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A Novel Crystallization-Induced Diastereomeric Transformation Based on a Reversible Carbon−Sulfur Bond Formation. Application to the Synthesis of a γ-Secretase Inhibitor

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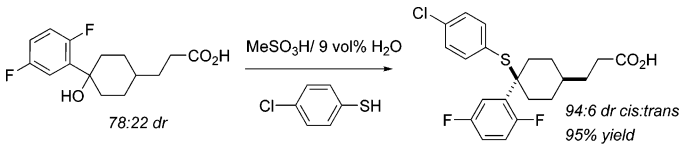

Crystallization-induced diastereomeric transformation

This paper describes a remarkably efficient process for the preparation of γ-secretase inhibitor **1**. The target is synthesized in only five steps with an overall yield of 58%. The key operation is a highly selective and practical, crystallization-driven transformation for the conversion of a mixture of tertiary benzylic alcohols into the desired sulfide diastereomer with 94:6 dr. This unprecedented process is based upon a reversible carbon−sulfur bond formation under acidic conditions.

Introduction

Alzheimer's disease (AD) is the most common of the neurodegenerative disorders.[1] In the elderly, it represents the most frequently occurring form of dementia, affecting 10% of individuals over 65 years of age and nearly half of those over 85. It is a progressive and ultimately fatal neurological disorder for which there is no effective treatment at present. The disease is characterized pathologically by cerebral plaques that contain the amyloid-β (Aβ) peptide and threadlike neuronal structures composed of the hyperphosphorylated TAU protein. Both Aβ and TAU are thought to be crucial to pathogenesis, but both genetic and biochemical evidence supports Aβ as the major causative pathway. It is expected that inhibition or modulation of γ-secretase activity in the CNS will decrease Aβ formation and thereby alter the underlying pathophysiology of AD. Thus, the complex γ-secretase enzyme has emerged as an attractive drug target. Several inhibitors of this enzyme have been discovered and shown to lower Aβ levels in preclinical models of AD.[2] Recent research at Merck[3] has identified compound **1** as a suitable γ-secretase inhibitor. We recently reported on an

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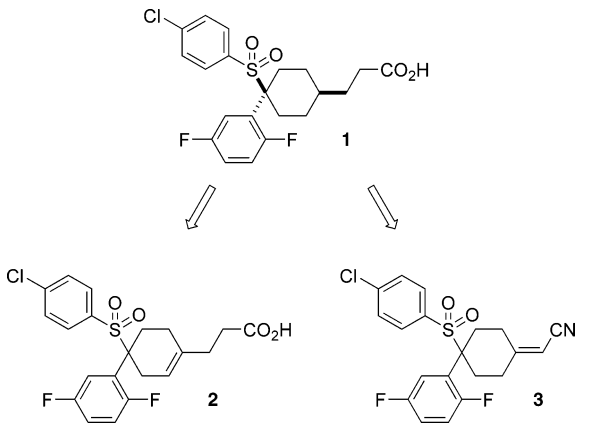
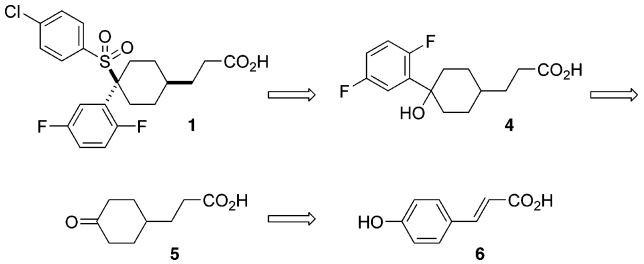
SCHEME 1



SCHEME 2



efficient stereoselective synthesis of this clinical candidate.[4] In this paper we report on a new and significantly more practical synthesis of **1**.

Compound **1** is an achiral 1,1,4-trisubstituted cyclohexane derivative. Crucial to the design of any successful synthesis is the control of the 1,4-cis relative stereochemistry between the propionic acid side chain and the 4-chlorophenylsulfonyl moiety. In our previous synthesis of this compound (Scheme 1), we developed two alternative strategies which achieved this goal. The first synthesis was based on the catalyst-controlled hydrogenation of racemic cyclohexene derivative **2** while the second used a conjugate hydride reduction of acrylonitrile derivative **3**. Unfortunately, we foresaw that both of these syntheses had limitations for implementation on a manufacturing scale. The hydrogenation route, although quite convergent (six linear steps), was not very selective (75:25 dr). The conjugate reduction route was highly stereoselective (>99.9:0.1 dr) but required a rather lengthy linear sequence of steps to introduce the propionic acid side chain.

Our new approach to the synthesis of **1** is based on a dramatically different analysis of the problem (Scheme 2). Disconnection of the carbon−sulfur bond at the tertiary stereogenic center reveals precursor **4**, with undefined stereochemistry at the benzylic position, as a key intermediate.[5] Access to **4** was envisaged to occur by a chemoselective organometallic aryl addition to the ketone moiety in ketoacid **5**. We thought that the latter compound would be available by improvement of the known reduction of the inexpensive **6**.[6] The key step in this analysis is the diastereoselective introduction of a sulfur-based nucleophile. At the outset of our activities we were hopeful that under acidic conditions, addition of 4-chlorothiophenol (4-CTP) to incipient cation **7** would favor the formation of the desired cis isomer **8** for stereoelectronic reasons (Scheme 3).[7]

In the event that the thiol addition proved unselective, however, we thought that we might be able to develop a novel crystallization-induced process for this transformation. Two fundamental requirements need to be satisfied in order to transform this hypothesis into reality. The desired sulfide **8** needs to be less soluble than diastereomer **9**. If this is the case, then conditions need to be identified under which **8** can be crystallized while simultaneously, the two diastereomers equilibrate.[8] Many crystallization-induced transformations[9] have been described in the literature, but most of them deal with salts or other aggregates.[10] Cases in which the diastereomeric set of stereocenters are part of the same molecule are much rarer[11−13] as are transformations in which the diastereomers are achiral.

