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Synthesis of oxazolidines using DMSO/P_4O_{10} as a formaldehyde equivalent

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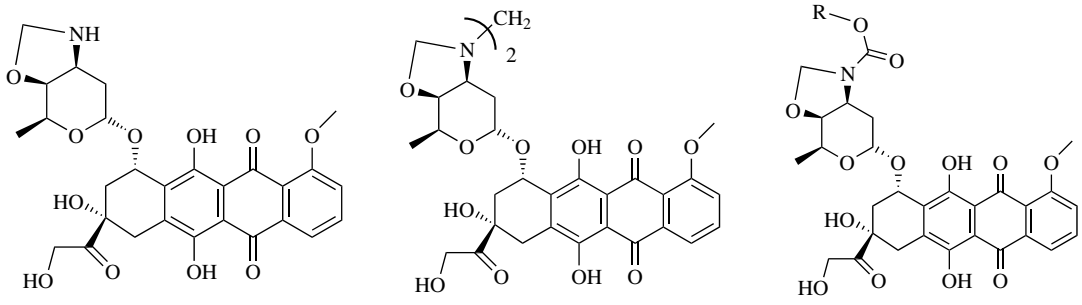
Abstract—Compounds containing a substituted oxazolidine ring were prepared in excellent yields in two steps from *cis* or *trans* 3-phenylglycidate. When an electron donating amine was used in the nucleophilic opening of an epoxide, treatment of the resulting β-amino-α-hydroxy ester with DMSO/P_4O_{10} led to the formation of *cis* or *trans* oxazolidines. This simple and practical procedure was readily adapted to the synthesis of enantiopure oxazolidines, using DMSO/P_4O_{10} because of the availability of the enantiopure halohydrins from enzymatic reduction of the β-chloro-α-ketoester.

1. Introduction

Substituted oxazolidines have been investigated extensively because of their importance as chiral auxiliaries in the synthesis of a variety of chiral compounds and as chain-protecting groups for amino alcohols.[1,2] Oxazolidine ring systems have been exploited successfully in medicinally valuable compounds, such as the anticancer prodrugs doxazolidine, doxoform, and doxaz carbamate (Fig. 1).[3] Thus, the construction of new oxazolidine skeletons continues to be pursued by many research groups.[4]

The most direct route to oxazolidines is the condensation of amino alcohols with either an aldehyde or acetone,[5] and such condensations of amino alcohols, including L-serine and L-cysteine methyl esters, with paraformaldehyde have been frequently employed, despite the fact that the yields are rather low.[6] Herein, we report a simple and direct



Doxazolidine (Doxaz) | Doxoform (Doxf) | Doxaz carbamate prodrug

Figure 1. Medicinally important prodrugs: doxazolidine and its derivatives.[3]

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method for the synthesis of racemic *cis*- and enantiopure *trans*-oxazolidines from phenylglycidate using DMSO/P_4O_{10} as a formaldehyde equivalent.

2. Results and discussion

At the beginning of this project, oxazolidines were not the target of our synthesis. Although its formation was not entirely unpredictable, it was unexpected. The initial target of our synthesis was 3-(4-methoxyphenylamino)-2-oxo-3-phenyl-propionic acid ethyl ester **5b**, which we planned to prepare via a simple three-step synthesis, as shown in Scheme 1. This route was appealing, since the precursor epoxide **1**, readily available in enantiopure forms,[7,8] allows access to both enantiomers of compound **5b**.

The synthesis started well: the zinc chloride-catalyzed[9] ring opening of *trans*-ethyl 3-phenyl glycidate **1**[10] with *p*-anisidine **2b** gave readily separable *anti*-β-amino alcohol **3b** and a small amount of α-amino alcohol (9:1 confirmed by GC–MS) in excellent yields (Scheme 1). In the following step, however, the reaction did not proceed along the projected route since all attempts to oxidize alcohol **3b** (Jones' reagent,[11] PCC, TEMPO/NaOCl,[12] and Dess–Martin reagent[13]) to **5b** under a variety of conditions gave unseparable mixtures of many compounds. Swern oxidation,[14] on the other hand, has been shown to be a favorable method for the oxidation of a few *t*-BOC-protected primary and secondary β-amino alcohols.[15,16] Although DMSO in hydrochloric acid had been used as a formaldehyde replacement (one-carbon source) in the synthesis of Tröger base,[17] we hoped that the P_4O_{10} in DMSO combination would favor oxidation, particularly in a reaction with a protected secondary amine.[18] In the attempted oxidation of the Boc-protected (R′ = Boc) alcohol **3b** with P_4O_{10} in DMSO, however, no **5b** product could be detected, although the same reaction with an unprotected **3b** (R′ = H) gave a single crystalline compound (85% yield), which was identified by ^1H and ^{13}C NMR as ethyl 3-(methoxyphenyl)-4-phenyl-oxazolidine-5-carboxylate **4b**. The structure of **4b** was confirmed by X-ray crystallographic analysis (Fig. 2).[19]

