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An efficient enantioselective synthesis of florfenicol via asymmetric aziridination

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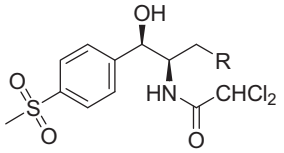
ABSTRACT

An efficient enantioselective synthesis of florfenicol is accomplished in 44.7% overall yield from commercially available *p*-(methylsulfonyl)benzaldehyde. Key features of this synthesis are the asymmetric aziridination reaction mediated by the Wulff's catalyst in situ derived from (*R*)-VANOL and diastereoselectively ring-opening of (2*S*,3*S*)-fluoroaziridine **13**.

1. Introduction

Since its discovery by Schering–Plough Corp. in 1979,[1] there has been continuous interest in developing efficient and economic process of florfenicol (**1**, Fig. 1),[2] a 3′-fluorinated derivative of thiamphenicol (**2**), due to its prominent superiority over **2** in antibacterial spectrum, antibacterial activity and comparatively lower side effect. To date, several asymmetric approaches toward the synthesis of **1** have been developed, such as Wu's asymmetric Sharpless epoxidation strategy and Lin's chemo-enzymatic cyanohydrination route.[3,4] However, it seems challenging to use these new methods for large scale syntheses. While the Schering–Plough resolution process developed in 1990 is still utilized with minor improvements via the key intermediate of D-*threo*-ethyl 2-amino-3-hydroxy-3-(4-(methylsulfonyl)phenyl) propanoate (D-Form ethyl ester) for large scale synthesis.[2a,5] Therefore, the continuous search for an asymmetric synthesis of **1** is of interest in the field.

Asymmetric aziridination has captured considerable attention in modern organic synthesis,[6] because it is an efficient and practical way to the enantioselective synthesis of chiral aziridines. The widespread application of these active intermediates in synthetic chemistry derives in large part from the fact that they readily undergo regio- and stereoselective ring-opening reaction with a variety of nucleophiles. Their interesting characteristics, combined with Davis's promising approach toward **2** via an important chiral aziridines intermediate promoted us to develop a facile and enantioselective synthesis of **1** using an improved Wulff's asymmetric aziridination strategy.[7,8] Herein, we report the results of our investigation.



florfenicol **1**: R = F
thiamphenicol **2**: R = OH

Fig. 1. The chemical structures of **1** and **2**.

2. Results and discussion

Our enantioselective synthesis of **1** was depicted in Scheme 1. Commercial available *p*-(methylsulfonyl)benzaldehyde (**3**) was refluxed with 1 equiv mol of benzhydrylamine in ethanol for 3 h to give corresponding benzhydryl imine **4** in excellent yield.

The following step was the key reaction of constructing two chiral centers of the target molecule **1**, utilizing Wulff asymmetric aziridination protocol. Thus, (2*S*,3*S*)-aziridine **11** was achieved from imine **4** in 93% yield with an enantiomeric purity of 85% ee and a cis/trans ratio of >50:1 in toluene at −10 °C in the presence of 10 mol % of the Wulff catalysts derived from (*R*)-VANOL ligand **5**