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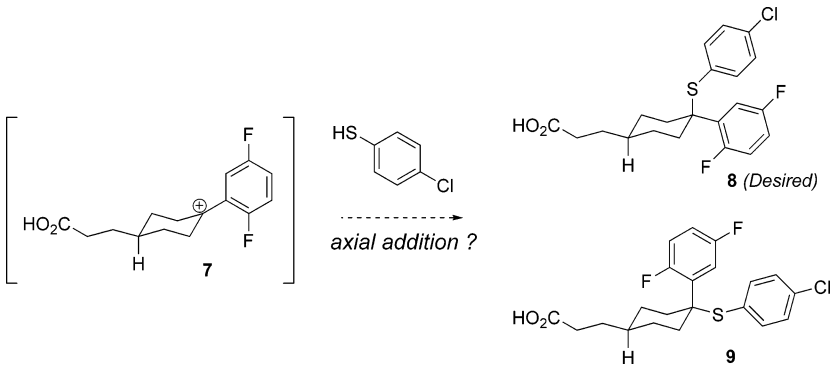
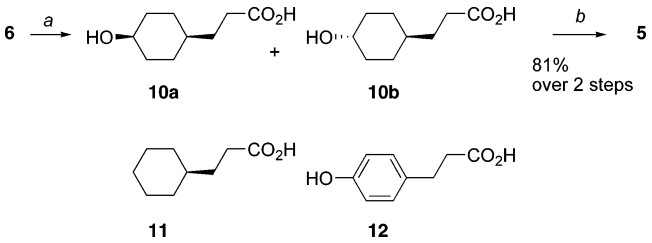
SCHEME 3

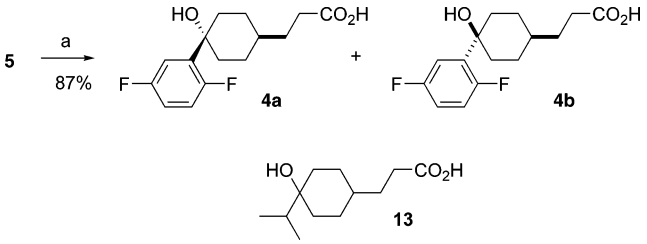


SCHEME 4 [a]



[a] Conditions: (a) 11.2 bar H_2 pressure, 5% Rh/Al_2O_3, IPAc, 80 °C. (b) $RuCl_3$, AcOH, 10-13 wt % NaOCl.

SCHEME 5 [a]



[a] (a) Conditions: *i*-PrMgCl, 1-bromo-2,5-difluorobenzene, THF, −30 °C then add solution of Mg salt of **5** generated using *i*-PrMgCl at <−50 °C.

To the best of our knowledge, reversible cleavage and formation of carbon−sulfur bonds have not been described in this context.

Results and Discussion

Synthesis of Ketoacid 5. A synthesis of **5** which provides the nine-carbon backbone of **1** has been described in the literature. Over-reduction of the readily available *trans-p*-coumaric acid **6** to diastereomeric alcohols **10a** and **10b** can be achieved in >85% yield (Scheme 4).[14] However, the reoxidation of this mixture to **5** is significantly less efficient.[15] We hoped, therefore, that the reduction of **6** could be halted at the stage of **5**.[16] A large number of heterogeneous catalytic reduction conditions were screened starting from either **6** or intermediate phloretic acid **12**. Under the best conditions we were able to identify (12 wt % of 5% Pd/Al_2O_3 in water containing 0.9 equiv of NaOH at 70 °C under 6.2 bar of hydrogen) that **6** was reduced to a 85:12:3 mixture of **5**, **10a**/**10b**, and **12**, respectively. Unfortunately, we could not isolate the desired **5** in pure form from this mixture.

We therefore developed a practical and high-yielding procedure which obviated the isolation of the mixture of **10a** and **10b**. Thus, hydrogenation of **6** in the presence of 5% Rh/Al_2O_3 in isopropyl acetate (iPAc) at 80 °C under 11.2 bar of hydrogen gave a 1.2−1.4:1 mixture of **10a** and **10b**, respectively, in 89% assay yield. The main impurity observed by GCMS was the over-reduced product **11** at around 5%; however, this was easily rejected in the eventual crystallization of ketoacid **5** (*vide infra*). After filtration of the catalyst, the mixture of **10a** and **10b** was oxidized with bleach and $RuCl_3$ catalysis under biphasic conditions[17] to afford **5** in 81% yield over the two steps.

Addition of the 1,4-Difluoroaryl Moiety. With the ketoacid **5** in hand, several protocols for the chemoselective addition of a 1,4-difluorophenyl moiety to the ketone moiety were investigated.[18] We favored a sacrificial protocol, whereby the carboxylic acid proton of **5** was removed by an 1 equiv of base, prior to the addition of the 1,4-difluorophenyl organometallic species. Initially, we prepared 2,5-difluorophenylmagnesium Grignard from the corresponding bromide by halogen exchange[19] with *i*-PrMgCl (Scheme 5). This reagent was then added to a solution of the magnesium salt of **5** at ≤−20 °C which had been generated using another sacrificial equivalent of *i*-PrMgCl at <−50 °C. The temperature for addition of the *i*-PrMgCl to generate the magnesium carboxylate salt is critical; above −50 °C, isopropyl addition is observed to the ketone moiety to give diastereomeric alcohols **13** (Scheme 5).[20] In early attempts, we obtained relatively low yields for carbinols **4** in this process (50−60%) which we ascribed to competitive ketone

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enolization.[21] However, detailed investigations showed that ketoacid **5** is hygroscopic. When the protocol was performed under rigorously dry conditions, excellent conversions (>90%) were observed. Using a pH-controlled extractive workup, isopropyl bromide, 1,4-difluorobenzene, unreacted 1-bromo-2,5-difluorobenzene, and other low-level impurities could be separated from carbinols **4**, which are soluble in aqueous NaOH. A 3.6:1 mixture of **4a** and **4b**, respectively, could be isolated in 87% yield after crystallization (Scheme 5).

