An Improved Industrial Synthesis of Florfenicol plus an Enantioselective Total Synthesis of Thiamphenicol and Florfenicol

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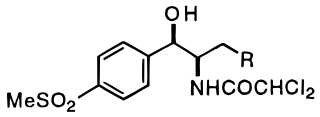
Introduction

Both thiamphenicol (**1**)[1] and its 3′-fluoro derivative, florfenicol (**2**)[2] are broad spectrum antibiotics possessing activity against many Gram negative and Gram positive microorganisms. The current industrial synthesis of florfenicol is based upon the established thiamphenicol process which starts with the condensation of *p*-(methylsulfonyl)benzaldehyde (**14**) and glycine.[3] The diol product from the reduction of the corresponding ester is resolved with unnatural D-(−)-tartaric acid affording optically pure D-(−)-*threo*-2-amino-1-(4-(methylsulfonyl)-phenyl)-1,3-propanediol (**3**). Various methods were developed to recycle the L-isomer, but they are generally lengthy and difficult to operate.[4] Since the discovery of florfenicol in 1979,[2] there has been renewed interest in developing asymmetric syntheses of thiamphenicol based structures.[5] A diastereoselective synthesis of thiamphenicol was reported by S. McCombie and T. L. Nagabhushan.[5a] However, the low enantioselectivity of the Sharpless epoxidation on (*Z*)-allylic alcohol derivatives flaws the approach.[6]



1 R =OH Thiamphenicol
2 R = F Florfenicol

We now report an improved version of the thiamphenicol-based synthesis of florfenicol which shortens our previous route[5b] by two steps. More importantly, we report the first enantioselective synthesis of 1′-(*R*,*R*)-(dichloromethyl)oxazoline **5**, an intermediate to both florfenicol and thiamphenicol. In the course of investigating the new synthesis, we have developed a clean inversion of the benzylic chiral center in 3′-(*S*,*R*)-(dichloromethyl)oxazoline **4a** and a regioselective epoxide opening with $CHCl_2CN$.

Results and Discussion

The use of benzonitrile as a protecting group in our previous report[5b] results in the inelegance of adding and removing an amide moiety only to later replace it with the desired one. Clearly, it would be shorter if dichloroacetonitrile could be used instead of benzonitrile to protect both the 1′-hydroxy and 2′-amino groups since the protecting group ends up as a part of the product. As shown in Scheme 1, we found that acids such as H_2SO_4 catalyze oxazoline formation at 70 °C. The resulting $(NH_4)_2SO_4$, in turn, promotes the isomerization of **4** to the desired **5** at 50−60 °C. These two stages of reaction temperature are necessary since the reaction takes place in two phases. The first is the actual condensation and cyclization at higher temperature to form a mixture of the two oxazolines. The second is the precipitation-driven equilibration of **4** to the desired internal oxazoline **5** at lower temperature. Filtration of the precipitate improves the ratio of **5**:**4** from 97:3 to 99.5:0.5. Following the fluorodehydroxylation procedure,[7] **5** was converted cleanly to the fluorinated oxazoline **6**. A selective hydrolysis procedure was developed to convert **6** to **2** in 86% yield. This process has been scaled up successfully to produce commercial florfenicol.

Having established **5** as a viable intermediate, we turned our attention to its enantioselective synthesis. As outlined in Scheme 2, the synthetic strategy is to regioselectively open the trans epoxide **7** with $CHCl_2CN$, forming 3′-(*S*,*R*)-(dichloromethyl)oxazoline **4a**. Our initial attempt to form the imidate under acidic conditions did not produce any desired product.[8] Under basic conditions, deprotonation of epoxy alcohol **7** with NaH followed by addition of $CHCl_2CN$ did yield some imidate which resulted in a few percent of **4a** upon acidification.[9] But the reaction mixture was complex. We suspected that two major side reactions were hindering the desired reaction. One is the simple deprotonation of $CHCl_2CN$ and the other the Payne rearrangement[10] to give **10**. Both of these side reactions could perhaps be circumvented by use of a less basic anion. Thus, we transmetalated alkoxy anion **8** to its zinc form, creating a weaker base but a better coordination metal. To our delight, **4a** was obtained as a major product in 65% yield. The imidate nitrogen anion **11** acts as a good nucleophile to attack the epoxide, producing **4a**. This completes a one-step epoxide opening in which both a carbon−oxygen and a carbon−nitrogen bonds are formed.

