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An Efficient Stereoselective Total Synthesis of All Stereoisomers of the Antibiotic Thiamphenicol through Ruthenium-Catalyzed Asymmetric Reduction by Dynamic Kinetic Resolution

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Thiamphenicol is a widely used antibiotic that exhibits activity against numerous Gram-positive and Gram-negative pathogens. Here, we describe the expedient synthesis of its four stereoisomers through a dynamic kinetic resolution that follows a ruthenium-catalyzed asymmetric hydrogenation or a hydrogen transfer reaction as the key step.

Introduction

Thiamphenicol (**1**) is a synthetic analogue of chloramphenicol (**2**), the *p*-nitro group of which is replaced by a methylsulfonyl group. Since its discovery more than 50 years ago, thiamphenicol (**1**) has been known for its antibacterial activity against many Gram-positive and Gram-negative microorganisms[1] (Figure 1). Currently, it is used as a human and veterinary antibiotic. The industrial process for the synthesis of (+)-thiamphenicol (**1**, 100 tons per year) involves a classical resolution step of racemic *threo*-2-amino-1-[4-(methylthio)phenyl]-1,3-propanediol (**3**), which in turn is prepared by a multistep sequence using unnatural D-(–)-tartaric acid as the resolving agent (Figure 1).[2]

Because the (1*R*,2*R*)-(–)-**3** enantiomer leads to the active isomer of thiamphenicol, various protocols have been developed to recycle the undesired (1*S*,2*S*)-(+)-**3** enantiomer.[3] However, most reported methods are difficult to operate and require several additional steps that are often accompanied by low chemical yields. As a result of the important biological properties of (+)-thiamphenicol (**1**) such as excellent tissue distribution, broad-spectrum antibacterial activity, low toxicity, and the potential for oral administration,[4] several syntheses have been described in the literature.[5] However, most of the reported routes introduce the absolute stereochemistry by using enantiomerically pure starting materials or stoichiometric amounts of chiral auxiliaries. Moreover, most of these methods often require long reaction sequences and multiple tedious purification steps.

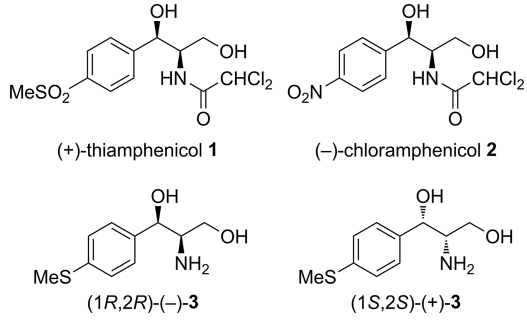

Figure 1. (+)-Thiamphenicol (**1**), its analogue (–)-chloramphenicol (**2**), and *threo*-2-amino-1-[4-(methylthio)phenyl]-1,3-propanediols (1*R*,2*R*)-(–)-**3** and (1*S*,2*S*)-(+)-**3**, which are involved in the preparation of **1**.

The dynamic kinetic resolution (DKR)[6] of α-amino-β-keto ester derivatives by using ruthenium-catalyzed asymmetric reductions has been reported by several groups,[7] including ourselves.[8] This technology is an elegant and powerful synthetic tool to prepare one enantiomer in a single chemical operation with high atom efficiency by using racemic starting materials that contain a labile stereocenter. As part of our ongoing research program directed towards the synthesis of bioactive molecules through transition-metal-catalyzed asymmetric reactions, we report herein a short, efficient, and stereoselective total synthesis of the four stereoisomers of the antibiotic thiamphenicol (**1**).

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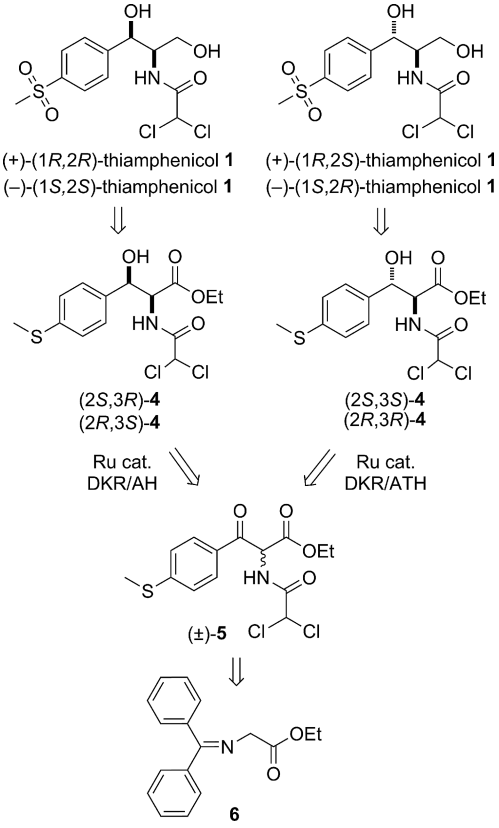
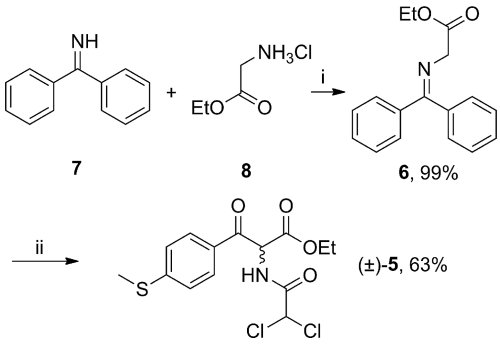
From a synthetic point of view, all isomers of thiamphenicol (**1**) can be obtained in three steps from racemic α-amido-β-keto ester **5**. As outlined in Scheme 1, the key step of our strategy involves a ruthenium-catalyzed asymmetric reduction of the ketone moiety of **5** to establish the essential *syn* and *anti* relationships of compounds (2*S*,3*R*)-**4**/(2*R*,3*S*)-**4** and (2*S*,3*S*)-**4**/(2*R*,3*R*)-**4**, respectively, with high diastereo- and enantioselectivities. This DKR process follows either an asymmetric hydrogenation (AH) or asymmetric transfer hydrogenation (ATH) pathway. The required pivotal intermediate **5** can in turn be easily prepared by α-acylation of imine **6** using 4-(methylthio)benzoyl chloride followed by acidic hydrolysis and treatment with dichloroacetic chloride (Scheme 1).



Scheme 1. Retrosynthetic analysis of thiamphenicol (**1**).

Results and Discussion

The required racemic α-amido-β-keto ester **5** was easily prepared according to the synthetic sequence shown in Scheme 2. Benzophenone Schiff base **6** was readily obtained from commercially available and inexpensive starting materials through the transamination reaction of benzophenone imine **7** with glycine ethyl ester hydrochloride (**8**).[9] This convenient and scalable procedure was carried out on a multigram scale by simply stirring equimolar amounts of the two reagents in dichloromethane at room temperature overnight. Filtration and aqueous workup provided benzophenone Schiff base **6** in 99% isolated yield. The acylation of **6** was then best achieved by the addition of the potassium salt of the benzophenone imine derivative to a precooled solution of 4-(methylthio)benzoyl chloride in tetrahydrofuran (THF) at –78 °C followed by a careful in situ acid hydrolysis.[10] The resulting α-amino-β-keto ester hydrochloride salt was treated immediately without purification with dichloroacetic chloride in the presence of Et_3N to give the desired racemic α-amido-β-keto ester **5** in 63% yield over the two steps.[11]