We were concerned that the 2,5-difluorophenyl Grignard reagent might be unstable and would generate the corresponding benzyne.[22,23] A study of the formation and stability of this reagent, however, showed that it was fully formed within 1 h and is stable for up to 4 h at <−10 °C. While we were unconcerned with the stereochemical outcome of the addition reaction, it is interesting to note that transmetalation of the Grignard reagent with cerium[24] resulted in a higher proportion of equatorial attack, leading to a 1:1.9 ratio of **4a** and **4b**, respectively.[25]

Further work on this transformation focused on attempts to make it more practical and economical. As mentioned above, we initially used 1 equiv of *i*-PrMgCl as the sacrificial base for carboxylate generation which required a temperature <−50 °C. Far more convenient was to treat **5** with equimolar amounts of triethylamine and anhydrous $MgCl_2$ in THF at ambient temperature. Filtration of the insoluble $Et_3N{\cdot}HCl$ salt yielded a solution of the magnesium salt of **5**, which could be directly used in the addition of 1,4-difluorophenyl Grignard. A practical metalation of 1,4-difluorobenzene was also seen as desirable as 1,4-difluorobenzene is 3-fold less expensive per mole than 1-bromo-2,5-difluorobenzene.[26] It was established that the 2-lithio species is best prepared (95% assay yield)[23] by the dropwise addition of 1,4-difluorobenzene to an equimolar solution of 1.1 equiv *n*-BuLi and TMEDA in THF at −70 °C.[27] When the order of addition was reversed (85% assay yield), the solution became very dark and viscous, which we attributed to benzyne formation. Other solvents (*t*-BuOMe, 1,2-dimethoxyethane) and additives (DABCO, pentamethyldiethylenetriamine) were significantly less effective for the metalation reaction. Above −60 °C the 2-lithio-1,4-difluorobenzene species begins to degrade, but below this temperature it appears reasonably stable. When 2.2 equiv of the resulting 2-lithio-1,4-difluorobenzene solution was added to a cold solution of **5**, the yield of **4a/b** was disappointingly low (35−45%). Subsequently, we found that a similar addition of 2-lithio-1,4-difluorobenzene to the magnesium salt of **5** (as generated from $Et_3N/MgCl_2$) resulted in much better yields (up to 85%). Interestingly, increasing the stoichiometry of the aryllithium relative to **5** enhanced the yield (Table 1, entries 1−4), even though in all cases the excess lithium reagent could be accounted for by HPLC assay. We speculate that this phenomenon might be the result of aryl lithium equilibration with the magnesium salt (i.e., $ArLi + RCO_2MgX \rightarrow RCO_2MgAr + LiCl$) rather than adding into the ketone moiety. The stereoselectivity in the addition of the aryl lithium reagent to the ketone shifted toward more equatorial attack when compared to the corresponding Grignard addition (1:1.4 vs 3.6:1 for **4a** and **4b**, respectively). It is believed that steric factors might explain this.[28]

TABLE 1. Addition of 2,5-Difluorophenyllithium to the Magnesium Salt of 5

entry	equiv ArLi (HPLC assay)	assay yield (%), **4a** + **4b**	isomer ratio, **4a**:**4b**
1	1.1	67	1:1.4
2	1.3	76	1:1.4
3	1.6	83	1:1.3
4	1.8	85	1:1.3

Diastereoselective Synthesis of Sulfide 8. The key transformation of our synthesis entails the diastereoselective reaction of 4-CTP with a mixture of **4a** and **4b** to provide the desired sulfide diastereomer **8** (Scheme 6). A large number[29] of Brønsted and Lewis acids were screened. The best stereoselectivity was obtained with $EtAlCl_2$ (a disappointing 60:40 dr at best), while the best chemical conversion was observed with BF_3 etherate (generating a 1:1 mixture of **8** and **9** in 93% isolated yield).

It was noted that styrene derivative **14** was invariably generated in these reactions. Similarly, we found that exposure of either pure **8** or **9** to the reaction conditions provided similar mixtures of **8**, **9**, **14**, and 4-CTP. This provided unequivocal proof for the reversible formation and cleavage of the critical carbon−sulfur bond under these conditions. With these results in hand, we shifted our attention toward the development of a crystallization-induced process. Solubility experiments[30] (Table 2) quickly showed that the desired sulfide **8** was less soluble than its diastereoisomer **9** in all solvent systems examined.

Several physical properties of **8** and **9** as well as of their 1:1 mixture were determined. The melting points of **8** and **9** are 144 and 127 °C, respectively, which correlates with the solubility

(20) For example, **13** is formed at *ca.* 1% at −45 °C, 4% at −25 °C, and 10% at 0 °C. ^1H NMR analysis of the magnesium salt (prepared by the addition of 0.98 equiv of a 2 M THF solution of *i*-PrMgCl, to a THF solution of **5** followed by concentration *in vacuo* and dissolution in d_6-DMSO) showed it to be stable at ambient temperature for at least 16 h.

(21) Residual ketoacid was always seen in the crude reaction mixtures after work-up.

(22) Selected references on 4-fluorobenzyne: (a) Liu, H.; Zhang, X.; Wang, C.; Guo, W.; Wu, Y.; Yang, S. *J. Phys. Chem. A* **2004**, *108*, 3356. (b) Maurin, P.; Ibrahim-Ouali, M.; Parrain, J.-L.; Santelli, M. *THEOCHEM* **2003**, *637*, 91. (c) Dkhar, P. G. S.; Lyngdoh, R. H. D. *Proc. Indian Acad. of Sci., Chem. Sci.* **2000**, *112*, 97. (d) Langenaeker, W.; De Proft, F.; Geerlings, P. *J. Phys. Chem. A* **1998**, *102*, 5944.

(23) For a detailed study on the stability of 2-lithio-1,4-difluorobenzene and the corresponding Grignard reagent, see Scott, J. P.; Brewer, S. E.; Davies, A. J.; Brands, K. M. J. *Synlett* **2004**, *9*, 1646.

(24) The physical form of the cerium chloride used in the transmetalation step is crucial in ensuring high yields. For a detailed investigation, see Conlon, D. A.; Kumke, D.; Moeder, C.; Hardiman, M.; Hutson, G.; Sailer, L. *Adv. Synth. Catal.* **2004**, *346*, 1307.

(25) The increasing proportion of equatorial vs axial attack on cyclohexananones, with increasing steric nucleophilic bulk has been noted, see (a) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994; pp 735-736, 880−887. (b) Reetz, M. T.; Haning, H.; Stanchev, S. *Tetrahedron Lett.* **1992**, *33*, 6963. (c) Molander, G. A.; Burkhardt, E. R.; Weinig, P. *J. Org. Chem.* **1990**, *55*, 4990. (d) Paquette, L. A.; Ra, C. S. *J. Org. Chem.* **1988**, *53*, 4978. (e) Reetz, M. T.; Kyung, S. H.; Hullman, M. *Tetrahedron* **1986**, *42*, 2931.

(26) Based on survey of potential commercial suppliers.

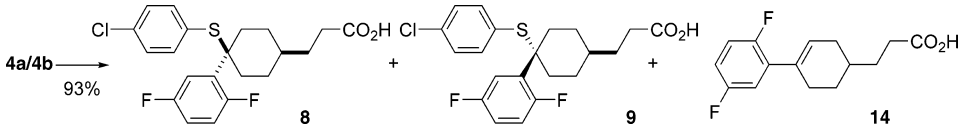
(27) 2-Lithio-1,4-difluorobenzene can also be prepared by halogen−metal exchange using *n*-BuLi according to the procedure of Butler, I. R.; Lindsell, W. E.; Preston, P. N. *J. Chem. Res. Synop.* **1981**, *7*, 185.

