# Stereoselective Synthesis of β-Hydroxyphenylalanines Using Imino 1,2-Wittig Rearrangement of Hydroximates

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**The imino 1,2-Wittig rearrangement of hydroximates containing a furan ring provides a novel method for the synthesis of β-hydroxy-α-amino acids. Upon treatment with LDA, hydroximates smoothly underwent the rearrangement to give *Z*-2-hydroxyoxime ethers in good yield, which were converted into both *cis*- and *trans*-oxazolidinones with high stereoselectivity. The *cis*- and *trans*-oxazolidinones were stereoselectively converted into *erythro*- and *threo*-β-hydroxyphenylalanines, respectively, *via* the oxidative cleavage of a furan ring, ring-opening of oxazolidinone, and deprotection.**

**Key words** imino Wittig rearrangement; hydroximate; imidate; amino acid; oxime ether

β-Hydroxy-α-amino acids are an important class of amino acids that are found in nature and as constituents of more complex natural products.[1—7] For example, β-hydroxytyrosine and β-hydroxyphenylalanine derivatives are found in clinically important glycopeptide antibiotics, such as Vancomycin and Teicoplanin. In addition, Lysobactin, which has shown antibiotic activity, contains five β-hydroxy-α-amino acids unit in the molecule. These densely functionalized amino acids are also useful building blocks for synthesis of β-lactams and sugars. Therefore, the synthesis of polypeptides and antibiotics containing β-hydroxy-α-amino acids are of interest to both synthetic and medicinal chemists. In recent years, we have developed a new imino 1,2-Wittig rearrangement of hydroximates which proceeds smoothly under basic conditions to give 2-hydroxyoxime ethers.[8—11] Part of the synthetic potentiality was demonstrated by the preparation of biologically important amino alcohols and the efficient synthesis of Cytoxazone.[11]

In this paper, we disclose a new convenient methodology for the preparation of β-hydroxy-α-amino acids using imino 1,2-Wittig rearrangement of hydroximates. Our approach is shown in Chart 1. We chose the hydroximates **1a**—**c** having ester, furan, and oxazoline moieties as substrates for imino 1,2-Wittig rearrangement. These functional groups are expected to readily convert into a carboxyl group. The hydroximates **1a**—**c** are treated with LDA to give 2-hydroxyoxime ethers **2** which are subjected to stereoselective reduction of imine moiety to afford both the *threo*- and *erythro*-amino alcohols **3**. Finally, the conversion of ester, furan, and oxazoline moieties into a carboxylic acid gives β-hydroxy-α-amino acids **4**.

## Results and Discussion

At first, we examined the preparation of the *Z*-hydroximates **1a**—**c** (Chart 2). According to the known procedure,[11—15] the acylation of methoxyamine hydrochloride with acid chloride **5a** followed by treatment of the resulting amide **6a** with carbon tetrabromide in the presence of triphenyl phosphine gave imidoyl bromides **7a** which was then converted into hydroximate **1a** by the treatment of sodium benzyloxide. Similarly, **1b** was prepared by the bromination of **6b** followed by the treatment of the resulting imidoyl bromide **7b** with sodium benzyloxide. The hydroximate **1c** was prepared from amino alcohol **8**[16,17] *via* construction of oxazolidine ring, amidation, bromination, and benzyloxylation.

Next, we investigated the 1,2-Wittig rearrangement reaction of hydroximates **1a**—**c** with LDA (Chart 3, Table 1). Upon treatment with 4 eq. of LDA, the rearrangement of hydroximate **1b** carrying furan ring proceeded smoothly at

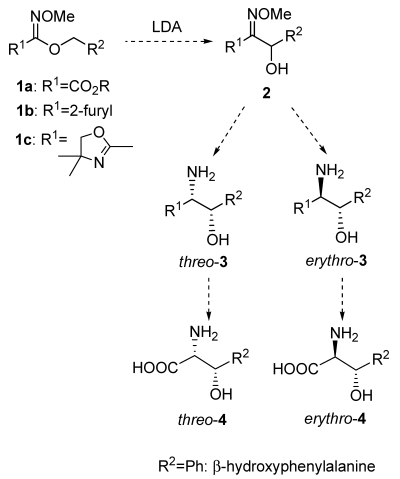
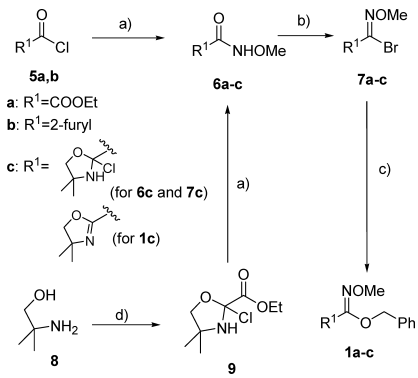



