CH_2Cl_2 (3 × 40 mL). The combined organic layer was washed with brine (40 mL) and then dried over $MgSO_4$. Filtration and rotary evaporation gave 7.52 g of a dark oil. Unreacted starting material was removed by Kugelrohr vacuum distillation at room temperature (0.1 mm), and then the iodoaniline was distilled at 62–70 °C (0.1 mm). The yellow, air-sensitive product (3.21 g) was crystallized from methanol to yield white plates (1.38 g, 11.2%): mp 76.5–78.5 °C (lit.[16] mp 77 °C); ^1H NMR (CD_2Cl_2) δ 7.44 (d, 2 H, J = 9 Hz, 3-H and 5-H), 6.48 (d, 2 H, J = 9 Hz, 2-H and 6-H), 2.89 (s, 6 H, CH_3); ^{13}C NMR (CD_2Cl_2) δ 151.0, 138.3, 115.4, 77.5, 40.6.

Comparitive Iodination Processes as Applied to Phenol. In all of the following cases the products were analyzed by capillary VPC vs naphthalene internal standard, with results as summarized in Table III.

NaI/Chloramine T Method. A solution of phenol (1.00 g) and sodium iodide (1.91 g) in *N,N*-dimethylformamide (32 mL) was treated with Chloramine T trihydrate (3.59 g) all at once, at 22 °C. The solution turned red and warmed to 24 °C. The mixture was stirred for 1 h at 21–24 °C, by which time the color had faded to pale yellow. The mixture was poured into water (100 mL), and the solution was acidified to pH 1 using 5% HCl. The solution was extracted with ethyl acetate (2 × 75 mL). The organic extracts were washed with 10% aqueous sodium thiosulfate (50 mL) and then brine (50 mL). The ethyl acetate solution was dried, and then the solvent was evaporated to afford 5.06 g damp, tan solid. The product was analyzed by VPC, which gave all of the yield data (Table III) except that for 2,4-diiodophenol. Since it coeluted with the *p*-toluenesulfonamide byproduct on VPC, 2,4-diiodophenol was isolated by flash chromatography (eluant 1:1 heptane–CH_2Cl_2), and this isolated yield is listed in Table III.

***tert*-Butyl Hypoiodite Method.** A solution of ICl (1.72 g) in THF (3 mL) was added dropwise over 5 min at 20–22 °C to a solution of potassium *tert*-butoxide (2.50 g) in *tert*-butyl alcohol (20 mL). The yellow slurry was cooled to 7 °C. A solution of phenol (1.00 g) in THF (2 mL) and *tert*-butyl alcohol (5 mL) was added dropwise over 15 min at 3–7 °C. The yellow slurry was stirred for 1 h at 0–5 °C and then for 1 h at ambient temperature. The mixture was poured into 59 mL of 10% sodium thiosulfate solution and acidified to pH 3 using 5% aqueous HCl. Ether (60 mL) was added, and the layers were separated. The organic layer was washed with brine (50 mL), dried, and filtered. Removal of the solvent in vacuo gave 2.06 g of an orange oil.

I_2/Methanol Method. Iodine (5.39 g) was added in portions over 1 h at −2 to 1 °C to a solution of phenol and sodium hydroxide (1.70 g) in methanol (50 mL). The colorless solution was stirred 20 min at 0 °C and then was acidified to pH 2 (5% HCl). The product was extracted into ether (75 mL). The ether layer was washed sequentially with 10% aqueous sodium thiosulfate (50 mL) and brine (50 mL). The ether layer was dried, then the solvent was removed in vacuo to give 4.05 g of a yellow oil.

ICl/Methanol Method. A solution of phenol (2.00 g) in methanol (50 mL) was treated with sodium carbonate (10.60 g). Iodine monochloride (3.45 g, 1.00 equiv) was added dropwise over 40 min at −1 to 4 °C. The colorless slurry was stirred for 1 h at 0 °C. The slurry was filtered, and the salt was washed with methanol (50 mL). The filtrate was treated with 10% sodium thiosulfate solution (25 mL) and then was adjusted to pH 7 using 3 N H_2SO_4. This mixture was extracted with ether (3 × 60 mL). The combined ether extracts were dried and filtered, and then the solvent was removed in vacuo to afford 4.65 g of a pale brown oil.