(28) The aryllithium reagent is most likely complexed with TMEDA in our reaction. Axial addition predominates in the addition of phenyllithium to 4-*tert*-butylcyclohexanone, see Ashby, E. C.; Noding, S. R. *J. Org. Chem.* **1979**, *44*, 4371.

(29) The following acid catalysts were screened in the reaction of 4-chlorothiophenol with **4a** and **4b** in dichloromethane: $Sc(OTf)_3$, $Ti(OEt)_4$, $BF_3{\cdot}Et_2O$, Et_2AlCl, $Zn(OTf)_2$, ZnI_2, $SnCl_2$, $SnCl_4$, $TiCl_4$, $InCl_2$, $InCl_3$, $LiClO_4$, $B(OMe)_3$, BEt_3, $EtAlCl_2$, $MeAlCl_2$, $AlCl_3$, $AlBr_3$, $MeSO_3H$, CF_3SO_3H, $(CF_3SO_2)_2NH$. Phenylthio ethers have been prepared previously from tertiary alcohols using ZnI_2 as the Lewis acid, see Guindon, Y.; Frenette, R.; Fortin, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 1357.

(30) A total of 47 solvents and solvent combinations were screened.

SCHEME 6 [a]



[a] Conditions: 1.4 equiv of 4-CTP, 1.3 equiv of $BF_3 \cdot Et_2O$, CH_2Cl_2, 0 °C.

TABLE 2. Solubility of Sulfide Diastereomers 8 and 9 in Various Solvents

		solubility, mg/mL[a]		solubility ratio
entry	solvent	**9**	**8**	**9:8**
1	*n*-heptane	0.58	0.46	1.26:1
2	methylcyclohexane	1.7	1.3	1.31:1
3	2,2,2-trifluoroethanol	2.5	1.6	1.56:1
4	hexafluorobenzene	5.5	4.4	1.25:1
5	α,α,α-trifluorotoluene	10.7	8.1	1.32:1
6	1,1,1,3,3,3-hexafluoro-2-propanol	13.6	10.5	1.30:1
7	acetonitrile	22.8	15.0	1.52:1

[a] Determined by HPLC assay.

TABLE 3. First Generation Crystallization-induced Process

			HPLC assay yield, %		
entry	acid (equiv)	solvent and additive (equiv)	**14**	**9**	**8**
1	$MeSO_3H$ (2)	c-$C_6H_{11}Me$	11	10	67
2	$MeSO_3H$ (2)	*c*-$C_6H_{11}Me$, 4-ClPhSH (2)	4	10	75
3	$MeSO_3H$ (0.6)	*n*-heptane, 4-ClPhSH (2)	2	4	96
4	CF_3SO_3H (0.1)	*n*-heptane, 4-ClPhSH (2)	2	4	93
5	CF_3SO_3H (0.1)	*n*-heptane, 4-ClPhSH (0.5)	1	3	95

data above. The 1:1 mixture of **8** and **9** has a melting point of 109 °C. Pure **8** and **9** show distinct XRPD patterns, while the XRPD of the 1:1 mixture can be interpreted as the sum of the two components (even though the peaks are relatively weak). The combination of these data strongly suggests that the mixture of these diastereomers can be expected to behave in an analogous manner to a racemic conglomerate.[10a] With suitable crystallization and reversible carbon−sulfur bond-formation conditions identified, the challenge became how to integrate these into a single vessel, viable process.

It was established that relatively small amounts of a strong Brønsted acid (e.g., methanesulfonic and trifluoromethanesulfonic acid) in apolar solvents such as *n*-heptane, methylcyclohexane, hexafluorobenzene, and trifluorotoluene were sufficient for an effective equilibration.[8] In more polar, Lewis basic solvents like acetonitrile and trifluoroethanol, no reaction took place. However, in the extremely polar and non-nucleophilic 1,1,1,3,3,3-hexafluoro-2-propanol, the cleavage was very facile.[31] On the basis of these observations, we developed a first-generation process, and salient results of our extensive screen of conditions are summarized in Table 3. A 1:1 mixture of **8** and **9** (prepared in a separate step using BF_3 etherate in dichloromethane, as mentioned above) suspended in methylcyclohexane was treated with 2 mol equiv of methanesulfonic acid at ambient temperature. We were delighted to find that after stirring overnight the ratio of **8** and **9** had increased to 6.7:1, respectively (entry 1). In addition, approximately 11% of **14** was also formed. Warming the mixture to 40 °C and addition of more 4-CTP (2 mol equiv) shifted the equilibrium further toward **8**, resulting in a 7.5:1 ratio of **8** to **9** (entry 2). Changing the solvent to *n*-heptane reduced the solubility further and enabled a reduction in the amount of acid required, providing an excellent 96:4 ratio for **8** to **9** (entry 3).

In spite of these encouraging results it was apparent during scale-up that uncontrolled crystallization of undesired **9** was occurring, thus lowering our selectivity. Methanesulfonic acid was identified as the likely culprit, as this acid is virtually immiscible in this system resulting in some phase separation. Switching to triflic acid overcame this limitation to some extent. This stronger acid is not necessarily more miscible, but only 0.1 mol equiv was required to effect comparable conversions, while also enabling a reduction in the amount of added 4-CTP (Table 3, entries 4 and 5). Nevertheless, scale-up still proved difficult, as significant gumming of the solids occurred under these conditions. To gain more insight into the system, the solubilities of **8** and **9** were determined as a function of the temperature, both in the absence and presence of 4-CTP (Figure 1). As expected, the addition of 4-CTP increased the absolute solubilities of **8** and **9**, but intriguingly the relative solubilities begin to diverge significantly above 60 °C. With these data in hand, the 1:1 mixture of **8** and **9** and 2 equiv of 4-CTP in heptane was warmed to 63 °C before 10 mol % triflic acid was added. When the resulting suspension was stirred at this temperature overnight and then allowed to cool to ambient temperature, a 97:3 dr of **8** and **9**, respectively, was obtained. The system was further optimized via addition of 5 vol % of toluene, to effect a slight increase in solubility of all components. The resulting process proved scaleable and afforded **8** in a reproducible 90% isolated yield with >99:1 dr.