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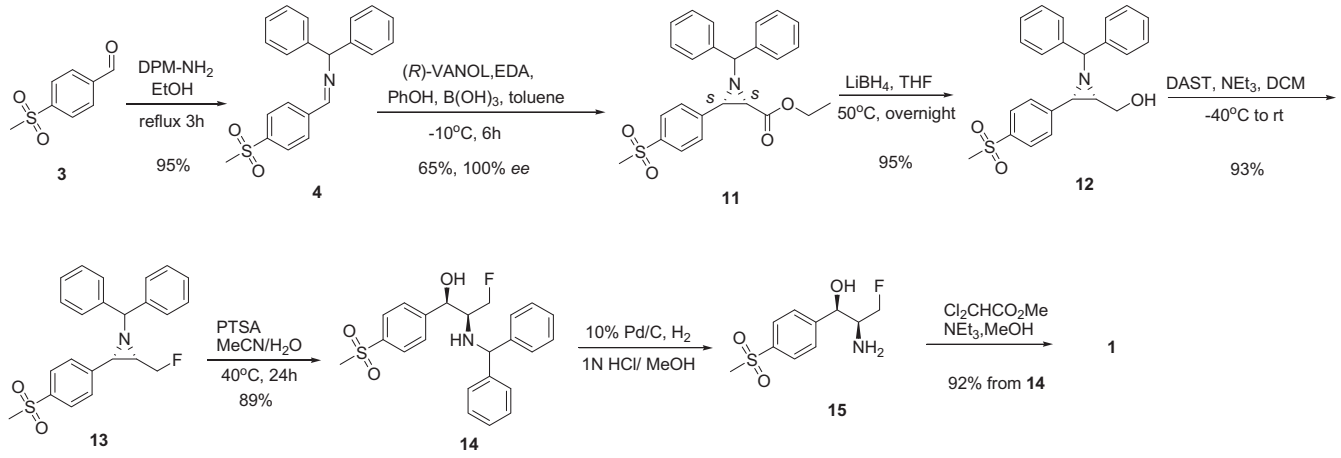
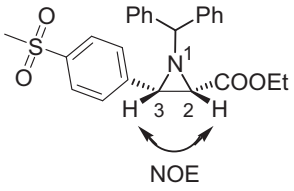


Scheme 1. The efficient and enantioselective synthesis of florfenicol **1**.

and triphenylborate. Its ee value could be increased up to 99.5% after a single crystallization from hexane/methylene chloride. Reduction of the loading of the catalyst from 10 mol % to 1 mol %, no obvious decrease in asymmetric induction, cis/trans ratio and yield were observed. Aziridine **11** was obtained in 91% yield with an enantiomeric purity of 82% ee and a cis/trans ratio of >50:1, when the loading of catalyst was 1 mol %. However, when the catalyst loading reduced to 0.5 mol %, both of the enantioselectivity and yield decreased distinctly to 56% ee and 78%, respectively. When the reaction scaled up to 10 mmol scale, the catalyst still works well. After recrystallized the crude product from hexane/methylene chloride twice, aziridine **5** was obtained in 65% yield with 100% ee.

The stereochemistry of (2*S*,3*S*)-aziridine **11** was confirmed by NMR experiment. The *J* values of the protons locating at aziridine ring (H_2–H_3) was 6.8 Hz, similarly to its analogous ((2*S*,3*S*)-ethyl 1-benzhydryl-3-phenylaziridine-2-carboxylate).[8a] Nuclear Overhauser enhancement spectroscopy (NOESY) relationship between H_2 and H_3 also indicated its cis configuration (Fig. 2). Furthermore, its structure was unambiguously ascertained via X-ray crystallography (Fig. 3).[9]



11.

Fig. 2. NOE correlation of **11**.

Additionally, other ligands (**6**–**10**, Table 1) have been examined for this asymmetric aziridination, and the results were listed in Table 1. As expected, VAPOL catalyst providing (2*S*,3*S*)-aziridine **11** with the similar results as VANOL catalyst in terms of stereoselectivity, chemical yield(Table 1, entry 2). Poor asymmetric induction was occurred by (*R*)-3,3′-diphenyl-BINOL ligand (**7**) with 34% ee, 85% yield, and >50:1 selectivity for the cis-diastereomer (Table 1, entry 3). Ligand **8**, (*R*)-3,3′-bis-9-anthracenyl-BINOL, provided product in 86% but no chiral induction was observed (Table 1, entry 4). The reaction was not proceeded with ligand **9**, whose 3,3′-positions were substituted by triphenylsily groups (Table 1, entry 5). Also, (4*R*, 5*R*)-TADDOL ligand **10**, an extraordinarily versatile diol ligand with large steric bulk, was ineffective to this asymmetric

