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Stereoselective syntheses of (−)-chloramphenicol and (+)-thiamphenicol

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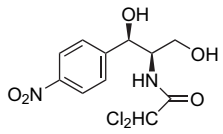
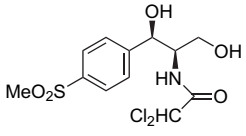
Abstract—Chloramphenicol and thiamphenicol have been enantioselectively synthesized using an asymmetric halohydrin reaction as a key step. In particular, halomethoxylation reaction was used, where *O*-methyl functions as a hydroxyl protecting group and eliminates an additional protection step.

1. Introduction

Chloramphenicol **1** is one of the oldest antibacterial agents, which was first isolated from *Streptomyces venezuelae* in 1947.[1] It is biologically active only as its 2*R*,3*R* enantiomer and might be the first antibiotic obtained commercially in optically active form by chemical synthesis. It is widely used as a broad spectrum antibiotic and has especially been effective in the treatment of typhi, dysentery, salmonella, rickettsia, and ocular bacterial infections.



1: (-)-chloramphenicol



2: (+)-thiamphenicol

Thiamphenicol **2** is an analogue of chloramphenicol and is active against both gram-positive and gram-negative microorganisms.[2] Due to the potent biological activity of compounds **1** and **2**, a number of chemical syntheses of racemic compounds and a few asymmetric syntheses have been described.[3–6] Herein, we report in detail the stereoselective syntheses of (−)-chloramphenicol **1** and (+)-thiamphenicol **2** using an asymmetric halohydrin (halohydroxylation as well as halomethoxylation) reaction as a key step.

Recently, a silver(I)-promoted asymmetric halohydrin (hydroxylation as well as halomethoxylation) reaction of chiral α,β-unsaturated carboxylic acids has been developed in our laboratory.[7] Accordingly, we anticipated that the Ag_2O-promoted asymmetric bromohydroxylation reaction of cinnamoyl substrate **3** containing oxazolidinone chiral auxiliary[8] at a lower temperature (e.g., −10 °C) might provide the carboxybromohydrin **4** as the major diastereomer with the desired stereochemistry for the synthesis of (−)-chloramphenicol. When the Ag_2O-promoted bromohydroxylation reaction of **3a** was performed at −10 °C instead of 0 °C (Table 1; entry 1), it gave, as anticipated, **4a** as the major diastereoisomer (entry 2). Unlike reaction at 0 °C (entry 4), $AgNO_3$-promoted reaction of **3a** also provided **4a** as a major isomer (entry 5). However, Ag_2O and $AgNO_3$-promoted bromohydroxylation of *p*-nitrocinnamoyl substrate **3b** showed poor diastereoselectivity (entries 6–9). The diastereoselectivity could not be improved by performing the reaction under a variety of reaction conditions.

Initially, the synthesis of chloramphenicol began with the α-bromo-β-hydroxy carbonyl compound **4a** (Scheme 1). Reaction of **4a** with NaN_3 in DMF at 25 °C gave the α-azido-β-hydroxy carbonyl compound **6a** (89%). Two-step reduction of azido carbonyl **6a** with $LiBH_4$ in THF–MeOH yielded azidodiol **7a** (90%) followed by reduction with hydrogen and Pd/C (10%) in MeOH under atmospheric pressure provided the amino alcohol **8a** in 99% yield. Compound **8a** would provide the (−)-chloramphenicol upon simple chemical modification by following the literature procedure,[4e] that requires an additional aryl nitration. Optical purity of **8a** was compared with previously reported values ($[\alpha]_D^{26}$ −26.0, *c* 1, MeOH; lit.[9] $[\alpha]_D^{22}$ −26.5, *c* 1, MeOH).

To avoid the nitration step, we initiated the synthesis of (−)-chloramphenicol from 4-nitrocinnamoyl compound **9a** containing Oppolzer's (2*R*)-bornanesultam[10] as a chiral

Keywords: Enantioselective synthesis; (−)-Chloramphenicol; (+)-Thiamphenicol; Asymmetric; Halohydrin reaction.
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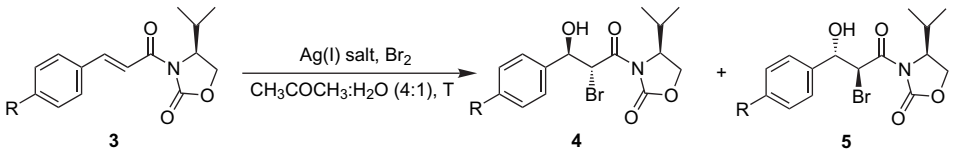
Table 1. Asymmetric bromohydroxylation of **3** under different reaction conditions[a]



Entry	Substrate	R	Ag(I) salt	T (°C)	Ratio[b] (**4**:**5**)	Yield[c] (%)
1	**3a**	H	Ag_2O	0	50:50	97
2	**3a**	H	Ag_2O	−10	72:28 (74:26)	93
3	**3a**	H	Ag_2O	−20	—	NR[d]
4	**3a**	H	$AgNO_3$	0	35:65 (34:66)	92
5	**3a**	H	$AgNO_3$	−10	64:36 (67:33)	93
6	**3b**	NO_2	Ag_2O	0	48:52	90
7	**3b**	NO_2	Ag_2O	−10	50:50	91
8	**3b**	NO_2	$AgNO_3$	0	47:53	92
9	**3b**	NO_2	$AgNO_3$	−10	50:50	90

[a] For **3a**: Ag_2O-promoted bromohydroxylation reactions were performed using 0.7 equiv of Ag_2O and 1.2 equiv of Br_2 in 20% aqueous acetone and $AgNO_3$-promoted bromohydroxylation were performed using 2.0 equiv of $AgNO_3$ and 1.2 equiv of Br_2, for **3b**: Ag_2O-promoted bromohydroxylation reactions were performed using 1.0 equiv of Ag_2O and 1.2 equiv of Br_2 in 20% aqueous acetone and $AgNO_3$-promoted bromohydroxylation were performed using 2.0 equiv of $AgNO_3$ and 2.0 equiv of Br_2.

