JOC*Article*

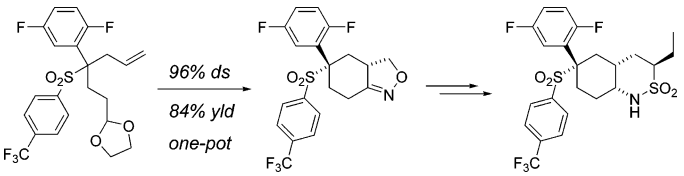
Practical Asymmetric Synthesis of a γ-Secretase Inhibitor Exploiting Substrate-Controlled Intramolecular Nitrile Oxide−Olefin Cycloaddition

Jeremy P. Scott,*,† Steven F. Oliver,*,† Karel M. J. Brands,† Sarah E. Brewer,† Antony J. Davies,† Andrew D. Gibb,† David Hands,† Stephen P. Keen,† Faye J. Sheen,† Robert A. Reamer,‡ Robert D. Wilson,† and Ulf-H. Dolling‡

Department of Process Research, Merck Sharp & Dohme Research Laboratories, Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, United Kingdom, and Department of Process Research, Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065

jeremy_scott@merck.com; steven_oliver@merck.com

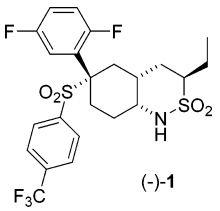
Received January 6, 2006



A practical asymmetric synthesis of the γ-secretase inhibitor (−)-**1** is described. As the key transformation, a highly diastereoselective intramolecular nitrile oxide cycloaddition forms the hexahydrobenzisoxazole core of **3** in four operations. Other aspects of the route include a highly stereoselective reduction of an isoxazole to form a *cis*-γ-amino alcohol, an efficient chemical resolution, a dianion cyclization to construct a sultam ring, and the α-alkylation of a sultam with excellent diastereoselectivity. In each instance, the relative stereochemistry was evolved by way of substrate-based induction with ≥96% ds. Kilogram quantities of the targeted drug candidate (−)-**1** were obtained, without recourse to chromatography, by way of 10 isolated intermediates and in 13% overall yield.

Introduction

Alzheimer's disease (AD) is a progressive and chronic neurodegenerative disease that leads to loss of intellect and memory in those afflicted. AD affects around 4.5 million people in the U.S. and 18 million people worldwide, and with the limited therapies currently available, this represents a major unmet medical need. One of the main pathological characteristics of this disease is the production of the 40−42 amino acid amyloid-β (Aβ) peptide,[1] in which the protease enzyme γ-secretase plays a critical role through cleavage of the β-amyloid precursor protein (βAPP). γ-Secretase, therefore, represents a potential target for AD therapeutic intervention, and as part of a program at Merck directed toward the identification of inhibitors of this enzyme,[2] (−)-**1** was selected for further development. We report herein an efficient and practical asymmetric synthesis of **1** that is amenable to multikilogram operation.



Results and Discussion

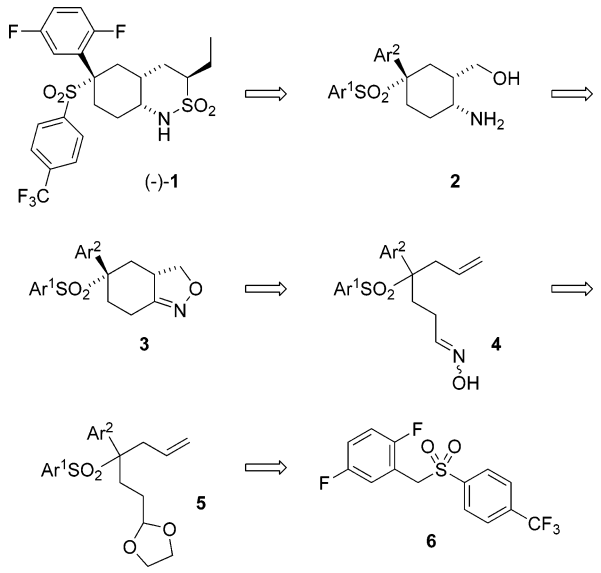
Retrosynthetic Analysis. γ-Secretase inhibitor **1** represents a significant synthetic challenge (Scheme 1). Key structural elements include a trisubstituted octahydro-1*H*-2,1-benzothiazine-2,2-dioxide core and an uncommon, sulfone-bearing carbon as one of four stereogenic centers. Our approach to the synthesis sought to exploit the tertiary sulfone stereocenter to control all relative stereochemistry in the molecule (Scheme 1).

† Merck Sharp & Dohme Research Laboratories.
‡ Merck Research Laboratories.

(1) (a) Jhee, S.; Shiovitz, T.; Crawford, A. W.; Cutler, N. R. *Expert Opin. Invest. Drugs* **2001**, *10*, 593−605. (b) Sambamurti, K.; Grieg, N. H.; Lahiri, D. K. *NeuroMol. Med.* **2002**, *1*, 1−31. (c) Hardy, J.; Higgins, G. A. *Science* **1992**, *256*, 184−185. (d) Tsai, J.-Y.; Wolfe, M. S.; Xia, W. *Curr. Med. Chem.* **2002**, *9*, 1087−1106.

10.1021/jo060033i CCC: $33.50
Published on Web 03/11/2006

SCHEME 1. Retrosynthetic Analysis[a]

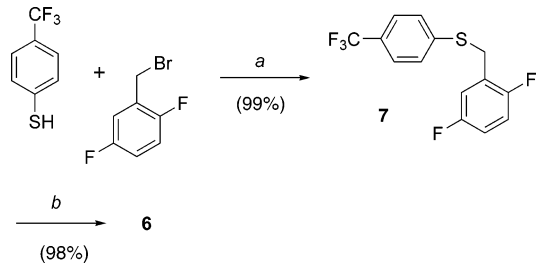


[a] Ar^1 = 4-trifluoromethylphenyl; Ar^2 = 2,5-difluorophenyl.

With late-stage construction of the sultam ring and substrate-controlled installation of the pendant ethyl substituent, γ-amino alcohol derivative **2** was identified as a key intermediate. This γ-amino alcohol enables an intramolecular [3+2] nitrile oxide−olefin cycloaddition (INOC)[3] disconnection by way of isoxazoline **3**, generated from oximes **4**. These in turn would be accessible from the dioxolane-bearing tertiary sulfone **5**, itself available by sequential alkylations of benzylaryl sulfone **6**. In the forward sense, analysis of the likely stereochemical outcome of the three key diastereoselective transformations (INOC, isoxazoline reduction, and ethylation) led us to expect the desired stereochemistry to evolve with substrate control relative to the tertiary sulfone in **5**. The enantioselective synthesis of **1** would, therefore, require either the preparation of a single enantiomer of **5** or a classical resolution.

