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New stereoselective synthesis of thiamphenicol and florfenicol from enantiomerically pure cyanohydrin: a chemo-enzymatic approach

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ABSTRACT

Thiamphenicol and florfenicol have been synthesized stereoselectively from enantiomerically pure 4-methylsulfanyl-mandelonitrile, which was obtained by hydrocyanation reaction of 4-methylsulfanyl-benzaldehyde catalyzed by (*R*)-hydroxynitrile lyase of *Badamu* (*Prunus communis* L. var. *dulcis* Borkh, almond from Xinjiang, China). It was found to be a highly effective bio-catalyst for this reaction after an extensive screening.

1. Introduction

Thiamphenicol **2**, a member of chloramphenicol **1** family (Fig. 1), is a broad spectrum antibiotics against many Gram negative and Gram positive microorganisms. Thiamphenicol possesses high in vivo activity for having a good property of unbinding with glucuronic acid in liver and has been used clinically. The first synthesis of racemic thiamphenicol was reported in 1950s.[1,2] Currently, commercially available optically active D-thiamphenicol is obtained by a resolution process with unnatural D-(−)-tartaric acid.[3,4] However, recycle of the L-isomer generated as a by-product in the resolution has been unsatisfactory due to the tedious and ineffective procedure. Florfenicol **3** (Fig. 1) is a fluorinated derivative of thiamphenicol, which was discovered in 1979.[5] Compared to thiamphenicol, florfenicol shows significant superiority in antibacterial spectrum, antibacterial activity, and considerably lower side effect, its antibacterial potency is 10 times higher than that of thiamphenicol. Since their discovery, there has been continuous interest in developing asymmetric synthesis of these two compounds.[6,7] Nagabhushan and co-workers[4b] reported a diastereospecific synthesis of thiamphenicol in racemic form. Schumacher and co-workers[8a] reported an asymmetric synthesis of florfenicol by using D-(−)-*threo*-2-amino-1-(4-methylthiophenyl)-1,3-propanediol or D-(−)-*threo*-2-amino-1-(4-methylsulfonylphenyl)-1,3-propanediol as the starting material. Clark and co-workers[8b] achieved a resolution of DL-*threo*-2-amino-1-(4-methylthiophenyl)-1,3-propanediol in its D-isomer in high ee value by using a protease from *Streptomyces griseus*. Later on, they[8c,d] disclosed a procedure for the synthesis of diastereomerically pure florfenicol, which was based on an intermediate, 1′-(*R*,*R*)-(dichloromethyl)oxazoline, obtained in the resolution process for thiamphenicol. In 1997, Wu and co-workers[8e] have developed a new asymmetric total synthesis of thiamphenicol and florfenicol based on the diastereoselective Sharpless epoxidation followed by a series of transformations to (3*S*,4*R*)-2-(dichloromethyl)-4,5-dihydro-α-[4-(methylsulfonyl)phenyl]-oxazole-4-methanol, a common intermediate for both thiamphenicol and florfenicol. In 2006, two Indian groups reported the stereoselective syntheses of (−)-chloramphenicol and (+)-thiamphenicol, respectively. Hajra and co-workers[8f] commenced the synthesis of (+)-thiamphenicol by using a silver(I)-promoted asymmetric bromomethoxylation of (2*R*)-*N*-[(2-methanesulfonyl-pheny)-

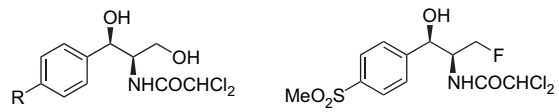

Figure 1.

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propenoyl]-bornanesultam to afford *anti*-(2*R*,2′*R*,3*R*)-*N*-[2′bromo-3′methoxy-3′(2-methnesulfonyl-phenyl)-propionyl]-bornanesultam, which, after a series of transformations, gave the target compound. Sudalai and co-workers[8g] performed the enantioselective synthesis of (+)-thiamphenicol by converting 4-(methylsulfanyl)-benzaldehyde into 1-(4-methylsulfanylphenyl)-2-propen-1-ol, which, after being converted into the corresponding sulfonyl derivative, was subjected to Sharpless asymmetric epoxidation. The epoxide was then converted into the target compound by a series of chemical manipulations.

The enzyme-catalyzed asymmetric syntheses of cyanohydrins have been remarkably developed by Effenberger[9] and Brussee.[10] β-Hydroxy-α-amino acids were diastereoselectively synthesized from cyanohydrins by Brussee and co-workers in 1992.[10b] As a result of our investigation of biologically catalyzed hydrocyanation of aldehydes and ketones,[11] we now report a new route to the asymmetric total synthesis of thiamphenicol and florfenicol starting from enantiomerically pure 4-methylsulfanyl-mandelonitrile.

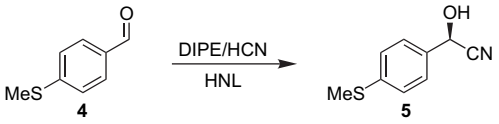
2. Results and discussion

2.1. Discovery of an enzyme source to catalyze highly enantioselective formation of the key starting compound 4-methylsulfanyl-mandelonitrile

As shown in Scheme 1, the enantioselective transformation of 4-methylsulfanyl-benzaldehyde to 4-methylsulfanyl-mandelonitirle is a key point in this synthesis. In our previous publications,[11] we reported a number of (*R*)-cyanohydrins formed in a bio-catalytic process, in which various (*R*)-hydroxynitrile lyase (HNL) containing plants were investigated and used as the crude enzyme source. However, these investigated plants were found to be unable to give the desired enantiomeric excess in 4-methylsulfanyl-mandelonitrile formation. Fortunately, after an extensive search and screening, we finally found that the kernel of *Badamu* (almond from Xingjiang, China) (*Prunus communis* L. var. *dulcis* Borkh)[12] is a highly effective enzyme source for our goal.