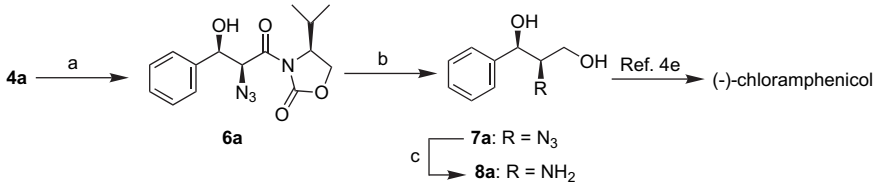
[b] Determined from the ^{1}H NMR spectrum of the crude reaction mixture. Ratios in the parentheses refer to the ratio of isolated **4** and **5** after column chromatography.

[c] Combined isolated yields of **4** and **5** after column chromatography.

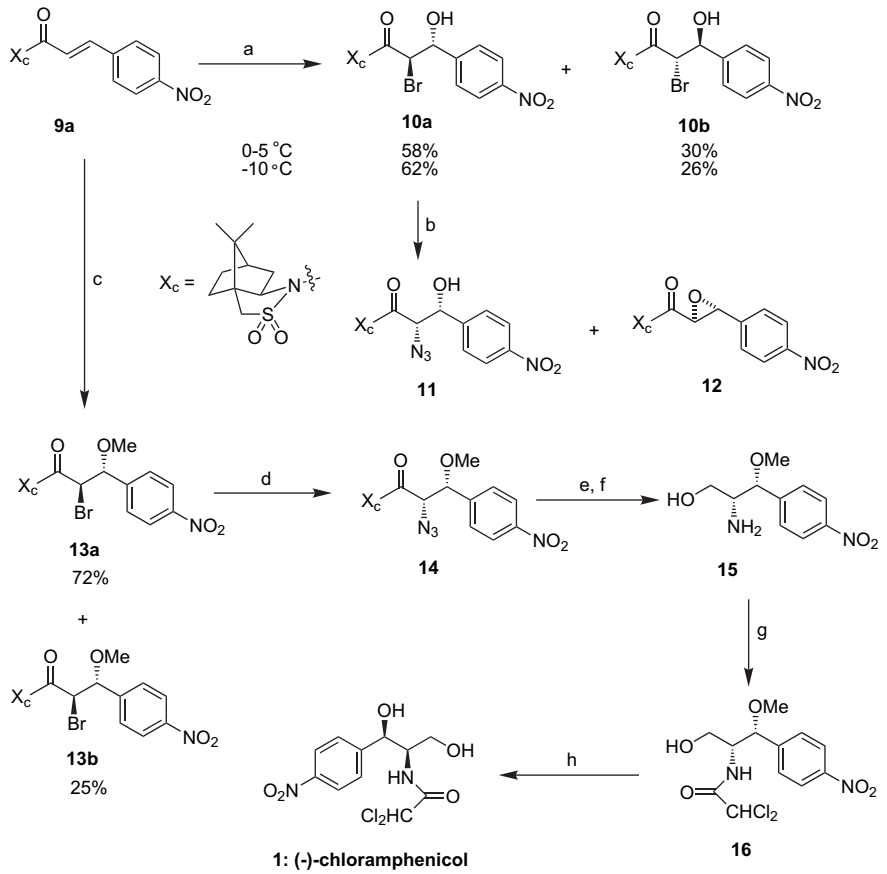
[d] >90% of **3a** was recovered.

auxiliary (Scheme 2). $AgNO_3$-promoted bromohydroxylation of **9a** with Br_2 in aqueous acetone provided the compound **10a** in 58% and 62% yields at 0 °C and at −10 °C, and the minor diastereomer **10b** in 30% and 26% yields, respectively. Unlike **4a**, reaction of **10a** with NaN_3 in DMF at 25 °C yielded a non-separable mixture (40:60) of azido carbonyl **11** and epoxy carbonyl compound **12**. The protection of β-hydroxyl functionality of **10a** was found to be essential for the replacement of bromide with azide.[4f] For this purpose and to eliminate an additional protection step we utilized our halomethoxylation reaction, where *O*-methyl functions as a hydroxyl protecting group. $AgNO_3$-promoted bromomethoxylation of **9a** with Br_2 in MeOH/CH_2Cl_2 at 0 °C gave the desired α-bromo-β-methoxy carbonyl compound **13a** in 72% yield along with minor diastereomer **13b** in 25% yield. There was no appreciable change in diastereoselectivity when the bromomethoxylation was performed at even lower temperature viz. −15 °C and −30 °C. It should be noted that the bromomethoxylation of the 4-nitrocinnamoyl substrate containing an oxazolidine chiral auxiliary (**3b**) showed, similar to the bromohydroxylation, poor diastereoselectivity (dr 52:48). Reaction of **13a** with NaN_3 in DMF at 60 °C gave the α-azido-β-methoxy carbonyl compound **14** in 92% yield. Two-step reduction of azido carbonyl **14** with $LiBH_4$ in THF followed by Ph_3P in H_2O–THF provided the amino alcohol **15** in 82% yield. N-acylation of **16** with Cl_2CHCO_2Me at 90 °C for 1 h yielded the compound **16**. Finally, demethylation of **16** with BBr_3 in CH_2Cl_2 at low temperature completed the intended synthesis of (−)-chloramphenicol. The specific optical rotation of the synthetic (−)-chloramphenicol **1** ($[\alpha]_D^{26}$ −25.4, *c* 1, EtOAc) was compared with previously reported[11] values ($[\alpha]_D^{23}$ −25.5, *c* 1, EtOAc).