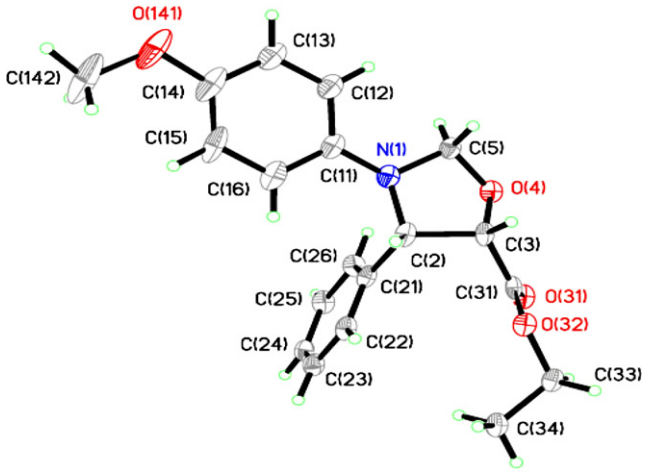
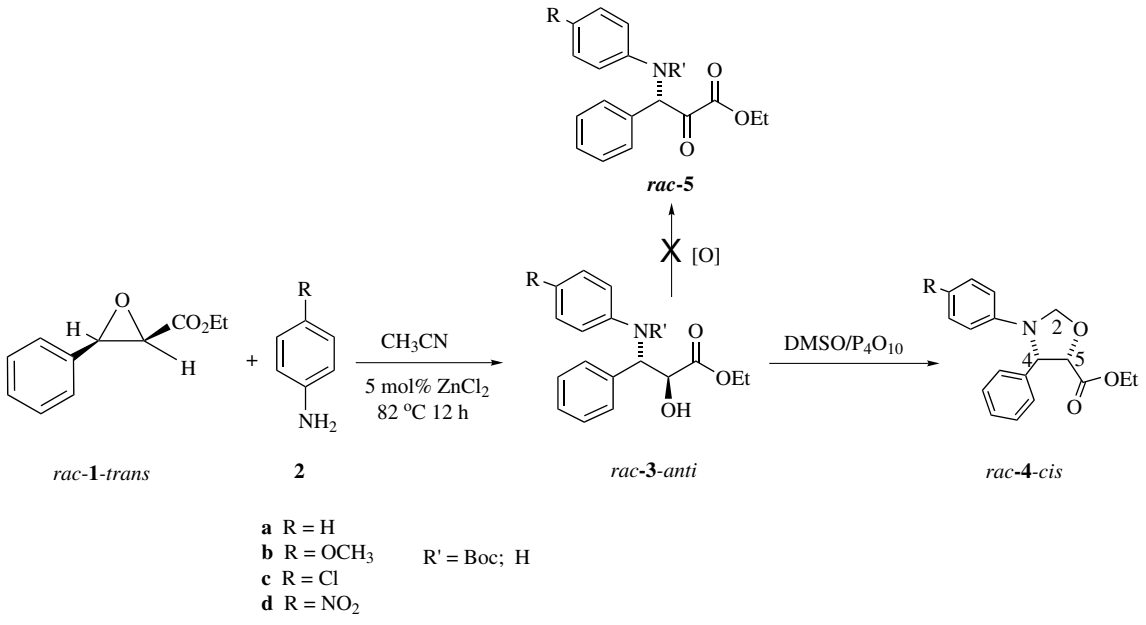


Figure 2. X-ray crystal structure of ethyl 3-(methoxyphenyl)-4-phenyl-oxazolidine-5-carboxylate **4b**.[19]

To investigate the generality of the oxazolidine formation, the reactions were performed with aniline **2a**, *p*-chloroaniline **2c**, and *p*-nitroaniline **2d**. Only *p*-chloroaniline **2c** turned out to be successful; *p*-nitroaniline **2d** failed to react with oxirane **1**, while aniline gave **3a** in good yield but failed to form oxazolidine **4a**. The results and yields of the products are summarized in Table 1.

The formation of oxazolidine **4b** can be explained as follows: it is generally accepted that in the oxidation of

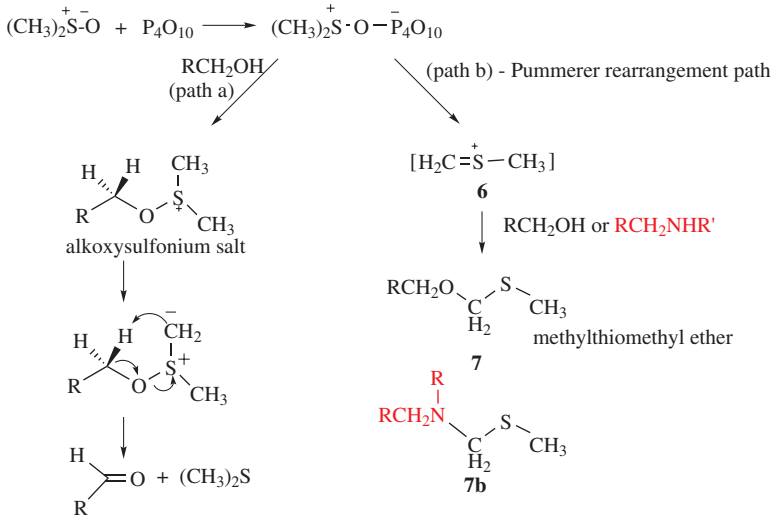


Scheme 1. Synthesis of *rac*-**4**-*cis*.

Table 1. Isolated yields of compounds **3** and **4**

Entry	2	3		4	
		Mp (°C)	Yield (%)	Mp (°C)	Yield (%)
a	Aniline	57.0–58.0	89	NR	
b	*p*-Anisidine	74.8–75.0	91	78.0–78.5	85
c	*p*-Chloroaniline	96.0–96.5	93	105.0–105.5	90
d	*p*-Nitroaniline	NR		—	

Note: NR = no reaction.



Scheme 2. Possible pathways for the reaction of activated DMSO with alcohols (or amines).

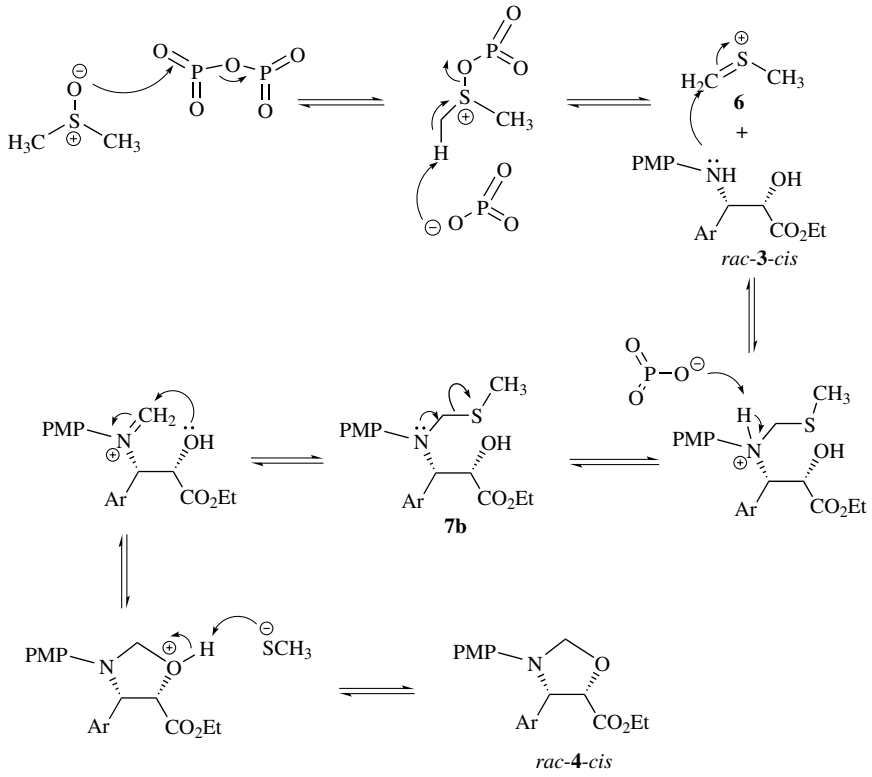
alcohols, dimethylsulfoxide (DMSO) is activated by a reaction with an electrophile (here phosphorous pentoxide) and that subsequent nucleophilic attack of an alcohol on the activated sulfoxonium intermediate leads to the formation of the alkoxysulfonium salt, which breaks down under basic conditions to give the carbonyl compound and dimethyl sulfide[20] (Scheme 2). It is also known that problems can arise when the formation of methylthiomethyl ether from the alcohol becomes an important competitive reaction.[21,22] Sulfonium ions, such as **6**, are recognized as intermediates in Pummerer rearrangements.[20]

