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A Practical Synthesis of a γ-Secretase Inhibitor

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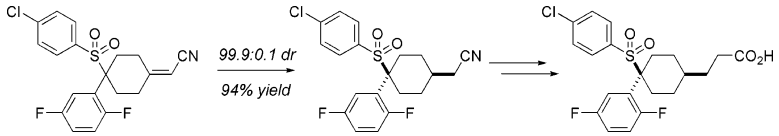

A practical and scaleable synthesis of the γ-secretase inhibitor **1** is reported. The inhibitor consists of a central trisubstituted cyclohexane core with appended propionic acid, 2,5-difluorophenyl, and 4-chlorophenylsulfonyl moieties. Two alternative synthetic strategies, proceeding by way of a common disubstituted cyclohexanone derivative **5**, were studied. In the preferred route, conjugate reduction of acrylonitrile derivative **4** with L-Selectride configures the desired relative stereochemistry of the cyclohexane core with >99.9:0.1 dr. A second strategy, based on catalyst-controlled hydrogenation of racemic cyclohexene derivative **2**, is more convergent but less diastereoselective (up to 75:25 dr). The common cyclohexanone intermediate **5** was constructed by a regioselective Diels−Alder condensation of a 1,1-disubstituted vinyl sulfone **6** with 2-trimethylsiloxybutadiene.

Introduction

Alzheimer's disease (AD) is a progressive and chronic neurodegenerative disorder that causes sufferers to lose their intellect, memory, and personality.[1] Aside from the societal costs, AD is rapidly becoming one of the most financially burdensome diseases to the healthcare systems of industrialized nations due to the aging demographic of the population. It is currently thought that AD pathogenesis is primarily driven by the accumulation of Aβ protein (the so-called amyloid hypothesis), and consequently, methods for Aβ reduction are the focus of several therapeutic strategies. As part of a program at Merck directed toward the identification of inhibitors for the enzyme γ-secretase,[2] **1** was selected as a preclinical candidate. We report herein an efficient and practical synthesis of **1** that is amenable to multikilogram operation.

Results and Discussion

Retrosynthetic Analysis. A central issue in the synthesis of inhibitor **1** is control of the desired 1,4-*cis* relative stereochemistry across the cyclohexane ring between the propionic acid and 4-chlorophenylsulfonyl side chains. We envisioned two potential strategies to address this issue, both of which proceeded by way of common cyclohexanone intermediate **5** (Scheme 1).

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(1) (a) Larner, A. *Expert Opin. Ther. Pat.* **2004**, *14*, 1403−1420. (b) Citron, M. *Nat. Rev. Neurosci.* **2004**, *5*, 677. (c) Parihar, M. S.; Hemnani, T. *J. Clin. Neurosci.* **2004**, *11*, 456. (d) Bullock, R. *Expert Opin. Investig. Drugs* **2004**, *13*, 303. (e) Esteban, J. A. *Trends Neurosci.* **2004**, *27*, 1. (f) Mani, R. B. *Statist. Med.* **2004**, *23*, 305. (g) Kornilova, A. Y.; Wolfe, M. S. *Annu. Rep. Med. Chem.* **2003**, *38*, 41. (h) Aguzzi, A.; Haass, C. *Science* **2003**, *302*, 814. (i) Lahiri, D. K.; Farlow, M. R.; Sambamurti, K.; Greig, N. H.; Giacobini, E.; Schneider, L. S. *Curr. Drug Targets* **2003**, *4*, 97. (j) Gurwitz, D. *Drug Dev. Res.* **2002**, *56*, 45. (k) Walter, J.; Haass, C. *Drug Dev. Res.* **2002**, *56*, 201. (l) Wolfe, M. S. *Nature Rev.* **2002**, 859. (m) Selkoe, D. J. *J. Clin. Invest.* **2002**, *110*, 1375. (n) Lahiri, D. K.; Farlow, M. R.; Greig, N. H.; Sambamurti, K. *Drug Dev. Res.* **2002**, *56*, 267.

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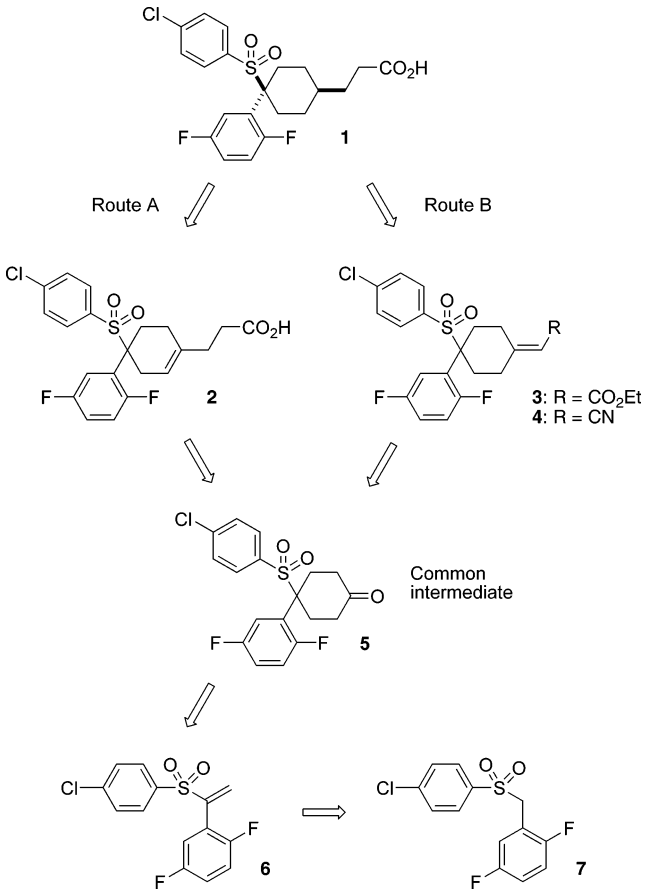
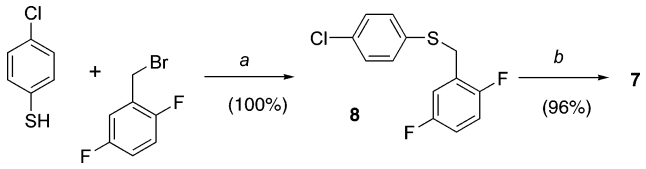
SCHEME 1



SCHEME 2[a]



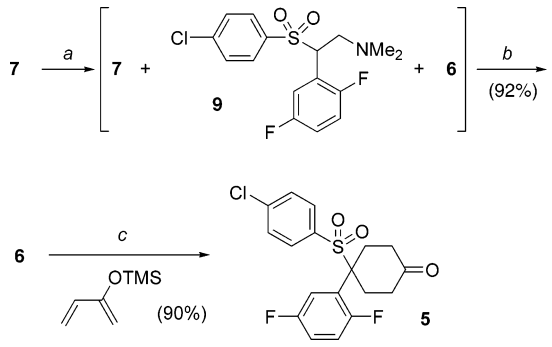
[a] Conditions: (a) 2 M NaOH, EtOH, < 20 °C; (b) Na_2WO_4, Aliquat 336, H_2O_2, PhMe, 45 °C.

