An Efficient Enantioselective Synthesis of Florfenicol Based on Sharpless Asymmetric Dihydroxylation

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Abstract: An efficient and highly enantioselective synthesis of florfenicol via a new intermediate *threo*-dihydroxy ester, with a Sharpless asymmetric dihydroxylation as the key step, is reported. A ring-opening/reduction strategy avoids the formation of a chlorinated byproduct that occurs in Schumacher's phenyloxazoline procedure. The overall yield of florfenicol by this new process is 23% based on 4-(methylsulfonyl)benzaldehyde.

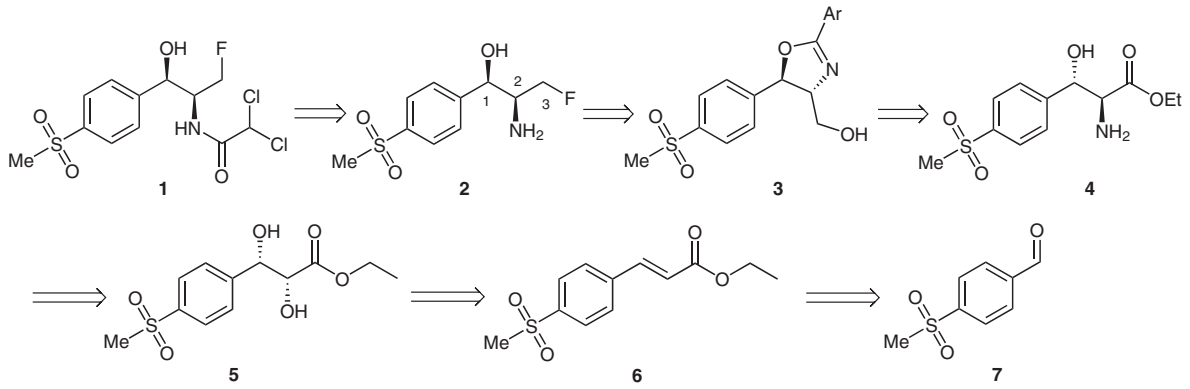
Key words: halogenation, heterocycles, asymmetric synthesis, sulfones, drugs

As part of our studies on asymmetric syntheses in the field of chiral pharmaceutical and natural products, the enantioselective synthesis of florfenicol (**1**), which has a unique structure and broad-spectrum antibacterial activity, has been an important target of our group.[1] We have recently developed two different asymmetric approaches to the synthesis of **1** that feature a vanadium-catalyzed asymmetric epoxidation[2] and an asymmetric catalytic aziridination strategy,[3] respectively. The main problem with these two strategies is the difficulty in recovering the chiral ligands that are used in the catalytic asymmetric transformations and which precludes the application of these processes in large-scale syntheses of florfenicol. There remains, therefore, a need for an efficient and economic approach to the synthesis of florfenicol. Here, we report an efficient and highly enantioselective route to florfenicol that uses a Sharpless asymmetric dihydroxylation[4] as its key step.

Our retrosynthetic plan for **1** is shown in Scheme 1. We hypothesized that intermediate fluoro compound **2** might be synthesized from alcohol **4** by inversion of the configuration of the hydroxyl group at the benzylic position via the intermediate oxazoline **3**. The stereocenters of (2*S*,3*S*)-**4** could be elaborated through a selective sulfonation/sodium azide substitution strategy.[5] The chiral dihydroxy ester **5** might be obtained from acrylate **6** by means of a Sharpless asymmetric dihydroxylation (AD).

Our enantioselective synthesis of florfenicol (**1**) commenced from commercially available 4-(methylsulfonyl)benzaldehyde (**7**). Knoevenagel condensation of **7** with malonic acid proceeding smoothly in the presence of piperidine to give (2*E*)-3-[4-(methylsulfonyl)phenyl]acrylic acid (**8**) in high yield (Scheme 2).[6] Refluxing of **8** with thionyl chloride in ethanol or methanol then gave the corresponding cinnamates **6** and **9** in excellent yields. When the reaction was carried out at room temperature, the desired products were not detected.

Sharpless asymmetric dihydroxylation of ethyl ester **6** with AD-mix-α reagent (1.4 g/mmol) and 1.0 equivalent of methanesulfonamide in a 1:1 mixture of *tert*-butanol and water at 25 °C for 20 hours gave the dihydroxy compound **5** in 95% yield and 98.7% enantiomeric excess



Scheme 1 Retrosynthetic analysis for florfenicol (**1**)

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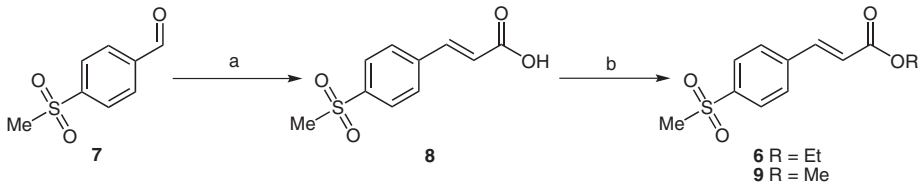
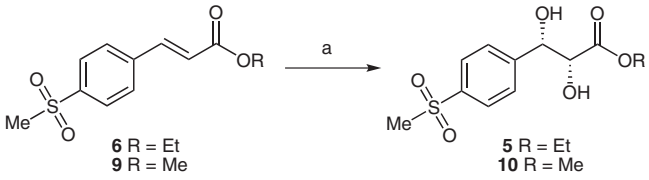


Scheme 2 *Reagents and conditions*: (a) malonic acid, piperidine, py, reflux, 2 h, 81%; (b) $SOCl_2$, ROH, reflux, overnight, 92% (for **6**), 93% (for **9**).