ICl/Acetonitrile Method. A solution of phenol (2.00 g) and sodium hydroxide (0.85 g, 1.00 equiv) in acetonitrile (50 mL), water (10 mL), and *tert*-butyl alcohol (1.73 g, 1.10 equiv) was treated with ICl (3.45 g, 1.00 equiv) dropwise over 35 min at −2 to 1 °C. The red reaction mixture was stirred for 2 h at 0–5 °C and then for 2 h at 20 °C. The mixture was treated with 10% sodium thiosulfate solution (75 mL) and then was acidified to pH 3 using 5% HCl. The mixture was extracted with ether (2 × 60 mL). The combined ether extracts were washed with saturated brine (50 mL) and then dried. The ether solution was filtered and concentrated in vacuo to give 4.05 g of an orange oil.

***tert*-Butyl Hypochlorite/NaI Method.** A solution of phenol (2.00 g) and sodium iodide (3.50 g, 1.10 equiv) in acetonitrile (50 mL) and water (10 mL) was treated with *tert*-butyl hypochlorite (2.54 g, 1.10 equiv) dropwise over 13 min at −2 to 2 °C. The red solution was stirred for 17 min at 0 °C and then was treated with 10% sodium thiosulfate solution (100 mL). The product was extracted into 150 mL of ether. The ether solution was washed with saturated brine (50 mL) and dried. The mixture was filtered and concentrated in vacuo to afford 4.52 g of a white semisolid.

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Notes

An Efficient Synthesis of Florfenicol

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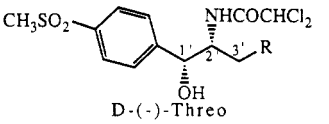
Florfenicol (**1**),[1] the 3′-fluoro derivative of the antibiotic thiamphenicol (**2**), is a broad spectrum antibiotic possessing activity against many Gram negative, Gram positive, and thiamphenicol-resistant microorganisms. Florfenicol is of interest as a veterinary product for use against diseases such as bovine mastitis and bovine shipping fever and for use in aqua culture.



1 R = F Florfenicol
2 R = OH Thiamphenicol

A highly efficient synthesis was required to produce large quantities for the competitive animal health market. Initially, florfenicol was synthesized from thiamphenicol.[1] The major drawback of this synthesis was a poor fluorination step. The fluorodehydroxylation of D-*threo*-1-(4-(methylsulfonyl)phenyl)-2-phthalimido-1,3-propanediol was accomplished with DAST, which gave a mixture of all three possible fluorinated products. Also, the hazards and

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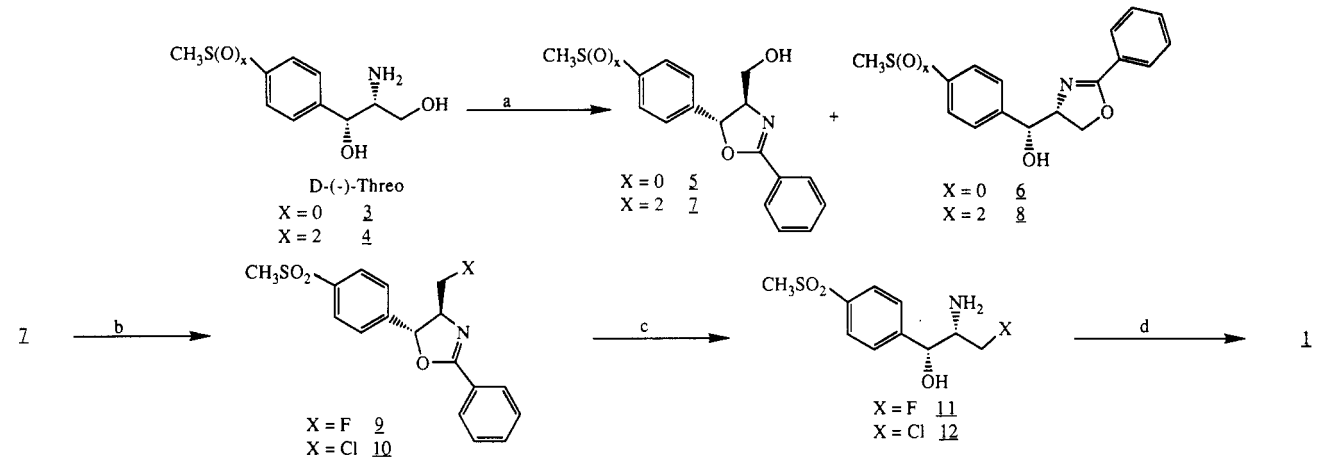
0022-3263/90/1955-5291$02.50/0

Scheme I[a]