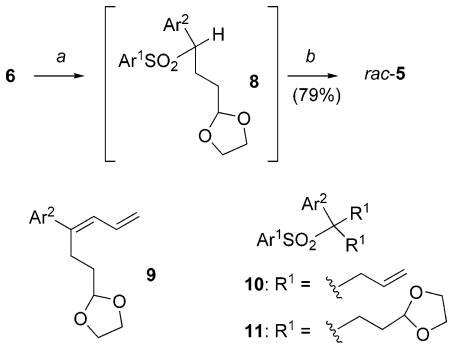
Construction of the Cycloaddition Precursor. Our synthesis began with the alkylation of commercially available 4-trifluoromethylthiophenol with 2,5-difluorobenzyl bromide (Scheme 2). A highly practical procedure involving the generation of the sodium thiolate with NaOH in aqueous EtOH and the addition of the bromide led to the desired sulfide **7** in excellent yield (99%). Oxidation to the corresponding sulfone **6**, using H_2O_2 in AcOH, proceeded in high yield (98%). In both of these processes, the crystalline product is filtered directly from the reaction mixture without extractive workup.

SCHEME 2 [a]



[a] Conditions: (a) 2 M NaOH, EtOH, $T \leq 15$ °C. (b) H_2O_2, AcOH, 40 °C.

SCHEME 3 [a]



[a] Conditions: (a) KO*t*-Bu, 2-(2-bromoethyl)-1,3-dioxolane, DMSO, $T < 20$ °C. (b) KO*t*-Bu, allyl bromide, DMSO, $T < 25$ °C. Ar^1 = 4-trifluoromethylphenyl; Ar^2 = 2,5-difluorophenyl.

The screening of solvent, base, and reagent stoichiometry led to the rapid definition of a practical one-pot procedure for the preparation of *rac*-**5** (Scheme 3). Exposing benzylaryl sulfone **6** to KO*t*-Bu in DMSO at ambient temperature, followed by the addition of 2-(2-bromoethyl)-1,3-dioxolane, afforded monoalkylated **8**. This intermediate was not isolated but was directly alkylated further by the formation of the anion with KO*t*-Bu in DMSO and quenching with allyl bromide. On addition of water, the desired *rac*-**5** could be crystallized directly from the reaction mixture in 79% overall yield. A reverse-addition protocol for the allylation step minimized the formation of the diene byproduct **9**, which was otherwise significant (up to 35%). Symmetrical dialkylated products **10** and **11** were only formed at low levels (<2%).

Several approaches to an enantioselective synthesis of **5** were investigated in parallel, with emphasis on the asymmetric allylation of alkyl sulfone **8**. Despite the wealth of Pd- and Mo-catalyzed asymmetric allylic alkylation processes reported,[4,5] no examples relate to chiral tertiary sulfone formation. Following an extensive ligand and precatalyst screen, Pd-catalyzed bond

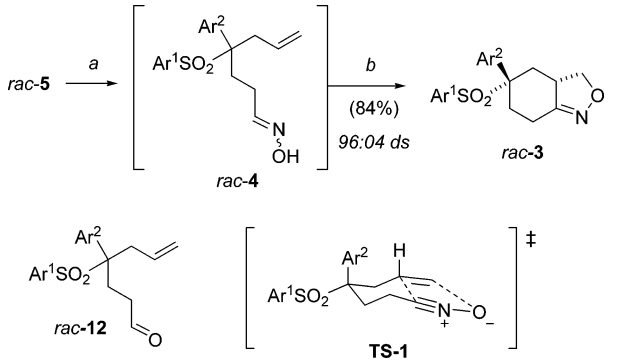
(2) (a) Shaw, D. E.; Best, J. D.; Dinnell, J.; Nadin, A.; Shearman, M. S.; Pattison, C.; Peachey, J.; Reilly, M. A.; Williams, B. J.; Wrigley, J. D. J.; Harrison, T. *Biorg. Med. Chem. Lett.* Submitted for publication. (b) Churcher, I.; Beher, D.; Best, J. D.; Castro, J. L.; Clarke, E. E.; Gentry, A.; Harrison, T.; Hitzel, L.; Kay, E.; Kerrad, S.; Lewis, H. W.; Morentin-Gutierrez, P.; Mortishire-Smith, R.; Oakley, P. J.; Reilly, M.; Shaw, D. E.; Shearman, M. S.; Teall, M. R.; Williams, S.; Wrigley, J. D. J. *Biorg. Med. Chem. Lett.* **2006**, *16*, 280−284. (c) Teall, M.; Oakley, P.; Harrison, T.; Shaw, D.; Kay, E.; Elliot. J.; Gerhard, U.; Castro, J. L.; Shearman, M.; Ball, R. G.; Tsou, N. N. *Biorg. Med. Chem. Lett.* **2005**, *15*, 2685−2688. (d) Churcher, I.; Ashton, K.; Butcher, J. W.; Clarke, E. E.; Harrison, T.; Lewis, H. D.; Owens, A. P.; Teall, M. R.; Williams, S.; Wrigley, J. D. J. *Biorg. Med. Chem. Lett.* **2003**, *13*, 179−183. (e) Churcher, I.; Williams, S.; Kerrad, S.; Harrison, T.; Castro, J. L.; Shearman, M. S.; Lewis, H. D.; Clarke, E. E.; Wrigley, J. D. J.; Beher, D.; Tang, Y. S.; Liu, W. *J. Med. Chem.* **2003**, *46*, 2275−2278.

(3) Reviews: (a) Jager, V.; Colinas, P. A. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Towards Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: New Jersey, 2003; Chapter 6. (b) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410−416. (c) Kanemasa, S.; Tsuge, O. *Heterocycles* **1990**, *30*, 719−736.

(4) (a) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813−5837. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (c) Trost, B. M.; Lee, C. B. In *Catalytic Asymmetric Synthesis II*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 8E, pp 593−650. (d) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis II*; Jacobsen, E. N., Pfaltz, A., Yamomoto, H., Eds.; Springer: Berlin, 1999; Chapter 24, pp 833−884.

(5) (a) Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104−1105. (b) Trost, B. M.; Dogra, K.; Franzini, M. *J. Am. Chem. Soc.* **2004**, *126*, 1944−1945. (c) Belda, O.; Moberg, C. *Acc. Chem. Res.* **2004**, *37*, 159−167.

SCHEME 4 [a]

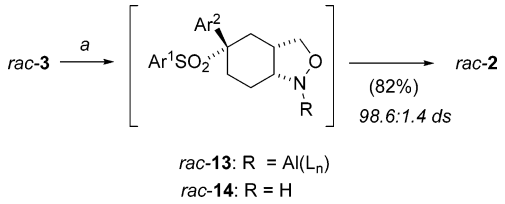


[a] Conditions: (a) $NH_2OH{\cdot}HCl$, EtOH, H_2O, 70 °C. (b) Chloramine-T hydrate, EtOH, H_2O, 50 °C. Ar^1 = 4-trifluoromethylphenyl; Ar^2 = 2,5-difluorophenyl.

formation to afford **5** was found to be possible under both neutral and basic conditions, however, all products were racemic.[6] Phase-transfer-catalyzed allylation of *rac*-**8** was also evaluated without significant success.[7] As a final approach, it was speculated that possible low-temperature configurational stability[8] of anions derived from (*R*)- or (*S*)-**8** would allow for allylation with minimal racemization. In studies using discrete enantiomers of **8**,[9] complete racemization was observed at −78 °C within 1 min under a range of conditions (solvent, additive, and concentration).[10] The in situ generation of the anion in the presence of allyl bromide also yielded racemic product. In the absence of a route to chiral **5**, attention shifted to employing a classical resolution of amino alcohol **2** to define the absolute stereochemistry.

