JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Enzymatic- and Iridium-Catalyzed Asymmetric Synthesis of a Benzothiazepinylphosphonate Bile Acid Transporter Inhibitor

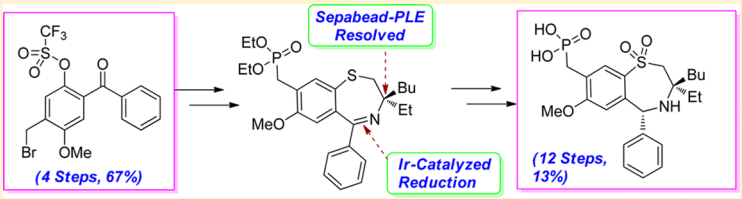
David J. Cowan,[†] Jon L. Collins,[†] Mark B. Mitchell,[†] John A. Ray,[†] Peter W. Sutton,[§] Amy A. Sarjeant,[‡] and Eric E. Boros*,[†]

[†]GlaxoSmithKline Research & Development, Five Moore Drive, Research Triangle Park, North Carolina 27709, United States

[§]GlaxoSmithKline Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, United Kingdom

[‡]Department of Chemistry, Northwestern University, 2145 Sheridan Road, Evanston, Illinois 60208, United States

Supporting Information



ABSTRACT: A synthesis of the benzothiazepine phosphonic acid **3**, employing both enzymatic and transition metal catalysis, is described. The quaternary chiral center of **3** was obtained by resolution of ethyl (2-ethyl)norleucinate (**4**) with porcine liver esterase (PLE) immobilized on Sepabeads. The resulting (*R*)-amino acid (**5**) was converted in two steps to aminosulfate **7**, which was used for construction of the benzothiazepine ring. Benzophenone **15**, prepared in four steps from trimethylhydroquinone **11**, enabled sequential incorporation of phosphorus (Arbuzov chemistry) and sulfur (Pd(0)-catalyzed thiol coupling) leading to mercaptan intermediate **18**. *S*-Alkylation of **18** with aminosulfate **7** followed by cyclodehydration afforded dihydrobenzothiazepine **20**. Iridium-catalyzed asymmetric hydrogenation of **20** with the complex of [Ir(COD)$_2$BArF] (**26**) and Taniaphos ligand **P** afforded the (3*R*,5*R*)-tetrahydrobenzothiazepine **30** following flash chromatography. Oxidation of **30** to sulfone **31** and phosphonate hydrolysis completed the synthesis of **3** in 12 steps and 13% overall yield.

INTRODUCTION

The apical sodium-dependent bile acid transporter (ASBT) is a protein highly expressed in the distal ileum of the gastrointestinal tract that helps maintain an enterohepatic balance of bile salts and cholesterol.[1−3] ASBT inhibitors promote conversion of cholesterol to bile acids in the liver and may serve as viable therapeutic agents for the treatment of hyperlipidemia.[4−6] Moreover, elevated intestinal levels of bile acids are known to induce secretion of gut hormone peptide GLP-1,[7] suggesting that a clinical ASBT inhibitor may ameliorate both blood glucose and cholesterol levels in humans. The goal of our ASBT inhibitor discovery program was to identify a potent, nonabsorbable ASBT inhibitor for treatment of type 2 diabetes.[8,9] Soluble and nonabsorbable ASBT[10,11] inhibitors were of particular interest because they localize the drug in the intestine (the locus of drug action) and minimize systemic side effects.

We initiated a medicinal chemistry effort targeting nonsystemic analogs of the clinical ASBT inhibitor 264W94[12,13] (**1**). Structure−activity work showed that acidic moieties joined by a methylene group to C-8 produced potent, soluble inhibitors with restricted absorption and good intestinal stability. These compounds were generally prepared from triflate intermediate **2** using in-house supplies of **1** as starting material. During the course of this work, phosphonic acid congener **3** emerged as a potential drug candidate, with potent ASBT inhibition activity (IC_{50} = 23 nM), good aqueous solubility (≥200 μg/mL), and low permeability (MDCK Papp = 7 nm/s).

The original synthesis of **3** (Scheme 1) and its congeners relied heavily on multikilogram stores of **1**. Nonselective mono-*O*-demethylation of **1** ($AlCl_3$/HCl) afforded a 1:1 mixture of 7-hydroxy-8-methoxy and 8-hydroxy-7-methoxy regioisomers from which the desired 8-hydroxy isomer was isolated by preparative chiral HPLC and converted to triflate **2**.[8,9] A five-step process starting with methoxy carbonylation of **2**, and ending with phosphonate hydrolysis, afforded the lead inhibitor **3**. In addition to the finite supply of **1**, the eight-step linear sequence used for installation of the phosphonic acid moiety (**1** → **3**), including a nonselective demethylation of **1**, was inefficient. The lead status of **3** at the time of this work prompted the team to investigate an alternative synthesis.

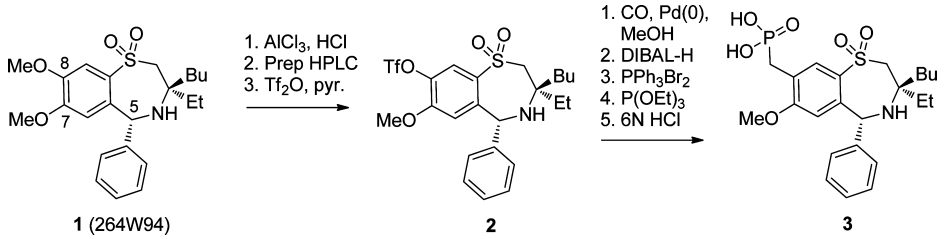
RESULTS AND DISCUSSION

The second generation approach to **3** is outlined in Figure 1. Formally, the route entailed reductive cyclo-condensation of a 2-mercaptobenzophenone with an (*R*)-(2-ethyl)norleucine derivative. Asymmetric imine reduction of the resulting dihydro-

Received: October 16, 2013
Published: November 20, 2013

   dx.doi.org/10.1021/jo402311e | *J. Org. Chem.* 2013, 78, 12726−12734

Scheme 1. First-Generation Synthesis of Phosphonic Acid 3 from ASBT Inhibitor 1



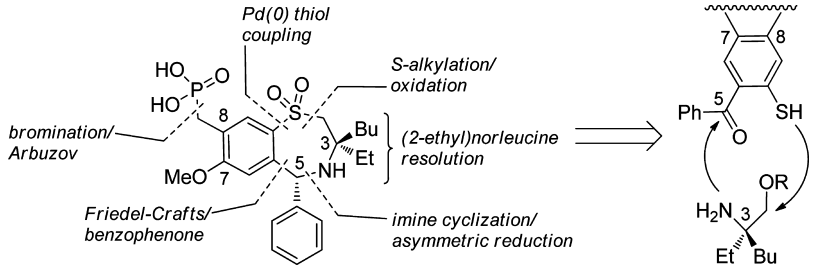
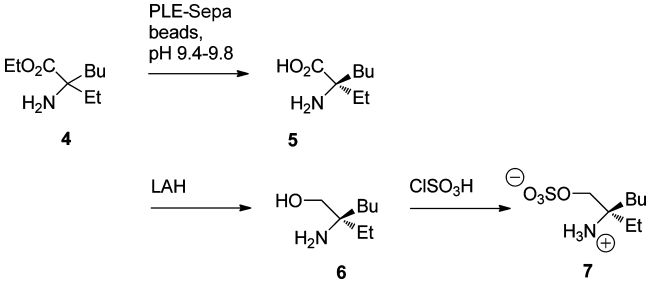


Figure 1. Key features of the second-generation pathway to **3**.

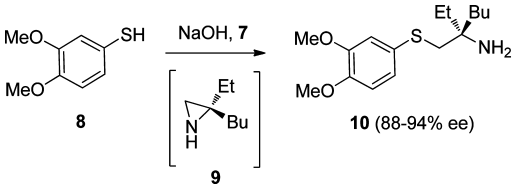
benzothiazepine, followed by sulfur oxidation and phosphonate hydrolysis, respectively would complete the synthesis.

The quaternary C3 stereocenter in **3** was derived by porcine liver esterase (PLE) resolution of (±)-ethyl (2-ethyl)-norleucinate (**4**) as previously described for the synthesis of **1** (Scheme 2).[12,14] PLE hydrolysis of **4** on the 10 g scale gave a 43%

Scheme 2. Enzymatic Hydrolysis of 4 and Synthesis of Aminosulfate 7



yield of **5** with 93% ee based on the aminosulfate derivatization sequence shown in eq 1. In our hands, filtration of the PLE



(1)

reaction mixture during workup could be slow owing to filter blockage by the enzyme and passage of fine particles into the filtrate. For this reason, the possibility of linking the PLE to a solid support was explored.

Enzyme immobilization was achieved in two steps by reacting powdered PLE with Sepabeads EC-EP[15−17] followed by deactivation of the remaining epoxy units on the polymer with glycine. Reaction times for Sepabead PLE hydrolysis of **4** to 37−42% substrate conversion were about 24 h, and removal of the immobilized enzyme by filtration was facile. The largest scale enzymatic resolution performed with Sepabead PLE was with 1.73 kg of **4** (9.21 mol) which afforded 4 mol of **5**.

Reduction of amino acid **5** with LAH gave (*R*)-(2-ethyl)-norleucinol (**6**) which was treated with chlorosulfonic acid to afford aminosulfate **7**.[12] More than 600 g of **7** were prepared in order to support ongoing medicinal chemistry studies and synthetic development work.

