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A concise synthesis of (−)-cytoxazone and (−)-4-*epi*-cytoxazone using chlorosulfonyl isocyanate

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Abstract—A concise synthesis of (–)-cytoxazone and its stereoisomer (–)-4-*epi*-cytoxazone, novel cytokine modulators, has been accomplished each in six steps from readily available *p*-anisaldehyde with good diastereoselectivity. Key steps in the synthesis include the regioselective and diastereoselective amination of *anti*- and *syn*-1,2-dimethyl ethers with chlorosulfonyl isocyanate and the subsequent regioselective cyclization of the diol to construct the oxazolidin-2-one core. The diastereoselectivity of amination reaction using CSI was explained by the Cieplak electronic model via S_N1 mechanism and neighboring group effect, leading to the retention of the configuration.

1. Introduction

Cytoxazone (**1**) containing a 4,5-disubstituted oxazolidin-2-one ring is a novel cytokine modulator that was isolated from *Streptomyces* sp., and was found to interfere with the productions of IL4, IL10, and IgG via the selective inhibition of the signaling pathway in Th2 cells. The absolute configuration of **1** was determined to be (4*R*,5*R*)-5-hydroxymethyl-4-*p*-methoxyphenyl-1,3-oxazolidin-2-one based on NMR, CD, and X-ray data,[1] and was unambiguously confirmed by the first total asymmetric synthesis reported by Nakata et al. (Fig. 1).[2a]

Due to its potent bioactivity, several methods of synthesizing (–)-cytoxazone and (–)-4-*epi*-cytoxazone have been reported. These include Sharpless asymmetric dihydroxylation and the introduction of amine,[2] Sharpless asymmetric aminohydroxylation,[3] asymmetric epoxidation and the regioselective introduction of azide,[4] the use of Petasis reaction,[5] asymmetric aldol reaction,[6] imino-1,2-Wittig rearrangement,[7] the addition of Grignard reagents to protected imines,[8] and the conjugated addition of chiral lithium amide.[9] Moreover, very recently, we reported a stereoselective synthesis of **1** via the regioselective and diastereoselective introduction of an *N*-protected amine group using chlorosulfonyl isocyanate (CSI) and subsequent regioselective cyclization to give the oxazolidin-2-one unit.[10] In this paper, we describe a concise synthesis of (–)-cytoxazone (**1**) and its stereoisomer (–)-4-*epi*-cytoxazone (**2**), based on the regioselective and diastereoselective reaction using CSI.[11]

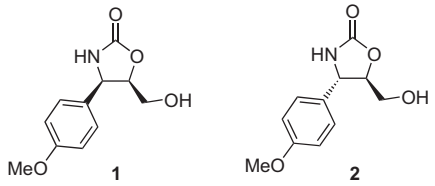

Figure 1. Structure of (−)-cytoxazone **1** and (−)-4-*epi*-cytoxazone **2**.

2. Results and discussion

Retrosynthetic analyses of **1** and **2** are shown in Scheme 1. Key steps for the synthesis of **1** and **2** are the regioselective and diastereoselective introduction of an *N*-protected amine group into *anti*-1,2-dimethyl ether **4** and *syn*-1,2-dimethyl ether **5** to give the protected *anti*-1,2-amino alcohol **3a** and *syn*-1,2-amino alcohol **3b**, respectively, using CSI and regioselective intramolecular cyclization. Compounds **4** and **5** can be easily prepared from commercially available *p*-anisaldehyde by using the chiral borane reagents.[12,13]

We first investigated the regioselectivity and diastereoselectivity of the reaction between CSI and *anti*- and *syn*-1,2-dimethyl ethers **4** and **5** prior to addressing the total synthesis of **1** and **2** (Scheme 2).

In initial studies, we examined the diastereoselectivity of the reaction of *anti*-1,2-dimethyl ether **4** with CSI. Treatment of **4** with CSI afforded *anti*-1,2-amino alcohol **3a** as the major product. The ratio of *anti*-1,2-amino alcohol **3a**

Keywords: Chlorosulfonyl isocyanate; Cytoxazone; 4-*epi*-Cytoxazone; Amination.
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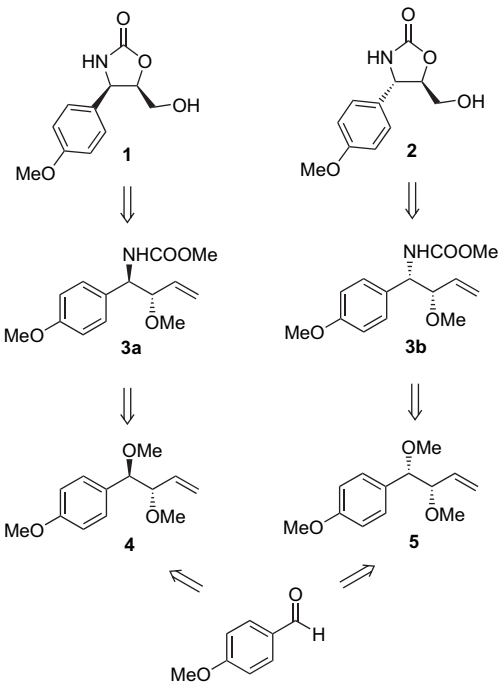


Scheme 1. Retrosynthetic analyses of **1** and **2**.

to *syn*-1,2-amino alcohol **3b** depended on solvent and temperature, as shown in Table 1.

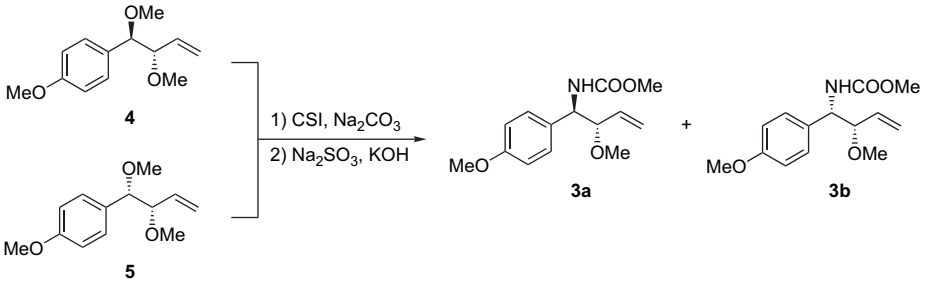
The reaction in methylene chloride at 0 °C gave a 5.7:1 inseparable mixture of diastereoisomers in 94% yield, and at −78 °C furnished a 7.0:1 ratio (entries 1 and 2). In particular, in toluene at −78 °C (entry 6), the highest diastereoselectivity of 27:1 was obtained in 95% yield. Table 1 shows that *anti*-stereoisomer of the 1,2-amino alcohol tends to be formed as the solvent polarity is reduced.

We also examined the reaction of *syn*-1,2-dimethyl ether **5** with CSI in various solvents and at different temperatures. The results are summarized in Table 2. In the case of **5**, *syn*-1,2-amino alcohol **3b** was obtained as the major product.

Although the ratio of stereoisomers was reduced versus *anti*-1,2-dimethyl ether case, reaction in hexane afforded a high diastereoselectivity of 1:9.3 in 91% yield.