[a] (a) Benzonitrile, ethylene glycol, K_2CO_3; (b) FPA (Ishikawa reagent), CH_2Cl_2; (c) 6 N HCl; (d) methyl dichloroacetate, Et_3N, MeOH.

expense of using DAST on a large scale are well known. More recently, a nine-step synthesis was employed to produce kilogram quantities of florfenicol.[2] The disadvantages of this route include a low overall yield and a resolution as the penultimate step. Several other syntheses of florfenicol have appeared,[3] including a recent one in the patent literature.[4] The drawbacks in the latter synthesis are two low-yielding steps: (1) a protection step which gives only 70% of the desired isomer and (2) a two-step fluorodehyroxylation in which the 3′-mesylate is displaced by fluoride ion in polyethylene glycol at 100 °C in 68% yield. None of the above syntheses were sufficiently cost-effective to produce the large quantities of 1 needed for clinical trials. This prompted the search for a high-yielding synthesis of florfenicol utilizing inexpensive starting material and reagents.

The synthesis described below (Scheme I) starts with either D-(−)-*threo*-2-amino-1-(4-(methylthio)phenyl)-1,3-propanediol (**3**) or D-(−)-*threo*-2-amino-1-(4-(methylsulfonyl)phenyl)-1,3-propanediol (**4**), both of which are commercially available. Prior to fluorination of the 3′-hydroxyl group, it was necessary to protect the 1′-hydroxyl and the 2′-amino groups. Of the various protecting groups evaluated (2-oxazolidinone, alkyl- and aryl-substituted 2-oxazolines), the phenyloxazoline was found to give the highest yield in the subsequent hydroxyl replacement step. Use of ethyl benzimidate HCl[4] to prepare the desired oxazoline **5** gave only a 70% yield, the remainder being the isomeric oxazoline **6**. The low yield and the need for large quantities of the reagent made this procedure impractical for large-scale synthesis. Although there are several procedures in the literature[5] for preparing oxazolines directly from the reaction of an amino alcohol with a nitrile, none of the standard reaction conditions gave the desired selectivity (yield >90%) for **5**. Recently, we have found that reaction of **3** or **4** with benzonitrile in ethylene glycol and/or glycerin with a catalytic amount of potassium carbonate at 105 °C gave **5** or **7** in >95% isolated yield. Under these conditions less than 0.5% of the undesired isomers (**6** or **8**) are formed.[6] This reaction is only effective when a polyhydric alcohol is used. When this reaction is run in other solvents, such as MeOH, i-PrOH, *n*-PrOH, *n*-BuOH, THF, *tert*-butyl methyl ether, CH_2Cl_2, or 1,2-dichloroethane, yields range from 0 to 83%. The best isomer ratio (1′:3′) in the above reactions was 8:1. A possible explanation for the high regiospecificity found with ethylene glycol is found in the recent literature where stacking of aromatic rings was shown to occur in water-like solvents such as ethylene glycol.[7] In our case, the stacking of the aromatic rings would position the cyano group over the benzylic hydroxyl, and thus initial attack would occur preferentially by the desired hydroxyl group. When **4** is used as the starting material, **7** was isolated in 95% yield from the reaction mixture by precipitation with water and after drying was used in the next step. When **3** was the starting material, the sulfide oxazoline **5** was oxidized to **7** with peracetic acid in >93% yield (two steps), without isolation of **5**. These yields have been reproduced on a 100-kg scale.

The vigorous two-step procedure mentioned earlier which was needed to displace the primary mesylate with fluoride ion is indicative of the difficulty of converting the 3′-hydroxyl group to a fluorine. A one-step procedure was desired and, initially, HF/SF_4 was evaluated. HF/SF_4 reactions are normally carried out at low temperature (−78 °C), but **7** was unaffected under these conditions.[8] Therefore, higher temperatures were used, and at 25 °C in a pressure reactor a greater than 95% yield of **9** was obtained. (When the benzylic hydroxyl group was not protected, fluorination at that position was favored.) Despite this high yield, the cost of SF_4 was prohibitive for a commercial process.