Enantiopurities of **7** were established by derivatization with the commercial aromatic mercaptan **8** followed by chiral SFC analysis. This reaction proceeds with retention of configuration through aziridine[18,19] intermediate **9** and afforded chiral aminosulfide **10** as an oil in good yield (eq 1). Chiral SFC analyses of **10** prepared from Sepabead PLE hydrolysis of **4** on the 50 g scale (37% substrate conversion) and 1.73 kg scale (42% substrate conversion) showed 94% ee and 88% ee, respectively.

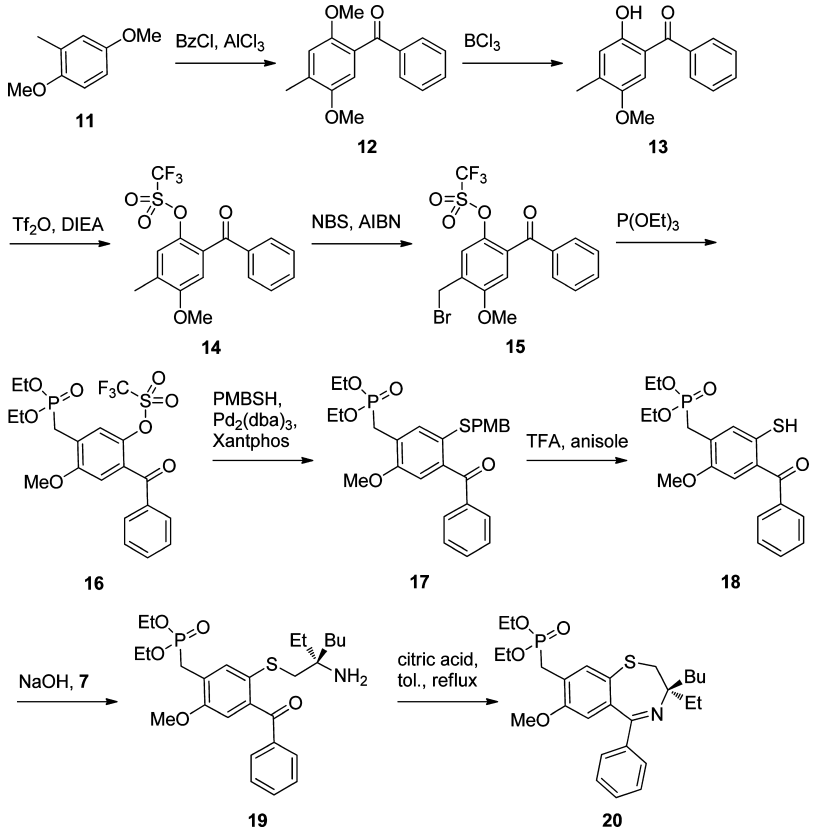
Construction of the requisite dihydrobenzothiazepine is illustrated in Scheme 3. Trimethylhydroquinone **11** was selected as the benzophenone synthon for the second-generation synthesis of **3**. This material was inexpensive and well-suited for Friedel−Crafts reaction with benzoyl chloride. The goal, at an appropriate point in the synthesis, was to convert the aryl methyl substituent in **11** to a dialkyl phosphonomethyl group through a sequential free radical bromination and Arbuzov[20] reaction sequence.

Reaction of **11** with benzoyl chloride in the presence of $AlCl_3$ proceeded in good yield to afford benzophenone **12**. Regioselective demethylation of the methoxyl group *ortho* to the ketone in **12** with BCl_3 gave the corresponding 2-hydroxybenzophenone **13** (72% overall yield). Boron complexation with the carbonyl oxygen in **12** directs the regioselectivity in this reaction.[21]

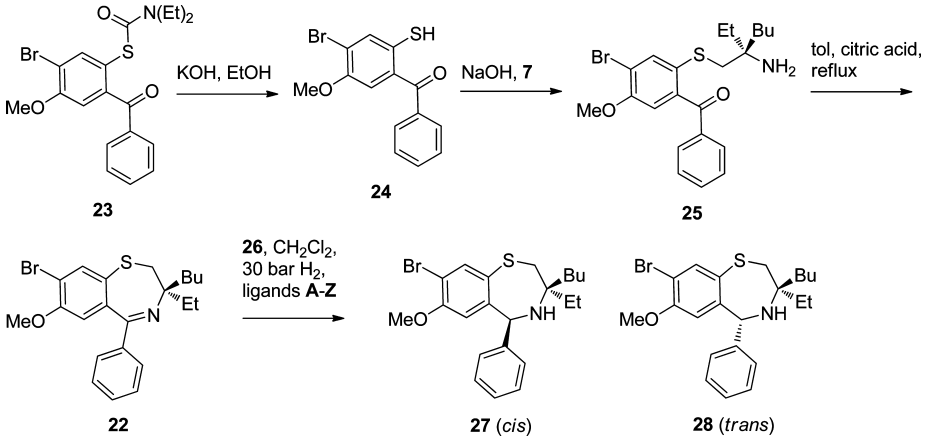
Synthesis of triflate **14** from phenol **13** was straightforward and set the stage for palladium-catalyzed coupling of a suitably protected thiol *ortho* to the carbonyl group. However, to avoid oxidative NBS conditions in the presence of divalent sulfur, the radical bromination and Arbuzov reactions were performed prior to the thiol coupling with the triflate functionality in place. We were pleased to find that NBS bromination of **14** proceeded smoothly to give bromomethyl intermediate **15** in good yield.

dx.doi.org/10.1021/jo402311e | J. Org. Chem. 2013, 78, 12726−12734

Scheme 3. Synthesis of Phosphonomethylbenzothiazepine 20



Scheme 4. Synthesis and Asymmetric Reduction of Bromobenzothiazepine 22



Benzylic bromide **15** was a pivotal intermediate in the synthesis of **3**. Its trifunctionality (benzylic bromide, triflate, and ketone) allowed sequential incorporation of phosphorus and sulfur and subsequent thiazepine ring closure. It is worth noting that reaction of **15** with other nucleophiles (e.g., amines, thiols, phenols, etc.) may afford access to additional 8-methylene-linked congeners in this family of ASBT inhibitors.

Treatment of **15** with triethylphosphite at 115 °C afforded phosphonate **16**. The crude material was initially an oil and did not crystallize despite considerable efforts. Flash chromatography of **16** did afford crystalline material (mp 53−56 °C) after storage for several weeks at 10−15 °C.

Introduction of the protected thiol group was accomplished by coupling **16** with *p*-methoxybenzyl mercaptan (PMBSH) in the presence of Xantphos, $Pd_2(dba)_3$, and Hunig's base.[22] This procedure was performed successfully on a 79 g scale and afforded **17** in 83% yield following crystallization. Removal of the PMB group in **17** with TFA/anisole afforded the corresponding thiol **18** which was used immediately in the next step without purification. *S*-Alkylation of **18** with aminosulfate **7** (prepared from the 1.725 kg scale resolution of **4**) afforded aminosulfide **19** which showed a 93:7 ratio of enantiomers by chiral normal phase HPLC/MS analysis.

Cyclodehydration of **19** under Dean−Stark conditions gave dihydrobenzothiazepine **20** in 38% overall yield (three steps) from **17**. We considered the synthesis of aminomercaptan **21** (R = Et; R′ = Bu)[23] which (if coupled to **16**) would improve

dx.doi.org/10.1021/jo402311e | J. Org. Chem. 2013, 78, 12726−12734

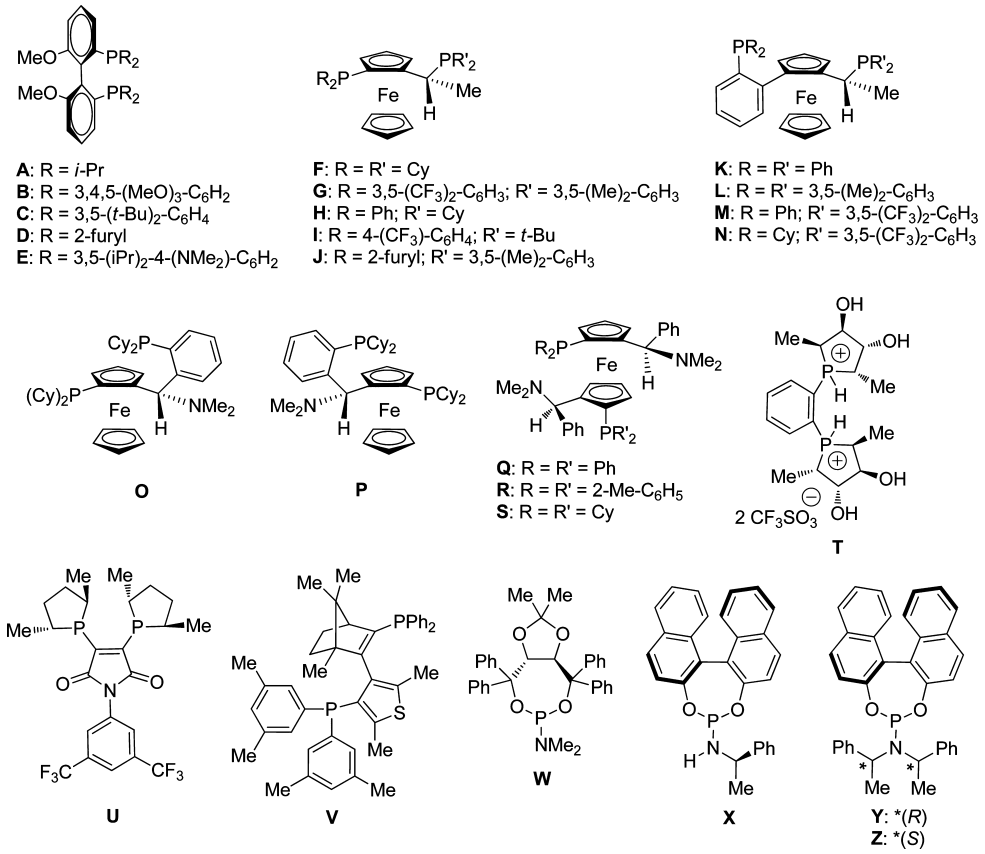
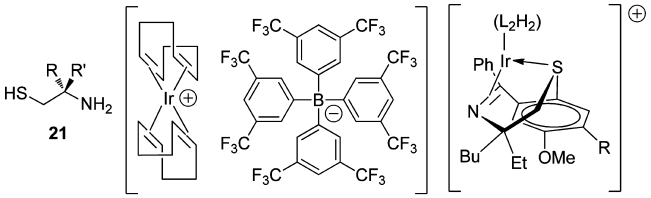


