Enantioselective Synthesis of AL-4414A, a Topically Active Carbonic Anhydrase Inhibitor

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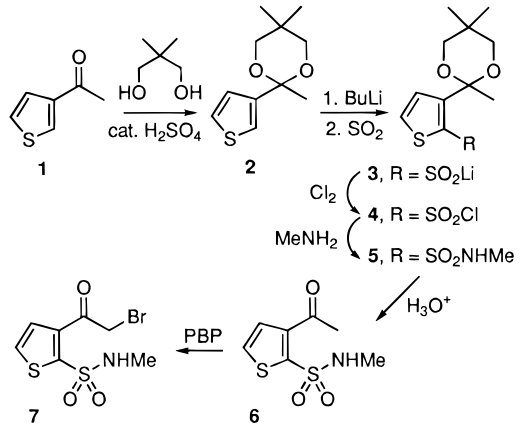
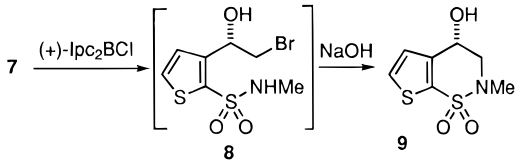
Systemically administered carbonic anhydrase inhibitors (CAIs) have long been used to control the elevated intraocular pressure associated with glaucoma.[1] However, the wide range of side effects associated with their use limits compliance, particularly among the elderly. Recently, the synthesis[2] and clinical evaluation[3] of several water-soluble topically active CAIs, having the potential to avoid these problems by local delivery of a lower dose, have been reported. AL-4414A, (*R*)-4-(ethylamino)-3,4-dihydro-2-methyl-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride, is a representative of a new class of topically active water-soluble CAIs[4] and was identified as a clinical candidate. Initial samples of AL-4414A were obtained by resolution of racemic material via the diastereomeric di-*p*-toluoyl-D-tartaric acid salts.[4] The lack of an efficient way to recycle the *S* enantiomer, as well as difficulties encountered in scale-up of the racemic synthesis, led us to develop the present synthesis in which α-bromo ketone **7** is reduced with (+)-*B*-chlorodiisopinocampheylborane ((+)-Ipc_2BCl),[5] and the resulting (*S*)-bromohydrin **8** is cyclized to form the thieno[3,2-*e*]thiazine ring system.

Ketal **2**,[4] obtained from 3-acetylthiophene (**1**) in 60−70% yield, was treated with BuLi[6] followed by SO_2 to give lithium sulfinate **3** (Scheme 1). Slow addition of **3** to excess aqueous Cl_2 produced sulfonyl chloride **4**. A simpler procedure, in which NCS was added to a suspension of **3** in THF, gave a side product suspected to be the symmetrical bis-sulfone[7] resulting from reaction of **3** with **4**. Without delay, **4** was added to a cold solution of $MeNH_2$ in THF to afford sulfonamide ketal **5**, which was hydrolyzed to give sulfonamide **6** in 70−80% overall yield after recrystallization. Bromination of **6** with pyridinium bromide perbromide (PBP) and catalytic HCl in THF provided **7** (70−80%).

Scheme 1



Scheme 2



Consonant with results documented for reductions of phenacyl halides,[5] (+)-Ipc_2BCl reduced bromo ketone **7** with excellent enantioselectivity (Scheme 2). Treatment of a solution of **7** in THF with (+)-Ipc_2BCl (2 equiv)[8] at −25 °C effected complete reduction in 18−24 h. Crude bromohydrin **8**, obtained after addition of diethanolamine to precipitate boron species,[5] cyclized to **9** on exposure to aqueous NaOH. When K_2CO_3 or DBU was used instead, **8** cyclized more slowly, allowing isolation of the presumed intermediate epoxide. Thieno[3,2-*e*]thiazine alcohol **9** was obtained in 75−85% yield after chromatography to remove α-pinene and a small amount of isopinocampheol. The ee of **9**, typically 92−94%, was increased to >98% by recrystallization from toluene. Upon esterification of **9** with (*R*)-(−)-α-methoxyphenylacetic acid, the thienyl proton resonances shifted upfield[9] (H-5, 0.6; H-6, 0.2 ppm) in accord with the expected[5] absolute configuration.