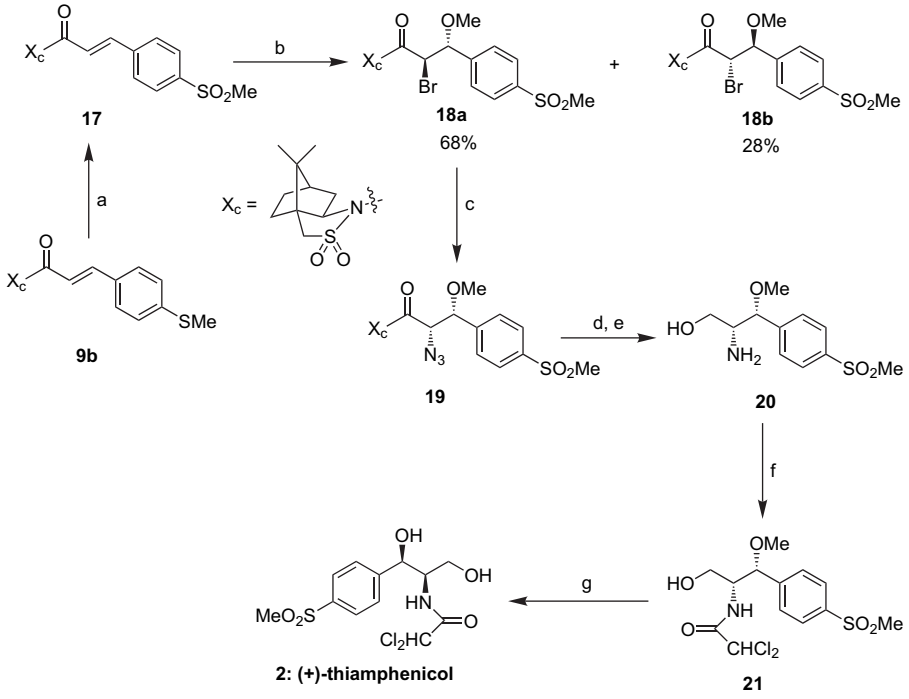
Similarly, the synthesis of (+)-thiamphenicol commenced (Scheme 3) with a Ag(I)-promoted asymmetric bromomethoxylation reaction of the substrate **17**, which afforded the α-bromo-β-methoxy carbonyl compound **18a** in 68% yield and a minor isomer **18b** (28%). Substrate **17** was obtained in 92% yield by MMPP oxidation of **9b**. Replacement of the bromide of **18a** by azide in DMF at 60 °C yielded the α-azido-β-methoxy carbonyl compound **19** in 92% yield. Reduction of the azido carbonyl **19** was performed in two steps with $LiBH_4$ in THF followed by Ph_3P in THF–H_2O to afford the amino alcohol **20**. Transformation of 3-hydroxy-protected 2-amino-1,3-propanediol **20** into (+)-thiamphenicol was readily accomplished by first forming the *N*-dichloroacetamide followed by demethylation. Treatment of **20** with the excess of Cl_2CHCO_2Me at 90 °C afforded **21** in 85% yield and (+)-thiamphenicol **2** was obtained in 84% isolated yield by demethylation of **21** with 2.2 equiv of BBr_3 in CH_2Cl_2. The identity and optical purity of the synthetic (+)-thiamphenicol **2** was confirmed by comparing with its spectral and physical properties with that of those reported in the literature ($[\alpha]_D^{26}$ +12.8, *c* 1, EtOH; lit.[2] $[\alpha]_D^{25}$ +12.9, *c* 1, EtOH).



Scheme 1. Reagents and conditions: (a) NaN_3, DMF, 25 °C, 4 h, 89%; (b) $LiBH_4$, THF–MeOH, 0 °C, 1 h, 90% and (c) Pd/C (10%), MeOH, H_2, rt, 12 h, 99%.



Scheme 2. Reagents and conditions: (a) $AgNO_3$, Br_2, acetone: H_2O (4:1), 30 min; (b) NaN_3, DMF, 25 °C, 4 h; (c) $AgNO_3$, Br_2, MeOH, 0 °C, 30 min, 72% (**13a**), 25% (**13b**); (d) NaN_3, DMF, 60 °C, 4 h, 92%; (e) $LiBH_4$, THF–MeOH; (f) Ph_3P, THF–H_2O, 25 °C, 5 h, 82% (for two steps); (g) Cl_2CHCO_2Me (excess), 90 °C, 1 h, 87% and (h) BBr_3, CH_2Cl_2, −78 °C to −20 °C, 10 h, 80%.



Scheme 3. Reagents and conditions: (a) MMPP, MeOH, rt, 2 h, 92%; (b) $AgNO_3$, Br_2, MeOH, 0 °C, 30 min, 68% (**18a**), 28% (**18b**); (c) NaN_3, DMF, 60 °C, 4 h, 92%; (d) $LiBH_4$, THF–MeOH; (e) Ph_3P, THF–H_2O, 25 °C, 5 h, 82% (for two steps); (f) Cl_2CHCO_2Me (excess), 90 °C, 1 h, 85% and (g) BBr_3, CH_2Cl_2, −78 °C to −20 °C, 10 h, 84%.

In conclusion, asymmetric halohydrin reaction—halohydroxylation and halomethoxylation—provides an efficient strategy for the synthesis of enantiomerically pure (−)-chloramphenicol and (+)-thiamphenicol. This strategy can also be extended toward synthesizing other structurally related compounds and analogues.

2. Experimental

2.1. General

All reactions were conducted using an oven-dried glassware under an atmosphere of Argon (Ar). Commercial grade reagents were used without further purification. Solvents were dried and distilled following usual protocols. Flash chromatography was carried out using Spectrochem Silica gel (230–400 mesh) purchased from Spectrochem, India. TLC was performed on aluminum-backed plates coated with Silica gel 60 with F_{254} indicator (Merck). Substrates **3** and **9** were synthesized by following the literature procedures.[8,10,12]

The ^{1}H NMR spectra were measured with Bruker-200 (200 MHz) and ^{13}C NMR spectra were measured with Bruker-200 (50 MHz) using $CDCl_3$, C_2D_6SO, CD_3OD, and CD_3CN. ^{1}H NMR chemical shifts are expressed in parts per million (δ) downfield to $CDCl_3$ (δ=7.26), C_2D_6SO (δ=2.49), CD_3OD (δ=3.30), and CD_3CN (δ=1.93); ^{13}C NMR chemical shifts are expressed in parts per million (δ) relative to the central $CDCl_3$ resonance (δ=77.0), C_2D_6SO (δ=39.7), CD_3OD (δ=49.0), and CD_3CN (δ=118.2 and 1.3). Coupling constants in ^{1}H NMR are expressed in Hertz. Elemental analyses were carried out on a Perkin–Elmer 2400-II. Melting points were measured in Toshniwal (India) melting point apparatus.