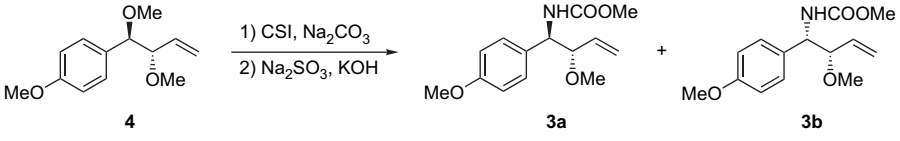
By reacting *anti*- and *syn*-1,2-dimethyl ethers with CSI, it was found that the stereochemistry of the major product was the same as that of the starting material, even though the reaction between CSI and *p*-methoxybenzylic methyl ether progresses via a carbocation intermediate and a S_N1 mechanism.

The results of these reactions can be explained as follows: First, regioselective substitution at the *p*-methoxybenzylic position is expected. This is because regioselectivity was controlled by the stability of the carbocation intermediate, i.e., the *p*-methoxybenzylic carbocation is more stable than the allyl carbocation.[14] Second, the formation of *anti*-1,2-amino alcohol **3a** from *anti*-1,2-dimethyl ether **4** can be explained by the Cieplak electronic model[11c,15] via a S_N1 mechanism. In this model, the vinyl group takes up an *anti* position to nucleophile attack (Fig. 2).



Scheme 2. CSI reactions of *anti*- and *syn*-1,2-dimethyl ethers **4** and **5** with CSI.

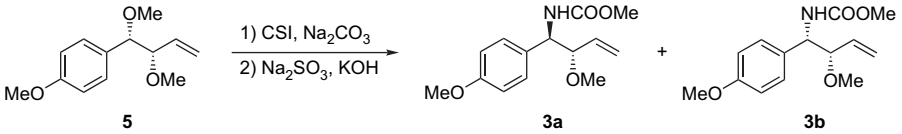
Table 1. Reactions of *anti*-1,2-dimethyl ether **4** with CSI in various solvents and at different temperatures



	Solvent	Temperature (°C)	Yield (%)[a]	Ratio (**3a**:**3b**)[b]
1	CH_2Cl_2	0	94	5.7:1
2		−78	92	7.0:1
3	$CHCl_3$	0	89	7.6:1
4	Et_2O	0	96	12:1
5	Toluene	0	94	16:1
6		−78	95	27:1
7	CCl_4	0	91	18:1
8	Hexane	0	67	13:1
9		−78	91	15:1

[a] Isolated yield of pure material.
[b] Isomer ratio determined by ^1H NMR.

Table 2. Reactions of *syn*-1,2-dimethyl ether **5** with CSI in various solvents and at different temperatures



5 **3a** **3b**

	Solvent	Temperature (°C)	Yield (%)[a]	Ratio (**3a**:**3b**)[b]
1	CH_2Cl_2	0	91	1.1:1
2		−78	92	1:1.1
3	$CHCl_3$	0	89	1:1.2
4	Et_2O	0	74	1:1.3
5	Toluene	0	84	1:1.4
6		−78	94	1:2.6
7	CCl_4	0	59	1:1.5
8	Hexane	0	81	1:4.8
9		−78	91	1:9.3

[a] Isolated yield of pure material.
[b] Isomer ratio determined by ^{1}H NMR.

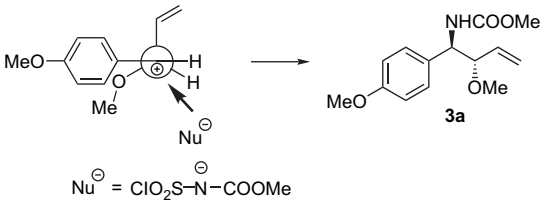


Figure 2. Cieplak electronic model of nucleophilic attack on the *p*-methoxybenzylic carbocation.

However, this mechanism cannot explain the formation of *syn*-stereoisomer as a major product in the case of *syn*-1,2-dimethyl ether.

Therefore, another mechanism for diastereoselectivity should be suggested. One plausible mechanism is offered by the neighboring group effect, as shown in Figure 3. This neighboring group (OMe) can use its electron pair to interact with the backside of the carbon atom undergoing substitution, and then nucleophile attack can only take place from the front side—thus leading to retention of configuration.[16]

Initial attack by the oxygen of *p*-methoxybenzylic methyl ether on CSI yields a *p*-methoxybenzylic carbocation. This attack is following an internal attack by the vicinal OMe to yield the oxiranium with an inversion of configuration at the *p*-methoxybenzylic carbon. This *p*-methoxybenzylic carbon atom, in turn, undergoes an ordinary S_N2 attack by $ClSO_2$–N^-–CO_2Me, with a second inversion of configuration. In this case, the configuration of the product is the same as that of the starting material. In case of *syn*-1,2-dimethyl ether **5**, the formation of *syn*-stereoisomer **3b** was slightly reduced due to the increasing steric repulsion

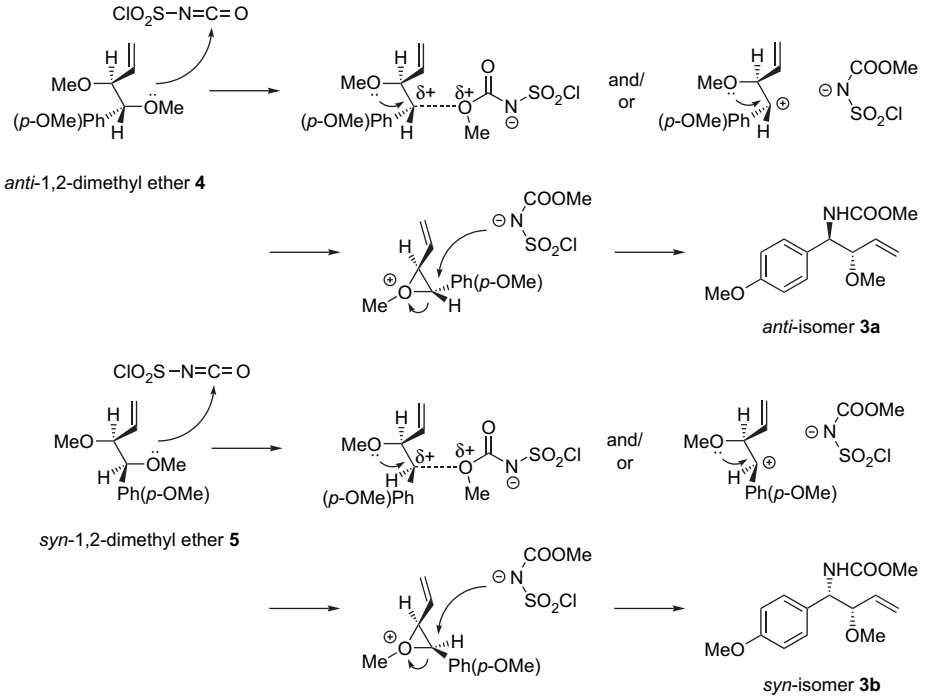
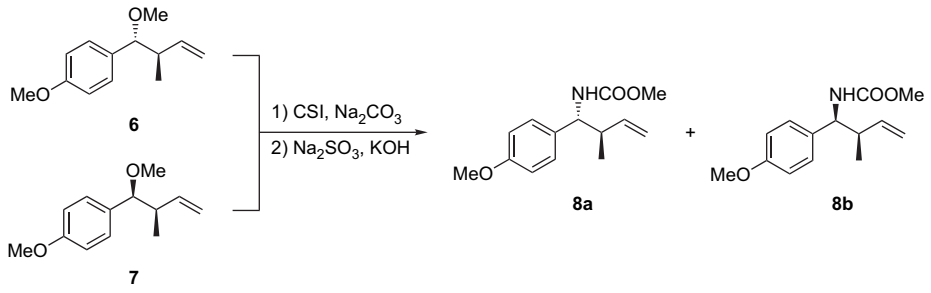


Figure 3. Neighboring group effect of nucleophilic attack on the *p*-methoxybenzylic carbocation.



