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Imino 1,2-Wittig rearrangement of hydroximates and its application to synthesis of cytoxazone

Okiko Miyata, Tomoko Koizumi, Hiroshi Asai, Ryuichi Iba and Takeaki Naito*

Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan

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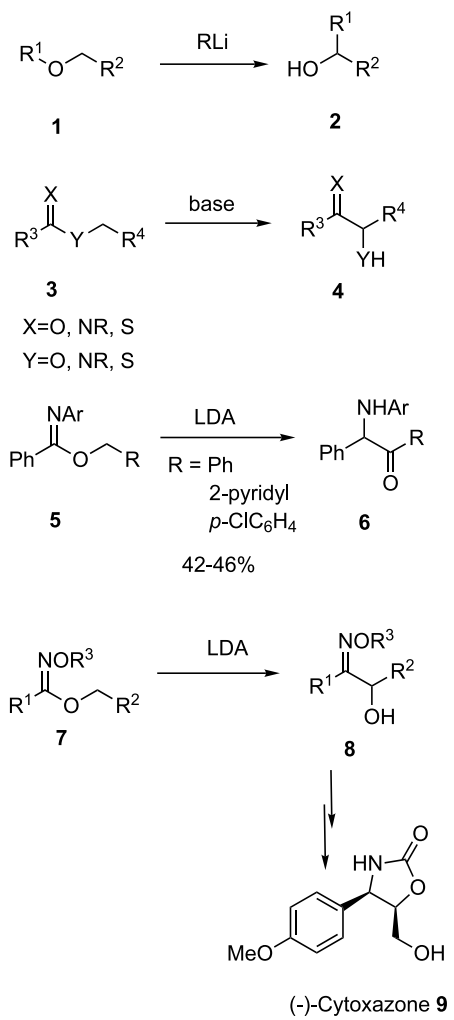
Abstract—The imino 1,2-Wittig rearrangement of hydroximates provides a novel method for the construction of 2-hydroxyoxime ethers. Upon treatment with LDA, *Z*-hydroximates smoothly underwent stereoselective rearrangement to give *Z*-2-hydroxyoxime ethers in good yield, which were converted into amino alcohols. On the other hand, the rearrangement of *E*-hydroximates gave a mixture of *E*- and *Z*-2-hydroxyoxime ethers. This method was successfully applied to a practical synthesis of cytoxazone.

1. Introduction

The 1,2-rearrangement of an ether **1** to its isomeric alcohol **2** which can occur upon metalation with excess organolithium reagent is well known as the 1,2-Wittig rearrangement (Scheme 1).[1] The synthetic utilization of the 1,2-Wittig rearrangement remains severely limited because of the rather low yields and restricted range of substrates. Recently, Tomooka's group[2] has modified the 1,2-Wittig rearrangement of ethers and applied this reaction to synthesis of natural products. There have been several papers published on the migration of the sp^2 carbon such as alkenyl,[3] carbonyl,[4] thiocarbonyl,[5] and iminyl[6] groups (**3**→**4**). Katritzky's,[6a] Uneyama's,[6b] and our groups[7] have developed a synthetically useful imino 1,2-Wittig rearrangement. Katritzky's group[6a] reported that the treatment of imidate **5** with a base gave the 2-aminoketones **6**, but in moderate yield (42–46%). On the other hand, we[7] found that the imino 1,2-Wittig rearrangement of benzyl and allyl *Z*-hydroximates (*N*-alkoxyimidate) **7** proceeded smoothly to give the 2-hydroxyoxime ethers **8**. This reaction provides a new entry to carbon–carbon bond formation. Furthermore, Uneyama's group[6b] synthesized biologically active compounds having a trifluoromethyl group via the imino 1,2-Wittig rearrangement.

We disclose herein the full details of the imino 1,2-Wittig rearrangement of benzyl and allyl hydroximates which are indispensable in the synthesis of amino alcohols, and application of this method to synthesis of cytoxazone **9**.[7] The amino alcohols are not only found in many biologically active compounds, but also are known to be important



Scheme 1.

Keywords: Imino Wittig rearrangement; Hydroximate; Imidate; Oxime ether; Cytoxazone.
* Corresponding author. Tel.: +81-78-441-7554; fax: +81-78-441-7556; e-mail address: taknaito@kobepharma-u.ac.jp

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intermediates for the synthesis of stereo-defined acyclic and other natural products.[8]

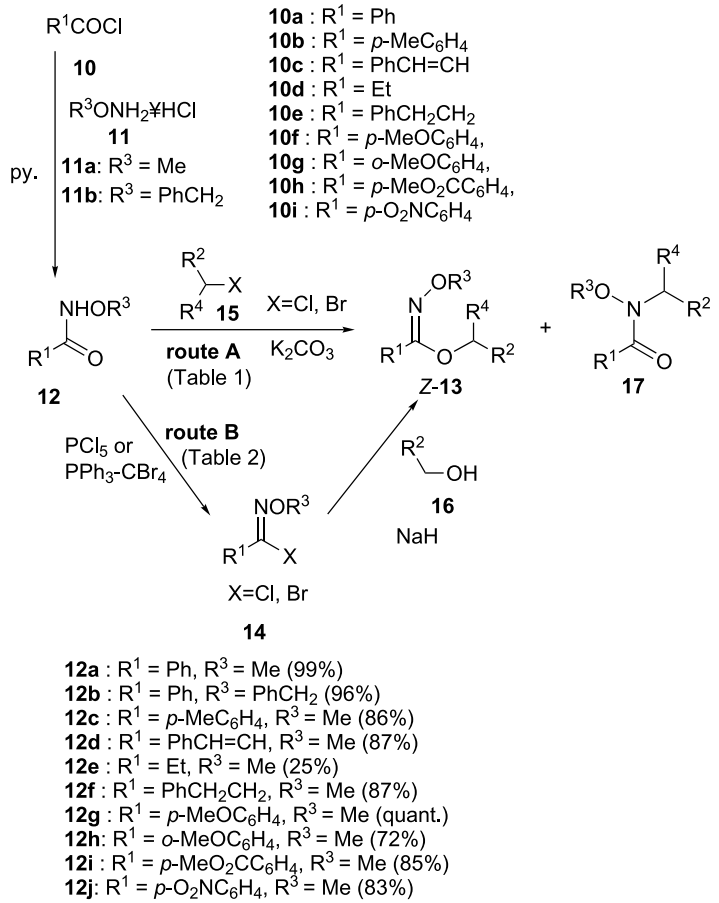
2. Results and discussion

2.1. Preparation and imino 1,2-Wittig rearrangement of *Z*-hydroximates 13

At first, we chose the *Z*-hydroximates **13** as the substrate of the imino 1,2-Wittig rearrangement.

According to the known procedure,[9] *Z*-**13** was prepared via two different routes (routes A and B) (Scheme 2). Route A to *Z*-**13** is accomplished via the alkylation of hydroxamates **12**, prepared from the corresponding acid chlorides **10** and alkoxyamines **11**. On the other hand, route B consists of two processes involving conversion of **12** into imidoyl halide **14** followed by treatment with alcohols **16** in the presence of a base.

We first examined the preparation of *Z*-**13** by route A (Table 1).



Scheme 2.

Table 1. Conversion of **12** into **13** by route A

Entry	Substrate	R^1	R^3	Alkyl halide				Product **13**, **17**	Yield (%)	Ratio *Z*-**13**:**17**
				15	R^2	R^4	X			
1	**12a**	Ph	Me	**15a**	Ph	H	Br	**a**	98	1:2.8
2	**12a**	Ph	Me	**15b**	CH_2=CH	H	Br	**b**	94	1:4.5
3	**12a**	Ph	Me	**15c**	MeO_2C	H	Br	**c**	28	1:0.1
4	**12a**	Ph	Me	**15d**	Me	H	Br	**d**	82	1:1.1
5	**12a**	Ph	Me	**15e**	*p*-$MeOC_6H_4$	H	Cl	**e**	74	1:6.4
6	**12a**	Ph	Me	**15f**	*p*-$O_2NC_6H_4$	H	Br	**f**	71	1:0
7	**12a**	Ph	Me	**15g**	Ph	Me	Br	**g**	82	1:2.8
8	**12b**	Ph	$PhCH_2$	**15a**	Ph	H	Br	**h**	89	1:2.6
9	**12c**	*p*-MeC_6H_4	Me	**15a**	Ph	H	Br	**i**	91	1:7.6
10	**12d**	PhCH=CH	Me	**15a**	Ph	H	Br	**j**	80	1:4.2
11	**12e**	Et	Me	**15a**	Ph	H	Br	**k**	40	1:2.3
12	**12f**	$PhCH_2CH_2$	Me	**15a**	Ph	H	Br	**l**	85	1:3.9
13	**12f**	$PhCH_2CH_2$	Me	**15b**	CH_2=CH	H	Br	**m**	97	1:8.0

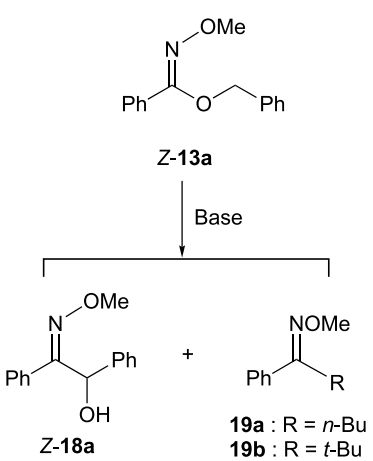
Table 2. Conversion of **12** into **13** by route B

Entry	Substrate	R^1	PCl_5 or PPh_3–CBr_4	Imidoyl halide			Alcohol		*Z*-**13**	Yield (%)
				14	R^1	X	**16**	R^2		
1	**12a**	Ph	PCl_5	**14a**	Ph	Cl	**16a**	Ph	**13a**	54
2	**12a**	Ph	PPh_3–CBr_4	**14b**	Ph	Br	**16b**	PhCH=CH	**13n**	59
3	**12g**	*p*-$MeOC_6H_4$	PPh_3–CBr_4	**14c**	*p*-$MeOC_6H_4$	Br	**16c**	CH_2=CH	**13p**	82
4	**12g**	*p*-$MeOC_6H_4$	PPh_3–CBr_4	**14c**	*p*-$MeOC_6H_4$	Br	**16b**	PhCH=CH	**13o**	56
5	**12h**	*o*-$MeOC_6H_4$	PPh_3–CBr_4	**14d**	*o*-$MeOC_6H_4$	Br	**16c**	CH_2=CH	**13q**	75
6	**12i**	*p*-$MeO_2CC_6H_4$	PPh_3–CBr_4	**14e**	*p*-$MeO_2CC_6H_4$	Br	**16c**	CH_2=CH	**13r**	52
7	**12j**	*p*-$O_2NC_6H_4$	PPh_3–CBr_4	**14f**	*p*-$O_2NC_6H_4$	Br	**16c**	CH_2=CH	**13s**	96

The alkylation of **12a** with benzyl bromide in the presence of potassium carbonate gave a 1:2.8 mixture of the *Z*-hydroximate **13a** and the alkoxyamide **17a** in 98% combined yield (entry 1). Similarly, **12b–f** gave *Z*-hydroximates **13b–m** accompanied with the formation of amides **17b–m** as shown in entries 2–13.

According to route B, *Z*-**13a**,**n–s** were prepared from **12a**,**g–j** via imidoyl halides **14a–f** (Table 2). The chlorination of hydroxamate **12a** with phosphorus pentachloride followed by treatment of the resulting imidoyl chloride **14a** with benzyl alcohol **16a** in the presence of sodium hydride gave the *Z*-hydroximate **13a** as the sole product in 54% yield (entry 1). Treatment of **12g–j** with triphenylphosphine and carbon tetrabromide followed by reaction of the resulting imidoyl bromide **14b–f** with sodium alcoholates, prepared from **16b**,**c**, gave the *Z*-hydroximates **13n–s** by the same reaction sequence (entries 2–7).

Next, we investigated the reaction of *Z*-hydroximate **13a** with various kinds of bases (Scheme 3, Table 3). The *Z*-hydroximate **13a** was treated with 1 equiv. of LDA in THF at −23 °C to give *Z*-2-hydroxyoxime ether **18a**, along with recovered *Z*-hydroximate **13a** (entry 1). When 2 equiv. of LDA was used, the reaction proceeded smoothly to give *Z*-**18a** in 89% yield (entry 2). Similarly, the reaction also occurred in either Et_2O or toluene to give *Z*-**18a** in moderate yield (entries 4 and 5). On the other hand, use of nucleophilic *n*-BuLi as a base gave the oxime ether **19a** in 54% yield without formation of the desired *Z*-2-hydroxyoxime ether **18a** (entry 6). In the case of *t*-BuLi, a mixture of *Z*-**18a** and **19b** was obtained (entry 7). The oxime ethers **19a**,**b** would be formed by the nucleophilic addition of a



Scheme 3.

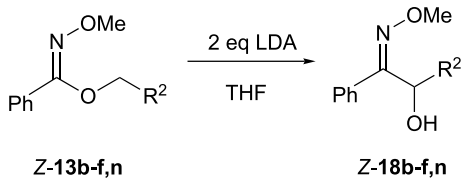
Table 3. Imino 1,2-Wittig rearrangement of *Z*-**13a**

Entry	Base (equiv.)	Solvent	*T* (°C)	Time (h)	Yield (%)	
					Z-**18a**	**19a**,**b**
1	LDA (1)	THF	−23	1	35	—
2	LDA (2)	THF	−23	0.5	89	—
3	LDA (2)	THF	−78	1	80	—
4	LDA (2)	Et_2O	−23	0.5	79	—
5	LDA (2)	PhMe	−23	0.5	62	—
6	*n*-BuLi (2)	THF	−23	1	—	54
7	*t*-BuLi (2)	THF	−23	1	19	23
8	LHMDS (2)	THF	−23	2	—[a]	—
9	PhLi (2)	THF	−23	2	—[a]	—

[a] The starting material was recovered.

base (*n*-BuLi or *t*-BuLi) to *Z*-**13a** followed by elimination of the benzyloxy anion. Treatment of *Z*-**13a** with either LHMDS (lithium hexamethyldisilazide) or phenyllithium did not give *Z*-**18a**, but the recovered *Z*-hydroximate **13a** (entries 8 and 9). It is clear that the conditions using LDA (2 equiv.) shown in entry 2 are suitable for the formation of rearranged product *Z*-**18a**.

The substituent effect at the R^2 position in the *Z*-oxime ether was then investigated in order to establish the generality of the rearrangement (Scheme 4, Table 4). The rearrangement of substrate *Z*-**13b** having a vinyl group at the R^2 position proceeded smoothly at −40 °C to give the *Z*-2-hydroxyoxime ether **18b** (entry 2). Similarly, *Z*-cinnamylhydroximate



Scheme 4.

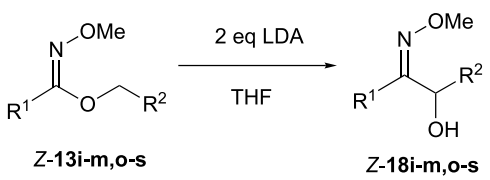
Table 4. Imino 1,2-Wittig rearrangement of *Z*-**13b–f**,**n**

Entry	Substrate	R^2	*T* (°C)	Time (h)	Yield (%)
1	*Z*-**13b**	CH_2=CH	−23	1.5	45
2	*Z*-**13b**	CH_2=CH	−40	3	60 (82)[a]
3	*Z*-**13n**	PhCH=CH	−40	0.5	50
4	*Z*-**13c**	CO_2Me	−50→0	8	—[b]
5	*Z*-**13d**	Me	−23	1.5	—[c]
6	*Z*-**13e**	*p*-$MeOC_6H_4$	−23	4	—[c]
7	*Z*-**13f**	*p*-$O_2NC_6H_4$	−40	3	—[b]

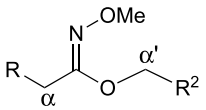
[a] Based on recovery of the starting material.
[b] Many spots were observed on TLC.
[c] The starting material was recovered.

13n underwent rearrangement to give the *Z*-2-hydroxyoxime ether **18n** (entry 3). However, when methoxycarbonyl, methyl, *p*-methoxyphenyl, and *p*-nitrophenyl groups are present at the R^2 position, no desired products were obtained (entries 4–7). In the case of *Z*-**13d** and *Z*-**13e**, the corresponding hydroximates were recovered while *Z*-**13c** and *Z*-**13f** gave a complex mixture, respectively.

We next investigated the substituent effect at the R^1 position (Scheme 5, Table 5). In the case of a substituted phenyl group having an electron-donating group, such as methyl and methoxyl groups, the rearrangement proceeded smoothly to give the products *Z*-**18i**, **18o**, **18p**, and **18q** (entries 1–4). However, the substrate *Z*-**13r** having a methoxycarbonyl group as an electron-withdrawing group on the benzene ring gave the desired product *Z*-**18r** in low yield while *Z*-**13s** having a nitro group did not give *Z*-**18s** but recovered Z-hydroximate **13s** (entries 5 and 6). The *Z*-cinnamylhydroximate **13j** gave the desired *Z*-oxime ether **18j** in good yield (entry 7). In order to extend the reaction to more reactive hydroximates which carry two methylene groups at the α- and α′-positions as shown in compound **A**, we next investigated the reaction of *Z*-hydroximates **13k–m** having an additional active methylene group at the α-position of the *N*-methoxyimino group, with LDA. Although the presence of two active methylene groups in these substrates *Z*-**13k–m** was expected to complicate the reaction, the rearrangement of the *Z*-hydroximates **13k–m** proceeded cleanly to give the rearranged products *Z*-**18k–m**



Z-**13i-m,o-s** *Z*-**18i-m,o-s**



A

Scheme 5.

