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A short enantioselective synthesis of (−)-chloramphenicol and (+)-thiamphenicol using tethered aminohydroxylation

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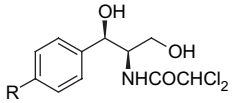
Abstract—An efficient enantioselective synthesis of (−)-chloramphenicol (**1**) and (+)-thiamphenicol (**2**) is described. These antibiotics have been synthesized from commercially available 4-nitrobenzaldehyde and 4-(methylthio)benzaldehyde, respectively, using tethered aminohydroxylation and Sharpless asymmetric epoxidation as the chirality inducing steps.

1. Introduction

(−)-Chloramphenicol **1** and (+)-thiamphenicol **2** (Fig. 1) are broad-spectrum antibiotics with a range of biological activities.[1] The antibiotic chloramphenicol is active only in its D-*threo* configuration and is especially effective in the treatment of typhus, dysentery and ocular bacterial infections.[2] (+)-Thiamphenicol **2**, a synthetic analogue of chloramphenicol **1**, is bacteriostatic for both Gram-positive and Gram-negative aerobes and for some anaerobes.[3] Owing to their potential biological activity, a number of syntheses have been described.[4–7]



R= NO_2; (-)-Chloramphenicol, **1**

R= SO_2Me; (+)-Thiamphenicol, **2**

Figure 1.

Sharpless asymmetric epoxidation has previously been used for the syntheses of **1** and **2**.[5c,d,j,7c,e] In one of these reports, the authors made use of a *Z*-cinnamyl alcohol for which the asymmetric epoxidation required a long reaction time.[5c] Further, in some cases, the use of *E*-cinnamyl alcohol resulted in the increase of the number of steps.[5d,7c,e] In another report, the use of Sharpless asymmetric epoxidation under kinetic resolution conditions required expensive, unnatural (−)-diisopropyl tartrate [(−)-DIPT].[5j] However, we are able to replace the unnatural (−)-diisopropyl tartrate with naturally occurring and cheaply available (+)-diisopropyl tartrate for the enantioselective syntheses of **1** and **2**.

The tethered aminohydroxylation (TA),[8] an intramolecular asymmetric aminohydroxylation of alkenes, has become a reliable method in recent years for achieving excellent levels of *syn* selectivity while providing at the same time complete control over the regio- and chemoselectivity of the oxidation. We describe herein a new, short approach for the stereoselective synthesis of (−)-chloramphenicol **1** and (+)-thiamphenicol **2** by employing two key reactions, namely, Sharpless asymmetric epoxidation[11] and the tethered aminohydroxylation.[8]

2. Result and discussion

Our synthesis of (−)-chloramphenicol **1** (Scheme 1) starts with the reaction of 4-nitrobenzaldehyde **3a** with divinylzinc[9] to give 1-(4-nitrophenyl)allyl alcohol **4a** in 68% yield. Allylic alcohol **4a** was then subjected to Sharpless asymmetric epoxidation under kinetic resolution conditions[10] using the naturally occurring (+)-diisopropyl tartrate [(+)-DIPT] to furnish the corresponding chiral allylic alcohol, 1-(***S***)-4-(nitrophenyl)-2-propen-1-ol **6a**, in 44% chemical yield and 98% ee (optical purity was determined by ^{1}H NMR analysis of the corresponding Mosher's ester **10a**, see Section 4 for details) along with the corresponding epoxide **7a** in 49% yield. Both chiral alcohol **6a** and epoxide **7a** could be easily separated by column chromatographic purification. Alcohol **6a** was then treated with trichloroacetyl isocyanate[11] in CH_2Cl_2 to give the corresponding isocyanate, which on treatment with K_2CO_3 and methanol in the presence of H_2O gave the carbamate **8a** in 90% yield.

The carbamate **8a** thus obtained was converted into the oxazolidinone **9a** by a tethered aminohydroxylation protocol[8b]

