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Asymmetric synthesis of (4*S*,5*S*)-2-oxo-4-phenyloxazolidine-5-carboxylic acid using a 1,2-addition of PhMgBr to an *N*-sulfinimine derived from (*R*)-glyceraldehyde acetonide and (*S*)-*t*-BSA

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ABSTRACT

We report an asymmetric synthesis of (4*S*,5*S*)-2-oxo-4-phenyloxazolidine-5-carboxylic acid via stereoselective addition of phenylmagnesium bromide (PhMgBr) to an *N*-sulfinimine derived from (*R*)-glyceraldehyde acetonide. (*S*)- and (*R*)-Glyceraldehyde acetonides, important chiral synthons in synthetic organic chemistry, are prepared from the corresponding epichlorohydrin using an identical synthetic methodology.

1. Introduction

3-Amino-3-phenylpropane-1,2-diol is a key chiral structural component in a variety of therapeutically active molecules, such as the side chain of Taxol[1] and its 2-oxazolidinone derivatives, such as cytoxazone and *epi*-cytoxazone.[2,7] The *syn*-β-aminoalcohols, such as 1,2-aminoindanols, serve as biologically active molecules as well as chiral ligands.[3] Only a few methods are available in the literature for the synthesis of chiral 3-amino-3-phenylpropane-1,2-diol, such as asymmetric epoxidations[1,4] or asymmetric dihydroxylations[5,6] of the corresponding cinnamyl alcohol or its ester followed by functional group transformations. Most of these reported methods are primarily applicable for the synthesis of *anti*-β-aminoalcohol[1] but are limited for directly obtaining *syn*-β-aminoalcohol (Fig. 1).

However, inversion at either stereogenic center of *anti*-β-amino alcohol can produce the corresponding *syn*-isomer, although there is the possibility of racemisation resulting in reduced yields.[1] Of course, *syn*-β-aminoalcohol itself can be synthesized using Sharpless asymmetric oxyamination[7a] (aminohydroxylation), conjugate addition of a chiral amine to a cinnamyl ester followed by diastereoselective enolate oxidation,[7b] and other methods[7] but sometimes achieving regioselectivity is a tedious task. There is thus felt a need by organic chemists to define a new methodology to synthesize *syn*-3-amino-3-phenylpropane-1,2-diol in high regioselectivity. Moreover, the ethyl ester of *syn*-(4*S*,5*S*)-2-oxo-4-phenyloxazolidine-5-carboxylic acid **1** can be epimerized to ethyl ester of *anti*-isomer **2** but not vice versa.[8] In this context we took upon

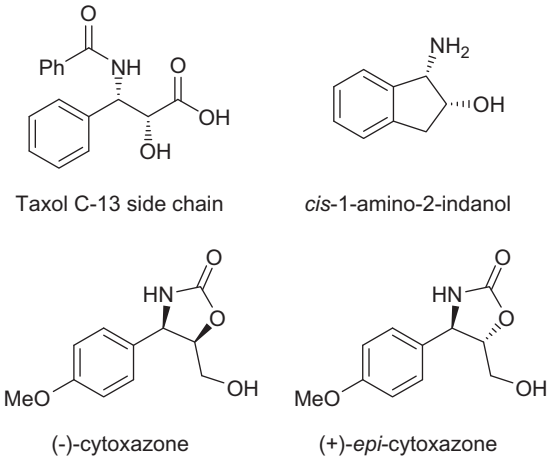

Figure 1. Structures of Taxol side chain, *cis*-1-amino-2-indanol, cytoxazone and *epi*-cytoxazone.

the asymmetric synthesis of *syn*-(4*S*,5*S*)-3-amino-3-phenylpropane-1,2-diol **11** followed by its oxidation to carboxylic acid **1** as the target.

Herein, we report an asymmetric synthesis of **1** via the stereoselective 1,2-addition of phenylmagnesium bromide (PhMgBr) to an *N*-sulfinimine[9] derived from (*R*)-glyceraldehyde acetonide followed by non-racemising oxidation of the primary alcohol to the corresponding carboxylic acid. These chiral glyceraldehyde acetonides are prepared from the commercially available corresponding epichlorohydrin (Scheme 1).