Hoping to avoid chromatographic purification of **9** on a multihundred gram scale, we studied the route shown in Scheme 3, wherein crude **9** is converted to amine **10** that is freed of pinene and other byproducts by extraction into aqueous acid. We planned to install the C-6 sulfonamide via electrophilic sulfonation of **10**, as reported[2a] for compound **12**. Both of these reactions proved inefficient. Although amine **10** could be obtained in acceptable yield from purified **9** via the mesylate or tosylate, the yield fell to 20−30% when crude **9** was used. Sequential treatment of **10** with $SO_3-H_2SO_4$, $SOCl_2$, and NH_4OH[2a] provided bis-sulfonamide **11** in only 25−35% yield; furthermore, the quench into aqueous ammonia was difficult to perform even on a small scale. An alternative approach to the sulfonyl chloride, direct chlorosulfonation with $ClSO_3H$, was unsuccessful.

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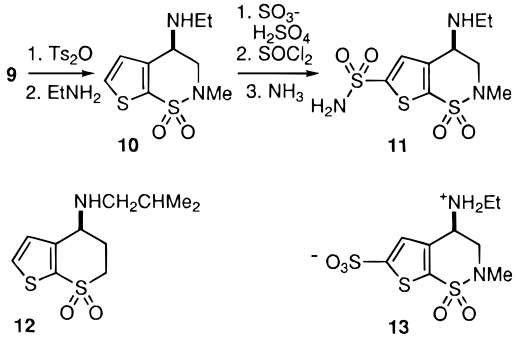
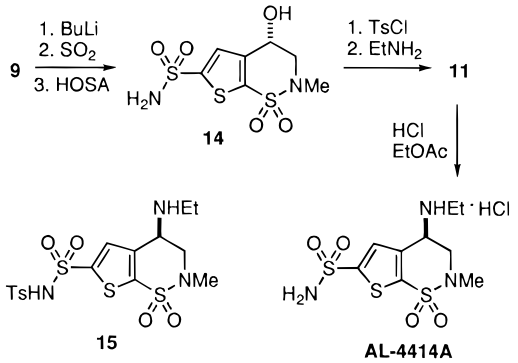
(1) Sugrue, M. F.; Smith, R. L. *Annu. Rep. Med. Chem.* **1985**, *20*, 83.
(2) (a) Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Turner Jones, E. T.; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 763. (b) Blacklock, T. J.; Sohar, P.; Butcher, J. W.; Lamanec, T.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 1672.
(3) Wilkerson, M.; Cyrlin, M.; Lippa, E. A.; Esposito, D.; Deasy, D.; Panebianco, D.; Fazio, R.; Yablonski, M.; Shields, B. *Arch. Ophthalmol.* **1993**, *111*, 1343 and cited references.
(4) Dean, T. R.; Chen, H.-H.; May, J. A. Alcon Laboratories, Inc. U.S. Patents 5,378,703 (3 Jan 1995); 5,240,923 (31 Aug 1993); 5,153,192 (6 Oct 1992).
(5) Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res* **1992**, *25*, 16.
(6) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: New York, 1992; p 607.
(7) This side product was distinct from **4** by TLC but had a similar ^1H NMR spectrum and reacted with $MeNH_2$ to form **5**: Backer, H. J. *Rec. Trav. Chim. Pays-Bas* **1951**, *70*, 254.
(8) At least 2 equiv of (+)-Ipc_2BCl were required for an acceptable reaction rate.
(9) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

S0022-3263(97)01550-8 CCC: $14.00

Scheme 3



Scheme 4



The C-6 sulfonic acid could be obtained in 55−60% yield, as zwitterion **13**, by treating **10** with fuming H_2SO_4 at rt. However, attempted conversion of **13** to the sulfonamide via the sulfonyl chloride, by treatment with $SOCl_2$ or $POCl_3$ followed by NH_4OH, gave only traces of **11**.