Keywords: Asymmetric synthesis; Asymmetric epoxidation; Kinetic resolution; Tethered aminohydroxylation.
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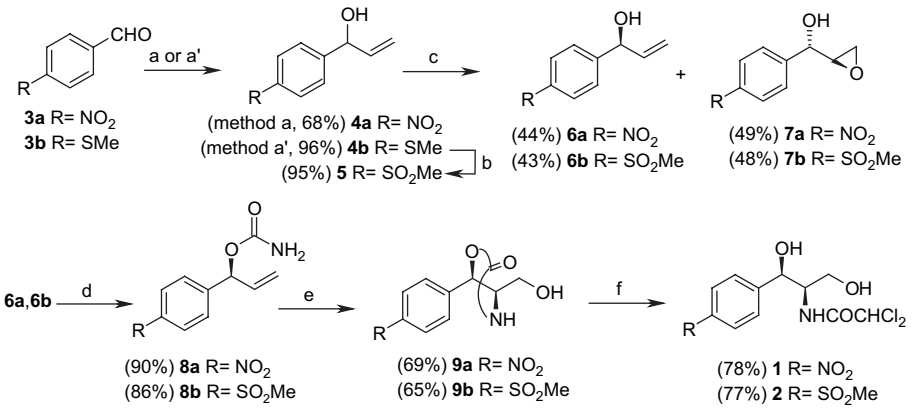

Scheme 1. Reagents and conditions: (a) divinylzinc, THF, Et_2O, −78–25 °C, 10 h; (a′) vinylmagnesium bromide, THF, 0–25 °C, 2 h; (b) oxone, THF/MeOH/H_2O (1:1:1), 0–25 °C, 30 min, 95%; (c) (+)-DIPT, $Ti(O^iPr)_4$, TBHP, CH_2Cl_2, −20 °C, 14–24 h; (d) (i) trichloroacetyl isocyanate, CH_2Cl_2, 0–25 °C, 2 h; (ii) K_2CO_3, MeOH, H_2O, 0–25 °C, 18 h; (e) $K_2Os(OH)_4O_2$, *t*-BuOCl, NaOH, EtN-*i*-Pr_2, *n*-PrOH/H_2O (1:1), 25 °C, 3 h; (f) (i) 1 N NaOH, MeOH, 25 °C, overnight; (ii) methyl dichloroacetate, 90 °C, 3 h.

using *tert*-butyl hypochlorite as the oxidant in the presence of potassium osmate, 0.08 M NaOH, diisopropyl ethylamine and propan-1-ol as the solvent. The reaction proceeded smoothly to furnish the protected aminoalcohol **9a** as a single isomer with complete regiocontrol and excellent *syn* selectivity (*syn*:*anti*>20:1, determined by ^{1}H NMR analysis) giving 69% yield. The compound **9a** was then hydrolyzed using 1 N NaOH in methanol[5h] to furnish the crude aminoalcohol, which was then taken in methyl dichloroacetate[4a,5h] and heated at 90 °C for 3 h to give (−)-chloramphenicol **1** in 78% yield. $[\alpha]_D^{25}$ −25.4 (*c* 1, EtOAc) [lit.[12] $[\alpha]_D^{23}$ −25.5 (*c* 1, EtOAc)]. The spectral data of **1** was in complete agreement with the reported values.[1b]

The same strategy was extended to the synthesis of (+)-thiamphenicol **2** (Scheme 1). Commercially available 4-(methylthio)benzaldehyde **3b** was converted to the allyl alcohol **4b** using vinylmagnesium bromide in THF.[5j] The thioether **4b** was then oxidized using oxone[13] to give the corresponding sulfonyl ester **5** in 95% yield. Allyl alcohol **5** was then subjected to Sharpless asymmetric epoxidation[10] using (+)-diisopropyl tartrate under kinetic resolution conditions to furnish the chiral alcohol **6b** in 43% yield and 98% ee (the optical purity was determined by ^{1}H NMR analysis of the corresponding Mosher's ester **10b**, see Section 4 for details) along with the epoxide **7b**. Both alcohol **6b** and epoxide **7b** could be easily separated by column chromatography. The carbamate **8b** obtained from **6b** under the same experimental conditions[11] as explained earlier was converted into the oxazolidinone **9b** using tethered aminohydroxylation.[8b] The desired isomer of the oxazolidinone **9b** was obtained with high stereoselectivity (*syn*:*anti*>20:1, determined by ^{1}H NMR analysis) giving 65% yield. Finally, the hydrolysis of **9b** with 1 N NaOH in methanol[5h] followed by the treatment with methyl dichloroacetate[4a,5h] gave the final product thiamphenicol **2** in 77% yield. $[\alpha]_D^{25}$ +12.7 (*c* 1, EtOH) [lit.[3] $[\alpha]_D^{25}$ +12.9 (*c* 1, EtOH)]. The spectral data of **2** was in complete agreement with the reported values.[5j,14]

3. Conclusion

In conclusion, we have achieved an efficient synthesis of (−)-chloramphenicol (overall yield 29%, 98% ee) and (+)-thiamphenicol (overall yield 34%, 98% ee) using tethered aminohydroxylation and Sharpless asymmetric epoxidation as the two key chirality inducing steps. The major advantages of this work are the use of naturally occurring (+)-DIPT for the kinetic resolution and the use of tethered aminohydroxylation for the induction of second chiral centre in the molecule in a highly diastereoselective fashion (dr=98:2).