Figure 2. Structures of bidentate phosphines (**A**–**V**) and monodentate phosphoramidites (**W**–**Z**) screened in combination with [Ir(COD)$_2$]BArF (**26**) for asymmetric hydrogenation of **22**.

synthetic convergence, but development priorities[24] precluded this investigation.



Asymmetric imine reduction of **20** was initially scoped with traditional Noyori ruthenium catalysts, including transfer hydrogenation with (*S*,*S*)-*p*TsDPEN-Ru(*p*-cymene)Cl[25] and hydrogenation in the presence of RuCl$_2$(*R*)-BINAP-(*S*,*S*)-DPEN.[26] None of the expected reduction products were observed, presumably owing to low catalytic reactivity with the substrate.

We next screened the effectiveness of cationic iridium complexes[27] for dihydrobenzothiazepine reduction, but to avoid the consumption of more phosphonate **20**, in-house stores of the bromo substrate **22** were employed. The synthesis of **22** and its asymmetric reduction are outlined in Scheme 4. Briefly, hydrolysis of the known thiocarbamate **23**[8] with KOH/EtOH afforded 2-mercaptobenzophenone **24**. *S*-Alkylation of **24** with aminosulfate **7** and cyclization of the resulting product (**25**) afforded benzothiazepine **22**.

Asymmetric hydrogenation of **22** was examined with a series of chiral cationic iridium complexes generated *in situ* from chiral ligands **A**–**Z** (Figure 2) and [Ir(COD)$_2$BArF] (**26**). The results of these experiments are shown in Table 1. An HPLC reference sample of the *cis*/*trans* mixture **27**/**28** (~1:1) was prepared by borane reduction of **22**, and an analytical sample of the desired *trans*-product (**28**) was isolated by silica gel chromatography. The relative stereochemistry of **28** was established by two-dimensional NOESY NMR experiments.

A number of the ligands shown in Figure 2, in combination with iridium complex **26**, quantitatively reduced the imine functionality of **22** under 30 bar (gauge) H_2, including biphenyl bis-phospine **B**, Walphos ligands **K**–**N**, Mandyphos ligand **R**, catASium ligand **V**, and Monophos **Z**. Of these catalysts, Walphos ligands **K**–**M** gave 60–70% selectivity for the *trans*-product (**28**). More significantly, complexes derived from **26** and Taniaphos ligands **O** and **P**, Monophos **Y**, and ROPhos ligand **T** all gave complete imine reduction with 85–90% diastereoselectivity.

Taniaphos[28,29] ligand **P** (Cy = cyclohexyl), in combination with **26**, gave 100% reduction of **22** with 90% *trans* product (**28**). It is important to note that the same reaction with Taniaphos ligand **O** (the enantiomer of **P**) gave 100% reduction and 88% *cis*-product (**27**). This indicates that the stereoselectivity of the reduction is controlled by the *Re*/*Si*-face of the imine substrate and is not significantly influenced by the quaternary stereocenter. Consequently, a silica gel chromatographic separation of the *cis*/*trans*-products following reduction will significantly enhance the enantiopurity of the desired *trans*-product.

Rophos[30] ligand **T** also gave 90% *cis*-product **27**, and the Monophos[31] ligand **Y**, which can offer cost of goods savings compared to chiral phosphines, gave clean imine reduction with 85% *trans*-product **28**. Because the antipode of Rophos ligand **T**

dx.doi.org/10.1021/jo402311e | J. Org. Chem. 2013, 78, 12726–12734

Table 1. Percent[a] Conversion and Products for Hydrogenation[b] of 22 to 27/28 with Chiral Iridium Catalysts Prepared *in situ* from [Ir(COD)$_2$]BArF (26) and Bidentate Phosphines (A–V)[c] or Monodentate Phosphoramidites (W–Z)[c]

ligand	% conversion (27 + 28)	% 27 (*cis*)	% 28 (*trans*)
A	73	43	30
B	100	45	55
C	73	38	35
D	24	12	12
E	76	26	52
F	78	34	44
G	23	10	13
H	78	34	44
I	85	44	41
J	11	5.8	5.5
K	100	30	70
L	100	31	69
M	100	40	60
N	100	47	53
O	100	88	12
P	100	10	90
Q	91	53	38
R	100	54	46
S	48	26	22
T	100	90	10
U	25	14	11
V	100	68	32
W	87	48	39
X	4.6	2.5	2.1
Y	100	15	85
Z	100	65	35

[a]Determined by HPLC. [b]See Experimental Section. [c]See Figure 2 for structures of ligands **A**–**Z**.

was not commercially available, we employed Taniaphos ligand **P** for asymmetric synthesis of **3**.

Anchimeric assistance by the divalent sulfur during iridium-catalyzed reduction of **22** does not explain the observed stereoselectivity, but is an intriguing possibility (see generalized transition structure **29**).[32] In fact, attempts to hydrogenate the sulfone derivative of **22** with the complex of **26** and ligand **P** failed to produce any imine reduction product, which is consistent with this hypothesis.

The final three steps in the synthesis of **3** are shown in Scheme 5. As anticipated, asymmetric hydrogenation of **20** with [Ir(COD)$_2$BArF] (**26**) and ligand **P** under 30 bar (gauge) H_2 gave predominantly *trans*-isomer **30** (100% conversion; *trans*/*cis* ratio 9:1), a result identical to that observed with the 8-bromo substrate (**22**). This reaction went to completion in 2 h (1–4 g scale of **18**) and also proceeded at a slower rate (24 h reaction time) under 4 bar (gauge) H_2 (95% imine reduction; *trans*/*cis* ratio 9:1). Separation of the unwanted *cis*-isomer by flash chromatography on silica gel afforded the pure diastereomer **30** in 73–85% yields. The desired *syn* orientation of the diaryl methine proton and *n*-butyl side chain in **30** was supported by a combination of NOE measurements and two-dimensional HMBC spectroscopy.

Oxidation of **30** with H_2O_2/TFA afforded sulfone **31**. The relative and absolute stereochemistry of **31** were confirmed by X-ray crystallography (Figure 3). In the solid state, the exocyclic phenyl substituent of **31**, although *trans* to the *n*-butyl side chain, is oriented slightly above the plane of the benzo ring which directs the benzylic methine proton toward the *pro*-(*S*) sulfonyl oxygen (O6 in Figure 3). The crystal structure of **31** also revealed an intermolecular hydrogen bond between the *pro*-(*R*) sulfonyl oxygen and the N–H proton of a neighboring molecule.

The final step in the synthesis of **3** entailed phosphonate hydrolysis of **31** in refluxing 6 N HCl. Evaporation of the solvent afforded the hydrochloride salt of the title compound as an amorphous solid (**3**·HCl) in 97% yield.

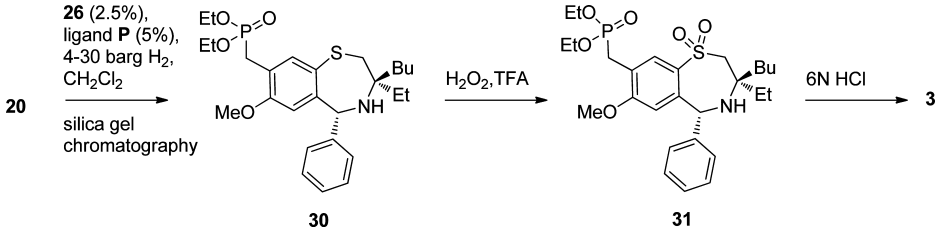
CONCLUSION

A convergent 12 step synthesis of benzothiazepinylphosphonic acid **3** was achieved through an unusual trifunctional benzophenone intermediate (**15**). The title synthesis represents a unique asymmetric pathway to this family of nonabsorbable ASBT inhibitors. Chemistry highlights included a Sepabead PLE-catalyzed synthesis of (*R*)-aminosulfate **7** and its two-step cyclocondensation with 2-mercapto-4-phosphonobenzophenone **18**. The synthesis culminated with an iridium-catalyzed asymmetric hydrogenation of dihydrothiazepine **20** followed by flash chromatography which afforded the desired (3*R*,5*R*)-diastereomer **30**. Absolute and relative stereochemistries of the title compound were confirmed by X-ray crystallographic analysis of the penultimate diethylphosphonate product (**31**). In addition, some synthetic convergence was achieved by incorporating the two stereocenters late in the pathway (after construction of the fully functionalized mercaptobenzophenone **18**). The medicinal chemistry and structure–activity relationships of **3** and related analogs are reported elsewhere.[9]

EXPERIMENTAL SECTION

Sepabead-Immobilized Porcine Liver Esterase. A fixed glass reactor equipped with a mechanical stirrer was charged with 1 M pH 7 sodium phosphate buffer (8.2 L, 8.2 mol). EC-EP Sepabeads (1646 g) and porcine liver esterase lyophilized powder (17 units/mg protein, 99 g) were added, and the mixture was stirred gently for 3 d at rt. The beads were collected by filtration. The reactor was cleaned and charged with a 3 M solution of aqueous glycine (8.2 L, 24.6 mol). This solution was charged with the beads from the filter and stirred gently for 3 d. The beads again were collected by filtration and air-dried on the filter for 30 min to afford the Sepabead-immobilized PLE (1622 g).