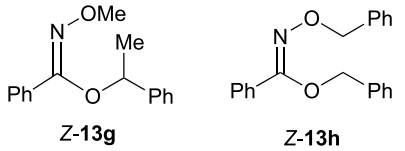
Table 5. Imino 1,2-Wittig rearrangement of *Z*-**13i–m,o–s**

Entry	Substrate	R^1	R^2	*T* (°C)	Time (h)	Yield (%)
1	*Z*-**13i**	*p*-MeC_6H_4	Ph	−23	0.5	89
2	*Z*-**13o**	*p*-$MeOC_6H_4$	PhCH=CH	−23	2	76
3	*Z*-**13p**	*p*-$MeOC_6H_4$	CH_2=CH	−78	0.5	82
4	*Z*-**13q**	*o*-$MeOC_6H_4$	CH_2=CH	−23	1	92
5	*Z*-**13r**	*p*-$MeO_2CC_6H_4$	CH_2=CH	−78	1	25
6	*Z*-**13s**	*p*-$O_2NC_6H_4$	CH_2=CH	−23	1.5	—[a]
7	*Z*-**13j**	PhCH=CH	Ph	−23	1.5	79
8	*Z*-**13k**	Et	Ph	−23	2.5	64
9	*Z*-**13l**	$PhCH_2CH_2$	Ph	−23	2.5	75 (89)[b]
10	*Z*-**13m**	$PhCH_2CH_2$	CH_2=CH	−40	2	64

[a] The starting material was recovered.
[b] Based on recovery of the starting material.

as the sole isolated product under similar conditions (entries 8–10).

Attempted rearrangement of both the substrate *Z*-**13g** having an active methine proton and *Z*-*O*-benzyloxyhydroximate **13h** was unsuccessful and the substrates *Z*-**13g** and *Z*-**13h** were mostly recovered (Fig. 1).

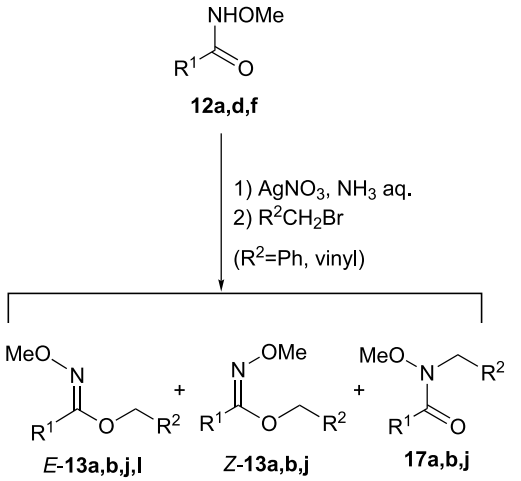


Z-**13g** *Z*-**13h**

Figure 1. *Z*-Hydroximates **13g** and **13h**.

2.2. Preparation and imino 1,2-Wittig rearrangement of *E*-hydroximates 13

This rearrangement was then applied to the *E*-hydroximates **13a**,**b**,**j**,**l** which were prepared as follows (Scheme 6). According to the reported procedure,[9] the reaction of hydroxamates **12a**,**d**,**f** with benzyl or allyl bromide in the presence of silver nitrate afforded the *E*-hydroximates **13a**,**b**,**j**,**l** as the major product but in low yield (Table 6).



E-**13a,b,j,l** *Z*-**13a,b,j** **17a,b,j**

Scheme 6.

The *E*/*Z*-geometries of hydroximates **13** were determined by ^{1}H NMR analysis (Fig. 2, Table 7). It is known[9] that the hydroximates exhibiting signals for the hydrogen Ha and Hb at lower field have *Z*-geometries while the hydroximates showing signals at higher field have *E*-geometries. From the fact that signals due to methoxy and allylic hydrogens of a minor product *Z*-**13a** (OMe: δ 3.94, 1′-H_2: δ 5.28) appeared in down-field compared with those of the major product *E*-**13a** (OMe: δ 3.83, 1′-H_2: δ 5.18), we deduced their stereostructures as shown. Similarly, the stereostructures of *Z*-**13b**,**j**,**l** and *E*-**13b**,**j**,**l** were determined.

Next, we investigated the rearrangement of *E*-hydroximates **13a** (Scheme 7, Table 8) which proceeded to give 41% combined yield of a 3:1 mixture of *E*-**18a** and *Z*-**18a** with recovery of the starting material *E*-**13a** (entry 1). Since equilibration between *E*-**18a** and *Z*-**18a** was not observed

Table 6. Preparation of *E*-hydroximates **13a**,**b**,**j**,**l**

Entry	Substrate	R^1	R^2	Products	Yield (%)	Ratio (*E*-**13**:*Z*-**13**:**17**)
1	**12a**	Ph	Ph	**a**	28	1:0.3:0.5
2	**12a**	Ph	CH_2=CH	**b**	42	1:0.2:0.1
3	**12d**	PhCH=CH	Ph	**j**	19	1:0.2:0.5
4	**12f**	$PhCH_2CH_2$	Ph	**l**	6	1:0:0

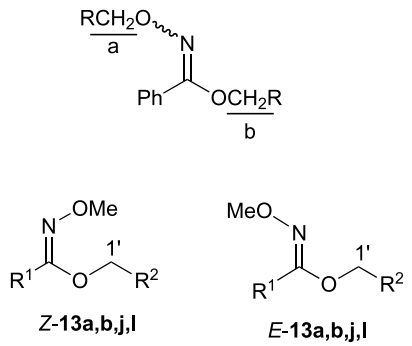
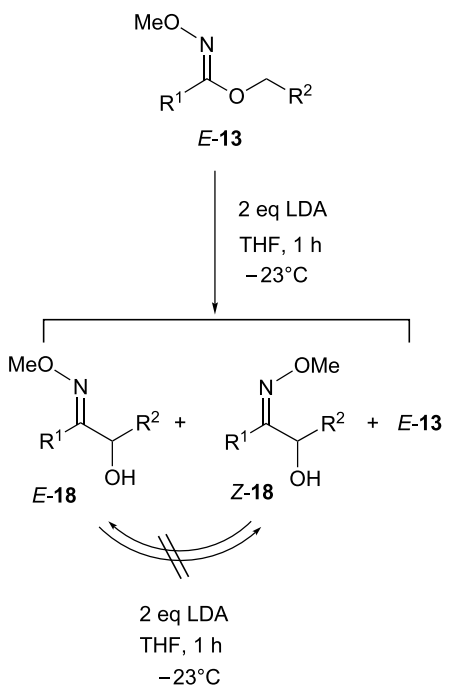


Figure 2. *Z*/*E*-Hydroximates **13**.

Table 7. ^{1}H NMR data of *Z*-**13a**,**b**,**j**,**l** and *E*-**13a**,**b**,**j**,**l**

	R^1	R^2	*Z*-**13** δ (ppm)		*E*-**13** δ (ppm)	
			OCH_3	$1'$-CH_2	OCH_3	$1'$-CH_2
a	Ph	Ph	3.94	5.28	3.83	5.18
b	Ph	CH_2=CH	3.91	4.71	3.80	4.66
j	PhCH=CH	Ph	3.91	5.29	3.86	5.14
l	$PhCH_2CH_2$	Ph	3.80	5.20	3.71	4.96



Scheme 7.

Table 8. Imino 1,2-Wittig rearrangement of *E*-hydroximates **13a**,**b**,**j**,**l**

Entry	Substrate	R^1	R^2	Yield		
				E-**18**	*Z*-**18**	*E*-**13**
1	*E*-**13a**	Ph	Ph	31	10	20
2	*E*-**13b**	Ph	CH_2=CH	12	7	44
3	*E*-**13j**	PhCH=CH	Ph	31	28	17
4	*E*-**13l**	$PhCH_2CH_2$	Ph	—	—	41

under the reaction conditions, both *E*-**18a** and *Z*-**18a** would be the kinetic products. Similarly, rearrangement of *E*-hydroximates **13b** and **13j** gave a mixture of *E*-**18b**,**j** and *Z*-**18b**,**j** (entries 2 and 3). The *E*-hydroximate **13l** having two types of active methylene protons did not give the rearranged products *E*-**18l** and *Z*-**18l** but gave a complex mixture with recovery of *E*-**13l** (entry 4).

The substituent effects on the rearrangement of hydroximates **13** can be summarized as follows.

(i) Stereostructure of oxime ether. In the case of *Z*-hydroximates **13**, the rearrangement proceeded stereoselectively to give *Z*-oxime ethers **18** as the sole product in good yield. On the other hand, the *E*-hydroximates **13** gave a mixture of *E*- and *Z*-oxime ethers **18** with no stereoselectivity.

(ii) Substituent effects at the R^1 position. The *Z*-hydroximates **13** having a substituted phenyl group, except for the nitrophenyl group, underwent the rearrangement. Particularly, the electron-donating group on the benzene ring accelerated the rearrangement. The reaction of *Z*-hydroximates **13k**–**m** having two types of active methylene groups also proceeded smoothly.

(iii) Substituent effects at the R^2 position. The phenyl, cinnamyl, and vinyl groups were effective for the rearrangement while the rearrangement of *Z*-hydroximates **13d**,**e** having methyl and *p*-methoxyphenyl groups did not proceed. Therefore, the *O*-methylene group having a moderately acidic hydrogen is required for the successful rearrangement.

(iv) Substituent effects at the R^3 position of alkoxyamino moiety. The hydroximate having a methyl group at the R^3 position underwent rearrangement while a benzyl group was not effective for the rearrangement.

2.3. Stereostructure determination of rearranged products

The stereostructure of rearranged products was established as follows (Fig. 3, Table 9). The *E*/*Z*-geometries of oxime ethers **18a** were determined by ^{1}H NMR spectroscopy.

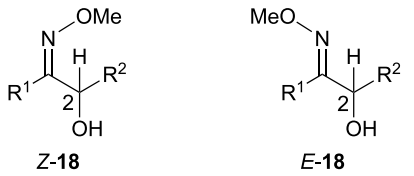


Figure 3. *Z*/*E*-Hydroxyoxime ethers **18**.

Table 9. ^{1}H NMR data of *Z*/*E*-2-hydroxyoxime ethers **18**

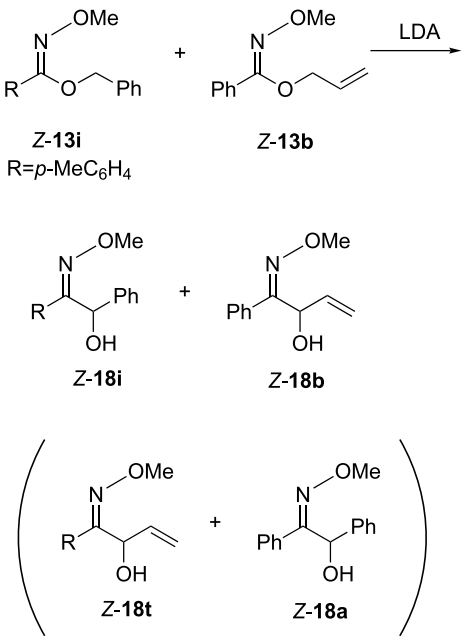
	R^1	R^2	2-H	
			Z-**18** δ (ppm)	*E*-**18** δ (ppm)
a	Ph	Ph	6.15	5.55
b	Ph	CH_2=CH	5.47	5.04
j	PhCH=CH	Ph	6.05	5.63

Karabatso's group[10] reported that the oxime ethers exhibiting signals for 2-H at lower field have *Z*-geometries while the oxime ethers showing signals at higher field have *E*-geometries. Signals due to hydrogen at the 2-position of *Z*-isomer **18a** (δ 6.15) appeared in down-field compared with those of *E*-isomer **18a** (δ 5.55). Similarly, the stereostructures of *Z*-**18b**,**j** and *E*-**18b**,**j** were established from their spectral data. Furthermore, the treatment of benzoin with methoxyamine gave a 1:4 mixture of the authentic *Z*-oxime ether **18a** and *E*-isomer **18a** according to the literature.[11] These spectral data were identical with those prepared from *E*-hydroximate **13a**.[11] Since the rearranged products *Z*-**18i**,**k**–**r** were obtained from *Z*-hydroximates **13i**,**k**–**r**, *Z*-**18i**,**k**–**r** were presumed to have *Z*-geometries.

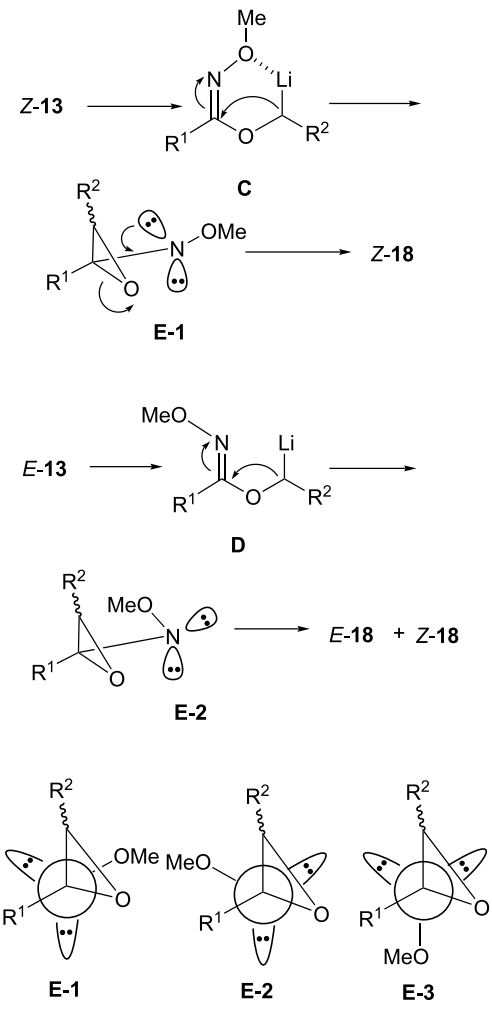
2.4. Plausible reaction pathway of the imino 1,2-Wittig rearrangement

In order to clarify the reaction pathway, we investigated the cross reaction (Scheme 8). A mixture of *Z*-**13i** and *Z*-**13b** was treated with LDA to give only a mixture of two products *Z*-**18i** and *Z*-**18b** without the formation of *Z*-**18t** and *Z*-**18a**. It suggests that the newly found rearrangement of hydroximates proceeds via an intramolecular process.

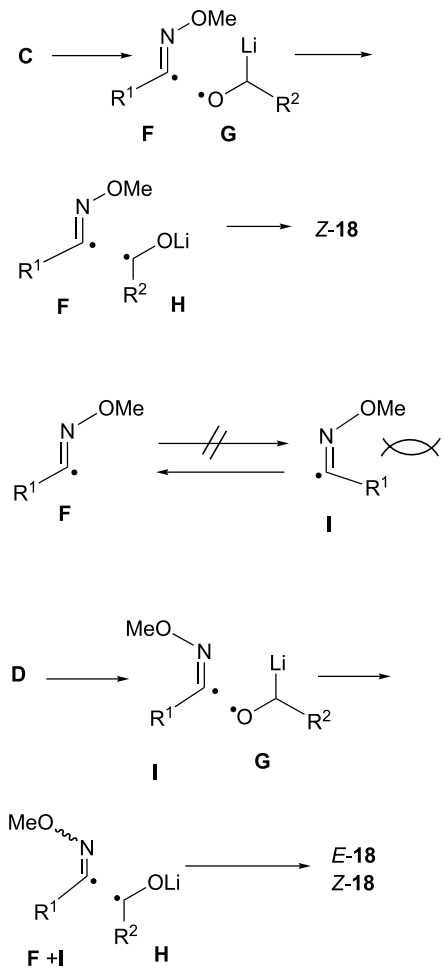
From the above results, we propose two possible reaction pathways for this rearrangement (Schemes 9 and 10). The first proposed reaction pathway is that rearrangement proceeds by an ionic addition–elimination process as proposed for the related 1,2-rearrangements (Scheme 9).[3] Grovenstein's group[3a] suggested that in the 1,2-Wittig rearrangement of benzyl propenyl ether, initial cyclization of the lithio ether, generated from benzyl propenyl ether, proceeds by *anti*-addition to give the epoxide and subsequent ring-opening of the epoxide occurs via *syn*-elimination to give the product with the same configuration at the disubstituted olefin. According to this mechanism, we propose a possible reaction pathway of the newly found imino Wittig rearrangement as follows. Treatment of **13** having *Z*-oxime ether with LDA gives the lithio ether **C** which would be stabilized by chelation with the methoxyl group. Then intramolecular addition of the resulting carbanion **C** to the imino double bond proceeds



Scheme 8.



Scheme 9.



Scheme 10.

in *anti*-fashion to give the epoxide **E-1** as shown in Newman's projection.

Finally, the epoxide **E-1** undergoes ring-opening reaction in *anti*-periplanar manner involving the nitrogen lone pair and C–O bond to afford the rearranged product *Z*-**18** with retention of configuration at the methoxyimino group.