The presence of **14** in all the reaction mixtures alerted us to the fact that it might actually serve as the initial reactant in this process. Dehydration of a mixture of **4a** and **4b** with excess TFA in CH_2Cl_2 provided pure **14** in an unoptimized 65% isolated yield. A similar screening process, as described above, identified a second generation process whereby a 1:1 mixture of 1,1,1,3,3,3-hexafluoro-2-propanol and perfluorinated butyltetrahydrofuran (FC-75)[32] was optimal for the crystallization-induced transformation. Thus, **14** and 1.1 equiv of 4-CTP were dissolved in the mixed solvent, and 10 mol % of triflic acid was added at 0 °C. Sulfides **8** and **9** are rapidly formed as a 1:1 mixture of solids within minutes. Further stirring (16 h) of this mixture at ambient temperature led to the desired turnover, and **8** was produced in 95% yield with 98.5:1.5 dr.

While we were delighted with the discovery of these unprecedented crystallization-induced processes, we were also keenly aware that an extra step was required, in the first instance to prepare the 1:1 mixture of **8** and **9**, and in the second instance

(31) A solvent quoted as possessing a higher polarity than water, see Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; VCH (UK) Ltd.: Cambridge, 1990; p 366.

(32) This solvent was chosen because it is miscible with 1,1,1,3,3,3-hexafluoro-2-propanol, without enhancing the solubility of **8** and **9**.

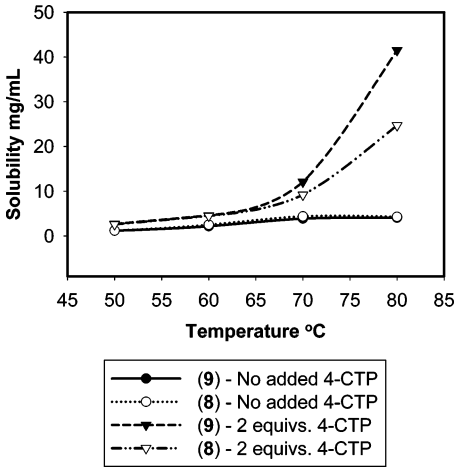


FIGURE 1. Variable temperature solubility curve of sulfides **8** and **9** with and without added 4-CTP in *n*-heptane.

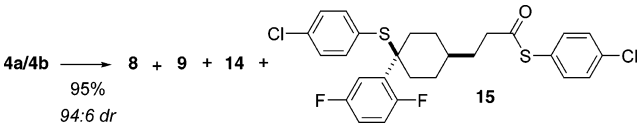
the dehydration to obtain **14**. It seemed obvious that the ultimate synthesis would use hydroxyacids **4a** and **4b** directly and generate **14** in situ. Indeed, development of such a third generation process proved to be feasible. Dissolution of **4a** and **4b** in $MeSO_3H$ resulted in rapid dehydration to **14**. Addition of a slight excess (1.2 equiv) of 4-CTP rapidly provided a 1:1 mixture of **8** and **9**. When an equal volume of water was added to the homogeneous reaction mixture, solids were produced immediately which, upon filtration, proved to be a mixture of **8** and **9** in a 53:47 dr with no appreciable styrene **14** content.[33] It was quickly discovered that the quantity of added water is critical. Insufficient water makes the medium too solubilizing, thus thwarting a productive crystallization. A surfeit of water reduces the solubility of **8** and **9** too much, thus preventing a productive turnover. Within a narrow range of optimum water amounts (9−13 vol %), equilibration can occur in the solution phase while most of the products are out of solution. Under these conditions it is just a matter of time before thermodynamic equilibrium is reached, producing predominantly crystalline **8**. Temperature proved another critical parameter for similar reasons, allowing further optimization of the process.

In a direct comparison on multigram scale it became apparent that the mode of agitation is also important in this process. Magnetic stirring provided better selectivity than overhead agitation (97:3 vs 94:6 dr). Obviously, on larger scale magnetic stirring is not practical, but the slightly lower selectivity resulting from overhead stirring can easily be corrected by a recrystallization of the isolated solids (*vide infra*). Thus, in the fully optimized third generation procedure, **4a** and **4b** are added to a solution of 1.1 equiv of 4-CTP in $MeSO_3H$ containing 9 vol % of water. After overnight stirring at 40 °C, dilution with 9 volumes of water, and filtration, the desired sulfide **8** can be obtained in 95% yield and 94:6 dr. The solid typically also contains 1% of thioester **15** (Scheme 7). This process proved to be scaleable and reproducible. In order to reduce the undesired diastereomer **9** as well as the other impurities to an insignificant level, the product was recrystallized from acetonitrile, which provided pure **8** (99.9:0.1 dr) with 92% yield recovery.[34]

(33) Thioethers have been prepared using dodecylbenzenesulfonic acid-catalyzed dehydration of alcohols, see Manabe, K.; Iimura, S.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 11971.

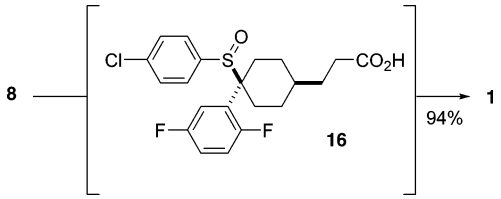
(34) The structures of **8** and **9** were confirmed by single-crystal X-ray crystallography. See Supporting Information for details.

SCHEME 7 [a]



[a] Conditions: 1.2 equiv of 4-CTP, 9.1 vol. of $MeSO_3H$, 0.9 vol. of H_2O, 40 °C.

SCHEME 8 [a]



[a] Conditions: 3.1 equiv of 27.5 wt % H_2O_2, AcOH, 50 °C.

Oxidation of 8 to 1. With all the key bonds of our target in place, we were left with an oxidation of a sulfide to sulfone. In our previous synthesis of **1**, we used a sodium tungstate-catalyzed hydrogen peroxide oxidation for a similar reaction.[4] Application of these conditions to the oxidation of **8** was less successful, resulting in poor reaction profiles and incomplete conversion. However, oxidation of **8** to **1** could be achieved much more cleanly, utilizing 27% hydrogen peroxide in acetic acid.[35] The temperature at which this oxidation sequence is carried out proved critical. As expected, the oxidation to the corresponding sulfoxide intermediate **16** is rapid (∼1 h at 50 °C), whereas the second oxidation to the sulfone requires an overnight age. When we attempted to accelerate the reaction by performing it above 60 °C, we obtained a relatively low yield (84%) for isolated **1**. A series of control experiments showed that at these temperatures, **16** is relatively unstable and eliminates 4-chlorophenylsulfenic acid with concomitant formation of styrene **14**. The latter is rapidly oxidized to a series of unidentified products which are rejected in the crystallization of **1**. When the temperature is maintained in the 45−50 °C range, this decomposition pathway is suppressed and **1** can be isolated in 94% yield after crystallization (Scheme 8).