We next studied the usefulness of FAR, Yarovenko's reagent,[9] to carry out this transformation. The Yarovenko reagent is known to effect fluorodehydroxylations under mild conditions; however, again only trace amounts of **9** were formed under the usual conditions. In efforts to drive the reaction to completion, higher temperature and various solvents, including THF, CH_3CN, acetone, *tert*-butyl

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(3) Jommi, G.; Ripa, A. Ripa, G.; Sisti, M. *Gazz. Chim. Ital.* **1985**, *115*, 653–658. Jommi, G.; Pagliarin, R.; Tavecchia, P.; Chiarino, D.; Fantucci, M. *Gazz. Chim. Ital.* **1986**, *116*, 485–489. Jommi, G.; Ripa, A.; Ripa, G.; Sisti, M. *Gazz. Chim. Ital.* **1988**, *118*, 75–76.
(4) Jommi, G.; Chiarino, D.; Pagliarin, R. U.S. Patent 4 743 700, 1988.
(5) Moersch, G. W.; Moore, A. C. U.S. Patent 2 759 001, 1956. Arlt, D.; Jautelat, M. U.S. Patent 4 216 162, 1980. Witte, H.; Selliger, W. U.S. Patent 3 813 378, 1974. Toth, I. T.; Bite, P.; Magyar, G.; Diszler, E.; Borsey, J.; Maderspach, A.; Polgari, I.; Elek, S.; Elekes, I. U.S. Patent 3 979 405, 1976.
(6) Schumacher, D. P.; Clark, J. E.; Murphy, B. L. European Patent Application 89309235.3, 1989.
(7) Kool, E. T.; Breslow, R. *J. Am. Chem. Soc.* **1988**, *110*, 1596–1597.
(8) Wang, C.-H. J. *Organic Reactions*; John Wiley and Sons, Inc.: New York, 1985; Vol. 34, pp 319–400.
(9) Sharts, C. M.; Sheppard, W. H. *Organic Reactions*; John Wiley and Sons, Inc.: New York, 1974; Vol. 21, pp 158–171.

methyl ether, toluene, DMF, EtOAc, and chlorobenzene, were evaluated, and we found that use of 1.3 equiv of FAR in methylene chloride at 100 °C in a pressure reactor gave a 90% yield of **9**. However, under all conditions and solvents evaluated, a persistent byproduct was formed in 7–80% yield. This compound was isolated and identified as the chloro derivative **10**. (Chlorination with the Yarovenko reagent has been noted previously and a mechanism proposed.[10] Our isolation of *N,N*-diethyldifluoroacetamide in reactions which gave large amounts of **10** supports this proposal.) The presence of **10** in the reaction mixture required column chromatography to obtain pure **9**. Addition of metal chlorides to FAR is known to promote chlorination; however, suppression of the formation of **10** could not be achieved by adding excess fluoride ion. Due to the difficulty in removing **10** from the product **9**, we then tried the Ishikawa reagent (FPA),[11] in which chlorination is no longer a possibility. Again, we found that more vigorous conditions than those described in the literature were needed (100 °C, CH_2Cl_2, 100 psi) to obtain **9** in >95% yield. Initially, we used distilled Ishikawa reagent, but it was found that the reagent formed in situ could be used directly with equally good results. This reagent provided the inexpensive, safe, and high-yielding fluorodehydroxylation that was needed.[12]

Although the fluorooxazoline **9** can be isolated from this reaction mixture by precipitation with 2-propanol, the methylene chloride solution of **9** can be used directly in the subsequent hydrolysis step. Various acids were evaluated for the hydrolysis of the oxazoline to the amine **11** and 6 N HCl at 100 °C was found to give the best result. The use of 1–2 N HCl gave **4** as a major byproduct and higher temperatures produced significant amounts of the chloro amine **12**. Careful control of the hydrolysis conditions (10 parts 6 N HCl, 100–102 °C) to minimize both byproducts provided **11** in 95% yield following extraction from the neutralized reaction mixture. Finally, conversion of **11** to **1** was accomplished in 98% yield as previously described using methyl dichloroacetate.[1] The product was recrystallized from 2-propanol–water to give **1** in an overall yield of 70% from **3**. All reactions have been run on at least a 25-kg scale.

In summary, an efficient synthesis of florfenicol from commercially available starting materials has been achieved, using low cost and safe reagents. This process has been used to produce 100-kg quantities of the antibiotic.

Experimental Section

Melting points were measured on a Büchi 510 instrument and are uncorrected. ^1H NMR were recorded on a Varian XL-200, 300, or 400 instrument and ^{13}C NMR were recorded on a Varian XL-300 instrument with tetramethylsilane as an internal standard. FAB mass spectra were determined on a Finnigan MAT 312 instrument and CI mass spectra on an Extranuclear ELQ-400-1 instrument. Rotations were measured on a Rudolph Research Autopol III polarimeter.