2.1.1. Halohydroxylation of substrates 3. To a solution of the substrate **3** (1 mmol) in 20% aqueous acetone (20 mL) Ag(I) [for **3a** Ag_2O (0.7 mmol) or $AgNO_3$ (1.2 mmol) and Br_2 (1.2 mmol); for **3b** Ag_2O (1.0 mmol) or $AgNO_3$ (2 mmol)] and Br_2 (2.0 mmol) were added, respectively, at 0–5 °C and allowed to stir for 20–30 min. The reaction mixture was extracted with Et_2O at least three times, washed with water, and dried over Na_2SO_4. The organic solution was filtered through a small Celite pad (otherwise locking problem or poor base line was found in the ^{1}H NMR of the crude mixture) and the filtrate was concentrated under vacuum. Flash column chromatography of the crude mixture using petroleum ether–EtOAc as eluent gave the desired carboxyhalohydrins in pure form. Compounds **4a** and **5a** were characterized by spectral analysis.[7b]

2.1.1.1. *anti*-(4*S*,2′*S*,3′*S*)-3-[2′-Bromo-3′-hydroxy-3′-(4-nitrophenyl)-propionyl]-4-(1-methylethyl)-2-oxazolidinone (4b). Colorless gummy liquid. $[\alpha]_D^{25}$ +52.91 (*c* 0.9, $CHCl_3$); FTIR (KBr): 3445 (br), 1778, 1682, 1626, 1519, 1385, 1344, 1299, 1230, 1204, 1143, 1100, 1057, 1030, 988, 975, 848, 750, 714, 669, 634, 532, 488 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.24 (d, *J*=8.7 Hz, 2H), 7.63 (d, *J*=8.7 Hz, 2H), 5.82 (d, *J*=8.1 Hz, 1H), 5.33 (d, *J*=8.1 Hz, 1H), 4.60–4.40 (m, 1H), 4.40–4.15 (m, 2H), 2.50–2.0 (m, 1H), 0.96 (d, *J*=2.0 Hz, 3H), 0.90 (d, *J*=2.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 171.7, 154.8, 148.6, 147.7, 127.3 (2C), 123.8 (2C), 74.7, 63.7, 59.1, 44.4, 28.8, 17.7, 14.5; Anal. Calcd for $C_{15}H_{17}BrN_2O_6$: C, 44.90; H, 4.27; N, 6.98. Found: C, 45.11; H, 4.58; N, 6.79%.

2.1.1.2. *anti*-(4*S*,2′*R*,3′*R*)-3-[2′-Bromo-3′-hydroxy-3′-(4-nitrophenyl)-propionyl]-4-(1-methylethyl)-2-oxazolidinone (5b). Colorless gummy liquid. $[\alpha]_D^{25}$ +5.15 (*c* 1, $CHCl_3$); FTIR (KBr): 3464 (br), 1780, 1705, 1523, 1388, 1348, 1205, 1107, 1051, 857, 754, 744, 699, 667, 614, 530 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.24 (d, *J*=11.2 Hz, 2H), 7.65 (d, *J*=11.2 Hz, 2H), 5.94 (d, *J*=7.7 Hz, 1H), 5.27 (d, *J*=7.7 Hz, 1H), 4.50–4.15 (m, 3H), 2.45–2.15 (m, 1H), 0.89 (d, *J*=7.0 Hz, 3H), 0.75 (d, *J*=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 171.8, 154.9, 148.3, 147.9, 126.9 (2C), 123.6 (2C), 74.6, 63.8, 58.8, 44.4, 28.5, 17.8, 14.6; Anal. Calcd for ($C_{15}H_{17}BrN_2O_6$+1.5·H_2O): C, 42.07; H, 4.71; N, 6.54. Found: C, 42.17; H, 4.93; N, 6.60%.

2.1.1.3. *syn*-(4*S*,2′*S*,3′*R*)-3-(2′-Azido-3′-hydroxy-3′-phenyl-propionyl)-4-(1-methylethyl)-2-oxazolidinone (6a). To a stirred solution of **5a** (0.40 g, 1.12 mmol) in 5 mL DMF at room temperature was added NaN_3 (0.108 g, 1.66 mmol) and stirred for 6 h. The reaction mixture was quenched with water and extracted with EtOAc (3× 50 mL). The combined organic layers were dried over Na_2SO_4. The organic phase was evaporated under reduced pressure and the crude reaction mixture was then purified by flash column chromatography to obtain pure **6a** (0.318 g, 89%) as a colorless gummy liquid. $[\alpha]_D^{26}$ +39.58 (*c* 1.0, $CHCl_3$); FTIR (KBr): 3483 (br), 2115, 1778, 1705, 1485, 1453, 1388, 1300, 1205, 1142, 1104, 1057, 1022, 974, 864, 757, 731, 704, 668, 614, 553, 531 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.52–7.20 (m, 5H), 5.39 (d, *J*=5.1 Hz, 1H), 5.17 (d, *J*=5.1 Hz, 1H), 4.35–3.95 (m, 3H), 2.50–2.25 (m, 1H), 0.89 (t, *J*=6.9 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 168.5, 153.4, 138.9, 128.5 (3C), 126.3 (2C), 74.4, 65.5, 63.8, 58.9, 28.2, 17.8, 14.5; Anal. Calcd for ($C_{15}H_{18}N_4O_4$+1·H_2O): C, 53.56; H, 5.99; N, 16.66. Found: C, 53.12; H, 5.65; N, 16.88%.