4. Experimental

4.1. General

Solvents were purified and dried by standard procedures before use;[15] petroleum ether of boiling range 60–80 °C was used. Melting points are uncorrected. Optical rotations were measured using sodium D line on a JASCO-181 digital polarimeter. Infrared spectra were recorded on Shimadzu FTIR-8400 spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on Bruker AV-200, AV-400 and BRX-500 NMR spectrometers, respectively. Elemental analysis was carried on a Carlo Erba CHNS-O analyzer.

4.2. 1-(4-Nitrophenyl)-2-propen-1-ol (4a)

To a stirred solution of vinylmagnesium bromide [prepared from vinyl bromide (8.49 g, 79.4 mmol) and magnesium (1.93 g, 79.4 mmol)] in THF (90 mL), freshly fused $ZnCl_2$ (5.40 g, 39.7 mmol) dissolved in THF (30 mL) was added at 0 °C under nitrogen atmosphere. This solution was stirred at 55 °C for 18 h, after which it was cooled to 10 °C and dry ether (150 mL) was added and stirred for 10 min. The reaction mixture was allowed to settle for 30 min. The supernatant liquid was transferred through a canula to another flask. This solution was allowed to cool to −78 °C, then 4-nitrobenzaldehyde **3a** (1.5 g, 9.92 mmol) in THF (20 mL) was added over a period of 15 min. The reaction mixture was allowed to warm to room temperature and stirring continued for 10 h. The reaction mixture was then quenched at −20 °C by the addition of aqueous ammonium chloride. The aqueous layer was extracted with ethyl acetate (3×100 mL) and the combined organic fractions collected and washed with water and brine solution, then dried over Na_2SO_4 and

concentrated under reduced pressure. The crude compound was purified by column chromatography using petroleum ether/EtOAc (8:2) to afford compound **4a** (1.21 g, 68%) as a pale yellow amorphous solid. Mp: 48–49 °C; IR ($CHCl_3$) ν_{max} 3433, 2858, 1606, 1519, 1348, 1217, 1108, 1041, 989, 854, 757 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.21 (d, J=8.8 Hz, 2H), 7.56 (d, J=8.5 Hz, 2H), 5.91–6.05 (m, 1H), 5.25–5.45 (m, 3H), 2.04 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.6, 147.1, 139.1, 126.9, 123.5, 116.6, 74.4. Anal. Calcd for $C_9H_9NO_3$ (179.18): C, 60.33; H, 5.06; N, 7.82. Found: C, 60.45; H, 5.09; N, 7.94%.

4.3. 1-(*S*)-(4-Nitrophenyl)-2-propen-1-ol (6a)

To a stirred suspension of powdered 4 Å molecular sieves (1.5 g) in dry CH_2Cl_2 (25 mL), $Ti(O^iPr)_4$ (1.27 g, 4.47 mmol) was added under nitrogen atmosphere. The reaction mixture was cooled to −20 °C and (+)-diisopropyl tartrate (1.25 g, 5.36 mmol) was added and stirred for 10 min, after which allyl alcohol **4a** (0.8 g, 4.5 mmol) dissolved in CH_2Cl_2 (20 mL) was added and stirred at −20 °C for 30 min. To the above solution *tert*-butyl hydroperoxide (0.22 g, 2.5 mmol) dissolved in toluene was added and stirred at −20 °C for 14 h. After completion of half of the reaction (monitored by TLC), the reaction mixture was quenched with 10% aqueous solution of tartaric acid (25 mL), after which stirring was continued for 1 h at −20 °C and 2 h at room temperature. The organic layer was separated, washed with water and dried over Na_2SO_4, and concentrated under reduced pressure. The residue was diluted with ether (75 mL) and stirred with 1 M NaOH (25 mL) for 1 h at 0 °C. The organic layer was then separated, washed with brine solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography using petroleum ether/EtOAc (8:2) to afford compound **6a** (0.35 g, 44%) as a pale yellow amorphous solid. Mp: 48–49 °C; $[\alpha]_D^{25}$ +41.3 (c 1, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3433, 2858, 1606, 1519, 1348, 1217, 1108, 1041, 989, 854, 757 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.21 (d, J=8.8 Hz, 2H), 7.56 (d, J=8.5 Hz, 2H), 5.91–6.05 (m, 1H), 5.25–5.45 (m, 3H), 2.04 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.6, 147.1, 139.1, 126.9, 123.5, 116.6, 74.4. Anal. Calcd for $C_9H_9NO_3$ (179.18): C, 60.33; H, 5.06; N, 7.82. Found: C, 60.45; H, 5.09; N, 7.94%.