The synthetic strategy using **4a** followed by an inversion was dictated by the fact that the more straightforward route—direct epoxidation to a precursor of **4**—required a cis allylic alcohol, and these are not reported to afford high ee's.[11] To invert **4a**, we took advantage of

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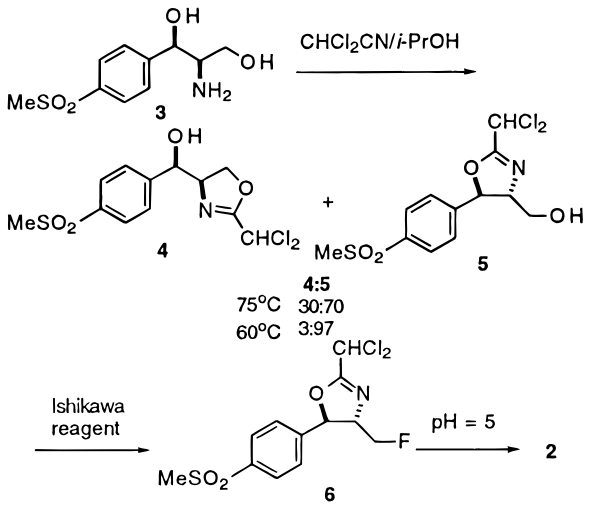
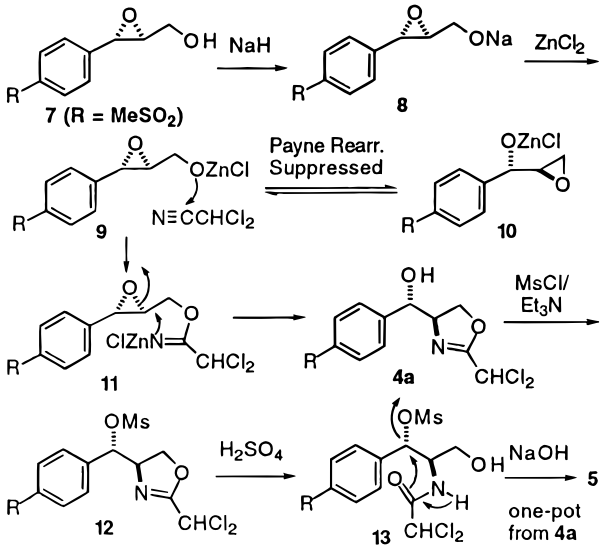
Scheme 1



Scheme 2

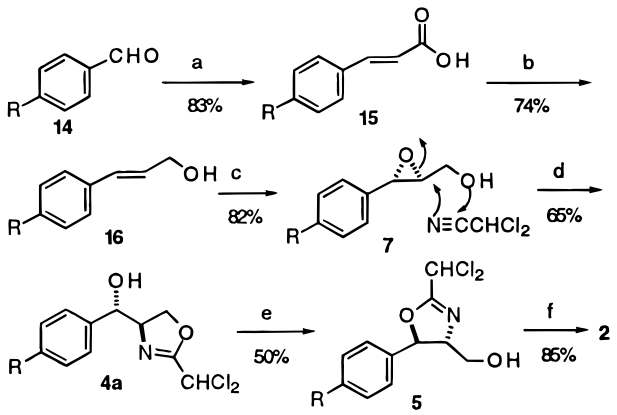


the neighboring amide group. First, mesylation of the benzylic alcohol in **4a** proceeds nicely to afford **12**. A pH adjustment with dilute H_2SO_4 hydrolyzes the oxazoline ring to the open form **13**. Re-adjustment of the pH to 10 with aqueous NaOH promotes the intramolecular SN_2 attack and produces 1′-oxazoline **5**. This transformation not only inverts the benzylic chiral center but also isomerizes **4a** to the internal oxazoline, exposing the primary alcohol to the fluorodehydroxylation. A brief study indicated that $EtSO_2$ gave a 50% overall yield of **5** from **4a** while $MeSO_2$ afforded a 45% yield.