In the case of attempted oxidation of alcohol **3b**, the formation of the alkoxysulfonium salt is probably very slow and the reaction preferentially follows path b (Scheme 2). The competing formation of oxazolidine **4b** (or **4c**) can be envisaged as outlined in Scheme 3. The unprotected, strongly nucleophilic β-amino group in compound **3b** (and **3c**) competes with the α-alcohol for the sulfonium ion **6**, but does not stop at the Pummerer rearrangement product, since ether **7b** not only possesses a potential leaving group (CH_3S^-) but also a neighboring electron-rich hydroxyl group. The proposed mechanism is supported by the fact that C-2 of the oxazolidine ring originates from DMSO, since it was established that the signal for this carbon atom at 83.43 ppm was enhanced (5×) when the reaction was performed in ^{13}C enriched DMSO.

The importance of the electron-rich amine group is confirmed by the fact that alcohol **3c** can be readily converted to **4c** in excellent yield, although no oxazolidine **4a** was detected in the cyclization of **3a**. The latter reaction gives a mixture of many products, which could not be identified. The reduced capacity to donate electrons, coupled with the vulnerability to oxidation of the non-substituted aniline, made this reaction unsuccessful. A poor electron donor, *p*-nitroaniline **2d**, did not react with epoxide **1**, even under forcing conditions (heating at 90 °C for 4 days) as shown in Table 1.

Other characteristics, which have an important bearing on the success of this reaction, are the reversibility and instability of the oxazolidine heterocycles toward hydrolysis, which often precludes their purification by chromatography. When run in dry, distilled DMSO, oxazolidines **4b** and **4c** crystallize from the reaction mixture in excellent yields. On the other hand, when the purification and drying of DMSO is not possible, as in the case in the reaction performed with ^{13}C-DMSO, the product does not crystallize spontaneously. During purification by flash chromatography, the proportion of ^{13}C-labeled oxazolidine **4b** in the mixture rapidly decreased (accompanied by the formation of several other unidentified products), resulting in a low yield of (still) impure **4b**.

Having optimized all steps leading to the formation of racemic *cis* oxazolidines, we turned to the synthesis of enantiopure *trans* products. β-Chloro-α-ketoester **8**, prepared according to the literature protocol,[23] was reduced using several carbonyl reductases from *Bacteroides fragilis*,[24] *Pyrococcus furiosus*,[25] *Candida magnoliae*,[26] and from *Sporobolomyces salmonicolor* (SSCR).[27,28] We found that



Scheme 3. Proposed pathway for the formation of oxazolidine **4**.

carbonyl reductase from *S. salmonicolor* (SSCR) gave (2*S*,3*S*)-**9** with >99% ee.[29] The enantiomeric excess of (2*S*,3*S*)-**9** was determined by chiral phase GC while the absolute configuration was assigned by comparing the retention times of a known sample from lipase resolution.[30] Overall, the formation of (2*S*)-α-hydroxy ester **9** is consistent with the enzyme-substrate docking studies of Hua et al.[28]

Ring closure of (2*S*,3*S*)-(+)-**9** gave (2*R*,3*R*)-(+)-methyl glycidate **10**. This epoxide is very sensitive to water and several protocols (NaOMe/MeOH,[24] K_2CO_3/DMF,[31] and K_2CO_3/MeOH[32]) were investigated to ensure a good yield. The K_2CO_3/MeOH method gave the best yield, provided that K_2CO_3 was added gradually. The product (2*R*,3*R*)-(+)-**10** was isolated as a colorless oil, in 85% yield. The *cis*-stereochemistry and absolute configuration were confirmed by ^{1}H NMR and specific rotation.[33†]

The availability, via enzymatic reductions, of enantiopure glycidate **10** provides access to the corresponding enantiopure β-amino alcohols and oxazolidines, which were not previously reported in the literature. The asymmetric aminolysis (Lewis acid catalyst $ZnCl_2$ at 82 °C) of (2*R*,3*R*)-(+)-**10** with amines **2b** and **2c** gave products (2*R*,3*S*)-(+)-**11b** and **11c**, respectively (Scheme 4). Both amino alcohols (3*R*,3*S*)-(+)-**11b** and **11c** reacted with dry DMSO in the presence of P_4O_{10} at room temperature to give (4*S*,5*R*)-(+)-**12b** and **12c** in excellent yields. Their melting points and specific rotations are listed in Table 2.

The *syn*-configuration of compounds (2*R*,3*S*)-(+)-**11b** and **11c** was deduced from their ^{1}H NMR spectra. The $J_{2,3}$ values of 2 Hz are considerably smaller than 3.2 Hz reported for *anti* isomers.[34] The following DMSO/P_4O_{10} ring closure gave both oxazolidine products in high yields and without a decrease in enantiopurity. Analysis by chiral HPLC showed a single peak (compared to two well-resolved peaks observed in the racemic products).