(Table 1, entry 1), whereas similar treatment of the corresponding methyl ester **9** gave the corresponding dihydroxy derivative **10** in only 52% yield (after extraction ten times with ethyl acetate) and 97.8% enantiomeric excess (entry 2). The yield of the methyl ester **10** was much lower than that of its ethyl counterpart **5** because of the greater solubility of the former in water; the calculated[7] octanol–water partition coefficient (log *P*) of **10** is –1.66 ± 0.41, which is much lower than that of **5** (–1.12 ± 0.41).

Because the more acidic α-hydroxy group reacted preferentially to form a monosulfonate,[5] selective sulfonation of



Scheme 3 *Reagents and conditions*: (a) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH–H_2O (1:1), r.t., 20 h.

Table 1 Results of the Sharpless AD Reaction of Cinnamates **6** and **9**

Entry[a]	Reactant	R	Products	Yield (%)[b]	ee (%)
1	**6**	Et	(2*R*,3*S*)-**5**	95	98.7[c]
2	**9**	Me	(2*R*,3*S*)-**10**	52	97.8[d]

[a] Reaction conditions: cinnamate (8.5 mmol), AD-mix-α and $MsNH_2$ (8.5 mmol), *t*-BuOH–H_2O (1:1), r.t., 20 h.
[b] Isolated yield after chromatography (silica gel).
[c] By HPLC [CHIRALPAK AD-H (25 cm × 0.46 cm i.d.); hexane–*i*-PrOH (80:20), 1.0 mL/min; UV wavelength: 220 nm; 35 °C].
[d] By HPLC [CHIRALPAK IA (25 cm × 0.46 cm i.d.); hexane–EtOH–Et_2NH (60:40:0.1), 0.8 mL/min; UV wavelength: 220 nm; 35 °C].

(2*R*,3*S*)-**5** with 1.0 equivalent of 4-nitrobenzenesulfonyl chloride in the presence of 2.0 equivalents of triethylamine in dichloromethane at 0–4 °C gave the α-hydroxy sulfonate **11** in 76% isolated yield (Scheme 4). Subsequently, sulfonate **11** underwent substitution with 1.2 equivalents of sodium azide in dry *N*,*N*-dimethylformamide under argon at 55 °C to give the (2*S*,3*S*)-α-azido β-hydroxy ester **12** and its (2*R*,3*S*)-epimer **12′** in a ratio of 3:1. Reduction of the mixture of **12** and **12′** with 10% Pd/C in ethanol under hydrogen at room temperature for two hours gave a mixture of the corresponding of amines **4** and **4′** in a ratio of 3:1. Treatment of this mixture with 4-methoxybenzoyl chloride in dichloromethane with subsequent separation by column chromatography gave the amides **13** and **13′** in 65 and 17% yields, respectively.

The structure of the (2*R*,3*S*)-sulfonate **11** was unambiguously determined by X-ray crystallography (Figure 1).[8]

Cyclization of amide **13** with thionyl chloride in anhydrous chloroform at 45 °C for 0.5 hours gave the *trans*-oxazoline **14** in 91% yield (Scheme 5). The inversion of

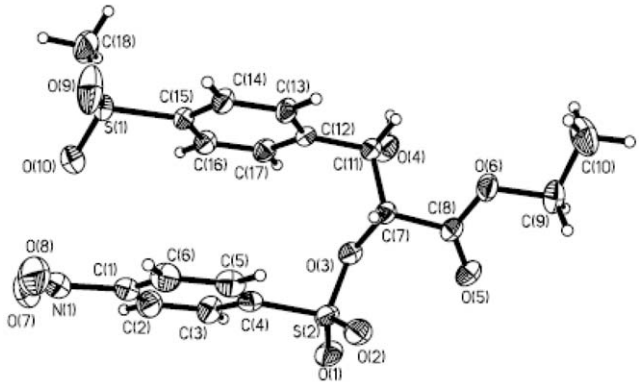
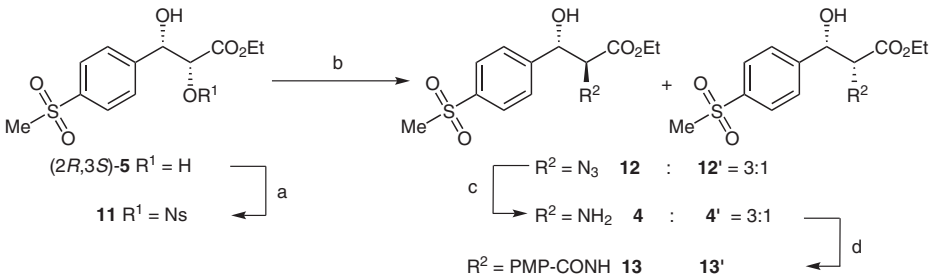
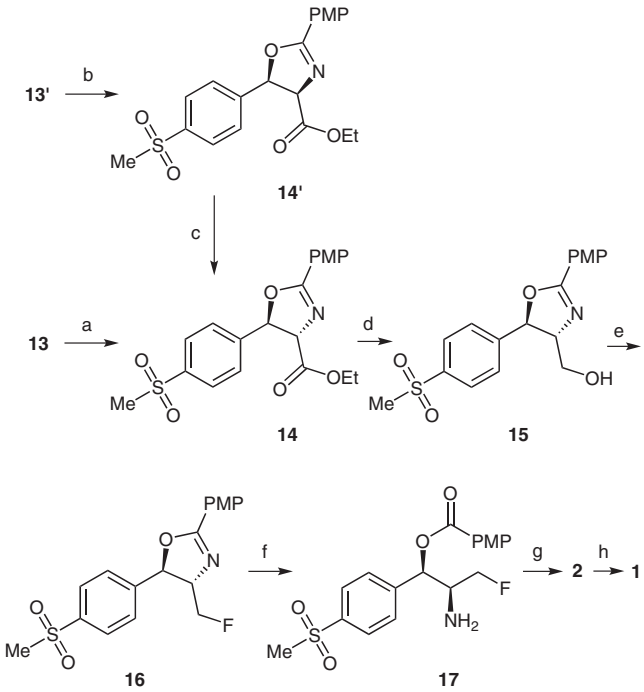