With the above developments, we were able to complete the enantioselective synthesis of **2** as expressed in Scheme 3. Thus, aldol condensation of **14** with malonic acid in the presence of pyridine and a catalytic amount of piperidine followed by dehydration and decarboxylation gave the trans cinnamic acid derivative **15**[12] in 83% yield. A two-step, one-pot procedure was developed for the reduction of acid **15**. First, the acid **15** was converted to its corresponding acid chloride and then treated with a solution of $NaBH_4$ in EtOH to produce trans allylic alcohol **16** in 74% yield. The isolated **16** was subjected to the Sharpless epoxidation conditions to give the (*S*,*S*)-epoxy alcohol **7** in 82% isolated yield. A 97% ee was

(12) *Organic Reactions*, Vol. 15, p 268.

Scheme 3[a]



[a] (a) Malonic acid, piperidine (0.2 equiv), pyridine, reflux, 2 h. (b) $SOCl_2$, reflux, 1 h, then $NaBH_4$, EtOH, 5 °C, 1 h. (c) Ti(OPr-*i*)$_4$ (0.2 equiv), L-DIP (0.2 equiv), *t*-BuOOH, 4 Å sieves, −20 to −15 °C, 2 h. (d) (i) NaH, THF, 5 °C, 30 min, (ii) $ZnCl_2$ (1.0 equiv), 5 °C, 30 min, (iii) $CHCl_2CN$ (1.5 equiv), 55 °C, 16 h. (e) (i) $EtSO_2Cl$, Et_3N, 5 °C, 3 h, (ii) H_2SO_4, 15 °C, 20 min, (iii) NaOH, 5 °C, 10 min. (f) (i) $CF_3CHCF_2NEt_2$ (Ishikawa reagent), CH_2Cl_2, sealed reflux, 1.5 h, (ii) HOAc, *i*-PrOH, reflux, 3 h.

obtained when 0.2 equiv of the catalyst was used whereas a 90% ee was achieved with 0.1 equiv of the catalyst. Following the novel epoxy alcohol opening procedure, **7** was regioselectively opened by a sequential addition of NaH, $ZnCl_2$, and $CHCl_2CN$ to afford oxazoline **4a** in 65% yield. The inversion was carried out according to the newly-discovered one-pot method to produce 50% of the desired 1′-(*R*,*R*)-oxazoline **5** which is identical to the authentic sample. The chiral purity was measured to be greater than 99.9%.

In summary, we have developed a shorter version of the resolution-based synthesis of florfenicol (**2**) which has proven robust enough for commercial use. We have also developed an enantioselective route to both thiamphenicol (**1**) and florfenicol (**2**).

Experimental Section

General. The ^1H and ^{13}C NMR spectra were taken in $CDCl_3$, and all reactions were carried out under nitrogen unless otherwise noted. Melting points were not corrected. All starting materials and reagents were purchased commercially and used as is without further purifications.