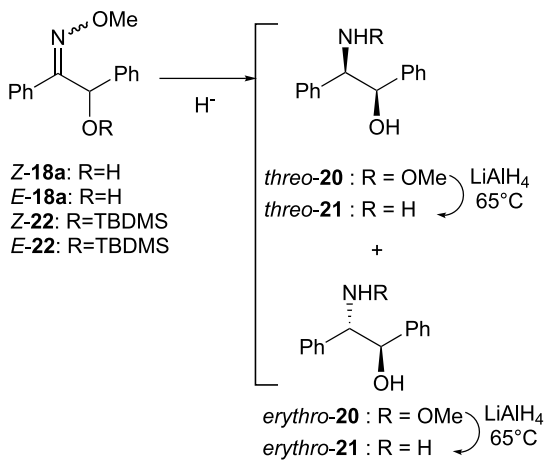
On the other hand, rearrangement of *E*-hydroximate **13** proceeded slowly and non-stereoselectively to give a mixture of *E*-**18** and *Z*-**18**. The treatment of *E*-**13** with LDA gives the lithio ether **D** which would not be stabilized by chelation with the methoxy group and then undergoes *anti*-addition to the imino group to give the epoxide **E-2**. Newman's projection shows that in the conformation **E-2**, the C–O bond and lone pair are not situated in *anti*-periplanar suitable for the E2 type of the final ring-opening reaction. Therefore, there would be two possible reaction pathways. One is E1cB type elimination from the conformation **E-2** which gives a mixture of *E*-**18** and *Z*-**18** products. The other is E2 type elimination from the conformational isomers **E-1** and **E-3** both of which gave the rearranged products *E*-**18** and *Z*-**18**, respectively.

The alternative is a radical mechanism as follows (Scheme 10). It is known that 1,2-Wittig rearrangement of the ethers proceeds not in a concerted fashion but *via* a radical dissociation–recombination mechanism.[2,12] The cyclic intermediate **C**, formed from *Z*-**13**, dissociates to the radical pair of the imidoyl radical **F** and the oxygen radical **G**, of which oxygen radical **G** isomerizes to carbon radical **H**. Recombination of the resulting radical pair of imidoyl radical **F** and carbon radical **H** occurs more rapidly than inversion of the imidoyl radical center **F** to geometrical isomer **I**, judging from the high degree of retention at the oxime ether group. On the rearrangement of *E*-hydroximate **13**, it is suggested that the isomerization of the imidoyl radical center **I**, formed from intermediate **D** isomerizes partially to the isomer **F** due to steric hindrance between the R^1 group and the methoxyl group in **I** during the course of the reaction.

However, we are unable to offer a detailed explanation of the reaction pathway at present.

2.5. Reduction of 2-hydroxyoxime ether

We next investigated the conversion of 2-hydroxyoxime ethers into 1,2-amino alcohols which are important and versatile synthetic intermediates for the preparation of a wide variety of natural products, drugs, and metal-binding ligands.[8] According to the reported procedure[13] for reduction of imines and oxime ethers, we examined the reduction of *Z*-**18a** using various types of reducing reagents (Scheme 11, Table 10). The reduction of *Z*-**18a** with $LiAlH_4$ proceeded smoothly at 0 °C to give a mixture of *threo*- and *erythro*-methoxyamino alcohols **20** in low yield with a ratio of 74:26, in addition to recovered starting material *Z*-**18** (entry 1). Further reduction of *threo*-**20** and *erythro*-**20** with $LiAlH_4$ in THF under reflux gave *threo*- and *erythro*-amino alcohols **21**, respectively, whose spectral data were identical with those reported.[13] The reduction of *Z*-**18a** with $LiAlH_4$ in boiling THF gave demethoxylated amino alcohols *threo*-**21** and *erythro*-**21** (entry 2). The reduction of *Z*-**18a** with $NaBH_4$ in the presence of zirconium tetrachloride gave *erythro*-**21** as a major product (entry 4). It is known[14] that TABH (tetramethylammonium triacetoxyborohydride) is used for the stereoselective reduction of 2-hydroxy-oxime ethers and -ketones. However, the reduction of *Z*-**18a** with TABH gave only a complex mixture (entry 5). *Z*-**18a** was



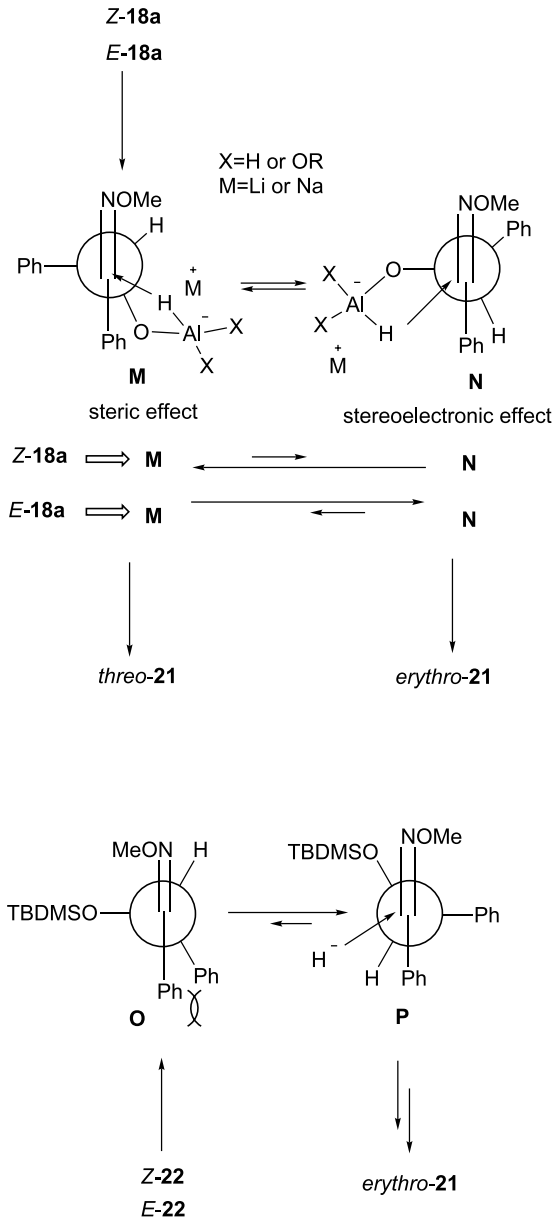
Scheme 11.

Table 10. Reduction of oxime ethers **18a** and **22**

Entry	Substrate	Reagent	*T* (°C)	Yield (%)	Ratio (*threo*-**21**:*erythro*-**21**:*threo*-**20**:*erythro*-**20**)
1	*Z*-**18a**	$LiAlH_4$	0	18	0:0:74:26
2	*Z*-**18a**	$LiAlH_4$	65	69	77:23:0:0
3	*Z*-**18a**	$NaBH_3CN/H^+$	Rt→65	61	69:31:0:0
4	*Z*-**18a**	$NaBH_4/ZrCl_4$	Rt	62	34:66:0:0
5	*Z*-**18a**	TABH	−35	—	—
6	*Z*-**18a**	SMEAH	80	74	83:17:0:0
7	*E*-**18a**	$LiAlH_4$	65	65	36:64:0:0
8	*E*-**18a**	SMEAH	80	—[a]	—
9[b]	*Z*-**22**	$LiAlH_4$	0	98	4:96:0:0
10[b]	*E*-**22**	$LiAlH_4$	0→rt	33	9:91:0:0

[a] Many spots were observed on TLC.
[b] Amino alcohols *threo*-**21** and *erythro*-**21** were obtained by reduction followed by treatment with *p*-TsOH.

treated with SMEAH (sodium bis(2-methoxyethoxy)-aluminum hydride) to give a mixture of *threo*-**21** and *erythro*-**21** with better selectivity than those in other agents (entry 6).



Scheme 12.

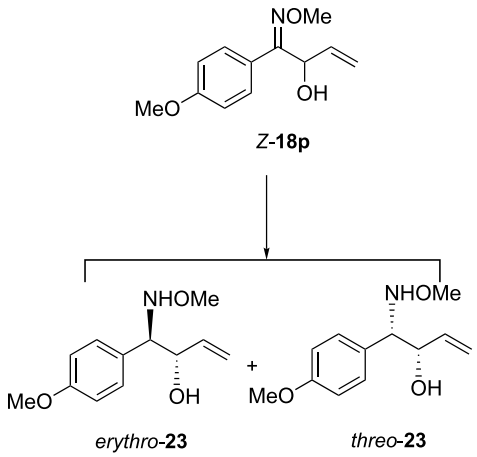
In the case of *E*-2-hydroxyoxime ether **18a**, the reduction with $LiAlH_4$ gave *threo*-**21** and *erythro*-**21** (entry 7) while the use of SMEAH as reducing reagent gave a complex mixture (entry 8).

We next investigated the reduction of silylated oxime ethers *Z*-**22** and *E*-**22**, prepared from the alcohol *Z*-**18a** and *E*-**18a**, respectively. The reduction of *Z*-**22** with $LiAlH_4$ followed by treatment of the resulting amine with *p*-TsOH gave *erythro*-**21** in good yield and with high diastereoselectivity (entry 9). Similarly, *erythro*-**21** was obtained diastereoselectively from *E*-**22**, but in poor yield (entry 10).

The observed stereoselectivity would be explained as follows (Scheme 12). The treatment of *Z*-**18a** with $LiAlH_4$ or SMEAH forms intermediate **M** or **N** which is complexed with the hydroxyl group in *Z*-**18a**. **N** is a conformation according to the Felkin–Anh model, but there is steric hindrance between the methoxyl group and the phenyl part in the conformation **N** because the oxime ether **18a** has *Z*-configuration. Therefore, the reduction of *Z*-**18a** would proceed via the conformation **M** by an intramolecular process to give *threo*-**21** as a major product. On the other hand, *E*-**18a** would exist preferably in the conformation **N** which is more stable than the conformation **M** because there is no steric hindrance between the methoxyl group and the phenyl group in the conformation **N**. Therefore, *E*-**18a** gave *erythro*-**21** as a major product. The protected 2-hydroxyoxime ethers *Z*-**22** and *E*-**22** would exist preferably in stable conformation **P** due to existence of steric hindrance between two phenyl groups in the conformation **O**. The hydride would attack the oxime ether by an intermolecular process to give *erythro*-**21** with high stereoselectivity.

2.6. Synthesis of cytoxazone

We then applied this methodology to the synthesis of cytoxazone **9**. Cytoxazone **9**[15] containing a 4,5-disubstituted 2-oxazolidinone ring was recently isolated from *Streptomyces* sp. and the absolute configuration was unambiguously established by the first total asymmetric synthesis reported recently by Nakata's group.[16] Cytoxazone **9** has shown a cytokine-modulating activity by inhibiting the signaling pathway of Th2 cells. Inhibitors of Th2-dependent cytokine production would be potent chemotherapeutic agents in the field of immunotherapy. Therefore, cytoxazone and its analogs have been a new



Scheme 13.

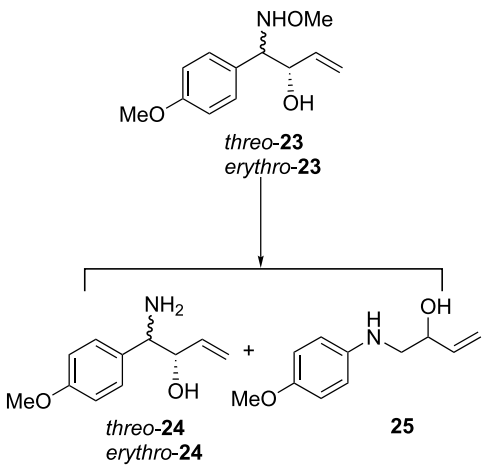
Table 11. Reduction of *Z*-2-hydroxyoxime ether **18p**

Entry	Reagent	Solvent	*T* (°C)	Yield (%)	Ratio (*erythro*-**23**:*threo*-**23**)
1	SMEAH	THF	−30	77	1.0:2.1
2	$LiAlH_4$	THF	0	68	1.0:1.2
3	$LiAlH_4$	Et_2O	0	77	2.1:1.0

subject of synthetic studies[17] for the development of a cytokine modulator.

We first investigated the reduction of oxime ether in *Z*-2-hydroxyoxime ether **18p** which was prepared in 82% yield by rearrangement of *Z*-hydroximate **13p** as described above (Scheme 13, Table 11). The reduction of *Z*-**18p** with SMEAH was carried out at −30 °C to give a 1.0:2.1 mixture of *erythro*- and *threo*-methoxyamino alcohols **23** as a result of reduction of the carbon–nitrogen double bond (entry 1). On the other hand, the reduction with $LiAlH_4$ in Et_2O gave the desired product *erythro*-**23** as the major isomer, but with low selectivity (entry 3).

Reductive demethoxylation of *threo*-**23** with $LiAlH_4$ at higher temperature gave *threo*-amino alcohol **24** as the sole product (Scheme 14, Table 12, entry 2) while the reduction



Scheme 14.

Table 12. Demethoxylation of methoxyamines **23**

Entry	Substrate	Reagent	Solvent	*T* (°C)	Yield (%)	
					24	**25**
1	*threo*-**23**	SMEAH	THF	65	52	33
2	*threo*-**23**	$LiAlH_4$	Et_2O	35	Quant.	—
3	*erythro*-**23**	SMEAH	THF	65	16	68
4	*erythro*-**23**	$LiAlH_4$	Et_2O	35	48	19

using SMEAH gave **25**[18] as a side product together with the desired product *threo*-**24** (entry 1). Similarly, reduction of *erythro*-**23** with $LiAlH_4$ gave *erythro*-amino alcohol **24** as a major product (entry 4).

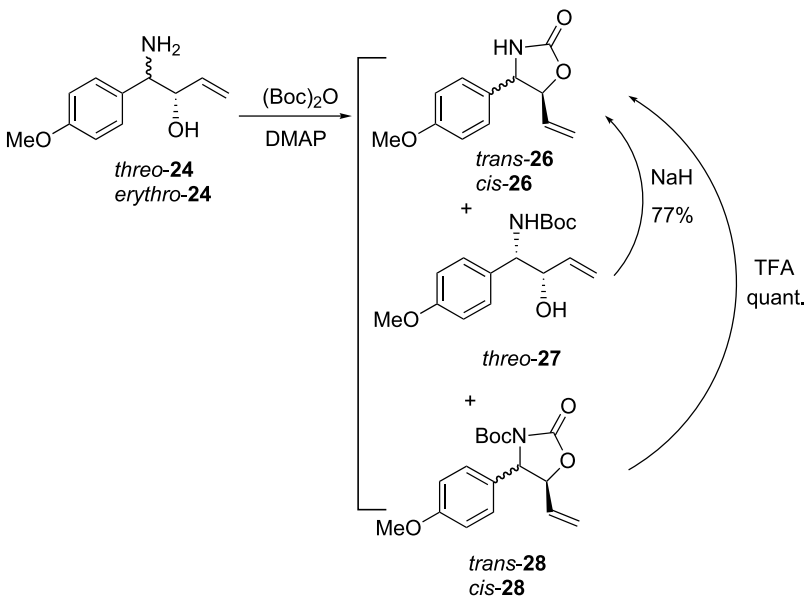
We next investigated conversion of amino alcohols *threo*-**24** and *erythro*-**24** into *trans*- and *cis*-oxazolidinones **26** (Scheme 15, Table 13). The treatment of *threo*-**24** with $(Boc)_2O$ (1.1 equiv.) in the presence of DMAP gave a mixture of *threo*-*N*-Boc-amino alcohol **27**, *trans*-*N*-Boc-oxazolidinone **28**, and *trans*-*N*-nor-oxazolidinone **26** (entry 1). Acylation of *threo*-**24** with 2.2 equiv. of $(Boc)_2O$ gave *trans*-*N*-Boc-oxazolidinone **28** as the sole product which was readily converted into *trans*-*N*-nor-**26** (entry 2). The *trans*-oxazolidinone **26** was also obtained from *threo*-**27** by the treatment with NaH. Similarly, the *erythro*-amino alcohol **24** was converted into *cis*-oxazolidinone **26** via *cis*-*N*-Boc-**28** (entry 3).

The *cis*/*trans*-stereostructures of oxazolidinones **26** were determined by ^1H NMR spectroscopy (Fig. 4, Table 14). It is known[19] that the oxazolidinones **29** exhibiting signals for 4-H and 5-H at lower field have *cis*-structure while the oxazolidinones **29** showing those at higher field have *trans*-structure. Signals due to 4-H and 5-H of *cis*-isomer **26** (4-H: δ 4.94; 5-H: δ 5.24) appeared in down-field compared with those of *trans*-isomer **26** (4-H: δ 4.55; 5-H: δ 4.68).

Figure 4. Structures of *trans*-**26**, **29** and *cis*-**26**, **29**.

We next investigated a simple method for conversion of rearranged product *Z*-**18p** into *cis*-oxazolidinone **28** (Scheme 16, Table 15). The treatment of *Z*-**18p** with $LiAlH_4$ (3 equiv.) gave a crude amino alcohol which was acylated with $(Boc)_2O$ to give a 2:1 mixture of *cis*- and *trans*-oxazolidinones **28** (entry 1). The use of either SMEAH or B_2H_6-pyridine brought about formation of *trans*-oxazolidinone **28** as a major product (entries 2 and 3). Attempted reduction of oxime ether **30** having the TBDMSO group, prepared by the treatment of *Z*-**18p** with TBDMSOTf, was unsuccessful (entry 4).