The plant originated enzyme source, shown in Table 1 (entry 4), was soaked in distilled water for 2 h, peeled, air-dried, and homogenized. The homogenate was defatted with ethyl acetate and washed with isopropyl ether to give a soft powder, which was stored in a refrigerator for use. A mixture of the crude enzyme-containing meal, aldehyde, and HCN in isopropyl ether was stirred at room temperature for 12 h.[9] Filtration, evaporation in vacuo, and chromatography on silica gel gave the cyanohydrin with 96% ee in 98% yield. Recrystallization from petroleum ether and diethyl ether gave 4-methylsulfanyl-mandelonitrile **5** as a colorless needle crystal with 99% ee in 86% yield.

Table 1
4-Methylsulfanyl-mandelonitrile formed under the catalysis of some representative (*R*)-HNL-containing plants as the enzyme source



Entry	HNL source	Yield[a] (%)	ee (%)[b]	Configuration
1	*Malus pumila* Mill., seeds	92	65	*R*
2	*Eriobotrya japonica* Lindl., seeds	70	74	*R*
3	*Prunus armeniaca* L., kernels	81	39	*R*
4	*Prunus communis* L. var. *dulcis* Borkh, kernels	98	96	*R*

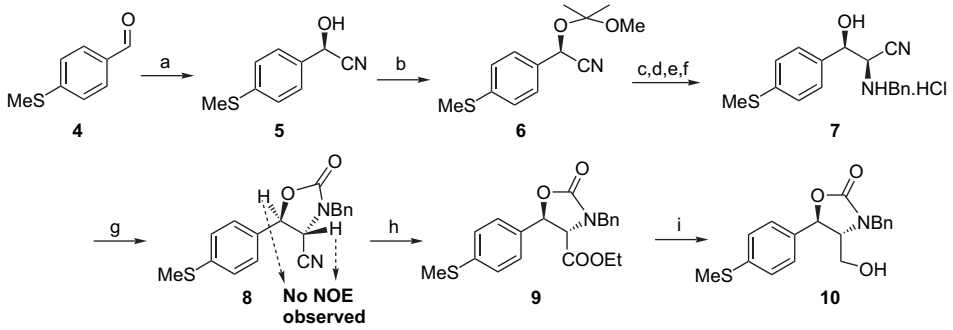
[a] Isolation yield on silica gel column.
[b] Determined on chiral HPLC after acetylation of the obtained cyanohydrins.

2.2. Syntheses of thiamphenicol and florfenicol starting from the enantiomerically pure 4-methylsulfanyl-mandelonitrile

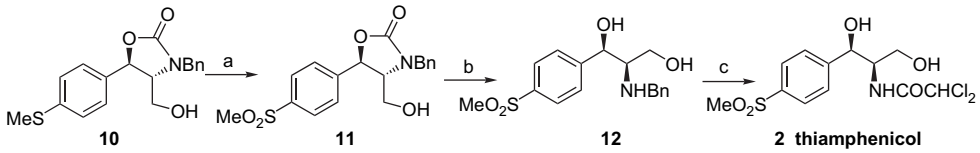
Both thiamphenicol and florfenicol have 1*R* chiral carbon and *threo* configuration. As shown in Scheme 1, the enantioselective formation of **5** establishes the 1*R* form stereochemistry. The subsequent transformations were performed by a modification of the procedure reported by Brussee and van der Gen.[10c] One-pot sequential manipulations of DIBAL reduction of the 2-methoxy-*iso*-propyl (MIP) protected (*R*)-cyanohydrin **6** at low temperature, benzylamine addition, and hydrocyanation generated the second chiral carbon in *threo* configuration almost exclusively to afford **7** in 75%. The diastereoselective ratio (dr) of this hydrocyanation reaction was found to be higher than 20:1 (determined by ^{1}H NMR, the *erythro* isomer's signals were not observed) when the reaction was conducted at 0 °C. Compound **7** was converted into the oxazolidone derivative **8** in an overnight reaction with 1,1′-carbonyl-diimidazole. The NOE and coupling constant of the oxazolidone **8** supported the assigned *threo* (trans) configuration[10b,13] of the major product. Conventional treatment of **8** produced **10**, which was used as a common intermediate for the formation of both of the target compounds.

As shown in Scheme 2, oxidation of **10** with *meta*-chloroperbenzoic acid (*m*-CPBA) converted the methylsulfanyl group into a methylsulfonyl group to give **11**, resulting in the formation of the skeleton of thiamphenicol. Hydrolysis with aqueous KOH, catalytic debenzylation, and acylation produced thiamphenicol in 26% overall yield starting from 4-methylsulfanyl-benzaldehyde **4**.

