6.09 mol) in anhydrous THF (8 L) was added to a stirred solution of **7** (1.51 kg, 4.02 mol) in anhydrous THF (28 L) keeping the temperature between −40 and −30 °C. The solution was stirred for 6 h at −35 to −25 °C, then allowed to warm to 20 °C over 15 h. TLC showed incomplete reaction. The solution was cooled to −30 °C and (+)-Ipc_2BCl (0.50 kg, 1.56 mol) was added. After 1 h the solution was concentrated and the residual oil was dissolved in Et_2O (15 L) and cooled to 10 °C. Diethanolamine (1.5 kg) was added over 10 min, forming a yellow precipitate. After 30 min the mixture was filtered and the precipitate was washed with Et_2O (3 × 1 L). 1 M NaOH (16 L) was added and the mixture was stirred at 20 °C for 15 h. The aqueous phase was separated and extracted with EtOAc (2 × 4L). The combined organic solutions were washed with 1 M HCl (10 L) and brine (10 L), dried ($MgSO_4$), filtered, and concentrated. The residual oil (2.77 kg) was combined with that from another run on the same scale and applied as a slurry in 10% EtOAc−hexane to a 30 × 50 cm silica gel column. The column was eluted at 250 mL/min with a gradient of 10% (60 L), 20% (20 L), 30% (20 L), 40% (20 L), 50% (20 L), and 70% EtOAc−hexane (40 L), followed by EtOAc (20 L), collecting 3-L fractions. The appropriate fractions were combined and concentrated to give 1.98 kg (83%) of **8a** as an oil. A sample was rechromatographed: $[\alpha]^{25}_D$ +4.0° (c = 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 3.31 (s, 3H), 3.38−3.91 (m, 5H), 4.16 (br s, 1H), 4.33 (dd, 1H, J = 16, 4), 4.57 (br s, 1H), 6.98 (s, 1H). Anal. Calcd for $C_9H_{12}NO_4S_2Cl$: C, 36.30; H, 4.06; N, 4.70. Found: C, 36.23; H, 4.05; N, 4.66.

3-Acetyl-5-chloro-2-thiophenesulfonamide (16). Chlorine was bubbled into a stirred solution of **2** (1.00 kg, 3.53 mol) in EtOAc (20 L) at 2−10 °C to form sulfenyl chloride **3**. The solution was purged with a stream of air for 1 h. Ammonia was bubbled in, keeping the temperature between 5 and 15 °C, to form sulfenamide **14**. The mixture was purged with air for 1 h. Water (5 L) was added and the solution was cooled to 15 °C. Sodium tungstate dihydrate (0.5 equiv, 583 g, 1.77 mol) was added, followed by 30% H_2O_2 (8 L) over 5 min. The mixture was heated at 35 °C for 2 h, then stirred at room temperature for 16 h. Water (5 L)

was added and the aqueous phase was separated. Water (5 L) was added to the organic phase, followed by solid $NaHSO_3$ with agitation, until peroxide test paper gave a negative test. The phases were separated and the organic solution was washed with saturated $NaHCO_3$ to pH 8, then with brine, dried (Na_2SO_4), filtered, and concentrated. The residual semisolid was triturated with MTBE to give a solid that was collected by filtration, washed with MTBE, and dried in air to give 597 g (71%) of **16**: mp 178−179 °C; ^{1}H NMR (DMSO-d_6) δ 2.55 (s, 3H), 7.70 (s, 1H), 7.72 (s, 2H, exchanges); ^{13}C NMR (DMSO-d_6) δ 30.0, 130.0, 131.5, 138.8, 145.9, 193.2. Anal. Calcd for $C_6H_6ClNO_3S_2$: C, 30.06; H, 2.52; N, 5.84; S, 26.75. Found: C, 30.19; H, 2.51; N, 5.80; S, 26.70.

3-Bromoacetyl-5-chloro-2-thiophenesulfonamide (17). To a stirred suspension of **16** (1.09 kg, 4.55 mol) and EtOAc (22 L) at 1 °C was added PBP (mfr. assay 98%, 1.30 kg, 4.00 mol) in one portion. H_2SO_4 (concentrated, 544 mL) was added over 10 min, causing the temperature to rise to 5 °C. The mixture was stirred for 1.5 h, water (5 L) was added, the mixture was stirred for 5 min, and the phases were separated. The organic solution was washed with brine to pH 3 (4 × 5 L required), dried over Na_2SO_4 (1 kg), filtered, and concentrated. The residue was triturated with CH_2Cl_2 (2 L) and chilled for 15 min. The solid was collected by filtration, washed with cold CH_2Cl_2 (2 L), and dried in air at room temperature to give 1.04 kg (72%) of **17**. A sample was recrystallized from CH_2Cl_2−EtOAc−hexane: mp 147−148 °C; ^{1}H NMR (acetone-d_6) δ 4.76 (s, 2H), 7.11 (br s, 2H, exchanges), 7.76 (s, 1H). Anal. Calcd for $C_6H_5NO_3S_2$-ClBr: C, 22.62; H, 1.58; N, 4.40; S, 20.13. Found: C, 22.66; H, 1.60; N, 4.35; S, 20.12.