We next converted *cis*- and *trans*-oxazolidinones **26** into (±)-cytoxazone **9** and (±)-4-*epi*-cytoxazone **31**



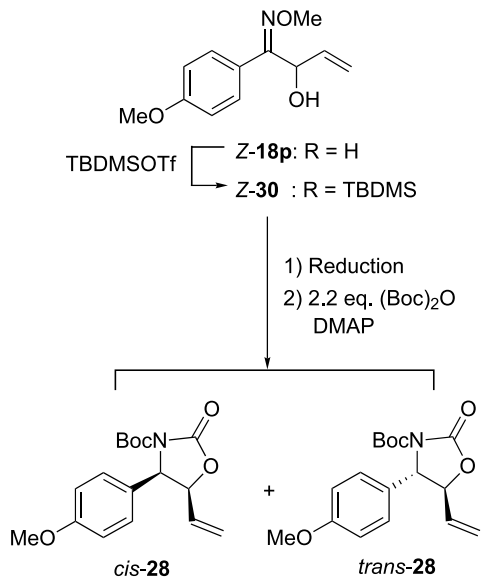
Scheme 15.

Table 13. Acylation of amino alcohols **24** with $(Boc)_2O$

Entry	Substrate	$(Boc)_2O$ (equiv.)	Yield (%)			
			trans-**26**	*threo*-**27**	*trans*-**28**	*cis*-**28**
1	*threo*-**24**	1.1	30	9	30	—
2	*threo*-**24**	2.2	—	—	82	—
3	*erythro*-**24**	2.2	—	—	—	44

(Scheme 17). The oxidation of *cis*-**26** with ozone followed by treatment with $NaBH_4$ gave (±)-cytoxazone **9**. Similarly, (±)-4-*epi*-cytoxazone **31** was obtained from *trans*-**26**.

Finally, we examined optical resolution of both (±)-**9** and (±)-**31** (Scheme 18). Acylation of (±)-**9** with (−)-camphanic chloride gave (4*R*,5*R*(*S*))-**32** and (4*S*,5*S*(*S*))-**32**. After separation of the diastereomers, the hydrolysis of (4*R*,5*R*)-oxazolidinone **32** gave (−)-cytoxazone **9**. Similarly, (+)-cytoxazone **9** was obtained from (4*S*,5*S*(*S*))-**32**. (−)-**9** was identical with natural (−)-cytoxazone **9** upon comparison of the spectral and physical data ($[\alpha]_D^{29}=-73.3$ (*c* 0.79, MeOH; lit.[15,16] $[\alpha]_D^{23}=-75.5$ (*c* 1.0, MeOH)) with those of authentic sample.[15,16] (±)-4-*epi*-cytoxazone **31** was converted into (−)-4-*epi*-cytoxazone **31** (($[\alpha]_D^{29}=-30.1$ (*c* 0.70, MeOH; lit.[16] ($[\alpha]_D^{23}=-30.4$ (*c* 1.0, MeOH)) and (+)-4-*epi*-cytoxazone **31** by the same reaction sequence.



Scheme 16.

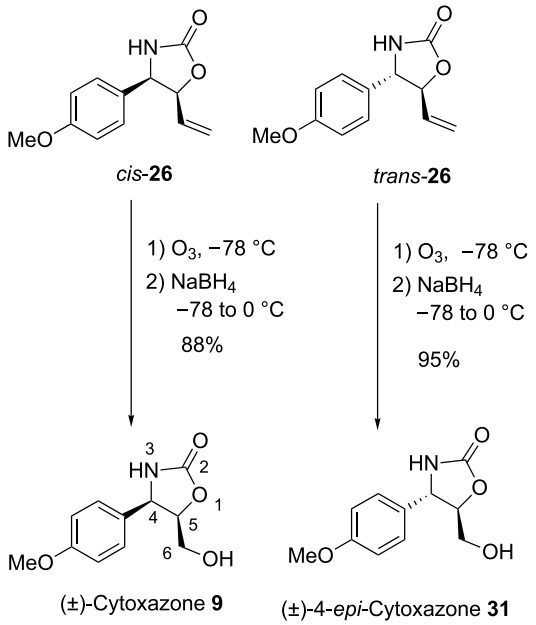
Our procedure would provide a practical synthetic method for cytoxazone and its stereoisomers which would be subjected to biological evaluations, particularly, as potent chemotherapeutic agents in the field of immunotherapy.

Table 14. ^1H NMR data of *trans*-**26**, **29** and *cis*-**26**, **29**

R	*trans*-**26**, **29** δ (ppm)				*cis*-**26**, **29** δ (ppm)			
	Compound	4-H	5-H	$J_{4,5}$	Compound	4-H	5-H	$J_{4,5}$
$PhCH_2OCH_2$	*trans*-**29a**	3.68	4.68	7	*cis*-**29a**	4.02	5.08	8
Me_2CHCH_2	*trans*-**29b**	3.58	4.50	7	*cis*-**29b**	3.94	5.01	7
$PhCH_2$	*trans*-**29c**	3.77	4.64	6	*cis*-**29c**	4.08	5.08	7
p-$MeOC_6H_5$	*trans*-**26**	4.55	4.68	8	*cis*-**26**	4.94	5.24	8

Table 15. Conversion of *Z*-**18p** and *Z*-**30** into *cis*-**28** and *trans*-**28**

Entry	Substrate	Reagent	Solvent	*T* (°C)	Yield (%)	Ratio (*cis*-**28**:*trans*-**28**)
1	*Z*-**18p**	$LiAlH_4$	Et_2O	0→35	81	2.1:1.0
2	*Z*-**18p**	(1) SMEAH	THF	−30		
		(2) $LiAlH_4$	Et_2O	35	49	1.0:2.1
3	*Z*-**18p**	(1) BH_3–py	10% HCl–EtOH	Rt		
		(2) $LiAlH_4$	Et_2O	35	44	1.0:2.3
4	*Z*-**30**	$LiAlH_4$	Et_2O	0	—	—



Scheme 17.

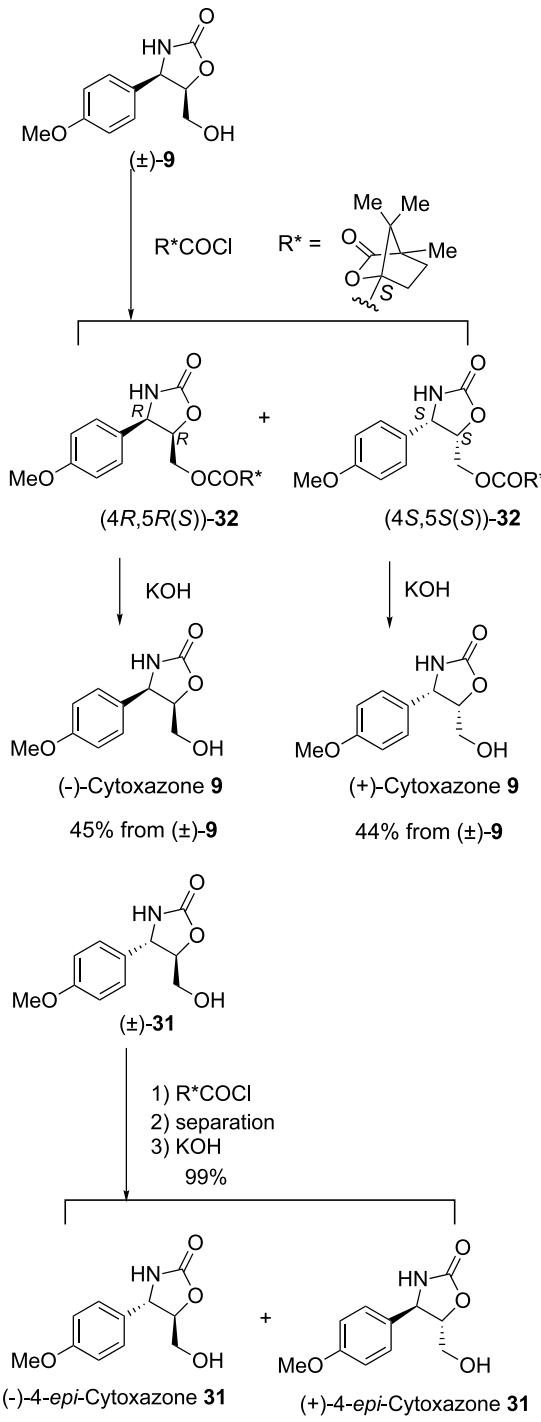
3. Conclusion

We have developed imino 1,2-Wittig rearrangement of the hydroximates. The feasibility of this rearrangement is dependent upon the structure of the substrates. The rearrangement of *Z*-hydroximates proceeded smoothly to give the 2-hydroxyoxime ether in good yield while the corresponding *E*-isomer gave a mixture of *E*- and *Z*-hydroxyoxime ethers. This method was successfully applied to the practical synthesis of cytoxazone.

4. Experimental

4.1. General

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 200, 300, or 500 MHz and at 75 MHz, respectively. IR spectra were recorded using FTIR apparatus. Mass spectra were obtained by EI method. Flash column chromatography (FCC) was preformed using E. Merck Kieselgel 60 (230–400 mesh). Medium-pressure column chromatography (MCC) was performed using Lober Größe B (E. Merck 310-25, Lichroprep Si60). Short column chromatography (SCC) was undertaken on a short glass filter using E. Merck Kieselgel 60 (230–400 mesh) under reduced pressure.



Scheme 18.

4.2. General procedure for preparation of the hydroxamates 12a–j

To a stirred solution of the corresponding acid chlorides **10** (36 mmol) in CH_2Cl_2 (360 mL) was added *N*-methoxyamine hydrochloride **11a** or *N*-benzyloxyamine hydrochloride **11b** (40 mmol) under a nitrogen atmosphere at room temperature. After the solution was stirred at the same temperature for 15 min, pyridine (84 mmol) was added dropwise to the reaction mixture at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was diluted with CH_2Cl_2 and washed with H_2O. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. Purification of the residue by FCC (hexane/AcOEt 1:1) afforded the hydroxamates **12a–j**.

4.2.1. *N*-Methoxybenzamide (12a).[20] A colorless oil; IR ($CHCl_3$) 3252 (NH), 1684 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.86 (3H, s), 7.37–7.53 (3H, m), 7.75 (2H, br d, J=7 Hz); HRMS (EI, *m/z*) calcd for $C_8H_9NO_2$ (M^+) 151.0633, found 151.0634.

4.2.2. *N*-(Phenylmethoxy)benzamide (12b).[21] Colorless crystals: mp 104–106 °C (hexane/$CHCl_3$) (lit.[21] mp 103–104 °C); IR ($CHCl_3$) 3253 (NH), 1684 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.04 (2H, s), 7.34–7.70 (10H, m), 8.53 (1H, br d); HRMS (EI, *m/z*) calcd for $C_{14}H_{13}NO_2$ (M^+) 227.0946, found 227.0952.

4.2.3. *N*-Methoxy-4-methylbenzamide (12c).[9b] Colorless crystals: mp 63–65 °C (hexane/$CHCl_3$) (lit.[9b] mp 70–71 °C); IR ($CHCl_3$) 3223 (NH), 1668 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (3H, s), 3.83 (3H, s), 7.18 and 7.67 (each 2H, br d, J=9 Hz), 9.80 (1H, br s); HRMS (EI, *m/z*) calcd for $C_9H_{11}NO_2$ (M^+) 165.0789, found 165.0777.

4.2.4. (*E*)-*N*-Methoxy-3-phenyl-2-propenamide (12d).[9a] Colorless crystals: mp 93–95 °C (hexane/$CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 3.85 (3H, s), 6.49 (1H, d, J=16 Hz), 7.60–7.28 (5H, m), 7.76 (1H, d, J=16 Hz), 8.65 (1H, br s); HRMS (EI, *m/z*) calcd for $C_{10}H_{11}NO_2$ (M^+) 177.0791, found 177.0766.

4.2.5. *N*-Methoxypropanamide (12e).[22] A colorless oil; IR ($CHCl_3$) 3221 (NH), 1676 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (3H, t, J=7.5 Hz), 2.14 (2H, br s), 3.76 (3H, s), 8.83 (1H, br s); HRMS (EI, *m/z*) calcd for $C_4H_9NO_2$ (M^+) 103.0632, found 103.0623.

4.2.6. *N*-Methoxy-3-phenylpropanamide (12f).[23] A colorless oil; IR ($CHCl_3$) 3241 (NH), 1690 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.38 and 2.96 (each 2H, t, J=7.5 Hz), 3.65 (3H, s), 7.15–7.33 (5H, m), 9.08 (1H, br s); HRMS (EI, *m/z*) calcd for $C_{10}H_{13}NO_2$ (M^+) 179.0946, found 179.0946.

4.2.7. *N*,4-Dimethoxybenzamide (12g).[9b,24] Colorless crystals: mp 105–107 °C (hexane/$CHCl_3$) (lit.[9b,24] mp 102–103 °C); IR ($CHCl_3$) 3261 (NH), 1680 (CON) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.86 and 3.88 (each 3H, s), 6.93 (2H, br d, J=8 Hz), 7.71 (2H, br d, J=8 Hz), 8.57 (1H, br s).

4.2.8. *N*,2-Dimethoxybenzamide (12h). A colorless oil; IR ($CHCl_3$) 3348 (NH), 1667 (CON) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.86 and 3.88 (each 3H, s), 6.97 (1H, br d, J=7.5 Hz), 7.10 (1H, br t, J=7.5 Hz), 7.48 (1H, td, J=7.5, 2 Hz), 8.20 (1H, dd, J=7.5, 2 Hz); HRMS (EI, *m/z*) calcd for $C_9H_{11}NO_3$ (M^+) 181.0739, found 181.0747.

4.2.9. Methyl 4-[(methoxyamino)carbonyl]benzoate (12i).[9b] Colorless crystals: mp 144–146 °C (hexane/$CHCl_3$) (lit.[9b] mp 142–144 °C); IR ($CHCl_3$) 3400 (NH), 1722 (COO), 1690 (CON) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.85 and 3.93 (each 3H, s), 7.84 (2H, br d, J=8 Hz), 8.05 (2H, br d, J=8 Hz), 8.78 (1H, br s).

4.2.10. *N*-Methoxy-4-nitrobenzamide (12j).[25] Colorless crystals: mp 176–177 °C (hexane/$CHCl_3$) (lit.[25] mp 180–181 °C); IR ($CHCl_3$) 3420 (NH), 1670 (CON) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.92 (3H, s), 7.82 (2H, br d, J=8 Hz), 8.30 (2H, br d, J=8 Hz), 8.83 (1H, br s).

4.3. General procedure for preparation of hydroximates 13 route A (Table 1)

To a solution of **12** (10 mmol) and K_2CO_3 (10 mmol) in acetone (50 mL) was added dropwise a solution of alkyl halides **15a–g** (10 mmol) in acetone (5 mL) under a nitrogen atmosphere at room temperature. After being stirred at room temperature for 24 h, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 7:1) afforded the hydroximates *Z*-**13a–m** and the amides **17a–m**.

4.3.1. Phenylmethyl (*Z*)-*N*-methoxybenzimidate (13a). A colorless oil; IR ($CHCl_3$) 1609 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.94 (3H, s), 5.28 (2H, s), 7.29–7.49 (8H, m), 7.66 (2H, br d, J=10 Hz); HRMS (EI, *m/z*) calcd for $C_{15}H_{15}NO_2$ (M^+) 241.1102, found 241.1130.

4.3.2. *N*-Methoxy-*N*-(phenylmethyl)benzamide (17a). A colorless oil; IR ($CHCl_3$) 1635 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.47 (3H, s), 4.92 (2H, s), 7.25–7.50 (8H, m), 7.70 (2H, br d, J=7 Hz); HRMS (EI, *m/z*) calcd for $C_{15}H_{15}NO_2$ (M^+) 241.1102, found 241.1103.

4.3.3. 2-Propenyl (*Z*)-*N*-methoxybenzimidate (13b). A colorless oil; IR ($CHCl_3$) 1604 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.91 (3H, s), 4.71 (2H, dt, J=6, 1.5 Hz), 5.24 (1H, dq, J=10.5, 1.5 Hz), 5.35 (1H, dq, J=17, 1.5 Hz), 6.00 (1H, ddt, J=17, 10.5, 6 Hz), 7.30–7.45 (3H, m), 7.60–7.73 (2H, m); HRMS (EI, *m/z*) calcd for $C_{11}H_{13}NO_2$ (M^+) 191.0946, found 191.0953.

4.3.4. *N*-Methoxy-*N*-(2-propenyl)benzamide (17b). A colorless oil; IR ($CHCl_3$) 1635 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.34 (3H, s), 4.11 (2H, dt, J=6 Hz), 5.04 (1H, dq, J=10, 1.5 Hz), 5.11 (1H, dq, J=17, 1.5 Hz), 5.74 (1H, ddt, J=17, 10, 6 Hz), 7.13–7.25 (3H, m), 7.44 (2H, br d, J=6 Hz).; HRMS (EI, *m/z*) calcd for $C_{11}H_{13}NO_2$ (M^+) 191.0946, found 191.0957.

4.3.5. Methyl (*Z*)-2-[1-(methoxyimino)-1-phenylmethoxy]acetate (13c). A colorless oil; IR ($CHCl_3$) 1761 (COO), 1613 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 and 3.88 (each 3H, s), 4.92 (2H, s), 7.32–7.43 (3H, m), 7.76–7.84 (2H, m); HRMS (EI, *m/z*) calcd for $C_{11}H_{13}NO_4$ (M^+) 223.0843, found 223.0829.