Scheme 3. CSI reactions of β-methyl homoallyl ethers **6** and **7** with CSI.

between the *p*-methoxyphenyl ring and the vinyl group oriented in the cis form.

As the polarity of the solvent decreased, the attack of the vicinal OMe (the neighboring group effect) become more rapid than nucleophile attack and the diastereoselectivity of 1,2-amino alcohol increased, and therefore, this reaction is more efficient in nonpolar solvents.

A methyl moiety instead of a methoxy group was introduced at the allylic position in order to confirm the neighboring group effect (Scheme 3).

The treatment of *threo*-ether **6** with CSI in methylene chloride furnished an 1:1.8 mixture of *threo*-stereoisomer **8a** and *erythro*-carbamate **8b** in 91% yield (entry 1). Other results are summarized in Table 3.

The reaction between CSI and compound **6** in toluene and hexane afforded a ratio similar to that obtained in methylene chloride (entries 2 and 3). In addition, in the case of the *erythro*-ether **7**, the ratio of diastereoisomers was similar to that obtained for the reaction between CSI and compound **6**.

The results shown in Table 3 reveal that the reaction between the β-methyl homoallyl ether and CSI is not affected by solvent and progresses through a free carbocation intermediate. Therefore, it is clear that the diastereoselectivity of the reaction between CSI and 1,2-dimethyl ethers **4** and **5** can be explained by the neighboring group effect and a partial S_N1 mechanism.

On the basis of the above results, the total synthesis of (–)-cytoxazone (**1**) was achieved from *p*-anisaldehyde as a starting material (Scheme 4).

p-Anisaldehyde was reacted with *B*-[3-((diisopropylamino)dimethylsilyl)allyl]diisopinocamphenylborane[12] (**9**), derived from (–)-*B*-methoxydiisopinocamphenyl borane and allyl(diisopropylamino)dimethylsilane, *n*-butyllithium, and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) in ether at 0 °C, to provide, upon workup with hydrogen peroxide under basic conditions, an optically pure (1*R*,2*S*)-*anti*-diol **10** with high enantioselectivity (95% ee via the Mosher ester) and diastereoselectivity (>99% ds) in 52% yield after recrystallization (toluene). Dimethylation of compound **10** with sodium hydride and iodomethane in tetrahydrofuran furnished the *anti*-1,2-dimethyl ether **4** in 96% yield. The key reaction is the regioselective and diastereoselective introduction of an *N*-protected amine group to compound **4** using CSI. The treatment of compound **4** with CSI in the presence of sodium carbonate in anhydrous toluene at −78 °C, followed by reduction of an *N*-chlorosulfonyl group with an aqueous solution of 25% sodium sulfite furnished the desired *anti*-1,2-amino alcohol **3a** with a high diastereoselectivity of 27:1 in 95% yield. The conversion of compound **3a** into the terminal primary alcohol **11** was achieved in 94% yield by ozonolysis of the double bond followed by sodium borohydride reduction.[17] The regioselective deprotection of the methyl ether of compound **11** with boron tribromide[18] in methylene chloride at 0 °C gave the desired diol **12** in 80% yield without affecting the *p*-methoxy group of the phenyl ring. Finally, the regioselective intramolecular cyclization of compound **12** using sodium hydride[7] in tetrahydrofuran at 0 °C, led to formation of (–)-cytoxazone (**1**) in 95% yield. Spectroscopic data and specific rotation data of **1** were in full agreement with values reported in the literature.[2a]

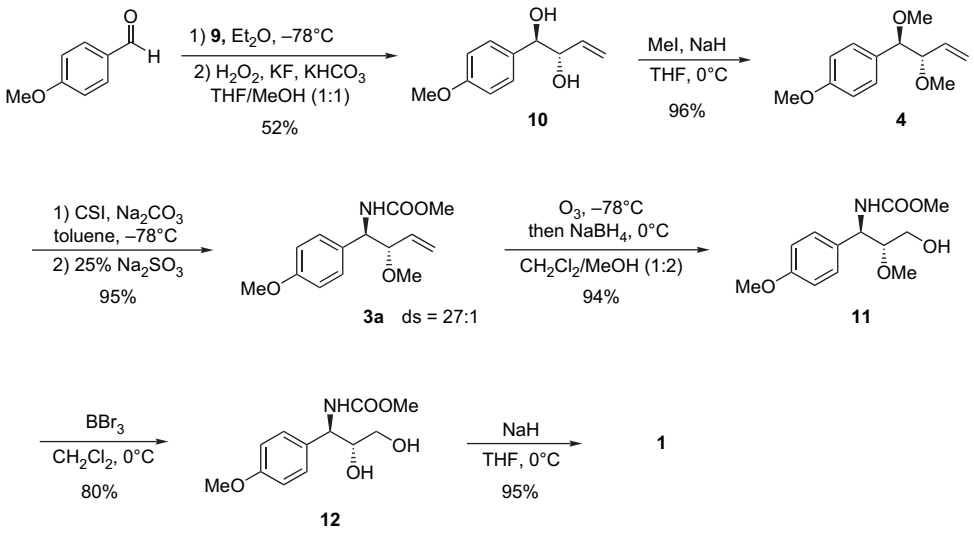
The total synthesis of (–)-4-*epi*-cytoxazone (**2**) was accomplished from *p*-anisaldehyde by using a sequence similar to that described for the synthesis of (–)-cytoxazone (Scheme 5).

Treatment of *p*-anisaldehyde with allylmethyl ether, (+)-*B*-methoxydiisopinocamphenyl borane,[13] and *sec*-BuLi in THF at −78 °C gave alcohol **13** with moderate enantioselectivity (80% ee via the Mosher ester) and high diastereoselectivity (>99% ds) in 63% yield. Alcohol **13** was then methylated with iodomethane in the presence of sodium hydride to afford *syn*-1,2-dimethyl ether **5** in 78% yield, and treatment of compound **5** with CSI in the presence of sodium carbonate in anhydrous hexane at −78 °C, followed by reduction of an *N*-chlorosulfonyl group with an aqueous solution of 25% sodium sulfite furnished the desired *syn*-1,2-amino alcohol **3b** in high diastereoselectivity of 1:9.3 in 91% yield. Ozonolysis of the double bond of **3b** followed by direct reduction of the resulting ozonide then gave the