D-(−)-*threo*-2-Phenyl-4-(4-(methylthio)phenyl)-2-oxazole-5-methanol (5). A suspension of 5 g (23.5 mmol) of **3** and 0.5 g (3.6 mmol) of K_2CO_3 in a mixture of 7.5 mL of ethylene glycol and 4.1 mL of glycerol was heated at 105 °C. Benzonitrile (4 mL, 39.2 mmol) was added, and the mixture was stirred at 105 °C for 18 h under a blanket of nitrogen. The resultant mixture was cooled and diluted with water. The product was collected by filtration, washed with water and hexane, and dried under vacuum to yield 6.9 g (HPLC purity 97%; yield 95%) (HPLC parameters: column, Zorbax C-8; mobile phase, 2:1:1 CH_3CN–CH_3OH–H_2O; flow rate, 1 mL/min; detection, 254 nm) of **5** as an off-white solid: mp 171–173 °C (lit.[4] mp 175–177 °C); ^1H NMR (200 MHz, DMSO-d_6) δ 2.48 (s, 3 H), 3.5–3.65 (m, 1 H), 3.65–3.8 (m, 1 H), 4.0–4.15 (m, 1 H), 5.04 (t, 1 H, J = 6 H), 5.52 (d, 1 H J = 6 Hz), 7.30 (s, 4 H), 7.45–7.65 (m, 3 H), 7.94 (d, 2 H, J = 9 Hz); ^{13}C NMR (300 MHz, DMSO-d_6) δ 14.6, 62.8, 76.7, 82.1, 126.0, 126.1, 126.2, 127.2, 127.9, 128.6, 131.5, 137.8, 137.9, 139.8, 162.0; mass spectrum m/e 300 $(M + 1)^+$, 282, 232; rotation (MeOH) $[\alpha]^{24.5}$ = 64.4°. Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.19; H, 5.72; N, 4.68; S, 10.71. Found: C, 68.00; H, 5.59; N, 4.62; S, 10.98.

D-*threo*-(−)-2-Phenyl-4-(4-(methylsulfonyl)phenyl)-2-oxazole-5-methanol (7). Method A. A mixture of glycerol (10 mL), K_2CO_3 (0.43 g, 3.1 mmol), and **4** (5.0 g, 20.4 mmol) was heated to 115 °C. Benzonitrile (3.5 mL, 3.5 g, 33.9 mmol) was added, and the mixture was stirred for 18 h at 115 °C. The reaction was cooled and diluted with water. The product was collected by filtration, washed with cold water and methylene chloride, and dried under vacuum to give 6.4 g (HPLC purity 97%; yield 95%) (HPLC parameters: column, Zorbax C-8; mobile phase, 1:1 CH_3CN–H_2O; flow rate, 1 mL/min; detection, 254 nm) of **7** as an off-white solid: mp 206–209 °C (lit.[4] mp 209–211 °C); ^1H NMR (200 MHz, DMSO-d_6) δ 3.22 (s, 3 H), 3.55–3.7 (m, 1 H), 3.7–3.85 (m, 1 H), 4.05–4.2 (m, 1 H), 5.12 (t, 1 H, J = 6 Hz), 5.69 (d, 1 H, J = 6 Hz), 7.45–7.7 (m, 5 H), 7.98 (d, 4 H, J = 9 Hz); ^{13}C NMR (300 MHz, DMSO-d_6) δ 43.4, 62.8, 77.0, 81.6, 126.1, 126.9, 127.5, 128.0, 128.6, 131.7, 140.2, 147.0, 162.0; mass spectrum, m/e 332 $(M + 1)^+$; rotation (DMF) $[\alpha]^{26}$ = 116.4°. Anal. Calcd for $C_{17}H_{17}NO_4S$: C, 61.61; H, 5.17; N, 4.23; S, 9.68. Found: C, 61.29; H, 5.08; N, 4.16; S, 9.83.