4.3.6. Methyl [(benzoyl)(methoxy)amino]acetate (17c). A colorless oil; IR ($CHCl_3$) 1753 (COO), 1648 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.60 and 3.80 (each 3H, s), 4.49 (2H, s), 7.38–7.51 (3H, m), 7.74 (2H, br d, *J*=8 Hz).

4.3.7. Ethyl (*Z*)-*N*-methoxybenzimidate (13d). A colorless oil; IR ($CHCl_3$) 1611 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (3H, t, *J*=7 Hz), 3.91 (3H, s), 4.25 (2H, q, *J*=7 Hz), 7.30–7.70 (5H, m); HRMS (EI, *m/z*) calcd for $C_{10}H_{13}NO_2$ (M^+) 179.0946, found 179.0955.

4.3.8. *N*-Ethyl-*N*-methoxybenzamide (17d). A colorless oil; IR ($CHCl_3$) 1633 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (3H, t, *J*=7 Hz), 3.57 (3H, s), 3.76 (2H, q, *J*=7 Hz), 7.35–7.48 (3H, m), 7.64 (2H, br d, *J*=10 Hz); HRMS (EI, *m/z*) calcd for $C_{10}H_{13}NO_2$ (M^+) 179.0946, found 179.0956.

4.3.9. (4-Methoxyphenyl)methyl (*Z*)-*N*-methoxybenzimidate (13e). A colorless oil; IR ($CHCl_3$) 1609 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.78 and 3.93 (each 3H, s), 5.21 (2H, s), 6.87 (2H, br d, *J*=9 Hz), 7.24–7.67 (7H, m).

4.3.10. *N*-Methoxy-*N*-[(4-methoxyphenyl)methyl]benzamide (17e). A colorless oil; IR ($CHCl_3$) 1634 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.45 and 3.80 (each 3H, s), 4.85 (2H, s), 6.89 (2H, br d, *J*=9 Hz), 7.28–7.48 (5H, m), 7.68 (2H, br d, *J*=9 Hz); HRMS (EI, *m/z*) calcd for $C_{16}H_{17}NO_3$+H (M^++1) 272.1286, found 272.1275.

4.3.11. (4-Nitrophenyl)methyl (*Z*)-*N*-methoxybenzimidate (13f). Colorless crystals: mp 67–68 °C (hexane/$CHCl_3$); IR ($CHCl_3$) 1609 (C=N), 1525, 1349 (NO_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.93 (3H, s), 5.39 (2H, s), 7.32–7.70 (7H, m), 8.24 (2H, br d, *J*=9 Hz); HRMS (EI, *m/z*) calcd for $C_{15}H_{14}N_2O_4$ (M^+) 286.0953, found 286.0964. Anal. calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79, found: C, 63.07; H, 4.64; S, 9.69.

4.3.12. 1-Phenylethyl (*Z*)-*N*-methoxybenzimidate (13g). A colorless oil; IR ($CHCl_3$) 1611 (C=N) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.63 (3H, d, *J*=6.5 Hz), 3.87 (3H, s), 5.70 (1H, q, *J*=6.5 Hz), 7.20–7.40 (8H, m), 7.59 (2H, br d, *J*=10 Hz); HRMS (EI, *m/z*) calcd for $C_{16}H_{17}NO_2$ (M^+) 255.1258, found 255.1237.

4.3.13. *N*-Methoxy-*N*-(1-phenylethyl)benzamide (17g). A colorless oil; IR ($CHCl_3$) 1634 (CON) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.70 (3H, d, *J*=7 Hz), 3.32 (3H, s, OMe), 5.65 (1H, q, *J*=7 Hz), 7.28–7.67 (10H, m); HRMS (EI, *m/z*) calcd for $C_{16}H_{17}NO_2$ (M^+) 255.1258, found 255.1266.

4.3.14. Phenylmethyl (*Z*)-*N*-(phenylmethoxy)benzimidate (13h). A colorless oil; IR ($CHCl_3$) 1611 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.15 and 5.30 (each 2H, s), 7.26–7.45 (13H, m), 7.66 (2H, br d, *J*=8 Hz); HRMS (EI, *m/z*) calcd for $C_{21}H_{19}NO_2$ (M^+) 317.1415, found 317.1416.

4.3.15. *N*-Phenylmethoxy-*N*-(phenylmethyl)benzamide[9c] (17h). Colorless crystals: mp 67–68 °C (hexane/$CHCl_3$) (lit.[9c] mp 66–67 °C); IR ($CHCl_3$) 1636 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.53 and 4.91 (each 2H, s), 6.90–7.70 (15H, m); HRMS (EI, *m/z*) calcd for $C_{21}H_{19}NO_2$ (M^+) 317.1415, found 317.1426.

4.3.16. Phenylmethyl (*Z*)-*N*-methoxy-4-methylbenzimidate (13i). A colorless oil; IR ($CHCl_3$) 1612 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.35 (3H, s), 3.92 (3H, s), 5.25 (2H, s), 7.10–7.56 (9H, m); HRMS (EI, *m/z*) calcd for $C_{16}H_{17}NO_2$ (M^+) 255.1259, found 255.1251.

4.3.17. *N*-Methoxy-4-methyl-*N*-(phenylmethyl)benzamide (17i). A colorless oil; IR ($CHCl_3$) 1634 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (3H, s), 3.47 (3H, s), 4.91 (2H, s), 7.16–7.65 (9H, m); HRMS (EI, *m/z*) calcd for $C_{16}H_{17}NO_2$ (M^+) 255.1259, found 255.1275.

4.3.18. Phenylmethyl (*Z*,*E*)-*N*-methoxy-3-phenyl-2-propenimidate (13j). A colorless oil; IR ($CHCl_3$) 1636, 1580 (C=N, C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.91 (3H, s), 5.29 (2H, s), 6.48 (1H, d, *J*=16 Hz), 7.05 (1H, d, *J*=16 Hz), 7.22–7.46 (10H, m); HRMS (EI, *m/z*) calcd for $C_{17}H_{17}NO_2$ (M^+) 267.1258, found 267.1286.

4.3.19. (*E*)-*N*-Methoxy-3-phenyl-*N*-phenylmethyl-2-propenamide (17j). A colorless oil; IR ($CHCl_3$) 1651 (CON), 1615 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.71 (3H, s), 4.92 (2H, s), 7.06 (1H, d, *J*=16 Hz), 7.80 (1H, d, *J*=16 Hz), 7.22–7.60 (10H, m); HRMS (EI, *m/z*) calcd for $C_{17}H_{17}NO_2$ (M^+) 267.1258, found 267.1242.

4.3.20. Phenylmethyl (*Z*)-*N*-methoxypropanimidate (13k). A colorless oil; IR ($CHCl_3$) 1638 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (3H, t, *J*=7.5 Hz), 2.23 (2H, q, *J*=7.5 Hz), 3.80 (3H, s), 5.19 (2H, s), 7.23–7.40 (5H, m); HRMS (EI, *m/z*) calcd for $C_{11}H_{15}NO_2$ (M^+) 193.1103, found 193.1113.

4.3.21. *N*-Methoxy-*N*-(phenylmethyl)propanamide (17k). A colorless oil; IR ($CHCl_3$) 1656 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (3H, t, *J*=7.5 Hz), 2.50 (2H, q, *J*=7.5 Hz), 3.61 (3H, s), 4.79 (2H, s), 7.23–7.37 (5H, m); HRMS (EI, *m/z*) calcd for $C_{11}H_{15}NO_2$ (M^+) 193.1103, found 193.1075.

4.3.22. Phenylmethyl (*Z*)-*N*-methoxy-3-phenylpropanimidate (13l). A colorless oil; IR ($CHCl_3$) 1634 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.48 and 2.84 (each 2H, m), 3.80 (3H, s), 5.20 (2H, s), 7.13–7.40 (10H, m); HRMS (EI, *m/z*) calcd for $C_{17}H_{19}NO_2$ (M^+) 269.1415, found 269.1420.

4.3.23. *N*-Methoxy-*N*-(phenylmethyl)-3-phenylpropanamide (17l). A colorless oil; IR ($CHCl_3$) 1653 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.80 and 3.01 (each 2H, m),

3.54 (3H, s), 4.79 (2H, s), 7.15–7.40 (10H, m); HRMS (EI, *m/z*) calcd for $C_{17}H_{19}NO_2$ (M^+) 269.1415, found 269.1420.

4.3.24. 2-Propenyl (*Z*)-*N*-methoxy-3-phenylpropanimidate (13m). A colorless oil; IR ($CHCl_3$) 1634 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.51 (2H, m), 2.89 (2H, m), 3.78 (3H, s), 4.63 (2H, dt, *J*=5.5, 1.5 Hz), 5.25 (1H, dq, *J*=10.5, 1.5 Hz), 5.33 (1H, dq, *J*=17, 1.5 Hz), 5.94 (1H, ddt, *J*=17, 10.5, 5.5 Hz), 7.17–7.32 (5H, m); HRMS (EI, *m/z*) calcd for $C_{13}H_{17}NO_2$ (M^+) 219.1258, found 219.1257.

4.3.25. *N*-Methoxy-*N*-(2-propenyl)-3-phenylpropanamide (17m). A colorless oil; IR ($CHCl_3$) 1638 (CON) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.75 (2H, m), 2.97 (2H, m), 3.61 (3H, s), 4.22 (2H, br d, *J*=6 Hz), 5.19 (1H, dq, *J*=10, 1.5 Hz), 5.23 (1H, dq, *J*=17, 1.5 Hz), 5.82 (1H, ddt, *J*=17, 10, 6 Hz), 7.15–7.32 (5H, m); HRMS (EI, *m/z*) calcd for $C_{13}H_{17}NO_2$ (M^+) 219.1258, found 219.1249.

4.4. Route B

Table 2, entry 1. To a solution of **12a** (0.5 mmol) in benzene (1 mL) was added phosphorus pentachloride (0.75 mmol) by small portion under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 2 h, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure to afford the crude hydroximoyl chloride **14a**. After being characterized by NMR spectra, **14a** was immediately subjected to the following reaction. To a suspension of NaH (60% oil suspension) (100 mg, 2.5 mmol) in THF was added benzyl alcohol **16a** (270 mg, 2.5 mmol) under a nitrogen atmosphere at 0 °C. After being stirred at room temperature for 20 min, a solution of the crude hydroximoyl chloride **14a** in THF (5 mL) was added at reflux. The reaction mixture was heated at reflux for a further 2 h, and then cooled at 0 °C, diluted with H_2O and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 7:1) afforded **13a** (65 mg, 54% from **12a**).

4.5. Route B

Table 2, entries 2–7. To a solution of **12a–j** (12.8 mmol) in MeCN (100 mL) was added Ph_3P (19.2 mmol) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 10 min, CBr_4 (19.2 mmol) was added to the reaction mixture. After refluxing for 3 h, the resulting solution was concentrated at reduced pressure. Purification of the residue by FCC (hexane→hexane/AcOEt 10:1) afforded the hydroximoyl bromide **14b–f**. After being characterized by NMR spectra, **14b–f** was immediately subjected to the following reaction. To a suspension of NaH (60% oil suspension) (32 mmol) in THF (40 mL) was added a solution of alcohols **16b,c** (48 mmol) in THF (40 mL) under a nitrogen atmosphere at 0 °C. After being stirred at room temperature for 20 min, a solution of the hydroximoyl bromide **14b–f** (16 mmol) in THF (80 mL) was added to reaction mixture at room temperature. After being stirred at the same temperature for 4 h, the reaction mixture was cooled at 0 °C, diluted with H_2O and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC afforded **13n–s**.

4.5.1. (*Z*)-*N*-Methoxybenzenecarboximidoyl bromide (14b).[9b] A colorless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 4.14 (3H, s), 7.40 (3H, m), 7.83 (2H, m).

4.5.2. (*Z*)-*N*,4-Dimethoxybenzenecarboximidoyl bromide (14c).[24] A colorless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 3.83 and 4.10 (each 3H, s), 6.89 (2H, br d, *J*=8 Hz), 7.77 (2H, br d, *J*=8 Hz).

4.5.3. (*Z*)-*N*,2-Dimethoxybenzenecarboximidoyl bromide (14d). A colorless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 3.88 and 4.11 (each 3H, s), 6.94 (1H, br d, *J*=7 Hz), 6.96 (1H, td, *J*=7, 1 Hz), 7.32 (1H, dd, *J*=7, 2 Hz), 7.39 (1H, td, *J*=7, 2 Hz).

4.5.4. Methyl (*Z*)-4-[bromo(methoxyimino)methyl]-benzoate (14e).[24] A colorless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 3.94 and 4.17 (each 3H, s), 7.89 (2H, br d, *J*=8 Hz), 8.05 (2H, br d, *J*=8 Hz).

4.5.5. (*Z*)-*N*-Methoxy-4-nitrobenzenecarboximidoyl bromide (14f).[26] A colorless oil; ^1H NMR (200 MHz, $CDCl_3$) δ 4.20 (3H, s), 7.90 (2H, br d, *J*=8 Hz), 8.25 (2H, br d, *J*=8 Hz).

4.5.6. 3-Phenyl-2-propenyl (*Z*)-*N*-methoxybenzimidate (13n). A colorless oil; IR ($CHCl_3$) 1609 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.95 (3H, s), 4.87 (2H, dd, *J*=6.5, 1.5 Hz), 6.36 (1H, dt, *J*=16, 6.5 Hz), 6.64 (1H, d, *J*=16 Hz), 7.27–7.41 (8H, m), 7.69–7.72 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.4, 72.1, 124.1, 126.6, 127.2, 128.0, 128.3, 128.5, 130.0, 130.9, 133.9, 136.3, 154.3; HRMS (EI, *m/z*) calcd for $C_{17}H_{17}NO_2$ (M^+) 267.1258, found 267.1257.

4.5.7. 2-Propenyl (*Z*)-*N*,4-dimethoxybenzimidate (13p). A colorless oil; IR ($CHCl_3$) 1609 (C=N) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.82 and 3.90 (each 3H, s), 4.70 (2H, dt, *J*=6, 2 Hz), 5.24 (1H, dq, *J*=10, 2 Hz), 5.34 (1H, dq, *J*=17, 2 Hz), 6.00 (1H, ddt, *J*=17, 10, 6 Hz), 6.88 (2H, br d, *J*=8 Hz), 7.63 (2H, br d, *J*=8 Hz); HRMS (EI, *m/z*) calcd for $C_{12}H_{15}NO_3$ (M^+) 221.1051, found 221.1059.

4.5.8. 3-Phenyl-2-propenyl (*Z*)-*N*,4-dimethoxybenzimidate (13o). A colorless oil; IR ($CHCl_3$) 1608 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.83 (3H, s), 3.93 (3H, s), 4.85 (2H, dd, *J*=6.5, 1.5 Hz), 6.36 (1H, dt, *J*=16, 6.5 Hz), 6.64 (1H, d, *J*=16 Hz), 6.89 (2H, br d, *J*=9 Hz), 7.28–7.40 (5H, m), 7.64 (2H, br d, *J*=9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.3, 62.3, 72.1, 113.8, 123.3, 124.3, 126.7, 128.0, 128.6, 128.8, 133.8, 136.3, 161.1; HRMS (EI, *m/z*) calcd for $C_{12}H_{15}NO_3$ (M^+) 221.1051, found 221.1059.

4.5.9. 2-Propenyl (*Z*)-*N*,2-dimethoxybenzimidate (13q). A colorless oil; IR ($CHCl_3$) 1610 (C=N) cm^{-1}; ^1H NMR

(200 MHz, $CDCl_3$) δ 3.86 and 3.90 (each 3H, s), 4.34 (2H, dt, J=5.5, 1.5 Hz), 5.16 (1H, dq, J=10.5, 1.5 Hz), 5.22 (1H, dq, J=17, 1.5 Hz), 5.90 (1H, ddt, J=17, 10.5, 5.5 Hz), 6.92 (1H, br d, J=7 Hz), 6.98 (1H, td, J=7, 1 Hz), 7.33 (1H, dd, J=7, 2 Hz), 7.42 (1H, td, J=7, 2 Hz); HRMS (EI, *m/z*) calcd for $C_{12}H_{15}NO_3$ (M^+) 221.1051, found 221.1027.

4.5.10. Methyl (*Z*)-4-[(methoxyimino)(2-propenyloxy)-methyl]benzoate (13r). A colorless oil; IR ($CHCl_3$) 1718 (COO), 1613 (C=N) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.82 and 3.90 (each 3H, s), 4.70 (2H, dt, J=6, 2 Hz), 5.24 (1H, dq, J=10, 2 Hz), 5.34 (1H, dq, J=17, 2 Hz), 6.00 (1H, ddt, J=17, 10, 6 Hz), 7.78 (2H, br d, J=8 Hz), 8.02 (2H, br d, J=8 Hz); HRMS (EI, *m/z*) calcd for $C_{13}H_{15}NO_4$ (M^+) 249.1000, found 249.1012.

4.5.11. 2-Propenyl (*Z*)-*N*-methoxy-4-nitrobenzimidate (13s). A colorless oil; IR ($CHCl_3$) 1611 (C=N) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.96 (3H, s), 4.86 (2H, dt, J=6, 2 Hz), 5.24 (1H, dq, J=10, 2 Hz), 5.34 (1H, dq, J=17, 2 Hz,), 6.00 (1H, ddt, J=17, 10, 6 Hz), 7.93 (2H, br d, J=8 Hz), 8.21 (2H, br d, J=8 Hz); HRMS (EI, *m/z*) calcd for $C_{11}H_{12}N_2O_4$ (M^+) 236.0796, found 236.0802.