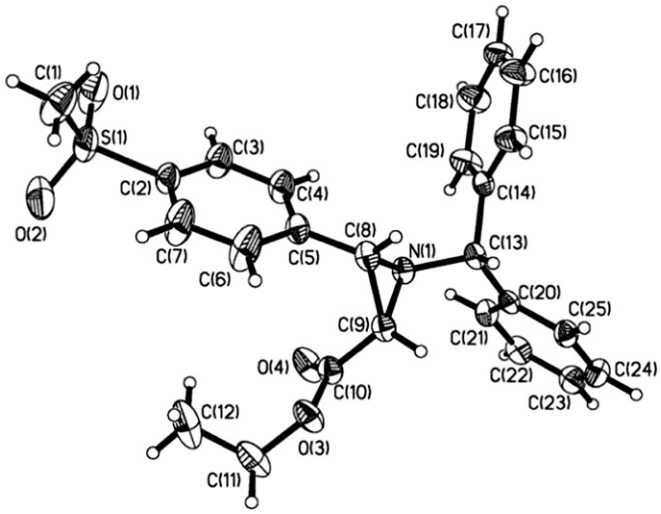


Fig. 3. ORTEP depiction of **11**.

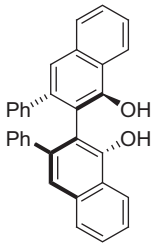
aziridination (Table 1, entry 6). The reaction solvents of this aziridination were examined. Toluene was the best choice among the tested solvents (toluene, CH_2Cl_2, THF) (entries 1 and 7–8). Better chiral induction was achieved at low reaction temperature (entries 1 and 9–10). While the reaction temperature decreased from −10 °C to −20 °C, no improvement in stereoselectivity was made (entry 11).

Under the optimized conditions, we next examined the asymmetric aziridination of *p*-methylthiobenzaldimine **16**. Surprisingly, this reaction was failed to take place and lead only to a 100% recovery of **16**, even the temperature was raised to room temperature (Scheme 2).

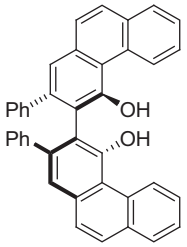
Chemoselective reduction of **11** with $LiBH_4$, prepared in situ from KBH_4 and anhydrous LiCl, in THF at 50 °C under N_2 gave (2*S*,3*S*)-aziridinol **12** in 95% yield. The Middleton fluorination of **12** with DAST ((diethylamino)sulfur trifluoride) in the presence of NEt_3 in CH_2Cl_2 at −40 °C to room temperature provided (2*S*,3*S*)-fluoroaziridine **13** in excellent yield.[10] It is worth mentioning that this fluorination reaction failed to proceed in the absence of the amine.

The ring-opening of **13** by treatment upon 1 equiv of PTSA worked well at 40 °C for 24 h in a mixed solvent of MeCN/H_2O to furnish benzhydryl (1*R*,2*S*)-fluoroalkamine **14** as a single diastereomer in 89% yield. The palladium-catalyzed hydrogenolysis

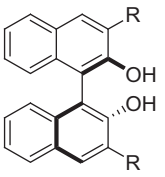
Table 1
Asymmetric aziridinationa of **4** mediated by the catalysts derived from ligands **5**–**10**[a]



5: (*R*)-VANOL

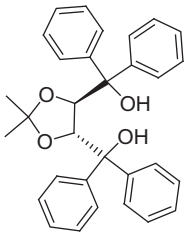


6: (*R*)-VAPOL



(*R*)-3,3'-substituted BINOLs

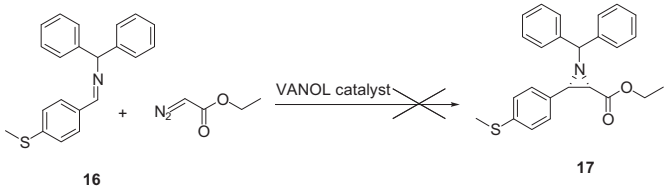
7: R = Ph
8: R = 9-anthracenyl
9: R = $SiPh_3$