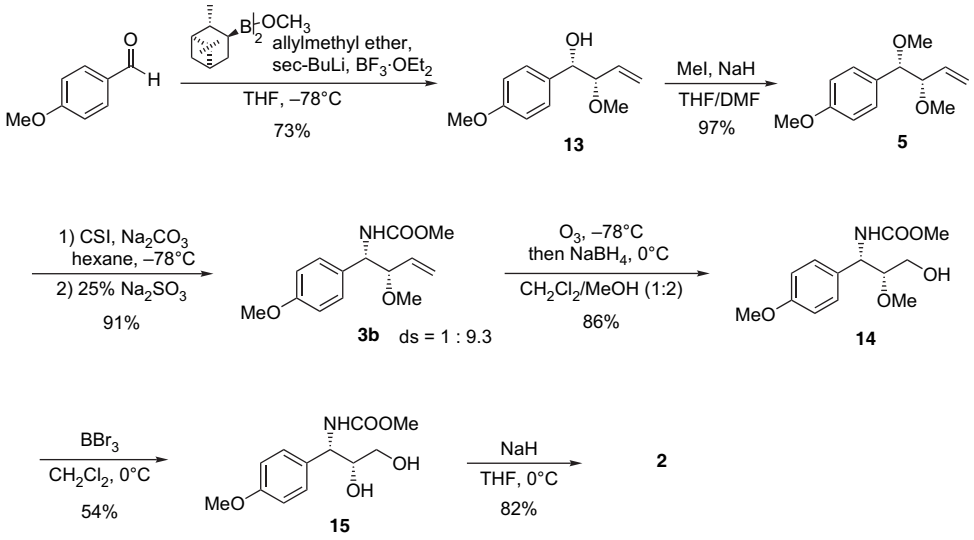
Table 3. Reactions of the β-methyl homoallyl ethers **6** and **7** with CSI in various solvents

	Ether	Solvent	Yield (%)[a]	Ratio (**8a**:**8b**)[b]
1	**6**	CH_2Cl_2	91	1:1.8
2		Toluene	83	1:1.7
3		Hexane	81	1:1.6
4	**7**	CH_2Cl_2	83	1:1.2
5		Toluene	88	1:1.7
6		Hexane	75	1:1.8

[a] Isolated yield of pure material.
[b] Isomer ratio determined from the ^{1}H NMR.



Scheme 4. Total synthesis of (−)-cytoxazone (**1**).



Scheme 5. Total synthesis of (−)-4-*epi*-cytoxazone (**2**).

primary alcohol **14** in 86% yield. The regioselective deprotection of the methyl ether of compound **14** with boron tribromide gave the desired diol **15** in 54% yield. Finally, the regioselective intramolecular cyclization of compound **15** afforded the (–)-4-*epi*-cytoxazone (**2**) as a crystalline form, mp 110–112 °C (EtOAc) [lit.[7b] 121–123 °C], which also had spectral properties (^{1}H and ^{13}C NMR) that were in full agreement with values reported in the literature.[7b]

3. Conclusion

In conclusion, we accomplished the total synthesis of (–)-cytoxazone (**1**) and its stereoisomer (–)-4-*epi*-cytoxazone (**2**), in six linear steps, starting from readily available *p*-anisaldehyde via the regioselective and diastereoselective introduction of an *N*-protected amine group using the reaction of *anti*- and *syn*-1,2-dimethyl ethers with CSI, and subsequently used regioselective cyclization to construct the oxazolidin-2-one ring. In addition, the optimum reaction conditions for the diastereoselective reaction of *anti*- and *syn*-1,2-dimethyl ethers with CSI were identified. Moreover, the retention of configuration is explained by the neighboring group effect and a partial S_N1 mechanism, and the described synthetic protocol using CSI can be applied to the formation of various natural products containing more complex amines.

4. Experimental

4.1. General

Commercially available reagents were used without additional purification, unless otherwise stated. All anhydrous solvents were distilled over CaH_2 or P_2O_5 or Na/benzophenone prior to reaction. All reactions were performed under an inert atmosphere of nitrogen or argon. Melting points were measured on a Gallenkamp melting point apparatus or Electrothermal IA9300 melting point apparatus and

were not corrected. Nuclear magnetic resonance spectra (^{1}H and ^{13}C NMR) were recorded on a Varian Unity Inova 500 MHz spectrometer for $CDCl_3$ solutions and chemical shifts are reported as parts per million (ppm) relative to, respectively, residual $CHCl_3$ δ_H (7.26 ppm) and $CDCl_3$ δ_C (77.0 ppm) as internal standards. Resonance patterns are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). In addition, the notation br is used to indicate a broad signal. Coupling constants (*J*) are reported in hertz (Hz). IR spectra were recorded on a Nicolet 205 Infrared spectrophotometer or Bruker Vector 22 Infrared spectrophotometer and are reported as cm^{-1}. Optical rotations were measured with a Jasco P1020 polarimeter. Thin layer chromatography was carried out using plates coated with Kieselgel $60F_{254}$ (Merck). For flash column chromatography, E. Merck Kieselgel 60 (230–400 mesh) was used. High-resolution mass spectra (HRMS) were recorded on a JEOL, JMS-505 or JMS-600 spectrometer using the chemical ionization (CI) method.

4.1.1. (1*R*,2*S*)-1-*p*-Methoxyphenylbut-3-ene-1,2-diol (10). To a stirred solution of allyl(diisopropylamino)dimethylsilane (5.10 mL, 20.86 mmol) in anhydrous Et_2O (25 mL) were added TMEDA (3.15 mL, 20.86 mmol) and *n*-BuLi (13.04 mL, 20.86 mmol, 1.6 M in hexane) at 0 °C under N_2. The solution was kept at 0 °C for 4 h and cooled to −78 °C. The reaction mixture was treated with (–)-*B*-methoxydiisopinocamphenyl borane (7.85 g, 24.83 mmol) in anhydrous Et_2O (5 mL) and stirred at −78 °C for 2 h. To this solution were added boron trifluoride etherate (3.43 mL, 27.03 mmol) and a solution of *p*-anisaldehyde (2.00 g, 14.69 mmol) in anhydrous Et_2O (5 mL). The reaction mixture was kept at −78 °C for 3 h. To this mixture were added THF (20 mL), MeOH (20 mL), KF (2.43 g, 41.87 mmol), $KHCO_3$ (4.19 g, 41.87 mmol), and 30% H_2O_2 (45 mL). The reaction mixture was stirred at room temperature for 20 h and cooled to 0 °C, and the excess H_2O_2 was quenched by the addition of $Na_2S_2O_3$. The mixture was diluted with EtOAc (100 mL) and filtered through Celite pad. The Celite pad was washed with EtOAc and the filtrate was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:1) and recrystallization (toluene) to give 1.48 g (52%) of diol **10** as a colorless crystal; R_f 0.25 (hexane/EtOAc 1:1); mp 87–89 °C; $[\alpha]_D^{29}$ −73.2 (*c* 0.1, $CDCl_3$); IR (CH_2Cl_2) 3408, 2954, 2837, 1612, 1514, 1463, 1303, 1248, 1176, 1116, 1032 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.93–1.99 (br, 1H), 2.30–2.37 (br, 1H), 3.81 (s, 3H), 4.25–4.33 (br, 1H), 4.66–4.70 (br, 1H), 5.24 (dd, 1H, *J*=10.5, 1.5 Hz), 5.31 (dd, 1H, *J*=17.0, 1.5 Hz), 5.83 (ddd, 1H, *J*=17.0, 10.5, 6.5 Hz), 6.89 (dd, 2H, *J*=7.0, 2.0 Hz), 7.29 (dd, 2H, *J*=7.0, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.52, 76.44, 77.53, 114.03, 118.07, 128.19, 132.12, 136.36, 159.59; Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.22; H, 7.29.