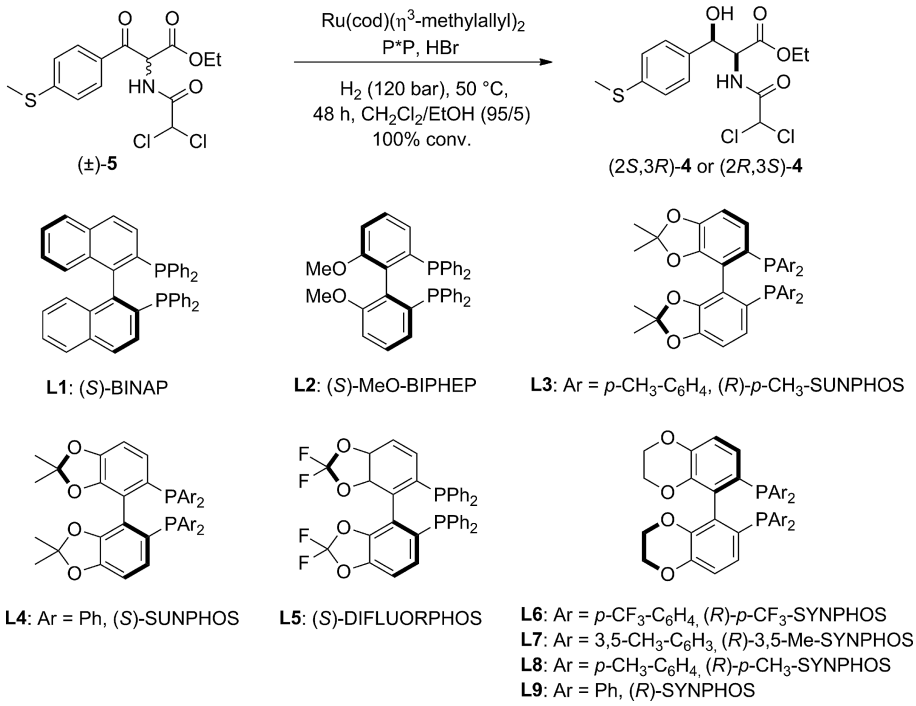
Scheme 2. Scalable synthesis of α-amido β-keto ester (±)-**5**. (i) CH_2Cl_2, room temp., 20 h; (ii) (1) potassium hexamethyldisilazide (KHMDS), 4-(methylthio)benzoyl chloride, THF, –78 °C, 2 h; (2) HCl (3 M) in H_2O; (3) dichloroacetic chloride, Et_3N, CH_2Cl_2, 0 °C to room temp.

With a reliable and straightforward method for the preparation of compound (±)-**5** in hand, we then focused our attention on the synthesis of the key amino alcohol **4**. It is well-established that *syn*-β-hydroxy-α-acylamino acid derivatives can be efficiently synthesized with high diastereo- and enantioselectivities from chirally labile α-amido-substituted β-keto esters by using a ruthenium-catalyzed asymmetric hydrogenation through a DKR.[7] Previous work[5f] shows that the hydrogenation reaction (1000 psi of H_2, 50 °C, and 66 h in CH_2Cl_2) of compound (±)-**5** with $Ru_2Cl_4[(R)\text{-BINAP}]_2{\cdot}N(C_2H_5)_3$ as the catalyst proceeded in 67% yield with a very low enantiomeric excess (*ee*) value of 15%. In contrast, we were pleased to find that the reduction could be efficiently performed by using in situ generated ruthenium(II) complexes, which are prepared by following our convenient procedure[12] that incorporates ligands **L1**–**L9** (Table 1). Thus, β-keto ester (±)-**5** was first subjected to a ruthenium-mediated asymmetric hydrogenation under 120 bar of H_2 at 50 °C in CH_2Cl_2 by using (*S*)-BINAP (**L1**)[13] This reaction provided the expected *syn*-β-hydroxy-α-acyl amino acid derivative (2*R*,3*S*)-**4** in 73% yield with an excellent diastereoselectivity [99:1 diastereomeric ratio (*dr*)] and moderate enantioselectivity [84:16 enantiomeric ratio (*er*); Table 1, Entry 1). Changing the ligand to (*S*)-MeO-BIPHEP (**L2**)[14] resulted in increased enantioselectivity (93:7 *er*) but a lower 56% yield (Table 1, Entry 2). Atropisomeric diphosphines (*R*)-*p*-CH_3-SUNPHOS (**L3**) and (*S*)-SUNPHOS (**L4**)[15] afforded (2*S*,3*R*)-**4** and (2*R*,3*S*)-**4**, respectively, with a high degree of enantioselectivity (97:3 and 95:5 *er*, respectively) and in good yields of 57 and 71% (Table 1, Entries 3 and 4). Electron-deficient ligands such as (*S*)-DIFLUORPHOS (**L5**) and (*R*)-*p*-CF_3-

SYNPHOS (**L6**) were also evaluated in the asymmetric hydrogenation of (±)-**5** (Table 1, Entries 5 and 6). (*S*)-DIFLUORPHOS (**L5**)[16] gave encouraging results with high enantioselectivity (96:4 *er*) and a yield of 83% (Table 1, Entry 5), whereas (*R*)-*p*-CF_3-SYNPHOS (**L6**) led to disappointing results (Table 1, Entry 6), which demonstrates that strongly electron-deficient ligands are not suitable for this reaction. Electron-rich ligands such as (*R*)-3,5-Me-SYNPHOS (**L7**) and (*R*)-*p*-Me-SYNPHOS[17b] (**L8**) afforded excellent diastereoselectivities of up to 99:1 but gave lower *er* values (80:20 and 90:10, respectively; Table 1, Entries 7 and 8). Finally, (*R*)-SYNPHOS (**L9**)[17] provided the desired *syn*-*N*-(dichloroacetyl)-3-[4-(methylthio)phenyl]serine ethyl ester (**4**) with excellent diastereoselectivity (>99:1 *dr*) and a high level of enantioselectivity (95:5 *er*; Table 1, Entry 9). The absolute and relative (*syn*) configurations of the hydrogenated products **4** were unambiguously determined by comparison with literature data.[5]

Alternatively, it is well-established that the ruthenium-catalyzed asymmetric hydrogen transfer reaction of α-amido-β-keto ester derivatives[18] allows efficient access to the corresponding *anti*-β-hydroxy-α-acylamino acids. During the last decade, asymmetric transfer hydrogenation (ATH)[19] has emerged as a practical and powerful alternative to asymmetric hydrogenation for the enantioselective reduction of carbonyl compounds. In this context, we have reported an enantio- and diastereoselective approach to α-alkoxy-substituted *syn*-β-hydroxy esters by using highly efficient catalytic ATH-DKR reactions and starting from the corresponding racemic β-keto esters.[20] Such an ATH process was then applied to racemic α-amido-β-keto ester (±)-**5** to provide the corresponding *anti*-β-hydroxy-α-acylamino acid derivative **4**. We started our investigation by screening various well-defined Noyori-type Ru^{II}-TsDPEN catalysts (i.e., **A**–**E**,[21] Table 2). These catalysts were easily prepared from the reaction of *N*-(4-tolylsulfonyl)-1,2-diphenylethylenediamine (Ts-DPEN) with the corresponding dimeric $[RuCl_2(\eta^6\text{-arene})]_2$ precursor.[22] Initial transfer hydrogenation experiments were carried out in dichloromethane at 50 °C for 48 h by using a substrate to catalyst molar ratio

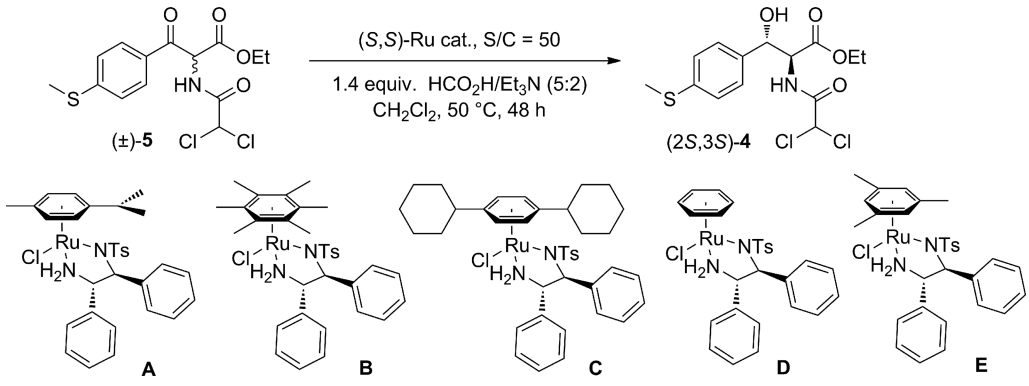
Table 1. Ru catalyzed asymmetric hydrogenation of **5** through DKR.[a]