Chart 1




*Reagents and conditions*: a) $NH_2OMe$•HCl, Py. (**6a**: 80%; **6b**: 97%; **6c**: 61%); b) $PPh_3$, $CBr_4$; c) BnOH, NaH (**1a**: 63%; **1b**: 90%; **1c**: 56% from **6a-c**); d) 1) ethyl oxalyl chloride **5a**, $Et_3N$, 2) $SOCl_2$, 71%.

Chart 2

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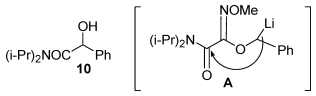
Chart 3

Table 1. Imino 1,2-Wittig Rearrangement of Hydroximates **1a**—**c**

| Entry | Substrate | $R^1$ | LDA (eq.) | Time (h) | $T$ (°C) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **1b** | 2-Furyl | 4 | 2 | −40 | 94 |
| 2 | **1c** | 4,4-Dimethyl-2-oxazolinyl | 2 | 1 | −20 | 50 |
| 3 | **1a** | COOEt | 2 | 1 | −78 | —[a] |

*a*) The amide **10** was obtained in 40% yield.




−40 °C to give **2b** in 94% yield (entry 1). Similarly, the reaction of hydroximate **1c** having oxazoline ring also occurred at −20 °C to give **2c** in moderate yield (entry 2). However, the reaction of hydroximate **1a** with an ester moiety did not give the desired 2-hydroxyoxime ether, but the mandelamide derivative **10** (entry 3). The spectral data of **10** were identical with those reported in the literature.[18,19] We proposed that the amide **10** would be formed *via* addition reaction of a carbanion to the carbonyl group as shown in the intermediate **A** which would be formed by the reaction of **1a** with LDA. Therefore, we employed **2b** and **2c** as intermediates for the synthesis of *β*-hydroxyphenylalanine.

We next investigated the reduction of oxime ether part in **2b** (Chart 4, Table 2). Recently, we have found[11] that the reduction of 2-hydroxyoxime ether with SMEAH (sodium bis(2-methoxyethoxy)aluminum hydride) gave *threo*-amino alcohol as a major product while *erythro*-amino alcohol was stereoselectively obtained in the reduction of the corresponding 2-silyloxyoxime ether with $LiAlH_4$. According to our previous studies,[11] the treatment of **2b** with SMEAH followed by acylation of the resulting *threo*-amino alcohol **12** with 2.2 eq. of $(Boc)_2O$ gave the *trans*-**13** with excellent stereoselectivity (entry 1). Interestingly, the reduction of silyl ether **11**, prepared from **2b**, with $LiAlH_4$ gave *cis*-**13** *via* *erythro*-amino alcohol **12** with high stereoselectivity (entry 2).

The *cis*/*trans*-stereostructures of oxazolidinones **13** were determined by the $^1$H-NMR spectroscopy. It is known[11—15] that the 4,5-disubstituted oxazolidinones exhibiting signals for 4-H and 5-H at lower field have *cis*-structure while the 4,5-disubstituted oxazolidinones showing those at higher field have *trans*-structure. From the fact that signals due to 4-H and 5-H of oxazolidinone **13** (4-H: $\delta$ 5.50; 5-H: $\delta$ 5.74) appeared in down-field compared with those of isomer **13** (4-H: $\delta$ 5.10; 5-H: $\delta$ 5.47), we deduced the former as *cis*- and the latter as *trans*-isomers, respectively.

The observed high stereoselectivity in the reduction of oxime ethers is explained as follows (Chart 5). The protected 2-hydroxyoxime ether **11** would exist in stable conformation **B** according to the Felkin–Anh model. The hydride would attack the oxime ether by an intermolecular process to give *erythro*-**14**, which is converted into *cis*-**13** *via* the cleavage of