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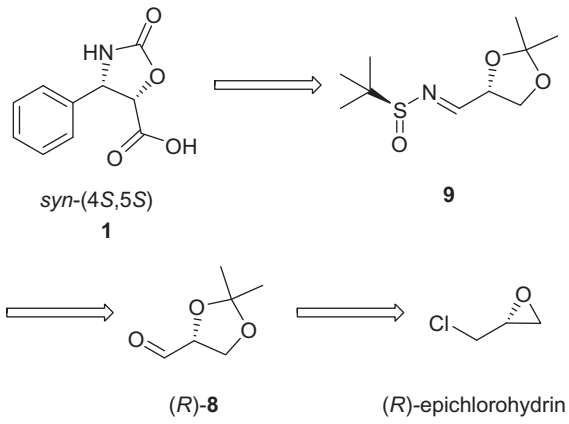
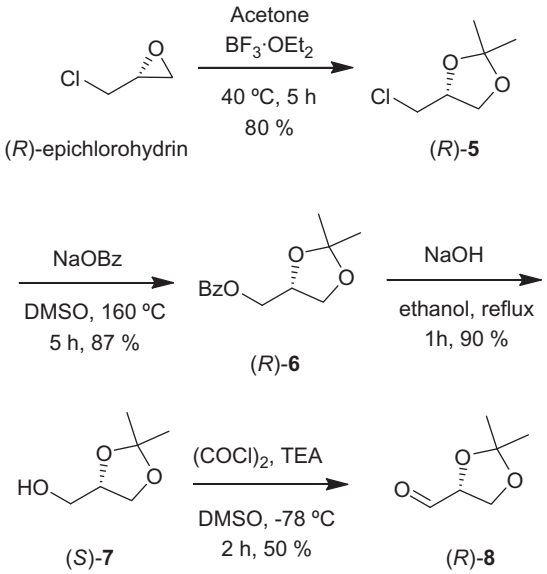


Scheme 1. Retrosynthesis of (4*S*,5*S*)-2-oxo-4-phenyloxazolidine-5-carboxylic acid, **1**.

2. Results and discussion

Both (*S*)- and (*R*)-glyceraldehyde acetonides are very important chiral synthons for the total synthesis of biologically active molecules and pharmaceutically important moieties.[10–12,21] The preparation of (*R*)-glyceraldehyde acetonide is well documented in the literature using D-mannitol,[13–16] whereas (*S*)-glyceraldehyde acetonide is synthesized from L-ascorbic acid.[17] To the best of our knowledge, no methods have so far been reported for the preparation of both (*S*)- and (*R*)-glyceraldehyde acetonide using an identical synthetic methodology. In this context, we decided to develop an efficient, simple, and identical synthetic strategy to prepare (*S*)- and (*R*)-glyceraldehyde acetonide and showed its application in the synthesis of the targeted compound **1**.

Accordingly, (*R*)-epichlorohydrin on reaction with acetone catalyzed by boron trifluoride etherate at 40 °C gave corresponding chloro compound, (*R*)-**5** which was further treated with sodium benzoate in dimethylsulfoxide (DMSO) at 160 °C to give benzoate ester (*R*)-**6** in good yield.[18,19] Hydrolysis of the *O*-benzoyl group in (*R*)-**6** using sodium hydroxide in ethanol gave protected glycerol (*S*)-**7** that was further oxidized to the desired (*R*)-glyceraldehyde acetonide (*R*)-**8** using Swern oxidation[20] (Scheme 2). The same synthetic approach was successfully applied to (*S*)-epichlorohydrin as well, yielding the (*S*)-glyceraldehyde acetonide (*S*)-**8**.



Scheme 2. Synthesis of (*R*)-glyceraldehyde acetonide from (*R*)-epichlorohydrin.

Among the various methods considered, nucleophilic 1,2-addition of an aryl or alkyl carbanion to an imine double bond is a versatile and popular method for the preparation of functionalizsed amines.[21] However, in this strategy both the yield and stereoselectivity were predominantly influenced by the electrostatic and steric factors of both substrates, that is, the imine and the nucleophile.[22a] Incorporation of a stereo-directing motif, such as chiral sulfinimines is evident for its potential to synthesize chiral amines in a stereoselective fashion.[22b] The aldehyde (*R*)-**8**, on reaction with (*S*)-*t*-butylsulfinamide [(*S*)-*t*-BSA] using $CuSO_4$ in dichloromethane at room temperature yielded (*S*,*E*)-*N*-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide **9** with 98.94% de (Scheme 3). No epimerisation at the α-center was detected by high performance liquid chromatography (HPLC) analysis of chiral sulfinimine **9**, which provides access to a diverse range of substituted imines. The de of **9** indirectly establishes the enantiomeric excess (ee) of (*R*)-**8**.