Figure 1 ORTEP diagram for (2*R*,3*S*)-sulfonate **11**



Scheme 4 Reagents and conditions: (a) 4-$O_2NC_6H_4SO_2Cl$, Et_3N, CH_2Cl_2, 0–4 °C, 10 h, 76%; (b) NaN_3, DMF, 55 °C, overnight; (c) H_2, 10% Pd/C, EtOH, r.t., 2 h; (d) 4-$MeOC_6H_4COCl$, Et_3N, CH_2Cl_2, 0–4 °C, 10 h, 65% for **13**; 17% for **13′** from **11**.

the configuration at the benzylic position of this compound from *S* to *R* was confirmed from the relationship between the signals from the H-4 and H-5 protons of **14** in its nuclear Overhauser effect (NOE) NMR spectra (Figure 2). The *cis*-oxazoline **14′** was similarly obtained by treatment of **13′** with thionyl chloride, and its configuration was also confirmed by NOE spectroscopy (Figure 2). The *trans*-oxazoline **14** could be prepared from **14′** in 85% yield (based on **13′**) by treatment with sodium ethoxide in a mixture of ethanol and tetrahydrofuran.



Scheme 5 Preparation of florfenicol from amide **13**. *Reagents and conditions*: (a) $SOCl_2$, $CHCl_3$, 45 °C, 0.5 h, 91%; (b) $SOCl_2$, $CHCl_3$, 45 °C, 0.5 h; (c) NaOEt, EtOH, THF, r.t., 1 h, 85% (from **13′**); (d) $NaBH_4$, $CaCl_2$, EtOH, 0 °C to r.t., 5 h, 82%; (e) Ishikawa's reagent ($F_3CCHFCF_2NEt_2$), CH_2Cl_2, sealed tube, 100 °C, 3 h, 92%; (f) 1 M HCl, THF, r.t., 3 h; (g) KBH_4, LiCl, THF, 50 °C, overnight; (h) $Cl_2CHCOCl$, NEt_3, CH_2Cl_2, EtOH, 0 °C, 3 h, 75% (three steps).

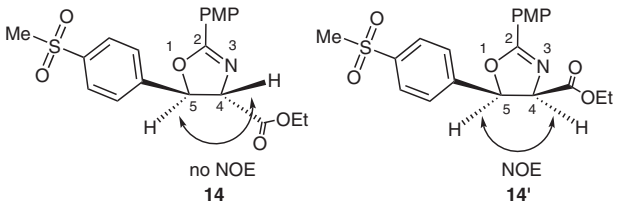


Figure 2 Nuclear Overhauser effect correlation of **14** and **14′**

Reduction of oxazoline **14** with calcium borohydride (prepared in situ from sodium borohydride and calcium chloride) in ethanol at 0 °C gave the alcohol **15** in 82% yield. This was converted into the fluoro compound **16** in 92% yield by fluorination with Ishikawa's reagent (*N*,*N*-diethyl-1,1,2,3,3,3-hexafluoropropylamine) in dichloromethane in a sealed tube at 100 °C.

Hydrolysis of fluoro compound **16** with 1 M hydrogen chloride in tetrahydrofuran at 45 °C for three hours and subsequent evaporation of the solvent gave the fluoro amine **17** as its hydrochloride salt,[9] which formed a colored ninhydrin chromophore on thin-layer chromatography and gave a precipitate on treatment with silver nitrate in aqueous solution. Reduction of the free amine **17** with lithium borohydride (prepared in situ from potassium borohydride and lithium chloride) in tetrahydrofuran gave the corresponding amine **2**. This mild preparation of amine **2** from oxazoline **16** avoids the formation of a chlorinated byproduct that occurs during Schumacher's phenyloxazoline strategy.[10]

Finally, florfenicol (**1**) was obtained in 91% yield by amidation of amine **2** with 1.03 equivalents of dichloroacetic chloride in a mixture of dichloromethane and ethanol at 0 °C for three hours; the total yield for the final three steps was 75%. The spectral data and physical characteristics of the product were in complete agreement with the reported values for florfenicol.[10]

In summary, we developed an efficient enantioselective route to florfenicol (**1**) in 23% overall yield via a new advanced intermediate *threo*-dihydroxy ester **5** and by using Sharpless AD as the key step.

Chiral HPLC was performed on a Shimadzu LC 20 with UV detector SPD-20A. Melting points were determined on a WRS-1 digital melting-point apparatus and are uncorrected. Optical rotations were recorded 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. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 and 100 MHz, respectively, in $CDCl_3$, MeOD, or DMSO-d_6 using TMS or the solvent (MeOD: ^1H, δ = 3.31 ppm; ^{13}C, δ = 49.0 ppm: DMSO-d_6, ^1H, δ = 2.49 ppm, ^{13}C, δ = 39.5 ppm: $CDCl_3$, ^{13}C, δ = 77.0 ppm) as the internal standard. ^{19}F NMR spectra were recorded on a Bruker DMX 500 spectrometer (470 MHz) using CCl_3F (^{19}F, δ = 0.0 ppm) as an external standard. IR spectra were recorded on a Nicolet FT-IR 4200 spectrometer as KBr pellets. Mass spectra were measured on a Waters Quattro Micromass instrument using electrospray ionization (ESI) techniques. Unless otherwise noted, all reactions were conducted in oven-dried glassware under an inert atmosphere of dried argon or N_2. THF was distilled from sodium/benzophenone. Toluene and CH_2Cl_2 were distilled from CaH_2. Cinnamic acid **8** was prepared according to the literature method.[6]

Ethyl (2*E*)-3-[4-(Methylsulfonyl)phenyl]acrylate (6)

A mixture of cinnamic acid **8** (22.6 g, 100 mmol) and EtOH (150 mL) was stirred at r.t. and $SOCl_2$ (14.2 mL, 200 mmol) was added dropwise. The mixture was then refluxed overnight, cooled to r.t., and concentrated. The residue was dissolved in CH_2Cl_2 (130 mL) and the resulting soln was washed with sat. aq $NaCO_3$ and brine then dried (Na_2SO_4), filtered, and concentrated. The residue was crystallized from EtOH–H_2O (1:1) to give yellow needles; yield: 23.3 g (92%); mp 93–94 °C.