As an alternative to electrophilic sulfonation, we turned to a lithiation/sulfonamidation procedure similar to that used for converting **2** to **7**. Sequential treatment of **10** with BuLi (2 equiv), SO_2, and hydroxylamine-*O*-sulfonic acid (HOSA)[10] provided **11** in low yield. This procedure suffered from poor solubility of the dianion of **10** in THF below −20 °C. When the lithiation was conducted at 0 °C, reversion to ketone **6** was observed.

In contrast to our experience with **10**, conversion of **9** to sulfonamide alcohol **14** worked well (Scheme 4). A solution of **9** in THF at ca. −70 °C was treated with 2.2 equiv of BuLi followed by excess SO_2 to produce the C-6 lithium sulfinate, which in turn reacted with HOSA to give **14** (65−75%). Conversion of **14** to **11** was accomplished in about 40% yield via the tosylate, which was treated directly with $EtNH_2$. The yield of **11** was limited by elimination and by formation of sulfonimide **15**, isolated in 24% yield from one run. Treatment of **11** with HCl, followed by recrystallization of the salt from aqueous EtOH, provided AL-4414A in 84% yield and >98% ee. Despite the need for chromatographic purification of the key intermediate **9**, this route readily afforded multihundred gram quantities of AL-4414A for toxicological and clinical evaluation.

Experimental Section

General Methods. Anhydrous THF, (+)-Ipc_2BCl, and pyridinium bromide perbromide (pyridinium tribromide, "tech, 90%", mfr. assay 98%) were used as received from Aldrich Chemical Co. 3-Acetylthiophene was obtained from Lancaster Synthesis. Temperatures recorded are those of the reaction mixture. Concentration refers to removal of volatile components by rotary evaporation at reduced pressure. Coupling constants (J) are reported in Hz. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA. Melting points are uncorrected. Enantiomeric excess (ee) was determined by HPLC using a Daicel OF analytical column with a mobile phase consisting of 1:1 hexane/i-PrOH, containing ca. 0.05% Et_3N. The *R* enantiomer of both **9** and **11** eluted first.

3-(2,5,5-Trimethyl-1,3-dioxan-2-yl)thiophene (2).[4] A mixture of 3-acetylthiophene (**1**) (400 g, 3.17 mol), 2,2-dimethyl-1,3-propanediol (4.76 mol, 492 g), and H_2SO_4 (0.5 mL) in toluene (2.6 L) was refluxed for 2 days with water removal (Dean−Stark trap) and then concentrated by distillation at 1 atm, removing 1.5 L of toluene. After the mixtured was cooled to rt under a drying tube, K_2CO_3 (50 g) was added, followed by saturated $NaHCO_3$ (1 L) and hexane (1 L). The organic phase was separated, and the aqueous phase was extracted with EtOAc (3 × 250 mL). The combined organic extracts were washed with brine (6 × 1 L), dried ($MgSO_4$), treated with decolorizing carbon, filtered through Celite 521, and concentrated. The residue was distilled through a 12 in. Vigreux column to provide 442 g (65%) of **2**: $bp_{0.1}$ 88 °C; mp 35−37 °C; IR (KBr) 3095, 2952, 2866, 1473, 1366, 1248, 1178, 1080, 1013, 841, 686 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31 (dd, 1H, J = 3, 5), 7.23 (dd, 1H, J = 1, 3), 7.02 (dd, 1H, J = 1, 5), 3.54 (d, 2H, J = 11), 3.39 (d, 2H, J = 11), 1.57 (s, 3H), 1.23 (s, 3H), 0.62 (s, 3H). Repeated attempts to secure a satisfactory microanalytical sample of **2** were not successful.