10: (*R*,*R*)-TADDOL

Entry	Ligands	Solvent	Temp (°C)	Conversion[b] (%)	Yield[c] (%)	cis/trans[b]	ee[d] (%)
1	**5**	Toluene	−10	100	93	>50:1	85
2	**6**	Toluene	−10	100	92	>50:1	84
3	**7**	Toluene	−10	100	85	>50:1	34
4	**8**	Toluene	−10	100	86	>50:1	0
5	**9**	Toluene	−10 to 25[e]	0	—	—	—
6	**10**	Toluene	−10 to 25[e]	0	—	—	—
7	**5**	CH_2Cl_2	−10	100	92	>50:1	83
8	**5**	THF	−10	82	71	>50:1	85
9	**5**	Toluene	25	100	92	>50:1	82
10	**5**	Toluene	0	100	92	>50:1	84
11	**5**	Toluene	−20	100	93	>50:1	85

[a] Unless otherwise specified, all reactions were run with 0.5 mmol of imine and 1.1 equiv of ethyl diazoacetate in the presence of 10 mol % of catalyst for 18 h. The catalyst was synthesized from ligands and triphenylborate, which was in situ prepared from PhOH and boric acid with the assistant of molecular sieve.
[b] Conversion and cis/trans selectivity were determined by ^{1}H NMR on the crude reaction mixture.
[c] Isolated yield after silica gel chromatography.
[d] Determined by HPLC on a Chiralpak AD-H column.
[e] The reaction mixture was stirred at −10 °C for 18 h, then 25 °C for another 18 h.



16 17

Scheme 2. The catalyst derived from (*R*)-VANOL ligand had no effect on imine **16**.

of **14** in 1 N HCl/MeOH afforded (1*R*,2*S*)-fluoroalkamine **15**, which, without purification, converted to florfenicol (**1**) in 92% overall yield (over two steps) upon treatment with methyl dichloroacetate under relatively mild conditions. The spectral data and physical characteristics of **1** were in complete agreement with the reported values.[4]

3. Conclusions

In conclusion, we have developed an efficient and enantioselective synthesis of **1** in 44.7% overall yield starting from *p*-(methylsulfonyl)benzaldehyde by employing asymmetric aziridination as the key step, which was mediated by the Wulff's catalyst. This process could have applications in large scale synthesis of **1** and its analogs.

4. Experimental section

4.1. General remarks

Melting points were determined on a WRS-1 digital melting point apparatus and were uncorrected. Optical rotations were obtained on a JASCO P1020 digital polarimeter. Elemental analyses were performed on a Carlo-Erba 1106 instrument, and the results of elemental analyses for C, H, N and S were within ±0.4% of the theoretical values. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker Avance 400 spectrometer (400, 100 MHz, respectively) in $CDCl_3$ or DMSO-d_6 using tetramethylsilane (TMS) or DMSO-d_6 (^{1}H δ 2.49) and $CDCl_3$ (^{13}C δ 77.0) or DMSO-d_6 (^{13}C δ 39.5) as internal standards. Chemical shifts are given in parts per million (ppm) relative to the residual signals of the solvent. IR spectra were recorded on a Nicolet FI-IR 4200 spectrometer as KBr pellets. Absorptions are given in cm^{-1}. Mass spectra were measured on a Waters Quattro Micromass instrument using electrospray ionization (ESI) techniques. Enantiomeric excesses (ee) of **11** was determined by HPLC analysis using a Chiralpak AD-H column, hexane/2-PrOH, 70:30; flow is 0.5 mL min^{-1}; λ=214 nm, t_R=20.8 min (major) and 16.1 min (minor)]. Unless otherwise noted all reactions were conducted in oven-dried glassware under inert atmosphere of dried Ar or N_2. THF was distilled from sodium/benzophenone, while toluene and CH_2Cl_2 from calcium hydride. The (*R*)-VANOL/VAPOL ligands were purchased from Aldrich, while ligands **7**–**10** were prepared according to known procedures from corresponding commercial starting materials.[11]