In the more convergent approach (route A), diastereoselective hydrogenation of racemic cyclohexene derivative **2** was hoped to afford **1** directly. The alternative approach (route B) was based on recognition that the 1,4-*cis* relationship of the propionic acid and 4-chlorophenylsulfonyl moieties could possibly be configured by a diastereoselective conjugate reduction of acrylate **3** or acrylonitrile **4**.[2] Common intermediate **5** was envisioned to arise by a regioselective Diels−Alder reaction of vinyl sulfone **6** with 2-trimethylsiloxybutadiene.

Preparation of Common Cyclohexanone Intermediate. The synthesis of vinyl sulfone **6** began with alkylation of commercially available 2,5-difluorobenzyl bromide with 4-chlorothiophenol (Scheme 2). A highly practical procedure was developed, involving generation of the sodium thiolate with NaOH in ethanol, followed by slow addition of the benzyl bromide. Addition of water allowed for direct crystallization of the sulfide **8** in quantitative yield.[3]

(3) Yields reported are of isolated materials corrected for purity as determined by reversed-phase HPLC assay versus authentic standards.

SCHEME 3[a]



[a] Conditions: (a) 1.5 equiv of *N*,*N*,*N*′,*N*′-tetramethylmethylenediamine, 1.5 equiv of acetic anhydride, DMF, 60 °C; (b) 1.6 equiv of acetic anhydride, DMF, 60 °C; H_2O; (c) xylenes, 130 °C; 3 M HCl, THF, 50 °C.

Several protocols for the oxidation of **8** were investigated. A sodium tungstate catalyzed hydrogen peroxide oxidation emerged as one of the most practical procedures (Scheme 2).[4] Dichloromethane, chlorobenzene, dichlorobenzene, and toluene were evaluated as solvents for a biphasic reaction with 2.5 equiv of aqueous hydrogen peroxide in the presence of 1.5 mol% of $Na_2WO_4 \cdot 2H_2O$ and 2 mol% of Aliquat 336 as phase-transfer catalyst. Toluene proved optimal with conversion of **8** complete within 45 min at 45 °C. After a reductive quench of the excess peroxide, heptane was used to effect direct crystallization of **7** from the organic layer in 96% isolated yield.[5]

Initially, vinyl sulfone **6** was prepared from **7** via a two-step procedure using Eschenmoser's salt.[6] However, we later identifed a more direct and practical one-pot procedure (Scheme 3).[7,8] Thus, after optimization it was discovered that warming a DMF solution of **7** with 1.5 equiv of *N*,*N*,*N*′,*N*′-tetramethylmethylenediamine and 1.5 equiv of acetic anhydride at 60 °C for 2.5 h yielded a mixture of **7**, **9**, and **6**. Slow addition over 4 h of an additional 1.6 equiv of acetic anhydride then led to full conversion to the desired **6**, which could be crystallized directly from the reaction mixture in 92% yield by the addition of water. The structure of **6** was confirmed by single-crystal X-ray crystallography.[9a] Addition of the full quantity of acetic anhydride at the reaction outset invariably led to incomplete consumption of **7**. Variable-temperature NMR studies presented insight into this issue. In DMF-d_7, the Mannich reagent $H_2C{=}NMe_2(OAc)$ is formed instantaneously upon addition of stoichiometric acetic anhydride to a solution of the diamine at 0 °C. This species is stable at ambient temperature for several

(4) (a) Blacklock, T. J.; Butcher, J. W.; Sohar, P.; Lamanec, T. R.; Grabowski, E. J. J. *J. Org. Chem.* **1989**, *54*, 3907. (b) Schultz, H. S.; Freyermuth, H. B.; Buc, S. R. *J. Org. Chem.* **1963**, *28*, 1140.

(5) Sulfone **7** can also be prepared in >90% yield by alkylation of 2,5-difluorobenzylbromide with 4-chlorobenzenesulfinic acid sodium salt in DMF; however, this salt is not commercially available on kilogram scale.

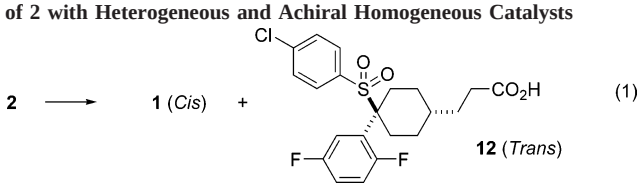
(6) Conditions: (a) LiHMDS, THF; $(Me_2NCH_2)I$; (b) MeI, IPAc then $NaHCO_3$.

(7) Scott, J. P.; Hammond, D. C.; Beck, E. M.; Brands, K. M. J.; Davies, A. J.; Dolling, Ulf-H.; Kennedy, D. J. *Tetrahedron Lett.* **2004**, *45*, 3345.

(8) (a) Gunda, T. E. *Synth. Commun.* **1992**, *22*, 2979. (b) DeSolms, S. J. *J. Org. Chem.* **1976**, *41*, 2650. (c) For a recent review of the Mannich reaction: Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044.

(9) Crystallographic data for this compound have been deposited at the Cambridge Crystallographic Data Centre. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data-request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033. (a) CCDC 236716. (b) CCDC 236717.

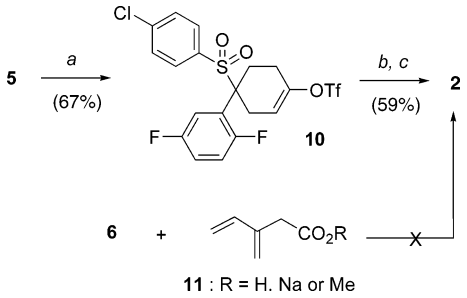
TABLE 1. Catalytic Hydrogenation of 2 with Heterogeneous and Achiral Homogeneous Catalysts



entry	catalyst	mol %	*P* (psig)	*T* (°C)	solvent	time/h	conversion/%[a]	**1**:**12** *(cis*/*trans)*[a]
1	5% Rh/C	5[b]	15	22	EtOAc	48	98	7:93
2	$(Ph_3P)_3RhCl$	15	90	22	1:1 EtOH/THF	22	11	38:62
3	Crabtree	10	90	22	CH_2Cl_2	16	5	11:89
4	(dppf)Rh(COD)BF_4[c]	20	90	22	MeOH	22	76	5:95
5	(dppp)Rh(COD)BF_4[c]	20	90	22	MeOH	22	74	2:98
6	(dppp)Ru(Cymene)Cl_2[c]	25	90	50	3:1 EtOH/ CH_2Cl_2	22	98	29:71

[a] Determined by HPLC assay. [b] Weight %. [c] 1.2 equiv of Et_3N added.