***N*-Methyl-3-acetyl-2-thiophenesulfonamide (6).** BuLi (1.32 mol, 574 mL of a 2.3 M hexane solution) was added to a stirred solution of **2** (255 g, 1.20 mol) in hexane (2 L) under N_2 over 10 min at −30 to −20 °C. The solution was allowed to warm to rt, kept at rt for 2 h, and then cooled to −40 °C and treated with SO_2 until an aliquot quenched into water was acidic (pH 4−5). The mixture was stirred overnight while being warmed to rt and then concentrated. The solid residue was dissolved in water (2 L) and added dropwise over 2 h to a vigorously stirred, 0 °C saturated solution of Cl_2 in water (4 L of Cl_2 was bubbled into the mixture during this operation). The mixture was stirred for a further 15 min, and then **4** was collected by filtration and washed with cold water. The moist sulfonyl chloride **4** was slurried in THF (1 L) and added over 15 min to a −10 °C saturated solution of $MeNH_2$ in THF (1.5 L). The mixture was allowed to warm to rt overnight and then concentrated to provide sulfonamide ketal **5**. The crude ketal was dissolved in a solution of acetone (1.8 L) and 2 M HCl (0.6 L) and stirred at rt for 3 d. Upon concentration, a white solid precipitated, which was collected by filtration, washed with water, and dried to provide 223 g (86%) of crude **6**. Another 10 g of crude **6** separated from the filtrate. Recrystallization from MeOH with carbon treatment provided 201 g (76%) of **6**: mp 102−103 °C; IR (KBr) 3322, 3093, 3076, 1677, 1506, 1391, 1355, 1337, 1244, 1166, 1120, 1066, 767, 689 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.59 (d, 1H, J = 5), 7.55 (d, 1H, J = 5), 6.16 (br, 1H), 2.70 (d, 3H, J = 5), 2.63 (s, 3H). Anal. Calcd for $C_7H_9NO_3S_2$: C, 38.34; H, 4.14; N, 6.39. Found: C, 38.41; H, 4.13; N, 6.42.

Data for **4**: ^1H NMR ($CDCl_3$) δ 7.73 (d, 1H, J = 5), 7.24 (d, 1H, J = 5), 3.58 (d, 2H, J = 10), 3.48 (d, 2H, J = 10), 1.81 (s, 3H), 1.27 (s, 3H), 0.71 (s, 3 H); MS (CI, Me_3CH) 311 (M + 1).

Data for **5**: ^1H NMR ($CDCl_3$) δ 7.50 (d, 1H, J = 5), 7.16 (d, 1H, J = 5), 5.30 (m, 1H), 3.52 (s, 4H), 2.80 (d, 3H, J = 5), 1.71 (s, 3H), 1.20 (s, 3H), 0.75 (s, 3H); MS (CI, Me_3CH) 306 (M + 1).

***N*-Methyl-3-(bromoacetyl)-2-thiophenesulfonamide (7).** Pyridinium bromide perbromide (524 g, ~1.64 mol, 0.9 equiv) was added in portions over 10 min to a stirred, 10 °C solution of **6** (398 g, 1.82 mol) in anhydrous THF (2 L) containing 1 mL of 12 M HCl. After 30 min, the mixture was allowed to warm to 13 °C, whereupon a precipitate formed. The mixture was cooled to 0 °C, kept at 0 °C for 1 h, and poured into ice−water (8 L). After the mixture was stirred for 30 min, the solid was collected by filtration and washed with water (4 L). The moist solid was added to EtOH (2 L), and the suspension was stirred for 30 min. The solid was collected by filtration and dried at rt under vacuum for 2 d to provide 403 g (74%) of **7**, which was used without further purification. The analytical sample was secured by recrystallization from toluene−MeOH: mp 118−119 °C; IR (KBr) 3310, 3106, 1675, 1503, 1394, 1323, 1250, 1171, 1160, 1125, 1063, 732, 697 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.95 (d, 1H,

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

$J = 5$), 7.81 (d, 1H, $J = 5$), 6.45 (br m, 1H), 4.78 (s, 2H), 2.68 (s, 3H). Anal. Calcd for $C_7H_8BrNO_3S_2$: C, 28.20; H, 2.69; N, 4.70. Found: C, 28.26; H, 2.67; N, 4.76.