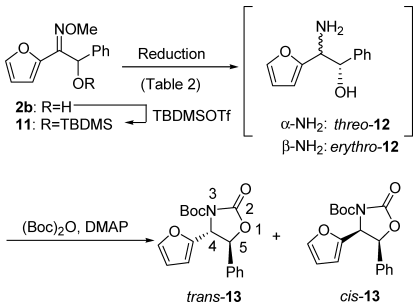



Chart 4

Table 2. The Reduction of Oxime Ethers **2b** and **11**

| Entry | Substrate | Reagent | Solv. | $T$ (°C) | Yield (%) | Ratio *trans*-**13** : *cis*-**13** |
|---|---|---|---|---|---|---|
| 1 | **2b** | SMEAH | THF | −30→65 | 67 | >99 : <1 |
| 2 | **11** | $LiAlH_4$ | $Et_2O$ | 0 | 59 | 3 : 97 |

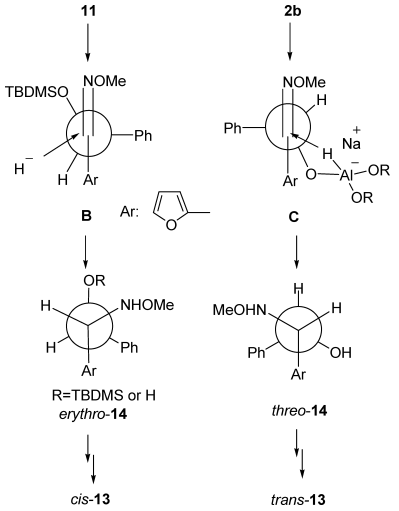
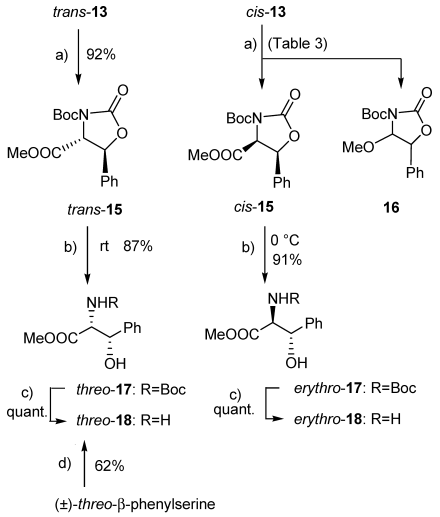



Chart 5

N–O bond followed by acylation. On the other hand, the treatment of **2b** with SMEAH forms aluminum complex **C** with a free hydroxyl group. The reduction of oxime ether part would proceed *via* the conformation **C** by an intramolecular process to give *threo*-**14** which is an intermediate for preparation of *trans*-**13**.

The *cis*- and *trans*-oxazolidinones **13** were converted into our target, *β*-hydroxyphenylalanine (Chart 6). The oxidative cleavage[20] of furan ring in *trans*-**13** with $RuO_4$ at room temperature followed by methylation of the resulting carboxylic acid with diazomethane in methanol gave the *trans*-ester **15**[21] in 92% yield from **13**. Then oxazolidinone **15** was subjected to the ring-opening[22] of oxazolidinone by using cesium carbonate at room temperature to give *threo*-**17**.[21] Finally, *threo*-**17** was deprotected by treatment with TFA to give *threo*-*β*-hydroxyphenylalanine methyl ester **18** in excellent yield. The spectral data of *threo*-**18** were identical with those reported in the literature.[23—25]

Additionally we confirmed that *threo*-**18** is also identical with the authentic sample prepared from the commercially available *threo*-(±)-*β*-phenylserine. Similarly, *cis*-**13** was




*Reagents and conditions*: a) 1) $RuCl_3 \cdot xH_2O$/ $NaIO_4$, rt, 2) $CH_2N_2$ in MeOH; b) $Cs_2CO_3$; c) TFA; d) $CH_2N_2$.

Chart 6

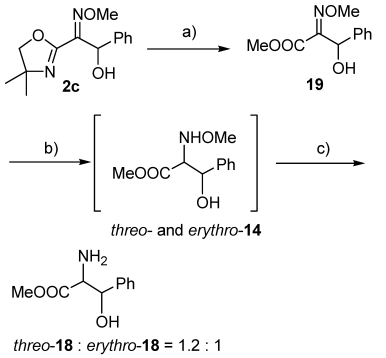
Table 3. The Oxidative Cleavage of *cis*-**13**

| Entry | Time (h) | *T* (°C) | *cis*-**15** (%) | **16** (%) |
|---|---|---|---|---|
| 1 | 1 | rt | 48 | 18 |
| 2 | 2 | 0 | 64 | 0 |