Intramolecular Nitrile Oxide−Olefin Cycloaddition (INOC) and Amino Alcohol Synthesis. Formation of isoxazoline **3** from tertiary sulfone **5** was envisaged by the deprotection of the dioxolane functionality, a conversion to the corresponding oximes **4**, an oxidation to the nitrile oxide, and a subsequent cycloaddition (Scheme 4). Initial studies of the acid-catalyzed deprotection of dioxolane **5** were problematic, with incomplete conversions and competitive degradation of aldehyde **12**. It was, however, found that exposing **5** to $NH_2OH{\cdot}HCl$ in $EtOH/H_2O$ at 70 °C for 2 h led directly to oximes **4** (1:1 *E*/*Z*), obviating the need to isolate **12**. Interestingly, on cooling to 50 °C and adding chloramine-T[11] to this product mixture, an in situ oxidation to the nitrile oxide occurred, followed by a spontaneous cycloaddition. The addition of water then allowed for direct crystallization of the desired *cis*-isoxazoline **3** in 84% yield for this unprecedented four-step one-pot sequence.[12] An examination of the crude reaction mixtures indicated that even at 50 °C **3** was formed with 96% ds,[13] and the diastereocontrol observed was consistent with the expected preferred transition state **TS-1** (Scheme 4).[14]

SCHEME 5 [a]



[a] Conditions: (a) DIBAH, THF, −5 °C, and then 50 °C. Ar^1 = 4-trifluoromethylphenyl; Ar^2 = 2,5-difluorophenyl.

A diastereoselective reduction of **3** to give amino alcohol **2** was expected to ensue through a sterically preferred exo approach to the isoxazoline of **3**, provided the imine moiety was reduced prior to the N−O bond cleavage. While $LiBH_4$, $BH_3{\cdot}Me_2S$, and Red-Al were promising, DIBAH proved to be the optimum reagent for this purpose, and a practical one-pot process was developed (Scheme 5).[15] The exposure of **3** to DIBAH (2.25 equiv) in THF at $T < 0$ °C afforded *N*-aluminoisoxazolidine **13** with excellent diastereocontrol (98.6% ds).[13] Heating this mixture to 50 °C then triggered N−O bond cleavage to afford **2** in 82% yield, following an aqueous workup to remove aluminum residues.[16]

With racemic **2** in hand, a survey of readily available chiral acids for a classical resolution was performed. Both dibenzoyl- and ditoluoyltartaric acids were promising leads, and the former was evaluated in detail (Table 1).[17] The dibenzoyl-D-hemitartrate salt of **2** was found to be the best. The performance of the resolution proved to be critically dependent on the use of ethereal solvents such as THF or DME (entries 2 and 5), possibly as the result of solvate formation.[18] Interestingly, amino alcohol **2** could also be successfully resolved using just 0.25 equiv of dibenzoyl-D-tartaric acid, however, yields were significantly reduced (entries 3 and 6).

Sultam Ring Synthesis and Final Elaboration. Our proposed routes to the sultam ring of **1** were based on methodology

(6) Summary of Pd-screening results: The diphosphines (*S*,*S*)-Et-DuPhos, (*S*,*S*)-Chiraphos, (*S*,*S*)-Diop, (*S*,*S*)-Dipamp, t-BuJOSIPHOS, and (*R*,*R*)-Norphos with LHMDS, $Pd(allyl)_2$, and allyl acetate afforded conversion to **5** (57−80%) in all cases racemically.

(7) (a) O'Donnell, M. J. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Oijima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 10, pp 727−755. (b) Lygo, B. *Rodd's Chemistry of Carbon Compounds*; Elsevier: Oxford, U.K., 2001; Vol. 5, pp 101−149. (c) Jones, R. A. *Quaternary Ammonium Salts. Their Use in Phase-Transfer Catalysis*; Academic Press: London, 2001.

(8) (a) Gais, H.-J.; Hellmann, G.; Gunther, H.; Lopez, F.; Lindner, H. J.; Braun, S. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1025−1027. (b) Raabe, G.; Gais, H.-J.; Flesichhauer, J. *J. Am. Chem. Soc.* **1996**, *118*, 4622−4630. (c) Corey, E. J.; Konig, H.; Lowry, T. H. *Tetrahedron Lett.* **1962**, *84*, 515−520.

(9) A preparative separation of the enantiomers of **8** was accomplished using 5% IPA in supercritical CO_2 (Chiralcel OD-H, 70 mL/min, 35 °C, 100 bar).

(10) The extent of the deprotonation of enantioenriched **8** (as determined by deuterium quenching) was found to closely correlate with the ee of the recovered **8**, and in situ trapping with allyl iodide afforded only *rac*-**5**.

(11) Hassner, A.; Rai, K. *Synthesis* **1989**, 57−59.

(12) Low levels (<1%) of competitive dehydration of the oximes **4** to the corresponding nitrile were observed in this process, and the latter was the major product when operating in EtOH in the absence of added water.

(13) Diastereoselection was determined by a reverse-phase HPLC assay of unpurified samples of the reaction mixtures. The undesired diastereoisomer remained in the mother liquors such that the isolated solid was >99% de.

(14) Related diastereocontrol in an INOC has been reported: Kozikowski, A. P.; MaloneyHuss, K. E. *Tetrahedron Lett.* **1985**, *26*, 5759−5762.

(15) Although the one-pot diastereoselective reduction of an isoxazoline to the corresponding γ-amino alcohol has been reported, an *N*-metalloisoxazolidine intermediate was not explicitly implicated: Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069−7071.

(16) Compound *rac*-**14** can be prepared using 1.2 equiv of DIBAH in CH_2Cl_2 (−50 °C). This solvent efficiently suppresses any subsequent N−O bond cleavage, which occurs on extended aging in THF.

(17) Other chiral acids that were screened (malic, tartaric, abietic, aspartic, glutamic, CSA, and mandelic) led to no crystalline material or the isolated salt was racemic.

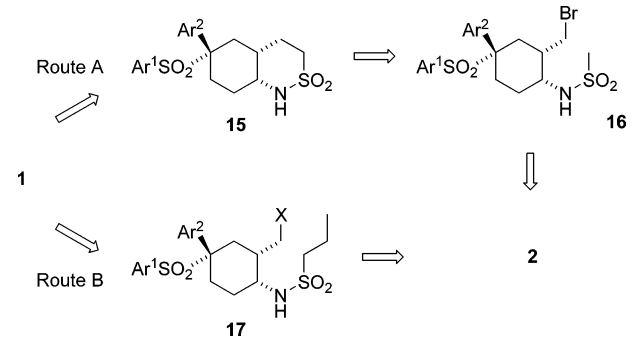
(18) Whilst the microscope examination of the intially formed slurries indicated crystalline material with needle morphology, the dry solid (45 °C in vacuo) is amorphous by XRPD, likely a result of desolvation.

TABLE 1. Study of Dibenzoyl-D-tartaric Acid Stoichiometry with *rac*-2 in THF and DME

entry	equiv of dibenzoyl-D-tartaric acid	solvent (mL g^{-1})	isolated yield (%) of hemitartrate salt	ee of isolated solid[a] (%)
1	1.0	THF (10)	38	73
2	0.5	THF (10)	42	87
3	0.25	THF (10)	36	94
4	1.0	DME (10)	44	95
5	0.5	DME (10)	42	98
6	0.25	DME (10)	36	98

[a] Enantiomeric excess determined by acetylation and HPLC assay.