4.1.2. (1*R*,2*S*)-1,2-Dimethoxy-1-*p*-methoxyphenylbut-3-ene (4). To a stirred solution of diol **10** (1.20 g, 6.18 mmol) in anhydrous THF (25 mL) were added NaH (0.54 g, 13.59 mmol, 60% in mineral oil) and MeI (1.15 mL, 18.53 mmol) at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 3 h, H_2O (30 mL) was added and the solution was extracted with EtOAc (50 mL). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 10:1) to afford 1.32 g (96%) of *anti*-1,2-dimethyl ether **4** as a colorless oil; R_f 0.40 (hexane/EtOAc 6:1); $[\alpha]_D^{29}$ −44.6 (*c* 0.1, $CDCl_3$); IR (neat) 2934, 2822, 1612, 1512, 1464, 1302, 1248, 1174, 1093, 1035 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.23 (s, 3H), 3.24 (s, 3H), 3.65 (dd, 1H, *J*=8.0, 5.0 Hz), 3.81 (s, 3H), 4.80 (d, 1H, *J*=5.0 Hz), 5.15 (dd, 1H, *J*=17.5, 1.5 Hz), 5.27 (dd, 1H, *J*=10.0, 1.5 Hz), 5.74 (ddd, 1H, *J*=17.5, 10.0, 8.0 Hz), 6.88 (dd, 2H, *J*=6.5, 2.0 Hz), 7.23 (dd, 2H, *J*=6.5, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.19, 56.80, 56.95, 85.51, 86.33, 113.41, 119.17, 128.99, 130.58, 134.69, 159.14; Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.33; H, 8.04.

4.1.3. (1*R*,2*R*)-2-Methoxy-1-*p*-methoxyphenylbut-3-en-1-ol (13). To a stirred solution of allylmethyl ether (2.0 g, 27.50 mmol) in anhydrous THF (15 mL) was added *sec*-BuLi (19.7 mL, 27.54 mmol, 1.4 M in cyclohexane) at −78 °C under N_2. The reaction mixture was treated with (+)-*B*-methoxydiisopinocamphenylborane (6.97 g, 22.04 mmol) in anhydrous THF (19 mL) and stirred at −78 °C for 1 h. To this solution were added boron trifluoride etherate (3.71 mL, 29.31 mmol) and a solution of *p*-anisaldehyde (3.0 g, 22.04 mmol) in anhydrous THF (3 mL). The reaction mixture was stirred at −78 °C for 3 h and then slowly warmed to room temperature. The reaction mixture was concentrated in vacuo. The residue was washed with pentane and the pentane layer decanted. The combined pentane layers were cooled at 0 °C and treated with ethanolamine (2.7 mL). After the reaction mixture was stirred at 0 °C for 2 h, the white turbid solution was filtered through Celite pad and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 3:1) to afford 3.35 g (73%) of **13** as a colorless oil; R_f 0.26 (hexane/EtOAc 3:1); $[\alpha]_D^{29}$ +15.8 (*c* 0.5, $CDCl_3$); IR (neat) 3468, 2936, 2834, 1614, 1512, 1464, 1303, 1249, 1175, 1097, 1035 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.20 (d, 1H, *J*=1.5 Hz), 3.38 (s, 3H), 3.60 (dd, 1H, *J*=8.0, 7.5 Hz), 3.80 (s, 3H), 4.44 (dd, 1H, *J*=8.0, 3.5 Hz), 5.07 (dd, 1H, *J*=17.5, 1.5 Hz), 5.17 (dd, 1H, *J*=17.5, 1.5 Hz), 5.51 (ddd, 1H, *J*=17.5, 10.5, 7.5 Hz), 6.85 (dd, 2H, *J*=7.0, 2.5 Hz), 7.25 (dd, 2H, *J*=7.0, 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.21, 56.76, 76.32, 87.60, 113.52, 119.63, 128.55, 131.77, 134.03, 159.28; HRMS (CI) calcd for $C_{12}H_{16}O_3$ [M+H$^+$] 209.1178, found 209.1172.

4.1.4. (1*R*,2*R*)-1,2-Dimethoxy-1-*p*-methoxyphenylbut-3-ene (5). To a stirred solution of **13** (3.67 g, 17.62 mmol) in anhydrous THF (36 mL) and DMF (36 mL) were added NaH (0.85 g, 21.15 mmol, 60% in mineral oil) and MeI (1.65 mL, 26.44 mmol) at 0 °C under N_2. The reaction mixture was stirred at room temperature for 1 h and quenched with H_2O (10 mL). The aqueous layer was extracted with EtOAc (50 mL). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 6:1) to afford 3.81 g (97%) of *syn*-1,2-dimethyl ether **5** as a colorless oil; R_f 0.28 (hexane/EtOAc 6:1); $[\alpha]_D^{29}$ +66.8 (*c* 0.1, $CDCl_3$); IR (neat) 2934, 2822, 1612, 1586, 1512, 1464, 1303, 1247, 1174, 1094, 1035 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.23 (s, 3H), 3.33 (s, 3H), 3.74 (dd, 1H, *J*=7.5, 6.5 Hz), 3.81 (s, 3H), 4.10 (d, 1H, *J*=6.5 Hz), 5.08 (dd, 1H, *J*=17.5, 1.5 Hz),

5.12 (dd, 1H, J=10.0, 1.5 Hz), 5.49 (ddd, 1H, J=17.5, 10.0, 7.5 Hz), 6.87 (dd, 2H, J=6.5, 2.0 Hz), 7.20 (dd, 2H, J=6.5, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.19, 56.88, 56.98, 85.76, 86.12, 113.51, 118.72, 129.08, 130.49, 134.84, 159.27; HRMS (CI) calcd for $C_{13}H_{18}O_3$ [M+H$^+$] 223.1334, found 223.1326.

4.1.5. (1*R*,2*R*)-1-Methoxy-1-*p*-methoxyphenyl-2-methylbut-3-ene (6). To a suspension of potassium *tert*-butoxide (0.58 g, 5.14 mmol) in anhydrous THF (5 mL) were added excess of *trans*-2-butene[19] and *n*-BuLi (3.21 mL, 5.14 mmol, 1.6 M in hexane) at −78 °C under N_2. The reaction mixture was stirred at −45 °C for 10 min and recooled to −78 °C. To this mixture was added (+)-*B*-methoxydiisopinocamphenyl borane (1.95 g, 6.17 mmol) in anhydrous Et_2O (3 mL) at −78 °C and the reaction mixture was stirred at −78 °C for 30 min. To this mixture were added boron trifluoride etherate (0.87 mL, 6.89 mmol) and a solution of *p*-anisaldehyde (0.70 g, 5.14 mmol) in anhydrous Et_2O (3 mL). The reaction mixture was stirred at −78 °C for 3 h, and then treated with 3 N NaOH (3.76 mL) and 30% H_2O_2 (1.54 mL), and the mixture was refluxed for 1 h. The organic layer was separated, washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 6:1) to give 0.64 g (65%) of (1*R*,2*R*)-1-*p*-methoxyphenyl-2-methylbut-3-en-1-ol as a colorless oil; R_f 0.40 (hexane/EtOAc 3:1); $[\alpha]_D^{29}$ +43.2 (*c* 0.2, $CDCl_3$); IR (neat) 3432, 2962, 2836, 1612, 1513, 1461, 1303, 1248, 1175, 1035 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (d, 3H, J=6.5 Hz), 2.06–2.11 (br d, 1H, J=2.5 Hz), 2.47 (ddq, 1H, J=8.0, 8.0, 6.5 Hz), 3.82 (s, 3H), 4.33 (dd, 1H, J=8.0, 2.5 Hz), 5.19 (dd, 1H, J=11.0, 1.5 Hz), 5.23 (dd, 1H, J=17.0, 1.5 Hz), 5.84 (ddd, 1H, J=17.0, 11.0, 8.0 Hz), 6.91 (dd, 2H, J=7.0, 2.0 Hz), 7.26 (dd, 2H, J=7.0, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.82, 46.63, 55.49, 77.75, 113.91, 116.89, 128.22, 134.86, 141.19, 159.39; HRMS (CI) calcd for $C_{12}H_{16}O_2$ [M+H$^+$] 193.1228, found 193.1226. To a stirred solution of (1*R*,2*R*)-1-*p*-methoxyphenyl-2-methylbut-3-en-1-ol (0.50 g, 2.60 mmol) in THF (10 mL) were added NaH (0.11 g, 2.86 mmol, 60% in mineral oil) and MeI (0.24 mL, 3.90 mmol) at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 3 h and quenched with H_2O (5 mL). The aqueous layer was extracted with EtOAc (20 mL). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The reaction mixture was purified by column chromatography (hexane/EtOAc 30:1) to give 0.51 g (95%) of the homoallyl ether **6** as a colorless oil; R_f 0.40 (hexane/EtOAc 15:1); $[\alpha]_D^{29}$ +82.8 (*c* 0.2, $CDCl_3$); IR (neat) 2976, 2932, 2835, 1612, 1512, 1463, 1302, 1249, 1173, 1091 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (d, 3H, J=7.0 Hz), 2.52 (ddq, 1H, J=8.0, 7.0, 7.0 Hz), 3.19 (s, 3H), 3.84 (s, 3H), 3.88 (d, 1H, J=8.0 Hz), 5.04 (dd, 1H, J=10.5, 1.5 Hz), 5.06 (dd, 1H, J=16.5, 1.5 Hz), 5.91 (ddd, 1H, J=16.5, 10.5, 7.0 Hz), 6.90 (dd, 2H, J=6.5, 2.0 Hz), 7.19 (dd, 2H, J=6.5, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.63, 44.58, 55.45, 56.96, 87.99, 113.73, 114.39, 128.85, 132.73, 141.71, 159.29; HRMS (CI) calcd for $C_{13}H_{18}O_2$ [M+H$^+$] 207.1385, found 207.1387.