Scheme 5. Asymmetric Reduction of 20 and Conversion to ASBT Inhibitor 3



dx.doi.org/10.1021/jo402311e | J. Org. Chem. 2013, 78, 12726–12734

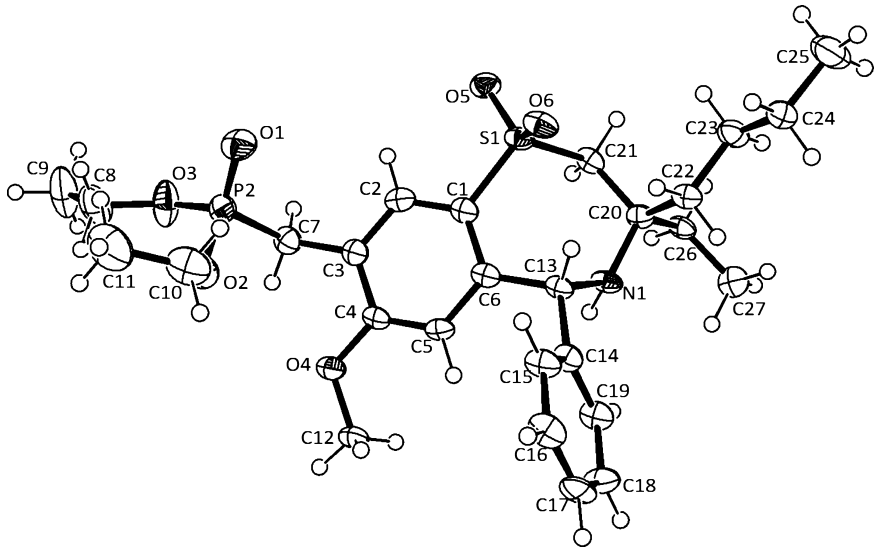


Figure 3. A view of the X-ray crystal structure of **31** showing the numbering scheme employed. Anisotropic atomic displacement ellipsoids for the non-hydrogen atoms are shown at the 50% probability level. Hydrogen atoms are displayed with an arbitrarily small radius.

2-Ethyl-D-norleucine (5). A fixed glass reactor equipped with a mechanical stirrer, pH stat, and metered 2 M NaOH pump was charged with racemic ethyl (2-ethyl)norleucinate (**4**) (1.725 kg, 9.211 mol) and water (8 L). To this stirred mixture was added the Sepabead-immobilized PLE (570 g), and the reaction mixture was stirred for 28 h at rt; the pH of the reaction mixture was maintained between 9.4 and 9.8 by automated pH stat addition of NaOH. PLE hydrolysis of **4** was monitored by ^{1}H NMR (CD_3OD) for production of EtOH in the organic phase. The immobilized enzyme was removed by filtration, and the filtrate was extracted with Et_2O (2 × 1.5 L). The combined ether layers were dried over $MgSO_4$, filtered, and concentrated to afford unreacted ester. The aqueous phase was neutralized to pH 6.8 with 2 M HCl and concentrated to a solid by rotovap. This material was further dried to a constant weight in a vacuum oven at 80 °C to afford 700 g of a white solid containing **5** (~640 g, 4.02 mol) and NaCl (~60 g, 1.5 mol). This material was used without further purification: ^{1}H NMR (D_2O, 400 MHz) δ 1.86−1.58 (m, 4H), 1.30−1.17 (m, 3H), 1.13−1.03 (m, 1H), 0.82 (t, J = 7.6 Hz, 3H), 0.78 (t, J = 7.2 Hz, 3H).

(*R*)-2-Amino-2-ethylhexan-1-ol (6). A 1 M solution of LAH in THF (3.24 L, 3.24 mol) was added dropwise over 2.5 h to a mechanically stirred slurry of **5** (400 g, 2.11 mol, ~8 wt % NaCl) in THF while the reaction temperature was maintained at around 5 °C. Following the addition, the reaction mixture was allowed to warm to rt over 1 h and then slowly heated to reflux. Reflux was maintained for 3 h, and the reaction mixture was allowed to cool to rt overnight. After the mixture was cooled to 5 °C, water (125 mL) followed by 15% NaOH (123 mL) and then water (369 mL) were added slowly dropwise while maintaining an internal temperature below 13 °C. The resulting slurry was stirred for 1 h at 5 °C, and the solids were removed by filtration. Rotary evaporation of the filtrate afforded **6** as a light yellow oil (334 g, 99% yield). This material was used without further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.30 (s, 2H), 1.89 (br, 3H), 1.50−1.16 (m, 8H), 0.90 (t, J = 7.0 Hz, 3H), 0.84 (t, J = 7.6 Hz, 3H).

(*R*)-2-Ammonio-2-ethylhexyl sulfate (7). Chlorosulfonic acid (254 mL, 3.79 mol) was added dropwise over 1 h to a stirred solution of **6** (500.5 g, 3.45 mol) in EtOAc (3 L). Some external cooling was applied during the chlorosulfonic acid addition to maintain the reaction temperature at or below 35 °C. The reaction mixture was maintained at 40 °C for 2 h and then cooled to 18 °C. Compound **7** was collected by filtration as a white solid and dried to a constant weight in a vacuum oven at rt (624 g, 80%): ^{1}H NMR (D_2O, 400 MHz) δ 4.02 (s, 2H), 1.72−1.56 (m, 4H), 1.32−1.18 (m, 4H), 0.88 (t, J = 7.4 Hz, 3H), 0.83 (t, J = 7.0 Hz, 3H).

(*R*)-3-(((3,4-Dimethoxyphenyl)thio)methyl)heptan-3-amine (10). In a typical procedure, a stirred mixture of **7** (500 mg, 2.22 mmol), **8** (567 mg, 3.33 mmol), water (4 mL), and toluene (4 mL) was purged with N_2 and then heated to reflux. A solution of NaOH (355 mg, 8.88 mmol) in water (4 mL) was added dropwise over 2 h. The reaction mixture was heated at reflux an additional 3 h and then stirred at 45 °C overnight. The layers were separated, and the toluene phase was washed with 1 N NaOH, dried over $MgSO_4$, and concentrated to an oil. This material was partitioned between 1 N HCl (7.5 mL) and Et_2O (10 mL) and stirred for 15 min to remove residual disulfide byproduct. The aqueous phase was cooled in an ice bath, basified with 1 N NaOH, and extracted with Et_2O. The organic phase was dried over $MgSO_4$, filtered, and concentrated to afford **10** (505 mg, 77% yield) as a colorless oil. Samples of **10** derived from the 50 g scale Sepabead PLE resolution of **4** and 1.725 kg scale Sepabead PLE resolution of **4** showed 94% ee and 88% ee, respectively, by chiral SFC: chiral AD-H column, 10% MeOH/CO_2/0.5% diethylamine, 140 bar, 40 °C, flow rate 2 mL/min. Spectral data for (±)-**10**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.01 (dd, J = 8, 2 Hz, 1H), 6.98 (d, J = 2 Hz, 1H), 6.79 (d, J = 8 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.95 (s, 2H), 1.55−1.15 (m, 10H), 0.88 (t, J = 7 Hz, 3H), 0.84 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.8, 148.0, 128.2, 123.8, 114.7, 111.4, 55.7, 54.6, 47.6, 38.4, 31.6, 25.6, 23.1, 13.9, 7.8; HRMS (TOF ES$^+$) $C_{16}H_{28}NO_2S$ calcd 298.1841, found 298.1843.

(2,5-Dimethoxy-4-methylphenyl)(phenyl)methanone (12). A round bottomed flask equipped with an overhead stirrer was charged with $AlCl_3$ (60.7 g, 455 mmol) and CH_2Cl_2 (300 mL). The stirred mixture was cooled in an ice bath, and a solution of benzoyl chloride (64 g, 455 mmol) in CH_2Cl_2 (300 mL) was added dropwise over 20 min. After stirring an additional 10 min, a solution of **11** (63 g, 414 mmol) in CH_2Cl_2 (300 mL) was added over 20 min. The resulting dark red reaction mixture was stirred for 1 h at ice bath temperature and then quenched by slow dropwise addition of conc. HCl (150 mL) with very slow mechanical stirring. The supernatant was decanted, and the remaining gum was triturated with CH_2Cl_2 (3 × 150 mL). The combined supernatants were washed with satd. $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The resulting material was triturated with heptane, and **12** was collected by filtration as a white solid (95 g, 90% yield): Mp 117−119 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (dd, J = 7.5, 1 Hz, 2H), 7.55 (t, J = 8 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 6.90 (s, 1H), 6.82 (s, 1H), 3.80 (s, 3H), 3.65 (s, 3H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.1, 151.5, 151.2, 138.1, 132.5, 131.0, 129.5, 127.9, 126.0, 114.8, 111.2, 56.1, 55.7, 16.6; ES$^+$ MS 257 (M + 1, 100); Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.10; H, 6.36.