SCHEME 6. Proposed Sultam Ring Constructions[a]

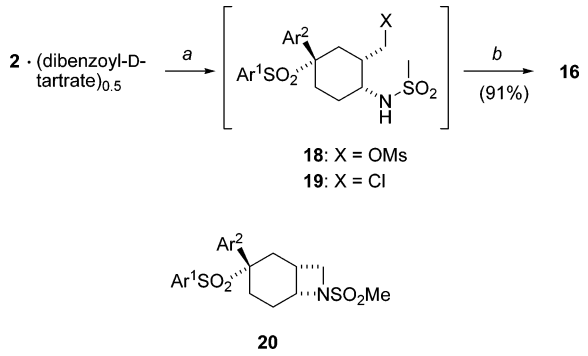


[a] Ar^1 = 4-trifluoromethylphenyl; Ar^2 = 2,5-difluorophenyl.

previously reported from these laboratories for the construction of sultams via sulfonamide dianion alkylation (Scheme 6).[19] In route A, diastereoselective α-ethylation of sultam **15**, or an appropriate *N*-protected derivative, would be required to arrive at **1**.[20,21] This would be preceded by the cyclization of the *N*,*C*-dianion generated from γ-bromomethanesulfonamide **16**, in turn derived from γ-amino alcohol **2**. In the more convergent approach (route B), a diastereoselective cyclization of an *N*,*C*-dianion of propanesulfonamide derivative **17** would be required. Despite extensive efforts, the latter cyclizations (**17**: X = Br, Cl, I, OTs, or benzenesulfonate) were found to be only moderately diastereoselective (≤69% ds).

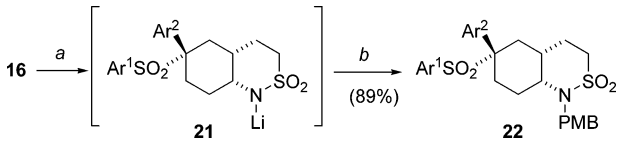
The desired sultam ring precursor was prepared from γ-amino alcohol **2** by *O*- and *N*-mesylation, followed by bromide displacement (Scheme 7).[19] Thus, exposure of the resolved hemitartrate salt of **2** to a biphasic mixture of NaOH and CH_2Cl_2, separation of the free base containing organic layer, followed by the addition of methanesulfonic anhydride and Et_3N afforded bismesylate **18**. This was not isolated, but aged with NaBr at elevated temperature following a solvent exchange to DMF. The addition of H_2O then allowed the direct crystallization of **16** from the reaction mixture in excellent yield (91%). The cyclization behavior of **16** had been demonstrated to be superior to **19**,[22] and our use of Ms_2O over MsCl was, therefore, guided by our desire to suppress the formation of **19**. Chloride **19** was always observed during the bromide displacement if MsCl had been employed (as a result of presumed chloride carry over) and was found to be responsible for downstream byproduct

SCHEME 7[a]



[a] Conditions: (a) NaOH, CH_2Cl_2, 25 °C, and then Ms_2O, Et_3N, T < 10 °C. (b) NaBr, DMF, 85 °C. Ar^1 = 4-trifluoromethylphenyl; Ar^2 = 2,5-difluorophenyl.

SCHEME 8[a]



[a] Conditions: (a) LDA, THF, T < −45 °C. (b) H_2O, and then PMBCl, DMAc, NaI, 25 °C. Ar^1 = 4-trifluoromethylphenyl; Ar^2 = 2,5-difluorophenyl.

formation. No azetidine byproduct **20** was detected in the preparation of **16**.

The addition of a THF solution of bromide **16** to LDA at T < −45 °C led to a clean cyclization to *N*-lithiosultam **21** with no competitive formation of azetidine **20** (Scheme 8).[23] Previously, we had shown that the direct ethylation of a dianion derived from sultam **15** was not viable to access **1**.[24] For this reason, **21** was protected in situ as the *p*-methoxybenzyl (PMB) derivative by quenching the excess LDA with a minimum of H_2O, followed by the addition of 4-methoxybenzyl chloride and sodium iodide in *N*,*N*-dimethylacetamide (DMAc). After overnight aging at ambient temperature, the conversion of **21** was complete and sultam **22** could be isolated in 89% yield.

The introduction of the final ethyl substituent was initially problematic due to significant degradation of the anion of **22** at −40 °C. This instability was compounded by a slow alkylation rate with EtI and unsatisfactory diastereoselection at this temperature. An in situ trapping protocol was, therefore, pursued, in which the EtI was added prior to any base. A striking

(19) Lee, J.; Zhong, Y.-L.; Reamer, R. A.; Askin, D. *Org. Lett.* **2003**, *5*, 4175−4177.

(20) Kaiser, E. M.; Knutson, P. L. A. *J. Org. Chem.* **1975**, *40*, 1342−1346.

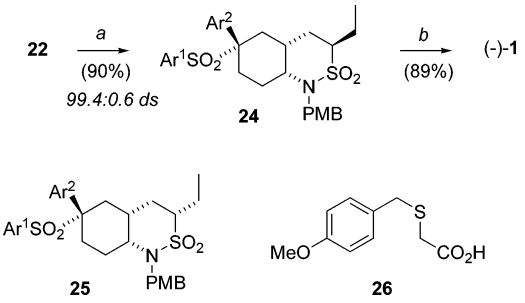
(21) Thompson, M. E. *J. Org. Chem.* **1984**, *49*, 1700−1703.

(22) Bromide **16** undergoes cyclization a temperature 20 °C cooler (−50 compared to −30 °C) than chloride **19** using LDA, affording a consequently improved impurity profile in isolated **22**.

(23) Azetidine **20** can be readily prepared by the cyclization of **16** with KO*t*-Bu in THF at 40 °C.

(24) An attempted direct ethylation of sultam **15** was thwarted by our inability to prepare the *N*,*C*-dianion, as indicated by deuterium incorporation studies. Profiles of deprotonations were also unsatisfactory at higher temperatures, presumably a result of competing aryl C−H abstraction.

SCHEME 9 [a]



[a] Conditions: (a) NaHMDS, EtI, THF, $T < 1$ °C. (b) MsOH, $HSCH_2CO_2H$, CH_2Cl_2, $T < 5$ °C. Ar^1 = 4-trifluoromethylphenyl; Ar^2 = 2,5-difluorophenyl.

metal counterion effect was observed. With the slow addition of NaHMDS at $T < 1$ °C to a THF solution of **22** and EtI, **24** formed with excellent diastereoselectivity (99.4% ds; Scheme 9). Following an aqueous workup and crystallization, pure **24** could be isolated in 90% yield. In contrast, the substitution of NaHMDS with LHMDS in the identical process led to formation of 10% of the undesired diastereomer **25**. Although the sense of diastereoselection is consistent with the sterically most favorable exo approach to the *cis*-bicyclic core, the origin of the dramatic counterion effect is currently not understood in detail.[25]