Conclusions

The γ-secretase inhibitor **1** can be synthesized starting from **6** in 58% overall yield using only five chemical steps. This remarkably efficient synthesis does not require the use of any protecting groups. The cornerstone of this new approach to **1** is a practical crystallization-driven transformation of a mixture of tertiary benzylic alcohols into the desired sulfide diastereomer with 94:6 dr. This unprecedented process is based upon a reversible, acid-catalyzed carbon−sulfur bond formation. In comparison to our two previously reported syntheses of **1**,[4b] the synthesis reported herein is significantly shorter, more efficient, and represents the potential basis for the manufacture of this compound.

Experimental Section

3-(4-Oxocyclohexyl)propanoic Acid (5).[15a] **Step A.** To a 40 L autoclave were charged *p*-coumaric acid **6** (3.33 kg, 20.0 mol), isopropyl acetate (iPAc) (30 L), and 5% Rh/Al_2O_3 (0.248 kg). The

(35) *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Ley, S. V., Eds.; Pergamon Press: Oxford, 1993; vol. 7, p 766 and references therein.

vessel was placed under 11.2 bar of hydrogen and heated at 80 °C for 18 h. The reaction mixture was cooled to ambient temperature and filtered through solka floc (500 g) using iPAc (2 × 3 L) as a rinse. The combined filtrates (containing a 1.2−1.4−1 mixture of **10a** and **10b**, respectively, at 89% yield according to GC analysis) were used directly in the next step.

Step B: To the iPAc solution from step A were charged $RuCl_3$ (42 g) and acetic acid (5.6 kg), and the reaction mixture was cooled to 5 °C. Sodium hypochlorite (10−13 w/v%, 26 kg, 23.76 mol) was added to this solution below the surface over 1.5 h, while maintaining the internal temperature in the 2−8 °C range. The resulting biphasic mixture was stirred in the 2−5 °C temperature range for 3 h until all of **10a** and **10b** had been consumed. The reaction mixture was quenched by the addition of a sodium bisulfite solution (1.0 kg in 5 L water) over 5 min and stirred for a further 10 min, and then 3 M hydrochloric acid (6.6 L) was added. The organic layer was separated, and the aqueous layer was extracted with iPAc (2 × 30L). The combined organic layers were washed with brine (5 L), dried over $MgSO_4$, and then concentrated to a total volume of 20 L while flushing with fresh iPAc (2 × 25 L). The resulting solution was then solvent switched to heptane (6 × 18 L), resulting in the crystallization of **5**. The product was filtered, washed with heptane (2 × 5 L) at ambient temperature, and dried to afford 3.07 kg of **5** (90%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.42 (t, J = 7.5 Hz, 2H), 2.43−2.29 (m, 4H), 2.06 (m, 2H), 1.77 (m, 1H), 1.67 (q, J = 7.5 Hz, 2H), 1.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.4, 179.4, 40.7, 35.5, 32.42, 32.0, 30.4; IR ν (cm^{-1}) 2932, 2859, 1692, 1417, 1326, 1273, 1210, 1110; mp 72−73 °C (lit. mp 55−58 °C); Anal. Calcd for $C_9H_{14}O_3$; C, 63.51; H, 8.29. Found: C, 63.49; H, 8.30.

3-[*cis*-4-(2,5-Difluorophenyl)-4-hydroxycyclohexyl]propanoic Acid (4b) and 3-[*trans*-4-(2,5-Difluorophenyl)-4-hydroxycyclohexyl]propanoic Acid (4a). Method A: 1-Bromo-2,5-difluorobenzene (157.3 g, 0.815 mol) was dissolved in THF (500 mL), degassed with N_2 (3×), and then cooled to −30 °C. A 2 M solution of isopropylmagnesium chloride in THF (400 mL, 0.80 mol) was then added dropwise over 35 min, while maintaining the temperature below −10 °C. The resultant opaque solution was aged for 1 h at −10 °C (*the Grignard reagent is stable for around 4 h when the temperature is maintained below −10 °C*). In a separate flask, **5** (85.1 g, 0.50 mol) was dissolved in THF (1000 mL) and degassed with N_2 (3×) before cooling to −58 °C. A 2 M solution of isopropylmagnesium chloride in THF (240 mL, 0.48 mol) was added dropwise over 40 min while maintaining the temperature below −55 °C. The resulting solution was aged for 30 min between −55 and −50 °C, warmed to −30 °C over 15 min, and held at this temperature until use (*this magnesium salt solution is stable according to ^{1}H NMR analysis when stored overnight at ambient temperature).* The solution of the magnesium salt was added to the solution of the Grignard reagent via cannula over 15 min while maintaining the internal temperature below −20 °C, followed by a rinse with THF (50 mL). The resulting thick slurry was aged for 45 min, while maintaining the temperature below −10 °C. The mixture was quenched by the addition of acetic acid over 5 min (86 mL, 1.50 mol) while maintaining the temperature below 5 °C. The mixture was aged for 10 min before warming to 10 °C, whereupon 1 M HCl (750 mL) was charged to the reaction mixture followed by toluene (750 mL). The organic layer was separated, washed with water (1.25 L), and then extracted with 1 M NaOH (1.25 L). Toluene (1.5 L) and 2 M HCl (700 mL) were added to the aqueous extract. The mixture was agitated for 5 min. The organic layer was separated, washed with water (2 × 1 L), and then concentrated to dryness *in vacuo*. The residue was recrystallized from toluene/heptane to afford 124 g of **4a** and **4b** (87%) as a 3.6:1.0 mixture, respectively. Pure diastereomers were obtained by preparative SFC separation: (Chiral Technologies 2.1 cm Chiralpak AD 20 μm column. 100 bar; 30% MeOH/CO_2 @ 70.00 mL/min; 35 °C and 215 nm. Feedstock concn. ∼200 mg/mL in IPA with 800 μL injections every 120 s). **3-[*cis*-4-(2,5-Difluorophenyl)-4-hydroxycyclohexyl]propanoic Acid (4b):** ^{1}H NMR (500 MHz, CD_3OD): δ 7.32 (ddd, J = 9.9, 6.7, 3.6 Hz, 1H), 7.04 (ddd, J = 11.3, 8.7, 4.5 Hz, 1H), 6.96 (dddd, J = 8.8, 7.3, 3.4, 3.4 Hz, 1H), 2.36 (m, 2H), 2.33 (t, J = 7.6 Hz, 2H), 2.00 (m, 2H), 1.76 (q, J = 7.6 Hz, 2H), 1.68 (m, 1H), 1.50 (dt, J = 14.1, 4.5 Hz, 2H), 1.36 (dq, J = 13.7, 4.5 Hz, 2H). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (ddd, J = 9.7, 6.5, 3.3 Hz, 1H), 7.00 (ddd, J = 11.5, 9.0, 4.7 Hz, 1H), 6.92 (dddd, J = 8.8, 7.3, 3.6, 3.6 Hz, 1H), 2.39 (t, J = 7.6 Hz, 2H), 2.34 (dd, J = 10.3, 3.7 Hz, 2H), 1.95 (m, 2H), 1.74 (q, J = 7.4 Hz, 2H), 1.68 (m, 1H), 1.62 (m, 2H), 1.33 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.0, 158.9 (dd, J = 243.1, 4.0 Hz), 156.8 (d, J = 239.1 Hz), 136.3 (dd, J = 12.9, 6.4 Hz), 117.6 (dd, J = 27.1, 8.6 Hz), 115.1 (dd, J = 24.0, 9.8 Hz), 114.6 (dd, J = 25.3, 5.5 Hz), 73.0 (d, J = 3.0 Hz), 33.6, 33.3, 32.5, 27.5, 26.9; IR ν (cm^{-1}) 2924, 2872, 1692, 1486, 1405, 1181, 1162,; mp 138−139 °C; Anal. Calcd for $C_{15}H_{18}F_2O_3$; C, 63.37; H, 6.38; F, 13.37. Found: C, 63.31; H, 6.34; F, 13.27.