(*S*)-(+)-4-Hydroxy-3,4-dihydro-2-methyl-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-Dioxide (9). A solution of (+)-Ipc$_2$BCl (900 g, 2.8 mol, 1.56 equiv) in anhyd THF (1 L) was added to a stirred solution of **7** (536 g, 1.80 mol) in anhyd THF (14 L) under N_2 at −35 to −25 °C. After 6 h at −25 °C, TLC indicated incomplete reduction, so 200 g of (+)-Ipc$_2$BCl was added. After an additional 2.5 h, 100 g of (+)-Ipc$_2$BCl was added, and the mixture was allowed to warm to rt overnight. Acetone (150 mL) was added and the mixture stirred for 30 min and then cooled to 10 °C. Diethanolamine (320 g) was added in portions, and the mixture was stirred for 6 h and then filtered through Celite 521. The filtrate was concentrated, removing 11 L of solvent. To the residue was added acetone (2 L), water (1 L), and 50% NaOH (120 mL). The temperature rose to 40 °C and then cooled to rt. The mixture was stirred overnight and then concentrated, and the remaining aqueous solution was extracted with EtOAc (4 L). After drying ($MgSO_4$), the extract was concentrated, leaving 1.5 kg of crude product. This material was purified by chromatography on silica gel (230−400 mesh), eluting with 30% EtOAc/hexane to remove α-pinene, and then with 50% EtOAc/hexane, followed by EtOAc, to secure **9** (319 g, 81%, 94% ee). Recrystallization from toluene afforded analytically pure material of >98% ee: mp 98−99 °C; IR (KBr) 1330, 1168, 1138, 1065, 962, 708 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.57 (d, 1H, $J = 5$), 7.15 (d, 1H, $J = 5$), 4.87 (m, 1H), 4.04 (dd, 1H, $J = 4, 15$), 3.76 (dd, 1H, $J = 5, 15$), 3.00 (s, 3H), 2.97 (d, 1H, $J = 7$); ^{13}C NMR ($CDCl_3$) δ 143.5, 132.5, 130.0, 126.8, 61.7, 56.0, 37.7; MS (CI, Me_3CH) *m*/*z* 220 (M + 1), 202 ((M + 1) − H_2O); $[\alpha]^{25}_D$ +21.6°(*c* = 1, MeOH). Anal. Calcd for $C_7H_9NO_3S_2$: C, 38.34; H, 4.14; N, 6.39. Found: C, 38.34; H, 4.13; N, 6.44.

(*R*)-α-Methoxyphenylacetate of 9. To a stirred solution of **9** (0.3 g, 1.4 mmol) in 5 mL of CH_2Cl_2 were added DMAP (0.02 g, 0.16 mmol), (*R*)-(−)-α-methoxyphenylacetic acid (0.27 g, 1.6 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.3 g, 1.6 mmol). After 1.5 h, the solution was washed with saturated KH_2PO_4 and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (25% EtOAc-hexanes) to give 0.3 g of ester: ^{1}H NMR ($CDCl_3$) δ 7.40 (d, 1H, $J = 5$), 7.34 (br s, 5H), 6.58 (d, 1H, $J = 5$), 5.89 (dd, 1H, $J = 3, 4$), 4.80 (s, 1H), 4.29 (dd, 1H, $J = 4.5, 16$), 3.71 (dd, 1H, $J = 3, 16$), 3.40 (s, 3H), 2.88 (s, 3H).