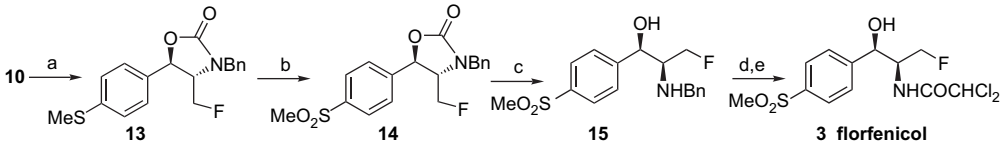
As shown in Scheme 3, fluorination of **10** with diethylaminosulfur trifluoride (DAST) gave the fluorinated derivative **13**. It is interesting that the alkaline ring opening of the oxazolidone ring in **15**, which was used by Brussee for the same conversion[10b] and used by us for the ring opening of **11**, caused cleavage of the F–C



Scheme 1. Synthesis of the common intermediate **10** for thiamphenicol and florfenicol. Reaction and conditions: (a) HCN/HNL, 98%, 96% ee; 86%, 99% ee after recrystallization; (b) MIP, $POCl_3$, 95%; (c) DIBAL; (d) $BnNH_2$; (e) NH_4Br, NaCN; (f) HCl, H_2O, ethanol; a through f, overall yield 75%; (g) $(im)_2CO$, TEA, 82%; (h) K_2CO_3, ethanol; then 1 N HCl, 91%; (i) $NaBH_4$, methanol, 85%.



Scheme 2. Synthesis of thiamphenicol **2** from intermediate **10**. Reaction and conditions: (a) *m*-CPBA, 90%; (b) 2 N KOH, reflux, 85%; (c) Pd/C, H_2, 90%; MeOH, $CHCl_2COOEt$, TEA, 100%.



Scheme 3. Synthesis of florfenicol **3** from intermediate **10**. Reaction and conditions: (a) DAST, THF, 85%; (b) *m*-CPBA, 90%; (c) 8 N H_2SO_4, 140 °C, 71%; (d) Pd/C, H_2 85%; (e) MeOH, $CHCl_2COOEt$, TEA, 100%.

bond. Careful study showed that substitution of the fluoro group by hydroxy group was quicker than ring opening of oxazolidone under the alkaline condition. Finally, the ring opening was accomplished with aqueous 8 N H_2SO_4 to give **16** in moderate yield. Florfenicol **3** was thus obtained in 18% overall yield starting from 4-methylsulfanyl-benzaldehyde **4**.

3. Conclusion

With the aid of (*R*)-hydroxynitrile lyase (HNL) in the kernel of *Badamu* (*Prunus communis* L. var. *dulcis* Borkh), we were able to obtain 4-methylsulfanyl-mandelonitrile in high chemical yield and high optical purity. With this cyanohydrin as the starting point, we have developed a new and efficient route to the asymmetric syntheses of thiamphenicol and florfenical, in 26% and 18% overall yields, respectively.

4. Experimental section

4.1. Material and methods

Prunus communis L. var. *dulcis* Borkh was obtained from Xinjiang, China. *Prunus armeniaca*, *Malus pumila*, and *Eriobotrya japonica* were purchased from market as fresh fruits. All other chemicals were of the highest purity, commercially available, and used without further purification unless otherwise mentioned. NMR spectra were recorded on a Bruker AM 300 spectrometer (300 MHz). The ^1H NMR chemical shifts are reported relative to 0 (TMS). ^{13}C NMR chemical shifts are reported relative to the center of the solvent resonance 77.0 ($CDCl_3$). Mass spectra were recorded on a Bruker APEXIII 7.0 TESLA FTMS using ESI mode. IR spectra were recorded on a Digital FTIR instrument. Optical rotations were measured using Perkin–Elemer 241 MC polarimeter or Jasco P-1030.

4.2. Preparation of defatted *Prunus communis* L. var. *dulcis* Borkh powder

Prunus communis L. var. *dulcis* Borkh (100 g) was soaked in distilled water (200 mL) for 4 h then air-dried, peeled, and homogenized in cold ethyl acetate. The resultant powder was collected by filtration, subsequently washed with ethyl acetate (2×100 mL) and di-*iso*-propyl ether (IPE) (2×60 mL), and stored in a refrigerator for use.

4.3. (*R*)-4-Methylsulfanyl-mandelonitrile (5)

In a well-ventilated hood, to a 25 mL round-bottomed flask were added 4-methylsulfanyl-benzaldehyde (400 mg, 2.6 mmol), the above-prepared *P. dulcis* Borkh kernel powder (150 mg), and HCN in IPE (1.5 equiv, 5 mL, added by a syringe) (caution: highly toxic! For details, see http://www.cdc.gov/niodh/ipcsneng/neng0492.html). The resulting mixture was stirred at room temperature for 12 h, filtered, and washed with ethyl acetate. The combined organic phase was washed with aqueous saturated $FeCl_3$ solution until the color of $FeCl_3$ kept unchanged, dried over Na_2SO_4, and evaporated under reduced pressure. Flash chromatography on silica gel (ethyl acetate/petroleum ether=1:2) of the residue gave the title compound as a white solid (yield 98%, ee=96%). Crystallization from petroleum ether and diethyl ether gave **5** as colorless crystals (920 mg, 86% yield, ee=99%).

Mp 73–74 °C; $[\alpha]_D^{20}$ 50.4 (*c* 0.83, $CHCl_3$), ee=99%. Determined on chiral HPLC after acetylation of the obtained cyanohydrins (Chiralcel AD, 15% IPA/hexanes, 0.7 mL/min, t_R (major)=11.1 min, t_R (minor)=12.1 min); FTIR (KBr): 3390, 2917, 1602, 1496, 1405, 1238, 1184, 1094, 1029, 1014, 932, 838, 801, 618, 502 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.50 (s, 3H, CH_3), 3.00 (br s, 1H, O*H*), 5.49 (s, 1H, C*H*OH), 7.29 (d, *J*=8.5 Hz, 2H, Ar), 7.43 (d, *J*=8.5 Hz, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.3, 63.2, 118.7, 126.5, 127.1, 131.7, 141.1; EIMS: *m*/*z* (rel intensity %) 181 (M^+, 2.5), 179 (M^+, 79), 162 (M^+−OH, 39), 153 (M^+−CN, 55), 152 (M^+−HCN, 100), 151 (M^+−HCN−H, 88), 132 (29), 123 (16), 109 (20), 105 (17), 91 (7), 77 (17). Anal. Calcd for C_9H_9NOS: C, 60.31; H, 5.06; N, 7.82. Found: C, 60.40; H, 5.06; N, 7.73. The acetylation was carried out by treating the cyanohydrin with acetyl chloride in pyridine to obtain a clear oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.15 (s, 3H, CH_3CO), 2.50 (s, 3H, SCH_3), 6.36 (s, 1H, C*H*O), 7.29 (d, *J*=8.5 Hz, 2H, Ar), 7.43 (d, *J*=8.5 Hz, 2H, Ar); EIMS: *m*/*z* (rel intensity %) 221 (M^+, 93), 179 (38), 162 (100), 161 (98), 151 (16), 147 (44), 146 (32), 132 (9).