(2-Hydroxy-5-methoxy-4-methylphenyl)(phenyl)methanone (13). A stirred solution of BCl_3 in CH_2Cl_2 (1 M, 351 mL, 351 mmol) was cooled to −15 °C, and a solution of **12** (72 g, 281 mmol) in CH_2Cl_2 (300 mL) was added dropwise. The resulting dark red reaction mixture

dx.doi.org/10.1021/jo402311e | J. Org. Chem. 2013, 78, 12726−12734

was allowed to warm to rt over 30 min and was then quenched by slow addition of MeOH (300 mL) followed by 1 M HCl (300 mL). The layers were separated, and the CH_2Cl_2 was washed with water, dried over $MgSO_4$, filtered, and concentrated to afford a yellow oil which was triturated with heptane. The product (**13**) was collected by filtration as a yellow crystalline solid (54 g, 80%): Mp 65−67 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.85 (s, 1H), 7.71 (dd, J = 8, 1 Hz, 2H), 7.60 (br t, J = 7.4 Hz, 1H), 7.52 (t, J = 8 Hz, 2H), 6.93 (s, 1H), 6.90 (s, 1H), 3.67 (s, 3H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.5, 157.8, 149.9, 138.2, 138.1, 131.6, 128.8, 128.2, 120.0, 116.2, 112.4, 55.6, 16.8; ES$^+$ MS 243 (M + 1, 100); Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.65; H, 5.87.

2-Benzoyl-4-methoxy-5-methylphenyl Trifluoromethanesulfonate (14). A solution of **13** (54 g, 223 mmol) in CH_2Cl_2 (400 mL) and DIEA (49 mL, 280 mmol) was cooled in an ice bath, and neat triflic anhydride (41 mL, 245 mmol) was added dropwise. The reaction mixture was stirred at ice-bath temperature for 1 h and then diluted with EtOAc (400 mL). The mixture was washed with 0.1 M NaOH and twice with 1 M HCl, dried over $MgSO_4$, filtered, and concentrated to afford **14** as a dark amber oil (78 g, 93%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (dd, J = 7.8, 1.3 Hz, 2H), 7.62 (t, $J \approx$ 7.5 Hz, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.16 (s, 1H), 6.96 (s, 1H), 3.84 (s, 3H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.6, 156.6, 139.4, 136.6, 133.5, 132.3, 130.3, 129.9, 128.3, 124.0, 118.3 (q, J_{CF} = 320 Hz), 111.4, 55.7, 16.2; ES$^+$ MS 375 (M + 1, 100); Anal. Calcd for $C_{16}H_{13}F_3O_5S$: C, 51.34; H, 3.50. Found: C, 51.18; H, 3.56.

2-Benzoyl-5-(bromomethyl)-4-methoxyphenyl Trifluoromethanesulfonate (15). A solution of **14** (71 g, 190 mmol) in 1,2-dichloroethane (600 mL) was charged with NBS (44g, 247 mmol) and benzoyl peroxide (1.2 g, 4.95 mmol), and the stirred reaction mixture was heated at reflux for 20 h. The solution was allowed to cool to rt, washed once with 10% Na_2SO_3 and once with 10% $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated to afford crude **15** (89 g, >100% theoretical) as a dark amber oil which was used without purification. This material crystallized on standing, and an analytical sample was obtained by trituration with heptane: Mp 91−94 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (d, J = 7.4 Hz, 2H), 7.65 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.61 Hz, 2H), 7.39 (s, 1H), 7.04 (s, 1H), 4.55 (s, 2H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.1, 156.2, 139.3, 136.2, 134.0, 133.4, 130.7, 130.1, 128.6, 124.5, 118.3 (q, J_{CF} = 321 Hz), 112.7, 56.4, 26.1; HRMS (TOF ES$^+$) Calcd for $C_{16}H_{13}(^{79}Br)F_3O_5S$: 452.9619 (M + 1). Found: 452.9619; Anal. Calcd for $C_{16}H_{12}BrF_3O_5S$: C, 42.40; H, 2.67; S, 7.07. Found: C, 42.33; H, 2.54; S, 7.07.

2-Benzoyl-5-((diethoxyphosphoryl)methyl)-4-methoxyphenyl Trifluoromethanesulfonate (16). A solution of **15** (89 g, assumed 190 mmol) in triethyl phosphite (77 g, 463 mmol) was heated in a 115 °C sand bath for 3 h. The solution was cooled to rt, diluted with CH_2Cl_2 (100 mL), and applied to a 600 g silica gel column. Nonpolar impurities were washed off the column with hexanes, and the eluent was switched to EtOAc to elute **16**. Desired EtOAc fractions were combined and washed with 1 M HCl and 10% $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated to afford **16** (80 g, 80% yield) as an oil which crystallized on standing to a light orange solid: Mp 53−56 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, J = 8 Hz, 2H), 7.63 (t, J = 8 Hz, 1H), 7.49 (t, J = 8 Hz, 2H), 7.38 (d, J_{HP} = 3 Hz, 1H), 7.02 (s, 1H), 4.10 (m, 4H), 3.86 (s, 3H), 3.31 (d, J_{HP} = 22 Hz, 2H), 1.30 (t, J = 7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 156.1 (d, $^3J_{CP}$ = 7 Hz), 139.3 (d, $^5J_{CP}$ = 4 Hz), 136.2, 133.7, 131.6 (d, $^3J_{CP}$ = 4 Hz), 129.9, 128.4, 125.9 (d, $^2J_{CP}$ = 10 Hz), 124.8 (d, $^4J_{CP}$ = 5 Hz), 118.2 (q, J_{CF} = 320 Hz), 112.1 (d, $^4J_{CP}$ = 3 Hz), 62.1 (d, $^2J_{CP}$ = 7 Hz), 56.1, 26.6 (d, $^1J_{CP}$ = 140 Hz), 16.1 (d, $^3J_{CP}$ = 6 Hz); ES$^+$ MS 511 (M + 1, 100); Anal. Calcd for $C_{20}H_{22}F_3O_8PS$: C, 47.06; H, 4.34. Found: C, 46.97; H, 4.44.

Diethyl 4-Benzoyl-2-methoxy-5-((4-methoxybenzyl)thio)-benzylphosphonate (17). A round-bottom flask equipped with an overhead stirrer and reflux condenser was charged with **16** (78.8 g, 154 mmol) and toluene, and the stirred solution was degassed with N_2 for 5 min and then charged with Xantphos (8.93 g, 15.44 mmol) and $Pd_2(dba_3)$ (7.1 g, 7.75 mmol). Degassing was continued for 5 min. 4-Methoxybenzyl mercaptan (PMBSH) (30 g, 195 mmol) was added, and the dark solution was degassed 5 min. The reaction mixture was heated at reflux for 18 h at which point HPLC showed 96% conversion. Additional PMBSH (9 g, 58 mmol) was added, and reflux was continued for 6 h. At this point, HPLC showed 98% conversion. The reaction mixture was allowed to cool to rt and diluted with 1 M HCl (500 mL) with rapid stirring. The mixture was filtered through Celite, and the filtrate layers were separated. The toluene phase was washed sequentially with 1 M HCl, 1 M NaOH, and 10% $NaHCO_3$, then dried over $MgSO_4$, filtered, and partially concentrated by rotovap until most of the toluene was removed. EtOAc (500 mL) was added, and about one-third of the solvent was removed by rotovap until crystallization ensued. The mixture was diluted with heptane (1 L) and cooled in an ice bath. The product (**17**) was collected by filtration as a pale orange solid (65 g, 82% yield): Mp 111−114 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71 (dd, J = 8, 1 Hz, 2H), 7.57 (t, J = 8 Hz, 1H), 7.46−7.40 (m, 3H), 7.02 (d, J = 9 Hz, 2H), 6.81 (s, 1H), 6.71 (d, J = 9 Hz, 2H), 4.07 (m, 4H), 3.89 (s, 2H), 3.81 (s, 3H), 3.76 (s, 3H), 3.24 (d, J_{HP} = 22 Hz, 2H), 1.29 (t, J = 7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.4, 158.4, 156.1 (d, $^3J_{CP}$ = 7 Hz), 142.5 (d, $^5J_{CP}$ = 4 Hz), 137.1, 136.5 (d, $^3J_{CP}$ = 6 Hz), 133.0, 129.9, 129.7, 129.0, 128.2, 124.2 (d, $^4J_{CP}$ = 4 Hz), 122.9 (d, $^2J_{CP}$ = 10 Hz), 113.4, 110.0 (d, $^4J_{CP}$ = 3 Hz), 61.8 (d, $^2J_{CP}$ = 7 Hz), 55.6, 55.0, 40.5, 26.4 (d, $^1J_{CP}$ = 139 Hz), 16.2 (d, $^3J_{CP}$ = 6 Hz); ES$^+$ MS 515 (M + 1, 100); Anal. Calcd for $C_{27}H_{31}O_6PS$: C, 63.02; H, 6.07. Found: C, 62.77; H, 6.07.