4.1.6. (1*S*,2*R*)-1-Methoxy-1-*p*-methoxyphenyl-2-methylbut-3-ene (7). The similar procedure for **6** was followed using *p*-anisaldehyde (0.70 g, 5.14 mmol), excess of *cis*-2-butene,[19] *n*-BuLi (3.21 mL, 5.14 mmol, 1.6 M in hexane), KO^{t}Bu (0.58 g, 5.14 mmol), (−)-*B*-methoxydiisopinocamphenyl borane (1.95 g, 6.17 mmol), and boron trifluoride etherate (0.87 mL, 6.89 mmol), and then treated with 3 N NaOH (3.76 mL) and 30% H_2O_2 (1.54 mL), and the mixture was refluxed for 2 h. The reaction mixture was purified by column chromatography (hexane/EtOAc 6:1) to give 0.66 g (67%) of (1*S*,2*R*)-1-*p*-methoxyphenyl-2-methylbut-3-en-1-ol as a colorless oil; R_f 0.40 (hexane/EtOAc 3:1); IR (neat) 3419, 2963, 2836, 1612, 1513, 1460, 1303, 1248, 1175, 1098 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (d, 3H, J=6.5 Hz), 1.83–1.90 (br, 1H), 2.56 (ddq, 1H, J=7.0, 6.5, 5.5 Hz), 3.81 (s, 3H), 4.54 (d, 1H, J=5.5 Hz), 5.03 (dd, 1H, J=16.0, 1.5 Hz), 5.05 (dd, 1H, J=10.5, 1.5 Hz), 5.72 (ddd, 1H, J=16.0, 10.5, 7.0 Hz), 6.87 (dd, 2H, J=6.5, 2.0 Hz), 7.22 (dd, 2H, J=6.5, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.64, 44.95, 55.53, 77.81, 113.72, 115.75, 127.97, 135.01, 140.59, 159.13; HRMS (CI) calcd for $C_{12}H_{16}O_2$ [M+H$^+$] 193.1228, found 193.1225. To a stirred solution of (1*S*,2*R*)-1-*p*-methoxyphenyl-2-methylbut-3-en-1-ol (0.50 g, 2.60 mmol) in THF (10 mL) were added NaH (0.11 g, 2.86 mmol, 60% in mineral oil) and MeI (0.24 mL, 3.90 mmol) at 0 °C under N_2. The reaction mixture was purified by column chromatography (hexane/EtOAc 30:1) to give 0.52 g (97%) of **7** as a colorless oil; R_f 0.40 (hexane/EtOAc 15:1); IR (neat) 2976, 2932, 2835, 1612, 1512, 1463, 1302, 1249, 1173, 1091 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (d, 3H, J=6.5 Hz), 2.51 (ddq, 1H, J=7.0, 7.0, 6.5 Hz), 3.21 (s, 3H), 3.83 (s, 3H), 3.90 (d, 1H, J=7.0 Hz), 4.90 (dd, 1H, J=16.0, 1.5 Hz), 4.92 (dd, 1H, J=10.5, 1.5 Hz), 5.65 (ddd, 1H, J=16.0, 10.5, 7.0 Hz), 6.88 (dd, 2H, J=6.5, 2.0 Hz), 7.15 (dd, 2H, J=6.5, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.87, 44.49, 55.43, 56.99, 87.68, 113.61, 114.61, 128.88, 134.79, 140.83, 159.18; HRMS (CI) calcd for $C_{13}H_{18}O_2$ [M+H$^+$] 207.1385, found 207.1381.

4.2. General procedure for the reaction of *p*-methoxybenzylic ethers with CSI

A stirred solution of Na_2CO_3 (6.75 mmol) in anhydrous solvent (12 mL) was adjusted to −78 °C, then CSI (4.50 mmol) and *p*-methoxybenzylic ether (3.00 mmol) were added under N_2. The reaction mixture was stirred at −78 °C, and quenched with H_2O (10 mL) when the reaction was completed (TLC monitoring), then extracted with EtOAc (10 mL×2). The organic layer was added to an aqueous solution of Na_2SO_3 (25%) and KOH (10%), and the reaction mixture was stirred at room temperature for overnight. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc).

4.2.1. (1*R*,2*S*)-Methyl *N*-(2-methoxy-1-*p*-methoxyphenylbut-3-enyl)carbamate (3a). The above general procedure was followed using *anti*-1,2-dimethyl ether **4** (0.70 g, 3.15 mmol), Na_2CO_3 (1.10 g, 10.39 mmol), and CSI (0.60 mL, 6.93 mmol) in anhydrous toluene (13 mL) at −78 °C. The reaction mixture was purified by column chromatography (hexane/EtOAc 3:1) to give 0.79 g (95%, *anti*:*syn*=27:1) of *anti*-1,2-amino alcohol **3a** as a white solid; R_f 0.28 (hexane/EtOAc 3:1); mp 93–95 °C; $[\alpha]_D^{29}$

−66.0 (*c* 0.1, $CDCl_3$); IR (CH_2Cl_2) 3330, 2938, 2836, 1710, 1612, 1514, 1464, 1296, 1246, 1181, 1101, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.32 (s, 3H), 3.66 (s, 3H), 3.81 (s, 3H), 3.86–3.93 (br, 1H), 4.72–4.80 (br, 1H), 5.26 (dd, 1H, *J*=11.0, 2.0 Hz), 5.29 (dd, 1H, *J*=17.5, 2.0 Hz), 5.35–5.42 (m, 1H), 5.50–5.60 (br, 1H), 6.86 (dd, 2H, *J*=8.0, 2.0 Hz), 7.23 (dd, 2H, *J*=8.0, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.37, 55.45, 57.08, 57.72, 85.08, 113.77, 119.71, 129.30, 131.17, 135.06, 156.52, 159.10; Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.50; H, 7.25; N, 5.33.