3. Conclusion

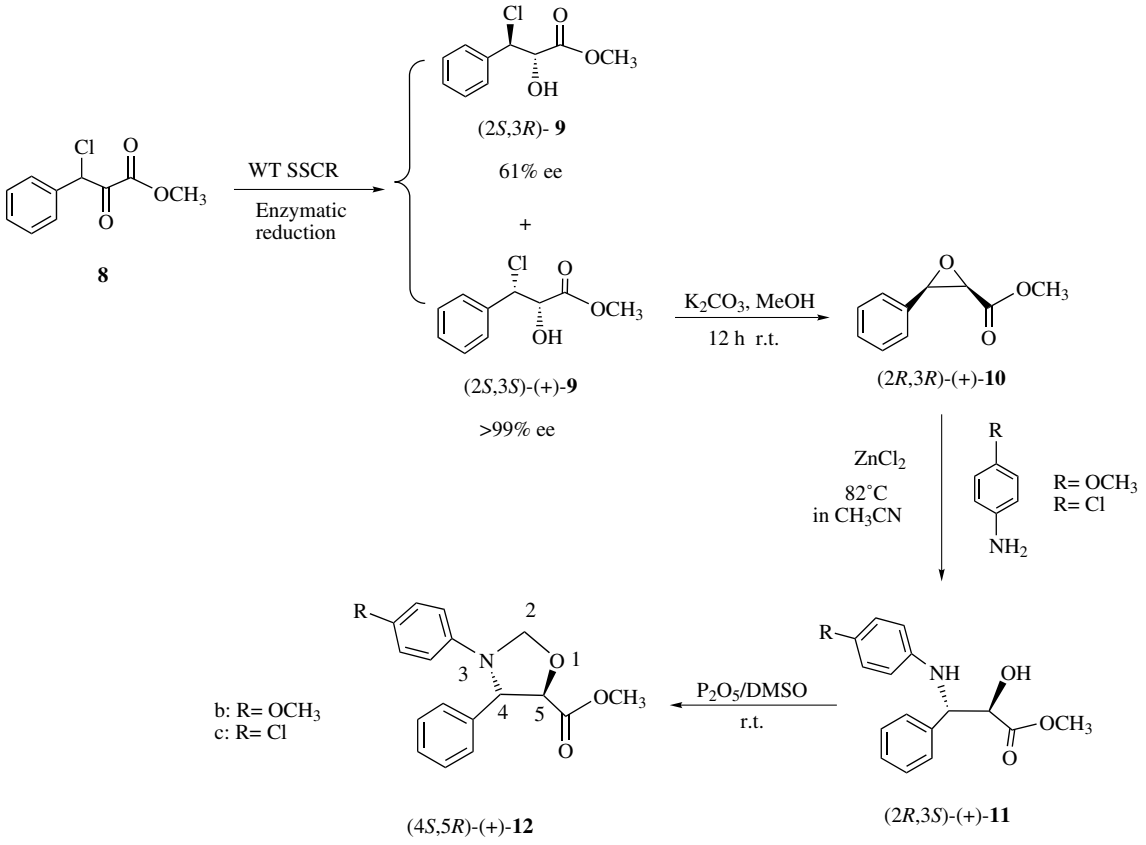
The method described in this paper allows the preparation of substituted oxazolidines from epoxide precursors, provided that the amines used to open the ring are good electron donors. An important aspect of this protocol is that it can be adapted for the synthesis of enantiopure oxazolidines, since enantiopure epoxides are available through the enzymatic reductions of α-chloro-β-ketoester.[8] The success of this methodology encourages future exploration of related reactions.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at room temperature on either a 400 or 500 MHz Bruker spectrometer and chemical shifts are reported in parts per

† The $J_{2,3}$ value of 4.6 Hz is consistent with a *cis*-configuration; $[\alpha]_D^{25} = +10.8$ (*c* 1.03, CH_2Cl_2); lit.[33] $J_{2,3} = 4.7$ Hz, $[\alpha]_D^{25} = +11$ (*c* 4.4, $CHCl_3$).



Scheme 4. Chemoenzymatic synthesis of oxazolidine **12.**

Table 2. Isolated yields, melting points, and optical rotations for compounds **11** and **12**

Entry	**2**	(2*R*,3*S*)-(+)-**11**			(4*S*,5*R*)-(+)-**12**		
		Mp (°C)	$[\alpha]_D^{25}$	Yield (%)	Mp (°C)	$[\alpha]_D^{25}$	Yield (%)
1	*p*-Anisidine (b)	76–77	+10.3	90	90–90.5	+48.7	86
2	*p*-Chloroaniline (c)	89–89.5	+7.9	92	93–93.5	+36.3	95

million using Me_4Si as internal standard. *J* values are expressed in Hertz. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. IR spectra were recorded as thin films on NaCl plates on a Mattson Satellite FT-IR spectrometer. The high resolution mass spectra were obtained on a Kratos MS50TC mass spectrometer. Optical rotations were measured on a Perkin–Elmer 241 Polarimeter operating at room temperature with energy source Na 589. The chiral HPLC analyses were performed on an Agilent 1100 series high-performance liquid chromatography system with (*S*,*S*)-Whelk-O 1 column (25 cm × 4.6 mm, Regis Technologies Inc.) using hexane/*iso*-propanol (90:10) as the mobile phase and a UV detector set at 254 nm. The chiral GC analysis was performed on an Agilent 5890 series II plus gas chromatography equipped with an autosampler, EPC, split/splitless injector, FID detector, and CP-Chirasil-Dex CB chiral capillary column (25 m × 0.25 mm). GC–EI-MS were performed on a SPB-5 GC column with an Agilent 5890 series gas chromatograph. Chiral GC program employed: the initial temperature 120 °C for 10 min, then increased 5 °C per min until final temperature 180 °C, then kept at 180 °C for 10 min, total run time 32 min.

4.1.1. Crystallography. The crystal intensity data were collected on a Bruker Smart 6000 diffractometer (rotating anode) at 100(2) K with Cu Kα (1.54178 Å) radiation. An absorption correction was made using multiscan SADABS while a SHELXTL system was used to solve and refine the structure and for the molecular graphics. Crystal data: $C_{19}H_{21}NO_4$, MW 327.37, triclinic $P\bar{1}$, $a = 5.7192(14)$, $b = 10.136(3)$, $c = 14.908(4)$ Å, $\alpha = 92.603(15)$, $\beta = 97.247(14)$, $\gamma = 105.463(14)°$, $V = 823.4(4)$ Å^3, $Z = 2$, $D_x = 1.320$ Mg m^{-3}.

