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Practical asymmetric synthesis of a novel γ-secretase inhibitor

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ABSTRACT

An efficient route to γ-secretase inhibitor hydroxyl thiophene sulfonamide **1** is described. The approach contains nine steps with an overall yield of 8%. The synthesis highlights a diastereoselective methylation using Evans' oxazolidinone method and a chiral Strecker reaction via Davis' sulfonimine protocol.

1. Introduction

Alzheimer's disease (AD) is the ost common cause of dementia in the elderly. AD affects millions of people worldwide and its direct and indirect costs are at least $100 billion annually. Common clinical symptoms of AD include cognitive decline, irreversible memory loss, disorientation, and language impairment.[1] One of the main pathological characteristics of AD is the accumulation and aggregation of β-amyloid protein (Aβ) into extracellular pertinacious plaques.[2] Formation of Aβ, which is composed of 40–42 amino acids, requires proteolytic cleavage of β-amyloid precursor protein (APP). Our project involves reduction of Aβ levels through inhibition of γ-secretase, a protease that cleaves APP to form Aβ.[3] Among our compounds of interest, compound **1** was shown to be a potent and selective γ-secretase inhibitor. Therefore, multi-gram preparation of compound **1** for further pre-clinical evaluations such as oral efficacy required a practical synthesis. Herein, we report a scalable asymmetric synthesis of γ-secretase inhibitor **1** (Fig. 1).[4]

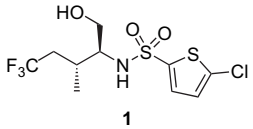

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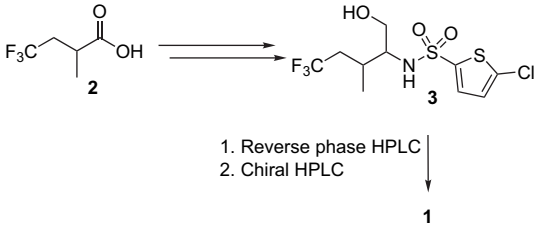
Figure 1.

2. Results and discussion

The original approach to prepare compound **1** involved an achiral synthesis,[4] which started from the commercially available carboxylic acid **2**. The desired compound **3** was obtained as a mixture of four stereoisomers via a six-step synthesis. The isolation of (1*S*,2*R*)-stereoisomer required two stages: (1) reverse phase HPLC to separate the diastereomers; (2) chiral HPLC to separate the enantiomers (Scheme 1).



Scheme 1.

Due to the inefficiency of this method to provide large-scale quantities of compound **1**, we embarked on a chiral synthetic route. Retrosynthetic analysis for the preparation of target compound **1** via a chiral route entails utilization of chiral amino acid **4** as a key intermediate (Scheme 2). We envisioned that the C-1 chiral center would be formed through a chiral Strecker reaction from chiral aldehyde **5**, an intermediate, which could be prepared from

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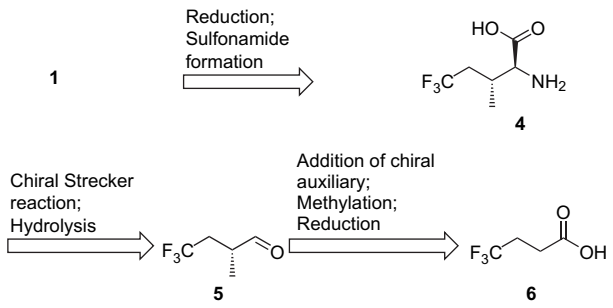
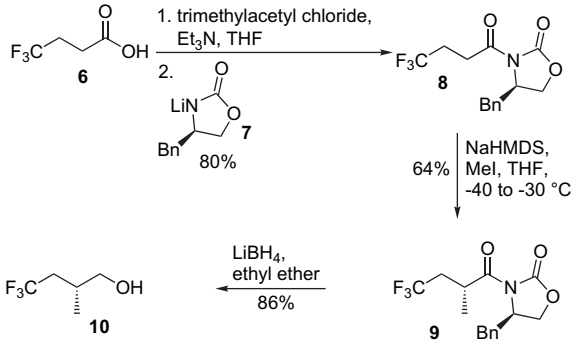
carboxylic acid **6** via Evans' methodology[5] by formation of chiral oxazolidinone followed by diasteroselective methylation and reduction.



Scheme 2.