(*S*)-3,4-Dihydro-6-chloro-4-hydroxy-4*H*-thieno[3,2-*e*]-1,2-thiazine-1,1-dioxide (18). Under N_2, a stirred suspension of **17** (855 g, 2.68 mol) and MTBE (12.5 L) was cooled to −40 °C using a dry ice/2-propanol bath. (+)-Ipc$_2$BCl (4.5 L of a 1.2 M solution in MTBE, 5.4 mol, 2 equiv) was added via a cannula over 30 min, causing the temperature to rise to −32 °C. After 3.5 h at −25 to −20 °C, reduction was complete. The bromohydrin solution was warmed to 0 °C and 1 M aqueous NaOH (11 L) was added over 10 min, causing the temperature to rise to 22 °C. The biphasic mixture was stirred vigorously at room temperature for 2 h. The phases were separated and the aqueous solution was extracted with MTBE (3 L), acidified to pH 1 using 12 M HCl, and extracted with EtOAc (2 × 4 L). The combined EtOAc extracts were washed with brine (3 L), dried (Na_2SO_4, 1 kg), filtered, and concentrated to about 1 L. Toluene (2 L) was added. Upon further concentration, removing EtOAc, the product crystallized and was collected by filtration, washed with toluene (2 L) and CH_2Cl_2 (2 L), and dried in air at room temperature to give 498 g (77%) of **18**. HPLC analysis of this material showed >98% chemical purity and >98% ee. A sample was recrystallized from $CHCl_3$: mp 126−127 °C; $[\alpha]^{25}_D$ −5.9° (c = 1, MeOH); ^{1}H NMR (DMSO-d_6) δ 3.35−3.50 (m, 1H), 3.55−3.68 (m, 1H), 4.58 (q, 1H, J = 7), 5.90 (d, 1H, J = 7, exchanges), 7.20 (s, 1H), 8.15 (br t, 1H, J = 6, exchanges); ^{13}C NMR (DMSO-d_6) δ 49.1, 61.7, 127.1, 132.7, 133.3, 146.6. Anal. Calcd for $C_6H_6NO_3S_2Cl$: C, 30.06; H, 2.52; N, 5.84. Found: C, 30.14; H, 2.56; N, 5.80.

(*S*)-3,4-Dihydro-6-chloro-4-hydroxy-2-(3-methoxypropyl)-4*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-Dioxide (8b). To a stirred mixture of **18** (350 g, 1.46 mol), DMSO (1.75 L), and K_2CO_3 (605 g, 4.38 mol) was added 3-bromopropyl methyl ether (268 g, 1.75 mol) in eight equal portions spaced 1 h apart. After a further 1.5 h the mixture was poured into saturated NaCl (18 L), extracted with MTBE (2 × 4 L), and the combined extracts were washed with 1 M NaOH (2 L), 1:1 bleach/water (2 L), and brine (2 L), dried over Na_2SO_4 (500 g), filtered, and concentrated to provide 427 g (94%) of **8b** as a light-yellow syrup. A sample was purified by chromatography on silica (5% acetone−CH_2Cl_2): $[\alpha]^{25}_D$ +11.4° (c = 1, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.83−2.04 (m, 2H), 3.25 (s, 3H), 3.28−3.81 (m, 6H), 4.08 (dd, 1H, J = 15, 4), 4.64 (br s, 1H), 6.96 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.9, 46.9, 53.5, 58.5, 61.3, 69.8, 126.0, 132.4, 135.9, 143.4. Anal. Calcd for $C_{10}H_{14}NO_4S_2Cl$: C, 38.52; H, 4.53; N, 4.49. Found: C, 38.65; H, 4.54; N, 4.47.