Entry	P*P	% Yield[b]	*dr* [*syn*/*anti*][c]	*er* [*syn*-**4**][d]
1	**L1**	73	99:1	84:16 [(2*R*,3*S*)-**4**]
2	**L2**	56	99:1	93:7 [(2*R*,3*S*)-**4**]
3	**L3**	57	99:1	97:3 [(2*S*,3*R*)-**4**]
4	**L4**	71	99:1	95:5 [(2*R*,3*S*)-**4**]
5	**L5**	83	98:2	96:4 [(2*R*,3*S*)-**4**]
6	**L6**	35	97:3	68:32 [(2*S*,3*R*)-**4**]
7	**L7**	60	99:1	80:20 [(2*S*,3*R*)-**4**]
8	**L8**	77	>99:1	90:10 [(2*S*,3*R*)-**4**]
9	**L9**	75	>99:1	95:5 [(2*S*,3*R*)-**4**]

[a] Reactions were conducted under 120 bar with substrate **5** [a 1 M solution in CH_2Cl_2/EtOH, 95:5; 1 mmol] and a substrate/catalyst (S/C) molar ratio of 33 (cod = 1,5-cyclooctadiene). [b] Isolated yield after flash column chromatography. [c] Determined by ^1H NMR analysis of the crude product. [d] Determined by chiral stationary phase-supercritical fluid chromatography (CSP-SFC).

Table 2. Screening of TsDPEN ruthenium (II) catalysts.[a]



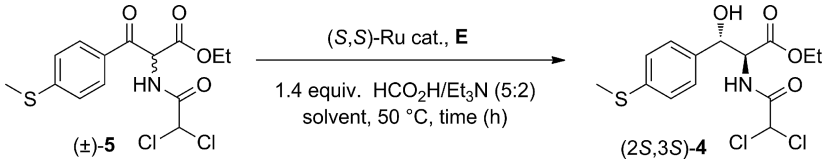
Entry	Ru catalyst	% Yield[b]	*dr* [*anti*/*syn*][c]	*er* [*anti*-**4**][d]
1	**A**	83	91:9	53:47
2	**B**	83	88:12	53:47
3	**C**	75	88:12	60:40
4	**D**	78	88:12	70:30
5	**E**	89	90:10	95:5

[a] Reactions were conducted at 50 °C with substrate **5** (1 M solution in CH_2Cl_2, 1 mmol) and a S/C molar ratio of 50 for 48 h. [b] Isolated yield after flash column chromatography. [c] Determined by ^{1}H NMR analysis of the crude product. [d] Determined by chiral stationary phase-supercritical fluid chromatography.

of 50:1 and a 5:2 azeotropic mixture of formic acid and triethylamine as the hydrogen source. As outlined in Table 2, complete conversions were achieved in all cases, and compound (2*S*,3*S*)-**4** was obtained in good yields that ranged from 75 to 89%.

The data in Table 2 clearly show that the diastereoselectivity of the reaction is only slightly affected by the nature of the η^6-arene ligand of the complex. This is in sharp contrast to the enantioselectivity, which is strongly influenced by the substituent on the Ru-arene ring. Indeed, the transfer hydrogenation of α-amido-β-keto ester (±)-**5** by using Noyori's RuCl[(*S*,*S*)-TsDPEN](*p*-cymene) catalyst **A** provided *anti*-amino alcohol (2*S*,3*S*)-**4** with an encouraging diastereoselectivity of 91:9 but a very disappointing enantiomeric ratio of 53:47 (Table 2, Entry 1). A similar result was obtained when the reaction was conducted with catalyst **B**, which contains hexamethylbenzene as a ligand (Table 2, Entry 2). In contrast, ruthenium complexes **C** and

Table 3. Optimization of the reaction conditions by using TsDPEN ruthenium catalyst **E**.[a]



Entry	Solvent	S/C	Time [h]	% Yield[b]	*dr* [*anti*/*syn*][c]	*er* [*anti*-**4**][d]
1	CH_2Cl_2	50	48	89	90:10	95:5
2	DCE	50	48	72	90:10	92:8
3	MeOH	50	48	82	92:8	92:8
4	*i*PrOH	50	48	88	93:7	92:8
5	acetone	50	48	67	88:12	93:7
6	CH_3CN	50	48	85	86:14	95:5
7	EtOAc	50	48	84	93:7	88:12
8	toluene	50	48	72	91:9	93:7
9	dioxane	50	48	80	93:7	92:8
10	THF	50	48	81	94:6	95:5
11	Et_2O	50	48	89	97:3	96:4
12	Et_2O[e]	50	0.5	91	97:3	96:4
13	Et_2O[e]	100	2	90	97:3	97:3
14	Et_2O[e]	200	4	87	97:3	97:3
15	Et_2O[e]	400	6	89	97:3	96:4

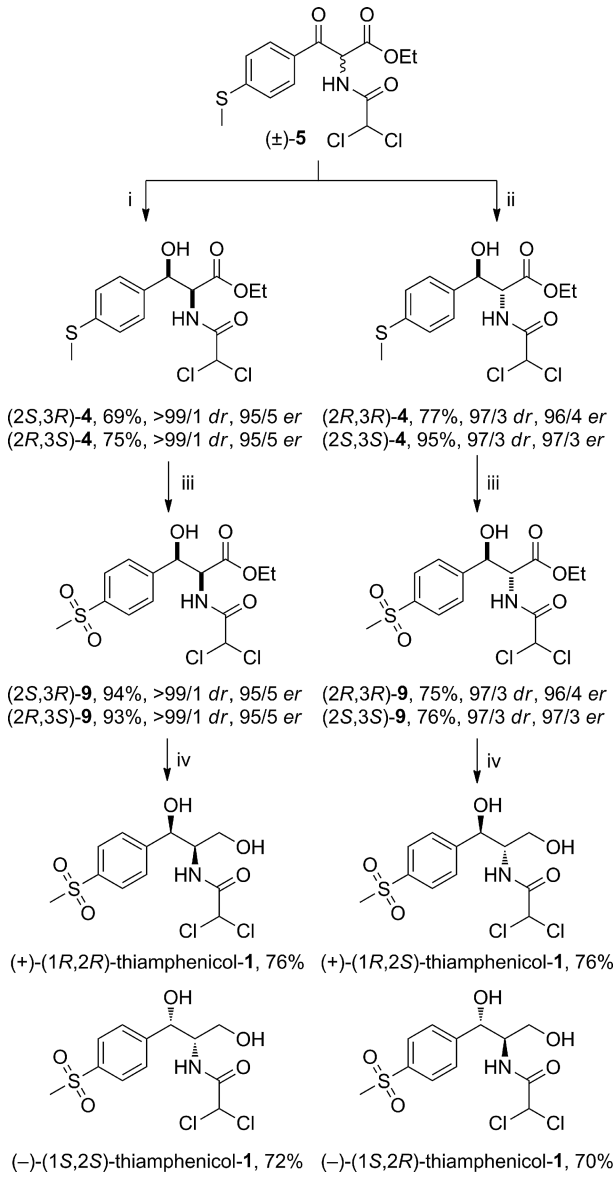
[a] Unless otherwise stated, reactions were conducted at 50 °C with substrate **5** (a 1 M solution, 1 mmol) and Ru catalyst **E** for 48 h. [b] Isolated yield after flash column chromatography. [c] Determined by ^{1}H NMR analysis of the crude product. [d] Determined by chiral stationary phase-supercritical fluid chromatography. [e] Reaction conducted under air.