4.5.12. (*Z*)-2-Hydroxy-1,2-diphenylethanone *O*-methyloxime (18a). Table 3, entry 2. A solution of *Z*-hydroximate **13a** (241 mg, 1 mmol) in THF (5 mL) was added with stirring at −23 °C to a LDA solution, prepared from diisopropylamine (0.28 mL, 2 mmol) and *n*-BuLi (1.65 M in hexane)(1.2 mL, 2 mmol) under nitrogen atmosphere. After being stirred at the same temperature for 30 min, the reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 7:1) afforded **18a** (214 mg, 89%) as colorless crystals, mp 76–78 °C (hexane/$CHCl_3$) (lit.[11] 77–77.5 °C). IR ($CHCl_3$) 3532 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.71 (1H, br d, J=9 Hz), 3.98 (3H, s), 6.15 (1H, d, J=9 Hz), 7.25–7.54 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.4, 71.1, 116.0, 127.3, 128.4, 129.4, 131.2, 139.9, 157.0; HRMS (EI, *m/z*) calcd for $C_{15}H_{15}NO_2$ (M^+) 241.1102, found 241.1112.

4.5.13. (*Z*)-1-Phenyl-1-pentanone *O*-methyloxime (19a). A solution of *Z*-hydroximate **13a** (241 mg, 1 mmol) in THF (5 mL) was added with stirring at −23 °C to a solution of *n*-BuLi (1.65 M in hexane)(1.2 mL, 2 mmol) in THF (30 mL) under nitrogen atmosphere. After being stirred at the same temperature for 1 h, the reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 7:1) afforded **19a** (103 mg, 54%) as a colorless oil. ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (3H, t, J=7 Hz), 1.59 (4H, m), 2.74 (2H, t, J=7.5 Hz), 3.97 (3H, s), 7.30–7.66 (5H, m); HRMS (EI, *m/z*) calcd for $C_{12}H_{17}NO$ (M^+) 191.1309, found 191.1294.

4.5.14. (*Z*)-1-Phenyl-2,2-dimethylpropan-1-one *O*-methyloxime (19b). According to the procedure given for **19a**, the treatment of **13a** (241 mg, 1 mmol) with *t*-BuLi (1.46 M in pentane) (1.37 mL, 2 mmol) gave **19b** (44 mg, 23%) as a colorless oil and **18a** (46 mg, 19%). **19b**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (9H, s), 3.89 (3H, s), 7.15–7.35 (5H, m). NOE was observed between methoxy group (δ 3.89) and *t*-butyl group (δ 1.24) in NOESY spectroscopy. HRMS (EI, *m/z*) calcd for $C_{12}H_{17}NO$ (M^+) 191.1309, found 191.1301.

4.6. Wittig rearrangement of *Z*-hydroximates 13b,i–r

According to the procedure given for **18a**, the treatment of *Z*-hydroximates **13b**,**i**–**r** with LDA at the temperature shown in Tables 4 and 5 gave **18b**,**i**–**r**.

4.6.1. (*Z*)-2-Hydroxy-1-phenyl-3-buten-1-one *O*-methyloxime (18b). Colorless crystals: mp 45–46 °C (hexane/$CHCl_3$); IR ($CHCl_3$) 3531 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.38 (1H, br d, J=9 Hz), 3.99 (3H, s), 5.24 (1H, dt, J=10.5, 2 Hz), 5.38 (1H, dt, J=17, 2 Hz), 5.47 (1H, ddt, J=9, 5, 2 Hz), 6.13 (1H, ddd, J=17, 10.5, 5 Hz), 7.30–7.40 (3H, m), 7.53–7.62 (2H, m); HRMS (EI, *m/z*) calcd for $C_{11}H_{13}NO_2$ (M^+) 191.0946, found 191.0951. Anal. calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33, found: C, 69.15; H, 6.81; N, 7.29.

4.6.2. (*Z*)-2-Hydroxy-1-(4-methylphenyl)-2-phenylethanone *O*-methyloxime (18i). A colorless oil; IR ($CHCl_3$) 3526 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.33 (3H, s), 3.77 (1H, br d, J=9.5 Hz), 3.97 (3H, s), 6.12 (1H, d, J=9.5 Hz), 7.13 (2H, br d, J=8 Hz), 7.23–7.45 (7H, m); HRMS (EI, *m/z*) calcd for $C_{16}H_{17}NO_2$ (M^+) 255.1258, found 255.1254.

4.6.3. (*Z*,*E*)-1-Hydroxy-1,4-diphenyl-3-buten-2-one *O*-methyloxime (18j). Colorless crystals: mp 98–100 °C (hexane/$CHCl_3$); IR ($CHCl_3$) 3532 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.63 (1H, br d, J=8 Hz), 3.93 (3H, s), 6.05 (1H, d, J=8 Hz), 6.82 (1H, d, J=16.5 Hz), 7.10 (1H, d, J=16.5 Hz), 7.23–7.46 (10H, m); HRMS (EI, *m/z*) calcd for $C_{17}H_{17}NO_2$ (M^+) 267.1258, found 267.1249. Anal. calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24, found: C, 76.34; H, 6.12; N, 5.28.

4.6.4. (*Z*)-1-Hydroxy-1-phenyl-2-butanone *O*-methyloxime (18k). A colorless oil; IR ($CHCl_3$) 3478 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (3H, t, J=7.5 Hz), 2.20 (1H, dq, J=16, 7.5 Hz), 2.34 (1H, dq, J=16, 7.5 Hz), 3.19 (1H, br d, J=6.5 Hz), 3.87 (3H, s), 5.81 (1H, d, J=6.5 Hz), 7.25–7.42 (5H, m); HRMS (EI, *m/z*) calcd for $C_{11}H_{15}NO_2$ (M^+) 193.1103, found 193.1085.

4.6.5. (*Z*)-1-Hydroxy-1,4-diphenyl-2-butanone *O*-methyloxime (18l). A colorless oil; IR ($CHCl_3$) 3521 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.45 and 2.60 (each 1H, ddd, J=15.5, 10, 6 Hz), 2.80 (2H, m), 2.97 (1H, br d, J=6 Hz), 3.88 (3H, s), 5.90 (1H, d, J=6 Hz), 7.10–7.42 (10H, m); HRMS (EI, *m/z*) calcd for $C_{17}H_{19}NO_2$ (M^+) 269.1415, found 269.1408.

4.6.6. (*Z*)-4-Hydroxy-1-phenyl-5-hexen-3-one *O*-methyloxime (18m). A colorless oil; IR ($CHCl_3$) 3475 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.53 (2H, m), 2.78 (1H, br d,

J=5.5 Hz), 2.86 (2H, t, J=8 Hz), 3.86 (3H, s), 5.20 (2H, m), 5.34 (1H, dt, J=17, 1 Hz), 5.97 (1H, ddd, J=17, 10, 5.5 Hz), 7.15–7.31 (5H, m); HRMS (EI, m/z) calcd for $C_{17}H_{19}NO_2$ (M^+) 269.1415, found 269.1408.

4.6.7. (*Z*,*E*)-2-Hydroxy-1,4-diphenyl-3-buten-1-one *O*-methyloxime (18n). A colorless oil; IR ($CHCl_3$) 1609 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.57 (1H, d, J=9 Hz), 4.02 (3H, s), 5.62 (1H, ddd, J=9, 5.5, 1.5 Hz), 6.46 (1H, dd, J=16, 5.5 Hz), 6.70 (1H, dd, J=16, 1.5 Hz), 7.25–7.40 (8H, m), 7.59–7.64 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.6, 71.0, 126.6, 127.3, 127.4, 127.9, 128.5, 128.5, 129.4, 131.4, 133.5, 136.4, 158.7; HRMS (EI, m/z) calcd for $C_{17}H_{17}NO_2$ (M^+) 221.1051, found 221.1059.

4.6.8. (*Z*,*E*)-2-Hydroxy-1-(4-methoxyphenyl)-4-phenyl-3-buten-1-one (18o). A colorless oil; IR ($CHCl_3$) 3530 (OH), 1608 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.60 (1H, d, J=9 Hz), 3.81 (3H, s), 4.01 (3H, s), 5.59 (1H, ddd, J=9, 6, 1.5 Hz), 6.47 (1H, dd, J=16, 6 Hz), 6.68 (1H, dd, J=16, 1.5 Hz), 6.89 (2H, br d, J=9 Hz), 7.21–7.40 (5H, m), 7.58 (2H, br d, J=9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.3, 62.5, 71.2, 113.9, 125.9, 126.6, 127.5, 127.8, 128.5, 128.7, 131.4, 136.5, 158.3, 160.6; HRMS (EI, m/z) calcd for $C_{18}H_{19}NO_3$ (M^+) 297.1364, found 297.1367.

4.6.9. (*Z*)-2-Hydroxy-1-(4-methoxyphenyl)-3-buten-1-one *O*-methyloxime (18p). Colorless crystals: mp 83–85 °C (hexane/$CHCl_3$); IR ($CHCl_3$) 3516 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.43 (1H, br d, J=9 Hz), 3.81 and 3.98 (each 3H, s), 5.24 (1H, dt, J=10, 2 Hz), 5.37 (1H, dt, J=17, 2 Hz), 5.44 (1H, ddt, J=9, 5, 2 Hz), 6.12 (1H, ddd, J=17, 10, 5 Hz), 6.88 (2H, br d, J=8 Hz), 7.53 (2H, br d, J=8 Hz); HRMS (EI, m/z) calcd for $C_{12}H_{15}NO_3$ (M^+) 221.1051, found 221.1065. Anal. calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33, found: C, 65.07; H, 6.71; N, 6.32.

4.6.10. (*Z*)-2-Hydroxy-1-(2-methoxyphenyl)-3-buten-1-one *O*-methyloxime (18q). A colorless oil; IR ($CHCl_3$) 3516 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.56 (1H, d, J=8.5 Hz), 3.86 and 3.98 (each 3H, s), 5.18 (1H, dt, J=10.5, 2 Hz), 5.34 (1H, dt, J=17, 2 Hz), 5.41 (1H, ddt, J=8.5, 5, 2 Hz), 6.06 (1H, ddd, J=17, 10.5, 5 Hz), 6.96 (2H, br d, J=8 Hz), 7.34 (2H, br d, J=8 Hz); HRMS (EI, m/z) calcd for $C_{12}H_{15}NO_3$ (M^+) 221.1051, found 221.1063.

4.6.11. Methyl (*Z*)-4-[[2-hydroxy-1-(methoxyimino)]-3-butenyl]benzoate (18r). A colorless oil; IR ($CHCl_3$) 3542 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.16 (1H, d, J=8.5 Hz), 3.92 and 4.03 (each 3H, s), 5.28 (1H, dt, J=10, 2 Hz), 5.41 (1H, dt, J=17, 2 Hz), 5.53 (1H, ddt, J=8.5, 6, 2 Hz), 6.13 (1H, ddd, J=17, 10, 6 Hz), 7.78 (2H, br d, J=8 Hz), 8.03 (2H, br d, J=8 Hz); HRMS (EI, m/z) calcd for $C_{13}H_{15}NO_4$ (M^+) 249.1000, found 249.0989.

4.7. General procedure for preparation of *E*-hydroximates (13a,b,j,l)

According to the literature procedure,[9c] to a solution of **12a**,**d**,**f** (10 mmol) in 95% EtOH (7.1 mL) and 29% NH_3 (0.65 mL) was added a solution of $AgNO_3$ (10 mmol) in H_2O (2.5 mL) under a nitrogen atmosphere at room temperature. The precipitated silver salt was separated from the solution by filtration, washed with acetone, and dried. To a suspension of the silver salt in Et_2O (3 mL) was added a solution of benzyl bromide or allyl bromide (6.0 mmol) in Et_2O (0.3 mL) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 24 h, the reaction mixture was filtered to remove AgBr. The filtrate was concentrated at reduced pressure and the residue was purified by MCC (hexane/AcOEt 3:1) to afford *E*-hydroximates **13a**,**b**,**j**,**l**, *Z*-hydroximates **13a**,**b**,**j**, and amides **17a**,**b**,**j** in the yields as shown in Table 6.

4.7.1. Phenylmethyl (*E*)-*N*-methoxybenzimidate (13a). A colorless oil; IR ($CHCl_3$) 1623 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.83 (3H, s), 5.18 (2H, s), 7.28–7.83 (10H, m); HRMS (EI, m/z) calcd for $C_{15}H_{15}NO_2$ (M^+) 241.1102, found 241.1077.

4.7.2. 2-Propenyl (*E*)-*N*-methoxybenzimidate (13b). A colorless oil; IR ($CHCl_3$) 1622 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.80 (3H, s), 4.66 (2H, dt, J=5.5, 1.5 Hz), 5.26 (1H, dq, J=10.5, 1.5 Hz), 5.40 (1H, dq, J=17, 1.5 Hz), 6.08 (1H, ddt, J=17, 10.5, 5.5 Hz), 7.35–7.80 (5H, m); HRMS (EI, m/z) calcd for $C_{11}H_{13}NO_2$ (M^+) 191.0946, found 191.0953.

4.7.3. Phenylmethyl (*E*,*E*)-*N*-methoxy-3-phenyl-2-propenimidate (13j). A colorless oil; IR ($CHCl_3$) 1637 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.86 (3H, s), 5.14 (2H, s), 7.12 (1H, d, J=16 Hz), 7.27 (1H, d, J=16 Hz), 7.26–7.53 (10H, m); HRMS (EI, m/z) calcd for $C_{17}H_{17}NO_2$ (M^+) 267.1258, found 267.1273.

4.7.4. Phenylmethyl (*E*)-*N*-methoxy-3-phenylpropanimidate (13l). A colorless oil; IR ($CHCl_3$) 1635 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.73 and 2.88 (each 2H, m), 3.71 (3H, s), 4.96 (2H, s), 7.15–7.39 (10H, m); HRMS (EI, m/z) calcd for $C_{17}H_{19}NO_2$ (M^+) 269.1415, found 269.1405.

4.8. Wittig rearrangement of *E*-hydroximates 13a,b,j,l

According to the procedure given for *Z*-**18a**, the treatment of *E*-hydroximates **13a**,**b**,**j**,**l** with LDA gave *E*-**18a**,**b**,**j** and *Z*-**18a**,**b**,**j** as shown in Table 8.

4.8.1. (*E*)-2-hydroxy-1,2-diphenylethanone *O*-methyloxime (18a). Colorless crystals: mp 66–67 °C (hexane/$CHCl_3$) (lit.[11] 66–67 °C); IR ($CHCl_3$) 3474 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.94 (3H, s), 3.97 (1H, d, J=5.5 Hz), 5.55 (1H, d, J=5.5 Hz), 7.08–7.28 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.5, 75.3, 127.0, 127.9, 128.0, 128.3, 129.0, 131.2, 139.9, 157.0; HRMS (EI, m/z) calcd for $C_{15}H_{15}NO_2$ (M^+) 241.1102, found 241.1106.

4.8.2. (*E*)-2-hydroxy-1-phenyl-3-butenone *O*-methyloxime (18b). A colorless oil; IR ($CHCl_3$) 3482 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.37 (1H, d, J=5.5 Hz), 3.90 (3H, s), 5.04 (1H, m), 5.14 (1H, dt, J=10, 1.5 Hz), 5.30 (1H, dt, J=17, 1.5 Hz), 5.78 (1H, ddd, J=17, 10, 6 Hz), 7.25–7.58 (5H, m); HRMS (EI, m/z) calcd for $C_{11}H_{13}NO_2$ (M^+) 191.0946, found 191.0951.

4.8.3. (*E*,*E*)-1-hydroxy-1,4-diphenyl-3-buten-2-one *O*-methyloxime (18j). A colorless oil; IR ($CHCl_3$) 3476 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.83 (1H, br s), 4.06 (3H, s), 5.63 (1H, br s), 6.90 (1H, d, J=17 Hz), 7.11 (1H, d, J=17 Hz), 7.25–7.48 (10H, m); HRMS (EI, *m*/*z*) calcd for $C_{17}H_{17}NO_2$ (M^+) 267.1258, found 267.1268. Anal. calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24, found: C, 76.20; H, 6.26; N, 5.36.

4.9. Wittig rearrangement of a mixture of *Z*-hydroximates 13i and 13b

According to the procedure given for *Z*-**18a**, the treatment of a mixture of *Z*-hydroximates **13i** and **13b** with LDA gave a mixture of *Z*-**18i** and *Z*-**18b**.

4.9.1. Conversion of *Z*-2-hydroxyoxime ether 18a into amino alcohols 20. Table 10, entry 1. To a solution of *Z*-**18a** (48 mg, 0.2 mmol) in THF (5 mL) was added $LiAlH_4$ (304 mg, 8 mmol) with stirring under a nitrogen atmosphere at 0 °C. After being stirred at the same reaction for 4 h, usual work-up followed by purification of the crude methoxyamino alcohol by MCC (hexane/AcOEt 1:1) afforded (*R* *,*R* *)-(±)-β-(methoxy)amino-α-phenylbenzeneethanol (**20**) (7 mg, 13%) and (*R* *,*S* *)-(±)-β-(methoxy)amino-α-phenylbenzeneethanol (**20**) (3 mg, 5%).

threo-**20** and *erythro*-**20** were immediately subjected to the following reduction.

threo-**20** A colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 3.27 and 6.32 (each 1H, br s), 3.49 (3H, s), 4.13 and 4.84 (each 1H, d, J=8.5 Hz), 7.15–7.32 (10H, m).

erythro-**20**. A colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 2.67 (1H, d, J=3 Hz), 3.51 (3H, s), 4.21 (1H, d, J=5 Hz), 5.07 (1H, dd, J=5, 3 Hz), 5.84 (1H, br s), 7.12–7.30 (10H, m).