(*S*)-3,4-Dihydro-4-hydroxy-2-(3-methoxypropyl)-4*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-Dioxide (11b). Under N_2, a solution of **8b** (1.06 kg, 3.42 mol) in anhydrous THF (27 L) was cooled to −70 °C using a dry ice/2-propanol bath. *n*-BuLi (7.7 mol, 2.3 equiv, 3.08 L of a 2.5 M hexane solution) was added dropwise over 2.5 h while the temperature was kept below −66 °C. After 1 h, SO_2 was introduced into the mixture until an aliquot quenched into water showed pH 4. The mixture was allowed to warm to room temperature overnight and then concentrated. The residue was dissolved in water (5 L), and this solution was added in one portion to a 0 °C solution of NaOAc·3H_2O (2.80 kg, 20.5 mol) and hydroxylamine-*O*-sulfonic acid (1.55 kg, 13.7 mol) in water (6 L), causing the temperature to rise to 25 °C. After being stirred for 15 h at room temperature the solution was extracted with EtOAc (3 × 4 L). The combined extracts were washed with saturated $NaHCO_3$ until basic, then with brine, dried (Na_2SO_4), filtered, and concentrated. CH_2Cl_2 (6 L) was added to the residual oil along with with 5 g of seed crystals, and the mixture was chilled and agitated to induce crystallization. The solid was collected by filtration, washed with CH_2Cl_2, and dried in air at room temperature to give 748 g (61%) of **11b** of 98.5% purity by HPLC. Another run starting with 700 g of **8b** yielded 552 g (69%) of **11b** of comparable purity. A sample was recrystallized from MeOH−H_2O: mp 111−113 °C; $[\alpha]^{23}_{405}$ +21.9° (c = 0.45, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.83 (pent, 2H, J = 7), 3.21 (s, 3H), 3.3−3.4 (m, 4H), 3.73 (dd, 1H, J = 15, 5.6), 3.92 (dd, 1H, J = 15, 4.5), 4.82 (br q, 1H, J = 5), 6.15 (d, 1H, J = 6, exchanges), 7.60 (s, 1H), 8.05 (s, 2H, exchanges); ^{13}C NMR (DMSO-d_6) δ 28.5, 46.6, 52.6, 57.9, 60.2, 68.8, 129.7, 135.4, 145.9, 148.8. Anal. Calcd for $C_{10}H_{16}N_2O_6S_3$: C, 33.69; H, 4.53; N, 7.86. Found: C, 33.61; H, 4.55; N, 7.77.

(*R*)-3,4-Dihydro-4-(ethylamino)-2-(3-methoxypropyl)-4*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-Dioxide (13b, AL-4862). A solution of **11b** (438 g, 1.23 mol), acetonitrile (4.0 L), and trimethyl orthoacetate (630 mL, 2.83

mol) was heated at reflux (85 °C) for 15 h. After cooling to 30 °C (4 h), the solution was concentrated and the imidate **12b** (563 g) was dissolved in anhydrous THF (2.2 L) and cooled to −10 °C under N_2. Et_3N (377 mL, 2.70 mol) and TsCl (469 g, 2.46 mol) were added. A precipitate formed and the temperature rose to −2 °C over 10 min. After 2 h, TLC indicated complete tosylation. 70% aqueous $EtNH_2$ (3.0 L, 37 mol) was added dropwise (0.4 L over 1 h, exothermic reaction with excess TsCl; then 2.6 L over 0.25 h), keeping the temperature below 11 °C. The mixture was stirred at room temperature for 15 h and cooled to −5 °C, and 12 M HCl (3.0 L) was added dropwise over 1 h causing a temperature rise to 50 °C. The cooled (25 °C) solution was washed with MTBE (2 × 2 L) and the combined washes were back-extracted with 1 M HCl (200 mL). The pH of the aqueous solution was adjusted to 8 over 1 h using solid $NaHCO_3$, causing a white solid to precipitate. After the solution was stirred overnight, the solid was collected by filtration and washed with water and dried to give 246 g of **13b**. The filtrates were extracted with EtOAc (2 × 4 L), the extract was dried ($MgSO_4$), filtered, and concentrated, and the residue was recrystallized from 2-propanol to provide an additional 40 g of **13b**, for a total yield of 286 g (61%) of **13b**. HPLC analysis of this material showed 97.4% purity and >99% ee. A sample was recrystallized from 2-propanol: mp 125−127 °C; $[\alpha]^{25}_{312.6}$ −26.1° ($c = 1$, pH 3 citric acid buffer); ^{1}H NMR (DMSO-d_6) δ 1.04 (t, 3H, $J = 7$), 1.83 (pent, 2H, $J = 7$), 2.5 (br s, 1H, exchanges), 2.60 (q, 2H, $J = 7$), 3.1−3.2 (m, 1H), 3.22 (s, 3H), 3.38 (t, 2H, $J = 7$), 3.3−3.5 (m, 1H), 3.80 (m, 2H), 4.12 (t, 1H, $J = 7$), 7.68 (s, 1H), 8.02 (br s, 2H, exchanges); ^{13}C NMR (DMSO-d_6) δ 15.6, 28.6, 40.0, 45.6, 49.0, 50.3, 57.9, 68.8, 129.8, 135.6, 146.6, 148.4. Anal. Calcd for $C_{12}H_{21}N_3O_5S_3$: C, 37.58; H, 5.48; N, 10.96. Found: C, 37.66; H, 5.56; N, 10.98.

Supporting Information Available

Infrared and mass spectra; experimental procedures and analytical data for **4**, **9**, **10**, **11a** and **13a**; analytical data for **3**, **5**, **12a**, **12b**, **14** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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