4.4. (1*R*,2*S*)-1-(4-Nitrophenyl)oxiranemethanol (7a)

White amorphous solid. Mp: 74–75 °C; $[\alpha]_D^{25}$ +60.8 (c 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 8.23 (d, J=9.0 Hz, 2H), 7.57 (d, J=9.0 Hz, 2H), 5.01 (br d, J=3.0 Hz, 1H), 3.20 (ddd, J=2.6, 3.0, 4.2 Hz, 1H), 2.88 (dd, J=2.6, 4.9 Hz, 1H), 2.72 (dd, J=4.2, 4.9 Hz, 1H), 2.45 (br s, 1H).

4.5. Preparation of Mosher's ester of 1-(*S*)-(4-nitrophenyl)-2-propen-1-ol (10a)

A two-neck 10 mL flask with septum was charged with (44 mg, 0.21 mmol) *N*,*N*′-dicyclohexylcarbodiimide (DCC), catalytic amount of 4-dimethylaminopyridine (DMAP) and CH_2Cl_2 (2 mL) under argon atmosphere. The flask was allowed to cool at 0 °C for 10 min and a solution of alcohol **6a** (32 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) was introduced through a syringe. It was allowed to stir for additional 10 min, followed by dropwise addition of (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (46 mg, 0.196 mmol) in CH_2Cl_2 (2 mL). This reaction mixture was then stirred at 0 °C for additional 1 h and then at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated sodium bicarbonate solution (50 mL), dried over Na_2SO_4 and then concentrated under reduced pressure to give Mosher's ester of the alcohol (53 mg, 70%) as a thick syrup. $[\alpha]_D^{25}$ +39.5 (c 0.4, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3158, 2952, 2927, 2850, 2250, 1753, 1606, 1519, 1495, 1348, 1268, 1242, 1217, 1153, 1122, 1015, 957, 911, 735, 650 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.15 (d, J=9 Hz, 2H), 7.32–7.53 (m, 7H), 6.48 (d, J=6.6 Hz, 1H), 5.90–6.06 (m, 1H), 5.36–5.47 (m, 2H), 3.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.27, 147.98, 144.53, 134.09, 133.87, 132.04, 129.79, 128.45, 127.68, 127.24, 123.86, 119.95, 77.06, 55.56. Anal. Calcd for $C_{19}H_{16}F_3NO_5$ (395.10): C, 57.72; H, 4.08; F, 14.42; N, 3.54. Found: C, 57.94; H, 3.82; F, 14.68; N, 3.21.

4.6. 1-(*S*)-(4-Nitrophenyl)allyl carbamate (8a)

To a stirred solution of alcohol **6a** (0.45 g, 2.5 mmol) in dichloromethane (12 mL) at 0 °C was added dropwise trichloroacetyl isocyanate (0.36 mL, 3 mmol). The resulting solution was stirred for 2 h and then concentrated in vacuo. The residue was diluted with MeOH (13 mL), cooled to 0 °C and a solution of potassium carbonate (1.04 g, 7.5 mmol) in H_2O (2.4 mL) was added. The resulting suspension was stirred at 0 °C for 2 h, then at room temperature for 16 h. The reaction was concentrated in vacuo, diluted with H_2O (50 mL) and brine (50 mL) and extracted with dichloromethane (2×50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by column chromatography using petroleum ether/EtOAc (6:4) to give **8a** (0.5 g, 90%) as a pale yellow crystalline solid. Mp: 101 °C; $[\alpha]_D^{25}$ +12.39 (c 1, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3471, 3280, 3178, 1724, 1620, 1514, 1386, 1346, 1328, 1215, 925, 854, 756 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.23 (d, J=8.8 Hz, 2H), 7.53 (d, J=8.7 Hz, 2H), 6.23 (d, J=6 Hz, 1H), 5.89–6.06 (m, 1H), 5.35 (t, J=7.3 Hz, 2H), 4.86 (br s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.5, 147.5, 146.3, 135.2, 127.5, 123.7, 118.2, 75.7. Anal. Calcd for $C_{10}H_{10}N_2O_4$ (222.22): C, 54.05; H, 4.54; N, 12.62. Found: C, 54.16; H, 4.50; N, 12.61%.