To control the final impurity levels, a robust procedure for the cleavage of the PMB group from **24** was required. An initial survey of acid-mediated deprotection in aprotic solvents indicated that, although high yields of **1** were readily obtained, they were typically accompanied by a myriad of PMB-derived byproducts. Speculating that an inefficient capture of the cation resulting from the PMB cleavage was occurring, a screen of sulfur-containing additives was initiated.[26] Thioglycolic acid ($HSCH_2CO_2H$) performed particularly well, and exposing **24** to 4.0 equiv of this additive with 3.0 equiv of MsOH in CH_2Cl_2 cleanly afforded **1** in quantitative assay yield (Scheme 9). This procedure had the additional benefit that the resulting byproduct **26** could be efficiently removed by a simple wash with aqueous base. Following crystallization, the desired drug candidate **1** could be isolated in 89% yield as an analytically pure compound.[27,28]

In summary, we have developed a practical asymmetric route to the γ-secretase inhibitor **1**, proceeding by way of 10 isolated intermediates (13% overall yield) and exploiting a diastereoselective INOC as key step. Aspects of the route which are of potentially more general synthetic utility follow: (1) the use of a dioxolane moiety as a masked nitrile oxide, exemplified by the transformation of **5** → **3**; (2) conditions for the one-pot diastereoselective reduction of an isoxazoline to the γ-amino alcohol by sequential imine and N−O bond reduction (**3** → **2**); and (3) acidic deprotection of a PMB-protected sulfonamide using thioglycolic acid as an efficient cation scavenger. The developed route is notable for the control of relative stereochemistry, with the three diastereoselective transformations proceeding with ≥96% ds under substrate-based induction in each instance.

(25) The observed diastereoselection is kinetic in origin under the conditions used, as prolonged aging in the presence of the 0.4 equiv of excess LHMDS or NaHMDS employed does not lead to any change in the ratio of **24**:**25**. In addition, under conditions of thermodynamic equilibration (KO*t*-Bu/*t*-BuOH, 80 °C), a 1:1 mixture of **24** and **25** afforded only a 97:3 ratio favoring **24**.

(26) Other trapping agents evaluated were thiourea, thiosemicarbazide, 2-thiobenzoic acid, *L*-methionine, and thioanisole. The use of protic solvents EtOH or IPA with 6 or 12 M HCl afforded high assay yields of **1**, however, impurity profiles were unsatisfactory.

(27) The PMB ether can also be removed by catalytic hydrogenolysis using a Degussa E101 NE/W, 20% Pd, 50% H_2O catalyst (70 psi, MeOH/AcOH, 10% w/t dry basis relative to **24**).

(28) The absolute stereochemistry of (−)-**1** was confirmed by X-ray crystallography. See Supporting Information.

Experimental Section

1,4-Difluoro-2-({[4-(trifluoromethyl)phenyl]thio}methyl)-benzene (7). 4-Trifluoromethylthiophenol (10.0 kg, 56.1 mol) was dissolved in EtOH (20.5 L) and cooled to 13 °C. Aqueous sodium hydroxide (2 M, 37.6 L, 75.2 mol) was added over 30 min, maintaining $T \leq 15$ °C. The resultant solution was aged for 15 min at 15 °C, and then a solution of 2,5-difluorobenzylbromide (11.4 kg, 55.1 mol) in EtOH (9.0 L) was added dropwise over 1 h, with $T \leq 15$ °C. The resultant slurry was cooled to 13 °C, and water (41.0 L) was added over 15 min at ≤15 °C. Filtration, washing of the product cake with EtOH/H_2O (1:2, 23.0 L) and water (2 × 23.0 L), and drying in vacuo at 40 °C for 18 h furnished the title compound as a white solid (16.6 kg, 99%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.64 (2H, d, J = 8.3 Hz), 7.55 (2H, d, J = 8.3 Hz), 7.27 (2H, m), 7.16 (1H, m), 4.36 (2H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.3 (dd, J = 2.2, 241.0 Hz), 156.9 (dd, J = 2.4, 242.1 Hz), 141.9 (q, J = 1.5 Hz), 128.4, 126.2 (q, J = 3.8 Hz), 126.7 (q, J = 32.0 Hz), 124.5 (q, J = 271.7 Hz), 126.4 (dd, J = 8.4, 17.6 Hz), 117.7 (dd, J = 4.0, 24.8 Hz), 117.4 (dd, J = 8.8, 24.6 Hz), 116.4 (dd, J = 8.6, 24.0 Hz), 29.7; mp 52−54 °C; Anal. Calcd for $C_{14}H_9F_5S$: C, 55.26; H, 2.98. Found: C, 54.85; H, 2.94.

1,4-Difluoro-2-({[4-(trifluoromethyl)phenyl]sulfonyl}methyl)-benzene (6). To a stirred solution of sulfide **7** (12.2 kg, 40.1 mol) dissolved in acetic acid (58 L) at ambient temperature was added hydrogen peroxide (5.05 kg, 27.5% w/t, 40.1 mol) over 35 min. The reaction was heated to 30 °C and aged at this temperature for 3 h. Further hydrogen peroxide (12.1 kg, 27.5% w/t, 96.2 mol) was added over 30 min, and then the mixture was aged at 40 °C for 18 h. The resultant slurry was cooled to <35 °C, and water (98 L) was added over 30 min. The slurry was aged 30 min at 25 °C and then filtered. The cake was washed with water (5 × 31 L) and then dried in vacuo at 45 °C to afford the title compound as a white solid (13.3 kg, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (2H, d, J = 8.7 Hz), 7.99 (2H, d, J = 8.7 Hz), 7.24 (2H, m), 7.15 (1H, m), 4.86 (2H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.9, (dd, J = 2.2, 240.7 Hz), 157.5 (dd, J = 2.4, 245.1 Hz), 142.4, 134.2 (q, J = 32.6 Hz), 129.8, 126.9 (q, J = 3.8 Hz), 123.7 (q, J = 272.7 Hz), 119.8 (dd, J = 3.4, 25.0 Hz), 118.2 (dd, J = 8.7, 24.0 Hz), 117.8 (dd, J = 9.0, 18.0 Hz), 117.5 (dd, J = 9.0, 24.8 Hz), 54.7; mp 119−120 °C; Anal. Calcd for $C_{14}H_9F_5O_2S$: C, 50.00; H, 2.70. Found: C, 49.92; H, 2.72.

2-(3-(2,5-Difluorophenyl)-3-{[4-(trifluoromethyl)phenyl]-sulfonyl}hex-5-en-1-yl)-1,3-dioxolane (5). Sulfone **6** (12.70 kg, 37.8 mol) in DMSO (33.8 L) was added to a solution of potassium *tert*-butoxide (4.66 kg, 41.5 mol) in DMSO (17 L) maintaining T < 25 °C. The resultant mixture was cooled to 15 °C, and 2-(2-bromoethyl)-1,3-dioxolane (7.85 kg, 43.4 mol) was added while maintaining T < 20 °C. The reaction mixture was aged at ambient temperature for 105 min and then cooled to 15 °C, and a solution of potassium *tert*-butoxide (6.77 kg, 60.3 mol) in DMSO (23.8 L) was added. The mixture was aged for 30 min and then added to a solution of allyl bromide (16.0 kg, 132 mol) in DMSO (34.8 L) while maintaining T < 25 °C. Water (36.0 L) was added at ambient temperature. The resultant slurry was filtered, and the solid was washed with a 2:1 mixture of DMSO/H_2O (16 kg) and then water (2 × 15 kg). Drying in vacuo afforded the title compound as a white solid (14.2 kg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H), 7.07 (m, 2H), 6.82 (ddd, J = 4.8, 9.0, 12.2 Hz, 1H), 5.92 (m, 1H), 5.28 (dq, J = 1.6,