D, which contain 1,4-dicyclohexylbenzene and benzene as the η^6-arene ligand, led to a significant increase in the enantiomeric ratio with *er* values of 60:40 and 70:30, respectively (Table 2, Entries 3 and 4). Finally, we were pleased to find that a dramatic enhancement in the enantioselectivity was observed when the RuCl[(*S*,*S*)-TsDPEN](mesitylene) catalyst **E** was used. Thus, (2*S*,3*S*)-**4** was obtained in 89% isolated yield with a good diastereomeric ratio of 90:10 and a promising enantiomeric ratio of 95:5 (Table 2, Entry 5).

Encouraged by these results, we set out to determine the optimal solvent to further improve the stereochemical outcome of the reaction with RuCl[(*S*,*S*)-TsTPEN](mesitylene) catalyst **E** and the formic acid/triethylamine (5:2) solution as the hydrogen source at 50 °C. The results from these experiments are presented in Table 3, which shows that this reaction is strongly solvent dependent. In the examined solvents, complete conversions were attained, and the reduced product (2*S*,3*S*)-**4** was obtained in moderate to good yields that ranged from 67 to 91%.

When the reaction was performed in 1,2-dichloroethane (DCE) instead of dichloromethane, the same diastereoselectivity was obtained with a slight drop in the enantioselectivity (Table 3, Entry 2 vs. 1). The diastereomeric ratio slightly increased when the reaction was performed in alcoholic solvents such as methanol and 2-propanol, but the enantiomeric ratio decreased to 92:8 in both cases (Table 3, Entries 3 and 4). Other polar solvents such as acetone, acetonitrile, and ethyl acetate gave compound (2*S*,3*S*)-**4** but with significantly less selectivity than that obtained in dichloromethane (Table 3, Entries 5–7 vs. 1). No improvement in the enantioselectivity was observed when the reaction was carried out in toluene, but the diastereomeric ratio increased to 91:9 (Table 3, Entry 8). Finally, ethereal solvents such as dioxane, THF, and diethyl ether proved to be the most suitable solvents with regard to both enantio- and diastereoselectivities, providing *anti*-amino alcohol (2*S*,3*S*)-**4** with enantiomeric ratios that ranged from 92:8 to 96:4 and diastereomeric ratios that varied from 93:7 to 97:3 (Table 3, Entries 9–11). With the goal of improving the reaction rate and taking into account the negative effect that CO_2 has on the kinetics of such a process,[23] we decided to run the ATH of (±)-**5** in refluxing ether with 2 mol-% of Ru catalyst **E** under an open atmosphere, rather than in a closed system, to remove the CO_2 generated during the reaction. Gratifyingly, under these reaction conditions, compound (±)-**5** was rapidly and fully converted into the desired reduced product (2*S*,3*S*)-**4** with a similar high selectivity in less than 30 min (Table 3, Entry 12, 91% yield, 97:3 *dr*, 96:4 *er*). This rate reduction effect from CO_2 may be attributed to its insertion into the Ru–H bond, thereby giving the inactive formate complex and limiting the concentration of the active ruthenium hydride species.[24] Interestingly, it was possible to further decrease the catalyst loading from a S/C molar ratio of 50 to 100, 200, and 400 without a significant change in the catalytic efficiency of the reaction, albeit longer reaction times were required. Indeed, in all cases, complete conversions were achieved, and compound (2*S*,3*S*)-**4** was obtained in good yields (87–90%) with a high diastereoselectivity of 97:3 *dr* and excellent enantioselectivities that ranged from 96:4 to 97:3 *er* (Table 3, Entries 13–15).

With an efficient synthetic route secured for each stereoisomer of amino alcohol **4**, all that remained to reach targeted (+)-thiamphenicol (**1**) and its isomers were a few functional group transformations. Toward this end, the asymmetric reduction of α-amido-β-keto ester (±)-**5** was carried out under the optimized reaction conditions. By using the ATH conditions, both *anti*-**4** isomers were obtained in good isolated yields with a high level of diastereoselectivity and excellent enantiomeric ratios of 96:4 and 97:3 for (2*R*,3*R*)-**4** and (2*S*,3*S*)-**4**, respectively. Subsequent oxidation with *meta*-chloroperoxybenzoic acid (*m*-CPBA)



Scheme 3. (i) [Ru(cod)(η^3-methylallyl)$_2$], (*R*)-**L9** or (*S*)-**L9**, aqueous HBr, H_2 (120 bar), CH_2Cl_2/EtOH (95:5), S/C = 33, 50 °C, 48 h; (ii) (*R*,*R*)-**E** or (*S*,*S*)-**E**, HCO_2H/Et_3N (5:2), Et_2O, S/C = 100, 50 °C, 1.5–3 h; (iii) *m*-CPBA, THF, room temp., 1 h; (iv) $NaBH_4$, MeOH, 0 °C, 1 h.

converted the methylsulfanyl into a methylsulfonyl group to give (2*R*,3*R*)-**9** in 75% yield and (2*S*,3*S*)-**9** in 76% yield. Finally, the reduction of esters **9** into primary alcohols **1** by treatment with sodium borohydride led to the formation of (1*R*,2*S*)-thiamphenicol (**1**) and (1*S*,2*R*)-thiamphenicol (**1**) in 76 and 70% yield, respectively (Scheme 3). Changing from an ATH to an AH process afforded the two *syn*-**4** isomers (2*S*,3*R*)-**4** and (2*R*,3*S*)-**4** in 69 and 75% yield, respectively. Finally, by using the same synthetic route as above, the two remaining isomers of thiamphenicol (**1**) were obtained in similar yields. The synthesis of the valuable (+)-(1*R*,2*R*)-thiamphenicol was thus completed in 54% overall yield from easily accessible (±)-**5**. The spectroscopic data of (+)-(1*R*,2*R*)-**1** were in complete agreement with reported literature values.[5]

Conclusions

In summary, we have achieved a short and practical total synthesis of the four stereoisomers of the antibiotic thiamphenicol (**1**) from inexpensive and commercially available starting materials. The key feature of our approach involves the enantioselective reduction of racemic α-amido-β-keto ester **5** through a dynamic kinetic resolution process to establish the essential *syn* or *anti* relationship of key amino alcohols **4**. For example, the application of the ruthenium-catalyzed asymmetric hydrogenation reaction of compound (±)-**5** by employing the in situ generated Ru^{II}-SYNPHOS catalyst provides efficient access to the corresponding *syn* isomers (2*S*,3*R*)-**4**/(2*R*,3*S*)-**4** in excellent yields (69–75%), with almost perfect diastereoselectivity (>99:1 *dr*) and high enantiomeric ratios of 95:5. On the other hand, the asymmetric transfer hydrogenation of racemic α-amido-β-keto ester **5** by using the RuCl[(η^6-mesitylene)(*S*,*S*)-TsDPEN] catalyst and a formic acid/triethylamine (5:2) solution as the hydrogen source allowed for the preparation of the corresponding *anti* isomers (2*R*,3*R*)-**4**/(2*S*,3*S*)-**4** in good yields with similar high diastereo- and enantioselectivities (97:3 *dr*, 96:4 and 97:3 *er*, respectively). Overall, our synthetic approach to the important antibiotic thiamphenicol (**1**) offers several advantages including: (i) flexibility, (ii) atom economy, (iii) operational simplicity, (iv) high chemical yields, and (v) high diastereo- and enantioselectivities.