(*R*)-4-(Ethylamino)-3,4-dihydro-2-methyl-2*H*-thieno[3,2-*e*]-1,2-thiazine 1,1-Dioxide (10). A solution of *p*-toluenesulfonic anhydride (7.40 g, 22.7 mmol) in CH_2Cl_2 (40 mL) was added over 10 min to a stirred, 5 °C solution of **9** (4.37 g, 20.0 mmol) and DMAP (3.16 g, 25.9 mmol) in CH_2Cl_2 (40 mL) under Ar. The mixture was stirred in ice for 15 min and then allowed to warm to rt over 2 h. Water was added, and after being stirred for 30 min, the mixture was partitioned between EtOAc and 0.2 M H_2SO_4. The organic phase was washed with water and brine, dried ($MgSO_4$), and concentrated to provide 6.32 g (85%) of crude tosylate: ^{1}H NMR ($CDCl_3$) δ 7.85 (d, 1H, $J = 8$), 7.52 (d, 1H, $J = 5$), 7.42 (d, 1H, $J = 8$), 6.78 (d, 1H, $J = 5$), 5.48 (m, 1H), 4.30 (dd, 1H, $J = 4, 16$), 3.82 (dd, 1H, $J = 2, 16$), 2.87 (s, 3H), 2.50 (s, 3H).

A solution of the crude tosylate (6.65 g, 17.8 mmol) in THF (35 mL) was added to ice-cold 70% aqueous $EtNH_2$ (200 mL), and the mixture was allowed to warm to rt over 5 h. EtOAc (500 mL) was added, and the solution was washed twice with water. The water washes were combined and back-extracted with EtOAc. The combined organic solutions were then extracted with 0.2 M H_2SO_4 (to pH 1), water, and brine, and the combined aqueous extracts were washed with EtOAc, basified with 50% NaOH, and extracted with CH_2Cl_2. After a water wash, the CH_2Cl_2 extract was dried ($MgSO_4$) and concentrated to give 2.52 g (57%) of **10**. The analytical sample was secured by recrystallization from toluene−MeOH: mp 99−100 °C; IR (KBr) 1344, 1326, 1316, 1189, 1162, 1136, 1103, 750, 624, cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.53 (d, 1H, $J = 5$), 7.12 (d, 1H, $J = 5$), 4.11−4.04 (m, 1H), 3.93−3.70 (m, 2H), 2.98 (s, 3H), 2.75 (q, 2H, $J = 7$), 1.35 (br, 1H), 1.13 (t, 3H, $J = 7$); $[\alpha]^{25}_D$ −14.8° (*c* = 1, MeOH). Anal. Calcd for $C_9H_{14}N_2O_2S_2$: C, 43.88; H, 5.73; N, 11.37. Found: C, 43.93; H, 5.76; N, 11.42.

(*R*)-4-(Ethylamino)-3,4-dihydro-2-methyl-1,1-dioxo-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonic Acid (13). Fuming H_2SO_4 (4 mL) was added to a stirred solution of **10** (3.0 g, 0.12 mol) in CH_2Cl_2 (5 mL). After 22 h at rt, the CH_2Cl_2 was decanted and the viscous residue poured onto ice, using water to rinse. The solution was adjusted to pH 7 with 0.5 M $Ba(OH)_2$, filtered through Celite 521, and concentrated. The residue was dissolved in EtOH, and the solution was concentrated to give 3.1 g (78%) of crude **13**.