Diethyl 4-Benzoyl-5-mercapto-2-methoxybenzylphosphonate (18). Compound **17** (20 g, 38.9 mmol) was dissolved in anisole (60 mL), and N_2 was passed through the solution continuously. Neat TFA (125 mL) was added dropwise over 15 min, and the reaction mixture was heated at reflux for 4 h. The TFA was removed by rotovap, and the remaining dark solution was diluted with TBME (400 mL) and washed with water (2 × 200 mL) and then extracted with previously degassed 2 M NaOH (4 × 75 mL). The combined NaOH layers were washed with TBME (2 × 200 mL) and filtered. The NaOH filtrate was cooled in an ice bath, and N_2 was bubbled through the solution continuously while acidifying with conc. HCl (60 mL). The aqueous mixture was extracted with TBME (2 × 200 mL), and the combined TBME layers were washed with pH 7.2 phosphate buffer (2 × 200 mL), dried over $MgSO_4$, filtered, and concentrated to afford thiol **18** (10.5 g, 69% crude yield) as a light amber oil which was used immediately without further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.97 (br s, 1H), 7.81 (dd, J = 8.4, 1.4 Hz, 2H), 7.62 (br t, J = 7.6 Hz, 1H), 7.50 (t, J = 8.0 Hz, 2H), 7.36 (d, J_{HP} = 3 Hz, 1H), 6.94 (s, 1H), 4.12 (dq, J_{HP} = 8, J = 7 Hz, 4H), 3.75 (s, 3H), 3.30 (d, J_{HP} = 22 Hz, 2H), 1.31 (t, J = 7 Hz, 6H); ES$^+$ MS 395 (M + 1, 100).

(*R*)-Diethyl 5-((2-Amino-2-ethylhexyl)thio)-4-benzoyl-2-methoxybenzylphosphonate (19). Crude **18** (10.5 g) was dissolved in toluene (40 mL) and degassed with N_2, and the aminosulfate **7** (6.57 g, 29.1 mmol) and water (9 mL) were added. The stirred mixture was heated to reflux, and 50% NaOH (5.5 mL, 104 mmol) was added dropwise over 1.5 h. Reflux was maintained for 30 min following the addition. Upon cooling to rt, the reaction mixture was extracted with TBME (2 × 100 mL) and the combined organic layers were washed with 10% $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated to afford **19** as an amber oil (11.6 g, 84% yield) which was used without further purification. An analytical sample was obtained as a light amber oil by flash chromatography on silica gel eluting with 0 → 20% EtOH/EtOAc: 86% ee by normal phase chiral HPLC (enantiomer ratio 93:7), Chiralpak IC column, hexane (0.1% dimethylaminoethanol)/EtOH eluent, flow rate 1 mL/min; $[\alpha]^{25}_D$ = −1.16° (c = 0.9, $CDCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, J = 8 Hz, 2H), 7.59 (t, J = 8 Hz, 1H), 7.54 (br d, J_{HP} = 3 Hz, 1H), 7.46 (t, J = 8 Hz, 2H), 6.82 (s, 1H), 4.09 (m, 4H), 3.82 (s, 3H), 3.27 (d, J_{HP} = 22 Hz, 2H), 2.81 (s, 2H), 1.37−1.17 (m, 6H), 1.30 (t, J = 7 Hz, 6H), 1.12 (m, 2H), 0.85 (t, J = 7 Hz, 3H), 0.74 (t, J = 8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.8, 156.3 (d, $^3J_{CP}$ = 7 Hz), 142.6 (d, $^5J_{CP}$ = 4 Hz), 137.3, 136.6 (d, $^3J_{CP}$ = 6 Hz), 133.3, 129.9, 128.5, 125.3 (d, $^4J_{CP}$ = 4 Hz), 123.3 (d, $^2J_{CP}$ = 10 Hz), 110.1 (d, $^4J_{CP}$ = 3 Hz), 62.0 (d, $^2J_{CP}$ = 6 Hz), 55.8, 54.5, 48.9, 38.4, 31.6, 26.6 (d, $^1J_{CP}$ = 139 Hz), 25.6, 23.2, 16.4 (d, $^3J_{CP}$ = 7 Hz), 14.0, 7.9; ES$^+$ MS 521 (M+1, 100); Anal. Calcd for $C_{27}H_{40}NO_5PS$: C, 62.17; H, 7.73; N, 2.69. Found: C, 62.22; H, 8.04; N, 3.08.

(*R*)-Diethyl ((3-Butyl-3-ethyl-7-methoxy-5-phenyl-2,3-dihydrobenzo[*f*][1,4]thiazepin-8-yl)methyl)phosphonate (20). To a solution of **19** (11 g, 21.09 mmol) in toluene (200 mL) was added citric acid (600 mg, 2.08 mmol), and the stirred solution was heated at reflux for 7 h; during the course of the reaction, water was azeotropically removed with the aid of a Dean−Stark trap. The reaction was allowed to cool to rt, diluted with EtOAc (100 mL), and washed with 1:1 10% $NaHCO_3$/brine. The aqueous phase was backextracted with EtOAc (100 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford an amber oil. This material was dissolved in hot heptane (500 mL) and filtered hot to remove some insoluble material. The filtrate was concentrated to about 100 mL, and the resulting slurry was stirred at ice-bath temperature for 3 h; the product (**20**) was collected by filtration as a white solid (5.8 g). The filtrate was concentrated, and the resulting material was purified by flash chromatography on silica gel eluting with 0−25% EtOAc/CH_2Cl_2 to afford an additional 1.2 g of **20** (combined yield = 7 g, 66% yield): Mp 87−89 °C; $[\alpha]^{25}_D$ = +6.05° (*c* = 1.62, $CDCl_3$); ^{1}H NMR (d_6-DMSO, 400 MHz) δ 7.50−7.35 (m, 6H), 6.64 (s, 1H), 3.95 (m, 4H), 3.62 (s, 3H), 3.23 (br d, $J_{HP} \approx$ 20 Hz, 2H), 3.20 (s, 2H), 1.60 (m, 1H), 1.50 (m, 1H), 1.47−1.18 (m, 4H), 1.14 (t, *J* = 7 Hz, 3H), 1.16 (t, *J* = 7 Hz, 3H) 1.14−1.03 (m, 2H), 0.84 (t, *J* = 7 Hz, 3H), 0.79 (t, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.7, 156.6 (d, $^3J_{CP}$ = 7 Hz), 142.4, 140.8 (d, $^5J_{CP}$ = 4 Hz), 135.0 (d, $^3J_{CP}$ = 6 Hz), 129.3, 128.8, 127.7, 127.6, 121.9 (d, $^2J_{CP}$ = 10 Hz), 112.7 (d, $^4J_{CP}$ = 3 Hz), 63.7, 61.9 (d, $^2J_{CP}$ = 7 Hz), 55.7, 48.9, 39.5, 33.1, 26.5 (d, $^1J_{CP}$ = 140 Hz), 25.9, 23.1, 16.2 (d, $^3J_{CP}$ = 6 Hz), 14.0, 8.4; ES$^+$ MS 504 (M + 1, 100); Anal. Calcd for $C_{27}H_{38}NO_4PS$: C, 64.39; H, 7.60; N, 2.78. Found: C, 64.55; H, 7.57; N, 2.81.

(*R*)-8-Bromo-3-butyl-3-ethyl-7-methoxy-5-phenyl-2,3-dihydrobenzo[*f*][1,4]thiazepine (22). Powdered KOH (54.2 g, 966 mmol) was added to a stirred suspension of **23**[8] (136 g, 322 mmol) in EtOH (1 L) at rt. The reaction mixture was heated at reflux for 3 h and then cooled to rt overnight. Most of the volatiles were removed by rotovap, and the remaining material was diluted with water (1.5 L) and extracted with Et_2O. The aqueous phase was acidified with 2 M HCl and extracted with TBME. The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford **24** (89.5 g, 86% crude yield) as a dark oil. This material was dissolved in toluene, a solution of **7** (56.7 g, 252 mmol) in water (440 mL) was added, and the biphasic mixture was heated to reflux. A solution NaOH (6.25 M, 160 mL, 1 mol) was added dropwise over 2 h. Reflux was maintained for an additional 3 h following the NaOH addition. The reaction mixture was allowed to cool to rt and stirred overnight. The layers were separated, and the toluene phase was washed with 1 M NaOH, dried over $MgSO_4$, filtered, and concentrated by rotovap to afford **25** as an oil. This material was dissolved in Et_2O (300 mL), and 1 M HCl (450 mL, 450 mmol) was added dropwise over 2 h with stirring. The slurry was stirred overnight, and the product (**25**·HCl) was collected by filtration as a tan solid (98.9 g, 81% yield). A 1 M solution of NaOH (300 mL, 300 mmol) was added dropwise to a stirred solution of **25**·HCl (114.7 g, 236 mmol) in toluene (1.1 L), and the mixture was stirred for 15 min. The layers were separated, citric acid (905 mg, 4.71 mmol) was added to the toluene phase, and the reaction mixture was heated at reflux for 20 h under Dean−Stark conditions. After cooling to rt, the mixture was washed with satd. $NaHCO_3$ solution, dried, and concentrated to afford **22** as a viscous oil (91 g, 63% overall yield from **23**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (s, 1H), 7.54 (br d, *J* = 8 Hz, 2H), 7.42−7.31 (m, 3H), 6.60 (s, 1H), 3.71 (s, 3H), 3.22 (s, 2H), 1.70−1.59 (m, 2H), 1.60−1.50 (m, 2H), 1.35−1.17 (m, 4H), 0.89 (t, *J* = 7.3 Hz, 3H), 0.86 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.0, 155.3, 142.4, 141.2, 136.7, 129.6, 129.5, 128.8, 127.8, 113.8, 112.2, 64.0, 56.4, 49.0, 39.9, 33.2, 26.0, 23.2, 14.1, 8.4; ES$^+$ MS 432 (M + 1, 100), 434 (M + 1, 100); Anal. Calcd for $C_{22}H_{26}BrNOS$: C, 61.11; H, 6.06; N, 3.24. Found: C, 61.52; H, 6.11; N, 3.14.