4.7. (5*R*,6*R*)-4-(Hydroxymethyl)-5-(4-nitrophenyl)-2-oxazolidinone (9a)

A fresh aqueous solution of sodium hydroxide (0.08 M, 0.9 equiv) was prepared. All but a few drops of this were added in one portion to a stirred solution of the allylic carbamate (0.222 g, 1 mmol) in propan-1-ol (12 mL). The solution was allowed to stir for 5 min, before freshly prepared *tert*-butyl hypochlorite (0.114 mL, 1 mmol) was added. The mixture was again allowed to stir for 5 min. To this was added diisopropyl ethylamine (5 mol %) in one portion. The mixture was allowed to stir for a further 5 min before the final addition of a solution of potassium osmate (4 mol %) in the remainder of the sodium hydroxide solution made earlier. The reaction was monitored by TLC and halted when

no further change was detected. The reaction was quenched by the addition of sodium sulfite (500 mg), and allowed to stir for 30 min. The mixture was extracted with ethyl acetate (2×50 mL). The combined organics were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica using petroleum ether/EtOAc (4:6) to give **9a** (0.16 g, 69%) as a gum. $[\alpha]_D^{25}$ −4.08 (*c* 1.1, EtOH); IR ($CHCl_3$) ν_{max} 3351, 2944, 2832, 2523, 1755, 1607, 1527, 1450, 1416, 1351, 1112, 666 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 8.33 (d, *J*=8.3 Hz, 2H), 7.75 (d, *J*=8.7 Hz, 2H), 6.96 (s, 1H), 5.61 (m, 1H), 4.49 (s, 1H), 3.81 (m, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 158.3, 148.6, 148.3, 127.3, 124.4, 78.6, 63.7, 62.1. Anal. Calcd for $C_{10}H_{10}N_2O_5$ (238.22): C, 50.42; H, 4.23; N, 11.77. Found: C, 50.36; H, 4.36; N, 11.86%.

4.8. (1*R*,2*R*)-2-(Dichloroacetamido)-1-(4-nitrophenyl)-1,3-propanediol (1)

A solution of 1 N NaOH was made in methanol. The above solution (10 mL) was added to **9a** (0.95 g, 0.4 mmol) and stirred overnight at room temperature. The reaction mixture was filtered and the filtrate concentrated in vacuum. The crude compound was taken in methyl dichloroacetate (2 mL) and heated at 90 °C for 3 h. The excess ester was removed under reduced pressure and the crude compound was purified by column chromatography using petroleum ether/EtOAc (3:7) to give the product **1** (0.1 g, 78%) as a white amorphous solid. Mp: 151–152 °C [lit.[11] 149.7–150.7 °C]; $[\alpha]_D^{25}$ −24.9 (*c* 1, EtOAc) [lit.[11] $[\alpha]_D^{23}$ −25.5 (*c* 1, EtOAc)]; IR ($CHCl_3$) ν_{max} 3420, 3020, 2929, 1686, 1604, 1523, 1454, 1403, 1348, 1216, 1049, 850 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.31 (d, *J*=9 Hz, 1H), 8.15 (d, *J*=8.3 Hz, 2H), 7.58 (d, *J*=8.5 Hz, 2H), 6.47 (s, 1H), 6.04 (br s, 1H), 4.83–5.05 (m, 2H), 3.90–3.95 (m, 1H), 3.56–3.61 (m, 1H), 3.33–3.40 (m, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 164.3, 150.1, 147.3, 128.2, 123.2, 70.6, 66.6, 61.6, 56.9. Anal. Calcd for $C_{11}H_{12}Cl_2N_2O_5$ (323.15): C, 40.89; H, 3.74; Cl, 21.94; N, 8.68. Found: C, 40.93; H, 3.82; Cl, 21.89; N, 8.66%.

4.9. 1-(4-Methylsulfanylphenyl)-2-propen-1-ol (4b)