Experimental Section

General Methods: All air- and water-sensitive reactions were carried out under argon. Tetrahydrofuran and diethyl ether were distilled from sodium-benzophenone. Dichloromethane, toluene, and triethylamine were distilled from calcium hydride. Reactions were monitored by thin layer chromatography that was carried out on precoated silica gel plates (E. Merck ref. 5554 60 F254) and visualized by using either an ultraviolet lamp (λ = 254 nm), a potassium permanganate solution [$KMnO_4$ (3 g), K_2CO_3 (20 g), AcOH (0.25 mL), and H_2O (300 mL)], a ninhydrin solution [ninhydrin (1 g), EtOH/H_2SO_4 (95:5, 100 mL)] or a Kagi–Mosher solution [*p*-anisaldehyde (8 mL), H_2SO_4 (16 mL), and AcOH (800 mL)]. The NMR spectroscopic data were recorded with a Bruker AC 300 (^{1}H NMR at 300 MHz and ^{13}C NMR at 75 MHz) instrument. Data are reported as follows: chemical shifts (δ), multiplicity [reported as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublets (dd), quartet of doublets (qd), broad (br.)], coupling constants, and integration. Melting points were measured on a Büchi apparatus. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. High resolution mass spectra were measured on a LTQ-Orbitrap (Thermo Fisher Scientific) at Pierre et Marie Curie University. CSP-SFC analyses were performed on a Berger apparatus fitted with a chiral Chiralcel OD-H column and Chiralpak IA, AD-H, and AS-H columns.

Ethyl 2-[(Diphenylmethylene)amino]acetate (6): A solution of benzophenone imine **7** (9.23 g, 51 mmol, 1 equiv.) and amino acid ester hydrochloride **8** (7.12 g, 51 mmol, 1 equiv.) in dry CH_2Cl_2 (170 mL) was stirred at room temp. for 20 h under argon. The reaction mixture was then filtered through a pad of Celite (rinsed with CH_2Cl_2), and the filtrate was concentrated to afford the desired product as a white solid (13.45 g, 99%), which was used in the next step without purification; m.p. 42–43 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.71–7.62 (m, 2 H), 7.51–7.30 (m, 6 H), 7.25–7.11 (m, 2 H), 4.27–4.14 (m, 4 H), 1.27 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.8, 170.6, 139.2, 135.9, 130.4, 128.8, 128.7, 128.6, 128.0, 127.6, 60.8, 55.6, 14.2 ppm.

Ethyl 2-(2,2-Dichloroacetamido)-3-[4-(methylthio)phenyl]-3-oxopropanoate (5): To a solution of Schiff base **6** (12.8 g, 48 mmol, 1 equiv.) in dry THF (240 mL) was added dropwise a solution of KHMDS (0.5 M in toluene, 96 mL, 48 mmol, 1 equiv.). After 30 min, the red solution was cannulated into a solution of 4-(methylthio)benzoyl chloride (9 g, 48 mmol, 1 equiv.) in dry THF (160 mL) at –78 °C. After 2 h, the reaction was quenched with HCl (3 M aqueous solution, 100 mL), and the resulting mixture was concentrated under reduced pressure. Water was added, and the benzophenone was extracted with diethyl ether. The aqueous phase was concentrated, and the resulting white solid was dissolved in dry MeOH. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give a solid that was triturated with diethyl ether and then dried under vacuum to afford the desired compound (10.54 g, 76%) as a white solid. This was used directly in the next step. The product (4 g, 14 mmol, 1 equiv.) was dissolved in dry CH_2Cl_2 (60 mL), and the solution was cooled to 0 °C under argon. Freshly distilled dichloroacetyl chloride (1.48 mL, 15.4 mmol, 1.1 equiv.) was then added dropwise followed by triethylamine (2.17 mL, 15.4 mmol, 1.1 equiv.). After 2 h at 0 °C, the mixture was stirred at room temp. for 3 h. The reaction mixture was then quenched with a saturated solution of NH_4Cl, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (petroleum ether/EtOAc, 85:15) to afford the pure α-acetamido-β-keto ester **5** (4.25 g, 83%) as a white solid; m.p. 111–113 °C; R_f = 0.66 (petroleum ether/ethyl acetate, 6:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.7 Hz, 2 H), 7.92 (d, *J* = 6.7 Hz, 1 H), 7.29 (d, *J* = 8.7 Hz, 2 H), 6.03 (s, 1 H), 6.04 (d, *J* = 6.7 Hz, 1 H), 4.23–4.12 (m, 2 H), 2.53 (s, 3 H), 1.17 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 188.6, 165.4, 163.7, 148.7, 129.9, 129.5, 124.6, 65.7, 62.76, 58.5, 14.4, 13.7 ppm. IR (neat): $\tilde{\nu}$ = 3262, 3081, 2986, 2359, 2335, 1731, 1685, 1666, 1587, 1554, 1370, 1350, 1256, 1212, 1092, 968, 813, 780, 705, 645 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{15}O_4NCl_2NaS$ 385.9991; found 385.9998.

Ethyl (2*S*,3*S*)-2-(2,2-Dichloroacetamido)-3-hydroxy-3-[4-(methylthio)phenyl]propanoate [(2*S*,3*S*)-4]: To a suspension (previously degassed by three vacuum–argon cycles) of α-acetamido-β-keto

ester **5** (427 mg, 1.17 mmol, 1 equiv.) and [RuCl(η^6-mesitylene)-{(*S*,*S*)-TsDPEN}] (7.3 mg, 0.0117 mmol, 0.01 equiv.) in anhydrous diethyl ether (2 mL) was added the azeotropic mixture HCOOH/NEt_3 (5:2, 0.1 mL, 1.64 mmol, 1.4 equiv.). The reaction mixture was equipped with a condenser open to air and stirred at 50 °C until no starting material was observed by TLC (1.5 h). After 30 min, the orange solution became clear, and then the reaction mixture was cooled to room temp. and neutralized by the addition of saturated $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. ^{1}H NMR analysis of the crude material showed a conversion of 97% and diasteroisomeric ratio (*anti*/*syn*) of 97:3. The crude product was purified by silica gel column chromatography (pentane/EtOAc, 7:3) to afford (2*S*,3*S*)-**4** (408 mg, 95%) as a white solid; m.p. 79–80 °C; R_f = 0.47 (petroleum ether/ethyl acetate, 6:4). $[\alpha]_D^{20}$ = –30.7 (*c* = 0.83, MeOH). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.87 (d, *J* = 8.3 Hz, 1 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 6.47 (s, 1 H), 5.15 (t, *J* = 4.8 Hz, 1 H), 5.03 (d, *J* = 4.8 Hz, 1 H), 4.77 (dd, *J* = 8.3, 5.2 Hz, 1 H), 4.10 (qd, *J* = 7.1, 2.4 Hz, 2 H), 2.48 (s, 3 H), 1.14 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 169.7, 164.4, 138.9, 138.2, 127.9, 126.7, 73.9, 67.2, 61.8, 60.0, 15.5, 14.3 ppm. IR (neat): $\tilde{\nu}$ = 3531, 3273, 2983, 2360, 2339, 1732, 1701, 1681, 1558, 1338, 1206, 811 cm^{-1}. SFC [Chiralcel AD-H; $scCO_2$ (sc = supercritical)/MeOH, 90:10; 7 mL min^{-1}; P = 150 bar; λ = 215 nm]: t_R = 3.65 min [*syn*-(2*R*,3*S*)], t_R = 5.06 min [*anti*-(2*R*,3*R*), minor isomer], t_R = 7.75 min [*syn*-(2*S*,3*R*)], and t_R = 8.52 min [*anti*-(2*S*,3*S*), major isomer, 94% ee_{anti}]. MS (CI, NH_3): *m*/*z* = 383.19 [M + NH_4]$^+$, 348.13 [M + H – H_2O]$^+$.