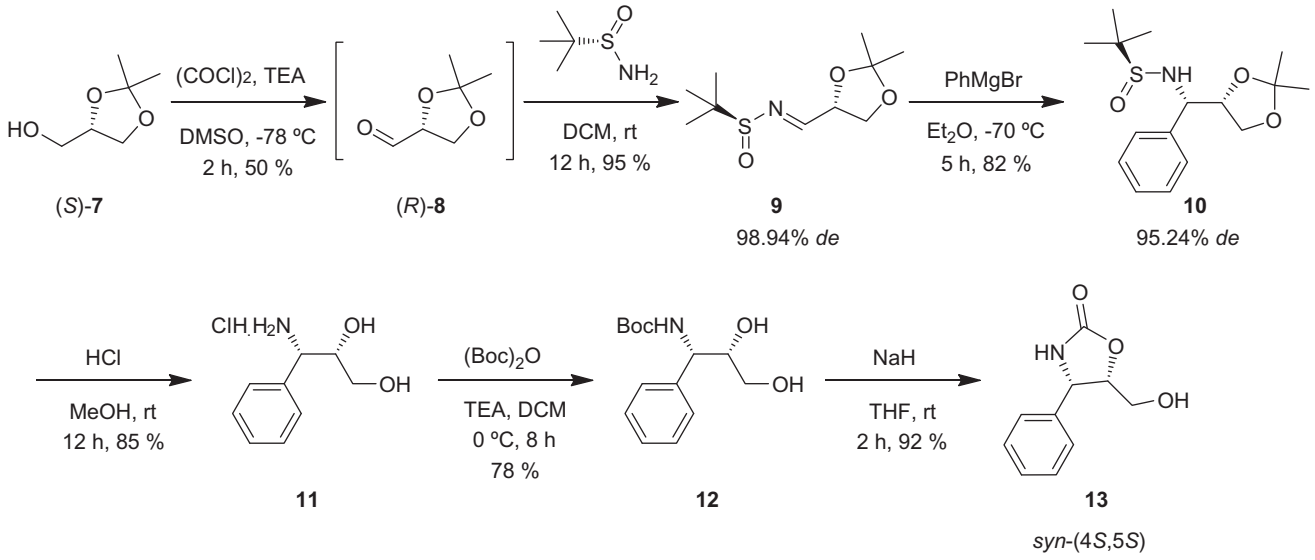
The 1,2-addition of phenylmagnesium bromide to benzyl imine derivative of (*S*)-**8** is reported in the literature but with low diastereoselectivity.[23] Alternatively, chiral *N*-sulfinimine was chosen as an auxiliary to achieve good de during the 1,2-addition to imine **9**. Chiral sulfinimine **9** upon treatment with PhMgBr in ether at −70 °C gave the (*S*)-*N*-((*S*)-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-(phenyl)methyl)-2-methylpropane-2-sulfinamide **10** with high diastereoselectivity (95.24% de by HPLC). Herein, the impact of temperature on stereoselectivity was studied (between 0 and −70 °C) and we obtained a maximum de of the targeted compound **10** at −70 °C. This reaction was scaled up to 50.0 g.

It is apparent that the 1,2-addition of PhMgBr to chiral sulfinimine **9** proceeds via transition state **9a** (Scheme 4). The stereoselectivity resulting from the addition of organometallic reagents to the C–N double bond of sulfinimines can generally be predicted by assuming chelated, chair-like transition states resulting from coordination of the metal ion with the sulfinyl oxygen.[21b]