To a stirred suspension of Mg (7.1 g, 296 mmol) in THF (75 mL), vinyl bromide (15.82 g, 147.81 mmol) in THF (45 mL) was added at 0 °C under nitrogen atmosphere over a period of 15 min and continued stirring at room temperature for a further 30 min. The reaction mixture was cooled to 0 °C and 4-(methylthio)benzaldehyde **3b** (7.5 g, 49.26 mmol) dissolved in THF (75 mL) was added over a period of 10 min. After the addition was completed, the reaction mixture was allowed to return to room temperature and stirring continued for another 2 h. The reaction mixture was quenched by the addition of aqueous ammonium chloride and extracted with ethyl acetate (3×100 mL). The combined organic fractions were collected and washed with water and brine solution, then dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by column chromatography using petroleum ether/EtOAc (8:2) to afford compound **4b** (8.5 g, 96%) as a thick syrup; IR ($CHCl_3$) ν_{max} 3398, 3078, 2981, 2920, 1639, 1598, 1492, 1431, 1404, 1219, 1093, 989, 927, 815 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.30 (d, *J*=8.7 Hz, 2H), 7.24 (d, *J*=8.7 Hz, 2H), 5.95–6.11 (m, 1H), 5.17–5.39 (m, 3H), 2.48 (s, 3H), 1.97 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.9, 139.4, 137.5, 126.7, 126.5, 114.9, 74.6, 15.74. Anal. Calcd for $C_{10}H_{12}OS$ (180.27): C, 66.63; H, 6.71; S, 17.79. Found: C, 66.79; H, 6.89; S, 17.68%.

4.10. 1-(4-Methylsulfonylphenyl)-2-propen-1-ol (5)

To a vigorously stirred solution of sulfide **4b** (3.78 g, 21 mmol) in THF (20 mL), MeOH (20 mL) and H_2O (20 mL) at 0 °C was added oxone (36 g, 59 mmol) portionwise. After 5 min at 0 °C, the white suspension was warmed to room temperature and stirred for 30 min. The reaction was poured into H_2O (200 mL) and extracted with CH_2Cl_2 (3×100 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude compound was purified by column chromatography using petroleum ether/EtOAc (6:4) to give sulfone **5** (4.25 g, 95%) as a white amorphous solid. Mp: 56.5–57.5 °C; IR ($CHCl_3$) ν_{max} 3481, 3020, 2927, 2360, 1639, 1598, 1407, 1303, 1149, 1087, 958, 761 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.91 (d, *J*=8.5 Hz, 2H), 7.58 (d, *J*=8.2 Hz, 2H), 5.99 (m, 1H), 5.23–5.43 (m, 3H), 3.03 (s, 3H), 2.20 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.0, 139.3, 139.1, 127.3, 127.1, 116.2, 74.34, 44.39. Anal. Calcd for $C_{10}H_{12}O_3S$ (212.27): C, 56.58; H, 5.69; S, 15.11. Found: C, 56.69; H, 5.76; S, 15.23%.

4.11. 1-(*S*)-(4-Methylsulfonylphenyl)-2-propen-1-ol (6b)

To a stirred suspension of powdered 4 Å molecular sieves (7 g) in dry CH_2Cl_2 (75 mL), $Ti(O^iPr)_4$ (3.12 g, 11 mmol) was added under nitrogen atmosphere. The reaction mixture was cooled to −20 °C and (+)-diisopropyl tartrate (3.1 g, 13.2 mmol) was added and stirred for 10 min, after which allyl alcohol **5** (2.3 g, 11 mmol) dissolved in CH_2Cl_2 (60 mL) was added and stirred at −20 °C for about 30 min. To the above solution *tert*-butyl hydroperoxide (0.59 g, 6.6 mmol) dissolved in toluene was added and stirred at −20 °C for about 24 h. After completion of half of the reaction (monitored by TLC), the reaction mixture was quenched with 10% aqueous solution of tartaric acid (80 mL), after which stirring was continued for 1 h at −20 °C and 2 h at room temperature. The organic layer was separated, washed with water and dried over Na_2SO_4 and concentrated under reduced pressure. The residue was diluted with ether (250 mL) and stirred with 1 M NaOH (100 mL) for about 1 h at 0 °C. The organic layer was then separated, washed with brine solution, dried over Na_2SO_4 and then concentrated under reduced pressure. The crude compound was purified by column chromatography using petroleum ether/EtOAc (6:4) to afford compound **6b** (1 g, 43%) as white amorphous solid. Mp: 56.5–57.5 °C; $[\alpha]_D^{25}$ +28.38 (*c* 1, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3481, 3020, 2927, 2360, 1639, 1598, 1407, 1303, 1149, 1087, 958, 761 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.91 (d, *J*=8.5 Hz, 2H), 7.58 (d, *J*=8.2 Hz, 2H), 5.99 (m, 1H), 5.23–5.43 (m, 3H), 3.03 (s, 3H), 2.20 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.0, 139.3, 139.1, 127.3, 127.1, 116.2, 74.34, 44.39. Anal. Calcd for $C_{10}H_{12}O_3S$ (212.27): C, 56.58; H, 5.69; S, 15.11. Found: C, 56.55; H, 5.61; S, 15.26%.