Screening Conditions for Asymmetric Hydrogenation of 22. Iridium catalysts were made *in situ* by mixing 1.1 equiv of chiral bidentate phosphine or 2.2 equiv of a chiral monodentate ligand (**A**−**Z**, Table 1) with Ir(COD)$_2$BArF (**26**) followed by addition of **22** (30 mg, 69 μmol) and CH_2Cl_2 (500 μL) (using a Flexiweigh dispensing robot). Reactions were performed in parallel using 2.5 mol % of preformed catalyst at 25 °C, 30 bar (gauge) H_2 for 16 h. The reaction mixtures were analyzed by direct injection HPLC to determine conversion and % de. An RRHT XDB C-18 4.6 mm × 50 mm 1.8 μm column was employed under the following conditions: 34→90% CH_3CN/water with 0.05% TFA; 5 min run; 4.5 mL/min; 60 °C. Compound **27** eluted at 3.6 min, and the desired *trans*-product (**28**) eluted at 3.8 min. Starting material (**22**) eluted at 3.9 min. The results of these experiments are shown in Table 1.

(3*R*,5*R*)-8-Bromo-3-butyl-3-ethyl-7-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (28). A 1 M solution of BH_3·THF (23 mL, 23 mmol) was added dropwise to a stirred solution of **22** (4.86 g, 11.24 mmol) in THF (25 mL) at rt. The reaction mixture was stirred for 3 h and then cooled to −15 °C and quenched by dropwise addition of MeOH (60 mL). The cold mixture was stirred for 15 min and then warmed to rt and concentrated by rotovap to afford an ∼1:1 mixture of diastereomers **27** and **28** (4.9 g, 100% yield). An analytical sample of the desired diastereomer (**28**) was obtained by flash chromatography on silica gel eluting with 0−3% EtOAc/heptane (compound **27** elutes after **28**) and was obtained as a colorless oil (100 mg, 230 μmol): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (s, 1H), 7.46−7.35 (m, 4H), 7.30 (t, *J* = 7 Hz, 1H), 6.11 (s, 1H), 5.74 (s, 1H), 3.51 (s, 3H), 2.77 (d, *J* = 14 Hz, 1H), 2.50 (d, *J* = 14 Hz, 1H), 2.11−2.00 (m, 1H), 1.71−1.60 (m, 1H), 1.46−1.38 (m, 2H), 1.35−1.25 (m, 23H), 1.19−1.09 (m, 2H), 0.88 (t, *J* = 8 Hz, 3H), 0.85 (t, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.2, 151.1, 143.6, 136.7, 129.0, 128.2, 127.6, 126.9, 111.8, 108.4, 57.4, 56.6, 55.8, 43.4, 33.3, 31.2, 25.0, 23.2, 14.1, 7.7; HRMS (TOF ES$^+$) $C_{22}H_{29}(^{79}Br)NOS$ calcd 434.1153, found 434.1153.

Diethyl (((3*R*,5*R*)-3-Butyl-3-ethyl-7-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]-thiazepin-8-yl)methyl)phosphonate (30). A mechanically stirred solution of **20** (1 g, 1.99 mmol), [Ir(COD)$_2$BArF] (**26**) (100 mg, 79 μmol), and Taniaphos ligand **Z** (Table 1) (60 mg, 84 μmol) in CH_2Cl_2 (35 mL) was hydrogenated at 25 °C and 30 bar (gauge) H_2 for 2 h (100% conversion, 80% de). The solution was concentrated, and the crude material was purified by flash chromatography on silica gel eluting with 0→30% EtOAc/CH_2Cl_2 to afford **30** as an off-white solid (850 mg, 85% yield). Performing this reaction at 4 bar (gauge) H_2 for 24 h effected 95% conversion with 80% de: Mp 88−91 °C; $[\alpha]^{25}_D$ = −37.3° (*c* = 1.34, $CDCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.51 (d, *J* = 3 Hz, 1H), 7.45−7.34 (m, 4H), 7.29 (m, 1H), 6.06 (s, 1H), 5.74 (s, 1H), 4.04 (m, 4H), 3.45 (s, 3H), 3.17 (dd, *J* = 20 Hz, J_{HP} = 15 Hz, 1H), 3.11 (dd, *J* = 20 Hz, J_{HP} = 15 Hz, 1H), 2.76 (d, *J* = 14 Hz, 1H), 2.47 (d, *J* = 14 Hz, 1H), 2.11−1.99 (m, 1H), 1.70−1.60 (m, 2H), 1.44−1.36 (m, 2H), 1.34−1.24 (m, 2H), 1.27 (t, *J* = 7 Hz, 3H), 1.26 (t, *J* = 7 Hz, 3H), 1.18−1.10 (m, 2H), 0.87 (t, *J* = 7 Hz, 3H); 0.85 (t, *J* = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 156.3 (d, $^3J_{CP}$ = 7 Hz), 150.4, 143.8, 135.1 (d, $^3J_{CP}$ = 6 Hz), 127.9, 127.5, 127.0 (d, $^4J_{CP}$ = 4 Hz), 126.5, 117.8 (d, $^2J_{CP}$ = 10 Hz), 110.4 (d, $^4J_{CP}$ = 3 Hz), 61.6 (d, $^2J_{CP}$ = 7 Hz), 56.4, 54.9, 43.2, 33.1, 30.9, 25.9 (d, $^1J_{CP}$ = 139 Hz), 24.8, 23.0, 16.1 (d, $^3J_{CP}$ = 7 Hz), 13.9, 7.6; MS (ES$^+$) 506 (M + 1, 100); Anal. Calcd for $C_{27}H_{40}NO_4PS$: C, 64.13; H, 7.97; N, 2.77. Found: C, 63.84; H, 7.82; N, 2.76.

Diethyl (((3*R*,5*R*)-3-Butyl-3-ethyl-7-methoxy-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepin-8-yl)methyl)-phosphonate (31). A solution of **30** (0.5 g, 989 μmol) in TFA (2 mL) was cooled to −20 °C, and 30% H_2O_2 (1.5 mL) was added dropwise. The reaction mixture was stirred at −15 to −20 °C for 3.75 h and at rt for 3 h. The reaction mixture was then stored at 15 °C for 3 d. The mixture was partitioned between EtOAc (30 mL) and water (30 mL), and the layers were separated. The organic phase was washed with 1 N NaOH (40 mL), and the combined aqueous phases were back extracted with EtOAc. The combined organic layers were washed with 10% Na_2SO_3, dried over $MgSO_4$, filtered, and concentrated to an oil which was triturated with heptane. The resulting off-white solid (**31**) was collected by filtration (421 mg, 79% yield): Mp 122−125 °C; $[\alpha]^{25}_D$ = −7.9° (*c* = 1.24, $CDCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (br d, J_{HP} = 2.7 Hz, 1H), 7.45−7.37 (m, 4H), 7.36−7.30 (m, 1H), 6.16 (s, 1H), 6.06 (s, 1H), 4.08 (m, 4H), 3.53 (s, 3H), 3.43 (d, *J* = 15 Hz, 1H), 3.20 (d, J_{HP} = 21.8 Hz, 2H), 3.01 (d, *J* = 15 Hz, 1H), 2.18 (br m, 1H), 1.86 (br m, 1H), 1.52 (m, 1H), 1.46 (m, 1H), 1.36−1.05 (m, 4H), 1.30 (t, *J* = 7 Hz, 3H), 1.29 (t, *J* = 7 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.83 (t, *J* = 7.2, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.3 (d, $^3J_{CP}$ = 6 Hz), 146.4 (d, $^5J_{CP}$ = 4 Hz), 141.6, 131.4 (d, $^4J_{CP}$ = 3 Hz), 130.7 (d, $^3J_{CP}$ = 5 Hz), 128.2, 127.6, 127.2,

118.9 (d, $^2J_{CP}$ = 8 Hz), 110.5 (d, $^4J_{CP}$ = 3 Hz), 63.6, 61.9 (d, $^2J_{CP}$ = 7 Hz), 61.8 (d, $^2J_{CP}$ = 7 Hz), 57.1, 55.3, 55.1, 33.9, 30.8, 26.1 (d, $^1J_{CP}$ = 140 Hz), 25.0, 22.7, 16.1 (d, $^3J_{CP}$ = 7 Hz), 13.8, 7.4; MS (ES$^+$) 538 (M + 1, 100); Anal. Calcd for $C_{27}H_{40}NO_6PS\cdot(0.5\ H_2O)$: C, 59.32; H, 7.56; N, 2.56; S, 5.87. Found: C, 59.43; H, 7.51; N, 2.58; S, 5.77.