2.1.1.4. *syn*-(2*R*,3*R*)-[2-Azido-3-hydroxy-3-phenyl-1-propanol] (7a). To a stirred solution of **6a** (0.40 g, 1.24 mmol) in 5 mL THF were added 1 mL MeOH followed by $LiBH_4$ (0.028 g, 1.24 mmol) at 0 °C under an argon atmosphere and stirred for 1 h. The reaction mixture was quenched with slow addition of H_2O at 0 °C and extracted with EtOAc (3×50 mL). The combined organic layers were dried over Na_2SO_4. The organic phase was evaporated under reduced pressure and the crude reaction mixture was then purified by flash column chromatography to obtain pure **7a** (0.215 g, 90%) as colorless gummy liquid. $[\alpha]_D^{26}$ +76.26 (*c* 1.0, $CHCl_3$); FTIR (KBr): 3393 (br), 2140, 2112, 1723, 1619, 1531, 1313, 1228, 1121, 1115, 994, 961, 835, 753, 610, 543 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.50–7.25 (m, 5H), 4.81 (d, *J*=6.0 Hz, 1H), 3.75–3.45 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.2, 128.6 (2C), 128.4, 126.3 (2C), 74.3, 68.7, 62.4; Anal. Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 56.17; H, 6.01; N, 21.34%.

2.1.1.5. *syn*-(2*R*,3*R*)-[2-Amino-3-hydroxy-3-phenyl-1-propanol] (8a). To a stirred solution of **7a** (0.20 g,

1.02 mmol) in 5 mL dry MeOH under hydrogen atmosphere (1 atm) was added Pd/C (10%) (0.015 g) at 0 °C under hydrogen atmosphere and stirred for 12 h at room temperature. The reaction mixture was filtered through a half-inch bed of Celite and the filtrate was evaporated under reduced pressure (at<40 °C) to obtain pure **8a** (0.168 g, 99%) as a colorless gummy liquid. $[\alpha]_D^{26}$ −26.0 (*c* 1, MeOH) [lit.[9] $[\alpha]_D^{22}$ −26.5 (*c* 1, MeOH)]; FTIR (KBr): 3372 (br), 1592, 1519, 1355, 1204, 1164, 1018, 883, 851, 766, 741, 612, 528, 519 cm^{-1}; ^1H NMR [200 MHz, $CDCl_3$:CD_3OD (3:1)]: δ 7.70–7.20 (m, 5H), 4.50 (d, *J*=8.6 Hz, 1H), 3.55–3.10 (m, 2H), 3.00–2.55 (m, 1H); ^{13}C NMR [50 MHz, $CDCl_3$:CD_3OD (1:1)]: δ 139.1, 128.5 (2C), 127.3 (3C), 70.1, 65.5, 62.3; Anal. Calcd for ($C_9H_{13}NO_2$+1·H_2O): C, 58.36; H, 8.16; N, 7.56. Found: C, 58.77; H, 8.10; N, 7.76%.

2.1.1.6. *anti*-(2*R*,2′*R*,3′*R*)-*N*-[2′-Bromo-3′-hydroxy-3′-(4-nitrophenyl)-propionyl]-bornanesultam (10a). Colorless gummy liquid. $[\alpha]_D^{25}$ −99.41 (*c* 0.8, $CHCl_3$); FTIR (KBr): 3495 (br), 1779, 1737, 1697, 1607, 1524, 1439, 1389, 1349, 1302, 1206, 1106, 1056, 983, 945, 857, 839, 754, 700, 670, 521 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.26 (d, *J*=8.7 Hz, 2H), 7.59 (d, *J*=8.7 Hz, 2H), 5.47 (d, *J*=6.4 Hz, 1H), 4.76 (d, *J*=6.4 Hz, 1H), 4.16–3.94 (m, 2H), 3.52 (d, *J*=1.8 Hz, 2H), 2.29–2.02 (m, 2H), 2.00–1.77 (m, 3H), 1.64–1.26 (m, 2H), 1.14 (s, 3H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$): 166.7, 147.8, 145.8, 127.9 (2C), 123.7 (2C), 75.3, 65.1, 52.6, 48.6, 47.7, 45.3, 44.3, 37.6, 32.9, 26.3, 19.9, 19.5; Anal. Calcd for $C_{19}H_{23}BrN_2O_6S$: C, 46.82; H, 4.76; N, 5.75. Found: C, 46.61; H, 4.98; N, 5.43%.

2.1.1.7. *anti*-(2*R*,2′*S*,3′*S*)-*N*-[2′-Bromo-3′-hydroxy-3′-(4-nitrophenyl)-propionyl]-bornanesultam (10b). Colorless gummy liquid. $[\alpha]_D^{25}$ −1.19 (*c* 0.75, $CHCl_3$); FTIR (KBr): 3448 (br), 1692, 1600, 1522, 1386, 1347, 1216, 1166, 1136, 1117, 1067, 856, 760, 699, 537, 499 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.25 (d, *J*=8.8 Hz, 2H), 7.60 (d, *J*=8.8 Hz, 2H), 5.31 (d, *J*=6.7 Hz, 1H), 4.83 (d, *J*=6.7 Hz, 1H), 4.17–3.92 (m, 2H), 3.56 (d, *J*=2.0 Hz, 2H), 2.30–2.00 (m, 2H), 2.00–1.76 (m, 3H), 1.68–1.25 (m, 2H), 1.15 (s, 3H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.8, 147.9, 145.9, 127.8 (2C), 123.6 (2C), 75.4, 65.4, 52.7, 48.6, 47.6, 45.2, 44.4, 37.8, 32.7, 26.1, 20.0, 19.6; Anal. Calcd for $C_{19}H_{23}BrN_2O_6S$: C, 46.82; H, 4.76; N, 5.75. Found: C, 47.19; H, 5.01; N, 5.76%.