FTIR (KBr): 1709, 1644, 1307, 1146, 968, 835, 773, 651, 528 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (t, *J* = 7.2 Hz, 3 H, C*H*$_3$), 3.08 (s, 3 H, SO_2CH_3), 4.29 (q, *J* = 7.2 Hz, 2 H, C*H*$_2$), 6.56 (d, *J* = 16 Hz, 1 H, COC*H*), 7.68–7.72 (m, 3 H, ArC*H* and ArH), 7.96 (d, *J* = 8.4 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.29, 44.45, 60.95, 122.17, 128.02, 128.66, 139.71, 141.47, 142.01, 166.13.

ESI-MS: *m/z* (%) = 255 $[M + H]^+$.

Anal. Calcd for $C_{12}H_{14}O_4S$: C, 56.68; H, 5.55; S, 12.61. Found: C, 56.60; H, 5.59; S, 12.57.

Methyl (2*E*)-3-[4-(Methylsulfonyl)phenyl]acrylate (9)

This compound was prepared by the same procedure as **6** to give yellow needles; yield: 22.3 g (93%): mp 128–129 °C.

FTIR (KBr): 3021, 2955, 2925, 1717, 1639, 1433, 1303, 1149, 966, 770, 651, 530 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.08 (s, 3 H, SO_2CH_3), 3.84 (s, 3 H, OCH_3), 6.56 (d, *J* = 16.4 Hz, 1 H, COC*H*), 7.70–7.74 (m, 3 H, ArC*H* and ArH), 7.97 (d, *J* = 8.4 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.46, 52.04, 121.68, 128.04, 128.70, 139.62, 141.55, 142.32, 166.57.

ESI-MS: *m/z* (%) = 241 $[M + H]^+$.

Anal. Calcd for $C_{11}H_{12}O_4S$: C, 54.99; H, 5.03; S, 13.35. Found: C, 54.93; H, 5.06; S, 13.31.

Ethyl (2*R*,3*S*)-2,3-Dihydroxy-3-[4-(methylsulfonyl)phenyl]propanoate (5)

$K_3[Fe(CN)_6]$ (8.33 g, 25.5 mmol), K_2CO_3 (3.50 g, 25.5 mmol), Sharpless ligand $(DHQ)_2PHAL$ (66 mg, 0.085 mmol), and K_2OsO_4 (6.3 mg, 0.017 mmol) were added to a mixture of *t*-BuOH (80 mL) and H_2O (80 mL), and the resulting mixture was stirred for 5 min. Acrylate **6** (2.16 g, 8.5 mmol) and $MeSO_2NH_2$ (808 mg, 8.5 mmol) were added and the mixture was stirred at r.t. for 20 h. $NaSO_3$ (12 g) was then added and the mixture was stirred for an additional 0.5 h. H_2O (200 mL) was added and the mixture was extracted with EtOAc (3 × 150 mL). The combined organic phase was dried (Na_2SO_4) and concentrated, and the residue was purified by flash column chromatography [silica gel, hexane–EtOAc (1:1 to 1:2)] to give a bright-yellow solid; yield: 2.33 g (95%, 98.7% ee); mp 154–155 °C; $[\alpha]_D^{20}$ +19.5 (*c* 0.66, THF).

FTIR (KBr): 3472, 3053, 3023, 2923, 2856, 1743, 1596, 1408, 1296, 1204, 1147, 1050, 959, 767, 562, 493 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.14 (t, *J* = 7.2 Hz, 3 H, CH_3), 3.18 (s, 3 H, SO_2CH_3), 4.07 (q, *J* = 7.2 Hz, 2 H, CH_2), 4.21 (dd, *J* = 7.2, 3.6 Hz, 1 H, COC*H*), 4.96 (dd, *J* = 5.6, 3.6 Hz, 1 H, ArC*H*), 5.37 (d, *J* = 7.6 Hz, 1 H, O*H*), 5.77 (d, *J* = 5.6 Hz, 1 H, O*H*), 7.62 (d, *J* = 8.0 Hz, 2 H, ArH), 7.85 (*J* = 8.4 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.55, 44.08, 60.73, 74.08, 75.44, 126.85, 128.06, 139.88, 148.64, 172.38.

ESI-MS: *m/z* (%) = 289 $[M + H]^+$.

Anal. Calcd for $C_{12}H_{16}O_6S$: C, 49.99; H, 5.59; S, 11.12. Found: C, 49.89; H, 5.56; S, 11.07.

Methyl (2*R*,3*S*)-2,3-Dihydroxy-3-[4-(methylsulfonyl)phenyl]propanoate (10)

This compound was prepared by the same procedure as **5** to give a bright-yellow solid; yield: 1.21 g (52%, 97.8% ee); mp 125–127 °C; $[\alpha]_D^{25}$ +27.9 (*c* 1.08, MeOH).