All solvents and chemicals were purchased from Sigma–Aldrich and Fisher Scientific (Canada). All solvents used were purified and dried by standard methods. DMSO was prepared by distillation over calcium hydride and stored over molecular sieves (4 Å).

4.2. Methyl 3-chloro-2-oxo-3-phenylpropanoate 8[23,30]

Methyl dichloroacetate (43.20 g, 0.302 mol) and benzaldehyde (32.0 g, 0.302 mol) were added dropwise into NaOMe (16.308 g, 0.302 mol) in diethyl ether (400 mL) at −10 °C under argon. After stirring for 6 h, the reaction mixture was warmed to room temperature and stirred overnight. The mixture was then quenched with 5% HCl solution and extracted twice with diethyl ether. The combined organic layer was washed with brine and dried over $MgSO_4$. After evaporation, the crude product was purified by flash chromatography with hexane and ethyl acetate (5:1) to give **8** (58.40 g, 90% yield) as a yellow oil; IR ($CHCl_3$): ν_{max}/cm^{-1} 3062, 2955, 1737 (very strong), 1454, 1245, 1062, 701; ^1H NMR (400 MHz, $CDCl_3$): δ 3.84 (3H, s, C*H*$_3$), 6.18 (1H, s, C*H*), 7.37–7.42 (5H, s, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$): δ 53.4 (O*C*H$_3$), 61.94 (*C*HCl), 129.7 (Ar–*C para*), 128.9 (Ar–*C meta*), 129.1 (Ar–*C ortho*), 132.8 (CAr–*C*), 160.4 (*C*OOCH$_3$), 184.6 (*C*O).

4.3. Enzymatic reduction of methyl 3-chloro-2-oxo-3-phenylpropanoate 8

Purified reductase from SSCR[27] (60 mg), D-glucose dehydrogenase (GDH) (60 mg), NADPH (60 mg) and glucose (2 g) were dissolved in 200 mL of 100 mM potassium phosphate buffer (pH 6.5) and then was added 1 g of **8** dissolved in 10 mL DMSO. The reaction mixture was stirred at room temperature overnight, extracted with ethyl acetate (3 × 200 mL), and dried over sodium sulfate. The reaction mixture was filtered, concentrated, and the residual crude mixture was purified by column chromatography (silica gel Merk 60 with a mixture of hexane/EtOAc 6:1) to give (2*S*,3*S*)-**9** (0.41 g, 41% yield, >99% ee) and (2*S*,3*R*)-**9** (0.50 g, 50% yield, 61% ee) as colorless oils.

4.3.1. (2*S*,3*S*)-(+)-Methyl-3-chloro-2-hydroxy-3-phenylpropanoate 9. Colorless oil, >99% ee. Only one diastereomer was observed by ^1H and ^{13}C NMR and GC analysis: $[\alpha]_D^{25} = +46$ (*c* 1.07, CH_2Cl_2) (lit.[30] $[\alpha]_D^{25} = +47$, *c* 1.4, $CHCl_3$). IR ($CHCl_3$) γ_{max}/cm^{-1}: 3484, 2954, 2920, 2850, 17428, 1453, 1263, 1214, 1118, 995, 905, 699; ^1H NMR (400 MHz, $CDCl_3$): δ 3.36 (1H, d, $J = 7.6$ Hz, CHO*H*), 3.88 (3H, s, OC*H*$_3$), 4.58 (1H, dd, $J = 7.4$ Hz, $J = 2.2$ Hz, C*H*OH), 5.35 (H, d, $J = 2.2$ Hz, ClC*H*), 7.42–7.57 (5H, m, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$): δ 53.2 (O*C*H$_3$), 63.7 (*C*HOH), 74.7 (*C*HCl), 128.8 (Ar–*C para*), 127.9 (Ar–*C meta*), 128.5 (Ar–*C ortho*), 137.5 (CAr–*C*), 171.7 (*C*O). HRMS: calcd for $C_{10}H_{11}ClO_3$ (M^+): 214.03967; found: 214.03974.

4.3.2. (2*S*,3*R*)-(+)-Methyl-3-chloro-2-hydroxy-3-phenylpropanoate 9. Colorless oil, 61% ee. IR ($CHCl_3$) γ_{max}/cm^{-1}: 3456, 3062, 3032, 2954, 1742, 1494, 1453, 1282, 1214, 1153; 1116, 699; ^1H NMR (400 MHz, $CDCl_3$): δ 3.1 (1H, s, O*H*), 3.71 (3H, s, OC*H*$_3$), 4.60 (1H, d, $J = 4.2$ Hz, C*H*OH), 5.26 (1H, d, $J = 4.2$ Hz, ClC*H*), 7.32–7.39 (5H, m, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$): δ 52.7 (O*C*H$_3$), 62.9 (*C*HOH), 75.4 (*C*HCl), 128.0 (Ar–*C para*), 128.4 (Ar–*C meta*), 128.9 (Ar–*C ortho*), 135.9 (CAr–*C*), 171.1 (*C*O). HRMS: calcd for $C_{10}H_{11}ClO_3$ (M^+): 214.03967; found: 214.03974.

4.4. (2*R*,3*R*)-(+)-Methyl 3-phenylglycidate 10

A solution of (2*S*,3*S*)-chlorohydrin **9** (1 g, 4.6 mmol) in 30 mL of methanol was added with K_2CO_3 (0.76 g, 5.52 mmol, 1.2 equiv) gradually and then was stirred at room temperature until the starting material was gone (12 h). The reaction mixture was quenched with NH_4Cl solution (25 mL) and extracted with ethyl acetate (3 × 25 mL). The combined organic layer was washed with brine, dried over sodium sulfate, and evaporated. The crude residue was purified by flash chromatography and eluted with 10% dry ether in hexane to give (2*R*,3*R*)-(+)-**10** (0.82 g, 85% yield) as a colorless oil. $[\alpha]_D^{25} = +10.8$ (*c* 1.03, CH_2Cl_2); lit.[30] $[\alpha]_D^{25} = +13$ (*c* 1.1, $CHCl_3$); lit.[33] $[\alpha]_D^{25} = +11$ (*c* 4.4, $CHCl_3$). IR ($CHCl_3$) γ_{max}/cm^{-1}: 3080, 3060, 2980, 2950, 1750, 1435, 1210; ^1H NMR (400 MHz, $CDCl_3$): δ 3.53 (3H, s, OC*H*$_3$), 3.83 (1H, d, $J = 4.7$ Hz, OC*H*), 4.25 (1H, d, $J = 4.7$ Hz, OC*H*), 7.26–7.41 (5H, m, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$): δ 52.0 (O*C*H$_3$), 55.8 (CO*C*HO), 57.5 (PhC*C*HO), 126.6 (Ar–*C para*), 128.1 (Ar–*C meta*), 128.5 (Ar–*C ortho*), 132.8 (CAr–*C*), 167.0 (*C*O).