The planned strategy was carried out initially on a small scale to verify the synthetic route and supply small quantities of material. As larger batches of the material were required, optimized scale-up efforts were essential, as will be described. In the first step, commercially available 4,4,4-trifluorobutyric acid **6** was converted into a mixed anhydride, and then reacted with lithiated oxazolidinone **7** to afford carboximide **8** (Scheme 3). The procedure entails formation of the mixed anhydride by addition of triethylamine and trimethylacetyl chloride to 4,4,4-trifluorobutyric acid **6** in THF.

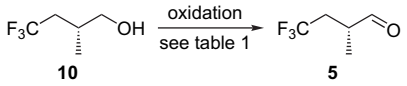


Scheme 3.

The resulting slurry is then added to a solution of lithiated oxazolidinone salt **7**. To ensure maximal transfer of the slurry to the oxazolidinone salt solution, we found that the concentration of mixed anhydride should be $\leq$0.93 M. The purification of carboximide **8** originally included tedious silica gel column chromatography. Alternatively, we found that **8** can be purified efficiently by crystallization with hexane/ethyl acetate.

Subsequent asymmetric methylation was carried out by anion formation with sodium bis(trimethylsilyl)amide in THF at $-40\,^{\circ}C$, followed by addition of iodomethane. The reaction temperature was then increased to $-30\,^{\circ}C$ and stirred for 5 h. In this manner, **9** was obtained as a single diastereomer in 64% yield. Treatment of **9** with $LiBH_4$ gave chiral alcohol **10** in 86% yield.

Oxidation of alcohol **10** to aldehyde **5** was initially performed with Dess–Martin reagent [6] (Scheme 4). We found that the yield of the oxidation was variable upon scale-up. Therefore, we screened other oxidation conditions including Swern oxidation,[7] trichloroisocyanuric acid/TEMPO,[8] $NaOBr_2$/TEMPO,[9] and $PhI(OAc)_2$/TEMPO.[10] The optimal conditions for oxidation were found to be $PhI(OAc)_2$/TEMPO, which was more reproducible than the Dess–Martin conditions and decreased the cost substantially (see Table 1). Due to the high volatility of aldehyde **5**, it was imperative to avoid loss of product due to co-evaporation with solvent. Therefore, the product was used in the next step without removal of work-up solvent.



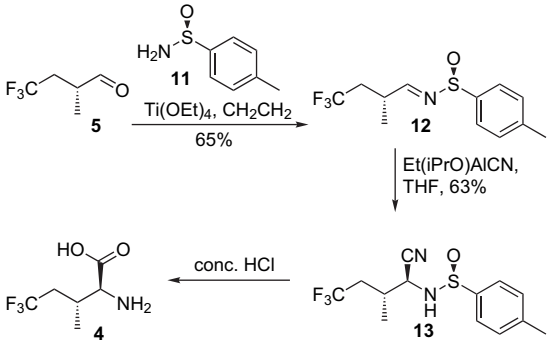
Scheme 4.

Table 1
Optimization of reaction conditions to convert alcohol **10** to aldehyde **5**

Entry	Oxidations	Results (yield)	Cost (supplier)
1	Swern[7]	Low conversion[a]	—
2	CYC/TEMPO[8]	No reaction	—
3	NaOCl/TEMPO[9]	No reaction	—
4	$PhI(OAc)_2$/TEMP[10]	Product 90%[b]	\$0.89/g (Sigma–Aldrich)
5	Dess–Martin[6]	Product 80%[b]	\$5.5/g (OmegaChem)

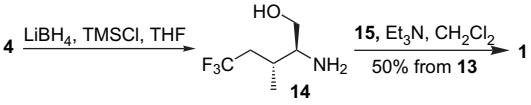
[a] Conversion: 20–30%.
[b] Yield estimated by NMR.

With chiral aldehyde **5** in hand, we embarked on the asymmetric synthesis of amino acid **4**. Many methods for the asymmetric synthesis of amino acids have been developed.[11,12] It was of interest to select a method that is amenable to large-scale application. We reasoned that the sulfinimine-mediated asymmetric Strecker method that was developed in the Davis group[13–15] would be appropriate due to the commercial availability and reasonable price of the sulfinamide chiral auxiliary (Scheme 5). Thus, condensation of (*S*)-(+)-toluenesulfinamide **11** with aldehyde **5** in the presence of $Ti(OEt)_4$ in dichloromethane provided sulfinimine **12**. The reaction of Et(*i*-OPr)AlCN with **12** afforded amino nitrile **13** with a diastereomeric ratio of 7:1. Crystallization of the crude product with ether/hexane (1:1) provided the product with an enhanced diastereomeric ratio of >100:1 as judged by ^1H NMR and HPLC. (The other diastereomer was not detected.) In the final step to form amino acid **4**, nitrile **13** was hydrolyzed with concentrated hydrochloric acid.