17.0 Hz, 1H), 5.20 (dq, J = 1.4, 10.2 Hz, 1H), 4.91 (t, J = 4.4 Hz, 1H), 3.93 (m, 4H), 3.30 (m, 1H), 3.12 (m, 1H), 2.51 (m, 2H), 2.02 (m, 1H), 1.58 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4 (dd, J = 2.0, 243.5 Hz), 158.1 (dd, J = 2.6, 249.0 Hz), 138.9 (m), 135.5 (q, J = 33.2 Hz), 131.8, 130.9, 125.5 (q, J = 3.6 Hz), 123.0 (dd, J = 7.2, 11.6 Hz), 123.0 (q, J = 273.1 Hz), 119.9, 118.7 (dd, J = 4.2, 25.8 Hz), 118.1 (dd, J = 8.6, 29.2 Hz), 118.0 (dd, J = 10.0, 23.8 Hz), 103.6, 71.9 (dd, J = 1.2, 4.6 Hz), 65.0 (d, J = 6.2 Hz), 36.2 (d, J = 6.6 Hz), 28.1, 25.5 (d, J = 5.6 Hz); mp 93−94 °C; Anal. Calcd for $C_{22}H_{21}F_5O_4S$: C, 55.46; H, 4.44. Found: C, 55.31; H, 4.38.

***cis*-5-(2,5-Difluorophenyl)-5-{[4-(trifluoromethyl)phenyl]sulfonyl}-3,3a,4,5,6,7-hexahydro-2,1-benzisoxazole (3).** Dioxolane **5** (28.0 kg, 58.8 mol) and hydroxylamine hydrochloride (5.31 kg, 76.0 mol) in a mixture of ethanol (140 L) and water (28 L) were aged at 70 °C for 2 h and then cooled to 50 °C. A solution of chloramine-T hydrate (20.1 kg, 88.2 mol) in a mixture of water (56 L) and ethanol (196 L) was then added, and the mixture was aged at 50 °C for 2 h before cooling to ambient temperature. The resultant slurry was filtered, and the solid was washed with a 4:1 mixture of EtOH/H_2O (20 L). Drying in vacuo furnished the title compound as a tan solid (21.4 kg, 84%). ^{1}H NMR (600.1 MHz, DMF-d_7, 350 K) δ 7.97 (d, J = 8.3 Hz, 2H), 7.77 (d, J = 8.3 Hz, 2H), 7.38−7.34 (om, 2H), 7.19 (m, 1H), 4.50 (dd, J = 10.2, 7.9 Hz, 1H), 3.88 (dd, J = 10.2, 7.9, 1H), 3.33 (ddd, J = 13.2, 5.3, 3.4 Hz, 1H), 3.30−3.17 (om, 2H), 2.85 (m, 1H), 2.25−2.18 (om, 2H), 2.13 (td, J = 12.8, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.0 (dd, J = 2.0, 249.3 Hz), 158.7 (dd, J = 2.5, 241.7 Hz), 157.4, 139.0, 134.8 (q, J = 32.4 Hz), 131.5, 126.5 (q, J = 3.6 Hz), 123.6 (q, J = 273.2 Hz), 119.9 (dd, J = 7.8, 11.4 Hz), 119.3 (3C, m), 72.9, 71.0 (m), 45.2, 35.1 (d, J = 6.4 Hz), 30.4 (d, J = 7.0 Hz), 21.3; mp 212−214 °C; Anal. Calcd for $C_{20}H_{16}F_5N0_3S$: C, 53.93; H, 3.62; N, 3.14. Found: C, 53.68; H, 3.60; N, 3.04.

((1*R*,2*S*,5*R*)- and ((1*S*,2*R*,5*S*)-2-Amino-5-(2,5-difluorophenyl)-5-{[4-(trifluoromethyl)phenyl]sulfonyl}cyclohexyl)methanol (2). Isoxazoline **3** (50.0 g, 112 mmol) was slurried in tetrahydrofuran (300 mL) and cooled to −5 °C. Diisobutylaluminum hydride (20 % w/t in toluene, 212 mL, 252 mmol) was added while maintaining T < −3 °C. The resultant solution was aged for 1.5 h, warmed to 50 °C for 1.5 h, and then recooled to 0 °C. Methanol (10 mL) was added while maintaining T < 15 °C, and then aqueous sodium hydroxide (2 M, 300 mL) was added. The mixture was stirred for 14 h, and then the layers were separated. The organic layer was distilled to a volume of 250 mL while toluene (250 mL) was added. The mixture was allowed to cool. The resultant slurry was filtered, and the solids were washed with toluene (50 mL). Drying in vacuo furnished the title compound as a white solid (40.9 g, 82%). ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C) δ 7.88 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H), 7.26 (m, 1H), 7.08 (m, 2H), 3.40 (m, 2H), 3.08 (m, 1H), 2.47 (m, 2H), 2.40 (d, J = 12.8 Hz, 1H), 2.25 (t, J = 12.8 Hz, 1H), 1.69 (m, 1H), 1.36 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.9 (dd, J = 2.8, 248.1 Hz), 158.5 (dd, J = 2.1, 241.3 Hz), 139.8, 134.3 (q, J = 32.4 Hz), 131.3, 126.3 (q, J = 3.8 Hz), 123.7 (q, J = 272.9 Hz), 121.9 (dd, J = 7.2, 12.4 Hz), 119.2 (dd, J = 4.6, 25.8 Hz), 118.9 (dd, J = 9.0, 29.2 Hz), 118.5 (dd, J = 10.0, 23.8 Hz), 72.6 (m), 63.7, 45.2, 40.7, 30.6, 26.1 (m), 23.7 (d, J = 7.4 Hz); mp 212−214 °C; Anal. Calcd for $C_{20}H_{20}F_5N0_3S$: C, 53.45; H, 4.49; N, 3.12. Found: C, 53.24; H, 4.41; N, 2.99.

((1*S*,2*R*,5*S*)-2-Amino-5-(2,5-difluorophenyl)-5-{[4-(trifluoromethyl)phenyl]sulfonyl}cyclohexyl)methanol D-Dibenzoyl Hemitartrate. To a solution of *rac*-**2** (7.5 kg, 16.7 mol) in THF (56.3 L) was added a solution of dibenzoyl-D-tartaric acid (2.99 kg, 8.34 mol) in IPAc (56.3 L) while maintaining T < 25 °C. The resultant mixture was aged overnight and filtered, and the solids were washed with THF/IPAc (1:1, 22.5 L), followed by THF (22.5 L). Drying in vacuo furnished the title compound as a white solid (4.05 kg, 39%, 96% ee). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.18−8.13 (m, 2H), 7.83−7.80 (m, 2H), 7.63−7.60 (m, 2H), 7.59−7.51 (m, 1H), 7.45−7.42 (m, 2H), 7.25−6.95 (m, 3H), 5.89 (s, 1H), 3.75−3.52 (m, 2H), 3.49−3.42 (m, 1H), 2.85−2.80 (m, 1H), 2.58−2.45 (m, 1H), 2.40−2.30 (m, 2H), 2.08−1.98 (m, 1H), 1.73−1.53 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, 70 °C) δ 168.7, 165.5, 159.0 (d, J = 250.0 Hz), 158.5 (d, J = 241.2 Hz), 139.7, 134.3 (q, J = 32.0 Hz), 133.4, 131.3, 130.6, 129.6, 128.8, 126.4 (q, J = 3.6), 123.7 (q, J = 273), 121.2 (m), 118.9 (3C, m), 72.7, 72.2 (m), 62.6, 46.0, 39.2, 27.6, 26.4, 24.0; mp 167−168 °C; $[\alpha]^{20}_D$ +5.35 (*c* 1.0, MeOH, >99% ee); enantiopurity was determined via supercritical fluid chromatography (Chiralpak AD, 0.7 mL/min, 150 bar CO_2, t = 0 min @ 11% MeOH, t = 12 → 20 min @ 17% MeOH, t_R = 11.0−11.7 and 12.1−12.7 min) following acetylation (MTBE/NaOH, concentrate MTBE extract, and dissolve in MeOH/Ac_2O).