Condensation of Amino Diol 3 with $CHCl_2CN$ to (4*R*,5*R*)-2-(Dichloromethyl)-5-[4-(methylsulfonyl)phenyl]oxazole-4-methanol (5). To a 500 mL three-neck flask equipped with a mechanical agitator and a thermometer were sequentially added at 25 °C 150 mL of 2-propanol, 50.4 g (458 mmol) of $CHCl_2CN$, 5 mL of concd H_2SO_4, and 100 g (408 mmol) of amino diol **3**. The mixture was heated to 70 °C for 1.5−2 h to complete the condensation. The resulting slurry was cooled to 50 °C and agitated at that temperature for an additional 14 h. The precipitate was cooled to 5 °C, filtered, and dried at 50 °C to give 119 g (88%) of **5**. The ratio of **5**:**4** in the isolated solid is 99.5:0.5 as determined by HPLC: $[\alpha]^{23.3}_D$ +11.1° (*c* 5.13, EtOH). ^1H NMR (DMSO-d_6): δ 8.00 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.3 Hz, 2H), 7.26 (s, 1H), 5.75 (d, J = 6.4 Hz, 1H), 5.18 (t, J = 5.6 Hz, 1H), 4.10−4.05 (m, 1H), 3.75−3.65 (m, 1H), 3.60−3.55 (m, 1H), 3.23 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 161.0, 146.0, 140.6, 127.8, 126.1, 83.0, 76.5, 61.8 (2 carbons by Hetcor), 43.5. IR (KBr, paraffin): 3350, 2930, 1670 cm^{-1}. Mp: 144−145 °C. Anal. Calcd for $C_{12}H_{13}Cl_2NO_4S$: C, 42.63; H, 3.88; N, 4.14. Found: C, 42.29; H, 4.11; N, 4.24. Analyses for the minor product **4**: $[\alpha]^{22.8}_D$ −150.3° (*c* 4.79, DMSO). ^1H NMR (DMSO-d_6): δ 7.81 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 8.2 Hz, 1H), 6.95 (s, 1H), 5.83 (d, J = 4.8 Hz, 1H), 4.81 (t, J = 4.0 Hz, 1H), 4.56−4.51 (m, 1H), 4.44−4.33 (m, 2H), 3.13 (s, 3H, Me). ^{13}C NMR (DMSO-d_6): δ

162.3, 148.4, 139.7, 127.8, 126.7, 71.8, 71.5, 70.7, 62.3, 43.9. IR (KBr, paraffin): 3250, 2950, 1660 cm^{-1}. Mp: 12.5−126.5 °C. Anal. Calcd for $C_{12}H_{13}Cl_2NO_4S$: C, 42.63; H, 3.88; N, 4.14. Found: C, 42.48; H, 4.04; N, 4.22.

Conversion of 5 to Florfenicol (2). To a 30 mL nonstirred Teflon tube were added 8.5 g of a 23% CH_2Cl_2 solution of CF_3-$CHCF_2NEt_2$ (Ishikawa reagent, 9 mmol) and 2.0 g (6 mmol) of **5**. The Teflon tube was inserted into an autoclave. The autoclave was sealed, heated to 100 °C in an oil-bath for 1−3 h, and cooled with an ice bath. The content was transferred into a 250 mL flask for hydrolysis. To the flask were added 0.35 g of KOAc to pH 5 and 2 mL of MeOH. Most of solvent in the flask was removed under vacuum. To the residue was added a 20 mL mixture of 2-propanol (IPA) and water (65:35). The IPA−water mixture was refluxed for 3 h to complete the hydrolysis. After removal of about half of the solvent under vacuum, the product began to crystallize. The precipitate was cooled to 5 °C, filtered, and dried at 50 °C to afford 2.0 g of florfenicol (**2**). Recrystallization from 2-propanol and water gave the final drug in >98% purity. The assays of the product obtained from this route are identical to that reported.[5b]

(*E*)-3-[4-(Methylsulfonyl)phenyl]propenic Acid (15). To a three-neck 3 L round bottom flask equipped with a condenser, a thermometer, and a mechanical agitator were added sequentially 596 g (2.99 mol) of malonic acid, 506 mL of pyridine, 30 mL of piperidine, and 300 g (1.49 mol) of *p*-(methylsulfonyl)-benzaldehyde **14**. The mixture was heated to 95−100 °C for 4 h, cooled to 25 °C, and quenched slowly into 3 L of an ice−HCl solution. The precipitate was filtered and dried at 50 °C to give 340 g of **15** as white crystals. The yield was 83% after correction for the purity. ^{1}H NMR (DMSO-d_6): δ 7.90 (d, J = 8.9 Hz, 2H), 7.87 (d, J = 8.9 Hz, 2H), 7.62 (d, J = 16 Hz, 1H), 6.65 (d, J = 16 Hz, 1H), 3.19 (s, 3H, Me). ^{13}C NMR (DMSO-d_6): δ 167.5, 142.2, 141.8, 139.5, 129.2, 127.8, 123.1, 43.7. IR (KBr, paraffin): 2940, 1680 cm^{-1}. Mp: 294−296 °C. Anal. Calcd for $C_{10}H_{10}H_4S$: C, 53.08; H, 4.45; S, 14.17. Found: C, 52.78; H, 4.66; S, 13.94.