Method B. A mixture of **3** (50.0 g, 0.234 mol) and K_2CO_3 (5.0 g, 0.036 mol) in ethylene glycol (75 mL) and glycerol (38 mL) was heated to 105 °C. Benzonitrile (40 mL, 40.4 g, 0.392 mol) was added, and the mixture was stirred at 105 °C for 18 h. The reaction mixture was cooled to 15 °C, and acetic acid (500 mL) was added. The mixture was vigorously stirred, and peracetic acid (150 mL) was added at a rate such that the temperature was maintained between 20 and 25 °C with external cooling. The mixture was stirred for 1 h following the complete addition of the peracetic acid and then poured into a cold, stirred mixture of 2 kg of ice, 400 g of 50% NaOH, and 50 g of sodium bisulfite, keeping the temperature < 20 °C. The pH was adjusted to 12, and the product was collected by filtration, washed with water and hexane, and dried under vacuum to give 74.5 g (HPLC purity 97%; yield 93%) of **7** as a white solid. The mother liquor was concentrated to a residue, which was dissolved in CH_2Cl_2 and chromatographed on silica gel eluted with 2% MeOH–98% CH_2Cl_2. Concentration of the appropriate fractions gave **8** as an off-white solid: mp 131–134 °C; ^1H NMR (200 MHz, DMSO-d_6) δ 3.18 (s, 3 H), 4.26–4.48 (m, 2 H), 4.54–4.67 (m, 1 H), 4.89 (t, 1 H, J = 5 Hz), 5.76 (d, 1 H, J = 5 Hz), 7.38–7.90 (m, 9 H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 43.4, 68.7, 71.5, 72.3, 126.1, 127.4, 127.5, 127.7, 128.4, 131.3, 139.1, 148.5, 163.1; mass spectrum, m/e 332 $(M + 1)^+$; rotation (MeOH) $[\alpha]_D$ = −52.7°. Anal. Calcd for $C_{17}H_{17}NO_4S$: C, 61.61; H, 5.17; N, 4.23; S, 9.68. Found: C, 61.44; H, 5.12; N, 4.00; S, 9.68.

D-(−)-*threo*-2-Phenyl-4-(fluoromethyl)-5-(4-(methylsulfonyl)phenyl)-2-oxazoline (9). To a suspension of **7** (30.0 g, 0.091 mol) in 300 mL of CH_2Cl_2 was added 21.4 mL (26.3 g, 0.118 mol) of Ishikawa reagent[13] at room temperature under nitrogen. The reaction mixture was enclosed in a pressure reactor and heated at 100 °C for 2 h. After cooling to near 0 °C, the vessel was opened and HPLC analysis of the solution gave 28.7 g (0.086 mol, yield 95%) of **9**. After being washed with water, this solution was used directly in the next step. Alternatively, the methylene chloride solution was washed twice with dilute aqueous NaOH and concentrated to a low volume, and **9** was precipitated by the addition of 2-propanol and hexane. The product was collected by filtration, washed with cold 2-propanol, and dried under vacuum to give **9** as a tan solid: mp 117–119 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 3.23 (s, 3 H), 4.3–4.5 (m, 1 H), 4.6–4.9 (m, 2 H), 5.8 (d, 1 H, J = 6 Hz), 7.5–7.7 (m, 5 H), 7.99 (d, 4 H, J = 9 Hz); ^{13}C NMR (300 MHz, DMSO-d_6) δ 43.4, 74.2, 74.5, 80.3, 80.4, 82.6, 84.8, 126.3, 126.5, 127.6, 128.0, 128.7, 132.0, 140.5, 146.1, 163.1;

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(11) (1,1,2,3,3,3-Hexafluoropropyl)diethylamine: Takaoka, A.; Iwagiri, H.; Ishikawa, N. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3377–3380.

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mass spectrum, m/z 334 $(M + 1)^+$. Anal. Calcd for $C_{17}H_{16}NO_3SF$: C, 61.24; H, 4.84; N, 4.20; F, 5.67; S, 9.62. Found: C, 61.42; H, 4.83; N, 4.15, F, 5.34, S, 9.68.

D-(−)-***threo*-1-(4-(Methylsulfonyl)phenyl)-2-amino-3-chloro-1-propanol (10).** To a suspension of **7** (0.5 g, 1.51 mmol) in 10 mL of CH_2Cl_2 was added 0.70 mL (0.83 g, 4.6 mmol) of Yarovenko reagent at room temperature under nitrogen. The reaction was enclosed in a pressure reactor and heated at 100 °C for 5 h. After cooling to near 0 °C, the vessel was opened and the solution was concentrated to a residue. The residue was dissolved in MeOH and chromatographed on silica gel eluted with 16:4:0.75:0.25 toluene–CH_2Cl_2–MeOH–MeOH saturated with NH_3 gas. Concentration of the appropriate fractions yielded **10** as a colorless oil: ^1H NMR (300 MHz, DMSO-d_6) δ 3.23 (s, 1 H), 3.93–4.03 (m, 1 H), 4.08–4.15 (m, 1 H), 4.45–4.5 (m, 1 H), 5.73 (d, 1 H, J = 7.5 Hz), 7.51–7.71 (m, 5 H), 7.95–8.03 (m, 4 H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 43.4, 47.2, 75.1, 81.8, 126.4, 126.5, 127.5, 128.1, 128.8, 132.1, 140.6, 145.9, 163.1; HRMS m/z calcd 350.0618, obsd 350.0646.