4.2.2. (1*R*,2*R*)-Methyl *N*-(2-methoxy-1-*p*-methoxyphenylbut-3-enyl)carbamate (3b). The above general procedure was followed using *syn*-1,2-dimethyl ether **5** (2.96 g, 13.32 mmol), Na_2CO_3 (6.35 g, 59.93 mmol), and CSI (3.48 mL, 39.95 mmol) in anhydrous hexane (67 mL) at −78 °C. The reaction mixture was purified by column chromatography (hexane/EtOAc 3:1) to afford 3.21 g (91%, *syn*:*anti*=9.3:1) of *syn*-1,2-amino alcohol **3b** as a white solid; R_f 0.28 (hexane/EtOAc 3:1); $[\alpha]_D^{29}$ +55.4 (*c* 0.1, $CDCl_3$); IR (neat) 3340, 2938, 2852, 1725, 1612, 1514, 1463, 1295, 1246, 1179, 1098 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.24 (s, 3H), 3.65 (s, 3H), 3.75–3.82 (br, 1H), 3.81 (s, 3H), 4.65–4.72 (br, 1H), 5.28 (dd, 1H, *J*=17.0, 1.0 Hz), 5.30 (dd, 1H, *J*=10.5, 1.0 Hz), 5.50–5.58 (br, 1H), 5.78 (ddd, 1H, *J*=17.0, 10.5, 7.5 Hz), 6.87 (dd, 2H, *J*=7.5, 2.0 Hz), 7.26 (dd, 2H, *J*=7.5, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.46, 55.50, 57.11, 58.07, 85.24, 113.93, 119.36, 128.39, 133.05, 135.53, 156.96, 159.08; Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.51; H, 7.25; N, 5.23.

4.2.3. (1*R*,2*R*)-Methyl *N*-(1-*p*-methoxyphenyl-2-methylbut-3-enyl)carbamate (8a) and (1*S*,2*R*)-methyl *N*-(1-*p*-methoxyphenyl-2-methylbut-3-enyl)carbamate (8b). The above general procedure was followed using **6** (50 mg, 0.24 mmol), Na_2CO_3 (58 mg, 0.55 mmol), and CSI (32 μL, 0.36 mmol) in CH_2Cl_2 (2 mL) at −78 °C. The reaction mixture was purified by column chromatography (hexane/EtOAc 3:1) to give inseparable mixture (55 mg, 91%) of *anti*-homoallyl ether **8a** and *syn*-homoallyl ether **8b** (ratio=1:1.8) as a white solid; **8a**: R_f 0.31 (hexane/EtOAc 3:1); ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (d, 3H, *J*=7.0 Hz), 6.86 (dd, 2H, *J*=8.5, 2.5 Hz), 2.60 (ddq, 1H, *J*=8.0, 7.0, 7.0 Hz), 3.66 (s, 3H), 3.82 (s, 3H), 4.58–4.65 (br, 1H), 4.95–5.05 (br, 1H), 5.06 (dd, 1H, *J*=10.5, 1.5 Hz), 5.09 (dd, 1H, *J*=16.0, 1.5 Hz), 5.60 (ddd, 1H, *J*=16.0, 10.5, 8.0 Hz), 6.86 (dd, 2H, *J*=8.5, 2.5 Hz), 7.12 (dd, 2H, *J*=8.5, 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.41, 43.42, 52.38, 55.50, 58.72, 113.85, 116.35, 128.53, 132.68, 139.96, 156.54, 159.01. Compound **8b**: IR (CH_2Cl_2) 3329, 2958, 2857, 1699, 1612, 1514, 1459, 1247, 1179, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.99 (d, 3H, *J*=6.5 Hz), 2.53 (ddq, 1H, *J*=8.0, 7.0, 6.5 Hz), 3.64 (s, 3H), 3.81 (s, 3H), 4.42–4.53 (br, 1H), 4.95–5.05 (br, 1H), 5.08 (dd, 1H, *J*=10.5, 1.5 Hz), 5.11 (dd, 1H, *J*=16.5, 1.5 Hz), 5.74 (ddd, 1H, *J*=16.5, 10.5, 8.0 Hz), 6.87 (dd, 2H, *J*=8.5, 2.5 Hz), 7.17 (dd, 2H, *J*=8.5, 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.79, 43.97, 52.36, 55.51, 59.01, 114.24, 116.47, 128.02, 133.76, 139.98, 156.64, 158.98; HRMS (CI) calcd for $C_{14}H_{19}NO_3$ [M+H$^+$] 250.1443, found 250.1451.

4.2.4. (2*R*,3*R*)-2-Methoxy-3-methoxycarbonylamino-3-*p*-methoxyphenylpropan-1-ol (11). Ozone was bubbled through a solution of *anti*-1,2-amino alcohol **3a** (0.70 g, 2.64 mmol) in anhydrous CH_2Cl_2 (10 mL) and MeOH (20 mL) at −78 °C until blue color persisted, the excess was then purged out with N_2 until decolorization, and $NaBH_4$ (1.00 g, 26.38 mmol) was added at −78 °C. The reaction mixture was slowly warmed to 0 °C, stirred at 0 °C for 1 h and concentrated in vacuo. The residue was dissolved in H_2O (30 mL) and EtOAc (50 mL), the organic layer was separated and washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:2) to give 0.67 g (94%) of alcohol **11** as a colorless syrup; R_f 0.21 (hexane/EtOAc 1:2); $[\alpha]_D^{29}$ −48.6 (*c* 0.1, $CDCl_3$); IR (CH_2Cl_2) 3390, 2951, 2836, 1704, 1612, 1514, 1463, 1295, 1247, 1180, 1115, 1063 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.20–2.28 (br, 1H), 3.43 (ddd, 1H, *J*=7.5, 5.5, 3.5 Hz), 3.46 (s, 3H), 3.50–3.56 (br d, 1H, *J*=2.0 Hz), 3.68 (s, 3H), 3.64–3.75 (br, 1H), 3.82 (s, 3H), 4.97–5.03 (br, 1H), 5.82 (br d, 1H, *J*=8.5 Hz), 6.89 (dd, 2H, *J*=7.0, 2.0 Hz), 7.25 (dd, 2H, *J*=7.0, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.59, 55.24, 55.55, 58.21, 61.19, 82.84, 114.28, 128.42, 131.52, 157.15, 159.24; HRMS (CI) calcd for $C_{13}H_{19}NO_5$ [M+H$^+$] 270.1341, found 270.1341.