A 1.5 g sample of this solid was dissolved in 50% aqueous MeOH (30 mL), and the pH of the solution was adjusted to 3 using 0.2 M H_2SO_4. The solution was filtered and concentrated to provide 1.05 g of a solid that was dissolved in hot MeOH (80 mL), treated with decolorizing carbon, filtered, and cooled to 0 °C. The solid that separated was collected by filtration, providing 0.1 g of **13**. Dilution of the filtrate with an equal volume of Et_2O, filtration, and concentration left a residue that, after trituration with MeOH (5 mL), provided another 0.4 g of **13**: mp 283−285 °C; IR (KBr) 3446, 3022, 2853, 1459, 1319, 1244, 1196, 1165, 1070 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.00 (br d, 2H, exchanges), 7.60 (s, 1H), 4.90 (br s, 1H), 4.04 (d, 2H, $J = 7$), 3.10 (br s, 2H), 2.86 (s, 3H), 1.22 (t, 3H, $J = 7$). Anal. Calcd for $C_9H_{14}N_2O_5S_3$: C, 33.11; H, 4.32; N, 8.58; S, 29.47. Found: C, 33.18; H, 4.34; N, 8.61; S, 29.38.

(*S*)-(−)-4-Hydroxy-3,4-dihydro-2-methyl-2*H*-thieno[3,2-*e*]-1,2-thiazine- 6-sulfonamide 1,1-Dioxide (14). BuLi (1.3 mol, 520 mL of a 2.5 M hexane solution) was added to a mechanically stirred solution of **9** (129.5 g, 0.591 mol) in anhyd THF (1.7 L) under N_2 over 40 min at −72 to −60 °C. The solution was allowed to warm to −23 °C over 4 h, and then SO_2 was introduced via a gas inlet tube for 30 min. The mixture was allowed to warm to 10 °C and then concentrated. The white solid obtained was dissolved in water (5 L) containing NaOAc·3H_2O (746 g, 5.49 mol). HOSA (300 g, 2.65 mol) was added, and the solution was stirred at rt for 24 h. $NaHCO_3$ was added to adjust the pH to 7, and the solution was extracted with EtOAc (2 × 1.5 L). The combined extracts were dried ($MgSO_4$) and concentrated to give a white solid, which was washed with CH_2Cl_2 (3 × 200 mL) and Et_2O (2 × 800 mL) and dried in air to a constant weight of 135 g (77%) of **14**, which was used without further purification. The analytical sample was secured by recrystallization from toluene−MeOH: mp 173−174 °C; IR (KBr) 3497, 3388, 3244, 1354, 1332, 1164, 1066, 1009, 965, 680, 614 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.05 (s, 2H), 7.60 (s, 1H), 6.16 (d, 1H, $J = 6$), 4.90−4.83 (m, 1H), 3.92 (dd, 1H, $J = 5, 15$), 3.69 (dd, 1H, $J = 6, 15$), 2.92 (s, 3H); $[\alpha]^{25}_D$ −1.4° (*c* = 1, MeOH). Anal. Calcd for $C_7H_{10}N_2O_5S_3$: C, 28.18; H, 3.38; N, 9.39. Found: C, 28.24; H, 3.44; N, 9.30.