Ethyl (2*R*,3*R*)-2-(2,2-Dichloroacetamido)-3-hydroxy-3-[4-(methylthio)phenyl]propanoate [(2*R*,3*R*)-4]: To a suspension (previously degassed by three vacuum–argon cycles) of α-acetamido-β-keto ester **5** (523 mg, 1.44 mmol, 1 equiv.) and [RuCl(η^6-mesitylene)-{(*R*,*R*)-TsDPEN}] (9 mg, 0.0144 mmol, 0.01 equiv.) in anhydrous diethyl ether (2 mL) was added the azeotropic mixture HCOOH/NEt_3 (5:2, 0.12 mL, 2.02 mmol, 1.4 equiv.). The reaction mixture was equipped with a condenser open to air and stirred at 50 °C for 3 h. After 30 min, the orange solution became clear. The reaction mixture was then cooled to room temp. and neutralized by the addition of saturated $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. ^{1}H NMR analysis of the crude material showed a conversion of 83% and a diasteroisomeric ratio (*anti*/*syn*) of 97:3. The crude product was purified by silica gel column chromatography (pentane/EtOAc, 7:3) to afford (2*R*,3*R*)-**4** (406 mg, 77%) as a white solid; m.p. 76–78 °C; R_f = 0.48 (petroleum ether/ethyl acetate, 6:4). $[\alpha]_D^{20}$ = +28.4 (*c* = 0.83, MeOH). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.86 (d, *J* = 8.3 Hz, 1 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 6.47 (s, 1 H), 5.14 (t, *J* = 4.8 Hz, 1 H), 5.03 (d, *J* = 4.8 Hz, 1 H), 4.77 (dd, *J* = 8.3, 5.2 Hz, 1 H), 4.10 (qd, *J* = 7.2, 2.2 Hz, 2 H), 2.48 (s, 3 H), 1.14 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 169.7, 164.4, 138.9, 138.3, 127.9, 126.7, 73.9, 67.2, 61.8, 60.1, 15.5, 14.3 ppm. IR (neat): $\tilde{\nu}$ = 3528, 3280, 2982, 2358, 2333, 1741, 1703, 1681, 1561, 1340, 1207, 809 cm^{-1}. SFC [Chiralcel AD-H; $scCO_2$/MeOH, 90:10); 7 mL min^{-1}; P = 150 bar; λ = 215 nm]: t_R = 3.65 min [*syn*-(2*R*,3*S*)], t_R = 5.06 min [*anti*-(2*R*,3*R*), major isomer, 92% ee_{anti}], t_R = 7.75 min [*syn*-(2*S*,3*R*)], t_R = 8.52 min [*anti*-(2*S*,3*S*), minor isomer]. MS (CI, NH_3): *m*/*z* = 383.21 [M + NH_4]$^+$, 348.15 [M + H – H_2O]$^+$.

Ethyl (2*S*,3*R*)-2-(2,2-Dichloroacetamido)-3-hydroxy-3-[4-(methylthio)phenyl]propanoate [(2*S*,3*R*)-4]: (*R*)-SYNPHOS (17.6 mg, 0.028 mmol, 0.022 equiv.) and [Ru(cod)(η^3-2-methylallyl)$_2$] (8 mg, 0.025 mmol, 0.02 equiv.) were placed in a reaction vessel, and the solids were purged with argon. Anhydrous acetone (2 mL), which was previously degassed by three vacuum–argon cycles, was added at room temperature. To this suspension was added dropwise methanolic HBr (0.138 N solution prepared by adding 48% aqueous HBr in degassed methanol, 400 μL, 0.044 equiv.), and the reaction mixture was stirred at room temperature for 30 min. The suspension immediately turned yellow, and then an orange precipitate appeared. The solvent was thoroughly evaporated under vacuum to give the [Ru{(*R*)-SYNPHOS}Br_2] complex as an orange-brown solid, which was used directly. Substrate **5** (300 mg, 0.82 mmol, 1 equiv.) was then added followed by previously degassed anhydrous CH_2Cl_2 (9.5 mL) and degassed EtOH (0.5 mL). The Schlenk vessel was degassed by three vacuum–argon cycles and placed under argon in a stainless steel autoclave. Argon was replaced with hydrogen by three cycles of pressurizing, and the pressure was adjusted to 120 bar. The autoclave was heated at 50 °C, and the stirring was maintained for 48 h. After cooling, the reaction mixture was concentrated under reduced pressure to afford the crude product (2*S*,3*R*)-**4**. ^{1}H NMR analysis of the crude material showed a conversion of 100% and a diasteroisomeric ratio (*syn*/*anti*) of >99:1. The residue was purified by flash chromatography (SiO_2, pentane/EtOAc, 7:3) to afford (2*S*,3*R*)-**4** (207 mg, 69%) as a white solid; m.p. 108–110 °C; R_f = 0.48 (petroleum ether/ethyl acetate, 6:4). $[\alpha]_D^{20}$ = +8.2 (*c* = 0.83, MeOH). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.82 (d, *J* = 8.8 Hz, 1 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 6.48 (s, 1 H), 5.37–5.35 (m, 1 H), 5.19 (dd, *J* = 4.5, 0.4 Hz, 1 H), 4.67 (dd, *J* = 8.8, 2.9 Hz, 1 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 2.47 (s, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 170.7, 165.3, 139.6, 139.4, 128.4, 127.5, 73.9, 68.0, 62.8, 60.7, 16.2, 15.2 ppm. IR (neat): $\tilde{\nu}$ = 3353, 2921, 2360, 2335, 1746, 1685, 1523, 1496, 1371, 1353, 1285, 1221, 1119, 1096, 1076, 1017, 869, 824, 813, 787, 769, 740, 695, 675, 662, 651, 642, 634, 618, 602 cm^{-1}. SFC [Chiralcel AD-H; $scCO_2$/MeOH, 90:10; 7 mL min^{-1}; P = 150 bar; λ = 215 nm]: t_R = 3.65 min [*syn*-(2*R*,3*S*), minor isomer], t_R = 5.06 min [*anti*-(2*R*,3*R*)], t_R = 7.75 min [*syn*-(2*S*,3*R*), major isomer, 90% ee_{syn}], t_R = 8.52 min [*anti*-(2*S*,3*S*)]. MS (CI, NH_3): *m*/*z* = 383.21 [M + NH_4]$^+$, 348.16 [M + H – H_2O]$^+$.

Ethyl (2*R*,3*S*)-2-(2,2-Dichloroacetamido)-3-hydroxy-3-[4-(methylthio)phenyl]propanoate [(2*R*,3*S*)-4]: (*S*)-SYNPHOS (17.6 mg, 0.028 mmol, 0.022 equiv.) and [Ru(cod)(η^3-2-methylallyl)$_2$] (8 mg, 0.025 mmol, 0.02 equiv.) were placed in a reaction vessel, and the solids were purged with argon. Anhydrous acetone (2 mL), which was previously degassed by three vacuum–argon cycles, was added at room temperature. To this suspension was added dropwise methanolic HBr (0.138 N solution prepared by adding 48% aqueous HBr in degassed methanol, 400 μL, 0.044 equiv.), and the reaction mixture was stirred at room temperature for 30 min. The suspension immediately turned yellow, and then an orange precipitate appeared. The solvent was thoroughly evaporated under vacuum to give the [Ru{(*S*)-SYNPHOS}Br_2] complex as an orange-brown solid, which was used directly. Substrate **5** (300 mg, 0.82 mmol, 1 equiv.) was then added followed by previously degassed anhydrous CH_2Cl_2 (9.5 mL) and degassed EtOH (0.5 mL). The Schlenk vessel was degassed by three vacuum–argon cycles and placed under argon in a stainless steel autoclave. Argon was replaced with hydrogen by three cycles of pressurizing, and the pressure was adjusted to 120 bar. The autoclave was heated at 50 °C, and the stirring was maintained for 48 h. After cooling, the reaction mixture was concentrated under reduced pressure to afford the crude product (2*R*,3*S*)-**4**. ^{1}H NMR analysis of the crude material showed a conversion of 100% and a diasteroisomeric ratio