4.12. (1*R*,2*S*)-1-(4-Methylsulfonylphenyl)oxirane-methanol (7b)

Thick syrup. $[\alpha]_D^{25}$ +47.3 (*c* 1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.91 (d, *J*=8.3 Hz, 2H), 7.59 (d, *J*=8.3 Hz, 2H), 4.96 (br d, *J*=3.0 Hz, 1H), 3.19 (m, 1H), 3.02 (s, 3H), 2.88 (dd, *J*=3.0, 5.2 Hz, 1H), 2.73 (dd, *J*=3.7, 5.2 Hz, 1H), 2.50 (br s, 1H).

4.13. Preparation of Mosher's ester of 1-(*S*)-(4-methylsulfonylphenyl)-2-propen-1-ol (10b)

A two-neck 10 mL flask with septum was charged with (44 mg, 0.21 mmol) *N*,*N*′-dicyclohexylcarbodiimide (DCC), catalytic amount of 4-dimethylaminopyridine (DMAP) and CH_2Cl_2 (2 mL) under argon atmosphere. The flask was allowed to cool at 0 °C for 10 min and a solution of alcohol **6b** (38 mg, 0.179 mmol) in CH_2Cl_2 (2 mL) was introduced through a syringe. It was allowed to stir for additional 10 min, followed by dropwise addition of (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (46 mg, 0.196 mmol) in CH_2Cl_2 (2 mL). This reaction mixture was then stirred at 0 °C for additional 1 h and then at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated sodium bicarbonate solution (50 mL), dried over Na_2SO_4 and then concentrated under reduced pressure to get Mosher's ester of the alcohol (53 mg, 70%) as a thick syrup. $[\alpha]_D^{25}$ +42.5 (*c* 0.4, MeOH); IR ($CHCl_3$) ν_{max} 3156, 3069, 2951, 2930, 2851, 2255, 1754, 1644, 1601, 1496, 1452, 1410, 1318, 1243, 1154, 1016, 957, 910, 737, 650 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.87 (d, *J*=8.5 Hz, 2H), 7.35–7.45 (m, 7H), 6.48 (d, *J*=6.5 Hz, 1H), 5.89–6.06 (m, 1H), 5.35–5.47 (m, 2H), 3.55 (s, 3H), 3.04 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.33, 147.44, 143.67, 140.73, 134.17, 131.99, 129.77, 128.43, 127.78, 127.24, 119.84, 77.31, 55.55, 44.44. Anal. Calcd for $C_{20}H_{19}F_3O_5S$ (428.42): C, 56.07; H, 4.47; F, 13.30; S, 7.48. Found: C, 57.24; H, 4.24; F, 13.06; S, 7.71.

4.14. 1-(*S*)-(4-(Methylsulfonyl)phenyl)allyl carbamate (8b)

To a stirred solution of alcohol **6b** (1 g, 4.7 mmol) in dichloromethane (23 mL) at 0 °C was added dropwise trichloroacetyl isocyanate (0.71 mL, 5.64 mmol). The resulting solution was stirred for 2 h and then concentrated in vacuo. The residue was diluted with MeOH (25 mL), cooled to 0 °C and a solution of potassium carbonate (1.95 g, 14.1 mmol) in H_2O (5 mL) was added. The resulting suspension was stirred at 0 °C for 2 h, then at room temperature for 16 h. The reaction was concentrated in vacuo, diluted with H_2O (50 mL) and brine (50 mL) and extracted with dichloromethane (2×50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude material was purified by column chromatography using petroleum ether/EtOAc (4:6) to give **8b** (0.99 g, 86%) as a white crystalline solid. Mp: 159 °C; $[\alpha]_D^{25}$ −10.23 (*c* 1, MeOH); IR (neat) ν_{max} 3421, 3265, 2906, 1720, 1608, 1406, 1379, 1298, 1145, 1041, 947, 769 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.93 (d, *J*=7.8 Hz, 2H), 7.58 (d, *J*=7.8 Hz, 2H), 6.84 (s, 1H), 6.61 (s, 1H), 6.10 (d, *J*=5.5 Hz, 1H), 5.97–6.04 (m, 1H), 5.32 (d, *J*=16.9 Hz, 1H), 5.22 (d, *J*=10.1 Hz, 1H), 3.20 (s, 3H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 155.7, 146.1, 140.2, 136.9, 127.5, 127.4, 117.0, 74.5, 43.7. Anal. Calcd for $C_{11}H_{13}NO_4S$ (255.30): C, 51.75; H, 5.13; N, 5.49; S, 12.56. Found: C, 51.79; H, 5.27; N, 5.40; S, 12.49%.