(((3*R*,5*R*)-3-Butyl-3-ethyl-7-methoxy-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepin-8-yl)methyl)phosphonic Acid Hydrochloride (3·HCl). A solution of **31** (62 mg, 115 μmol) in 6 M HCl (2 mL) was heated at 120 °C in a sealed tube for 20 h. The solution was concentrated by rotovap to afford **3**·HCl as an amorphous off-white solid (58 mg, 97% yield): $[\alpha]^{25}_D$ = +47.6° (*c* = 1.56, CH_3OH); ^{1}H NMR (CD_3OD, 400 MHz) δ 8.15 (br d, *J* = 2 Hz, 1H), 7.71−7.60 (m, 4H), 6.62 (s, 1H), 6.54 (s, 1H), 4.04 (d, *J* = 16 Hz, 1H), 3.64 (s, 3H), 3.57 (d, *J* = 16 Hz, 1H), 3.30−3.15 (m, 2H), 2.88 (m, 1H), 2.23−2.12 (m, 2H), 1.72 (m, 1H), 1.52−1.41 (m, 3H), 1.03 (t, *J* = 7 Hz, 3H), 0.95 (t, *J* = 7 Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 162.8, 135.1, 134.6, 132.7, 132.2, 131.8, 131.0, 130.8, 125.3, 115.2, 66.7, 59.5, 59.4, 56.8, 31.8, 30.0, 28.9 (d, $^1J_{CP}$ = 138 Hz), 26.0, 23.8, 14.3, 8.3; MS (ES$^+$) 482 (M + 1, 100); HRMS (TOF ES$^+$) $C_{23}H_{33}NO_6PS$ calcd 482.1766, found 482.1767; Anal. Calcd for $C_{23}H_{32}NO_6PS\cdot(HCl)\cdot(0.5\ H_2O)$: C, 52.42; H, 6.50; N, 2.66; S, 6.08. Found: C, 52.48; H, 6.90; N, 2.60; S, 5.80.

■ ASSOCIATED CONTENT

Supporting Information

NMR Spectra for compounds **3**, **5**−**7**, (±)-**10**, **14**−**20**, **22**, **28**, **30**−**31** and X-ray crystal structure data for compound **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: eric.e.boros@gsk.com.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank Professor Scott E. Denmark (Department of Chemistry, University of Illinois) for helpful discussions during the course of this work. We also thank Douglas J. Minick, Timothy D. Spitzer, Eric S. Wentz, and Yang Zhao for their analytical support.

■ REFERENCES

(1) Alrefai, W. A.; Gill, R. K. *Pharm. Res.* **2007**, *24*, 1803−1823.
(2) Kosters, A.; Karpen, S. J. *Xenobiotica* **2008**, *38*, 1043−1071.
(3) Dawson, P. A.; Lan, T.; Rao, A. *J. Lipid Res.* **2009**, *50*, 2340−2357.
(4) Tollefson, M. B.; Kolodziej, S. A.; Fletcher, T. R.; Vernier, W. F.; Beaudry, J. A.; Keller, B. T.; Reitz, D. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3727−3730.
(5) Kurata, H.; Suzuki, S.; Ohhata, Y.; Ikeda, T.; Hasegawa, T.; Kitayama, K.; Inaba, T.; Kono, K.; Kohama, T. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1183−1186.
(6) Liu, H. T.; He, H. W.; Bai, X. G.; Wang, J. X.; Xu, C. L.; Cai, S. Y.; Shao, R. G.; Wang, Y. C. *Molecules* **2013**, *18*, 6883−6897.
(7) Chen, L.; Yao, X.; Young, A.; McNulty, J.; Anderson, D.; Liu, Y.; Nystrom, C.; Croom, D.; Ross, S.; Collins, J.; Rajpal, D.; Hamlet, K.; Smith, C.; Gedulin, B. *Am. J. Physiol. Endocrinol. Metab.* **2012**, *302*, E68−E76.
(8) Aquino, C. J.; Collins, J. L.; Cowan, D. J.; Wu, Y. Benzothiazepine Derivatives as Ileal Bile Acid Transporter (iBAT) Inhibitors and Their Preparation and Use for the Treatment of Metabolic Disorders, International Patent WO2011/13715, 2011; *Chem. Abstr.* **2011**, *155*, 615381.
(9) Wu, Y.; Aquino, C. J.; Cowan, D. J.; Anderson, D. L.; Ambroso, J. L.; Bishop, M. J.; Boros, E. E.; Chen, L.; Cunningham, A.; Dobbins, R. L.; Feldman, P. L.; Harston, L. T.; Kaldor, I. W.; Klein, R.; Liang, X.; McIntyre, M. S.; Merrill, C. L.; Patterson, K. M.; Prescott, J. S.; Ray, J. A.; Roller, S. G.; Yao, X.; Young, A.; Yuen, J.; Collins, J. L. *J. Med. Chem.* **2013**, *56*, 5094−5114.
(10) Tremont, S. J.; Lee, L. F.; Huang, H. C.; Keller, B. T.; Banerjee, S. C.; Both, S. R.; Carpenter, A. J.; Wang, C. C.; Garland, D. J.; Huang, W.; Jones, C.; Koeller, K. J.; Kolodziej, S. A.; Li, J.; Manning, R. E.; Mahoney, M. W.; Miller, R. E.; Mischke, D. A.; Rath, N. P.; Fletcher, T.; Reinhard, E. J.; Tollefson, M. B.; Vernier, W. F.; Wagner, G. M.; Rapp, S. R.; Beaudry, J.; Glenn, K.; Regina, K.; Schuh, J. R.; Smith, M. E.; Trivedi, J. S.; Reitz, D. B. *J. Med. Chem.* **2005**, *48*, 5837−5852.
(11) Huang, H. C.; Tremont, S. J.; Lee, L. F.; Keller, B. T.; Carpenter, A. J.; Wang, C. C.; Banerjee, S. C.; Both, S. R.; Fletcher, T.; Garland, D. J.; Huang, W.; Jones, C.; Koeller, K. J.; Kolodziej, S. A.; Li, J.; Manning, R. E.; Mahoney, M. W.; Miller, R. E.; Mischke, D. A.; Rath, N. P.; Reinhard, E. J.; Tollefson, M. B.; Vernier, W. F.; Wagner, G. M.; Rapp, S. R.; Beaudry, J.; Glenn, K.; Regina, K.; Schuh, J. R.; Smith, M. E.; Trivedi, J. S.; Reitz, D. B. *J. Med. Chem.* **2005**, *48*, 5853−5868.
(12) Brieaddy, L. E. Preparation of 1,4-Benzothiazepine-1,1-dioxides as Hypolipemics, International Patent WO 96/05188, 1996; *Chem. Abstr.* **1996**, *125*, 114724.
(13) Root, C.; Smith, C. D.; Sundseth, S. S.; Pink, H. M.; Wilson, J. G.; Lewis, M. C. *J. Lipid Res.* **2002**, *43*, 1320−1330.
(14) Liu, W.; Ray, P.; Benezra, S. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 553−559.
(15) Mateo, C.; Abian, O.; Fernández-Lorente, G.; Pedroche, J.; Fernández-Lafuente, R.; Guisan, J. M. *Biotechnol. Prog.* **2002**, *18*, 629−634.
(16) Hilterhaus, L.; Minow, B.; Müller, J.; Berheide, M.; Quitmann, H.; Katzer, M.; Thum, O.; Antranikian, G.; Zeng, A. P.; Liese, A. *Bioprocess Biosyst. Eng.* **2008**, *31*, 163−171.
(17) Percent loading and reuse of Sepabead PLE were not evaluated.
(18) Li, X.; Chen, N.; Xu, J. *Synthesis* **2010**, 3423−3428.
(19) Buckley, B. R.; Patel, A. P.; Wijayantha, K. G. U. *J. Org. Chem.* **2013**, *78*, 1289−1292.
(20) Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415−430.
(21) Nagaoka, H.; Schmid, G.; Iio, H.; Kishi, Y. *Tetrahedron Lett.* **1981**, *22*, 899−902.
(22) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587−4590.
(23) For the synthesis of aminomercaptan **23** (R = R′ = Me), see: Wu, W. L.; Burnett, D. A.; Greenlee, W. J. Pyranochromene Derivatives as γ-Secretase Inhibitors and Their Preparation and Use for the Treatment of Neurodegenerative Diseases, International Patent WO 2012/138678 A1, 2012; *Chem. Abstr.* **2012**, *157*, 577330.
(24) During the course of this work a (3-amino)pentanedioic acid analog of **3** (GSK2330672) was selected as a suitable clinical candidate.[9]
(25) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916−4917.
(26) Cobley, C. J.; Henschke, J. P. *Adv. Synth. Catal.* **2003**, *345*, 195−201.
(27) Imamoto, T.; Iwadate, N.; Yoshida, K. *Org. Lett.* **2006**, *8*, 2289−2292.
(28) Tappe, K.; Knochel, P. *Tetrahedron: Asymmetry* **2004**, *15*, 91−102.
(29) Godard, C.; Ruiz, A.; Claver, C. *Helv. Chim. Acta* **2006**, *89*, 1610−1622.
(30) Kesselgruber, M.; Thommen, M. Phospholane Salts and Their Use in Enantioselective Hydrogenation, International Patent WO 2004/098772 A2, 2004; *Chem. Abstr.* **2004**, *141*, 428385.
(31) Mršić, N.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *J. Am. Chem. Soc.* **2009**, *131*, 8358−8359.
(32) Sulfide-coordinating iridium hydride complexes are known; see: Herrera, V.; Fuentes, A.; Rosales, M.; Sánchez-Delgado, R. A.; Bianchini, C.; Meli, A.; Vizza, F. *Organometallics* **1997**, *16*, 2465−2471.