3-[*trans*-4-(2,5-Difluorophenyl)-4-hydroxycyclohexyl]propanoic Acid (4a). ^{1}H NMR (500 MHz, CD_3OD): δ 7.35 (ddd, J = 9.9, 6.4, 3.1 Hz, 1H), 7.01 (ddd, J = 11.3, 8.9, 4.6 Hz, 1H), 6.94 (dddd, J = 8.8, 7.4, 3.6, 3.6 Hz, 1H), 2.35 (t, J = 7.6 Hz, 2H), 2.21 (td, J = 13.5, 3.8 Hz, 2H), 1.70 (br d, J = 13.7 Hz, 2H), 1.63 (m, 2H), 1.59 (q, J = 7.4 Hz, 1H), 1.51 (m, 2H), 1.41 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD): δ 178.0, 160.4 (dd, J = 239.6, 1.9 Hz), 157.1 (dd, J = 239.8, 2.2 Hz), 140.3 (dd, J = 14.6, 6.2 Hz), 118.5 (dd, J = 28.0, 8.5 Hz), 115.5 (dd, J = 24.3, 9.2 Hz), 115.1 (dd, J = 26.2, 5.3 Hz), 73.3 (d, J = 5.3 Hz), 37.7, 37.0 (d, J = 4.5 Hz), 33.5, 32.7, 29.2; IR ν (cm^{-1}) 3391, 2937, 2868, 1707, 1481, 1416, 1277, 1266, 1183; mp 113−114 °C; Anal. Calcd for $C_{15}H_{18}F_2O_3$; C, 63.37; H, 6.38; F, 13.37. Found: C, 63.36; H, 6.37; F, 13.29.

Method B: The Grignard reagent is prepared in the same way as for method A. The magnesium salt solution is prepared as follows: 3-(4-oxo-cyclohexyl)propanoic acid **5** (7 g, 41.1 mmol) was dissolved in THF (56 mL) and degassed with N_2 (3×) before cooling to 4 °C. Magnesium chloride (3.92 g, 41.1 mmol) was added in one portion. The resulting solution was aged for 5 min followed by the dropwise addition of triethylamine (5.73 mL, 41.1 mmol) over 15 min. The resulting suspension was aged for 1 h at ambient temperature, cooled to 1 °C, and filtered under a nitrogen atmosphere. The filter cake was washed with THF (20 mL). The combined filtrates were used as in method A.

Method C: TMEDA (13.7 mL, 90.5 mmol) was dissolved in THF (100 mL) and degassed (3×) with N_2. The solution was cooled to −65 °C, and *n*-butyl lithium (36.2 mL, 90.5 mmol) was added over 10 min while maintaining the internal temperature below −60 °C. The resulting pale yellow solution was aged for 10 min below −60 °C. 1,4-Difluorobenzene (8.5 mL, 82.3 mmol) was added over 15 min while maintaining the internal temperature below −55 °C. The resulting solution was aged for 1 h at −60 °C. A solution of the magnesium salt of **5** (prepared as in method B) was added to the organolithium solution over 20 min while maintaining the temperature below −55 °C. The reaction mixture was allowed to warm to −30 °C over 1 h and then quenched with acetic acid (9.5 mL) keeping the internal temperature below −20 °C. After warming to 10 °C, 2 M HCl (190 mL) and toluene (190 mL) were added to the reaction mixture. After stirring for 10 min and warming to ambient temperature, the organic phase was separated and washed with water (90 mL) to give a 1:1.4 mixture of **4a** and **4b**, respectively, in 78% combined yield based on HPLC assay.

3-[4-(2,5-Difluorophenyl)cyclohex-3-en-1-yl]propanoic Acid (14). Diastereomeric alcohols **4a** and **4b** (2.5 g, 8.79 mmol) were suspended in dichloromethane (39 mL), and the resulting solution was cooled to −2 °C. Trifluoroacetic acid (10.03 g, 87.9 mmol) was added over 1 h while maintaining internal temperature below 5 °C. The resulting suspension was allowed to warm to ambient temperature, whereupon it gradually became homogeneous. The reaction was quenched by the addition of water (50 mL). The solution was then extracted with iPAc (150 mL). The organic layer was washed with water (50 mL) and brine (50 mL), dried with

Na_2SO_4, and concentrated to dryness *in vacuo*. The crude product was recrystallized from iPAc to afford 1.39 g of **14** (65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.1 (br.s, 1H), 7.05−6.75 (m, 3H), 2.55−2.25 (m, 5H), 1.95−1.65 (m, 5H), 1.45−1.35 (1H, m). ^{13}C NMR (100 MHz, CD_2Cl_2) δ 180.6, 158.5 (d, J = 260 Hz), 155.9 (d, J = 241 Hz), 132.7, 132.3 (dd, J = 7.7, 16.3 Hz), 128.1, 116.6 (dd, J = 8.7, 26.1 Hz), 115.4 (dd, J = 5.1, 23.8 Hz), 114.1 (dd, J = 8.7, 23.8 Hz), 32.4, 32.0, 31.7, 31.0, 28.7, 28.2 (d, J = 3.2 Hz); IR ν (cm^{-1}) 2915, 2859, 1699, 1584, 1493, 1479, 1415, 1324, 1279, 1232, 1207, 1170; mp 78−79 °C; Anal. Calcd for $C_{15}H_{16}F_2O_2$; C, 67.66; H, 6.06; F, 14.27. Found: C, 67.48; H, 6.03; F, 14.15.