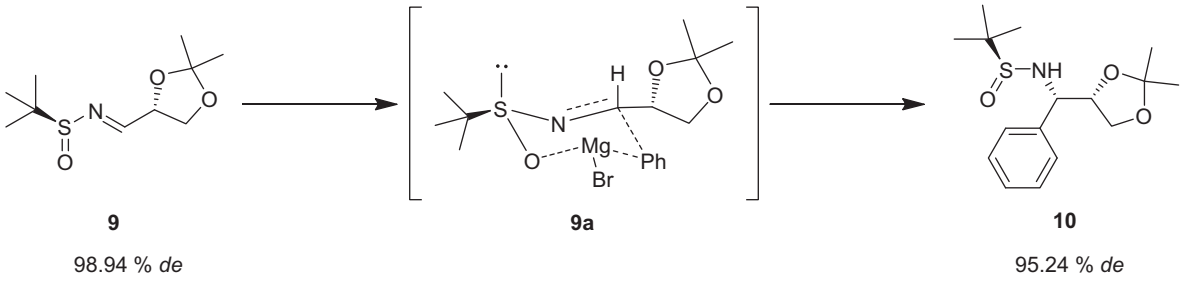
Deprotection of the *t*-butylsulfonyl group and 1,3-dimethyl acetal in **10** was performed in acidic media (methanolic HCl) to give *syn*-β-aminoalcohol **11**. The amine functionality in **11** was protected as *N*-Boc derivative **12**. The next step in the sequence is the formation of 2-oxazolidinone. The *N*-Boc protective group was advantageously utilizsed for the formation of an oxazolidinone ring, thereby avoiding the protection and deprotection of the primary hydroxyl group. Thus, compound **12**, on exposure to NaH in THF cyclizsed regioselectively to **13**. Alcohol **13** has been confirmed to exist in a *threo* configuration (*syn* product) by the characteristic H4 and H5 signals that appear in the ^{1}H NMR spectra and is in agreement with the reported values of similar compounds.[2b,8] Since the absolute stereochemistry of (*R*)-**8** and *t*-BSA were known, the identity of the stereocenters of **13** was elucidated and confirmed to be (4*S*,5*S*).

To oxidize the primary alcohol of compound **13**, into the respective acid **1** in a non-racemising way, various methods were attempted, such as ruthenium catalyzed $NaIO_4$, PCC, PDC, $KMnO_4$, and others. After numerous efforts, we finally developed a simple and feasible method using cost effective reagent CrO_3 (Jones' method) to oxidize compound **13** into corresponding carboxylic acid **1** in moderate yields ~55% (Scheme 5) and these are summarized in Table 1. Racemic, *syn*- and *anti*-carboxylic acids **1** were prepared as reference standards by following the literature procedure on similar compounds.[24] Chiral and chemical HPLC methods were developed to characterize and determine the % of ee or de in the final compound **1**. The possibility of racemization during oxidation was ruled out as HPLC showed the enantiomeric purity of the respective carboxylic acid **1** to be 99% ee. Compound **1** has been utilized to synthesize *cis*-1-amino-2-indanol.[3c]

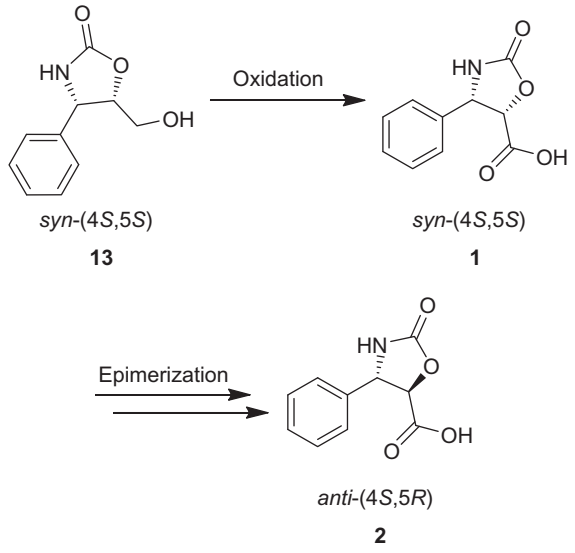
The ester of **1** (*syn*) can be epimerized to the respective *anti*-isomer but not vice versa. Earlier, the ethyl ester of **1** (*syn* racemic)



Scheme 3. Synthesis of *syn*-(4*S*,5*S*)-5-(hydroxymethyl)-4-phenyloxazolidin-2-one **13**.



Scheme 4. Mechanistic pathway for the addition of PhMgBr to convert sulfinimine **9** into sulfinamine **10**.



Scheme 5. Oxidation of **13** into corresponding carboxylic acid **1**.

had been epimeried to its ethyl ester of the *anti*-isomer **2** (racemic).[8] Thus, this strategy is diverse enough to produce both *syn*- and *anti*-isomers as per the requirements. Moreover, the stereocenters in **2** are similar to the Taxol side chain.[25]

3. Conclusion

In conclusion, three objectives of the present research work have been addressed. (i) Synthetically important intermediates (*S*) and (*R*)-glyceraldehyde acetonides have been prepared from the corresponding chiral epichlorohydrin using identical synthetic methodology. (ii) We have established the diastereoselectivity (de) during the Grignard reaction onto (*S*,*E*)-*N*-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide **9**. (iii) A simpler, non-racemising method has been developed to oxidize alcohol **13** into the respective carboxylic acid **1**.