4.5. General procedure for the epoxide ring opening

A mixture of ethyl (or methyl) 3-phenyl glycidate (5 mmol, 1 equiv) and *p*-substituted aniline **2** (5 mmol, 1 equiv) was dissolved in acetonitrile (20 mL). Dry $ZnCl_2$ (34 mg, 0.25 mmol) (1.25 mmol %) was added and the resulting mixture was stirred under a nitrogen atmosphere for 12–28 h at 82 °C. Removal of the solvent gave a residue, which was extracted with ethyl acetate (50 mL) and washed with a saturated solution of sodium bicarbonate (20 mL), water, and brine. After drying over anhydrous magnesium sulfate and removal of the solvent, the residue was purified by chromatography over ultrapure silica gel using hexane/ethyl acetate (2:1) to give the product.

4.5.1. *anti*-(±)-Ethyl 2-hydroxy-3-phenyl-3-(phenylamino)-propanoate 3a. White powder, 89% yield; mp: 57–58 °C; IR ($CHCl_3$) γ_{max}/cm^{-1}: 3404, 3054, 2982, 2934, 1736, 1298, 1603, 1504, 1214, 1106, 1026, 868, 750, 694, 561, 509; ^1H NMR (500 MHz, $CDCl_3$): δ 1.31 (3H, t, $J = 7.3$ Hz, C*H*$_3$), 2.10 (1H, s, O*H*), 2.91 (1H, N*H*), 4.22 (3H, m, $J = 7.1$ Hz, C*H*$_2$), 4.71 (1H, d, $J = 3.7$ Hz, NHC*H*), 4.92 (1H, d, $J = 3.7$ Hz, C*H*OH), 6.67 (2H, d, $J = 7.9$ Hz, Ar*H*–*N*), 6.73 (1H, d, $J = 7.4$ Hz, Ar*H*–*N*), 7.14 (2H, d, $J = 7.9$ Hz, Ar*H*–*N*), 7.34 (5H, m, Ar*H*). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.1 (OCH$_2$*C*H$_3$), 59.6 (*C*HNH), 62.0 (O*C*H$_2$CH$_3$), 73.6 (*C*HCO), 113.9 (NHAr–*C ortho*), 118.1 (NHAr–*C para*), 127.6 (Ar–*C ortho*), 128.5 (Ar–*C meta*), 129.2 (NHAr–*C meta*), 137.2 (Ar–*C*–CH), 146.2 (Ar–*C*–NH), 172.1 (*C*O); HRMS: calcd for $C_{17}O_3NH_{19}$ (M^+): 285.13635; found: 285.13651.

4.5.2. *anti*-(±)-Ethyl 3-(4-methoxyphenylamino)-2-hydroxy-3-phenylpropanoate 3b. Yellow crystals, 91% yield; mp: 74.8–75 °C; IR ($CHCl_3$) γ_{max}/cm^{-1}: 3285, 2979, 2936, 2471, 1737, 1511, 1258, 1217, 1028, 701; ^1H NMR (500 MHz, $CDCl_3$): δ 1.23 (3H, t, $J = 7.3$ Hz, C*H*$_3$), 2.91 (2H, d, $J = 7.6$ Hz, N*H*), 3.68 (3H, s, OC*H*$_3$), 4.16 (3H, m, $J = 7$ Hz, C*H*$_2$ and O*H*), 4.63 (1H, d, $J = 3.4$ Hz,

NHC*H*), 4.78 (1H, d, $J = 3.4$ Hz, C*H*OH), 6.70 (2H, d, $J = 6$ Hz, Ar*H*), 6.58 (2H, d, $J = 6$ Hz, Ar*H*), 7.25 (5H, m, Ar*H*). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.1 (OCH_2CH_3), 55.7 (OCH_3), 60.6 (*C*HNH), 73.5 (*C*HCO), 61.9 (OCH_2CH_3), 114.8 (NHAr–*C ortho*), 115.5 (NHAr–*C meta*), 127.6 (Ar–*C ortho*), 128.4 (Ar–*C meta*), 136.1 (Ar–*C*–NH), 140.5 (Ar–*C*–CH), 152.5 (Ar–*C*–OCH_3), 172.3 (*C*O); EI-MS, *m*/*z*: M^+: 315, 211 $(M-103)^+$, 103 $(M-211)^+$, 77, 89. HRMS: calcd for $C_{18}O_4NH_{21}$ (M^+): 315.14706; found: 315.14686.

4.5.3. *anti*-(±)-Ethyl 3-(4-chlorophenylamino)-2-hydroxy-3-phenylpropanoate 3c. Yellow crystals, 93% yield; mp: 96–96.5 °C; IR ($CHCl_3$) γ_{max}/cm^{-1}: 3473, 3400, 3029, 2981, 2932, 1936, 1600, 1453, 1245, 1210, 1095, 1024, 816, 720, 700; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (3H, t, $J = 6.7$ Hz, CH_3), 2.92 (1H, d, $J = 7.3$ Hz, N*H*), 4.15 (3H, m, $J = 7.3$ Hz, CH_2 and O*H*), 4.63 (1H, d, $J = 3.7$ Hz, NHC*H*), 4.78 (1H, d, $J = 3.7$ Hz, C*H*OH), 6.51 (2H, d, $J = 8.6$ Hz, Ar*H*), 6.70 (2H, d, $J = 8.6$ Hz, Ar*H*), 7.25 (5H, m, Ar*H*). ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.1 (OCH_2CH_3), 59.6 (*C*HNH), 62.1 (OCH_2CH_3), 73.4 (*C*HCO), 115.0 (NHAr–*C ortho*), 122.6 (NHAr–*C para*), 127.4 (Ar–*C ortho*), 128.5 (Ar–*C meta*), 129.0 (NHAr–*C meta*), 136.6 (Ar–*C*–CH), 144.7 (Ar–*C*–NH), 171.8 (*C*O); HRMS: calcd for $C_{17}H_{18}ClO_3N$ (M^+): 319.09649; found: 319.09753.