4.4. (*R*)-*O*-Methoxy-*iso*-propyl-4-methylsulfanyl-mandelonitrile (6)

To a round-bottomed flask were added compound **5** (900 mg, 5.0 mmol), 2-methoxypropene (2 mL, 20 mmol), diethyl ether (5 mL), and $POCl_3$ (20 mg, 0.1 mmol). The resulting mixture was stirred at room temperature for 2 h. Et_3N (1 mL) was added and stirring was continued for 30 min. The organic phase was washed with aqueous saturated NaCl solution (3×50 mL), dried (Na_2SO_4), and evaporated under reduced pressure. Flash chromatography on silica gel (ethyl acetate/petroleum ether=1:10) afforded **6** as a yellow oil (1.09 g, 96% yield).

$[\alpha]_D^{20}$ 25.2 (*c* 0.83, $CHCl_3$) (Chiralcel AD, 2% IPA/hexanes, 0.7 mL/min, t_R (major)=14.1 min, t_R (minor)=17.7 min); FTIR (KBr): 2993, 2924, 2835, 1594, 1562, 1495, 1438, 1378, 1268, 1216, 1146, 1095, 1014, 876, 838, 813, 766, 544 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.4 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 2.50 (s, 3H, SCH_3), 3.2 (s, 3H, OCH_3), 5.42 (s, 1H, C*H*), 7.25–7.41 (m, 4H, Ar–*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.3, 24.3, 24.9, 49.8, 60.9, 102.8, 119.2, 126.4, 127.5, 129.9, 140.4;

EIMS: *m*/*z* (rel intensity %) 251 (M^+, 1.63), 219 ($M^+-H-OCH$, 2.01), 179 (100.00), 162 (76.27), 151 (21.93), 132 (82.14), 109 (22.98), 105 (28.48), 86 (49.45), 45 (27.76); HRMS calcd for $C_{13}H_{17}NO_2S$: *m*/*z* 251.0980, found: 251.0973.

4.5. (2*R*,3*R*)-2-Benzylamino-3-hydroxy-3-(4-methylsulfanylphenyl)-propionitrile·HCl (7)

Under argon atmosphere, to a dried three-necked flask containing **6** (3.6 g, 14 mmol) and anhydrous diethyl ether (90 mL) was added dropwise DIBAL-H (35 mL, 1 M in toluene) at −70 °C. The mixture was stirred at the same temperature for 2.5 h and then was added NH_4Br (3.43 g) in MeOH (50 mL). After removal of the dry ice/acetone bath was added benzylamine (7.5 mL). The mixture was stirred at room temperature for 1 h, cooled in an ice bath, and was added a solution of NH_4Br (4.2 g) and NaCN (2.1 g) in MeOH (90 mL) (caution must be taken: HCN formed in situ!) and stirred for another 1.5 h. MeOH was removed below 30 °C, and then aqueous 2 N NaOH (100 mL) was added and extracted with diethyl ether (4×60 mL). The combined organic phase was washed with water (2×15 mL) and aqueous saturated NaCl solution (2×15 mL), and dried (Na_2SO_4). Column chromatography on silica gel (ethyl acetate/petroleum ether=1:6) to remove the benzylamine afforded pale yellow oil, which was dissolved in EtOH (100 mL) and then 1 N HCl (20 mL) was added. Evaporation under reduced pressure to remove the ethanol and co-evaporation with toluene gave a pale yellow solid. Crystallization from *iso*-PrOH produced **7** as white crystals (3.46 g, 75% yield). Mp 156–158 °C (decomposed); $[\alpha]_D^{20}$ −36.4 (*c* 0.85, CH_3OH); FTIR (KBr): 3308, 3037, 2920, 2703, 2621, 2532, 2322, 1683, 1602, 1496, 1439, 1404, 1329, 1312, 1286, 1236, 1192, 1091, 1066, 1050, 1029, 966, 816, 748, 697, 625 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz): δ 2.52 (s 3H), 4.47 (AB, *J*=28 Hz, 2H), 4.70 (d, *J*=9 Hz, 1H), 5.11 (d, *J*=9 Hz, 1H), 7.33–7.58 (m, 9H); ESIMS: *m*/*z* (rel intensity %): 299.0 (M^++H); HRMS calcd for $C_{17}H_{19}OSN_2$ (M+H): *m*/*z* 299.1218, found: 299.1213. Because of the low solubility and equilibrium between amine and ammonium salt, we failed to collect a clear ^{13}C NMR of **7**. Therefore, 100 mg of **7** was neutralized with NaOH to afford the corresponding free base as a clear oil. $[\alpha]_D^{20}$ −113.8 (*c* 0.85, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 2.47 (s, 3H, SC*H*$_3$), 3.56 (d, *J*=7.8 Hz, 1H, C*H*CN), 3.93 (dd, *J*=69.0, 13.2 Hz, 2H, Ar–C*H*$_2$), 4.66 (d, *J*=7.8 Hz, 1H, C*H*OH), 7.23 (d, *J*=8.1 Hz, 2H, Ar–*H*), 7.31–7.34 (m, 7H, Ar–*H*), de>20 (^1H NMR does not show the *erythro* isomer); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 15.5, 51.2, 56.5, 73.0, 117.9, 126.4, 127.3, 127.8, 128.3, 128.7, 134.7, 137.6, 139.6; the *erythro* isomer could be isolated with 5% yield when the hydrocyanation reaction was conducted at room temperature. ^1H NMR ($CDCl_3$, 300 MHz): δ 2.49 (s, 3H, SC*H*$_3$), 3.66 (d, *J*=3.6 Hz, 1H, C*H*CN), 4.47 (dd, *J*=81.9, 13.5 Hz, 2H, Ar–C*H*$_2$), 4.94 (d, *J*=3.6 Hz, 1H, C*H*OH), 7.23–7.38 (m, 9H, Ar–*H*).