4. Experimental

4.1. General

Melting points were determined on Buchi 540 melting point apparatus and are uncorrected. FT-IR spectra were recorded as KBr pellet on Nicolet 380 FT-IR Instrument (Model Thermo Electron Corporation-Spectrum One), ^{1}H and ^{13}C NMR (proton decoupled) spectra were recorded on a Varian 400 MHz spectrometer using DMSO-d_6 or $CDCl_3$ as solvent and tetramethylsilane (TMS) as the internal standard. Mass spectra were recorded on Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375 °C. All the organic extracts were dried over sodium sulfate after work-up.

The dry reactions were carried out under a nitrogen atmosphere with magnetic/mechanical stirring. Unless otherwise mentioned,

Table 1
Attempted conditions to oxidize alcohol **13** into acid **1**

Solvent number	Oxidising agent	Solvent	Yield (%)	Remarks
1	PCC	DMF	—	No reaction
2	PDC	DMF	18	Incompletion
3	$KMnO_4$	Acetone	—	Decomposed
4	$NaIO_4$, $RuCl_2$	CCl_4, CH_3CN	10	Low yield
5	$NaIO_4$, TEMPO and $RuCl_2$	Acetone	13	Incompletion
6	CrO_3, H_2SO_4 (Jones oxidation)	Acetone, H_2O	55	Completed

all solvents and reagents used were of LR grade. TLC was performed on precoated silica-gel plates, which were visualized using UV light and sulfuric acid/ethanol (5:95) charring. Flash column-chromatography was carried out on silica gel (230–400 mesh) unless otherwise stated.

4.2. Preparation of (*R*)-4-(chloromethyl)-2,2-dimethyl-1,3-dioxolane (*R*)-5

To a solution of (*R*)-epichlorohydrin (50.0 g, 0.540 mol) and acetone (500 mL), $BF_3{\cdot}OEt_2$ (0.5 mL) was added at 0 °C (ice bath). After stirring for 1 h, the reaction mixture was heated to 40 °C and again stirred for 5 h. After concentration under reduced pressure compound (*R*)-**5** was obtained as a colorless oil (65.12 g, yield: 80%). Bp 63 °C/37 Torr. IR (Neat) ν_{max}: 2988, 1066, 845 cm^{-1}. δ_H ($CDCl_3$, 300 MHz): 1.37 (s, 3H), 1.45 (s, 3H), 3.50 (m, 1H), 3.56–3.61 (m, 1H), 3.87–3.91 (m, 1H), 4.10–4.15 (m, 1H), 4.3–4.34 (m,1H). δ_C ($CDCl_3$, 125 MHz) δ: 25.1, 26.6, 44.3, 67.2, 75.2, 109.8. $[\alpha]_D^{25} = +35.9$ (*c* 5.3, C_6H_6). ESI MS for (M) = 150.0 and 151.0 (M^+).

4.3. Preparation of ((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl) methyl benzoate (*R*)-6

A mixture of (*R*)-**5** (60.0 g, 0.398 mol), sodium benzoate (114.6 g, 0.796 mol), and anhydrous DMSO (900 mL) was stirred at rt for 10 min. Then, the reaction mixture was heated to 160 °C and again stirred for 5 h. The reaction was allowed to cool rt, diluted with 10% aqueous Na_2CO_3 solution (900 mL), and extracted with CH_2C1_2 (3 × 200 mL). The dried (Na_2SO_4) organic extracts were concentrated in vacuo and the oily residue was distilled at reduced pressure to afford compound (*R*)-**6** as a colorless oil (81.0 g, yield: 87%). Bp 120–130 °C/0.5 Torr. IR ($CHCl_3$) ν_{max}: 1066, 1722, 844 cm^{-1}. δ_H ($CDCl_3$, 300 MHz): 1.36 (s, 3H), 1.46 (s, 3H), 3.88 (dd, 1H, *J* = 5.9, 8.4 Hz), 4.15 (dd, 1H, *J* = 6.6, 8.4 Hz), 4.36 (dd, 1H, *J* = 5.5, 11.4 Hz), 4.41 (dd, 1H, *J* = 4.8, 11.4 Hz), 4.43–4.57 (m, 1H), 7.43–7.46 (m, 1H), 8.05–8.07 (m, 2H). δ_C ($CDCl_3$, 125 MHz): 25.4, 26.7, 65.0, 66.4, 73.6, 109.8, 128.3, 129.6, 129.6, 133.0, 166.2. $[\alpha]_D^{25} = +7.35$ (*c* 1.0, $CHCl_3$). ESI MS for (M^+) = 237.08.