SCHEME 4[a]



[a] Conditions: (a) LDA, THF, −50 °C then 2-[*N*, *N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine, 25 °C; (b) $PdCl_2(PPh_3)_2$, 3-ethoxy-3-oxopropylzinc bromide, THF, 55 °C; (c) LiOH, THF, 65 °C.

hours. However, upon addition of further acetic anhydride decomposition of the Mannich reagent is observed. Thus, when the acetic anhydride is added slowly it presumably preferentially reacts with the intermediate **9** rather than the initially formed iminium salt.

The Diels−Alder reaction of vinyl sulfone **6** with 2-trimethylsiloxybutadiene[10] proceeded at an acceptable rate in xylenes at 130 °C. Hydrolysis of the intermediate silyl enol ether with HCl in THF/xylenes then afforded **5** in high yield (Scheme 3).[7] Both an excess of diene (2 equiv) and low water content of the initial reaction mixture (<50 μg mL^{-1}) were found to be critical in effecting reproducible and complete conversion of **6** within a reasonable time frame (16 h). An azeotropic distillation of xylenes was therefore incorporated prior to addition of the diene. At the reaction conclusion, a further distillation was employed in order to remove the excess 2-trimethylsiloxybutadiene remaining in solution. This minimized formation of polymeric material resulting from degradation of the diene during the acidolysis. Crystallization then afforded cyclohexanone **5** in 90% yield. A single-crystal X-ray structure[9b] indicated that the 4-chlorophenylsulfonyl group adopts an equatorial position in **5**. Thus, cyclohexanone **5** could be prepared in four steps with 79% overall yield.

Preparation of Cyclohexene Propionic Acid (Route A). The attachment of the propionic side chain to access cyclohexene derivative **2** was achieved in three steps from cyclohexanone **5** (Scheme 4). Enolization with LDA followed by quenching with 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine afforded enol triflate **10** in 67% yield.[11] Negishi coupling of the latter with commercially obtained 3-ethoxy-3-oxopropylzinc bromide[12] followed by ester hydrolysis yielded the desired racemic hydrogenation substrate **2** (59% over two steps). An alternative approach to **2**, based on the Diels−Alder condensation of vinyl sulfone **6** with dienes **11** (R = H, Na, or Me), was unsuccessful under a variety of thermal and Lewis acid promoted conditions.

Hydrogenation Studies. Initial hydrogenation studies of racemic cyclohexene acid **2** employing heterogeneous Cu-, Ni-, Pd-, Pt-, Ru-, or Rh-based catalysts were complicated by competitive dechlorination of the arylsulfone moiety, particularly at elevated hydrogen pressures (90 psig). Moreover, diastereoselection was generally in the undesired sense, with *trans* relative stereochemistry predominant. For example, using 5% Rh/C in EtOAc afforded a 93:7 dr at 98% conversion for the undesired *trans* cyclohexane diastereomer **12** with 3% dechlorination (Table 1, entry 1). Achiral homogeneous catalysts were also examined, but these typically displayed low reactivity and a similar preference for the undesired diastereomer **12** (Table 1, entries 2−6). The addition of amines did not appear to have a substantial impact on the diastereoselectivity of the hydrogenation.[13]

The selectivity observed with the heterogeneous catalysts and achiral homogeneous catalysts studied indicated strong substrate control governing the facial approach in the reduction of **2**. In an effort to overcome this preference by exploiting reagent control, hydrogenation catalysts bearing chiral ligands were examined. Although diverse metal/ligand combinations were examined, ruthenium modified by axially chiral ligands provided the best results (Table 2).[14] Gratifyingly, several ligands now afforded the desired *cis*-isomer **1** as the major component albeit that the highest selectivities (up to 75:25 dr) were still moderate.

(10) (a) Tamura, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955. (a) Jung, M. E.; McCombs, C. A. *Tetrahedron Lett.* **1976**, *34*, 2935. (b) Jung, M. E.; McCombs, C. A. *Org. Synth.* **1978**, *58*, 163. (c) Jung, M. E.; McCombs, C. A.; Taked, Y.; Pan, Y-G. *J. Am. Chem. Soc.* **1981**, *103*, 6677.

(11) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

(12) Tamura, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955.

(13) Zhang, M.; Azhu, L.; Ma, X.; Dai, M.; Lowe, D. *Org. Lett.* **2003**, *5*, 1587.

(14) Hydrogenations with catalysts derived from rhodium or iridium did not indicate any reversal in substrate control, yielding **12** as the major product in each case examined.

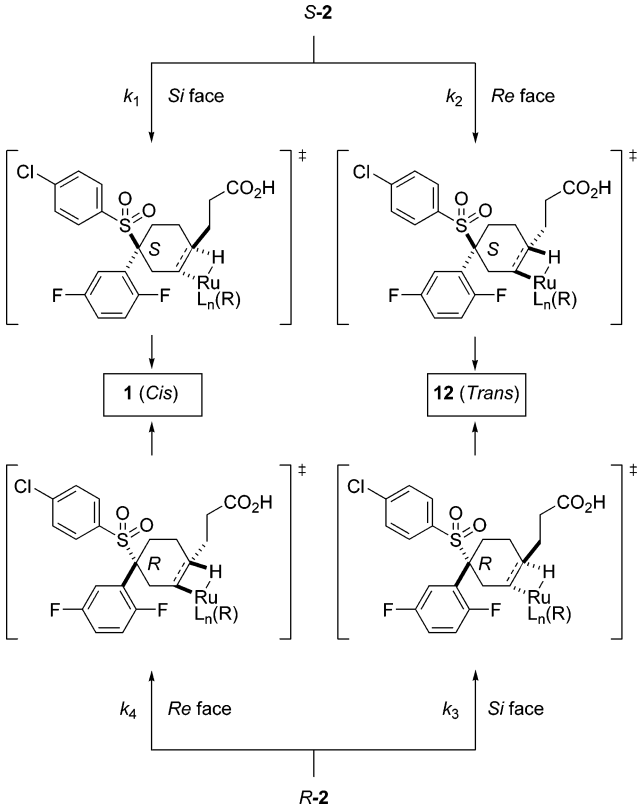
(15) (Ligand)$RuCl_2$(cymene) complexes were prepared according to the literature: Mashima, K.; Kusano, K.; Sate, N.; Matsumura, N.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 3064.