Scheme 5.

Completion of the synthesis involved reduction of amino acid **4** with $LiBH_4$/TMSCl to afford amino alcohol **14**, and then treatment of this compound with 5-chlorothiophene-2-sulfonyl chloride **15** in the presence of triethylamine to give target compound **1** (Scheme 6). Crystallization with ethyl acetate/heptane (1:4) gave target **1** as a single crystal form in 86% yield.



Scheme 6.

3. Conclusion

In conclusion an efficient and practical asymmetric synthesis of biologically active hydroxyl thiophene sulfonamide **1** was developed. The challenge of the synthesis of this compound involved formation of two chiral centers. Asymmetric methylation via Evan's oxazolidinone method provided the *R*-configuration of the C-2 chiral center and a sulfinimine-mediated asymmetric Strecker reaction was used to install the *S*-configuration of the C-1 chiral center. Target compound **1** was ultimately prepared in 9 steps with an overall yield of 8%. Crystallization gave the target molecule as single crystal form with 99% chemical purity and 98.5% ee.

4. Experimental

4.1. General

All reagents and solvents were purchased from commercial sources and used without further purification. ^{1}H NMR spectra were recorded on a Varian Unity Plus 40 spectrometer. The chemical shifts are reported in parts per million downfield from zero, and coupling constants are reported in hertz (Hz). Mass spectra were recorded on either a Hewlett-Packard 5995A, a Finnigan Trace MS or a Micromass LCT spectrometer. C, H, N combustion analyses were determined on either a Perkin–Elmer 2400 analyzer or were performed by Robertson Microlit (Madison, NJ). HPLC was performed on Agilent systems with solvents indicated. Enantiomeric excess (ee) was determined by chiral HPLC of two enantiomers.

4.2. (4*R*)-4-Benzyl-3-(4,4,4-trifluorobutanoyl)-1,3-oxazolidin-2-one (8)

Reaction mixture 1: to a solution of 4,4,4-trifluorobutyric acid (**6**, 199 g, 1.40 mol), triethylamine (205 mL, 1.47 mol), and THF (1.5 L) at 0 °C was added trimethylacetyl chloride (177 g, 1.47 mol) and the resulting slurry was stirred at 0 °C for 1 h. Reaction mixture 2: to a solution of (*R*)-4-benzyl-oxazolidin-2-one (272 g, 1.53 mol) in THF (2 L) at −78 °C was added a solution of *n*-butyllithium (2.5 N in hexane, 614 mL, 1.53 mol). The mixture was stirred at −78 °C for 1 h and then the slurry from reaction mixture 1 was carefully added. The mixture was then stirred for 3 days at room temperature, diluted with ethyl acetate (4.3 L), and washed sequentially with 2 N HCl (1 L) and saturated aqueous $NaHCO_3$ (4 L). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to afford a yellow oil. The crude product was passed through a short silica gel pad, washed with hexane/ethyl acetate, 10:1, and concentrated to give a light yellow oil. Crystallization with hexane/ethyl acetate, 10:1 (500 mL) provided 336 g (80%) of **8** as a white solid. HPLC purity: 97.6% (254 nm, area %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (s, 1H), 7.33 (t, J=4 Hz, 2H), 7.27 (t, J=4 Hz, 1H), 7.23 (t, J=4 Hz, 2H), 4.65–4.69 (m, 1H), 4.33(t, J=8 Hz, 2H), 4.22 (dd, J=8, 4 Hz, 1H), 3.08–3.18 (m, 1H), 3.03 (dd, J=8, 4 Hz, 1H), 2.93 (dd, J=8, 4 Hz, 1H). ^{13}C NMR δ 170.5, 154.1, 136.1, 130.1, 129.2, 127.9 (q, CF_3), 127.5, 67.0, 55.0, 37.3, 28.8, 28.3 (q). MS $[M-H]^-$ m/z 300. Anal. Calcd for $C_{14}H_{14}F_3NO_3$: C, 55.82; H, 4.68; N, 4.65. Found: C, 56.03; H, 4.67; N, 4.62.