3-[*cis*-4-[(4-Chlorophenyl)sulfanyl]-4-(2,5-difluorophenyl)cyclohexyl]propanoic Acid (8). 4-Chlorothiophenol was slurried in methanesulfonic acid (1070 mL) at ambient temperature. The solids were solubilized by warming to 38 °C. Water (118 mL) was added over 45 min while maintaining the temperature below 40 °C. A mixture of **4a** and **4b** (106.8 g, 0.376 mol) was added to the reaction mixture in one portion. After 10 min the mixture was seeded with sulfide **8** (1 g) and stirred between 36 and 42 °C overnight. After cooling to ambient temperature, water (1.07 L) was added over 50 min while maintaining the temperature below 40 °C. The suspension was then cooled to ambient temperature, aged for 30 min, and filtered. The filter cake was washed with water (5 L) and dried in vacuo at 40 °C overnight to afford 152 g of **8** (95%, containing 6% of the trans diastereomer **9**). Recrystallization from CH_3CN affords >99.9:0.1 dr. **3-[*cis*-4-[(4-Chlorophenyl)sulfanyl]-4-(2,5-difluorophenyl)cyclohexyl]propanoic Acid (8):** ^{1}H NMR (500 MHz, C_6D_6): δ 6.80 (m, 2H), 6.74 (m, 2H), 6.58 (m, 1H), 6.49−6.43 (m, 2H), 2.18−2.14 (m, 4H), 1.57 (m, 2H), 1.51 (q, J = 7.5 Hz, 2H), 1.33−1.27 (m, 4H), 0.95 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6): δ 181.0, 158.8 (dd, J = 241.6, 2.0 Hz), 158.0 (dd, J = 247.6, 2.4 Hz), 138.3, 136.6 (dd, J = 10.6, 6.5 Hz), 135.9, 131.1, 129.2, 118.1 (dd, J = 27.5, 8.7 Hz), 115.4 (dd, J = 25.2, 4.9 Hz), 115.0 (dd, J = 23.8, 9.4 Hz), 54.7 (d, J = 4.1 Hz), 36.6, 34.7 (d, J = 4.6 Hz), 32.0, 32.0, 28.4; IR ν (cm^{-1}) 2924, 2855, 1698, 1584, 1484, 1474, 1411, 1290, 1187, 1091; mp 144−145 °C; Anal. Calcd for $C_{21}H_{21}ClF_2O_2S$; C, 61.38; H, 5.15; F, 9.25; Cl, 8.63; S, 7.80. Found: C, 61.29; H, 5.17; F, 9.20; Cl, 8.69; S, 7.62. Pure **9** was obtained by preparative SFC separation: (Chiralpak AD column. 200 Bar; 4% MeOH for 4 min then ramp to 40% MeOH @ 2% per min with a 3 min hold at 40% MeOH; 1.5 mL/min; 35 °C; 25 min run time). **3-[*trans*-4-[(4-chlorophenyl)sulfanyl]-4-(2,5-difluorophenyl)cyclohexyl]propanoic Acid (9):** ^{1}H NMR (500 MHz, C_6D_6): δ 12.28 (br s, 1H), 6.86 (m, 2H), 6.82 (m, 2H), 6.54−6.49 (m, 2H), 6.43 (m, 1H), 2.48 (br s, 2H), 1.93 (t, J = 7.5 Hz, 2H), 1.57 (td, J = 13.4, 2.5 Hz, 2H), 1.30 (d, J = 13.4 Hz, 2H), 1.08 (q, J = 7.5 Hz, 2H), 0.98 (m, 1H), 0.63 (m, 2H). ^{13}C NMR (125 MHz, C_6D_6): δ 181.2, 159.0 (dd, J = 241.3, 1.8 Hz), 158.3 (dd, J = 247.6, 2.4 Hz), 139.2, 136.3, 131.5 (dd, J = 11.1, 6.5 Hz), 130.4, 129.1, 118.5 (dd, J = 28.2, 8.5 Hz), 117.0 (dd, J = 24.9, 5.1 Hz), 115.4 (dd, J = 23.8, 9.6 Hz), 54.7 (d, J = 3.9 Hz), 39.2 (br s), 36.8, 32.0, 31.4, 30.0; IR ν (cm^{-1}) 2923, 2850, 1697, 1571, 1492, 1474, 1412, 1181; mp 126−127 °C; Anal. Calcd for $C_{21}H_{21}ClF_2O_2S$; C, 61.38; H, 5.15. Found: C, 61.37; H, 4.91. The structures of **8** and **9** were confirmed by single-crystal X-ray crystallography; see Supporting Information for details.

3-[*cis*-4-[(4-Chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexyl]propanoic Acid (1). Sulfide **8** (119 g) was dissolved in acetic acid (965 mL) at 50 °C. A hydrogen peroxide solution (27.5 wt %, 110 mL) was added dropwise over 10 min. The reaction mixture was maintained at this temperature overnight. The solution was cooled to ambient temperature, and water (220 mL) was added dropwise over 10 min until the solution became turbid. At this point, authentic **1** (8.6 g) was added as a seed and the resulting slurry was aged for 20 min, before additional water (1710 mL) was added over 40 min. After stirring at ambient temperature for 1 h, the crystals were collected by filtration, washed with water (1930 mL), and dried *in vacuo* at 40 °C to afford 129.5 g of **1** (94% yield). ^{1}H and ^{13}C NMR and HPLC data for **1** were in full accord with those that have been previously reported.[4b]

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Supporting Information Available: X-ray crystallographic (CIF) files and ORTEP plots for **8** and **9**. ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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