D-(−)-***threo*-1-(4-(Methylsulfonyl)phenyl)-2-amino-3-fluoro-1-propanol (11).** The CH_2Cl_2 solution of **9** was added over 0.5 h to 300 mL of 6 N HCl heated at near reflux, allowing the CH_2Cl_2 to distill from the reaction vessel. After removal of the CH_2Cl_2, the reaction mixture was heated at 100–105 °C for 12 h. The solution was cooled and extracted twice with dichloroethane. The aqueous layer was adjusted to pH 12, and the product was extracted into CH_2Cl_2. The CH_2Cl_2 solution was dried over Mg_2SO_4, filtered, and concentrated to a residual solid of 24.0 g (HPLC 85%, 0.0826 mol) (HPLC parameters: column, Zorbax C-8; mobile phase, 20:1 0.05 M pH3 phosphate buffer: CH_3CN; flow rate, 1 mL/min; detection, 254 nm). An analytical sample was prepared by crystallization from CH_2Cl_2: mp 111–113 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 1.54 (br s, 2 H), 2.9–3.1 (m, 1 H), 3.2 (s, 3 H), 4.05–4.5 (m, 2 H), 4.69 (d, 1 H, J = 6 Hz), 5.69 (br s, 1 H), 7.61 (d, 2 H, J = 9 Hz), 7.88 (d, 2 H, J = 9 Hz); ^{13}C NMR (300 MHz, DMSO-d_6) δ 43.0, 55.7, 55.9, 70.6, 83.2, 85.4, 125.9, 126.9, 138.6, 149.1; mass spectrum, m/z 248 $(M + 1)^+$; rotation (MeOH) $[\alpha]^{26} = -36.5°$. Anal. Calcd for $C_{10}H_{14}NO_3SF$: C, 48.56; H, 5.71; N, 5.67; F, 7.68; S, 12.97. Found: C, 48.22; H, 5.48; N, 5.58; F, 7.93; S, 13.08.

D-(−)-***threo*-1-(4-(Methylsulfonyl)phenyl)-2-amino-3-chloro-1-propanol Hydrochloride (12).** A solution of **9** (3.0 g, 9.0 mmol) in 15 mL of 12 N HCl was heated at 130 °C for 22 h. After cooling, the solution was concentrated to a residue, which was triturated with 2-propanol, filtered, and dried, yielding 2.61 g of **12**·HCl as a white solid: mp 189–192 °C; NMR (200 MHz, DMSO-d_6) δ 3.21 (s, 3 H), 3.35–3.5 (m, 1 H) 3.6–3.75 (m, 1 H), 3.87 (dd, 1 H, J = 8, 4 Hz), 4.83–4.95 (m, 1 H), 6.69 (d, 1 H, J = 6 Hz), 7.68 (d, 2 H, J = 9 Hz), 7.95 (d, 2 H, J = 9 Hz), 8.48 (br s, 2 H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 42.6, 43.4, 56.2, 70.0, 127.1, 127.9, 140.5, 145.9; HRMS m/z calcd 264.0461, obsd 264.0451; rotation (MeOH) $[\alpha]_D = 4.1°$.