converted into *cis*-ester **15** (Table 3). The oxidation of *cis*-**13** with $RuO_4$ at room temperature and subsequent methylation afforded a mixture of *cis*-**15** and methoxyoxazolidinone **16**, the latter of which would be obtained *via* addition of MeOH to acyliminium formed by unexpected oxidative C–C bond cleavage at 4-position (entry 1). The stereostructure of **16** have not been established. When the reaction was carried out at 0 °C, only desired product *cis*-**15** was obtained (entry 2). The *cis*-ester **15** was treated with cesium carbonate at room temperature to give a mixture of *erythro*- and *threo*-**17** as the result of the epimerization at 2-position. On the other hand, the reaction proceeded smoothly even at 0 °C to give the desired product *erythro*-**17**[21] as a sole product which was converted into *erythro*-$\beta$-hydroxyphenylalanine methyl ester **18** by the deprotection. The spectral data of *erythro*-**18** were identical with those reported in the literature.[25,26]

We next investigated the preparation of *threo*- and *erythro*-**18** from 2-hydroxyoxime ether **2c** having oxazoline ring (Chart 7). The alcoholysis of **2c** with methanol in the presence of sulfuric acid gave the ester **19** in low yield. The attempted reduction of oxime ether moiety and hydrogenolysis of N–O bond in **19** using catalytic reduction were unsuccessful, but the oxime ether **19** was recovered. The treatment of oxime ether **19** with tributyltin hydride[27] in the presence of boron trifluoride-diethyl etherate followed by cleavage[28,29] of N–O bond in the resulting methoxyamine **14** afforded a 1.2 : 1 mixture of *threo*- and *erythro*-**18** in low yield, which were identical with the respective sample prepared from **2b**. Thus, **2c** with oxazoline ring was converted into methyl $\beta$-hydroxyphenylalaninate but in less satisfactory overall yield.

In conclusion, we have now established a new strategy for stereoselective synthesis of $\beta$-hydroxyphenylalanine *via* imino 1,2-Wittig rearrangement of hydroximate carrying




*Reagents and conditions*: a) 5% $H_2SO_4$/MeOH, 24%; b) $Bu_3SnH/BF_3{\cdot}Et_2O$, 28%; c) $Mo(CO)_6$, 12%.

Chart 7

furan ring which was employed as a synthon for an ester. The further applications of this imino 1,2-Wittig rearrangement to asymmetric synthesis of $\beta$-hydroxy-$\alpha$-amino acids are in progress.

## Experimental

**General** Melting point is uncorrected. $^1$H-NMR spectra were recorded at 200, 300, or 500 MHz. IR spectra were recorded using FTIR apparatus. Mass spectra were obtained by EI method. Flash column chromatography (FCC) was performed 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). Preparative TLC (PTLC) was performed on precoated Silica gel 60F-254 plates (0.5 mm, thick, Merck).

**Preparation of Hydroxamates 6a, b**[11] To a stirred solution of the acid chloride (90 mmol) in $CH_2Cl_2$ (900 ml) was added *N*-methoxyamine hydrochloride (99 mmol) under a nitrogen atmosphere at room temperature. After the solution was stirred at the same temperature for 15 min, pyridine (20.7 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 hydroxamates **6a**, **b**.

**Ethyl [(Methoxyamino)oxo]acetate (6a)**[30] A colorless oil; IR ($CHCl_3$) cm$^{-1}$: 3357, 1767, 1717. $^1$H-NMR (200 MHz, $CDCl_3$) $\delta$: 1.40 (3H, t, $J$=7 Hz), 3.86 (3H, s), 4.38 (2H, q, $J$=7 Hz), 9.60 (1H, br s). HR-MS (EI) *m*/*z*: 147.0554 (Calcd for $C_5H_9NO_4$ ($M^+$): 147.0531). These spectral data are identical with those reported.[30]

***N*-Methoxy-2-furancarboxamide (6b)**[31] A colorless oil; IR ($CHCl_3$) cm$^{-1}$: 3222, 1640. $^1$H-NMR (200 MHz, $CDCl_3$) $\delta$ 3.88 (3H, s), 6.52 (1H, dd, $J$=4, 2 Hz), 7.21 (1H, dd, $J$=4, 1 Hz), 7.48 (1H, dd, $J$=2, 1 Hz), 9.20 (1H, br s). These spectral data are identical with those reported.[31]