4.2. *N*-(4-(Methylsulfonyl)benzylidene)diphenylmethanamine (4)

p-(Methylsulfonyl)benzaldehyde **3** (1.83 g, 10 mmol) and benzhydrylamine (1.84 g, 10 mmol) were stirred and refluxed in 30 mL EtOH for 3 h, then cooled to room temperature. After filtration and dried, **4** was obtained as yellowish needles (3.32 g, 95% yield). Mp 139–140 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.06 (3H, s, SO_2CH_3), 5.67 (1H, s, Ph_2CH), 7.26 (2H, m, Ar), 7.24–7.41 (8H, m, Ar), 8.02 (4H, m, Ar), 8.49 (1H, s, N=C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=44.52, 78.08, 127.30, 127.62, 127.71, 128.61, 129.22, 141.05, 142.14, 143.27, 158.91 ppm. ESI-MS: (*m*/*z*)=350 $[M+H]^+$. FTIR (KBr): ν_{max}=3052, 3009, 2918, 1640, 1491, 1310, 1150, 768, 698 cm^{-1}. Anal.

Calcd for $C_{21}H_{19}NO_2S$: C, 72.18; H, 5.48; N, 4.01; S, 9.18. Found: C, 71.06; H, 5.52; N, 3.95; S, 9.22.

4.3. *N*-(4-(Methylthio)benzylidene)diphenylmethanamine (16)

Compound **16** was prepared in the same procedure as **4**, white powder, 91% yield. Mp 99–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.54 (3H, s, SC*H*$_3$), 5.64 (1H, s, Ph$_2$C*H*), 7.28–7.46 (12H, m, Ar), 7.80 (2H, d, *J*=8.4 Hz, Ar), 8.41 (1H, s, N=C*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.34, 77.92, 125.84, 127.03, 127.75, 128.50, 128.84, 133.16, 142.25, 144.02, 160.18 ppm. ESI-MS: (*m*/*z*)=318 $[M+H]^+$. FTIR (KBr): ν_{max}=: 3078, 3021, 2915, 2856, 1637, 1590, 1491, 1024, 809, 755, 699 cm^{-1}. Anal. Calcd for $C_{21}H_{19}NS$: C, 79.45; H, 6.3; N, 4.41; S, 10.10. Found: C, 79.32 H, 6.06; N, 4.38; S, 10.06.

4.4. (2*S*,3*S*)-Ethyl 1-benzhydryl-3-(4-(methylsulfonyl)phenyl) aziridine-2-carboxylate (11)