D-(−)-***threo*-1-(4-(Methylsulfonyl)phenyl)-2-(dichloroacetamido)-3-fluoro-1-propanol (1).** A solution of 11.1 g (HPLC purity 97%, 43.9 mmol) of **11**, 6.12 mL (4.44 g, 43.9 mmol) of Et_3N, and 22.7 mL (31.4 g, 0.220 mol) of methyl dichloroacetate in 110 mL of dry methanol was stirred at room temperature for 18 h. The HPLC analysis of the solution gave 15.4 g (43.0 mmol, 98% yield) of **11**. The reaction mixture was concentrated to a low volume and precipitated by the addition of toluene and H_2O. The product was collected by filtration, washed with H_2O, and dried under vacuum to afford 16.8 g (HPLC purity 90%, 42.2 mmol, 96% yield) of crude **1**. The precipitate was recrystallized from 2-propanol/H_2O and dried under vacuum to yield 13.4 g (HPLC purity 98%, 36.7 mmol, 84% yield) (HPLC parameters: column, Zorbax C-8; mobile phase, 2:1 H_2O–CH_3CN; flow rate, 1 mL/min; detection, 254 nm) of **1** as a white solid: mp 152–154 °C (lit.[1] mp 153–154 °C); NMR (400 MHz, DMSO-d_6) δ 3.17 (s, 3 H), 4.2–4.5 (m, 2 H), 4.55–4.75 (m, 1 H), 5.00 (m, 1 H), 6.17 (d, 1 H, J = 9 Hz), 6.46 (s, 1 H), 7.62 (d, 2 H, J = 9 Hz), 7.87 (d, 2 H, J = 9 Hz), 8.62 (d, 1 H, J = 9 Hz); ^{13}C NMR (300 MHz, DMSO-d_6) δ 43.5, 54.4, 54.7, 66.1, 69.2, 81.1, 83.4, 126.4, 127.0, 139.4, 147.8, 163.6, mass spectrum, m/e 360 $(M + 1)^+$, 358, 342, 340; rotation (DMF) $[\alpha]^{26} = 17.9°$. Anal. Calcd for $C_{12}H_{14}NO_4Cl_2SF$: C, 40.23; H, 3.94; N, 3.91; Cl, 19.80; F, 5.30; S, 8.95. Found: C, 40.48; H, 3.93; N, 3.86; Cl, 19.76; F, 5.39; S, 8.95.

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Synthesis and Reactions of α-Chloro β,γ-Unsaturated Esters. 2. Application to the Synthesis of Dihydrojasmone, *cis*-Jasmone, Desoxyallethrolone, and Novel Cyclopentenones

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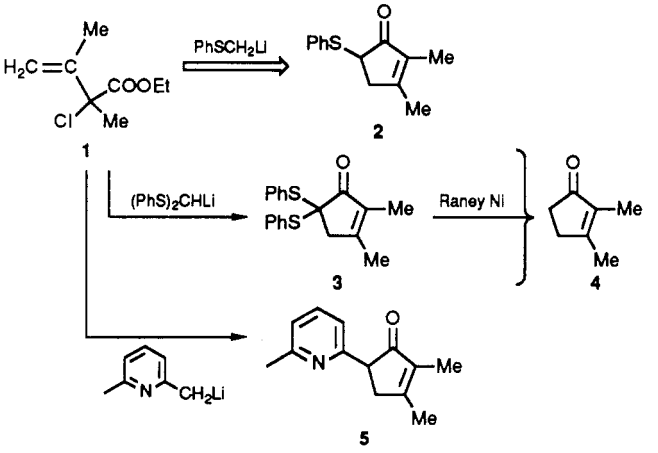
In the preceding paper in this series, we described the syntheses and reactions of four new α-chloro β,γ-unsaturated esters.[1] It was shown that a substituted cyclopentenone can be synthesized by the reaction of 2-lithio-1,3-dithiane with ethyl 2-chloro-2,3-dimethyl-3-butenoate (**1**). As an extension of this novel reaction, we were interested in applying this route for the synthesis of several substituted cyclopentenones. We have now found that other sulfur and nitrogen stabilized carbanions undergo this reaction with allylic halide **1**. Thus (bis(phenylthio)methyl)lithium,[2] ((phenylthio)methyl)lithium,[3] and 2-(lithiomethyl)-6-methylpyridine[4] can be used as the nucleophile in this reaction. Cyclopentenones **2** and **3** undergo desulfurization with Raney nickel at room temperature almost instantaneously and quantitatively. ((Phenylthio)methyl)lithium is the preferred reagent for this transformation due to the ease of removal of sulfur.



In order to extend this reaction to other fully substituted allylic halides similar to **1**, the ene–ester enolate of ethyl 2-chloro-3-methyl-3-butenoate[1] was alkylated with allyl/alkyl halides to give the desired allylic halides:[5]

1, R = Me, yield 76%; **6**, R = $PhCH_2$, yield 63%; **7**, R = CH_2=$CHCH_2$, yield 68%; **8**, R = $(Me)_2C$=$CHCH_2$, yield 56%; **9**, R = EtCH=$CHCH_2$, yield 78%; **10**, R = $CH_3(CH_2)_4$, yield 70%

Two more highly substituted 2-chloro-2-methyl-3-butenoates were prepared by the reaction of hypochlorous

†This work was completed at Petrolite Corp., St. Louis, MO, and is covered by a pending U.S. patent assigned to Petrolite Corp.

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