TABLE 2. Catalytic Hydrogenation of 2 with Ruthenium Catalysts and Axially Chiral Ligands

entry	ligand[a]	conversion[b]/%	**1**:**12** *(cis/trans)*[b]
1	*rac*-Binap	>99	66:34
2	*R*-Binap	98	52:48
3	*rac*-TolBinap	93	67:33
4	*rac*-XylBinap	95	73:27
5	*rac*-Synphos	91	74:26
6	*rac*-P-Phos	>99	75:25
7	*R*-P-Phos	>99	53:47

[a] Conditions: (ligand)$RuCl_2$(cymene),[15] Et_3N, S/C 2−4:1, 90 psig H_2, 50 °C, 3:1 EtOH/ CH_2Cl_2, 22 h. [b] Determined by HPLC assay.

SCHEME 5. Stereochemical Outcomes in the Ruthenium-Catalyzed Reduction of 2



Interestingly, early screening results indicated racemic catalysts were required to achieve the highest levels of diastereoselectivity observed. For example, *rac*-Binap and enantiomerically enriched *R*-Binap provided 66% and 52% of **1**, respectively (Table 2, entries 1 and 2). Similarly, *rac*-P-Phos and enantiomerically enriched *R*-P-Phos provided 75% and 53% of **1**, respectively (Table 2, entries 6 and 7). The interpretation of these observations is complex, given that for each enantiomer of catalyst there are four diastereomeric transition states, and thus four distinct rates should be considered for racemic **2** (Scheme 5).[16] The desired *cis* selectivity requires *si* face approach with the *S*-enantiomer of **2**, while *re* face approach is necessary for *R*-**2**. One rationale which is consistent with all observed results is that the reaction satisfies the following criteria (Scheme 5): (1) A given enantiomer of catalyst selects for a matched prochiral face regardless of the absolute configuration

(16) The regiochemistry in the transition states for ruthenium hydride addition to **2** are likely to be identical, but have been assigned arbitrarily pending further mechanistic experimentation.

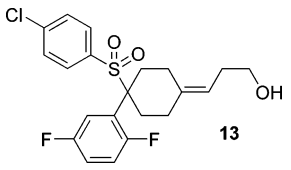


FIGURE 1. Alternative exocyclic olefin substrate.

of **2** (e.g., with *R*-enantiomer of catalyst, *si* facial attack > *re* facial attack, or $k_1 > k_2$ and $k_3 > k_4$). (2) Each of the enantiomeric catalysts exhibit kinetic resolution on the substrate (i.e., for a given enantiomer of catalyst k_1 and k_2 are greater than k_3 and k_4). (3) The prochiral facial selectivity of each catalyst enantiomer toward each substrate enantiomer is roughly equivalent in magnitude (i.e., $k_1/k_2 \approx k_3/k_4$). In addition, the observation that the diastereoselectivity of reductions conducted with enantiomerically enriched catalyst at low conversion of **2** was similar to that of reductions with racemic catalysts at high conversion (for example, the reduction with ((*R*)-P-Phos)Ru-(Cymene)Cl_2 at 21% conversion yielded an 81:19 ratio of **1** and **12**, respectively) also corroborates the above rationale.[16]

As an alternative strategy, extensive hydrogenation screening on the reduction of achiral alcohol **13** (Figure 1), which bears an exocyclic olefin, was also performed with a variety of ligand/catalyst combinations. Diastereoselection was at best 67:33 favoring the desired diastereomer (20 mol % Ir black, EtOAc, 1 atm H_2).

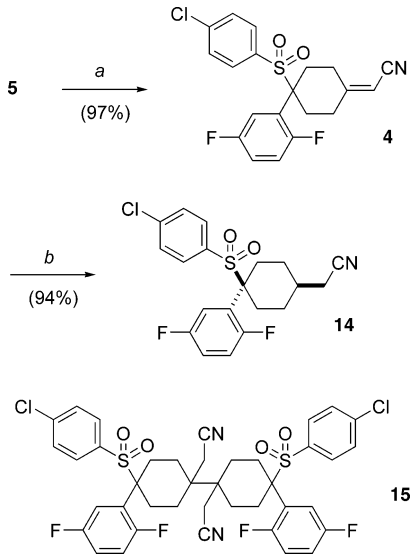
HWE Olefination and Conjugate Reduction (Route B). The modest selectivity of the above hydrogenation approach was not suitable for the synthesis of **1** on large scale. Therefore, we decided to investigate the alternative approach which was outlined above (Scheme 1, route B). The reduction of 4-*tert*-butylcyclohexanones with hindered hydride reagents is well documented to afford the axial alcohol products predominantly.[17] Consequently, assuming a preference for the 4-chlorophenylsulfonyl moiety to occupy an equatorial orientation, we expected to obtain good *cis* diastereoselectivity in a similar reduction of **3** or **4**.[18] Initial experiments using the unsaturated ester **3** indeed showed that good *cis* selectivity could be achieved. However, the yields in these experiments were low, presumably due to competing and/or consecutive 1,2-reduction processes. This led to examination of the acrylonitrile derivative **4** as it was expected that 1,2-reduction pathways would be less favored with this substrate. Compound **4** was readily prepared in 97% yield via Horner−Emmons−Wadsworth olefination of cyclohexanone **5** with diethyl (cyanomethyl)phosphonate[19] employing KO-*t*-Bu as base (Scheme 6). L-Selectride showed the best selectivity among several hydride reagents which were screened for this reaction. Initially, a reaction protocol was examined in which L-Selectride was slowly added to a cold solution of **4** in THF. Under these conditions, the diastereoselection was found to be uniformly excellent with >99:1 dr in favor of the desired *cis*

(17) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.