4.4.1. 1 mmol scale. Phenol (56.4 mg, 0.6 mmol), boric acid (12.4 mg, 0.2 mmol), and molecular sieve (20 mg) were added to a flame-dried flask cooled under argon and then added 2 mL anhydrous toluene. The mixture was stirred and heated to reflux overnight. Then cooled to room temperature and (*R*)-VANOL (21.9 mg, 0.05 mmol) was added. The mixture was heated to 80 °C for 1 h. After slow evaporation of the solvent, a vacuum (0.5 mmHg) was applied for 30 min with the temperature maintained at 80 °C. The resulting catalyst was dissolved in anhydrous toluene (1 mL) and transferred via syringe to a suspension of imine **4** (349 mg, 1 mmol) in anhydrous toluene (1 mL) under argon. The reaction mixture was stirred for 10 min at room temperature, and then cooled to −10 °C, treated with ethyl diazoacetate (110 μL, 1.1 mmol). Some gas was emitted. The reaction was stirred at this temperature for 18 h, and then warmed up at room temperature for 1 h. After removal of the toluene, the ^{1}H NMR of the crude product revealed aziridine **11** with a cis/trans ratio >50:1 and less than 5% of acyclic side products. Purification by column chromatography on silica gel with hexane/ethyl acetate (2:1 to 1:1) gave aziridine **11** (405 mg, 93% yield, 85% ee). Recrystallization from hexane: CH_2Cl_2 gave **11** as white needles (292 mg, 67% yield, 99.5% ee). Mp 122–123 °C. $[\alpha]_D^{25}$ −20.9 (*c* 1.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.00 (3H, t, *J*=7.0 Hz, CH$_2$C*H*$_3$), 2.70 (1H, d, *J*=6.4 Hz, C*H*COOEt), 3.00 (3H, s, SO$_2$C*H*$_3$), 3.24 (1H, d, *J*=6.8 Hz, ArC*H*), 3.95 (2H, q, *J*=7.0 Hz, C*H*$_2$CH$_3$), 3.98 (1H, s, Ph$_2$C*H*), 7.19–7.58 (10H, m, Ar), 7.62 (2H, d, *J*=8.4 Hz, Ar), 7.82 (2H, d, *J*=8.4 Hz, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.03, 44.50, 46.86, 47.25, 60.94, 77.63, 126.95, 127.11, 127.46, 127.69, 128.64, 128.68, 128.92, 139.51, 141.52, 141.93, 142.16, 167.07 ppm. ESI-MS: (*m*/*z*) (%)=436 $[M+H]^+$. FTIR (KBr): ν_{max}=3026, 2918, 1736, 1600, 1453, 1314, 1299, 1210, 1149, 747, 560 cm^{-1}. Anal. Calcd for $C_{25}H_{25}NO_4S$: C, 68.94; H, 5.79; N, 3.22; S, 7.36. Found: C, 68.80; H, 5.73; N, 3.19; S, 7.31.

4.4.2. 10 mmol scale. 10 mmol scale procedure for **4** was same as 1 mmol scale one, except for the workup. The crude product was recrystallized from hexane: CH_2Cl_2 for two times to furnish **11** as white needles (2.82 g, 65% yield, 100% ee).

4.5. ((2*S*,3*S*)-1-Benzhydryl-3-(4-(methylsulfonyl)phenyl)aziridin-2-yl)methanol (12)

KBH_4 (745 mg, 13.8 mmol) and LiCl (584 mg, 13.8 mmol) were stirred and refluxed in anhydrous THF (20 mL) under N_2 for 2 h. Then cooled to room temperature, and the THF solution of aziridine **11** (2.00 g, 4.6 mmol, >99% ee) was added dropwise. After the addition, the mixture was heated at 50 °C overnight. Then cooled to room temperature, 30 mL H_2O was added and stirred for 1 h. Then extracted by EA (3×50 mL), combined, dried over Na_2SO_4, filtrated, condensed in vacuum, and purified silica gel with hexane/ethyl acetate (2:1 to 1:1) to afford aziridinol **12** as a white solid (1.71 g, 95% yield). Mp 193–195 °C. $[\alpha]_D^{25}$ +166.8 (*c* 1.06, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.34 (1H, q, C*H*CH$_2$OH), 3.04–3.05 (4H, m, SO$_2$C*H*$_3$ and ArC*H*), 3.38 (2H, d, *J*=6.4 Hz, C*H*$_2$OH), 3.92 (1H, s, Ph$_2$C*H*), 7.19–7.51 (10H, m, Ar), 7.58 (2H, d, *J*=8.4 Hz, Ar), 7.85 (2H, d, *J*=8.4 Hz, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=44.54, 45.94, 47.96, 60.34, 78.29, 127.20, 127.28, 127.34, 127.40, 127.70, 128.52, 128.57, 128.83, 139.16, 142.38, 143.05, 143.30 ppm. ESI-MS: (*m*/*z*) (%)=394 $[M+H]^+$. FTIR (KBr): ν_{max}=3478, 3055, 2923, 1597, 1397, 1307, 1293, 1146, 1028, 704, 569 cm^{-1}. Anal. Calcd for $C_{23}H_{23}NO_3S$: C, 70.20; H, 5.89; N, 3.56; S, 8.15. Found: C, 70.08; H, 5.92; N, 3.49; S, 8.08.