FTIR (KBr): 3456, 3368, 3030, 3014, 2929, 1759, 1445, 1299, 1144, 1062, 968, 781, 738, 539 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.18 (s, 3 H, $SOCH_3$), 3.63 (s, 3 H, OCH_3), 4.25 (dd, *J* = 7.2, 3.2 Hz, 1 H, COC*H*), 4.99 (dd, *J* = 5.6, 3.2 Hz, 1 H, ArC*H*), 5.37 (d, *J* = 7.6 Hz, 1 H, O*H*), 5.76 (d, *J* = 6.4 Hz, 1 H, O*H*), 7.63 (d, *J* = 8.4 Hz, 2 H, ArCH), 7.86 (d, *J* = 8.4 Hz, 2 H, ArCH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 44.10, 52.05, 73.91, 75.37, 126.84, 128.02, 139.86, 148.65, 172.89.

ESI-MS: *m/z* (%) = 275 $[M + H]^+$.

Anal. Calcd for $C_{11}H_{14}O_6S$: C, 48.17; H, 5.14; S, 11.69. Found: C, 48.09; H, 5.11; S, 11.63.

Ethyl (2*R*,3*S*)-3-Hydroxy-3-[4-(methylsulfonyl)phenyl]-2-{[(4-nitrophenyl)sulfonyl]oxy}propanoate (11)

4-$O_2NC_6H_4SO_2Cl$ (2.43 g, 11 mmol) was added to a soln of (2*R*,3*S*)-**5** (3.17 g, 11 mmol) and Et_3N (2.3 mL, 16.5 mmol) in CH_2Cl_2 (110 mL) at 0 °C under argon, and the mixture was stirred for 10 h. Additional CH_2Cl_2 (50 mL) was added and the mixture was washed sequentially with 1 M aq HCl (3 × 30 mL), sat. aq $NaHCO_3$ (20 mL), and brine (20 mL). The organic phase was dried (Na_2SO_4), filtered, and then concentrated under vacuum. The residue was mixed with CH_2Cl_2 (20 mL) and the mixture was refluxed for 2 h, cooled to r.t., and filtered to give a white solid; yield: 3.95 g (76%); mp 195–196 °C; $[\alpha]_D^{25}$ +64.5 (*c* 1.04, THF).

FTIR (KBr): 3573, 3107, 2991, 2982, 2940, 1746, 1541, 1351, 1310, 1149, 1089, 1036, 836, 743, 535, 418 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.19 (t, *J* = 7.2 Hz, 3 H, CH_3), 3.11 (s, 3 H, SO_2CH_3), 4.19 (q, *J* = 7.2 Hz, 2 H, CH_2), 5.23 (dd, *J* = 5.2, 2.4 Hz, ArC*H*), 5.41 (d, *J* = 2.8 Hz, 1 H, C*H*), 6.34 (d, *J* = 5.6 Hz, 1 H, O*H*), 7.48 (d, *J* = 8.4 Hz, 2 H, ArH), 7.59 (d, *J* = 8.4 Hz, 2 H, ArH), 7.78 (d, *J* = 8.8 Hz, 2 H, ArH), 8.18 (d, *J* = 8.8 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.40, 43.75, 62.26, 71.75, 82.92, 124.85, 126.79, 127.57, 129.45, 140.19, 140.82, 145.50, 150.88, 166.73.

ESI-MS: *m/z* (%) = 474 $[M + H]^+$.

Anal. Calcd for $C_{18}H_{19}NO_{10}S_2$: C, 45.66; H, 4.04; N, 2.96; S, 13.54. Found: C, 45.58; H, 4.09; N, 2.91; S, 13.50.

The structure of **11** was confirmed by X-ray crystallography.[8]

Ethyl (2*S*,3*S*)-3-Hydroxy-2-[(4-methoxybenzoyl)amino]-3-[4-(methylsulfonyl)phenyl]propanoate (13) and Ethyl (2*R*,3*S*)-3-Hydroxy-2-[(4-methoxybenzoyl)amino]-3-[4-(methylsulfonyl)phenyl]propanoate (13′)

A soln of disulfone **11** (1.84 g, 3.9 mmol) and NaN_3 (305 mg, 4.7 mmol) in anhyd DMF (10 mL) was stirred at 55 °C under N_2 overnight and then the solvent was distilled off. The residue was diluted with CH_2Cl_2 (50 mL), washed with brine (2 × 20 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum to afford a mixture of the crude azides **12** and **12′** (3:1 by ^{1}H NMR) as a bright yellow oil that was used directly in the next step without further purification.

The crude mixture of **12** and **12′** was dissolved in EtOH (50 mL), 10% Pd/C (200 mg) was added, and the mixture was stirred under H_2 at r.t. for 2 h. The mixture was then filtered and concentrated under vacuum to afford a mixture of crude **4** and **4′** (3:1 by ^{1}H NMR) as a bright yellow oil. This mixture was used directly in the next step without further purification.

Et_3N (1.08 mL, 7.8 mmol) and the mixture of **4** and **4′** were dissolved in EtOH (100 mL) and a soln of 4-$MeOC_6H_4COCl$ (663 mg, 3.9 mmol) in CH_2Cl_2 (20 mL) was added at 0 °C. The mixture was stirred for 10 h and then the solvent was evaporated under vacuum. The residue was diluted with CH_2Cl_2 (100 mL) and the soln was washed sequentially with 0.1 M HCl (40 mL) and brine (40 mL) then dried (Na_2SO_4), filtered, and concentrated in a vacuum. The residue was purified by flash column chromatography [silica gel, hexane–EtOAc (1:1)] to give **13** [yield: 1.07 g (65% from 11)] and **13′** [yield: 0.28 g (17%)] as white solids.

13

Mp 154–155 °C; $[\alpha]_D^{25}$ +22.3 (*c* 0.47, THF).