(18) (a) For a detailed study and rationalisation of the conformational bias of aryl, arylsulfonyl geminally substituted tertiary carbon centers, see: Scott, J. P.; Mullens, P. R.; Brewer, S. E.; Brands, K. J. M.; Chilenski, J. R.; Davies, A. J.; Gibb, A. D.; Lieberman, D. R.; Oliver, S. F.; Dolling, U-H. *Org. Biomol. Chem.* **2006**, *4*, 1806. (b) For the application of this conformational bias in an intramolecular nitrile oxide-olefin cycloaddition, see: Scott, J. P.; Oliver, S. F.; Brands, K. J. M.; Brewer, S. E.; Daves, A. J.; Gibb, A. D.; Hands, D.; Keen, S. P.; Sheen, F. J.; Reamer, R. A.; Wilson, R. D.; Dolling, U. H. *J. Org. Chem.* **2006**, *71*, 3086.

(19) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

SCHEME 6[a]

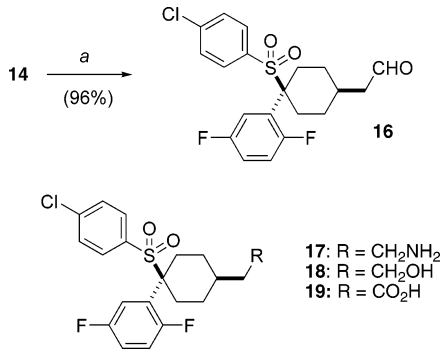


[a] Conditions: (a) $(EtO)_2P(O)CH_2CN$, KO-*t*-Bu, THF, −5 °C; (b) L-Selectride, THF, $-60 < T < -55$ °C; H_2O_2, NaOH, NaCl, H_2O, 5 °C; >99.9:0.1 dr.

diasteromer **14** at temperatures as high as −10 °C and was >99.9:0.1 dr under the preferred conditions.[20] However, under these conditions a set of impurities were formed at unacceptably high levels (6−8%) which burdened our downstream chemistry. After isolation of these impurities as a mixture of stereoisomers via chromatography their structures were tentatively assigned as **15** on the basis of NMR and LC−MS data.[21] Speculating on the possible intermediacy of radical intermediates in the formation of **15** from **4**, the reduction was carried out in the presence of radical traps. However, no change in the reaction performance was observed with addition of either 1,1-azobis-(cyclohexanecarbonitrile) or nitrosobenzene. Interestingly, when 75 mol % of Et_3B was added to the reaction, dimers **15** were reduced from the typical 6−8%, to only 1%. However, this eroded the *cis*/*trans* selectivity to 85:15. Given that the formation of **15** should be bimolecular in **4** or intermediates derived thereof, a reverse addition protocol in which **4** is slowly added to L-Selectride would be expected to reduce the formation of **15**. Gratifyingly, the reverse addition reduced the formation of **15** to only 1−2% at −55 °C with no attendant erosion of diastereocontrol. Following an oxidative workup to remove boron residues, nitrile **14** was isolated in 94% yield.

Wittig Homologation and Final Elaboration. With the desired *cis* relative stereochemistry established, final elaboration to the desired drug candidate **1** now required the conversion of the acetonitrile moiety in **14** to a propionic acid. Among several tactics which were considered, reduction of **14** to the corresponding aldehyde followed by a one-carbon homologation and an oxidation appeared most expedient. Thus, DIBAH reduction of **14** to **16** was accomplished under carefully defined conditions to control the impurity profile (Scheme 7). Addition of 1.1 equiv

SCHEME 7[a]



[a] Conditions: (a) DIBAH, PhMe, $-40 < T < -45$ °C; MeOH then citric acid.

of DIBAH to a toluene solution of **14** between −40 and −45 °C reproducibly led to full conversion. Performing the reduction at higher temperatures led to significant formation of primary amine **17**. Quenching of the cold toluene solution with MeOH was then carried out to avoid formation of primary alcohol **18**. If an aqueous quench was used directly, **18** was observed at significant levels presumably due to reduction of aldehyde **16**, liberated following imine hydrolysis, with unquenched DIBAH. Rigorous degassing of the reaction and quench solutions were employed as a further precaution in order to minimize inadvertent oxidation of **16** to the corresponding carboxylic acid **19**. Using this optimized protocol, aldehyde **16** was obtained in 96% yield and used directly in the next step.

Following a screen of reported protocols[22] for the one-carbon homologation of aldehydes, the classical Wittig homologation with methoxymethyltriphenylphosphorane[23,24] emerged as the only viable solution. Implicit in the use of this reagent would be the necessity to find a purification protocol to remove the stoichiometric triphenylphosphine oxide byproduct. The unstable bright red phosphorus ylid required for this reaction was generated from $[Ph_3PCH_2OMe]Cl$ in THF between −40 to −30 °C with KO-*t*-Bu (Scheme 8). A dry toluene solution of freshly prepared aldehyde **16** was then added and the reaction mixture allowed to warm to ambient temperature in order to effect thermal elimination of the observable intermediate oxaphosphetanes to the corresponding enol ethers **20**. The latter were formed as a 1:1 mixture of *E*/*Z* isomers. After a quench the solvent was changed from THF to DMF and the enol ethers were hydrolyzed with HCl at 45 °C. Addition of an optimized amount of water to the crude reaction mixture then led to direct crystallization of **21** which could be isolated in 87% yield with near complete rejection of triphenylphosphine oxide.

In the final step **21** was oxidized to **1** using a biphasic sodium chlorite/sulfamic acid protocol (Scheme 8).[25] Dichloromethane provided the best conversion and purity among several solvents

(20) (a) Diastereoselection was determined by reversed-phase HPLC analysis. (b) The $NaBH_4$ reduction of **4** afforded a 67:33 *trans*/*cis* mixture from which the *trans* isomer could be separated chromatographically.

(21) LC−MS confirmed the dimeric nature of **15** and the quaternary-quaternary carbon connectivity *β*- to the nitrile groups was supported by ^1H and ^{13}C NMR studies that indicated the presence of two sets of four quaternary carbon signals and isolated AB proton quartets consistent with methylenes adjacent to the nitrile functions.

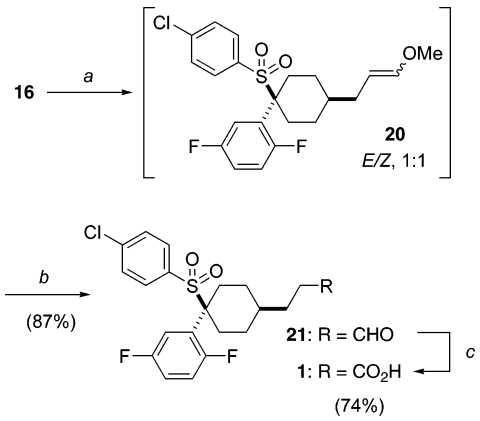
(22) (a) Martin, S. F.; Gompper, R. *J. Org. Chem.* **1974**, *39*, 2814. (b) Kluge, A. F.; Cloudsdale, I. S. *J. Org. Chem.* **1979**, *44*, 4847. (c) Magnus, P.; Roy, G. *J. Chem. Soc., Chem. Commun.* **1979**, 822. (d) Broekhof, N. L. J. M.; Jonkers, F. L.; van der Gen, A. *Tetrahedron Lett.* **1980**, *21*, 2671. (e) Broekhof, N. L. J. M.; Jonkers, F. L.; van der Gen, A. *Tetrahedron Lett.* **1979**, *20*, 2433.