4.5.4. (2*R*,3*S*)-(+)-Methyl 3-(4-methoxyphenylamino)-2-hydroxy-3-phenylpropanoate 11b. Yellow crystals, 90% yield; $[\alpha]_D^{25} = +10.3$ (*c* 0.99, CH_2Cl_2); >99% ee; mp: 76–77 °C; IR ($CHCl_3$) γ_{max}/cm^{-1}: 3285, 2979, 2936, 2471, 1737, 1511, 1258, 1217, 1028, 701; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.69 (3H, s, CH_3), 3.74 (3H, s, OCH_3), 4.47 (1H, d, $J = 2.4$ Hz, NHC*H*), 4.84 (1H, d, $J = 2.4$ Hz, C*H*OH), 6.50 (2H, d, $J = 8.8$ Hz, Ar*H*), 6.63 (2H, d, $J = 8.8$ Hz, Ar*H*), 7.25–7.36 (5H, m, Ar*H*). ^{13}C NMR (126 MHz, $CDCl_3$): δ 52.3 (O*C*H$_3$), 55.7 (O*C*H$_3$), 60.0 (*C*HNH), 74.7 (*C*HCO), 114.7 (NHAr–*C ortho*), 115.4 (NHAr–*C meta*), 127.0 (Ar–*C ortho*), 128.6 (Ar–*C meta*), 136.1 (Ar–*C*–NH), 140.4 (Ar–*C*–CH), 152.3 (Ar–*C*–OCH_3), 173.3 (*C*O); HRMS: calcd for $C_{17}O_4NH_{19}$ (M^+): 301.13141; found: 301.13142.

4.5.5. (2*R*,3*S*)-(+)-Methyl 3-(4-chlorophenylamino)-2-hydroxy-3-phenylpropanoate 11c. Colorless crystals, 92% yield; $[\alpha]_D^{25} = +7.9$ (*c* 1.36, CH_2Cl_2); >99% ee; mp: 89–89.5 °C; IR ($CHCl_3$) γ_{max}/cm^{-1}: 3473, 3400, 3029, 2981, 2932, 1936, 1600, 1453, 1245, 1210, 1095, 1024, 816, 720, 700; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.6 (3H, s, CH_3), 3.14 (1H, O*H*), 4.49 (1H, d, $J = 2.0$ Hz, NHC*H*), 4.79 (1H, d, $J = 2.0$ Hz, C*H*OH), 6.45 (2H, d, $J = 8.6$ Hz, Ar*H*), 7.05 (2H, d, $J = 8.6$ Hz, Ar*H*), 7.24–7.33 (5H, m, Ar*H*). ^{13}C NMR (126 MHz, $CDCl_3$): δ 53.1 (O*C*H$_3$), 59.0 (*C*HNH), 74.5 (*C*HCOH), 115.0 (NHAr–*C ortho*), 122.6 (NHAr–*C para*), 127.8 (Ar–*C ortho*), 128.7 (Ar–*C meta*), 129.0 (NHAr–*C meta*), 138.8 (Ar–*C*–CH), 144.7 (Ar–*C*–NH), 173.2 (*C*O); HRMS: calcd for $C_{16}H_{16}ClO_3N$ (M^+): 305.08187; found: 305.08065.

4.6. General procedure for the formation of oxazolidines 4 and 12

Phosphorus pentoxide (568 mg, 2 mmol, calculated with P_4O_{10}, MW = 284) was added to dry dimethylsulfoxide (3 mL) and ultrasonicated for 10 min. Compound **3** or **11** (1 mmol) in dimethylsulfoxide (2 mL) was then added and the resulting mixture was stirred at room temperature until TLC indicated complete conversion (24 h). The reaction mixture was quenched with cooled saturated sodium bicarbonate solution (20 mL) followed by a small amount of water. The mixture was extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with water (3×40 mL) to remove unreacted dimethylsulfoxide, then washed with brine, dried over magnesium sulfate, filtered, concentrated, and separated by flash chromatography on silica gel and then crystallized from hexane and ethyl acetate to give colorless crystals.

4.6.1. *cis*-(±)-Ethyl 3-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate 4b. Yellow crystals, 85% yield; mp: 78–78.5 °C; IR ($CHCl_3$) γ_{max}/cm^{-1}: 2980, 2930, 2836, 1746, 1514, 1244, 1200, 1038; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (3H, t, $J = 7.3$ Hz, CH_3), 3.88 (2H, dd, $J = 7.3$ Hz, CH_2), 3.74 (3H, s, OCH_3), 5.59 (1H, d, $J = 1.9$ Hz, NCHO), 5.01 (1H, d, $J = 1.9$ Hz, NCHO), 4.94 (1H, d, $J = 7.3$ Hz, NCH), 4.90 (1H, d, $J = 7.3$ Hz, COH), 6.74 (2H, d, $J = 6.9$ Hz, ArH), 6.42 (2H, d, $J = 6.9$ Hz, ArH), 7.29 (5H, m, ArH); ^{13}C NMR (126 MHz, $CDCl_3$): δ 13.7 (OCH_2CH_3), 55.7 (OCH_3), 61.0 (OCH_2CH_3), 64.4 (NCHC), 83.4 (NCH_2O), 81.7 (OCHC), 115.0 (NAr–C *ortho*), 114.1 (NAr–C *meta*), 152.5 (NAr–C *para*), 127.6 (Ar–C *para*), 128.4 (Ar–C *meta*), 128.2 (Ar–C *ortho*), 138.8 (Ar–C–CH), 168.1 (CO); GC–MS (SPB-5 column)-MS. RT = 10.65 minute. EI-MS, *m*/*z*: M^+ 327, 73, 77, 86, 91,105, 118, 122. HRMS: calcd for $C_{19}O_4NH_{21}$ (M^+): 327.14706; found: 327.14743.