***N*-((1*R*,2*S*,4*S*)-2-Bromomethyl-4-(2,5-difluorophenyl)-4-{[4-(trifluoromethyl)phenyl]sulfonyl}cyclohexyl)methanesulfonamide (16).** To a slurry of ((1*R*,2*S*,5*R*)-2-amino-5-(2,5-difluorophenyl)-5-{[4-(trifluoromethyl)phenyl]sulfonyl}cyclohexyl)methanol D-dibenzoyl hemitartrate (4.10 kg, 3.3 mol) in CH_2Cl_2 (76.0 kg) was added 0.4 N NaOH (23.5 kg, 9.4 mol), and the resultant mixture was aged for 45 min. The lower organic layer was separated, washed with water (13 kg), and then reduced in volume to 12 L by distillation at atmospheric pressure. Triethylamine (1.67 kg, 16.5 mol) was added, followed by a solution of methanesulfonic anhydride (2.83 kg, 16.3 mol) in methylene chloride (11 kg) while maintaining T < 10 °C. DMF (30 kg) was then added, and the mixture was distilled to remove the CH_2Cl_2 and to reach a volume of 34 L. Sodium bromide (1.34 kg, mol) was added, and the batch was heated to 85 °C for 7 h. DMF (7 kg) was added, followed by water (35 L), to crystallize the product. The resultant slurry was filtered, and the solid was washed with water (2 × 5 L). Drying in vacuo furnished the title compound as an off-white solid (3.49 kg, 91%, >99% ee). ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C) δ 7.89 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 8.4 Hz, 2H), 7.28 (m, 1H), 7.15 (d, J = 7.3 Hz, 1H), 7.10 (m, 2H), 3.68 (m, 1H), 3.62 (dd, J = 6.6, 10.1 Hz, 1H), 3.52 (br t, J = 8.2 Hz, 1H), 2.97 (s, 3H), 2.79 (br m, 1H), 2.60 (br m, 1H), 2.45 (m, 1H), 2.22 (t, J = 13.5 Hz, 1H), 2.03 (m, 1H), 1.82 (m, 1H), 1.43 (m, 1H);^{13}C NMR (100 MHz, DMF-d_7, 5 °C) δ 158.9 (dd, J = 2.8, 247.5 Hz), 158.6 (dd, J = 2.0, 239.5 Hz), 138.9 (m), 134.5 (q, J = 33.0 Hz), 131.5, 126.3 (m), 123.6 (q, J = 273.1), 120.7 (m), 118.9 (3C, m), 70.9 (d, J = 3.9 Hz), 49.9, 40.6, 39.7, 35.4, 28.6 (m), 24.2, 23.9 (m); mp 200−201 °C; $[\alpha]^{20}_D$ −26.9 (*c* 1.0, MeOH, >99% ee); Anal. Calcd for $C_{21}H_{21}BrF_5N0_4S_2$: C, 42.72; H, 3.59; N, 2.37. Found: C, 42.81; H, 3.55; N, 2.24. The separation of the enantiomers was accomplished by HPLC analysis (Chiralpak AD, 2.0 mL/min, 90% hexane, 10% EtOH, t_R = 13.2, 17.9 min).

(4a*S*,6*S*,8a*R*)-6-(2,5-Difluorophenyl)-1-(4-methoxybenzyl)-6-{[4-(trifluoromethyl)phenyl]sulfonyl}octahydro-1*H*-2,1-benzothiazine 2,2-Dioxide (22). THF (14.7 kg) was cooled to less than −60 °C, and hexyllithium (5.2 kg of a 2.28 M solution in hexane, 16.8 mol) was added at T < −20 °C. Diisopropylamine (1.78 kg, 17.6 mol) was then added while maintaining T < −20 °C. The resultant solution was cooled to −60 °C, and then a solution of **16** (3.22 kg, 5.45 mol) in THF (4.8 kg) was added while maintaining T < −45 °C. The resultant solution was aged for 3 h, and then water (0.11 kg, 6.15 mol) was added while maintaining T < −40 °C. The solution was allowed to warm to −20 °C, and a solution of NaI (0.42 kg, 2.80 mol) in DMAc (8.66 kg) was added, followed by *para*-methoxybenzyl chloride (1.58 kg, 10.1 mol). The mixture was warmed to room temperature and aged to reach full conversion. A solution of HCl [1.64 L of concentrated HCl (specific gravity 1.18) diluted with 17 L of water, 19.4 mol] was added while maintaining T < 50 °C. Toluene (44.3 kg) was added, and the layers were separated. The organic layer was washed with water (3 × 8.9 kg) and then distilled to reach a volume of 22.5 L, adding toluene as necessary to reach a residual THF content of <2 mol % (^{1}H NMR). Heptane (12.6 kg) was added, and the resultant slurry was filtered and washed with a 1:1 mixture of toluene and heptane

(2.8 kg of each), followed by heptane (2.8 kg). Drying in vacuo furnished the title compound as tan solid (3.05 kg, 89%, >99% ee). ^{1}H NMR (400 MHz, DMSO-d_6, 85 °C) δ 7.85 (d, J = 8.2 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.30−7.23 (m, 1H), 7.13−7.05 (m, 2H), 6.92 (d, J = 8.5 Hz, 2H), 4.53 (d, J = 16.6 Hz, 1H), 4.11 (d, J = 16.6 Hz, 1H), 3.82 (s, 3H), 3.50 (br s, 1H), 3.35 (dt, J = 3.7, 13.7 Hz, 1H), 3.25−3.18 (m, 1H), 2.69−2.60 (m, 1H), 2.48−2.40 (m, 1H), 2.38−2.25 (m, 1H), 2.21−2.11 (m, 2H), 2.10−2.01 (m, 1H), 1.79−1.68 (m, 2H), 1.40−1.28 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, 85 °C) δ 159.2 (d, J = 247 Hz), 159.1, 158.7 (d, J = 240 Hz), 139.5, 134.5 (q, J = 32 Hz), 131.3, 130.8, 129.4, 126.2 (q, J = 3.0 Hz), 123.8 (q, J = 272 Hz), 121.5 (dd, J = 7.0, 12.0 Hz), 119.5−118.6 (3C, overlapping resonances), 114.5, 71.8, 58.3, 55.8, 45.5, 44.9, 32.4, 28.7 (d, J = 7.0 Hz), 28.1, 25.3, 24.5; mp 230−231 °C; $[\alpha]^{20}_D$ −7.58 (*c* 1.0, CH_3CN, >99% ee); Anal. Calcd for $C_{29}H_{28}F_5N0_5S_2$: C, 55.32; H, 4.48; N, 2.22. Found: C, 55.20; H, 4.48; N, 2.15. Separation of enantiomers was accomplished by HPLC analysis (Chiralpak AD, 1.0 mL/min, 60% hexane, 40% EtOH, t_R = 9.8, 16.9 min).