4.2.5. (2*R*,3*R*)-3-Methoxycarbonylamino-3-*p*-methoxyphenylpropane-1,2-diol (12). To a stirred solution of alcohol **11** (0.50 g, 1.86 mmol) in anhydrous CH_2Cl_2 (20 mL) was added BBr_3 (2.04 mL, 2.04 mmol, 1.0 M in CH_2Cl_2) at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 30 min, quenched with saturated $NaHCO_3$ aqueous solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL×3). The combined organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:4) to give 0.38 g (80%) of diol **12** as a white solid; R_f 0.31 ($CHCl_3$/MeOH 6:1); mp 81–84 °C; $[\alpha]_D^{29}$ −60.0 (*c* 0.1, $CDCl_3$); IR (CH_2Cl_2) 3347, 2953, 2836, 1699, 1612, 1514, 1462, 1296, 1248, 1179, 1101, 1031 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.42–2.48 (br, 1H), 2.62–2.72 (br, 1H), 3.67 (s, 3H), 3.60–3.75 (br, 2H), 3.80 (s, 3H), 3.84–3.93 (br d, 1H, *J*=13.5 Hz), 4.72 (dd, 1H, *J*=8.0, 7.0 Hz), 5.40–5.46 (br, 1H), 6.90 (dd, 2H, *J*=9.5, 2.0 Hz), 7.25 (dd, 2H, *J*=9.5, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.73, 55.54, 57.04, 63.53, 74.04, 114.48, 128.75, 130.94, 157.48, 159.53; Anal. Calcd for $C_{12}H_{17}NO_4$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.34; H, 6.73; N, 5.39.

4.2.6. (4*R*,5*R*)-5-Hydroxymethyl-4-*p*-methoxyphenyl-1,3-oxazolidin-2-one [(−)-cytoxazone] (1). To a stirred solution of diol **12** (0.30 g, 1.18 mmol) in anhydrous THF (12 mL) was added NaH (52 mg, 1.29 mmol, 60% in mineral oil) at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 2 h and quenched with H_2O (10 mL), then extracted with EtOAc (10 mL×2). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:4) to give 0.25 g (95%) of (−)-cytoxazone (**1**) as a white solid; R_f 0.37 ($CHCl_3$/MeOH 6:1); mp 118–120 °C; $[\alpha]_D^{24}$ −70.9 (*c* 0.1, MeOH); ^1H NMR (500 MHz, DMSO-d_6) δ 2.94–2.99 (m, 2H), 3.75

(s, 3H), 4.70 (ddd, 1H, J=8.5, 7.5, 4.5 Hz), 4.81 (t, 1H, J=5.0 Hz), 4.90 (d, 1H, J=8.5 Hz), 6.93 (dd, 2H, J=8.5, 3.0 Hz), 7.15 (dd, 2H, J=8.5, 3.0 Hz), 8.03–8.06 (br, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 55.81, 56.92, 61.76, 80.77, 114.39, 128.74, 129.99, 159.47, 159.72; HRMS (CI) calcd for $C_{11}H_{14}NO_4$ [M+H$^+$] 224.0923, found 224.0925.

4.2.7. (2*S*,3*R*)-2-Methoxy-3-methoxycarbonylamino-3-*p*-methoxyphenylpropan-1-ol (14). Ozone was bubbled through a solution of *syn*-1,2-amino alcohol **3b** (2.15 g, 8.10 mmol) in anhydrous CH_2Cl_2 (20 mL) and MeOH (40 mL) at −78 °C until blue color persisted, the excess was then purged out with N_2 until decolorization, and $NaBH_4$ (0.77 g, 20.25 mmol) was added at −78 °C. The reaction mixture was slowly warmed to 0 °C, stirred at 0 °C for 2 h and concentrated in vacuo. The residue was dissolved in H_2O (40 mL) and EtOAc (70 mL), the organic layer was separated and washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:2) to give 1.88 g (86%) of alcohol **14** as a colorless syrup; R_f 0.30 (hexane/EtOAc 1:2); $[\alpha]_D^{29}$ +64.1 (c 0.1, $CDCl_3$); IR (neat) 3336, 2922, 2856, 2357, 1702, 1608, 1510, 1456, 1373, 1241, 1180, 1107, 1028 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05–2.07 (br, 1H), 3.29 (s, 3H), 3.50 (ddd, 1H, J=11.5, 7.0, 2.5 Hz), 3.60 (dd, 1H, J=11.5, 7.0 Hz), 3.60–3.71 (m, 4H), 3.81 (s, 3H), 4.88–4.91 (br, 1H), 5.50 (br d, 1H, J=8.0 Hz), 6.89 (dd, 2H, J=7.5, 2.0 Hz), 7.27 (dd, 2H, J=7.5, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.65, 54.39, 55.49, 59.47, 61.39, 84.34, 114.21, 128.03, 132.52, 157.55, 159.17; HRMS (CI) calcd for $C_{13}H_{20}NO_5$ [M+H$^+$] 270.1341, found 270.1342.

4.2.8. (2*S*,3*R*)-3-Methoxycarbonylamino-3-*p*-methoxyphenylpropane-1,2-diol (15). To a stirred solution of alcohol **14** (1.65 g, 6.13 mmol) in anhydrous CH_2Cl_2 (61 mL) was added BBr_3 (7.4 mL, 7.36 mmol, 1.0 M in CH_2Cl_2) at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 4 h, quenched with saturated $NaHCO_3$ aqueous solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (15 mL×3). The combined organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:4) to give 0.74 g (54%) of diol **15** as a white solid; R_f 0.28 ($CHCl_3$/MeOH 10:1); mp 110–113 °C; $[\alpha]_D^{29}$ +16.3 (c 1.0, $CDCl_3$); IR (neat) 3352, 2956, 1690, 1615, 1543, 1517, 1464, 1345, 1300, 1251, 1180, 1095, 1032, 1008 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.64–1.81 (br, 2H), 3.56 (dd, 1H, J=11.0, 6.0 Hz), 3.62 (dd, 1H, J=11.0, 4.5 Hz), 3.70 (s, 3H), 3.81 (s, 3H), 3.94–3.98 (br, 1H), 4.78–4.81 (br, 1H), 5.41–5.43 (br, 1H), 6.91 (d, 2H, J=7.5 Hz), 7.26 (d, 2H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 52.74, 55.54, 56.31, 64.02, 75.21, 114.50, 128.13, 131.86, 157.81, 159.45; HRMS (CI) calcd for $C_{12}H_{18}NO_5$ [M+H$^+$] 256.1185, found 256.1186.

4.2.9. (4*R*,5*S*)-5-Hydroxymethyl-4-*p*-methoxyphenyl-1,3-oxazolidin-2-one [(−)-4-*epi*-cytoxazone] (2). To a stirred solution of diol **15** (0.60 g, 2.66 mmol) in anhydrous THF (13 mL) was added NaH (0.13 g, 3.19 mmol, 60% in mineral oil) at 0 °C under N_2. The reaction mixture was stirred at 0 °C for 4 h and quenched with H_2O (12 mL), then extracted with EtOAc (18 mL×2). The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 1:4) to give 0.43 g (82%) of (–)-4-*epi*-cytoxazone (**2**) as a white solid; R_f 0.27 (CH_2Cl_2/MeOH 15:1); mp 110–112 °C (EtOAc); $[\alpha]_D^{28}$ −22.8 (c 0.5, MeOH); IR (neat) 3256, 2962, 1746, 1725, 1614, 1515, 1417, 1305, 1252, 1175, 1102, 1023 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 3.73 (ddd, 1H, J=12.0, 6.0, 4.0 Hz), 3.82 (s, 3H), 3.84 (ddd, 1H, J=12.0, 6.0, 4.0 Hz), 4.27 (dt, 1H, J=6.0, 4.0 Hz), 4.79 (d, 1H, J=6.5 Hz), 6.93 (br s, 1H), 6.98 (d, 1H, J=8.5 Hz), 7.35 (d, 1H, J=8.5 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 54.95, 57.04, 61.84, 84.92, 114.41, 127.75, 133.29, 158.26, 160.01; HRMS (CI) calcd for $C_{11}H_{14}NO_4$ [M+H$^+$] 224.0923, found 224.0923.

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