Table 10, entry 2. To a solution of *Z*-**18a** (48 mg, 0.2 mmol) in THF (5 mL) was added $LiAlH_4$ (304 mg, 8 mmol) with stirring under a nitrogen atmosphere at 0 °C. After being heated at reflux for 6 h, usual work-up followed by purification of the crude amino alcohol by SCC (AcOEt/MeOH 10:1) afforded of (*R* *,*R* *)-(±)-β-amino-α-phenylbenzeneethanol (**21**) (23 mg, 53%) as colorless crystals, mp 127–129 °C (EtOH) (lit.[13a] mp 129–131 °C) and (*R* *,*S* *)-(±)-β-amino-α-phenylbenzeneethanol (**21**) (7 mg, 17%) as colorless crystals, mp 164–165 °C (EtOH) (lit.[13a] mp 166.5–168 °C). The spectral data of *threo*-**21** and *erythro*-**21** are identical with those reported.[14a]

threo-**21**. ^1H NMR (300 MHz, $CDCl_3$) δ 3.99 (1H, d, J=6.5 Hz), 4.66 (1H, d, J=6.5 Hz), 7.10–7.40 (10H, m). *erythro*-**21**. ^1H NMR (300 MHz, $CDCl_3$) δ 4.18 (1H, d, J=6 Hz), 4.76 (1H, d, J=6 Hz), 7.10–7.40 (10H, m).

Table 10, entry 3. To a solution of *Z*-**18a** (48 mg, 0.2 mmol) in MeOH (1 mL) was added $NaBH_3CN$ (10 mg, 0.15 mmol) and methanolic solution of 2 M HCl with stirring at 0 °C. The pH of reaction mixture was maintained at approximately pH 3 at 0 °C for 2 h. After being heated at reflux for 5 h, the reaction mixture was cooled to 0 °C, made pH 9 by addition of 2 M aqueous KOH, and extracted with Et_2O. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by SCC (MeOH/AcOEt 1:10) afforded *threo*-**21** (18 mg, 42%) and *erythro*-**21** (8 mg, 19%).

Table 10, entry 4. A solution of $ZrCl_4$ (61 mg, 0.26 mmol) and $NaBH_4$ (40 mg, 1.05 mmol) in THF (1 mL) was stirred under a nitrogen atmosphere at room temperature for 20 h. A solution of *Z*-**18a** (48 mg, 0.2 mmol) in THF (2 mL) was added to the reaction mixture. After being stirred at room temperature for 2 days, the reaction mixture was made pH 9 by addition of 29% NH_3 and extracted with AcOEt. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by SCC (MeOH/AcOEt 1:10) afforded *threo*-**21** (9 mg, 21%) and *erythro*-**21** (17 mg, 41%).

Table 10, entry 6. To a solution of *Z*-**18a** (48 mg, 0.2 mmol) in benzene (2 mL) was added SMEAH (70% in toluene) (404 mg, 2 mmol) under nitrogen atmosphere at room temperature. After being heated at reflux for 3 h, the reaction mixture was cooled to room temperature. To the reaction mixture was added 20% H_2SO_4 and the solution was filtered to remove the precipitate. The filtrate was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by SCC (MeOH/AcOEt 1:10) afforded *threo*-**21** (26 mg, 61%) and *erythro*-**21** (6 mg, 13%).

4.9.2. Demethoxylation of *threo*-20 and *erythro*-20. The reduction of *threo*-**20** and *erythro*-**20** (48.5 mg each, 0.2 mmol) with $LiAlH_4$ (304 mg, 8 mmol) under the conditions shown in Table 10, entry 2 gave *threo*-**21** and *erythro*-**21** (43 mg each, quant.), respectively.

4.9.3. Conversion of *E*-2-hydroxyoxime ether 18a into amino alcohols 21. Table 10, entry 7. According to the procedure given for *threo*-**21** and *erythro*-**21** in Table 10, entry 2, the reduction of *E*-**18a** (48 mg, 0.2 mmol) with $LiAlH_4$ (304 mg, 8 mmol) gave *threo*-**21** (10 mg, 23%) and *erythro*-**21** (18 mg, 42%).

4.9.4. (*Z*)-2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1,2-diphenylethanone *O*-methyloxime (22). To a solution of *Z*-**18a** (482 mg, 2 mmol) in CH_2Cl_2 (10 mL) was added 2,6-lutidine (0.47 mL, 4 mmol) and then added dropwise a solution of TBDMSOTf (0.69 mL, 3 mmol) in CH_2Cl_2 (1 mL). After being stirred at room temperature for 1 h, the reaction mixture was diluted with H_2O and extracted with AcOEt. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 1:1) afforded *Z*-**22** (710 mg, quant.) as colorless crystals, mp 81–81 °C (hexane/$CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ −0.14 and 0.00 (each 3H, s), 0.72 (9H, s), 3.97 (3H, s), 6.58 (1H, s), 7.03–7.45 (10H, m); HRMS (EI, *m*/*z*) calcd for $C_{21}H_{31}NO_2Si$ (M^+) 355.1966, found 355.1944. Anal. calcd for $C_{21}H_{31}NO_2Si$: C, 70.94; H, 8.22; N, 3.94, found: C, 70.79; H, 8.41; S, 3.91.

4.9.5. (*E*)-2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1,2-diphenylethanone *O*-methyloxime (22). According to the

procedure given for *Z*-**22**, the silylation of *E*-**18a** (482 mg, 2 mmol) with TBDMSOTf (0.69 mL, 3 mmol) gave *E*-**22** (710 mg, quant.) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 and 0.14 (each 3H, s), 0.91 (9H, s), 3.87 (3H, s), 5.67 (1H, s), 7.00–7.32 (10H, m); HRMS (EI, *m*/*z*) calcd for $C_{21}H_{31}NO_2Si$ (M^+) 355.1966, found 355.1962.

4.9.6. Reduction of *Z*-22 with $LiAlH_4$. Table 10, entry 9. To a solution of *Z*-**22** (71 mg, 0.2 mmol) in THF (5 mL) was added $LiAlH_4$ (304 mg, 8 mmol) with stirring under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 7 h, usual work-up afforded the crude amine. To a solution of crude amine in MeOH (5 mL) was added *p*-TsOH (3.8 mg, 0.02 mmol). After being stirred at room temperature for 3 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by SCC (MeOH/AcOEt 1:10) afforded *threo*-**21** (2 mg, 4%) and *erythro*-**21** (40 mg, 94%) which were identical with the respective sample prepared by reduction of *Z*-**18a** with $LiAlH_4$ shown in Table 10, entry 2.

4.9.7. Reduction of *E*-22 with $LiAlH_4$. Table 10, entry 10. To a solution of *E*-**22** (71 mg, 0.2 mmol) in THF (5 mL) was added $LiAlH_4$ (304 mg, 8 mmol) with stirring under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 7 h, usual work-up afforded the crude amine. To a solution of crude amine in MeOH (5 mL) was added *p*-TsOH (3.8 mg, 0.02 mmol). After being stirred at room temperature for 3 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by SCC (MeOH/AcOEt 1:10) afforded *threo*-**21** (2 mg, 3%) and *erythro*-**21** (13 mg, 30%).

4.9.8. Reduction of *Z*-2-hydroxyoxime ether 18p. Table 11, entry 1. To a solution of *Z*-**18p** (100 mg, 0.45 mmol) in THF (10 mL) was added SMEAH (65% in toluene) (0.67 mL, 2 mmol) under a nitrogen atmosphere at −30 °C. After being stirred at the same temperature for 1.5 h, the reaction mixture was diluted with 10% aqueous NaOH and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 2:1) afforded (*R* ∗ ,*S* ∗)-(±)-α-ethenyl-4-methoxy-β-methoxy-aminobenzeneethanol (**23**) (111 mg, 25%) as a colorless oil and (*R* ∗ ,*R* ∗)-(±)-α-ethenyl-4-methoxy-β-methoxyaminobenzeneethanol (**23**) (229 mg, 52%) as a colorless oil. *erythro*-**23** and *threo*-**23** were immediately subjected to the following reduction.

threo-**23**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (1H, br s), 3.55 and 3.80 (each 3H, s), 4.06 (1H, d, *J*=7 Hz), 4.45–4.52 (1H, m), 5.16 (1H, dt, *J*=10, 2 Hz), 5.27 (1H, dt, *J*=17, 2 Hz), 5.71 (1H, ddd, *J*=17, 10, 6 Hz), 5.88 (1H, br s), 6.87 (2H, br d, *J*=8 Hz), 7.27 (2H, br d, *J*=8 Hz).

erythro-**23**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.94 (1H, br s), 3.46 and 3.79 (each 3H, s), 3.84 (1H, d, *J*=7.5 Hz), 4.36 (1H, br dd, *J*=7.5, 5.5 Hz), 5.05 (1H, dt, *J*=10, 2 Hz), 5.21 (1H, dt, *J*=17, 2 Hz), 5.67 (1H, ddd, *J*=17, 10, 5.5 Hz), 6.13 (1H, br s), 6.85 (2H, br d, *J*=8 Hz), 7.25 (2H, br d, *J*=8 Hz).

Table 11, entry 2. To a solution of *Z*-**18p** (22 mg, 0.1 mmol) in THF (2.5 mL) was added $LiAlH_4$ (11.5 mg, 0.3 mmol) with stirring under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 2 h, usual work-up afforded the crude amino alcohol. Purification of the crude amino alcohol by MCC (hexane/AcOEt 2:1) afforded *erythro*-**23** (7.3 mg, 31%) and *threo*-**23** (8.8 mg, 37%).

Table 11, entry 3. To a solution of *Z*-**18p** (100 mg, 0.45 mmol) in Et_2O (10 mL) was added $LiAlH_4$ (51.8 mg, 1.35 mmol) with stirring at 0 °C. The reaction mixture was stirred at the same temperature for 2 h. Work-up afforded the crude amino alcohols. Purification of the crude amino alcohols by MCC (hexane/AcOEt 2:1) afforded *erythro*-**23** (53 mg, 52%) and *threo*-**23** (25 mg, 25%).

4.9.9. Demethoxylation of *threo*-23 and *erythro*-23. Table 12, entry 1. To a solution of *threo*-**23** (117 mg, 0.5 mmol) in THF (10 mL) was added SMEAH (65% in toluene) (1.38 mL, 2.2 mmol) under a nitrogen atmosphere at room temperature. After being heated at reflux for 2 h, the reaction mixture was diluted with 10% aqueous NaOH and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by SCC (hexane/AcOEt 5:1→AcOEt/MeOH 5:1) afforded (*R* ∗ ,*R* ∗)-(±)-β-amino-α-ethenyl-4-methoxybenzeneethanol (**24**) (52 mg, 52%) as a colorless oil and 1-(4-methoxyphenylamino)-3-buten-2-ol (**25**) (38 mg, 33%) as a colorless oil.

threo-**24**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24 (3H, br s), 3.73 (1H, d, *J*=6.5 Hz), 3.80 (3H, s), 4.10 (1H, br dd, *J*=6.5, 5 Hz), 5.11 (1H, dt, *J*=10, 2 Hz), 5.25 (1H, dt, *J*=17, 2 Hz), 5.77 (1H, ddd, *J*=17, 10, 5 Hz), 6.86 (2H, br d, *J*=8 Hz), 7.24 (2H, br d, *J*=8 Hz).

25. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.86 (2H, br s), 3.16 (1H, dd, *J*=14, 7 Hz), 3.26 (1H, dd, *J*=14, 4.5 Hz), 3.75 (3H, s), 4.31–4.40 (1H, m), 5.24 (1H, dt, *J*=10, 2 Hz), 5.38 (1H, dt,*J*=17, 2 Hz), 5.92 (1H, ddd, *J*=17, 10, 2 Hz), 6.63 (2H, br d, *J*=8 Hz), 6.78 (2H, br d, *J*=8 Hz); HRMS (EI, *m*/*z*) calcd for $C_{11}H_{15}NO_2$ (M^+) 193.1102, found 193.1098.

Table 12, entry 2. To a solution of *threo*-**23** (117 mg, 0.5 mmol) in Et_2O (10 mL) was added $LiAlH_4$ (38 mg, 5 mmol) with stirring under a nitrogen atmosphere at 0 °C. After being heated at reflux for 2 h, work-up afforded the crude amino alcohols. Purification of the crude amino alcohols by SCC (hexane/AcOEt 5:1→AcOEt/MeOH 5:1) afforded *threo*-**24** (96 mg, quant.).

Table 12, entries 3 and 4. According to the procedure given for reduction of *threo*-**23**, the reduction of *erythro*-**23** with either SMEAH or $LiAlH_4$ afforded (*R* ∗ ,*S* ∗)-(±)-β-aminoα-ethenyl-4-methoxybenzeneethanol (**24**) as a colorless oil and **25** in the yield shown in Table 12, entries 3 and 4.

erythro-**24**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90 (3H, br s), 3.80 (3H,s), 3.96 (1H, br d, *J*=5 Hz), 4.22 (1H, br dd, *J*=6,

5 Hz), 5.21 (1H, dt, *J*=10, 1.5 Hz), 5.31 (1H, dt, *J*=17, 1.5 Hz), 5.71 (1H, ddd, *J*=17, 10, 6 Hz), 6.88 (2H, br d, *J*=8 Hz), 7.26 (2H, br d, *J*=8 Hz).

4.9.10. Acylation of *threo*-24. Table 13, entry 1. To a solution of *threo*-**24** (74 mg, 0.38 mmol) in MeCN (6 mL) was added DMAP (45 mg, 0.38 mmol) and $(Boc)_2O$ (91 mg, 0.42 mmol) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 2 h, the reaction mixture was concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 2:1) afforded *trans*-5-ethenyl-4-(4-methoxyphenyl)-2-oxazolidinone (**26**) (25 mg, 30%), 1,1-dimethylethyl (*R* ∗ ,*R* ∗)-(±)-*N*-[2-hydroxy-*N*-(4-methoxyphenyl)-3-butenyl]carbamate (**27**) (10 mg, 9%), and 1,1-dimethylethyl *trans*-5-ethenyl-4-(4-methoxyphenyl)-2-oxo-3-oxazolidinecarboxylate (**28**) (36 mg, 30%).

trans-**26**. Colorless crystals, mp 150–151 °C (hexane/$CHCl_3$); IR ($CHCl_3$) 3451 (NH), 1759 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.81 (3H, s), 4.55 (1H, d, *J*=8 Hz), 4.68 (1H, ddt, *J*=8, 7, 2 Hz), 5.22 (1H, dt, *J*=16, 2 Hz), 5.33 (1H, dt, *J*=10.5, 2 Hz), 5.96 (1H, ddd, *J*=16, 10.5, 7 Hz), 6.10 (1H, br s), 6.91 (2H, br d, *J*=8 Hz), 7.25 (2H, br d, *J*=8 Hz); HRMS (EI, *m*/*z*) calcd for $C_{12}H_{13}NO_3$ (M^+) 219.0895, found 219.0913. Anal. calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39, found: C, 65.44; H, 5.92; N, 6.33.

threo-**27**. A colorless oil; IR ($CHCl_3$) 1707 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.40 (9H, br s), 2.32 (1H, br s), 3.80 (3H, s), 4.30–4.39 (1H, m), 4.58–4.70 (1H, m), 5.20 (1H, dt, *J*=10, 1.5 Hz), 5.27 (1H, br d, *J*=8 Hz), 5.33 (1H, dt, *J*=17, 1.5 Hz), 5.84 (1H, ddd, *J*=17, 10, 5 Hz), 6.90 (2H, br d, *J*=8 Hz), 7.22 (2H, br d, *J*=8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 55.2, 75.7, 79.7, 113.9, 116.5, 127.9, 137.3, 156.1, 158.9.

trans-**28**. Colorless crystals, mp 126–128 °C (hexane/$CHCl_3$); IR ($CHCl_3$) 1811 (OCONCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.30 (9H, s), 3.82 (3H, s), 4.66 (1H, dt, *J*=5.5, 2 Hz), 4.79 (1H, d, *J*=5.5 Hz), 5.35 (1H, dt, *J*=10, 2 Hz), 5.40 (1H, dt, *J*=17, 2 Hz), 5.95 (1H, ddd, *J*=17, 10, 6 Hz), 6.93 (2H, br d, *J*=8 Hz), 7.24 (2H, br d, *J*=8 Hz); HRMS (EI, *m*/*z*) calcd for $C_{17}H_{21}NO_5$ (M^+) 319.1420, found 319.1409. Anal. calcd for $C_{17}H_{21}NO_5{\cdot}1/10H_2O$: C, 63.58; H, 6.65; N, 4.36, found: C, 63.58; H, 6.63; N, 4.30.

Table 13, entry 2. To a solution of *threo*-**24** (19.3 mg, 0.1 mmol) in MeCN (1.5 mL) were added DMAP (12 mg, 0.1 mmol) and $(Boc)_2O$ (48 mg, 0.22 mmol) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 2 h, the reaction mixture was concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 3:1) afforded *trans*-**28** (26 mg, 82%).