FTIR (KBr): 3497, 3384, 3332, 3223, 3018, 2977, 2925, 1748, 1634, 1607, 1506, 1293, 1263, 1148, 1023, 772, 558 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.6 Hz, 3 H, C*H*$_3$), 3.03 (s, 3 H, SO_2CH_3), 3.86 (s, 3 H, OCH_3), 4.28 (q, *J* = 7.2 Hz, 2 H, C*H*$_2$), 5.19 (dd, *J* = 3.2, 6.4 Hz, 1 H, COC*H*), 5.35 (d, *J* = 5.2 Hz, 1 H, ArC*H*), 5.49 (s, 1 H, O*H*), 6.86 (d, *J* = 5.6 Hz, 1 H, N*H*), 6.94 (d, *J* = 8.4 Hz, 2 H, ArH), 7.48 (d, *J* = 8.4 Hz, 2 H, ArH), 7.73 (d, *J* = 8.4 Hz, 2 H, ArH), 7.88 (d, *J* = 8.4 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.07, 44.45, 55.51, 59.74, 62.36, 74.71, 114.02, 124.82, 127.19, 127.22, 129.19, 139.87, 146.26, 162.97, 168.28, 169.03.

ESI-MS: *m/z* (%) = 422 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{23}NO_7S$: C, 57.00; H, 5.50; N, 3.32; S, 7.61. Found: C, 56.89; H, 5.53; N, 3.28; S, 7.57.

13′

Mp 165–167 °C, $[\alpha]_D^{25}$ +90.4 (*c* 1.12, THF).

FTIR (KBr): 3452, 3362, 3020, 2979, 2924, 1728, 1632, 1533, 1504, 1299, 1258, 1147, 1024, 848, 770, 573, 554 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 6.8 Hz, 3 H, C*H*$_3$), 2.97 (s, 3 H, SO_2CH_3), 3.82 (s, 3 H, OCH_3), 4.06 (s, 1 H, O*H*), 4.16–4.26 (m, 2 H, C*H*$_2$), 5.02 (dd, *J* = 8.8, 2.8 Hz, 1 H, COC*H*), 5.42 (d, *J* = 2.4 Hz, 1 H, ArC*H*), 6.89 (d, *J* = 9.2 Hz, 2 H, ArH), 6.90 (d, *J* = 8.8 Hz, 1 H, N*H*), 7.55 (d, *J* = 8.0 Hz, 2 H, ArH), 7.62 (d, *J* = 8.8 Hz, 2 H, ArH), 7.77 (d, *J* = 8.4 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.13, 44.51, 55.48, 58.38, 62.22, 73.55, 113.91, 125.50, 127.11, 127.37, 128.97, 139.89, 146.46, 162.70, 167.31, 170.09.

ESI-MS: *m/z* (%) = 422 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{23}NO_7S$: C, 57.00; H, 5.50; N, 3.32; S, 7.61. Found: C, 56.89; H, 5.45; N, 3.29; S, 7.56.

Ethyl (4*S*,5*R*)-2-(4-Methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1,3-oxazole-4-carboxylate (14)

*Method 1 (from amide **13**)*: Amide **13** (2.02 g, 4.8 mmol) was added to a soln of $SOCl_2$ (0.67 mL, 9.6 mmol) in $CHCl_3$ (10 mL). The mixture was stirred at 45 °C for 0.5 h then cooled to r.t. and concentrated. The residue was dissolved in CH_2Cl_2 (30 mL) and the soln was carefully poured into a mixture of sat. aq $NaHCO_3$ (30 mL) and ice (150 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phase was dried (Na_2SO_4), filtered, and concentrated under vacuum to give a residue that was purified by flash column chromatography [silica gel, hexane–EtOAc (2:1)] to give a bright yellow oil; yield: 1.75 g (91%); $[\alpha]_D^{25}$ –71.8 (*c* 1.24, $CHCl_3$).

FTIR (KBr): 2982, 2929, 1738, 1644, 1608, 1513, 1314, 1257, 1150, 1080, 957, 767, 550 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.36 (t, *J* = 7.2 Hz, 3 H, C*H*$_3$), 3.05 (s, 3 H, SO_2CH_3), 3.86 (s, 3 H, OCH_3), 4.29–4.38 (m, 2 H, C*H*$_2$), 4.71 (d, *J* = 7.6 Hz, 1 H, COC*H*), 5.92 (d, *J* = 7.6 Hz, 1 H, ArC*H*), 6.95 (d, *J* = 8.8 Hz, 2 H, ArH), 7.59 (d, *J* = 8.4 Hz, 2 H, ArH), 7.97 (d, *J* = 8.4 Hz, 2 H, ArH), 8.01 (d, *J* = 8.8 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.24, 44.54, 55.49, 62.20, 77.12, 81.95, 113.96, 118.88, 126.42, 128.13, 130.62, 140.70, 146.08, 162.89, 165.08, 170.62.

ESI-MS: *m/z* (%) = 404 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{21}NO_6S$: C, 59.54; H, 5.25; N, 3.47; S, 7.95. Found: C, 59.42; H, 5.18; N, 3.44; S, 7.91.

*Method 2 (from amide **13′**)*: Crude oxazole **14′** [prepared from **13′** (2.02 g, 4.8 mmol) by the same procedure as **14**] was added to a soln of NaOEt (326 mg, 0.48 mmol) in a mixture of absolute EtOH (50 mL) and THF (50 mL). The resulting mixture was stirred at r.t. for 1 h then concentrated under vacuum. The residue was dissolved in CH_2Cl_2 (50 mL) and washed successively with 5% aq $NaHCO_3$ (30 mL) and brine (20 mL) then dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by flash column chromatography [silica gel, hexane–EtOAc (2:1)] to give a bright yellow oil [yield: 1.64 g (85% from **13′**), together with **14′** as a white solid: yield 36 mg (1.9% yield from **13′**).