(E)-[4-(Methylsulfonyl)phenyl]propenol (16). To an oven-dried 250 mL three-neck flask was charged 96 mL (1.35 mol) of $SOCl_2$ and 50 g (0.225 mol) of (*E*)-3-[4-(methylsulfonyl)phenyl]-propenic acid (**15**). The reaction mixture was heated to reflux for 1 h. The excess $SOCl_2$ was removed *via* azeotropic distillation with CH_2Cl_2, and the residue was made into a 100 mL CH_2Cl_2 solution. This solution was then added dropwise to precooled (5 °C) 42 g (1.1 mol) of $NaBH_4$ in EtOH. The resulting mixture was agitated at 10 °C for 1 h, quenched slowly into an ice−HCl solution, and extracted with 3 × 300 mL of CH_2Cl_2. The product began to crystallize after concentration of the organic layer. The precipitate was filtered and dried at 50 °C to give 28 g of **16** (74% yield) with a solution yield of 94%. ^{1}H NMR: δ 7.80 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H), 6.62 (d, J = 16.2 Hz, 1H), 6.55 (dt, J = 16.2, 3.8 Hz, 2H), 4.96 (t, J = 5.0 Hz, 1H, OH), 4.12−4.10 (m, 1H), 3.14 (s, 3H, Me). ^{13}C NMR (DMSO-d_6) δ 142.3, 139.2, 135.5, 127.7, 127.0, 126.8, 61.5, 43.9. IR ((paraffin): 3520, 3340, 2930, 1420 cm^{-1}. Mp: 126−127 °C. Anal. Calcd for $C_{10}H_{12}O_3S$: C, 56.59; 5.70; S, 15.1. Found: C, 56.36; H, 5.70; S, 15.1.

(*S,S*)-3-[4-(Methylsulfonyl)phenyl]-2,3-epoxypropyl Alcohol (7). To an oven-dried 500 mL three-neck flask with a thermometer and a mechanical agitator at −20 °C were added sequentially 8 g of 4 Å molecular sieves powder, 1.74 g (7.4 mmol) of diisopropyl L-tartrate, and 2.16 g (7.4 mmol) of Ti(OPr-*i*)$_4$. The reaction mixture was agitated at −20 °C for 30 min. To the resulting mixture were added dropwise 8.1 g (37 mmol) of **8** dissolved in 500 mL of CH_2Cl_2 and 13.4 mL of 3.0 M *t*-BuOOH in 2,2,4-trimethylpentane. The reaction was stirred at −20 °C for 4 h, quenched with 6.0 mL of Me_2S, and filtered. After addition of 250 mL of saturated NaF, the filtrate was stirred at ambient temperature for 16 h, filtered through a pad of Celite, extracted with 3 × 100 mL of CH_2Cl_2, and washed with 2 × 100 mL of water. After concentration of the organic layer, the precipitate was filtered and dried at 50 °C to give 7.15 g (82% yield) of **7** as white crystals. The ee was determined to be 99.9% on a Chiralcel OJ column with hexane:2-propanol:acetonitrile (50:50:1) as the mobile phase. The (*R,R*)-isomer was also prepared by following the same procedure. ^{1}H NMR: δ 7.92 (d, J = 8 Hz, 2H), 7.49 (d, J = 8 Hz, 2H), 4.10 (dd, J = 17, 3 Hz, 1H), 4.04 (s, 1H), 3.85 (dd, J = 17, 3 Hz, 1H), 3.20−3.17 (m, 1H), 3.05 (s, 3H), 1.88 (bs, 1H). ^{13}C NMR: δ 143.4, 140.2, 127.6, 126.5, 62.9, 60.7, 54.5, 44.5. Mp: 104−106 °C. IR (paraffin): 3300, 2940, 1600 cm^{-1}. Anal. Calcd for $C_{10}H_{12}O_4S$: C, 52.62; H, 5.30; S, 14.04. Found: C, 52.60; H, 5.27; S, 14.36.