4.4. Preparation of ((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (*S*)-7

A mixture of (*R*)-**6** (60.0 g, 0.3253 mol), EtOH (300.0 mL), and NaOH (12.1 g, 0.304 mol) with water (120.0 mL), was stirred at rt for 10 min. Then, the reaction mixture was heated to 90 °C and stirred again for 1 h. The reaction mass was allowed to cool rt and extracted with CH_2C1_2 (3 × 200 mL). The dried (Na_2SO_4) organic extracts were distilled in vacuo to give compound (*S*)-**7** as a colorless oil (30.1 g, yield: 90%). Bp 80–90 °C/20 Torr. IR (Neat) ν_{max}: 3450, 1390, 1380, 1050, 840 cm^{-1}; δ_H ($CDCl_3$, 300 MHz): 1.36 (s, 3H), 1.46 (s, 3H), 3.58 (dd, 1H, *J* = 3.6, 11.6 Hz), 3.68 (dd, 1H, *J* = 4.0, 11.6 Hz), 3.78 (ddd, 1H, *J* = 1.0, 3.8, 7.81 Hz), 4.03 (ddd, 1H, *J* = 1.0, 4.1, 7.8 Hz), 4.27–4.19 (m, 1H). δ_C ($CDCl_3$, 125 MHz): 25.3, 26.7, 63.0, 65.8, 76.2, 109.8. $[\alpha]_D^{25} = +14.4$ (*neat*) ESI MS for (M^+) = 132.9.

4.5. Preparation of (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (*R*)-8

Freshly distilled DMSO (37.5 g 0.48 mol), diluted in 50 mL of anhydrous DCM, was added drop wise to a well stirred solution of oxalyl chloride (27.9 g, 0.22 mol) in anhydrous DCM (50 mL) maintained at −78 °C. The mixture became yellow and (*S*)-glycerol acetonide (*S*)-**7** (26.4 g, 0.20 mol) diluted with 100 mL of anhydrous DCM was introduced drop wise to the solution which was then stirred for 15 min. Next, TEA (101 g, 1.0 mol) was added dropwise and the mixture was heated to rt. Water (500 mL) and DCM (500 mL) were added to the reaction mass. The organic layer was washed with water (250 mL) and the combined aqueous layer was extracted with dichloromethane (3 × 500 mL). The combined organic layer was dried over (Na_2SO_4) filtered and the solvent was evaporated under reduced pressure to give 16.0 g of crude material which was rapidly purified by fractional distillation (bath temperature 60–90 °C, 3 mm Hg) to give compound (*R*)-**8** as colorless oil (13 g, yield: 50%). IR ($CHCl_3$) ν_{max}: 3390, 2969, 2929, 1736, 1460, 1379, 1254, 1200, 1157, 1042, 829.2 cm^{-1}. δ_H ($CDCl_3$, 300 MHz): 1.44 (s, 3H), 1.49 (s, 3H), 3.91 (d, 1H), 4.2 (d, 1H), 4.4 (m, 1H), 9.55 (d, *J* = 1.8 Hz, 1H). δ_C ($CDCl_3$, 125 MHz): 24.7, 25.8, 65.1, 79.5, 110.8, 201.4. $[\alpha]_D^{25} = +53.8$ (*c* 2.0, $CHCl_3$). ESI MS for (M^+) = 131.02.