4.3. (4*R*)-4-Benzyl-3-[(2*R*)-4,4,4-trifluoro-2 methylbutanoyl]-1,3-oxazolidin-2-one (9)

To a solution of sodium bis(trimethylsilyl)amide (1 M in THF, 1.03 L, 1.03 mol) in THF (3 L) at −40 °C was added a precooled solution of **8** (282 g, 936 mmol) in THF (3.5 L) dropwise over 1.5 h. Then iodomethane (87.5 mL, 1.40 mol) was added slowly at −50 °C. The reaction mixture was warmed to −30 °C and stirred for 5 h. To the solution was added saturated aqueous NH_4Cl (3 L). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to afford a yellow oil. The crude product was passed through a short silica gel column (hexane/ethyl acetate, 8:1) to afford 189 g (estimated yield 64%) of **9** as a light yellow oil, which was used directly in the next step. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (s, 1H), 7.30 (t, J=4 Hz, 2H), 7.25 (t, J=4 Hz, 1H), 7.19 (d, J=4 Hz, 2H), 4.66–4.70 (m, 1H), 4.37 (t, J=4 Hz, 1H), 4.25 (dd, J=8, 4 Hz, 1H), 3.89–3.96 (m, 1H), 2.93–3.00 (m, 1H), 2.69–2.80 (m, 1H), 2.35–2.51 (m, 1H), 1.22 (d, J=8 Hz, 3H). ^{13}C NMR δ 178.0, 153.6, 136.1, 130.2, 129.2, 127.7 (q, CF_3), 127.6, 67.0, 55.0, 37.2, 35.8 (q), 32.4, 18.3. MS $[M]^+$ m/z 315. HRMS (ESI) [M+H] calcd for $C_{15}H_{16}F_3NO_3$ 316.1159; found 316.1155.

4.4. (2*R*)-4,4,4-Trifluoro-2-methyl-butan-1-ol (10)

To a solution of **9** (189 g, 600 mmol) and water (10.8 mL, 600 mmol) in ethyl ether (2.5 L) at 0 °C was added a solution of lithium borohydride (2 M in THF, 300 mL, 600 mmol). After 30 min, the reaction mixture was warmed to room temperature and stirred for 3 days. The mixture was quenched with methanol (500 mL) and then sodium hydroxide (1 N, 4 L) was added. The mixture was extracted with ethyl ether (3×500 mL) and the combined organic extracts were washed with water and brine, then dried over anhydrous sodium sulfate, filtered, and concentrated to 500 mL. The crude product was passed through a short silica gel column (petroleum ether/ethyl ether, 1:1), and concentrated to afford 107 g of a solution of **10** in petroleum ether/ethyl ether (69% by NMR, estimated yield: 86% yield). The petroleum ether/ethyl ether solution of **10** was used directly in the next step. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.49 (br s, 1H), 3.21–3.26 (m, 1H), 3.14–3.18 (m, 1H), 2.58–2.62 (m, 1H), 2.29–2.40 (m, 1H), 1.97–2.04 (m, 1H), 4.36–4.39 (t, J=4 Hz, 1H), 4.25 (dd, J=8, 4 Hz, 1H), 3.89–3.96 (m, 1H), 2.93–3.00 (m, 1H), 2.69–2.80 (m, 1H), 2.35–2.51 (m, 1H), 0.82 (d, J=8 Hz, 3H). ^{13}C NMR δ 127.9 (q, CF_3), 65.1, 35.7 (q), 30.4, 16.3. MS $[M]^+$ m/z 142.

4.5. (2*R*)-4,4,4-Trifluoro-2-methyl-butanal (5)

4.5.1. Method 1 (Dess–Martin)

To a solution of **10** (107 g, 520 mmol, 69% by NMR) in dichloromethane (1 L) at 0 °C was added Dess–Martin reagent (263 g, 621 mmol) in portions over 30 min. The reaction mixture was warmed to room temperature and stirred for 5 h. To the solution were added saturated $Na_2S_2O_3$ (3 L) and saturated $NaHCO_3$ (3 L) and the mixture was stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2×300 mL). The organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to a 1.5 L solution of **5** in dichloromethane (0.28 M by NMR, estimated yield 80%). The solution of **5** was used directly in the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 2.66–2.70 (m, 2H), 2.00–2.10 (m, 1H), 1.25 (d, J=8 Hz, 3H). MS $[M]^+$ m/z 140.