4.15. (5*R*,6*R*)-4-(Hydroxymethyl)-5-(4-(methylsulfonyl)phenyl)-2-oxazolidinone (9b)

A fresh aqueous solution of sodium hydroxide (0.08 M, 0.9 equiv) was prepared. All but a few drops of this were added in one portion to a stirred solution of the allylic carbamate (0.76 g, 3 mmol) in propan-1-ol (30 mL). The solution was allowed to stir for 5 min, before freshly prepared *tert*-butyl hypochlorite (0.4 mL, 3 mmol) was added. The mixture was again allowed to stir for 5 min. To this was added diisopropyl ethylamine (5 mol %) in one portion. The mixture was allowed to stir for a further 5 min before the final addition of a solution of potassium osmate (4 mol %) in the remainder of the sodium hydroxide solution made earlier. The reaction was monitored by TLC and halted when no further change was detected. The reaction was quenched by the addition of sodium sulfite (1.5 g), and allowed to stir for 30 min. The mixture was extracted with ethyl acetate (2×50 mL). The combined organics were washed with brine, dried over sodium sulfate and concentrated under reduced pressure. The crude material was purified by flash column chromatography on silica using petroleum ether/EtOAc (2:8) to give **9b** (0.53 g, 65%) as a pale yellow amorphous solid. Mp: 152 °C; $[\alpha]_D^{25}$ +9.74 (*c* 1.16, MeOH); IR (neat) ν_{max} 3259, 3020, 2929, 2399, 2360, 1716, 1602, 1407, 1299, 1215, 1149, 1089, 1026, 954, 769 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 7.98 (d, *J*=8.5 Hz, 2H), 7.95 (br s, 1H), 7.62 (d, *J*=8.3 Hz, 2H), 5.45 (d, *J*=3.9 Hz, 1H), 5.20 (t, *J*=5.3 Hz, 1H), 3.46–3.59 (m, 3H), 3.22 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.1, 146.0, 140.8, 127.8, 126.6, 77.8, 62.6, 61.3, 43.7. Anal. Calcd for $C_{11}H_{13}NO_5S$ (271.30): C, 48.69; H, 4.83; N, 5.17; S, 11.82. Found: C, 48.62; H, 4.94; N, 5.23; S, 11.76%.

4.16. (1*R*,2*R*)-2-(Dichloroacetamido)-1-[(4-methylsulfonyl)phenyl]-1,3-propanediol (2)

A solution of 1 N NaOH was made in methanol. The above solution (10 mL) was added to **9b** (0.14 g, 0.4 mmol) and stirred overnight at room temperature. The reaction mixture was filtered and the filtrate concentrated in vacuum. The crude compound was taken in methyl dichloroacetate (2 mL) and heated at 90 °C for 3 h. The excess ester was removed under reduced pressure and the crude compound was purified by column chromatography using petroleum ether/EtOAc (1:9) to give the product **2** (0.11 g, 77%) as a white amorphous solid. Mp: 164–165 °C [lit.[2] 164.3–166.3 °C]; $[\alpha]_D^{25}$ +12.5 (*c* 1, EtOH) [lit.[2] $[\alpha]_D^{25}$ +12.9 (*c* 1, EtOH)]; IR (neat) ν_{max} 3481, 3407, 3242, 3082, 3020, 2925, 1699, 1562, 1406, 1282, 1215, 1145, 1033, 906, 806, 767 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 7.93 (d, *J*=8.5 Hz, 2H), 7.71 (d, *J*=8.2 Hz, 2H), 7.70 (d, *J*=8.2 Hz, 1H), 6.41 (s, 1H), 5.31 (d, *J*=2.4 Hz, 1H), 5.27 (d, *J*=3.8 Hz, 1H) 4.28 (t, *J*=4.7 Hz, 1H), 4.10–4.20 (m, 1H), 3.77–3.89 (m, 1H), 3.63–3.72 (m, 1H), 3.10 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 164.42, 149.59, 140.95, 127.85,

127.77, 71.21, 67.51, 62.08, 57.99, 44.34. Anal. Calcd for $C_{12}H_{15}Cl_2NO_5S$ (356.23): C, 40.46; H, 4.24; Cl, 19.9; N, 3.93, S, 9.0. Found: C, 40.59; H, 4.38; Cl, 19.85; N, 4.05; S, 8.96%.

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