4.6. (4*R*,5*R*)-2,3,4,5-Tetrahydro-5-(4-methylsulfanylphenyl)-2-oxo-3-benzyl-4-oxazole-carbonitrile (8)

In a stirred solution of **7** (0.6 g, 1.8 mmol) in methylene chloride (7 mL) was added triethylamine (0.1 mL). The mixture was stirred for 30 min, *N*,*N*′-carbonyldiimidazole (0.6 g, 3.6 mmol) was added, and stirring was continued overnight. Water (5 mL) was added under stirring for phase separation. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3×30 mL). The combined organic phase was washed with 0.1 N HCl and dried over anhydrous sodium sulfate. Evaporation under reduced pressure gave a crude (0.32 g). Crystallization from a mixture of methylene chloride and petroleum ether (1:8) afforded **8** (276 mg, 86% yield) as white crystals.

$[\alpha]_D^{20}$ 160.1 (*c* 0.81, $CHCl_3$); FTIR (KBr): 3087, 3030, 2921, 1748, 1602, 1495, 1437, 1410, 1364, 1325, 1181, 1039, 1050, 1014, 991, 808, 760, 670, 564 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 3H, SC*H*$_3$), 4.06 (d, *J*=6.3 Hz, 1H, C*H*CN), 4.20 (d, *J*=14.9 Hz, 1H, Ar–CH*H*), 5.02 (d, *J*=14.9 Hz, 1H, Ar–CH*H*), 5.57 (d, *J*=6.3 Hz, 1H, C*H*O), 7.15–7.38 (m, 9H, Ar–*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 46.4, 51.9, 113.7, 124.8, 125.6, 127.5, 127.9, 128.3, 130.6, 132.5, 140.6, 154.5; EIMS: *m*/*z* (rel intensity %) 324 (M^+), 286 (0.57), 243 (0.52), 215 (1.81), 175 (14.70), 151 (2.77), 91 (100), 77 (4.73), 65 (41.498.08); HRMS (MALDI) calcd for $C_{18}H_{17}N_2O_2S^+$: *m*/*z* 325.1005, found: 325.1020.

4.7. Ethyl (4*R*,5*R*)-2,3,4,5-tetrahydro-5-(4-methylsulfanylphenyl)-2-oxo-3-benzyl-4-oxazolecarboxylate (9)

A mixture of **8** (121 mg, 0.37 mmol) and potassium carbonate in 96% ethanol (3.2 mL) was stirred at room temperature for 6 h. Potassium carbonate was removed by filtration and to the filtrate was added hydrochloric acid (1 N, 3.5 mL). The solution was stirred for 30 min and then was added saturated aqueous sodium bicarbonate (4 mL). The mixture was diluted with methylene chloride (30 mL) and water (30 mL), and the organic phase was separated. The aqueous phase was extracted with methylene chloride (2×30 mL). The combined organic phase was washed with water and dried over sodium sulfate. Removal of the solvent gave a crude product, which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=4:1) to afford **9** (99 mg, 80% yield) as a yellow oil.

Mp 64–65 °C; $[\alpha]_D^{20}$ 154.4 (*c* 0.90, $CHCl_3$); FTIR (KBr): 1752, 1602, 1495, 1436, 1417, 1289, 1226, 1182, 1091, 1064, 1043, 819, 757, 704, 617, 500 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (t, *J*=7.2 Hz, 3H, C*H*$_3$), 2.47 (s, 3H, SC*H*$_3$), 3.90 (d, *J*=5.4 Hz, 1H, C*H*COOEt), 4.21–4.30 (m, 3H, Ar–C*H*H and OC*H*$_2$), 4.96 (d, *J*=14.4 Hz, 1H, Ar–C*H*H), 5.42 (d, *J*=5.4 Hz, 1H, C*H*O), 7.14–7.31 (m, 9H, Ar–*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 15.3, 47.3, 62.2, 63.4, 76.6, 125.8, 126.4, 128.1, 128.3, 128.8, 134.3, 134.7, 140.0, 157.0, 168.9. Anal. Calcd for $C_{20}H_{21}NO_4S$: C, 64.67; H, 5.70; N, 3.77. Found: C, 64.85; H, 5.76; N, 3.62. HRMS (MALDI) calcd for $C_{20}H_{21}NO_4SNa$: *m*/*z* 394.1084, found: 394.1085.