4.5.2. Method 2 (TEMPO/(PhI(OAc)$_2$))

To a solution of **10** (65 g, 457 mmol) in dichloromethane (1 L) at 0 °C was added TEMPO (10.7 g, 68 mmol) and iodobenzene diacetate (177 g, 548 mmol) in small portions. The reaction mixture was warmed to room temperature and stirred for 6 h. To the solution was added saturated $Na_2S_2O_3$ (1.5 L) and saturated $NaHCO_3$ (1.5 L) and it was stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2×300 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to a 1.2 L solution of **5** in dichloromethane (0.28 M by NMR, estimated yield 90%), which was used directly in the next step.

4.6. (*S*)-*N*-[(3*R*)-Methyl-4,4,4-trifluorobutylidene]-*p*-toluenesulfinamide (12)

To a solution of **5** (27.6% in dichloromethane, 1.5 L, 414 mmol) at room temperature were added titanium(IV) ethoxide (286 mL, 1366 mmol) and (*S*)-(+)-toluenesulfinamide (**11**, 64 g, 414 mmol) slowly. The reaction mixture was heated to reflux for 5 h. Then the mixture was poured into ice water (3 L) and filtered through Celite. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by silica gel chromatography (hexane/ethyl ether, 6:1–4:1) to afford 75 g (65% yield) of **12** as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (d, J=8 Hz, 1H), 7.52 (d, J=12 Hz, 2H), 7.36 (d, J=12 Hz, 2H), 2.87–2.98 (m, 1H), 2.68–2.84 (m, 1H), 2.37–2.56 (m, 1H), 2.35 (s, 3H), 1.16 (d, J=12 Hz, 3H). ^{13}C NMR δ 195.5, 165.4, 141.6, 129.8, 126.9 (q, CF_3), 124.4, 35.4 (q), 33.8, 20.8, 16.4. MS $[M+H]^+$ m/z 278. Anal. Calcd for $C_{12}H_{14}F_3NOS$: C, 51.97; H, 5.09; N, 5.05. Found: C, 52.16; H, 4.88; N, 5.23.

4.7. *N*-[(1*S*,2*R*)-1-Cyano-4,4,4-trifluoro-2-methylbutyl]-4-methylbenzenesulfinamide (13)

To a solution of Et_2AlCN (1 M in toluene, 810 mL, 810 mmol) in THF (800 mL) at 0 °C was added isopropyl alcohol (66 mL, 810 mmol) and the mixture was stirred for 20 min. The resultant solution of Et(*i*-OPr)AlCN was then cooled to −38 °C and a solution of **12** (75 g, 270 mmol) in THF (1.2 L) was added over 30 min. Then the reaction mixture was warmed to 0 °C and stirred for 15 min. The reaction was quenched with saturated NH_4Cl (3 L) at −30 °C. Then the mixture was stirred for 1.5 h and allowed to warm to 8–10 °C. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to afford the crude product (78 g), which was purified by recrystallization (hexane/ethyl ether, 1:1) to afford 52 g (63% yield) of **13** as a white crystal. HPLC purity: 98.9% (254 nm, area %); ee: 99% (ee was determined by chirally pure samples of (1*S*,2*R*) and (1*R*,2*R*)). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (d, J=8 Hz, 1H), 7.56 (d, J=8 Hz, 2H), 7.42 (d, J=8 Hz, 2H), 4.35 (m, 1H), 2.4–2.54 (m, 2H), 2.40 (s, 3H), 2.17–2.38 (m, 1H). 1.11 (d, J=4 Hz, 3H). ^{13}C NMR δ 141.9, 141.4, 130.3, 126.3 (q, CF_3), 126.2, 119.1, 48.1, 35.8 (q), 32.5, 21.5, 15.9. MS $[M+H]^+$ m/z 305. Anal. Calcd for $C_{13}H_{15}F_3N_2OS$: C, 51.31; H, 4.97; N, 9.20. Found: C, 52.07; H, 4.94; N, 9.08.