(23) (a) Levine, S. G. *J. Am. Chem. Soc.* **1958**, *80*, 6150. (b) Anderson, C. L.; Soderquist, J. A.; Kabalka, G. W. *Tetrahedron Lett.* **1992**, *33*, 6915.

(24) Incomplete conversion of aldehyde **16**, likely due to competing enolization, was observed with methoxymethyldiphenyl phosphine oxide under a variety of conditions: Earnshaw, C.; Wallis, C. J.; Warren, S. *J. Chem. Soc., Chem. Commun.* **1977**, 314.

(25) Lindgren, B. O.; Nilsson, T. *Acta. Chem. Scand.* **1973**, *27*, 888.

SCHEME 8[a]



[a] Conditions: (a) Ph_3PCH_2OMeCl, KO-*t*-Bu, THF, $-40 < T < -30$ °C; (b) 2 M HCl, DMF, 45 °C; (c) $NaClO_2$, NH_2SO_3H, CH_2Cl_2, 25 °C.

examined for this reaction and the desired drug candidate **1** was obtained in 74% yield after crystallization.

In summary, we have developed a practical, scaleable, and high-yielding (45% over nine steps) chemical process for the synthesis of drug candidate **1**. Notable features are the novel synthesis of vinyl sulfone **6**, its regioselective Diels−Alder condensation with 2-trimethylsiloxybutadiene and the highly diastereoselective conjugate reduction of acrylonitrile **4**. A second more convergent strategy based on a homogeneous catalytic reduction of cyclohexene derivative **2** was also developed but was only moderately diastereoselective.

Experimental Section

2-[[(4-Chlorophenyl)sulfonyl]methyl]-1,4-difluorobenzene (7). A mixture of sodium tungstate dihydrate (1.83 g, 5.54 mmol) as a solution in water (36.6 mL), 1 M sulfuric acid (2.50 mL), sulfide **8** (100 g, 0.37 mol), and Aliquat 336 (2.99 g, 7.39 mmol) in toluene (500 mL) was heated to 45 °C, and 27.5% aqueous hydrogen peroxide (114.2 mL) was added slowly. The mixture was cooled, and the unreacted peroxide was quenched by addition of 20 wt % sodium metabisulfite solution (120 mL). The layers were separated and the organic phase washed with water (190 mL) and concentrated to a total volume of 200 mL. Heptane (400 mL) was added and the resulting mixture cooled to 0 °C and filtered. The wet cake was washed with 2:1 heptane/toluene (200 mL) and then heptane (200 mL). The solid was dried in vacuo at 40 °C to furnish the title compound (108 g, 96%): ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.55−7.50 (m, 2H), 7.44−7.36 (m, 2H), 7.02−6.91 (m, 2H), 6.90−6.83 (m, 1H), 4.29 (s, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 157.3 (d, J = 242 Hz), 156.1 (d, J = 244 Hz), 140.8, 136.4, 130.0, 129.4, 118.8 (dd, J = 3, 25 Hz), 117.7 (dd, J = 8, 24 Hz), 117.2 (dd, J = 8, 17 Hz), 116.7 (dd, J = 9, 24 Hz), 55.4; IR ν (cm^{-1}) 1497, 1315, 1203, 1160, 1083; mp 96−98 °C. Anal. Calcd for $C_{13}H_9ClF_2O_2S$; C, 51.58; H, 3.00; F, 12.55. Found: C, 51.44; H, 2.92; F, 12.57.

2-[1-[(4-Chlorophenyl)sulfonyl]ethenyl]-1,4-difluorobenzene (6). Sulfone **7** (17.1 kg, 55.4 mol) was dissolved in DMF (159.6 kg), and *N*,*N*,*N*′,*N*′-tetramethyldiaminomethane (8.66 kg, 84.7 mol) was added. Acetic anhydride (8.65 kg, 84.7 mol) was added over 5 min and the reaction aged at 60 °C for 2.5 h. Further acetic anhydride (9.23 kg, 90.4 mol) as a solution in DMF (16.1 kg) was added over 4 h, and the mixture was aged for 18 h at 60 °C. Water (188 kg) was then added dropwise to crystallize the product. The solids were filtered, and the cake was washed sequentially with a mixture of DMF and water (16.1 kg of DMF and 17.1 kg of water) and water (68.4 kg). Drying overnight in vacuo at 40 °C under a nitrogen stream furnished the title compound (16.2 kg, 92%): ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.57−7.50 (m, 2H), 7.38−7.32 (m, 2H), 7.12−7.03 (m, 1H), 7.02−6.93 (m, 1H), 6.92−6.83 (m, 1H), 6.77 (s, 1H), 6.03 (s, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 156.8 (d, J = 242 Hz), 154.9 (d, J = 244 Hz), 143.0, 140.5, 136.8, 130.1, 129.9, 129.4, 120.9 (dd, J = 9, 18 Hz), 118.1−117.9 (m, 2C), 116.9 (dd, J = 8, 25 Hz); IR ν (cm^{-1}) 1571, 1494, 1390, 1314, 1143, 1084; mp 110−112 °C. Anal. Calcd for $C_{14}H_9ClF_2O_2S$; C, 53.43; H, 2.88; F, 12.07. Found: C, 53.16; H, 2.85; F, 11.97. The structure was additionally confirmed by single-crystal X-ray crystallography.[9a]