2.1.1.8. *anti*-(2*R*,2′*R*,3′*R*)-*N*-[2′-Bromo-3′-methoxy-3′-(4-nitrophenyl)-propionyl]-bornanesultam (13a). To a stirred solution of **9a** (0.50 g, 1.28 mmol) in 5 mL MeOH and 1.5 mL CH_2Cl_2 (0–5 °C) were added $AgNO_3$ (0.435 g, 2.56 mmol) and Br_2 (0.409 g, 2.56 mmol) and allowed to stir at that temperature for 20–30 min. The reaction mixture was quenched with water and extracted with EtOAc (3×50 mL). The combined organic layers were dried over Na_2SO_4. The organic phase was evaporated under reduced pressure and the crude reaction mixture was then purified by flash column chromatography to obtain pure **13a** (0.42 g, 72%) as white solid. Mp 153–155 °C; $[\alpha]_D^{26}$ −89.74 (*c* 1.0, $CHCl_3$); FTIR (KBr): 1696, 1608, 1524, 1456, 1384, 1347, 1218, 1167, 1136, 1101, 967, 857, 834, 758, 698, 558, 535, 500 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.24 (d, *J*=8.7 Hz, 2H), 7.60 (d, *J*=8.7 Hz, 2H), 4.79 (s, 2H), 4.15–3.95 (m, 2H), 3.52 (d, *J*=1.1 Hz, 2H), 3.22 (s, 3H), 2.30–2.05 (m, 2H), 2.00–1.80 (m, 3H), 1.55–1.30 (m, 2H), 1.15 (s, 3H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.1, 148.1, 144.4, 129.2 (2C), 123.3 (2C), 82.1, 64.8, 58.0, 52.7, 48.7, 47.7, 45.1, 44.3, 37.7, 32.5, 26.2, 20.4, 19.6; Anal. Calcd for $C_{20}H_{25}BrN_2O_6S$: C, 47.91; H, 5.03; N, 5.59. Found: C, 47.88; H, 5.02; N, 5.86%.

2.1.1.9. *anti*-(2*R*,2′*S*,3′*S*)-*N*-[2′-Bromo-3′-methoxy-3′-(4-nitrophenyl)-propionyl]-bornanesultam (13b). Colorless gummy liquid. $[\alpha]_D^{24}$ +5.31 (*c* 0.9, $CHCl_3$); FTIR (KBr): 3422 (br), 1686, 1522, 1384, 1347, 1302, 1216, 1166, 1136, 1116, 1066, 1041, 993, 856, 760, 699, 614, 533, 498 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.24 (d, *J*=8.7 Hz, 2H), 7.62 (d, *J*=8.7 Hz, 2H), 4.95 (d, *J*=6.5 Hz, 1H), 4.81 (d, *J*=6.5 Hz, 1H), 4.17–3.92 (m, 2H), 3.53–3.51 (m, 2H), 3.21 (s, 3H), 2.32–2.03 (m, 2H), 2.00–1.81 (m, 3H), 1.56–1.27 (m, 2H), 1.15 (s, 3H), 0.99 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.2, 148.0, 144.2, 128.9 (2C), 123.3 (2C), 82.9, 65.3, 57.7, 52.7, 48.6, 47.9, 45.7, 44.5, 37.7, 32.5, 26.7, 20.2, 19.6; Anal. Calcd for ($C_{20}H_{25}BrN_2O_6S$+1·H_2O): C, 46.25; H, 5.24; N, 5.39. Found: C, 46.19; H, 5.19; N, 5.48%.

2.1.1.10. *syn*-(2*R*,2′*S*,3′*R*)-*N*-[2′-Azido-3′-methoxy-3′-(4-nitrophenyl)-propionyl]-bornanesultam (14). To a stirred solution of **13a** (0.50 g, 1.05 mmol) in 10 mL DMF at 60 °C was added NaN_3 (0.11 g, 1.50 mmol) and stirred for 8 h at 60 °C. The reaction mixture was quenched with water and extracted with EtOAc (3×50 mL). The combined organic layers were dried over Na_2SO_4. The organic phase was evaporated under reduced pressure and the crude reaction mixture was then purified by flash column chromatography to obtain pure **14** (0.48 g, 92%) as white solid. Mp 152–154 °C; $[\alpha]_D^{26}$ −76.57 (*c* 1.0, $CHCl_3$); FTIR (KBr): 2140, 2111, 1711, 1607, 1519, 1333, 1216, 1166, 1135, 1106, 1067, 831, 761, 541 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.21 (d, *J*=6.8 Hz, 2H), 7.59 (d, *J*=6.8 Hz, 2H), 4.90 (d, *J*=5.7 Hz, 1H), 4.50 (d, *J*=5.7 Hz, 1H), 4.00–3.80 (m, 2H), 3.45 (s, 2H), 3.30 (s, 3H), 2.25–1.60 (m, 5H), 1.50–1.10 (m, 2H), 0.90 (s, 3H), 0.68 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.6, 148.3, 143.9, 128.8 (2C), 123.7 (2C), 83.4, 65.9, 65.2, 57.8, 53.0, 48.4, 47.5, 44.7, 37.9, 32.7, 26.4, 20.0, 19.7; Anal. Calcd for $C_{20}H_{25}N_5O_6S$: C, 51.83; H, 5.44; N, 15.11. Found: C, 51.89; H, 5.34; N, 14.89%.

2.1.1.11. *syn*-(2*R*,3*R*)-[2-Amino-3-methoxy-3-(4-nitrophenyl)-1-propanol] (15). To a stirred solution of **14** (0.30 g, 0.72 mmol) in 5 mL THF were added 1 mL MeOH followed by $LiBH_4$ (0.017 g, 0.72 mmol) at 0 °C under an argon atmosphere and stirred for 1 h. The reaction mixture was quenched with slow addition of H_2O at 0 °C and extracted with EtOAc (3×40 mL). The combined organic layers were dried over Na_2SO_4. The organic phase was evaporated under reduced pressure and the crude reaction mixture was taken in 5 mL THF and 1 mL H_2O mixture, to that Ph_3P (0.226 g, 0.86 mmol) was added and stirred for 12 h in dark. The reaction mixture was diluted with EtOAc (50 mL) and evaporated under reduced pressure. The crude compound was purified by column chromatography to afford pure **15** (0.106 g, 82%) as a colorless gummy liquid. $[\alpha]_D^{26}$ −65.59 (*c* 1.0, $CHCl_3$); FTIR (KBr): 3367 (br), 1605, 1522, 1348, 1108, 854, 829, 753, 701, 617, 542 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.22 (d, *J*=8.7 Hz, 2H), 7.49 (d, *J*=8.7 Hz, 2H), 4.25 (d, *J*=6.5 Hz, 1H), 3.60–3.40 (m,

1H), 3.40–3.10 (m, 2H), 3.24 (s, 3H), 2.94 (br s, NH), 2.40 (br s, OH); ^{13}C NMR ($CDCl_3$): δ 147.7, 146.9, 128.0 (2C), 123.7 (2C), 84.1, 62.8, 58.2, 57.4; Anal. Calcd for ($C_{10}H_{14}N_2O_4$+1.5·H_2O): C, 47.43; H, 6.77; N, 11.06. Found: C, 47.43; H, 6.28; N, 11.39%.