(*syn*/*anti*) of >99:1. The residue was purified by flash chromatography (SiO_2, pentane/EtOAc, 7:3) to afford (2*R*,3*S*)-**4** (226 mg, 75%) as a white solid; m.p. 120–122 °C; R_f = 0.46 (petroleum ether/ethyl acetate, 6:4). $[\alpha]_D^{20}$ = –9.2 (*c* = 0.83, MeOH). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.86 (d, *J* = 8.5 Hz, 1 H), 7.39 (d, *J* = 8.4 Hz, 2 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 6.49 (s, 1 H), 5.35 (d, *J* = 2.8 Hz, 1 H), 5.24 (br. s, 1 H), 4.67 (dd, *J* = 8.5, 2.8 Hz, 1 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 2.47 (s, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 170.7, 165.3, 139.6, 139.4, 128.4, 127.5, 73.8, 67.9, 62.8, 60.7, 16.2, 15.2 ppm. IR (neat): $\tilde{\nu}$ = 3348, 2925, 2360, 2339, 1744, 1685, 1523, 1494, 1372, 1355, 1284, 1221, 1119, 1094, 1078, 1018, 825, 815, 786, 768, 692, 669, 651, 637, 615, 604 cm^{-1}. SFC [Chiralcel AD-H; scCO$_2$/MeOH, 90:10; 7 mL min^{-1}; P = 150 bar; λ = 215 nm]: t_R = 3.65 min [*syn*-(2*R*,3*S*), major isomer, 90% *ee*$_{syn}$], t_R = 5.06 min [*anti*-(2*R*,3*R*)], t_R = 7.75 min [*syn*-(2*S*,3*R*), minor isomer], t_R = 8.52 min [*anti*-(2*S*,3*S*)]. MS (CI, NH$_3$): *m*/*z* = 383.22 [M + NH$_4$]$^+$, 348.16 [M + H – H$_2$O]$^+$.

General Procedure for the Synthesis of Ethyl 2-(2,2-Dichloroacetamido)-3-hydroxy-3-[4-(methylsulfonyl)phenyl]propanoate (9): To a solution of ester **4** (1 equiv.) in anhydrous THF (0.17 M) was added *m*CPBA (2.5 equiv.) at 0 °C in one portion, and the mixture was stirred at room temp. for 1 h. The reaction was quenched by the addition of a saturated solution of $Na_2S_2O_3$. The biphasic solution was stirred at room temp. for 30 min, and then a saturated solution of $NaHCO_3$ was added. The THF was removed by rotary evaporation, and then H_2O and EtOAc were added to the resulting mixture. The aqueous phase was then extracted with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, pentane/EtOAc, 1:1) to give pure product **9** as a white solid.

(2*S*,3*S*)-9: Yield 76%; m.p. <38 °C (low melting solid). R_f = 0.17 (petroleum ether/ethyl acetate, 5:5). $[\alpha]_D^{20}$ = –23.9 (*c* = 0.38, MeOH). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 8.06 (d, *J* = 8.1 Hz, 1 H), 7.94 (d, *J* = 8.3 Hz, 2 H), 7.74 (d, *J* = 8.3 Hz, 2 H), 6.50 (s, 1 H), 5.39 (d, *J* = 4.8 Hz, 1 H), 5.31 (t, *J* = 4.8 Hz, 1 H), 4.83 (dd, *J* = 8.1, 4.8 Hz, 1 H), 4.14–4.03 (m, 2 H), 3.11 (s, 3 H), 1.10 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 169.2, 164.4, 147.7, 141.5, 128.2, 127.9, 73.7, 67.2, 61.9, 60.0, 44.4, 14.2 ppm. IR (neat): $\tilde{\nu}$ = 3394, 3311, 2924, 2854, 1737, 1692, 1550, 1301, 1143 cm^{-1}. SFC [Chiralcel AD-H; scCO$_2$/MeOH, 91:9; 6 mL min^{-1}; *P* = 150 bar; λ = 215 nm]: t_R = 5.62 min [*anti*-(2*R*,3*R*), minor isomer], t_R = 6.22 min [*syn*-(2*R*,3*S*)], t_R = 8.47 min [*syn*-(2*S*,3*R*)], t_R = 18.72 min [*anti*-(2*S*,3*S*), major isomer, 94% *ee*$_{anti}$]. MS (CI, NH$_3$): *m*/*z* = 415.06 [M + NH$_4$]$^+$, 381.11 [M + H – H$_2$O]$^+$.

(2*R*,3*R*)-9: Yield 75%; m.p. <38 °C (low melting solid). R_f = 0.16 (petroleum ether/ethyl acetate, 5:5). $[\alpha]_D^{20}$ = +28.7 (*c* = 0.39, MeOH). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 8.06 (d, *J* = 8.2 Hz, 1 H), 7.94 (d, *J* = 8.5 Hz, 2 H), 7.73 (d, *J* = 8.1 Hz, 2 H), 6.50 (s, 1 H), 5.39 (d, *J* = 4.8 Hz, 1 H), 5.31 (t, *J* = 4.8 Hz, 1 H), 4.83 (dd, *J* = 8.2, 4.8 Hz, 1 H), 4.14–4.03 (m, 2 H), 3.11 (s, 3 H), 1.10 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 169.2, 164.4, 147.7, 141.5, 128.2, 127.9, 73.7, 67.2, 61.9, 60.03, 44.4, 14.2 ppm. IR (neat): $\tilde{\nu}$ = 3390, 3313, 2925, 2854, 1733, 1682, 1556, 1297, 1148 cm^{-1}. SFC [Chiralcel AD-H; scCO$_2$/MeOH, 91:9; 6 mL min^{-1}; P = 150 bar; λ = 215 nm]: t_R = 5.62 min [*anti*-(2*R*,3*R*), major isomer, 92% *ee*$_{anti}$], t_R = 6.22 min [*syn*-(2*R*,3*S*)], t_R = 8.47 min [*syn*-(2*S*,3*R*)], t_R = 18.72 min [*anti*-(2*S*,3*S*), minor isomer]. MS (CI, NH$_3$): *m*/*z* = 415.04 [M + NH$_4$]$^+$.

(2*S*,3*R*)-9: Yield 94%; m.p. 145–147 °C. R_f = 0.17 (petroleum ether/ethyl acetate, 5:5). $[\alpha]_D^{20}$ = +12.7 (*c* = 0.83, MeOH). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.93–7.89 (m, 3 H), 7.75 (d, *J* = 8.1 Hz, 2 H), 6.45 (s, 1 H), 5.57 (dd, *J* = 4.8, 2.6 Hz, 1 H), 5.50 (dd, *J* = 4.8, 0.7 Hz, 1 H), 4.84 (dd, *J* = 9.2, 2.6 Hz, 1 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 3.08 (s, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 170.4, 165.3, 148.5, 142.2, 128.8, 128.7, 73.7, 67.8, 63.0, 60.2, 45.1, 15.2 ppm. IR (neat): $\tilde{\nu}$ = 3389, 3306, 2924, 1741, 1692, 1555, 1301, 1143 cm^{-1}. SFC [Chiralcel AD-H; scCO$_2$/MeOH, 91:9; 6 mL min^{-1}; P = 150 bar; λ = 215 nm]: t_R = 5.62 min [*anti*-(2*R*,3*R*)], t_R = 6.22 min [*syn*-(2*R*,3*S*), minor isomer]; t_R = 8.47 min [*syn*-(2*S*,3*R*), major isomer, 90% *ee*$_{syn}$], t_R = 18.72 min [*anti*-(2*S*,3*S*)]. MS (CI, NH$_3$): *m*/*z* = 415.22 [M + NH$_4$]$^+$, 381.24 [M + H – H$_2$O]$^+$.