4.9.11. 1,1-Dimethylethyl *cis*-5-ethenyl-4-(4-methoxyphenyl)-2-oxo-3-oxazolidinecarboxylate (36). Table 13, entry 3. According to the procedure given for *trans*-**28** (Table 13, entry 2), the acylation of *erythro*-**24** (15 mg, 0.075 mmol) with $(Boc)_2O$ (33 mg, 0.075 mmol) gave *cis*-**28** (11 mg, 44%) as colorless crystals, mp 130–132 °C (hexane/$CHCl_3$); IR ($CHCl_3$) 1812 (OCONCOO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (9H, s), 3.81 (3H, s), 5.13 (1H, dd, *J*=10, 2 Hz), 5.14–5.29 (4H, m), 6.88 (2H, br d, *J*=8 Hz), 7.07 (2H, br d, *J*=8 Hz); HRMS *m*/*z*: calcd for $C_{17}H_{21}NO_5$ (M^+) 319.1420, found 319.1409. Anal. calcd for $C_{17}H_{21}NO_5{\cdot}1/10H_2O$: C, 63.58; H, 6.65; N, 4.36, found: C, 63.54; H, 6.53; N, 4.34.

4.9.12. Conversion of *threo*-27 into *trans*-26. To a suspension of NaH (60% in oil) (3.3 mg, 0.08 mmol) in THF (1 mL) was added a solution of *threo*-**27** (20 mg, 0.068 mmol) in THF (1 mL) under a nitrogen atmosphere at 0 °C. After being stirred at room temperature for 4 h, the reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 1:1) afforded *trans*-**26** (10 mg, 77%).

4.9.13. Conversion of *trans*-28 into *trans*-26. To a solution of *trans*-**28** (51 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) was added TFA (0.013 mL) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 3 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$, extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 1:1) afforded *trans*-**26** (35 mg, quant.).

4.9.14. *cis*-5-Ethenyl-4-(4-methoxyphenyl)-2-oxazolidinone (26). According to the procedure given for *trans*-**26**, the treatment of *cis*-**28** (51 mg, 0.16 mmol) with TFA (0.02 mL, 0.19 mmol) afforded *cis*-**26** (35 mg, quant.) as colorless crystals, mp 113–114 °C (hexane/$CHCl_3$); IR ($CHCl_3$) 3448 (NH), 1760 (NCOO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.81 (3H, s), 4.94 (1H, d, *J*=8 Hz), 5.13 (1H, dd, *J*=10, 2 Hz), 5.24 (1H, dd, *J*=8, 6.5 Hz), 5.27 (1H, ddd, *J*=17, 10, 6.5 Hz), 5.34 (1H, dd, *J*=17, 2 Hz), 5.45 (1H, br s), 6.90 (2H, br d, *J*=8 Hz), 7.13 (2H, br d, *J*=8 Hz); HRMS (EI, *m*/*z*) calcd for $C_{12}H_{13}NO_3$ (M^+) 219.0895, found 219.0913. Anal. calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39, found: C, 65.44; H, 6.03; N, 6.35.

4.9.15. (*Z*)-2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-(4-methoxyphenyl)-3-buten-1-one *O*-methyloxime (30). According to the procedure given for *Z*-**22**, the silylation of *Z*-**18p** (221 mg, 2 mmol) with TBDMSOTf (0.34 mL, 1.5 mmol) gave *Z*-**30** (384 mg, quant.) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ −0.14 and 0.03 (each 3H, s), 0.77 (9H, s), 3.81 and 3.91 (each 3H, s), 5.21 (1H, dt, *J*=10, 2 Hz), 5.49 (1H, dt, *J*=17, 2 Hz), 5,92 (1H, dt, *J*=3.5, 2 Hz), 6.07 (1H, ddd, *J*=17, 10, 3.5 Hz), 6.92 (2H, br d, *J*=8 Hz), 7.54 (2H, br d, *J*=8 Hz); HRMS (EI, *m*/*z*) calcd for $C_{18}H_{29}NO_3Si$ (M^+) 335.1916, found 335.1932.

4.9.16. *N*-Boc-oxazolidinones *cis*-28 and *trans*-28 from *Z*-18p. Table 15, entry 1. To a suspension of $LiAlH_4$ (764 mg, 20.1 mmol) in Et_2O (30 mL) was added a solution of *Z*-**18p** (1.5 g, 6.7 mmol) in Et_2O (30 mL) with stirring under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 2.5 h, $LiAlH_4$ (2.5 g, 67 mmol) was added to the reaction mixture. After being heated at

reflux for 4 h, usual work-up afforded the crude amino alcohols **24**. To a solution of the crude amino alcohols in MeCN (65 mL) were added DMAP (977 mg, 6.7 mmol) and $(Boc)_2O$ (4.7 g, 20.1 mmol) at room temperature. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated at reduced pressure. Purification of the residue by FCC (hexane/AcOEt 2:1) afforded *cis*-**28** (1.08 g, 55%) and *trans*-**28** (507 mg, 26%).

Table 15, entry 2. To a solution of *Z*-**18p** (100 mg, 0.45 mmol) in THF (10 mL) was added SMEAH (65% in toluene) (0.67 mL, 2 mmol) under a nitrogen atmosphere at −30 °C. After being stirred at the same temperature for 2 h, the reaction mixture was diluted with 10% aqueous NaOH and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure to give the crude methoxyamino alcohols. To a solution of the crude methoxyamino alcohols in Et_2O (10 mL) was added $LiAlH_4$ (171 mg, 4.5 mmol) at 0 °C. After being heated at reflux for 4 h, work-up afforded the crude amino alcohols **24**. To a solution of the crude amino alcohols in MeCN (10 mL) were added DMAP (55 mg, 0.45 mmol) and $(Boc)_2O$ (98 mg, 0.45 mmol) at room temperature. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 2:1) afforded *cis*-**28** (23 mg, 16%) and *trans*-**28** (47 mg, 33%).

Table 15, entry 3. To a solution of *Z*-**18p** (23 mg, 0.1 mmol) in EtOH (3 mL) were added BH_3–pyridine (0.1 mL, 0.33 mmol) and an ethanolic solution of HCl (10%, 0.5 mL) under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 2 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure to give the crude methoxyamino alcohols. To a solution of the crude methoxyamino alcohols in Et_2O (3 mL) was added $LiAlH_4$ (38 mg, 1 mmol) at 0 °C. After being heated at reflux for 4 h, usual work-up afforded the crude amino alcohols **24**. To a solution of the crude amino alcohols in MeCN (2 mL) were added DMAP (24 mg, 0.1 mmol) and $(Boc)_2O$ (48 mg, 0.2 mmol) at room temperature. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 2:1) afforded *cis*-**28** (4.2 mg, 13%) and *trans*-**28** (9.8 mg, 31%).

4.9.17. (±)-Cytoxazone (9). Ozone was bubbled into a solution of *cis*-**26** (147 mg, 0.67 mmol) in CH_2Cl_2 (20 mL) with stirring under a nitrogen atmosphere at −78 °C. After being stirred at the same temperature for 1.5 h, MeOH (10 mL) and $NaBH_4$ (134 mg, 3.35 mmol) were added to the reaction mixture. After being stirred at room temperature for 2 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure to give the crude cytoxazone which was recrystallized from AcOEt to afforded (±)-cytoxazone **9** (131 mg, 88%) as colorless crystals, mp 120–123 °C (lit.[15,16] 122–123 °C (4*R*,5*R*-**9**)), IR (KBr) 3475 and 3250 (OH, NH), 1713 (NCOO) cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 2.97 (2H, m), 3.75 (3H, s), 4.69 (1H, ddd, *J*=8, 7, 4 Hz), 4.80 (1H, t, *J*=7 Hz), 4.90 (1H, d, *J*=7 Hz), 6.93 (2H, br d, *J*=8 Hz), 7.14 (2H, br d, *J*=8 Hz), 8.05 (1H, br s); HRMS (EI, *m*/*z*) calcd for $C_{11}H_{13}NO_4$ (M^+) 223.0844, found 223.0861. The spectral data of synthetic (±)-**9** was identical with those of natural cytoxazone.

4.9.18. (±)-4-*epi*-Cytoxazone (31). According to the procedure given for (±)-**9**, the oxidation of *trans*-**26** (200 mg, 0.91 mmol) with ozone followed by reduction of the resulting ozonide with $NaBH_4$ (182 mg, 4.55 mmol) gave (±)-4-*epi*-cytoxazone **31** (193 mg, 95%) as colorless crystals, mp 161–163 °C (AcOEt) (lit.[16] 161.5–162.5 °C (4*S*,5*R*-**31**)), IR (KBr) 3688 and 3456 (OH, NH), 1760 (NCOO) cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 3.71 (1H, ddd, *J*=12, 6.5, 4.5 Hz), 3.80 (3H, s), 3.83 (1H, ddd, *J*=12, 5.5, 4 Hz), 4.25 (1H, br dt, *J*=6.5, 4.5 Hz), 4.29 (1H, dd, *J*=6.5, 5.5 Hz), 4.78 (1H, d, *J*=6.5 Hz), 6.91 (1H, br s), 6.96 (2H, br d, *J*=8 Hz), 7.33 (2H, br d, *J*=8 Hz); HRMS (EI, *m*/*z*) calcd for $C_{11}H_{13}NO_4$ (M^+) 223.0844, found 223.0842. The spectral data of (±)-**31** was identical with those reported.[16]

4.9.19. Acylation of (±)-9 with (−)-camphanic chloride. To a solution of (±)-**9** (85 mg, 0.38 mmol) in CH_2Cl_2 (4.5 mL) were added Et_3N (45 mg, 0.45 mmol), DMAP (4.6 mg, 0.036 mmol), and (−)-camphanic chloride (87 mg, 0.38 mmol) under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 3 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 2:1) afforded (4*R*,5*R*(*S*))-**32** (67 mg, 44%) as a colorless oil and (4*S*,5*S*(*S*))-**32** (69 mg, 45%) as a colorless oil.

[4-(4-Methoxyphenyl)-2-oxo-oxazolidin-5-yl]methyl [1*S*-[1α(4*R* ∗ ,5*R* ∗),4β]-4,7,7-trimethyl-3-oxo-2-oxabicyclo-[2.2.1]heptane-1-carboxylate ((4*R*,5*R*(*S*))-**32**): IR ($CHCl_3$) 3450 (NH), 1768 (NCOO, COO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ:0.92 and 1.03 and 1.11 (each 3H, s), 1.68 (1H, ddd, *J*=13, 9, 5 Hz), 1.91 (1H, ddd, *J*=12, 11, 5 Hz), 2.05 (1H, ddd, *J*=12, 9, 5 Hz), 2.35 (1H, ddd, *J*=13, 11, 5 Hz), 3.80 (3H, s), 3.88–4.02 (2H, m), 5.01–5.10 (2H, m), 5.38 (1H, br s), 6.93 (2H, br d, *J*=8 Hz), 7.24 (2H, br d, *J*=8 Hz); HRMS (EI, *m*/*z*) calcd for $C_{21}H_{25}NO_7$ (M^+) 403.1629, found 403.1620.

[4-(4-Methoxyphenyl)-2-oxo-oxazolidin-5-yl]methyl [1*S*-[1α(4*S* ∗ ,5*S* ∗),4β]-4,7,7-trimethyl-3-oxo-2-oxabicyclo-[2.2.1]heptane-1-carboxylate ((4*S*,5*S*(*S*))-**32**): IR ($CHCl_3$) 3436 (NH), 1764 (NCOO, COO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ:0.90, 1.03 and 1.10 (each 3H, s), 1.68 (1H, ddd, *J*=13, 8, 4 Hz), 1.91 (1H, ddd, *J*=12, 10, 4 Hz), 2.00 (1H, ddd, *J*=12, 8, 4 Hz), 2.37 (1H, ddd, *J*=13, 10, 4 Hz), 3.80 (3H, s), 3.86 (1H, dd, *J*=11, 3 Hz), 3.98 (1H, dd, *J*=11, 8 Hz), 5.01–5.10 (2H, m), 5.38 (1H, br s), 6.93 (2H, br d, *J*=8 Hz), 7.24 (2H, br d, *J*=8 Hz); HRMS (EI, *m*/*z*) calcd for $C_{21}H_{25}NO_7$ (M^+) 403.1629, found 403.1622.

4.9.20. (−)-Cytoxazone (9). To a solution of (4*R*,5*R*(*S*))-ester **32** (12 mg, 0.03 mmol) in MeOH (0.8 mL) was added 1 M methanolic KOH (0.34 mL) at room temperature. After

being stirred at room temperature for 30 min, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 1:2) afforded (−)-**9** (7 mg, 99%) as colorless crystals, mp 121–123 °C (AcOEt), $[\alpha]_D^{29}=-73.3$ (*c* 0.51, MeOH) (lit.[15,16] −75.7 (*c* 1.0, MeOH).

The spectral and physical data of (−)-**9** are identical with those reported.[15,16]

4.9.21. (+)-Cytoxazone (9). According to the procedure given for (−)-**9**, the hydrolysis of (4*S*,5*S*(*S*))-ester **32** (12 mg, 0.03 mmol) with KOH gave (+)-**9** (7 mg, 99%) as colorless crystals, mp 121–123 °C (AcOEt), $[\alpha]_D^{29}=+75.0$ (*c* 0.51, MeOH).

4.9.22. Acylation of (±)-31 with (−)-camphanic chloride. To a solution of (±)-**31** (81 mg, 0.36 mmol) in CH_2Cl_2 (4 mL) were added Et_3N (43 mg, 0.43 mmol), DMAP (4.4 mg, 0.036 mmol), and (−)-camphanic chloride (82 mg, 0.38 mmol) under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 3 h, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 2:1) afforded (4*S*,5*R*(*S*))-**32** (64 mg, 44%) as a colorless oil and (4*R*,5*S*(*S*))-**32** (65 mg, 45%) as a colorless oil.

[4-(4-Methoxyphenyl)-2-oxo-oxazolidin-5-yl]methyl [1*S*-[1α(4*S* ∗ ,5*R* ∗),4β]-4,7,7-Trimethyl-3-oxo-2-oxabicyclo-[2.2.1]heptane-1-carboxylate ((4*S*,5*R*(*S*))-**32**): IR ($CHCl_3$) 3460 (NH), 1769 (NCOO, COO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ*:0.94, 1.07 and 1.12 (each 3H, s), 1.70 (1H, ddd, *J*=13, 8, 4 Hz), 1.93 (1H, ddd, *J*=11, 10, 4 Hz), 2.06 (1H, ddd, *J*=11, 8, 4 Hz), 2.45 (1H, ddd, *J*=13, 10, 4 Hz), 3.80 (3H, s), 4.40–4.52 (2H, m), 4.56 (1H, dd, *J*=7, 6 Hz), 4.68 (1H, d, *J*=6 Hz), 5.67 (1H, br s), 6.93 (2H, br d, *J*=8 Hz), 7.27 (2H, br d, *J*=8 Hz,); HRMS (EI, *m*/*z*) calcd for $C_{21}H_{25}NO_7$ (M^+) 403.1629, found 403.1614.

[4-(4-Methoxyphenyl)-2-oxo-oxazolidin-5-yl]methyl [1*S*-[1α(4*R* ∗ ,5*S* ∗),4β]-4,7,7-trimethyl-3-oxo-2-oxabicyclo-[2.2.1]heptane-1-carboxylate ((4*R*,5*S*(*S*))-**32**): IR ($CHCl_3$) 3448 (NH), 1768 (NCOO, COO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ*:0.99, 1.06 and 1.11 (each 3H, s), 1.68 (1H, ddd, *J*=13, 8, 4 Hz), 1.91 (1H, ddd, *J*=11, 10, 4 Hz), 2.05 (1H, ddd, *J*=11, 8, 4 Hz), 2.35 (1H, ddd, *J*=13, 10, 4 Hz), 3.80 (3H, s), 4.35–4.42 (1H, m), 4.52–4.62 (2H, m), 4.71 (1H, d, *J*=6 Hz), 5.01–5.10 (2H, m), 5.63 (1H, br s,), 6.93 (2H, br d, *J*=8 Hz), 7.24 (2H, br d, *J*=8 Hz); HRMS (EI, *m*/*z*) calcd for $C_{21}H_{25}NO_7$ (M^+) 403.1629, found 403.1614.

4.9.23. (+)-4-*epi*-Cytoxazone (31). To a solution of (4*S*,5*R*(*S*))-ester **32** (18 mg, 0.045 mmol) in MeOH (1.5 mL) was added 1 M methanolic KOH (0.5 mL) at room temperature. After being stirred at room temperature for 30 min, the reaction mixture was diluted with H_2O and extracted with $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 1:2) afforded (+)-**31** (10 mg, 99%) as colorless crystals, mp 121–123 °C (AcOEt), $[\alpha]_D^{28}=+30.0$ (*c* 0.87, MeOH).

4.9.24. (−)-4-*epi*-Cytoxazone (31). According to the procedure given for (−)-**9**, the hydrolysis of (4*R*,5*S*(*S*))-ester **32** (18 mg, 0.045 mmol) with KOH gave (−)-**31** (7 mg, 99%) as colorless crystals, mp 121–123 °C (AcOEt), $[\alpha]_D^{29}=-30.1$ (*c* 0.70, MeOH) (lit.[16] −30.4 (*c* 1.0, MeOH).

The spectral and physical data of (−)-**9** are identical with those reported.[16]

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