4.6. Preparation of (*S*,*E*)-*N*-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylene)-2-methylpropane-2-sulfinamide 9

To a solution of aldehyde (*R*)-**8** (30.0 g, 0230 mol) in DCM (300 mL), (*S*)-*t*-butylsulfinamide (33.4 g, 0.276 mol), and anhydrous $CuSO_4$ (110.1 g, 0.69 mol) was added and stirred at rt for 10 min. Then, the reaction mixture was heated to 40 °C and again stirred for 12 h, the reaction mass was allowed to cool rt and filtered. The organic solution was dried with (Na_2SO_4) distilled under vacuo to give compound **9** as oil (51.0 g, yield: 95%). Ee (98.9%) was determined by Chemical HPLC (X-BRIDGERP-18), 0.02 M ammonium bicarbonate pH 7 with ACOH and ACN, gradient program, 1 mL/min, major enantiomer (*R*) tr = 9.338 min, minor enantiomer (*S*) tr = 8.90 min. IR ($CHCl_3$) ν_{max}: 3280, 1376.1, 1153, 1063 cm^{-1}. δ_H (DMSO, 300 MHz): 1.19 (s, 9H), 1.44 (s, 3H), 1.50 (s, 3H), 3.99–4.04 (m, 1H), 4.18–4.23 (m, 1H), 4.89–4.93 (m, 1H), 7.87 (d, 1H). δ_C (DMSO, 125 MHz): 25.2, 26.3, 56.5, 66.5, 76.2, 109.8, 168.0. $[\alpha]_D^{25} = +63.7$ (*c* 1.0, EtOH). ESI MS for (M^+) = 234.05.

4.7. Preparation of (*S*)-*N*-((*S*)-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)(phenyl)methyl)-2-methyl propane-2-sulfinamide 10

A solution of chiral imine **9** (50.0 g, 0.214 mol) in diethyl ether (200 mL) was added dropwise over a period of 30 min to a stirred solution of phenylmagnesium bromide 3.0 M solution in diethyl ether (186.2 mL, 0.257 mol) at −78 °C under argon. After being stirred for 15 h at room temperature, the reaction mixture was poured into saturated aqueous NH_4C1 (300 mL). The organic layer separated and the aqueous layer extracted with ether (2 × 300 mL). The combined organic layer was dried over anhydrous ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the residue by flash chroma-

tography (ethyl acetate/hexane 1:3) afforded compound **10** as a white solid (54.74 g, yield: 82%). De (96.5%) was determined by Chemical HPLC (Chiralpack AD-H), hexane/EtOH 40:60, 1 mL/min, major *syn*-isomer (*S*,*S*) tr = 4.00 min, minor *anti*-isomer (*R*,*S*) tr = 3.83 min. Mp: 127–130 °C. IR (KBr) $\nu_{max:}$ 3292, 1464, 1066 cm^{-1}. δ_H (DMSO, 300 MHz): 1.07 (s, 9H), 1.22 (s, 3H), 1.32 (s, 3H), 3.94–4.04 (m, 2H), 4.23 (dd, 1H), 4.30–4.36 (m, 1H), 5.33 (d, 1H, ex.D_2O), 7.26–7.35 (m, 5H). δ_C (DMSO, 75 MHz): ~25.3, 26.5, 55.2, 61.5, 66.0, 78.0, 109.2, 127.1, 127.6, 128.6, 140.5. $[\alpha]_D^{25} = +77.2$ (*c* 1.0, EtOH). ESI MS for (M^+ +Na) = 334.13.

4.8. Preparation of (2*S*,3*S*)-3-amino-3-phenylpropane-1,2-diol hydrochloride 11

To a solution of protected chiral amine **10** (50.0 g, 0.160 mol) in methanol (100 mL) was added dropwise a solution of MeOH/HCl (10%) (88.0 mL, 0.240 mol) over a period of 30 min. The solution was stirred for 12 h at room temperature and then concentrated in vacuo. The amine hydrochloride was obtained as a white solid after precipitation from ether and was used without further purification. Compound **11** was obtained as a white solid (27.7 g, yield: 85%). Mp 255 °C. IR (KBr) ν_{max}: 3352, 3089, 1577, 1488, 1386.9, 1058.7, 702.2 cm^{-1}. δ_H (DMSO, 300 MHz): 2.99–3.05 (1H, dd, *J* = 6.9, 11.6 Hz), 3.14–3.20 (1H, dd, *J* = 6.0, 11.1), 3.89–3.95 (1H, ddd, *J* = 4.3, 5.4, 6.4), 4.28 (1H, d, *J* = 6.0), 7.36–7.42 (m, 5H). δ_C (D_2O, 100 MHz): 134.8, 131.8, 131.4, 130.3, 73.3, 64.7, 58.8. $[\alpha]_D^{25} = +3.7$ (*c* 1.05, MeOH). ESI MS for (M^+) = 168.02.