4.8. (4*R*,5*R*)-2,3,4,5-Tetrahydro-5-(4-methylsulfanylphenyl)-2-oxo-3-benzyl-4-oxazole-methanol (10)

To an ice-cooled solution of **9** (0.95 g, 2.6 mmol) in methanol (50 mL) was added sodium borohydride (0.6 g, 15 mmol). The reaction mixture was warmed to room temperature and stirred for 2 h. Then water (20 mL) was added and methanol was removed under reduced pressure. The residue was extracted with ethyl acetate (160 mL). The organic phase was washed with water (2×10 mL) and saturated brine (2×10 mL), and dried over sodium sulfate. Removal of the solvent gave a crude product (0.89 g). Crystallization from methanol afforded **10** (0.72 g, 85% yield) as a white crystal. $[\alpha]_D^{20}$ 101.5 (*c* 1.2, $CHCl_3$); FTIR (KBr): 3398, 2945, 2916, 2897, 1717, 1602, 1495, 1450, 1434, 1417, 1367, 1249, 1197, 1109, 1081, 1059, 1006, 961, 828, 753, 707, 672, 634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.45 (s, 3H, SC*H*$_3$), 2.90 (br, 1H, O*H*), 3.47–3.50 (m, 1H, C*H*N), 3.57 (dd, *J*=12.6, 3.6 Hz, 1H, C*H*$_2$O), 3.81 (dd, *J*=12.6, 3.6 Hz, 1H, C*H*$_2$O), 4.61 (dd, *J*=134, 15.6 Hz, 2H, Ar–C*H*$_2$), 5.36 (d, *J*=6.3 Hz, 1H, C*H*O), 7.15–7.32 (m, 9H, Ar–*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.6, 51.3, 56.6, 73.1, 117.9, 126.5, 127.3, 127.8, 128.3, 128.7, 134.8, 137.6, 139.6. Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.63; H, 5.83; N, 4.17. HRMS (MALDI) calcd for $C_{18}H_{19}NO_3SNa$: *m*/*z* 352.0978, found: 352.0973.

4.9. (4*R*,5*R*)-2,3,4,5-Tetrahydro-5-(4-methylsulfonylphenyl)-2-oxo-3-benzyl-4-oxazole-methanol (11)

To a solution of **10** (140 mg, 0.42 mmol) in tetrahydrofuran (15 mL) was added *m*-chloroperbenzoic acid (350 mg, 1.2 mmol).

The mixture was stirred at temperature for 2 h. The solvent was removed by rotatory evaporator. The residue was dissolved in ethyl acetate (100 mL). The solution was washed with saturated aqueous sodium sulfite (10 mL), water (10 mL), and saturated brine (2×10 mL), and dried over sodium sulfate. Column chromatography on silica gel (petroleum ether/ethyl acetate=1:2) afforded **11** (145 mg, 94% yield) as a white solid.

$[\alpha]_D^{20}$ 91.3 (*c* 1.42, $CHCl_3$); FTIR (KBr): 3495, 1738, 1725, 1454, 1422, 1324, 1305, 1247, 1153, 1087, 1055, 952, 775, 709, 669, 589, 564 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.50 (br, 1H, O*H*), 3.06 (s, 3H, SO_2CH_3), 3.49–3.53 (m, 1H, C*H*N), 3.70 (dd, *J*=12.0, 3.0 Hz, 1H, CH_2O), 3.84 (dd, *J*=12.0, 3.0 Hz, 1H, CH_2O), 4.61 (dd, *J*=110, 15.3 Hz, 2H, Ar–CH_2), 5.50 (d, *J*=5.7 Hz, 1H), 7.28–7.37 (m, 5H, Ar–*H*), 7.49 (d, *J*=8.7 Hz, 2H, Ar–*H*), 7.90 (d, *J*=8.7 Hz, 2H, Ar–*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.4, 46.8, 60.2, 64.0, 126.5, 127.9, 128.1, 128.3, 129.1, 135.72, 140.9, 144.9, 157.9; ESIMS: *m*/*z* ($M+Na^+$) (384.10); HRMS (MALDI) calcd for $C_{18}H_{20}NO_5S^+$: *m*/*z* 362.1057, found: 362.1063.

4.10. (2*R*,3*R*)-2-Benzylamino-3-(4-methylsulfonylphenyl)-propane-1,3-diol (12)

To a solution of **11** (110 mg, 0.30 mmol) in ethanol (5 mL) was added aqueous potassium hydroxide (4 N, 5 mL). The mixture was heated in reflux under argon atmosphere for 45 min and cooled to room temperature. Ethanol was evaporated and the residue was extracted with methylene chloride (3×30 mL). The combined organic phase was washed with water (8 mL) and saturated brine (2×8 mL), and dried over sodium sulfate. Purification of the crude product by column chromatography on silica gel (ethyl acetate) afforded **12** (98 mg, 96% yield) as a white solid.

$[\alpha]_D^{20}$ −47.1 (*c* 1.5, ethanol); FTIR (KBr): 3467, 2927, 1653, 1600, 1456, 1406, 1307, 1150, 1089, 958, 771, 701, 544 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.74–2.76 (m, 1H, C*H*N), 3.05 (s, 3H, SO_2CH_3), 3.43 (dd, *J*=11.4, 3.9 Hz, 1H, CH_2O), 3.70 (dd, *J*=44, 13.2 Hz, 2H, Ar–CH_2), 3.75 (dd, *J*=11.4, 3.9 Hz, 1H, CH_2O), 4.74 (d, *J*=6.9 Hz, 1H, C*H*O), 7.22–7.35 (m, 5H, Ar–*H*), 7.58 (d, *J*=9.0 Hz, 2H, Ar–*H*), 7.90 (d, *J*=9.0 Hz, 2H, Ar–*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.51, 51.63, 63.30, 63.56, 71.29, 71.35, 79.24, 81.47, 127.58, 127.79, 128.16, 128.68, 139.05, 140.10, 147.95; ESIMS: *m*/*z* ($M+H^+$) 336.15; HRMS (ESI) calcd for $C_{17}H_{22}NO_4S$: *m*/*z* 336.1264, found: 336.1271.