2.1.1.12. 2,2-Dichloro-*N*-[1-hydroxymethyl-2-methoxy-2-(4-nitrophenyl)-ethyl]-acetamide (16). Compound **15** (0.15 g, 0.66 mmol) was taken in 25 mL of $Cl_2CHCOOMe$ and stirred at 90 °C for 45 min and after the completion of reaction, unreacted $Cl_2CHCOOMe$ was evaporated under reduced pressure, the crude material was then purified by column chromatography to obtain pure **16** (0.193 g, 87%) as a colorless gummy liquid. $[\alpha]_D^{26}$ −60.97 (*c* 1.0, $CHCl_3$); FTIR (KBr): 3403, 1685, 1607, 1522, 1464, 1348, 1217, 1087, 1015, 859, 811, 754, 725, 702, 666, 542 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.23 (d, *J*=8.7 Hz, 2H), 7.50 (d, *J*=8.7 Hz, 2H), 7.05 (d, *J*=8.5 Hz, NH), 5.80 (s, 1H), 4.73 (d, *J*=3.1 Hz, 1H), 4.20–4.00 (m, 1H), 3.82 (d, *J*=5.3 Hz, 2H), 3.37 (s, 3H), 1.95 (br s, OH); ^{13}C NMR ($CDCl_3$): δ 164.2, 147.7, 145.4, 127.5 (2C), 123.7 (2C), 80.9, 66.1, 61.9, 57.8, 56.3; Anal. Calcd for $C_{12}H_{14}Cl_2N_2O_5$: C, 42.75; H, 4.19; N, 8.31. Found: C, 42.07; H, 4.45; N, 8.79%.

2.1.1.13. (−)-Chloramphenicol (1). To a stirred solution of **16** (0.15 g, 0.42 mmol) in 5 mL DCM at –78 °C was added 1 M solution of BBr_3 in DCM (1.11 mL, 1.11 mmol) and the temperature was raised to –20 °C under an argon atmosphere and stirred for 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (3×40 mL). The combined organic layers were dried over Na_2SO_4. The organic phase was evaporated under reduced pressure and the crude reaction mixture was purified by column chromatography to afford pure (−)-chloramphenicol **1** (0.115 g, 0.34 mmol) as white solid. Mp 150–152 °C [lit.[11] 149.7–150.7 °C]; $[\alpha]_D^{26}$ −25.16 (*c* 1.0, EtOAc) [lit[11] $[\alpha]_D^{23}$ −25.5 (*c* 1, EtOAc)]. Spectroscopic data consistent with that reported in the literature.[4i]

2.1.1.14. (2*R*)-*N*-[(2-Methanesulfonyl-phenyl)-propenoyl]-bornanesultam (17). To a stirred solution of **9b** (2.0 g, 5.13 mmol) in 25 mL of dry MeOH at room temperature were added magnesium mono peroxy phthalate (6.0 g, 12.82 mmol) and stirred for 2 h. The reaction mixture was filtered through one-inch bed of Celite, the filtrate was taken and the MeOH was evaporated under reduced pressure. The gummy material was dissolved in EtOAc and washed with saturated $NaHCO_3$ solution; the organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude compound was purified by column chromatography to afford pure **17** (2 g, 92%) as white solid. Mp 170–172 °C; $[\alpha]_D^{25}$ −97.48 (*c* 0.5, $CHCl_3$); FTIR (KBr): 1676, 1629, 1408, 1334, 1309, 1236, 1219, 1150, 1136, 1116, 1089, 1066, 987, 959, 830, 781, 768, 663, 541, 499 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.94 (d, *J*=8.3 Hz, 2H), 7.77 (d, *J*=15.6 Hz, 1H), 7.73 (d, *J*=8.3 Hz, 1H), 7.26 (d, *J*=15.6 Hz, 1H), 4.10–3.90 (m, 1H), 3.52 (d, *J*=5.3 Hz, H), 3.05 (s, 3H), 2.15 (d, *J*=6.8 Hz, 2H), 2.10–1.75 (m, 3H), 1.55–1.25 (m, 2H), 1.19 (s, 3H), 0.99 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 163.3, 142.6, 141.6, 139.4, 129.1 (2C), 127.9 (2C), 121.1, 65.2, 53.1, 48.6, 47.8, 44.6, 44.3, 38.3, 32.8, 26.4, 20.7, 19.8; Anal. Calcd for $C_{20}H_{25}NO_5S_2$: C, 56.71; H, 5.95; N, 3.31. Found: C, 56.99; H, 6.01; N, 3.56%.

2.1.1.15. *anti*-(2*R*,2′*R*,3′*R*)-*N*-[2′-Bromo-3′-methoxy-3′-(2-methanesulfonyl-phenyl)-propionyl]-bornanesultam (18a). White solid. Mp 185–187 °C; $[\alpha]_D^{26}$ −81.49 (*c* 1.0, $CHCl_3$); FTIR (KBr): 1696, 1409, 1385, 1336, 1309, 1219, 1151, 1117, 1099, 1058, 958, 754, 571, 534 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.96 (d, *J*=8.2 Hz, 2H), 7.64 (d, *J*=8.2 Hz, 2H), 4.78 (s, 2H), 4.10–3.90 (m, 1H), 3.52 (s, 2H), 3.22 (s, 3H), 3.08 (s, 3H), 2.20–2.05 (m, 2H), 2.00–1.80 (m, 3H), 1.60–1.30 (m, 2H), 1.15 (s, 3H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.2, 143.5, 140.8, 129.3 (2C), 127.3 (2C), 82.4, 64.9, 58.1, 52.8, 48.8, 47.8, 45.3, 44.4 (2C), 37.4, 32.6, 26.3, 20.6, 19.8; Anal. Calcd for $C_{21}H_{28}BrNO_6S_2$: C, 47.19; H, 5.28; N, 2.62. Found: C, 46.97; H, 5.42; N, 2.99%.