4-[(4-Chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexanone (5). A solution of vinyl sulfone **6** (100 g, 0.32 mol) in xylenes (500 mL) was azeotropically dried via distillation at 38 °C, 20 mmHg, until 300 mL of solvent had been removed. 2-Trimethylsilyloxybutadiene (90.4 g, 0.64 mol) was then added under a nitrogen atmosphere, and the mixture was heated to 130 °C for 16 h. The mixture was distilled in vacuo to remove residual diene, while a constant volume was maintained by the addition of xylenes (400 mL). The mixture was cooled to 50 °C, and THF (500 mL) and 3 M HCl (424 mL, 1.27 mol) were added. The mixture was then aged at this temperature for 2 h. The layers were separated, and the organic layer was washed with water (300 mL) and then concentrated by atmospheric distillation until 350 mL of solvent had been removed. The solution was allowed to cool until crystallization started, and then heptane (600 mL) was added and the resulting mixture was allowed to cool to ambient temperature. The solids were filtered and washed sequentially with heptane/xylenes (3:1, 200 mL) and then heptane (200 mL). Drying overnight in vacuo at 40 °C furnished the title compound (110 g, 90%): ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.39−7.32 (m, 4H), 7.23−7.05 (m, 2H), 6.94−6.84 (m, 1H), 2.95−2.83 (m, 2H), 2.48−2.35 (m, 4H), 2.18−2.04 (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 206.3, 158.8 (d, J = 242 Hz), 141.2, 133.3, 131.6, 129.1, 118.9−118.4 (m, 5C), 69.0, 37.0, 29.7; IR ν (cm^{-1}) 1716, 1576, 1498, 1306, 1142, 1089; mp 176−178 °C; HRMS (+ESI) calcd for $C_{18}H_{19}ClF_2NO_3S$ ($M + NH_4$) requires 402.0742, found 402.0749. The structure was additionally confirmed by single-crystal X-ray crystallography.[9b]

[4-[(4-Chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexylidene]acetonitrile (4). To a solution of potassium *tert*-butoxide (1.0 M in THF, 2.76 kg, 3.06 mol) in THF (2.1 L) at −5 °C was added diethyl (cyanomethyl)phosphonate (566 g, 3.20 mol), keeping the temperature constant. The resulting orange solution was aged for 60 min, and a solution of **5** (1.07 kg, 2.78 mol) in THF (3.9 L) was added maintaining the temperature below 0 °C. The reaction was then allowed to warm to ambient temperature. After the reaction was complete (approximately 20 h at 22 °C), MTBE (3.7 L) and water (6.8 L) were added. The organic layer was washed with brine and then concentrated to 3 L at atmospheric pressure. Further MTBE was added (3.4 L) and the solution concentrated to ca. 1.7 L. This was repeated again with 3.4 L of MTBE, and after reduction to ca. 1.7 L, the contents were allowed to cool. At 37 °C the product began to crystallize. Heptane (4 L) was added over 30 min and the resultant slurry aged at 22 °C for 1 h and then cooled to 0 °C for 1 h. The resulting solid was filtered, washed with MTBE/heptane (1:4) and heptane, and finally dried in vacuo at 37 °C to furnish the title compound (1100 g, 97%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.9 Hz, 2H), 7.36 (d, J = 8.8 Hz, 2H), 7.25−7.06 (m, 2H), 6.94−6.87 (m, 1H), 5.12 (s, 1H), 3.05−3.03 (m, 1H), 2.92−2.86 (m, 2H), 2.54−2.50 (m, 1H), and 2.30−2.03 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 160.0 (dd, J = 2.5, 11.3 Hz), 157.6 (dd, J = 2.4, 6.5 Hz), 141.3, 133.1, 131.6, 129.0, 120.2 (dd, J = 7,11 Hz) 118.9−118.4 (m, 3C), 94.5, 69.8, 31.1, 30.4 (t, J = 7 Hz), 28.5, 27.0; IR ν (cm^{-1}) 2216, 1635, 1576, 1495, 1473, 1306, 1149, 1086; mp 155.4−155.9 °C. Anal. Calcd for $C_{20}H_{16}ClF_2NO_2S$; C, 58.90; H, 3.95; N, 3.43. Found: C, 58.78; H, 3.98; N, 3.36.

***cis*-4-[(4-Chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexaneacetonitrile (14).** L-Selectride (1.0 M in tetrahydrofuran, 100 g, 113 mmol) was cooled to −60 °C. A solution of **4** (40 g, 98 mmol) in THF (200 mL) was added over 90 min, maintaining the temperature at −60 °C. The solution was aged for 60 min and then slowly quenched over 60−90 min into a solution of sodium chloride (30 g) in water (160 mL) containing concd sodium hydroxide (46 wt % solution; 1.1 g) and 27 wt % aqueous hydrogen peroxide (50 mL) at −5 °C. A solution of sodium metabisulphite (11.9 g) in water (100 mL) was added, and the resulting mixture was allowed to warm to 23 °C. Further sodium metabisulfite (6.0 g) in water (50 mL) was added and the solution aged for 10 min. The solution was diluted with isopropyl acetate (300 mL) and the aqueous layer removed. The organic layer was diluted with isopropyl acetate (254 mL) and washed with water (254 mL). The organic layer was distilled to a total volume of 150 mL as further isopropyl acetate (300 mL) was added. The solution was then reconcentrated to a final volume of 200 mL, and then heptane (500 mL) was introduced over 30 min. After the solution was cooled to ambient temperature, the solids were filtered, washed with heptane (100 mL), and then dried in vacuo at 45 °C to afford the title compound (38.6 g, 94%): ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.44−7.41 (m, 2H), 7.36−7.32 (m, 2H), 7.13−7.04 (m, 2H), 6.94−6.87 (m, 1H), 2.53 (d, J = 8.0 Hz, 2H), 2.55−2.38 (m, 4H), 2.09−2.03 (m, 1H), 1.93−1.86 (m, 2H) and 1.71−1.62 (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 159.9 (dd, J = 2.5, 29.3 Hz), 157.5 (dd, J = 2.3, 22.9 Hz), 140.8, 133.5, 131.5, 128.9, 118.8, 118.6−118.2 (m, 2C), 117.9 (dd, J = 10, 23 Hz), 69.9 (d, J = 4.1 Hz), 30.1, 25.7, 25.7, 20.9; IR ν (cm^{-1}) 1580, 1495, 1304, 1190, 1144, 1082; mp 161.2−163.2 °C. Anal. Calcd for $C_{20}H_{18}ClF_2NO_2S$; C, 58.61; H, 4.43; N, 3.42. Found: C, 58.61; H, 4.46; N, 3.31.