4.11. Thiamphenicol (2)

To a solution of **12** (35 mg, 0.10 mmol) in ethanol (3 mL) were added concd hydrochloric acid (0.05 mL) and 10% Pd/C (20 mg). The hydrogenation was carried out at room temperature in atmospheric hydrogen for 2 h. The catalyst was separated via filtration and ethanol was removed. To the residue were added anhydrous methanol (1 mL), ethyl dichloroacetate (0.2 mL, 1.5 mmol), and triethylamine (25 μL). The mixture was stirred at 30 °C for 6 h. The solvent was removed by evaporation. Purification of the crude product by column chromatography on silica gel (methylene chloride/methanol=9:1) afforded **2** (38 mg, 96% yield) as a white solid.

Mp 164–165 °C; $[\alpha]_D^{20}$ 12.5 (*c* 0.38, ethanol) (lit.[1] mp 164.3–166.3 °C; $[\alpha]_D^{20}$ 12.9 (*c* 1.0, ethanol)); FTIR (KBr): 3493, 3449, 3258, 3080, 2918, 1691, 1561, 1408, 1281, 1144, 1067, 1034, 974, 808, 771, 753, 684, 545 cm^{-1}; ^1H NMR (300 MHz, CD_3OD): δ 3.07 (s, 3H, SO_2CH_3), 3.59 (dd, *J*=10.8, 6.0 Hz, 1H, CH_2O), 3.81 (dd, *J*=10.8, 7.2 Hz, 1H, CH_2O), 4.10–4.14 (m, 1H, C*H*N), 5.14 (d, *J*=3.3 Hz, 1H, C*H*O), 6.23 (s, 1H, $CHCl_2$), 7.66 (d, *J*=8.4 Hz, 2H, Ar–*H*), 7.88 (d, *J*=8.4 Hz, 2H, Ar–*H*); ^{13}C NMR (75 MHz, CD_3OD): δ 43.1, 57.2, 60.9, 66.1, 70.1, 126.8, 126.9, 139.5, 149.0, 165.1; HRMS (MALDI) calcd for $C_{12}H_{15}NO_5SCl_2Na$: *m*/*z* 377.99402, found: 377.9937.

4.12. (4*R*,5*R*)-5-(4-Methylsulfanylphenyl)-2-oxo-3-benzyl-4-fluoromethyl-oxazolidine (13)

Under argon atmosphere, to a flask containing **10** (255 mg, 0.77 mmol) was added anhydrous THF (10 mL). To the resultant solution, DAST (0.3 g, 1.8 mmol) was then added slowly via a syringe. The reaction mixture was stirred at room temperature for 12 h. The reaction was quenched by adding 2 N NaOH (10 mL) and extracted with ethyl acetate (3×30 mL). The combined organic phases were washed with water (8 mL) and saturated brine (2×8 mL), and dried over sodium sulfate. The solvent was removed and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate=4:1) to afford **13** (260 mg, 90% yield) as a yellow solid.

$[\alpha]_D^{20}$ 132.2 (*c* 0.65, $CHCl_3$); FTIR (KBr): 3004, 2878, 2737, 2626, 1771, 1754, 1559, 1459, 1371, 1216, 1108, 1038, 933, 750, 698, 548 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.45 (s, 3H, SCH_3), 3.57–3.66 (m, 1H, C*H*N), 4.26 (d, *J*=15.0 Hz, 1H, Ar–CH_2), 4.31–4.62 (m, 2H, CH_2F), 4.89 (d, *J*=15.0 Hz, 1H, Ar–CH_2), 5.20 (d, *J*=6.6 Hz, 1H, C*H*O), 7.15–7.37 (m, 9H, Ar–*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.3, 46.7, 61.9 (d, J_{C-C-F}=15.1 Hz), 75.7 (d, J_{C3-F}=4.4 Hz), 80.4 (d, J_{C-F}=132 Hz), 126.2, 126.5, 127.9, 128.1, 128.8, 134.0, 135.3, 140.1, 157.4. Anal. Calcd for $C_{18}H_{18}FNO_2S$: C, 65.24; H, 5.47; N, 4.23. Found: C, 65.04; H, 5.63; N, 4.02. HRMS (EI) calcd for $C_{18}H_{18}NO_2FS$: *m*/*z* 331.1042, found: 331.1045.

4.13. (4*R*,5*R*)-5-(4-Methylsulfonylphenyl)-2-oxo-3-benzyl-4-fluoromethyl-oxazolidine (14)

To a solution of **14** (150 mg, 0.45 mmol) in THF (6 mL) was added *m*-perbenzoic acid (250 mg, 0.90 mmol). The reaction mixture was stirred at room temperature for 2 h and concentrated to remove THF. The residue was dissolved in ethyl acetate (100 mL). The solution was washed with saturated sodium sulfite (10 mL), water (10 mL), and saturated brine (2×10 mL), and dried over sodium sulfate. Removal of the solvent followed by column chromatography on silica gel (petroleum ether/ethyl acetate=3:2) afforded **14** (149 mg, 89% yield) as a white solid.