4.6.2. *cis*-(±)-Ethyl 3-(4-chlorophenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate 4c. Colorless crystals, 90% yield; mp: 105–105.5 °C; IR ($CHCl_3$) γ_{max}/cm^{-1}: 2982, 2902, 2836, 1760, 1744, 1599, 1493, 1469, 1341, 1201, 1097, 1041, 809, 737, 699, 504; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (3H, t, $J = 7.1$ Hz, CH_3), 3.70 (1H, m, $J = 3.6$ Hz, CH_2), 3.86 (1H, m, $J = 3.6$ Hz, CH_2), 4.92 (1H, d, $J = 7.8$ Hz, OC*H*), 4.96 (1H, d, $J = 7.8$ Hz, NC*H*), 5.04 (1H, d, $J = 1.8$ Hz, NC*H*O), 5.56 (1H, d, $J = 1.8$ Hz, NC*H*O), 6.35 (2H, d, $J = 8.7$ Hz, Ar*H*), 6.74 (2H, d, $J = 8.7$ Hz, Ar*H*), 7.29 (5H, m, Ar*H*); ^{13}C NMR (126 MHz, $CDCl_3$): δ 13.7 (OCH_2CH_3), 61.2 (OCH_2CH_3), 63.6 (N*C*HC), 82.6 (N*C*H$_2$O), 81.6 (O*C*HC), 113.8 (NAr–*C ortho*), 123.1 (Ar–*C para*), 127.5 (Ar–*C meta*), 128.6 (Ar–*C ortho*), 129.2 (NAr–*C meta*), 137.1 (Ar–*C*–CH), 142.5 (NAr–*C para*), 167.6 (*C*O); HRMS: calcd for $C_{18}O_3NClH_{18}$ (M^+): 331.09829; found: 331.09753.

4.6.3. (4*S*,5*R*)-(+)-Methyl 3-(4-methoxyphenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate 4–12b. Colorless crystals, 86% yield; $[\alpha]_D^{25} = +48.7$ (*c* 1.02, CH_2Cl_2); >99% ee; mp: 90–90.5 °C; IR ($CHCl_3$) γ_{max}/cm^{-1}: 2982, 2902, 2836, 1760, 1744, 1599, 1493, 1469, 1341, 1201, 1097, 1041, 809, 737, 699, 504; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.68

(3H, s, CH_3), 3.79 (3H, s, OCH_3), 4.59 (1H, d, $J = 3.0$ Hz, OCH), 4.85 (1H, d, $J = 3.0$ Hz, NCH), 5.24 (1H, d, $J = 1.6$ Hz, NCHO), 5.38 (1H, d, $J = 1.6$ Hz, NCHO), 6.35 (2H, d, $J = 8.8$ Hz, ArH), 7.10 (2H, d, $J = 8.8$ Hz, ArH), 7.29 (5H, m, ArH); ^{13}C NMR (126 MHz, $CDCl_3$): δ 51.8 (OCH$_3$), 54.2 (OCH$_3$), 64.7 (NCHC), 82.8 (NCH$_2$O), 84.2 (OCHC), 114.1 (NAr–*C ortho*), 123.2 (Ar–*C para*), 126.2 (Ar–*C meta*), 128.7 (Ar–*C ortho*), 129.2 (NAr–*C meta*), 140.2 (Ar–*C*–CH), 142.6 (NAr–*C para*), 167.6 (*C*O); HRMS: calcd for $C_{18}O_4NH_{19}$ (M^+): 313.13141; found: 313.13145.

4.6.4. (4*S*,5*R*)-(+)-Methyl 3-(4-chlorophenyl)-4-phenyl-1,3-oxazolidine-5-carboxylate 12c. Colorless crystals, 95% yield; $[\alpha]_D^{25} = +36.3$ (*c* 0.55, CH_2Cl_2); >99% ee; mp: 93–93.5 °C; IR ($CHCl_3$) γ_{max}/cm^{-1}: 2982, 2902, 2836, 1760, 1744, 1599, 1493, 1469, 1341, 1201, 1097, 1041, 809, 737, 699, 504; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (3H, s, CH_3), 4.63 (1H, s, OCH), 4.88 (1H, s, NCH), 5.24 (1H, s, NCHO), 5.38 (1H, s, NCHO), 6.35 (2H, d, $J = 7.1$ Hz, ArH), 7.10 (2H, d, $J = 7.1$ Hz, ArH), 7.25–7.36 (5H, m, ArH); ^{13}C NMR (126 MHz, $CDCl_3$): δ 52.6 (OCH$_3$), 64.6 (NCHC), 82.7 (NCH$_2$O), 84.0 (OCHC), 114.0 (NAr–*C ortho*), 123.2 (Ar–*C para*), 126.1 (Ar–*C meta*), 128.1 (Ar–*C ortho*), 129.2 (NAr–*C meta*), 140.1 (Ar–*C*–CH), 142.4 (NAr–*C para*), 170.8 (*C*O); HRMS: calcd for $C_{17}O_3NClH_{16}$ (M^+): 317.08188; found: 317.08177.

4.7. (^{13}C) Ethyl 3-(4-methoxyphenyl)-4-phenyl-1, 3-oxazolidine-5-carboxylate (^{13}C)-4b

Phosphorus pentoxide (568 mg, 2 mmol calculated with P_4O_{10}, MW = 284) was added to dry dimethylsulfoxide (2 mL) containing ^{13}C-DMSO (5%) and ultrasonicated for 10 min. Compound **3b** (315 mg, 1 mmol) in dimethylsulfoxide (3 mL) containing ^{13}C-DMSO (5%) was added and the resulting mixture was stirred at room temperature until TLC indicated complete conversion (24 h). The reaction was quenched with cooled saturated sodium bicarbonate solution followed by a small amount of water. The mixture was extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with water (3×40 mL) to remove unreacted dimethylsulfoxide, then washed with brine, dried over magnesium sulfate, filtered, concentrated, and separated by flash chromatography on silica gel with hexane/ethyl acetate to give a yellow product, which was highly enriched but not pure (^{13}C)-**4b**.

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