4.8. (2*S*,3*R*)-2-Amino-5,5,5-trifluoro-3-methylpentanoic acid hydrochloride (4)

To a round bottom flask charged with concentrated HCl (750 mL) was added **13** (52 g, 171 mmol) in small portions and the reaction mixture was heated to reflux for 3 days. The mixture was cooled to room temperature and washed with ethyl ether (3×1 L). The aqueous layer was concentrated to afford 50 g (estimated yield 99%) of **4** as a yellow solid, which was used directly in the next step. HPLC purity: 98.9% (254 nm, area %). ^{1}H NMR (400 MHz, D_2O) δ 3.96 (d, J=4 Hz, 1H), 2.52–2.62 (m, 1H), 2.29–2.43 (m, 1H), 2.12–2.26 (m, 1H), 1.01 (d, J=4 Hz, 3H). ^{13}C NMR δ 171.0, 126.7 (q, CF_3), 57.0, 36.6, 28.9 (q), 14.6. MS $[M-H]^-$ m/z 184. HRMS (ESI) [M+H] calcd for $C_6H_{11}F_3NO_2$ 186.0736; found 186.0738.

4.9. (2*S*,3*R*)-2-Amino-5,5,5-trifluoro-3-methylpentan-1-ol (14)

To a mixture of lithium borohydride (2 M in THF, 270 mL, 540 mmol) and chlorotrimethylsilane (137 mL, 1080 mmol) in THF (2.7 L) at 0 °C was added **4** (50 g, 170 mmol) in small portions. Then the reaction mixture was allowed to warm to room temperature and stirred for 3 days. The reaction was quenched with methanol (500 mL) at 0 °C and then aqueous sodium hydroxide (1 N, 1.5 L) was added. The mixture was extracted with chloroform (3×500 mL) and the combined organic extracts were washed with water and brine, dried over anhydrous sodium sulfate, filtered, and concentrated to afford 28 g of **14** (estimated yield 96%) as a colorless oil, which was used directly in the next step. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.50 (br, 1H), 3.20–3.31 (m, 1H), 3.11–3.18 (m, 1H), 2.56–2.62 (m, 1H), 2.30–2.46 (m, 1H), 1.94–2.04 (m, 1H), 1.84–1.93 (m, 1H), 1.50 (br s, 2H), 0.82 (d, J=8 Hz, 3H). ^{13}C NMR δ, 126.6 (q, CF_3), 63.1, 58.9, 29.8, 27.4 (q), 15.9. MS $[M-H]^-$ m/z 170. HRMS (ESI) [M+H] calcd for $C_6H_{12}F_3NO$ 172.0944; found 172.0945.

4.10. 5-Chloro-*N*-[(1*S*,2*R*)-4,4,4-trifluoro-1-(hydroxymethyl)-2-methylbutyl]thiophene-2-sulfonamide (1)

To a mixture of **14** (28 g, 164 mmol), triethylamine (23 mL, 164 mmol) in dichloromethane (280 mL) at 0 °C was added a solution of 5-chlorothiophene sulfonyl chloride (**15**, 35.5 g, 164 mmol) in dichloromethane (280 mL). The reaction mixture was warmed to room temperature and stirred for 2 days. To the solution was added aqueous HCl (0.1 N, 1.5 L). The aqueous layer was extracted with dichloromethane (2×500 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. The product was purified by silica gel column chromatography (hexane/ethyl acetate, 8:1–4:1) to afford 30 g of **1** as a white solid (50% yield from **13**). Recrystallization: to a mixture of heptane and ethyl acetate (4:1) was added **1** (30 g) in small portions. The mixture was heated to reflux (about ~104 °C) until a clear solution was obtained. Then the resulting solution was heated for 1 h. The solution was seeded with a good crystal and then the solution was allowed to cool to room temperature and stirred for 12 h. The crystals were filtered and dried to afford 25.7 g (86%) of **1** as a white crystal. HPLC purity: 99.6% (254 nm, area %); ee: 99% (ee was determined by comparison to chirally pure samples of *SR* and *RR*). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.66 (d, J=8 Hz, 1H), 7.56 (d, J=8 Hz, 2H), 7.42 (d, J=8 Hz, 2H), 4.35 (m, 1H), 2.40–2.54 (m, 2H), 2.40 (s, 3H), 2.17–2.38 (m, 1H). 1.11 (d, J=4 Hz, 3H). ^{13}C NMR δ 141.5, 134.9, 132.1, 128.5, 128.3 (q, CF_3), 60.5, 59.4, 36.8 (q), 28.2, 14.3. MS $[M-H]^-$ m/z 350. Anal. Calcd for $C_{10}H_{13}ClF_3NO_3S_2$: C, 34.14; H, 3.72; N, 3.98. Found: C, 34.13; H, 3.5; N, 3.89.

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