$[\alpha]_D^{20}$ 99.0 (*c* 1.10, $CHCl_3$); FTIR (KBr): 2970, 2923, 1746, 1457, 1421, 1308, 1212, 1150, 1089, 1041, 1032, 956, 825, 756, 706, 582 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.05 (s, 3H, SO_2CH_3), 3.59–3.68 (m, 1H, C*H*N), 4.27 (d, *J*=15.3 Hz, 1H, Ar–CH_2), 4.31–4.62 (m, 2H, CH_2F), 4.86 (d, *J*=15.3 Hz, 1H, Ar–CH_2), 5.37 (d, *J*=6.0 Hz, 1H, C*H*O), 7.25–7.34 (m, 5H, Ar–*H*), 7.48 (d, *J*=8.4 Hz, 2H, Ar–*H*), 7.95 (d, *J*=8.4 Hz, 2H, Ar–*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.4, 47.0, 61.8 (d, J_{C-C-F}=19 Hz), 75.2 (d, J_{C3-F}=4.1 Hz), 80.4 (d, J_{C-F}=132 Hz), 126.4, 128.0, 128.2, 128.4, 129.1, 135.1, 141.3, 144.0, 157.0; ESIMS: *m*/*z* ($M+Na^+$) 386.10; HRMS (MALDI) calcd for $C_{18}H_{19}NO_4FS^+$: *m*/*z* 364.1019, found: 364.1013.

4.14. (1*R*,2*R*)-1-(4-Methylsulfonylphenyl)-2-benzylamino-3-fluoro-1-propanol (15)

To a solution of **14** (60 mg, 0.165 mmol) in dioxane (3 mL) was added 8 N sulfuric acid (3 mL). The solution was heated in a sealed tube under argon atmosphere at 140 °C for 6 h. After being cooled to room temperature, the tube was cooled in an ice-water bath and aqueous 4 N sodium hydroxide (14 mL) was added. The mixture was extracted with methylene chloride (3×30 mL). The combined organic phase was washed with water (8 mL) and saturated brine (2×8 mL), and dried over sodium sulfate. Removal of the solvent followed by column chromatography on silica gel (petroleum

ether/ethyl acetate=1:1) afforded **13** (42 mg, yield 75%) as a white solid.

$[\alpha]_D^{20}$ −79.2 (*c* 1.10, $CHCl_3$); FTIR (KBr): 3469, 3311, 2924, 1599, 1456, 1318, 1148, 1087, 962, 838, 775, 746, 547 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.71–2.83 (m, 1H, C*H*N), 3.05 (s, 3H, SO_2CH_3), 3.83 (dd, *J*=56.0, 12.9 Hz, 2H, Ar–CH_2), 4.10–4.60 (m, 2H, CH_2F), 4.62 (d, *J*=7.9 Hz, 1H, C*H*O), 7.28–7.35 (m, 5H, Ar–*H*), 7.59 (d, *J*=8.4 Hz, 2H, Ar–*H*), 7.92 (d, *J*=8.4 Hz, 2H, Ar–*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.5, 51.6, 63.4 (d, J_{C-C-F}=19 Hz), 71.3 (d, J_{C3-F}=4.6 Hz), 80.4 (d, J_{C-F}=168 Hz), 127.6, 127.8, 128.2, 128.7, 139.1, 140.1, 148.0; ESIMS: *m*/*z* ($M+H^+$) 338.0; HRMS (ESI) calcd for $C_{17}H_{21}N_1O_3FS$: *m*/*z* 338.1221, found: 338.1221.

4.15. Florfenical (3)

To a solution of **15** (22 mg, 0.065 mmol) in ethanol (3 mL) were added concd sulfuric acid (0.05 mL) and 10% Pd/C (12 mg). The suspension was hydrogenated under atmospheric hydrogen at room temperature for 2 h. The Pd/C was separated via filtration and ethanol was removed by evaporation. Anhydrous methanol (1 mL) was added to the residue. To the solution were added ethyl dichloroacetate (0.12 mL) and triethylamine (15 μL). The reaction mixture was stirred at 30 °C for 6 h. Removal of the solvent followed by purification of the residue on silica gel (petroleum ether/ethyl acetate=1:1) afforded **14** (19 mg, 96% yield) as a white solid.

Mp 151–152 °C; $[\alpha]_D^{20}$ −18.0 (*c* 0.35, DMF) (lit.[5b] mp 151–152 °C, $[\alpha]_D^{20}$ −18.4 (*c* 0.5, DMF)); FTIR (KBr): 3455, 3320, 2931, 1683, 1535, 1276, 1190, 1150, 1091, 1018, 859, 809, 769, 537 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.17 (s, 3H, CH_3), 4.26–4.33 (m, 1H, C*H*NHCO), 4.44–4.76 (m, 2H, CH_2F), 4.99 (d, *J*=2.4 Hz, 1H, C*H*OH), 6.46 (s, 1H, CO*H*Cl_2), 7.62 (d, *J*=8.4 Hz, 2H, Ar–*H*), 7.85 (d, *J*=8.4 Hz, 2H, Ar–*H*), 8.62 (d, *J*=9 Hz, 1H, N*H*CO); ^{13}C NMR (75 MHz, DMSO-d_6): δ 44.1, 55.1 (d, J_{C-C-F}=19 Hz), 66.7, 69.8 (d, J_{C3-F}=5.3 Hz), 82.8 (d, J_{C-F}=169 Hz), 127.0, 127.6, 140.0, 148.4, 164.2; ESIMS: *m*/*z* ($M+Na^+$) 380.0; HRMS (ESI) calcd for $C_{12}H_{14}N_1O_4FSCl_2Na$: *m*/*z* 399.9897, found: 379.9906.

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Supplementary data

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