14′

Mp 209–211 °C, $[\alpha]_D^{25}$ –243.3 (*c* 1.06, $CHCl_3$).

FTIR (KBr): 3001, 2982, 2907, 2844, 1733, 1645, 1517, 1308, 1261, 1190, 1147, 1086, 1018, 839, 767, 545 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, *J* = 7.2 Hz, 3 H, C*H*$_3$), 3.04 (s, 3 H, SO_2CH_3), 3.63–3.84 (m, 2 H, C*H*$_2$), 3.90 (s, 3 H, OCH_3), 5.32 (d, *J* = 10.8 Hz, 1 H, COC*H*), 5.97 (d, *J* = 10.8 Hz, 1 H, ArC*H*), 6.99 (d, *J* = 8.4 Hz, 2 H, ArH), 7.55 (d, *J* = 8.0 Hz, 2 H, ArH), 7.94 (d, *J* = 8.4 Hz, 2 H, ArH), 8.04 (d, *J* = 8.4 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.67, 44.48, 55.49, 61.13, 74.00, 81.74, 114.00, 118.84, 127.37, 127.57, 130.65, 140.76, 142.56, 162.96, 166.19, 168.75.

ESI-MS: *m/z* (%) = 404 $[M + H]^+$.

Anal. Calcd for $C_{20}H_{21}NO_6S$: C, 59.54; H, 5.25; N, 3.47; S, 7.95. Found: C, 59.47; H, 5.21; N, 3.42; S, 7.89.

{(4*R*,5*R*)-2-(4-Methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1,3-oxazol-4-yl}methanol (15)

$NaBH_4$ (1.12 g, 29.6 mmol) was added to a soln of oxazole **14** (1.49 g, 3.7 mmol) and $CaCl_2$ (1.64 g, 14.8 mmol) in EtOH (80 mL) at 0 °C. The mixture was stirred for 5 h then H_2O (20 mL) was added and the mixture was stirred for a further 1 h. The mixture was then filtered and the filtrate was concentrated. The residue was diluted with EtOAc (300 mL), washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by flash column chromatography [silica gel hexane–EtOAc (1:3)] to give a white solid; yield: 1.10 g (82%); mp 153–154 °C; $[\alpha]_D^{25}$ –143.4 (*c* 0.203, $CHCl_3$).

FTIR (KBr): 3190, 2957, 2920, 2859, 1645, 1515, 1302, 1259, 1144, 1097, 778, 557, 54 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.20 (s, 3 H, SO_2CH_3), 3.53–3.60 (m, 1 H, CH_aH_b), 3.73–3.79 (m, 1 H, CH_aH_b), 3.82 (s, 3 H, OCH_3), 4.03–4.07 (m, 1 H, NC*H*), 5.08 (t, *J* = 5.2 Hz, 1 H, O*H*), 5.64 (d, *J* = 6.4 Hz, 1 H, ArC*H*), 7.04 (d, *J* = 8.8 Hz, 2 H, ArH), 7.59 (d, *J* = 8.4 Hz, 2 H, ArH), 7.90 (d, *J* = 8.8 Hz, 2 H, ArH), 7.95 (d, *J* = 8.4 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 44.06, 55.91, 63.56, 77.54, 82.08, 114.57, 119.85, 126.63, 128.04, 130.36, 140.74, 147.79, 162.43, 162.45.

ESI-MS: *m/z* (%) = 362 $[M + H]^+$.

Anal. Calcd for $C_{18}H_{19}NO_5S$: C, 59.82; H, 5.30; N, 3.88; S, 8.87. Found: C, 59.75; H, 5.26; N, 3.83; S, 8.83.

(4*S*,5*R*)-4-(Fluoromethyl)-2-(4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1,3-oxazole (16)

A 50-mL tube was charged with a 23% CH_2Cl_2 soln of $F_3CCHFCF_2NEt_2$ (Ishikawa's reagent; 12.75 g, 13.5 mmol) and oxazole **15** (3.25 g, 9 mmol) at r.t. under N_2. The tube was sealed and heated at 100 °C for 3 h then cooled to r.t. CH_2Cl_2 (100 mL) was added and the organic phase was washed successively with sat. aq $NaHCO_3$ (2 × 30 mL) and brine, dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by flash column chromatography [silica gel, hexane–EtOAc (1:1)] to give a white solid; yield: 3.03 g (92%); mp 117–118 °C; $[\alpha]_D^{25}$ –165.8 (*c* 1.03, $CHCl_3$).

FTIR (KBr): 2954, 2900, 2839, 1653, 1513, 1310, 1255, 1141, 1011, 773, 560, 543 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.04 (s, 3 H, SO_2CH_3), 3.86 (s, 3 H, OCH_3), 4.29–4.39 (m, 1 H, NC*H*), 4.51–4.83 (m, 2 H,CH_2), 5.62 (d, *J* = 6.8 Hz, 1 H, ArC*H*), 6.95 (d, *J* = 8.8 Hz, 2 H, ArH), 7.54 (d, *J* = 8.4 Hz, 2 H, ArH), 7.94–7.98 (m, 4 H, ArH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.53, 55.48, 74.98 (d, *J* = 20.8 Hz, FCH_2CH), 81.92 (d, *J* = 3.3 Hz, FCH_2CHCH), 83.93 (d, *J* = 172 Hz, FCH_2), 114.00, 119.07, 126.27, 128.12, 130.41, 140.53, 146.67, 163.79, 164.70.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –228.0 (s, 1 F).

ESI-MS: *m/z* (%) = 364 $[M + H]^+$.

Anal. Calcd for $C_{18}H_{18}FNO_4S$: C, 59.49; H, 4.99; N, 3.85; S, 8.82. Found: C, 59.37; H, 4.96; N, 3.81; S, 8.78.