(2*R*,3*S*)-9: Yield 93%; m.p. 145–147 °C. R_f = 0.16 (petroleum ether/ethyl acetate, 5:5). $[\alpha]_D^{20}$ = –11.3 (*c* = 0.83, MeOH). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.92–7.89 (m, 3 H), 7.74 (d, *J* = 8.3 Hz, 2 H), 6.45 (s, 1 H), 5.57 (d, *J* = 2.4 Hz, 1 H), 5.50 (br. s, 1 H), 4.84 (dd, *J* = 9.2, 2.4 Hz, 1 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 3.08 (s, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]-acetone): δ = 170.4, 165.3, 148.5, 142.2, 128.7, 128.7, 73.6, 67.8, 63.0, 60.2, 45.1, 15.2 ppm. IR (neat): $\tilde{\nu}$ = 3311, 2360, 2340, 1739, 1715, 1691, 1653, 1557, 1541, 1522, 1508, 1491, 1474, 1457, 1395, 1372, 1342, 1305, 1269, 1201, 1146, 1092, 1018, 957, 810, 791, 747, 678, 623 cm^{-1}. SFC [Chiralcel AD-H; scCO$_2$/MeOH, 91:9; 6 mL min^{-1}; P = 150 bar; λ = 215 nm]: t_R = 5.62 min [*anti*-(2*R*,3*R*)], t_R = 6.22 min [*syn*-(2*R*,3*S*), major isomer, 90% *ee*$_{syn}$], t_R = 8.47 min [*syn*-(2*S*,3*R*), minor isomer], t_R = 18.72 min [*anti*-(2*S*,3*S*)]. MS (CI, NH$_3$): *m*/*z* = 415.22 [M + NH$_4$]$^+$, 381.25 [M + H – H$_2$O]$^+$.

General Procedure for the Synthesis of 2,2-Dichloro-*N*-{1,3-dihydroxy-1-[4-(methylsulfonyl)phenyl]propan-2-yl}acetamide (Thiamphenicol, 1): To a solution of ester **9** (1 equiv.) in distilled MeOH (0.1 M) was added $NaBH_4$ (5 equiv.) in one portion at 0 °C. The reaction mixture was stirred at 0 °C until no starting material was observed by TLC (1 h). The methanol was then evaporated, and then H_2O and brine were added at 0 °C. The resulting mixture was warmed to room temp., and the aqueous phase was extracted with EtOAc. The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH, 9:1) to give the desired product **1** as a white solid.

(1*S*,2*R*)-1: Yield 70%; m.p. 126–130 °C. R_f = 0.21 (CH_2Cl_2/MeOH, 9:1). $[\alpha]_D^{20}$ = –6.45 (*c* = 0.31, MeOH). ^{1}H NMR (300 MHz, [D$_6$]-acetone): δ = 7.90 (d, *J* = 8.4 Hz, 2 H), 7.74–7.69 (m, 1 H), 7.70 (d, *J* = 8.4 Hz, 2 H), 6.30 (s, 1 H), 5.11 (d, *J* = 4.8 Hz, 1 H), 5.05 (t, *J* = 6.2 Hz, 1 H), 4.16–4.09 (m, 2 H), 3.94–3.87 (m, 1 H), 3.71–3.65 (m, 1 H), 3.08 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 164.3, 149.3, 141.2, 128.4, 127.9, 73.5, 67.6, 61.0, 58.0, 44.4 ppm. IR (neat): $\tilde{\nu}$ = 3464, 3223, 3074, 1674, 1563, 1289, 1143, 1089, 1040, 770 cm^{-1}. MS (CI, NH$_3$): *m*/*z* = 373.09 [M + NH$_4$]$^+$. HRMS (ESI): calcd. for $C_{12}H_{15}O_5NCl_2NaS$ 377.9940; found 377.9940.

(1*R*,2*S*)-1: Yield 76%; m.p. 126–128 °C. R_f = 0.20 (CH_2Cl_2/MeOH, 9:1). $[\alpha]_D^{20}$ = +4.2 (*c* = 0.26, MeOH). ^{1}H NMR (300 MHz, [D$_6$]-acetone): δ = 7.90 (d, *J* = 8.5 Hz, 2 H), 7.74–7.69 (m, 1 H), 7.70 (d, *J* = 8.5 Hz, 2 H), 6.31 (s, 1 H), 5.12–5.10 (m, 1 H), 5.07–5.03 (m, 1 H), 4.17–4.10 (m, 2 H), 3.90 (dd, *J* = 10.9, 4.5 Hz, 1 H), 3.68 (d, *J* = 10.9 Hz, 1 H), 3.08 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]-acetone): δ = 164.3, 149.3, 141.2, 128.4, 127.9, 73.5, 67.6, 61.0, 58.0, 44.4 ppm. IR (neat): $\tilde{\nu}$ = 3460, 3223, 3073, 1671, 1563, 1285, 1040, 765 cm^{-1}. MS (CI, NH$_3$): *m*/*z* = 373.08 [M + NH$_4$]$^+$. HRMS (ESI): calcd. for $C_{12}H_{15}O_5NCl_2NaS$ 377.9940; found 377.9941.

(1*R*,2*R*)-1: Yield 76%, m.p. 162–163 °C; ref.[1a] m.p. 164–167 °C. R_f = 0.20 (CH_2Cl_2/MeOH, 9:1). $[\alpha]_D^{20}$ = +7.6 (*c* = 0.25, MeOH). ^{1}H

NMR (300 MHz, [D$_6$]acetone): δ = 7.89 (d, J = 8.4 Hz, 2 H), 7.69 (d, J = 8.4 Hz, 2 H), 7.54 (d, J = 8.7 Hz, 1 H), 6.38 (s, 1 H), 5.30 (br. s, 1 H), 5.18 (br. s, 1 H), 4.27 (br. s, 1 H), 4.17–4.13 (m, 1 H), 3.80 (t, J = 10.3 Hz, 1 H), 3.68 (dd, J = 10.3, 5.2 Hz, 1 H), 3.08 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 164.5, 149.6, 141.0, 127.9, 127.8, 71.3, 67.5, 62.1, 58.0, 44.4 ppm. IR (neat): $\tilde{\nu}$ = 3489, 3443, 3252, 2920, 1692, 1559, 1276, 1139, 770 cm^{-1}. MS (CI, NH_3): m/z = 373.09 [M + NH_4]$^+$.

(1*S*,2*S*)-1: Yield 72%, m.p. 161–163 °C; ref.[1a] m.p. 164–167 °C. R_f = 0.19 (CH_2Cl_2/MeOH, 9:1). $[\alpha]_D^{20}$ = –9.2 (c = 0.25, MeOH). ^{1}H NMR (300 MHz, [D$_6$]acetone): δ = 7.89 (d, J = 8.4 Hz, 2 H), 7.69 (d, J = 8.4 Hz, 2 H), 7.56 (d, J = 8.6 Hz, 1 H), 6.38 (s, 1 H), 5.30 (s, 1 H), 5.20 (s, 1 H), 4.29 (s, 1 H), 4.18–4.12 (m, 1 H), 3.80 (t, J = 7.9 Hz, 1 H), 3.68 (dd, J = 10.0, 5.0 Hz, 1 H), 3.08 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]acetone): δ = 164.5, 149.6, 140.9, 127.9, 127.8, 71.2, 67.5, 62.1, 58.0, 44.4 ppm. IR (neat): $\tilde{\nu}$ = 3489, 3448, 3252, 2916, 1687, 1563, 1280, 1143, 774 cm^{-1}. MS (CI, NH_3): m/z = 373.10 [M + NH_4]$^+$.

Supporting Information (see footnote on the first page of this article): NMR spectra of **1**, **4**–**6**, and **9** as well as SFC chromatograms of **4** and **9**.

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