4.6. (2*S*,3*S*)-1-Benzhydryl-2-(fluoromethyl)-3-(4-(methylsulfonyl) phenyl)aziridine (13)

Compound **12** (1.50 g, 3.82 mmol) and NEt_3 (1.06 mL, 7.64 mmol) were dissolved in anhydrous CH_2Cl_2 (10 mL) under Ar. Then cooled to −40 °C, DAST (0.94 mL, 7.64 mmol) was added dropwise via syringe. After the addition, the reaction mixture was warmed to room temperature and stirred for 8 h. The reaction was quenched by adding 5% $NaHCO_3$ (40 mL) and extracted with ethyl acetate (3×100 mL). The combined organic phases were dried over sodium sulfate. The solvent was removed and the residue was purified by flash column chromatography on silica gel with hexane/ethyl acetate (2:1 to 1:1) to afford fluoroaziridine **13** as white solid (1.40 g, 93% yield). Mp 165–168 °C. $[\alpha]_D^{25}$ +101.7 (*c* 1.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.44 (1H, q, C*H*CH$_2$F), 3.03 (3H, s, SO$_2$C*H*$_3$), 3.10 (1H, d, ArC*H*), 3.96 (1H, s, Ph$_2$C*H*), 3.97–4.41 (2H, m, C*H*$_2$F), 7.18–7.50 (10H, m, Ar), 7.56 (2H, d, *J*=8.4 Hz, Ar), 7.86 (2H, d, *J*=8.4Hz, Ar) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=44.47, 44.84 (d, *J*=28.4 Hz, *C*HCH$_2$F), 45.22 (d, *J*=3.8 Hz, ArCHCHCH$_2$F), 77.89, 81.19 (d, *J*=166 Hz, *C*H$_2$F), 127.14, 127.29, 127.46, 128.54, 128.58, 139.30, 142.38, 142.55 ppm. ESI-MS: (*m*/*z*) (%)=396 $[M+H]^+$. FTIR (KBr): ν_{max}=3024, 2925, 1600, 1453, 1307, 1146, 993, 706, 570, 535 cm^{-1}. Anal. Calcd for $C_{23}H_{22}FNO_2S$: C, 69.85; H, 5.61; N, 3.54; S, 8.11. Found: C, 69.77; H, 5.57; N, 3.50; S, 8.06.

4.7. (1*R*,2*S*)-2-(Benzhydrylamino)-3-fluoro-1-(4-(methylsulfonyl) phenyl)propan-1-ol (14)

Compound **13** (2.00 g, 5.06 mmol) and PTSA (0.96 g, 5.06 mmol) were dissolved in MeCN (10 mL) and H_2O (10 mL). The mixture was stirred at 40 °C for 24 h, then cooled to room temperature and evaporated the solvent. The residue was dissolved in 100 mL CH_2Cl_2 and washed by 1% aq $NaHCO_3$ (100 mL) and brine (50 mL). The organic solvent was dried over Na_2SO_4, condensed in vacuum and purified silica gel with hexane/ethyl acetate (2:1 to 1:1) to afford protected fluoroalkamine **14** as a white solid (1.86 g, 89% yield). Mp 142–144 °C. $[\alpha]_D^{25}$ +70.6 (*c* 1.05, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.70–2.83 (1H, m, NC*H*CH$_2$F), 3.04 (3H, s, SO$_2$C*H*$_3$), 4.11–4.26 (1H, m, C*H*$_a$H$_b$F), 4.48–4.68 (1H, m, CH$_a$*H*$_b$F), 4.74 (1H, d, *J*=7.6 Hz, ArC*H*OH), 4.92 (1H, s, Ph$_2$C*H*), 7.22–7.36 (10H, m, Ar), 7.51 (2H, d, *J*=8.4 Hz, Ar), 7.89 (2H, d, *J*=8.4 Hz, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ=44.54, 61.06 (d, *J*=18.2 Hz, *C*HCH$_2$F), 64.53, 71.72 (d, *J*=4.3 Hz, ArCHCHCH$_2$F), 80.21 (d, *J*=168 Hz, *C*H$_2$F), 127.03, 127.45, 127.51, 127.66, 127.69, 127.85, 128.84, 139.99, 141.96, 143.30, 147.95. ESI-MS: (*m*/*z*) (%)=414 $[M+H]^+$. FTIR (KBr): ν_{max}=3479, 3372, 3023, 2923, 2850, 1597, 1493, 1453, 1290, 1143, 1085, 957, 772, 752, 706, 698, 563 cm^{-1}. Anal. Calcd for $C_{23}H_{24}FNO_3S$: C, 66.81; H, 5.85; N, 3.39; S, 7.75. Found: C, 66.68; H, 5.89; N, 3.41; S, 7.71.