(3*R*,4a*S*,6*S*,8a*R*)-6-(2,5-Difluorophenyl)-3-ethyl-1-(4-methoxybenzyl)-6-{[4-(trifluoromethyl)phenyl]sulfonyl}octahydro-1*H*-2,1-benzothiazine 2,2-Dioxide (24). A solution of **22** (2.97 kg, 4.7 mol) and ethyl iodide (1.03 kg, 6.60 mol) in THF (26.3 kg) was cooled to −5 °C. Sodium bis(trimethylsilylamide) (1.0 M in THF, 5.97 kg, 6.60 mol) was then added while maintaining T < 1 °C. The mixture was aged for 80 min, and then an aqueous citric acid solution (0.55 kg citric acid, 2.84 mol in 28.3 kg water) was added while maintaining T < 8 °C. Methyl *tert*-butyl ether (22 kg) was added, and the layers were allowed to settle. The organic layer was washed with water (8.91 kg) and then distilled at atmospheric pressure to a volume of 34 L. The mixture was further distilled, adding 2-propanol (80.2 kg) to reach a final volume of 34 L. The resultant slurry was cooled and filtered, and the solid was washed with 2-propanol (2.70 kg). Drying in vacuo furnished the title compound as a white solid (2.74 kg, 90%, >99% ee). ^{1}H NMR (400 MHz, DMSO-d_6, 85 °C) δ 7.87 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 7.2 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.31−7.25 (m, 1H), 7.18−7.03 (m, 2H), 6.94−6.90 (d, J = 8.0 Hz, 2H), 4.55 (d, J = 17.2 Hz, 1H), 4.17 (d, J = 16.8 Hz, 1H), 3.81 (s, 3H), 3.49−3.48 (m, 1H), 3.28−3.19 (m, 1H), 2.70−2.61 (m, 1H), 2.52−2.43 (m, 1H), 2.20−1.92 (m, 5H), 1.75−1.67 (m, 2H), 1.60−1.49 (m, 1H), 1.38−1.28 (m, 1H), 1.10 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 85 °C) δ 159.2 (d, J = 245 Hz), 159.1, 158.7 (d, J = 241 Hz), 139.5, 134.5 (q, J = 32.0 Hz), 131.3, 130.9, 129.4, 126.3 (d, J = 3.0 Hz), 123.8 (q, J = 272 Hz), 121.4 (dd, J = 12.0, 20.0 Hz), 119.5−118.5 (3C, overlapping resonances), 114.5, 71.9, 57.7, 56.2, 55.8, 45.0, 34.0, 33.0, 29.0 (d, J = 6.1 Hz), 25.3, 24.5, 21.7, 11.0; mp 188−189 °C; $[\alpha]^{20}_D$ −23.9 (*c* 1.0, MeOH, >99% ee); Anal. Calcd for $C_{31}H_{32}F_5N0_5S_2$: C, 56.61; H, 4.90; N, 2.13. Found: C, 56.50; H, 4.89; N, 2.06. Separation of enantiomers was accomplished by HPLC analysis (Chiralpak AD, 0.7 mL/min, 60% hexane, 40% EtOH, t_R = 10.5, 14.5 min).

(3*R*,4a*S*,6*S*,8a*R*)-6-(2,5-Difluorophenyl)-3-ethyl-6-{[4-(trifluoromethyl)phenyl]sulfonyl}octahydro-1*H*-2,1-benzothia-zine 2,2-Dioxide (1). To a stirred solution of **24** (2.74 kg, 4.16 mol) in CH_2Cl_2 (18 L) at 0 °C was added thioglycolic acid (1.53 kg,16.6 mol). A solution of methanesulfonic acid (1.21 kg, 12.5 mol) in CH_2Cl_2 (2 L) was added while maintaining T < 5 °C. The reaction was then aged 30 min, and then a 2 M NaOH solution (18 L, 36 mol) was added while maintaining T < 10 °C. The lower organic layer was diluted with IPAc (35 L), and the combined organic layers were washed sequentially with 2 M NaOH (18 L, 36 mol) and water (17 L). The organic layer was distilled to a volume of 15 L, and further IPAc (20 L) was added. The solution was again distilled to a volume of 15 L, and then heptane (12.5 L) was added to crystallize the product. The solid was isolated by filtration and washed with a 2:1 heptane/IPAc mixture (5 L). Drying in vacuo furnished the title compound as a white solid (1.97 kg, 89%, >99 wt %, >99% ee). ^{1}H NMR (400 MHz, DMSO-d_6, 85 °C) δ 7.88 (2H, d, J = 7.9 Hz), 7.65 (d, J = 7.6 Hz, 2H), 7.30−7.23 (m, 1H), 7.22−7.05 (m, 2H), 7.00−6.95 (m, 1H), 3.48−3.40 (m, 1H), 2.96−2.89 (m, 1H), 2.63−2.38 (m, 4H), 2.10−1.95 (m, 1H), 1.90−1.79 (m, 3H), 1.65−1.35 (m, 3H), 1.05 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 85 °C) δ 159.2 (d, J = 248 Hz), 158.4 (d, J = 240 Hz), 139.6, 134.5 (q, J = 32.0 Hz), 131.3, 126.3 (q, J = 3.0 Hz), 123.8 (q, J = 272 Hz), 121.3 (dd, J = 7.0, 90 Hz), 119.5−118.5 (3C, overlapping resonances), 72.3 (d, J = 4.0 Hz), 55.7, 52.1, 35.1, 31.9, 38.0 (d, J = 7.0 Hz), 26.6, 24.0, 21.9, 11.2; mp 247−248 °C; $[\alpha]^{20}_D$ −52.6 (*c* 1.0, MeOH, >99% ee); Anal. Calcd for $C_{23}H_{24}F_5N0_4S_2$: C, 51.39; H, 4.50; N, 2.61. Found: C, 51.28; H, 4.47; N, 2.54. Separation of enantiomers was accomplished by HPLC analysis (Chiralpak AD, 1.5 mL/min, 60% hexane, 40% EtOH, t_R = 4.3, 10.4 min).

Acknowledgment. We thank Andrew Kirtley, Sophie Aillaud, Mirlinda Biba, Jennifer Chilenski, Arlene McKeown, Jimmy Dasilva, Christopher J. Welch, and Peter Yehl for technical support. We thank Mike S. Ashwood, Khateeta M. Emerson, John S. Edwards, and Adrian Goodyear for pilot plant support.

Supporting Information Available: Details of the stereochemical assignment of **3** and the X-ray structure of **1**. This material is available free of charge via the Internet at http://pubs.asc.org.

JO060033I