(*R*)-4-(Ethylamino)-3,4-dihydro-2-methyl-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-Dioxide (11). Et_3N (155 mL, 1.11 mol) and *p*-TsCl (211 g, 1.11 mol) were added to a stirred, −10 °C solution of **14** (330 g, 1.11 mol) in anhyd THF (6.6 L), and the mixture was allowed to warm to rt over 18 h. TLC analysis indicated incomplete tosylation, so another 0.5 equiv each of Et_3N and *p*-TsCl were added. This was repeated 8 h later, and the mixture was then stirred at rt for another 24 h. The mixture was cooled to 10 °C, and anhyd $EtNH_2$ (1.19 L, 16.5 equiv) was added slowly, keeping the temperature below 15 °C. After 36 h at rt, the solution was concentrated. Residual THF was removed by adding EtOAc (2 L) and concentration. Upon attempted partition of the residue between 1 M HCl (6 L) and Et_2O (2 L), a precipitate, believed to be AL-4414A, separated. The material was collected by filtration, washed with Et_2O (1.5 L), and dried to provide 114 g of "solid A." The aqueous phase was removed from the filtrate and extracted with Et_2O, and the combined organic phases were back-extracted with 1 M HCl. The aqueous solutions were combined, and the pH was adjusted to 9−10 using concd NH_4OH. After NaCl (300 g) was added, the solution was extracted with EtOAc, and the combined extracts were washed with water and brine. Solid A was partitioned between EtOAc (1.6 L) and concd NH_4OH. The aqueous phase was removed, and the EtOAc solution was washed with water. The combined EtOAc solutions were dried ($MgSO_4$) and concentrated to leave a solid residue, which was dissolved in a boiling solution of EtOAc (2 L) and CH_2Cl_2 (3 L). Crystallization occurred as the solution was cooled to rt overnight. The solid was collected by filtration, washed with CH_2Cl_2, and dried under vacuum to provide 96.9 g of **11**. A second crop, 52.6 g, was obtained for a total yield of 149.5 g (42%) of **11**: >98% ee; mp 130−132 °C; IR (KBr) 3354, 3326, 2965, 1327, 1165, 651 cm^{-1};

^{1}H NMR (DMSO-d_6) δ 8.01 (s, 2H, exchanges), 7.67 (s, 1H), 4.14 (m, 1H), 3.77 (m, 1H), 2.89 (s, 3H), 2.58 (m, 3H, 1H exchanges), 1.02 (t, 3H, J = 7); ^{13}C NMR (DMSO-d_6) δ 148.5, 146.5, 134.4, 129.8, 52.7, 48.7, 39.9, 36.2, 15.6; MS (CI, Me_3CH) 326 (M + 1). Anal. Calcd for $C_9H_{15}N_3O_4S_3$: C, 33.22; H, 4.65; N, 12.91. Found: C, 33.36; H, 4.59; N, 13.00.

Data for sulfonimide **15**: ^{1}H NMR (DMSO-d_6) δ 9.3−9.0 (br, 2H, exchanges), 7.80 (s, 1H), 7.59 (d, 2H, J = 8), 7.22 (d, 2H, J = 8), 4.87 (br, 1H), 4.1−4.0 (m, 2H), 3.15−3.0 (br, 2H), 2.89 (s, 3H), 2.32 (s, 3H), 1.23 (t, 3H, J = 7).

(*R*)-4-(Ethylamino)-3,4-dihydro-2-methyl-2*H*-thieno[3,2-*e*]-1,2-thiazine-6-sulfonamide 1,1-Dioxide Hydrochloride (AL-4414A). A mixture of **11** (232 g) and decolorizing carbon (76 g) in EtOAc (5 L) was stirred for 1 h and filtered through Celite 521. A 1.5 M solution of HCl in EtOAc was added to the stirred, pale yellow filtrate resulting in precipitation of the hydrochloride. After being stirred for 1 h, the material was collected by filtration, washed with EtOAc and Et_2O, and dried under vacuum to provide 247 g (96%) of AL-4414A. Recrystallization from aqueous EtOH provided two crops totalling 217 g (88% recovery): mp 261−263 °C dec; IR (KBr) 3385, 3071, 2683, 1353, 1157, 652 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.0 (br, 2H, exchanges), 8.24 (s, 1H), 8.20 (s, 2H, exchanges), 4.93 (br, 1H), 4.15 (m, 2H), 3.02 (br, 2H), 2.92 (s, 3H), 1.27 (t, 3H, J = 7); ^{13}C NMR (DMSO-d_6) δ 149.6, 137.6, 136.6, 129.7, 49.1, 47.2, 11.5; $[\alpha]^{25}_D$ +14.5° (c = 1, H_2O). Anal. Calcd for $C_9H_{16}ClN_3O_4S_3$: C, 29.87; H, 4.46; N, 11.61. Found: C, 29.81; H, 4.53; N, 11.55.

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