(3*S,4R*)-2-(Dichloromethyl)-4,5-dihydro-α-[4-(methylsulfonyl)phenyl]oxazole-4-methanol (4a). To a 1 L three-neck oven-dried flask with a condenser and a mechanical agitator were added sequentially 6.1 g (153 mmol) of NaH (60%) and 90 mL of THF. To the cooled suspension at 5 °C was added dropwise 300 mL of a THF solution of 30 g (128 mmol) of (*S,S*)-3-[4-(methylsulfonyl)phenyl]-2,3-epoxy alcohol **7**. The resulting mixture was agitated at 5 °C for 30 min to form the sodium anion. To the above solution was added 17.8 g (128 mmol) of dry $ZnCl_2$ dissolved in 250 mL of THF. After 30 min of agitation at 5 °C, 17.0 g (153 mmol) of $CHCl_2CN$ in 10 mL of THF and 1 g of 4 Å sieves was added dropwise into the flask. The contents were heated to 55 °C for 16 h, cooled to 25 °C, and quenched with aqueous $NaHCO_3$. The product was extracted with 4 × 400 mL of EtOAc, washed with brine, and concentrated under vacuum. The product solidified after addition of 50 mL of IPA and was filtered and dried at 55 °C to give 16.0 g of **4a**. The solution yield was 65% as assayed by HPLC *vs* an external standard. The crude product was recrystallized from methyl isobutyl ketone to afford **4a** with a 97% purity. $[\alpha]^{22.8}_D$ −43.8° (*c* 4.69, DMSO). ^{1}H NMR: δ 7.93 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 6.26 (s, 1H), 5.14 (d, J = 4.0 Hz, 1H), 4.57 (ddd, J = 8.7, 7.9, 4.0 Hz, 1H), 4.46 (dd, J = 9.7, 7.9 Hz, 1H), 4.28 (dd, J = 9.7, 8.7 Hz, 1H), 3.05 (s, 3H), 2.60 (bs, 1H). ^{13}C (DMSO-d_6): δ 162.4, 148.9, 139.9, 127.7, 127.1, 72.6, 72.1, 70.2, 62.4, 43.8. IR (KBr, (paraffin): 3240 (OH), 2900, 1650 cm^{-1}. Mp: 156.5−157.5 °C. Anal. Calcd for $C_{12}H_{13}Cl_2NO_4S$: C, 42.63; H, 3.88; N, 4.14. Found: C, 42.39; H, 4.16; N, 4.15.

(4*R*,5*R*)-2-(Dichloromethyl)-5-[4-(methylsulfonyl)-phenyl]oxazole-4-methanol (5). To an oven-dried 100 mL flask were charged at 25 °C sequentially 3.5 g (10 mmol) of **4a**, 5 mL of pyridine, and 2.8 mL of Et_3N. To the cooled mixture at 5 °C was added dropwise 0.95 mL (12 mmol) of $MeSO_2Cl$. The resulting solution was stirred at 5 °C for 2 h, and the pH was then adjusted to 2.0 with 3.0 N H_2SO_4. Then 5 mL of THF was added to make the hydrolysis homogeneous. The reaction was warmed to 25 °C for 10 min and treated with 50% NaOH to pH 12.5 to complete the cyclization. The reaction mixture was extracted with 3 × 40 mL of EtOAc, washed with brine, and concentrated to give crude **5**. An analytical sample was purified by flash column chromatography. The solution yield was 40−45%, and a 50% yield was obtained when $EtSO_2Cl$ was used. The ee was determined to be >99.9% on a J. T. Baker Chiralcel OJ column with hexane:2-propanol:acetonitrile (69:30:1) as the mobile phase. The assays of this product are identical to that of the authentic sample.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and IR spectra for **2**, **4**, **4a**, **5**, **7**, **15**, and **16**, also chiral HPLC chromatograms for **5** and **7** (26 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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