***cis*-4-[(4-Chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexaneacetaldehyde (16).** Nitrile **14** (6.00 kg, 13.0 mol) was slurried in toluene (65.5 kg) and the resulting mixture cooled to approximately −45 °C. Diisobutylaluminium hydride (1.0 M in toluene, 15.0 L, 15 mol) was added maintaining the temperature at −40 °C. The solution was aged for 60 min at −40 °C, and then MeOH (2.4 L) was added such that the temperature remained below −35 °C. The resulting solution was allowed to warm to −10 °C and then added into a citric acid solution (14.4 kg in 66 kg of water). Toluene (5.3 kg) was used to rinse. The biphasic mixture was vigorously stirred overnight, and then the layers were separated. The organic layer was washed with a solution of $NaHCO_3$ (6.35 kg) in water (83 kg) and then with water (59 kg). The toluene solution was concentrated to approximately 40 L, filtered, and then diluted to a final volume of approximately 120 L with further toluene (69.2 kg). The assay yield was 5.13 kg (96%). This solution was held overnight before concentrating to a final volume of 24.5 L: ^{1}H NMR (400 MHz, CD_2Cl_2) δ 9.65 (t, 1H, J = 1.7 Hz), 7.32−7.20 (m, 4H), 6.98−6.88 (m, 2H), 6.85−6.72 (m, 1H), 2.57−2.45 (dd, J = 1.7, 7.2 Hz, 2H), 2.45−2.10 (m, 5H) and 1.68−1.35 (m, 4H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ, 201.6 (d, J = 7 Hz), 160.0 (d, J = 47 Hz), 157.5 (d, J = 39 Hz), 140.7, 133.5, 131.6, 128.9, 118.7 (dd, J = 4, 25 Hz), 118.3 (dd, J = 8, 29 Hz), 117.8 (m, 2C), 70.5, 46.5, 26.3, 25.5; IR ν (cm^{-1}) 1716, 1576, 1498, 1476, 1311, 1190, 1142, 1152, 1083; mp 100.0−102.0 °C. Anal. Calcd for $C_{20}H_{19}ClF_2O_3S$; C, 58.18; H, 4.64. Found: C, 58.10; H, 4.63.

***cis*-4-[(4-Chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexanepropanal (21).** Methoxymethyltriphenylphosphonium chloride (6.6 kg, 19.3 mol) was slurried in THF (29.7 kg) and cooled to −60 °C. KO-*t*-Bu (16.2 kg, 18.0 mol) was then added such that the internal temperature did not exceed −30 °C. Aldehyde **16** (5.13 kg in toluene, total volume 24.5 L) was then added over 20 min maintaining the internal temperature below −20 °C. Further toluene (1 L) was used to rinse. The mixture was aged for 30 min at below −20 °C before warming to ambient temperature and stirring for 2.0 h. Acetic acid (0.35 kg) was added followed by water (50.3 kg). The layers were separated, and the organic layer was washed with brine. The volume was reduced to 22 L under vacuum before DMF (53.5 kg) was added, and the mixture was reconcentrated under vacuum to a final volume of 61 L. A mixture of concd HCl (1.22 kg) and water (9.3 kg) was then added, and the mixture was warmed to 45 °C for 2 h. After cooling, H_2O (25.5 kg) was added to crystallize the product. The solids were isolated by filtration and washed with a mixture of DMF and water (4.7 and 5.0 kg, respectively), then water (2 × 15.0 kg). The solids were then dried in vacuo at 50 °C to give the title compound (5.6 kg, 87%): ^{1}H NMR (400 MHz, CD_2Cl_2) δ 9.67 (t, J = 1.5 Hz, 1H), 7.45−7.40 (m, 2H), 7.37−7.33 (m, 2H), 7.13−7.05 (m, 2H), 6.94−6.87 (m, 1H), 2.47 (dt, J = 1.6, 7.3 Hz, 2H), 2.44−2.37 (m, 4H) 1.81 (q, J = 7.4 Hz, 2H), 1.74−1.70 (m, 2H) and 162−1.47 (m, 3H). ^{13}C NMR (100 MHz, CD_2Cl_2) δ, 202.0 160.0 (dd, J = 2.4, 52 Hz), 157.5 (dd, J = 2.4, 45 Hz), 140.6, 133.8, 131.3, 128.7, 122.4 (dd, J = 7.3, 11 Hz) 118.8 (dd, J = 4.6, 26 Hz), 118.2 (dd, J = 8.6, 29 Hz), 117.6 (dd, J = 10, 24 Hz) 70.8 (d, J = 4.0 Hz), 42.1, 31.7, 26.0, 25.4 (d, J = 6.7 Hz), 24.2; IR ν (cm^{-1}) 1714, 1576, 1496, 1301, 1294, 1190, 1141, 1084; mp 145.9−146.8 °C. Anal. Calcd for $C_{21}H_{21}ClF_2O_3S$; C, 59.08; H, 4.96. Found: C, 59.07; H, 4.91.

***cis*-4-[(4-Chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexanepropanoic Acid (1).** To a mixture of crude aldehyde **21** (650 g, 1.52 mol) in CH_2Cl_2 (6 L) and H_2O (6 L) was added sulfamic acid (216 g, 2.21 mol). Sodium chlorite (180 g in 3.13 L water, 2.0 mol) was added slowly over 30 min maintaining the internal temperature below 30 °C. The phases were separated, and the organic layer was washed with an aqueous $Na_2S_2O_5$ solution (157 g in 20 L water) and water (20 L) and then dried (Na_2SO_4). The solution was concentrated in vacuo and the residue recrystallized from isopropyl acetate/heptane to afford the title compound (482 g, 74%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.1 (br.s, 1H), 7.37−7.30 (m, 4H), 7.09−6.99 (m, 2H), 6.85−6.79 (m, 1H), 2.39 (br. t, J = 7.6 Hz, 6H), 1.85−1.79 (q, J = 7.5 Hz, 2H), 1.73−1.69 (m, 2H), 1.63−1.58 (m, 1H) and 1.53−1.45 (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 179.3 (d, J = 8 Hz), 160.0 (dd, J = 2.3, 53 Hz), 157.5 (dd, J = 2.3, 44 Hz), 140.6, 133.7, 131.5, 128.8, 122.2 (m, 1C), 118.7 (dd, J = 4.5, 26 Hz), 118.2 (dd, J = 8.5, 29 Hz), 117.7 (dd, J = 10, 24 Hz), 70.8 (d, J = 4.1 Hz), 32.1, 31.6, 26.8, 25.9, 25.4 (d, J = 6.4 Hz); IR ν (cm^{-1}) 2935, 2873, 1692, 1583, 1495, 1476, 1306, 1277, 1193, 1139, 1082; mp 166.6−167.5 °C. Anal. Calcd $C_{21}H_{21}ClF_2O_4S$; C, 56.95; H, 4.78. Found: C, 56.97; H, 4.74.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. ORTEP plots and CIF files for **5** and **6**. Experimental procedures and characterization data for **2**, **8**, **10**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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