4.8. Florfenicol 1

To a solution of the fluoroalkamine **14** (1.30 g, 3.15 mmol) in 1 N HCl (1.5 mL) and MeOH (15 mL) was added 10% Pd/C (130 mg) and the mixture was stirred for 6 h at room temperature in a hydrogen atmosphere under atmospheric pressure. The mixture was filtrated over a Celite pad, and the filtrate was concentrated in vacuo. The residue was dissolved in 10 mL CH_2Cl_2, and extracted by 1 N HCl (3×5 mL). Combined the aqueous phase, and neutralized by aq $NaHCO_3$, then extracted by CH_2Cl_2 (3×20 mL). The combined organic phases were dried over sodium sulfate. After filtrated and condensed in vacuum, crude white oily vicinal fluoroalkamine **15** was obtained. The residue was dissolved in MeOH (10 mL), then methyl dichloroacetate (1.54 mL, 14.8 mmol) and triethylamine (0.88 mL, 6.3 mmol) were added. The mixture was refluxed for 3 h. Removal of the solvent followed by purification of the residue on silica gel with hexane/ethyl acetate (2:1 to 1:1) afforded **1** as a white solid (1.04 g, 92% yield). Mp 151–152 °C. $[\alpha]_D^{25}$ −18.3 (*c* 0.51, DMF) (lit.[4] mp 151–152 °C, $[\alpha]_D^{25}$ −18.0 (*c* 0.35, DMF)). ^{1}H NMR (400 MHz, DMSO-d_6): δ=3.16 (3H, s, SO_2CH_3), 4.26–4.78 (3H, m, CH_2F/NC*H*), 4.99 (1H, m, ArC*H*), 6.15 (1H, d, *J*=4.4 Hz, O*H*), 6.47 (1H, s, C*H*Cl_2), 7.62 (2H, d, *J*=8.4 Hz, Ar), 7.85 (2H, d, *J*=8.4 Hz, Ar), 8.60 (1H, d, *J*=8.8 Hz, N*H*) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ=44.1, 55.1 (d, *J*=19.4 Hz, *C*HCH_2F), 66.8, 69.8 (d, *J*=6.1 Hz, ArCHCHCH_2F), 82.8 (d, *J*=168.9 Hz, *C*H_2F), 127.0, 127.6, 140.0, 148.4, 164.2 ppm. ESI-MS: (*m*/*z*) (%)=358 $[M+H]^+$. FTIR (KBr): ν_{max}=3453, 3321, 3033, 2989, 1684, 1535, 1290, 1276, 1149, 1017, 769 cm^{-1}. Anal. Calcd for $C_{12}H_{14}Cl_2FNO_4S$: C, 40.24; H, 3.94; N, 3.91; S, 8.95 Found: C, 40.07; H, 3.97; N, 3.87; S, 8.92.

Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.09.052.

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