4.9. Preparation of *tert*-butyl (1*S*,2*S*)-2,3-dihydroxy-1-phenylpropylcarbamate 12

To a solution of chiral amino alcohol **11** (25.0 g, 0.122 mol) in DCM (100.0 mL), TEA (31.1 g, 0.305 mol) and $(Boc)_2O$ (29.28 g, 0.134 mol) added slowly under an argon atmosphere at 0 °C. After the reaction mixture was stirred at rt for 8 h, The organic layer was dried over (Na_2SO_4) and concentrated in vacuo to give compound **12** as a white solid (25.6 g, yield: 78%), which was recrystallized from EtOAc/hexane: mp 116–118 °C. IR (KBr) ν_{max}: 3376, 1684 cm^{-1}. δ_C (DMSO, 300 MHz): 1.35 (s, 9H), 3.21–3.24 (m, 2H), 3.64–3.68 (m, IH), 4.53–4.61 (dd, 2H, *J* = 8.4, 14.1), 4.67 (d, *J* = 5.1, 1H), 7.13–7.28 (m, 5H). δ_C (DMSO, 75 MHz): 28.2, 56.3, 62.7, 74.3, 77.8, 126.4, 127.5, 140.8, 154.8. $[\alpha]_D^{25} = +51.0$ (*c* 0.65, $CHC1_3$). ESI MS for (M^+) = 290.1.

4.10. Preparation of (4*S*,5*S*)-5-(hydroxyl methyl)-4-phenyl-oxazolidin-2-one 13

To a solution of compound **12** (25.0 g, 0.0935 mol) in anhydrous THF (100 mL) was added sodium hydride (5.81 g, 1.0 mol (60% w/w in mineral) at room temperature and the mixture was stirred under a nitrogen atmosphere for 2 h. The reaction mixture was concentrated, CH_2Cl_2 was added, washed with aqueous saturated NH_4Cl solution, brine, and dried over (Na_2SO_4). The organic layer was concentrated by rotary evaporation and the residue was purified by flash column chromatography to give compound **13** as a white solid (16.2 g, yield: 92%). Mp: 106 °C. IR (KBr) ν_{max}: 3314, 1745 cm^{-1}. δ_H (DMSO, 300 MHz): 2.94–3.03 (ddd, 2H), 4.71–4.75 (d, 1H), 4.78–4.81 (d, 1H), 4.98 (d, 1H), 7.40–7.23 (m, 5H), 8.09 (s, 1H). δ_C (DMSO, 125 MHz): 159.0, 137.4, 128.3, 128.0, 126.8, 79.8, 61.0, 56.7. $[\alpha]_D^{25} = +71.8$ (*c* 1.0, EtOH). ESI MS for (M^-) = 192.0.

4.11. Preparation of *syn*-(4*S*,5*S*)-2-oxo-4-phenyloxazolidine-5-carboxylic acid 1

A solution of **13** (10.0 g, 0.051 mol) in acetone (200.0 mL) was added dropwise to a Jones' reagent [prepared from chromium (VI) trioxide (9.3 g, 0.093 mol), concd H_2SO_4 (10.0 mL), H_2O (20.0 mL)] in acetone (100.0 mL) at 0 °C. The mixture was stirred for 3 h and isopropanol (50.0 mL) was added to the reaction mixture and stirred for 0.5 h. The organic layer was evaporated, and then diluted with water (250.0 mL), after which were added 100 mL of 2 M $NaHCO_3$. The organic layer was separated and dried over Na_2SO_4, and evaporated to give **1** as a white solid (5.8 g, yield: 55%). The diastereoselectivity dr (99.14%) was determined by Chiral HPLC (Chiralpack AD-H), hexane/EtOH/IPA/0.2 mL TFA (840:120:40:0.2 mL TFA) 1 mL/min, major diastereomer (*S*,*S*) tr = 14.0 min, minor diastereomer (*S*,*R*) tr = 10.3 min. Mp = 245–248 °C. IR (KBr) ν_{max}: 3279, 1748, 1715 cm^{-1}. δ_H (DMSO, 300 MHz): 12.93 (br, 1H), 8.32 (s, 1H), 7.25 (m, 5H), 5.17–5.31 (dd, 2H). δ_C (DMSO, 125 MHz): 38.8, 57.3, 77.0, 128.0, 128.4, 128.9, 137.2, 158.0, 168.2. $[\alpha]_D^{25} = +63.3$ (*c* 1.20, DMF). ESI MS for (M^++Na) = 230.0.

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