Florfenicol (1; 2,2-Dichloro-*N*-{(1*S*,2*R*)-1-(fluoromethyl)-2-hydroxy-2-[4-(methylsulfonyl)phenyl]ethyl}acetamide)

A soln of oxazole **16** (1.82 g, 5 mmol) in THF (20 mL) and 1 M HCl (10 mL) was stirred at 45 °C for 3 h and then concentrated to give **17** as its hydrochloric acid salt. This salt was dissolved in 5% $NaHCO_3$ (30 mL) and the soln was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phase was washed with brine (40 mL), dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was added to a soln of $LiBH_4$ in THF, prepared in situ from KBH_4 (810 mg) and LiCl (634 mg) in THF (20 mL). The mixture was stirred overnight at 40 °C, cooled, mixed with H_2O (2 mL), and stirred for an additional 2 h. The solvent was then removed and the residue was diluted with CH_2Cl_2 (50 mL). The organic phase was extracted with 1 M HCl (3 × 30 mL) and the pH of the combined aqueous phase was adjusted to neutral with concd aq $NaHCO_3$. The soln was then extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phase was dried (Na_2SO_4), filtered, and concentrated under vacuum to give the crude product **2** as a bright-yellow oil.

Crude product **2** and Et_3N (2.0 mL, 14.3 mmol) were dissolved in EtOH (100 mL) and the mixture was stirred at 0 °C. A soln of $Cl_2CHCOCl$ (757 mg, 5.15 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 1 h, and the mixture was stirred for an additional 3 h. The solvent was removed under reduced pressure and the residue was diluted with CH_2Cl_2 (100 mL). The resulting soln was washed successively with 0.1 M HCl (50 mL), 5% aq $NaHCO_3$ (30 mL), and brine (30 mL). The organic phase was then dried (Na_2SO_4), filtered, and concentrated under vacuum to give a residue that was purified by flash column chromatography [silica gel, hexane–EtOAc (1:1)] to give **1** as a white solid; yield: 1.34 g (75%).

17·HCl

Mp 179–180 °C; $[\alpha]_D^{25}$ +88.8 (*c* 0.414, MeOH).

FTIR (KBr): 3594, 3455, 2928, 2898, 2849, 2649, 2521, 1704, 1604, 1309, 1262, 1159, 1102, 1024, 771 cm^{-1}.

^1H NMR (400 MHz, MeOD): δ = 3.15 (s, 3 H, SO_2CH_3), 3.90 (s, 3 H, OCH_3), 4.17–4.80 (m, 3 H, CH_2 and NC*H*), 6.28 (d, *J* = 9.2 Hz, 1 H, ArC*H*), 7.06 (d, *J* = 8.8 Hz, 2 H, ArH), 7.83 (d, *J* = 8.0 Hz, 2 H, ArH), 8.07 (d, *J* = 8.0 Hz, 2 H, ArH), 8.14 (d, *J* = 8.4 Hz, 2 H, ArH).

^{13}C NMR (100 MHz, MeOD): δ = 42.85, 54.46 (d, *J* = 17.7 Hz, N*C*H), 54.78, 72.56 (d, *J* = 5.3 Hz, Ar*C*H), 80.22 (d, *J* = 171 Hz, F*C*H_2), 113.71, 120.73, 128.00, 128.19, 131.94, 141.45, 141.86, 164.54, 164.73.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –235.2 to –234.9 (m, 1 F).

ESI-MS: *m/z* (%) = 382 $[M - Cl]^+$.

Anal. Calcd for $C_{18}H_{21}ClFNO_5S$: C, 51.74; H, 5.07; N, 3.35; S, 7.67. Found: C, 51.68; H, 5.02; N, 3.31; S, 7.63.

2

^1H NMR (400 MHz, DMSO-d_6): δ = 1.42 (br s, 2 H, NH_2), 2.98–3.04 (m, 1 H, NH_2CH), 3.18 (s, 3 H, CH_3), 4.11–4.44 (m, 2 H, FCH_2), 4.68 (d, *J* = 3.6 Hz, 1 H, C*H*OH), 5.68 (br s, 1 H, O*H*), 7.60 (d, *J* = 8.0 Hz, 2 H, ArH), 7.86 (d, *J* = 8.0 Hz, 2 H, ArH).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –229.5 to –229.2 (m, 1 F).

1

Mp 151–152 °C; $[\alpha]_D^{25}$ –18.3 (*c* 0.51, DMF).

FTIR (KBr): 3453, 3321, 3033, 2989, 1684, 1535, 1290, 1276, 1149, 1017, 769 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.16 (s, 3 H, SO_2CH_3), 4.26–4.78 (m, 3 H, CH_2F/NC*H*), 4.99 (m, 1 H, ArC*H*), 6.15 (d, *J* = 4.4 Hz, 1 H, O*H*), 6.47 (s, 1 H, $CHCl_2$), 7.62 (d, *J* = 8.4 Hz, 2 H, Ar), 7.85 (d, *J* = 8.4 Hz, 2 H, Ar), 8.60 (d, *J* = 8.8 Hz, 1 H, N*H*).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 44.1, 55.1 (d, *J* = 19.4 Hz, $CHCH_2F$), 66.8, 69.8 (d, *J* = 6.1 Hz, Ar*C*HCHCH_2F), 82.8 (d, *J* = 168.9 Hz, CH_2F), 127.0, 127.6, 140.0, 148.4, 164.2.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –224.4 to –224.1 (m, 1 F).

ESI-MS: *m/z* (%) = 358 $[M + H]^+$.

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.

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(7) Calculated by using *ACD ChemSketch* software. This software can be downloaded from http://www.acdlabs.com.

(8) Crystallographic data for compound **11** have been deposited with the accession number CCDC 830167, and can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk; Web site: www.ccdc.cam.ac.uk/conts/retrieving.html.

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