2.1.1.16. *anti*-(2*R*,2′*S*,3′*S*)-*N*-[2′-Bromo-3′-methoxy-3′-(2-methanesulfonyl-phenyl)-propionyl]-bornanesultam (18b). Colorless gummy liquid. $[\alpha]_D^{25}$ −69.47 (*c* 0.96, $CHCl_3$); FTIR (KBr): 1697, 1412, 1388, 1361, 1333, 1309, 1221, 1144, 1121, 1106, 1062, 1021, 968, 845, 734, 563, 519 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.95 (d, *J*=8.3 Hz, 2H), 7.66 (d, *J*=8.3 Hz, 2H), 4.94 (d, *J*=6.2 Hz, 1H), 4.82 (d, *J*=6.2 Hz, 1H), 4.11–3.89 (m, 1H), 3.54–3.51 (m, 2H), 3.23 (s, 3H), 3.07 (s, 3H), 2.22–2.05 (m, 2H), 2.03–1.81 (m, 3H), 1.60–1.28 (m, 2H), 1.14 (s, 3H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.3, 143.4, 140.8, 129.9 (2C), 127.1 (2C), 82.3, 65.0, 58.0, 52.9, 48.7, 47.6, 45.1, 44.2, 37.5, 32.5, 26.2, 20.4, 19.6; Anal. Calcd for ($C_{21}H_{28}BrNO_6S_2$+0.5·H_2O): C, 46.41; H, 5.38; N, 2.58. Found: C, 46.70; H, 5.51; N, 2.63%.

2.1.1.17. *syn*-(2*R*,2′*S*,3′*R*)-*N*-[2′-Azido-3′-methoxy-3′-(2-methanesulfonyl-phenyl)-propionyl]-bornanesultam (19). Colorless gummy liquid. $[\alpha]_D^{26}$ −67.35 (*c* 1.0, $CHCl_3$); FTIR (KBr): 2925, 2112, 1725, 1691, 1409, 1311, 1218, 1151, 1104, 959, 767, 536 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.92 (d, *J*=8.1 Hz, 2H), 7.62 (d, *J*=8.1 Hz, 2H), 4.90 (d, *J*=5.5 Hz, 1H), 4.49 (d, *J*=5.5 Hz, 1H), 4.10–3.85 (m, 1H), 3.45 (s, 2H), 3.36 (s, 3H), 3.07 (s, 3H), 2.20–1.80 (m, 5H) 1.50–1.10 (m, 2H), 1.98 (s, 3H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.6, 142.9, 140.9, 128.7 (2C), 128.0 (2C), 83.5, 65.1, 57.6, 52.9, 48.8, 47.8, 45.4, 44.5 (2C), 38.2, 32.7, 26.3, 20.2, 19.8; Anal. Calcd for $C_{21}H_{28}N_4O_6S_2$: C, 50.79; H, 5.68; N, 11.28. Found: C, 51.11; H, 5.97; N, 11.67%.

2.1.1.18. *syn*-(2*R*,3*R*)-[2-Amino-3-methoxy-3-(4-methanesulfonyl-phenyl)-1-propanol] (20). Colorless gummy liquid. $[\alpha]_D^{26}$ −61.97 (*c* 1.0, $CHCl_3$); FTIR (KBr): 3370 (br), 2931, 1598, 1465, 1408, 1303, 1149, 1088, 960, 833, 772, 547, 505 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.94 (d, *J*=8.3 Hz, 2H), 7.52 (d, *J*=8.3 Hz, 2H), 4.89 (br s, 1H), 4.22 (d, *J*=6.3 Hz, 1H), 3.60–3.20 (m, 2H), 3.24 (s, 3H), 3.07 (s, 3H), 3.05–2.80 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 146.0, 140.0, 128.1 (2C), 127.5 (2C), 84.3, 62.9, 58.2, 57.3, 44.4; Anal. Calcd for ($C_{11}H_{17}NO_4S$+1·H_2O): C, 47.64; H, 6.91; N, 5.05. Found: C, 47.33; H, 7.03; N, 4.89%.

2.1.1.19. 2,2-Dichloro-*N*-[1-hydroxymethyl-2-methoxy-2-(4-methanesulfonyl-phenyl)-ethyl]-acetamide (21). White solid. Mp 112–114 °C; $[\alpha]_D^{26}$ −55.68 (*c* 1.0, $CHCl_3$); FTIR (KBr): 3495, 3278, 3003, 1692, 1547, 1409,

1301, 1289, 1149, 1086, 1073, 808, 772, 686, 557, 544 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.93 (d, J=8.3 Hz, 2H), 7.52 (d, J=8.3 Hz, 2H), 7.05 (d, J=8.8 Hz, 1H), 5.82 (s, 1H), 4.70 (d, J=3.2 Hz, 1H), 4.20–3.90 (m, 1H), 3.78 (d, J=5.5 Hz, 2H), 3.35 (s, 3H), 3.05 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 164.2, 144.6, 140.1, 127.6 (2C), 127.5 (2C), 80.7, 66.2, 61.7, 57.8, 56.5, 44.3; Anal. Calcd for $C_{13}H_{17}Cl_2NO_5S$: C, 42.17; H, 4.63; N, 3.78. Found: C, 41.87; H, 4.72; N, 3.90%.

2.1.1.20. (+)-Thiamphenicol (2). White solid. Mp 163–165 °C [lit.[2] 164.3–166.3 °C]; $[\alpha]_D^{26}$ +12.61 (*c* 1.0, EtOH) [lit.[2] $[\alpha]_D^{25}$ +12.9 (*c* 1, EtOH)]. Spectroscopic data consistent with that reported in the literature.[4i]

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