**Ethyl 2-Chloro-4,4-dimethyl-2-oxazolidinecarboxylate (9)** To a stirred solution of 2-amino-2-methylpropanol **8** (8.94 g, 0.1 mol) and $Et_3N$ (18 ml, 0.13 mol) in $CH_2Cl_2$ (100 ml) was added a solution of ethyl oxalyl chloride **5a** (13.6 g, 0.1 mol) in $CH_2Cl_2$ (50 ml) under a nitrogen atmosphere at room temperature. After the solution was stirred at the same temperature for 5 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 to afford the crude amide. A solution of the crude amide in $SOCl_2$ (40 ml, 0.5 mol) was stirred at room temperature for 24 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic phase was washed with water, dried over $Na_2SO_4$, and concentrated at reduced pressure. The residue was purified by MCC (hexane/AcOEt 3 : 1) to afford **9** (14.6 g, 71%) as a colorless oil; IR ($CHCl_3$) cm$^{-1}$: 3404, 1737. $^1$H-NMR (200 MHz, $CDCl_3$) $\delta$: 1.39 (3H, t, $J$=7 Hz), 1.47 (6H, s), 3.82 (2H, s), 4.33 (2H, q, $J$=7 Hz), 7.05 (1H, br s). MS (EI) *m*/*z*: 207 ($M^+$), 209 ($M^+$+2).

**2-Chloro-*N*-methoxy-4,4-dimethyl-2-oxazolidinecarboxamide (6c)** To a stirred solution of **9** (2.1 g, 10 mmol) in MeOH (150 ml) was added *N*-methoxyamine hydrochloride (250 mg, 3 mmol) under a nitrogen atmosphere at room temperature. After the solution was stirred at the same temperature for 15 min, pyridine (2.4 ml, 3 mmol) was added dropwise to the reaction

mixture at 0 °C. After being stirred at room temperature for 24 h, the reaction mixture was diluted with $CHCl_3$ and washed with $H_2O$. The organic phase was dried over $Na_2SO_4$ and concentrated at reduced pressure. Purification of the residue by MCC (hexane/AcOEt 3 : 1) afforded **6c** (1.29 g, 62%) as a colorless oil; IR ($CHCl_3$) $cm^{-1}$: 3369, 1652. $^1$H-NMR (200 MHz, $CDCl_3$) $\delta$: 1.47 (6H, s), 3.80 (2H, s), 3.84 (3H, s), 7.35 (1H, br s). MS (EI) *m/z*: 208 ($M^+$), 210 ($M^+$+2).

**Preparation of Hydroximates 1a—c** To a solution of **6a—c** (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 **7a—c**. After being characterized by NMR spectra, **7a—c** were 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 benzyl alcohol (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 **7a—c** (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 **1a—c**.

**Ethyl [Bromo(methoxyimino)methyl]acetate (7a)** A colorless oil; $^1$H-NMR (200 MHz, $CDCl_3$). $\delta$: 1.38 (3H, t, *J*=6 Hz), 4.20 (3H, s), 4.40 (2H, q, *J*=6 Hz).

***N*-Methoxy-2-furancarboximidoyl Bromide (7b)** A colorless oil; $^1$H-NMR (200 MHz, $CDCl_3$) $\delta$: 4.15 (3H, s), 6.48 (1H, dd, *J*=4, 2 Hz), 6.89 (1H, dd, *J*=4, 1 Hz), 7.52 (1H, dd, *J*=2, 1 Hz).

**2-Chloro-*N*-methoxy-4,4-dimethyl-2-oxazolidinecarboximidoyl Bromide (7c)** A colorless oil; $^1$H-NMR (200 MHz, $CDCl_3$) $\delta$: 1.49 (6H, s), 3.82 (2H, s), 4.11 (3H, s), 6.60 (1H, br s).

**Ethyl (*Z*)-[(Methoxyimino)(phenylmethoxy)]acetate (1a)** A colorless oil; IR ($CHCl_3$) $cm^{-1}$: 1732, 1649. $^1$H-NMR (200 MHz, $CDCl_3$) $\delta$: 1.30 (3H, t, *J*=7 Hz), 3.96 (3H, s), 4.30 (2H, q, *J*=7 Hz), 5.32 (2H, s), 7.31—7.47 (5H, m). HR-MS (CI) *m/z*: 238.1084 (Calcd for $C_{12}H_{15}NO_4$+1 ($QM^+$): 238.1079).

**Phenylmethyl (*Z*)-*N*-Methoxy-2-furancarboximidate (1b)** A colorless oil; IR ($CHCl_3$) $cm^{-1}$: 1609. $^1$H-NMR (200 MHz, $CDCl_3$) $\delta$: 3.95 (3H, s), 5.29 (2H, s), 6.38 (1H, dd, *J*=3.5, 2 Hz), 6.62 (1H, dd, *J*=3.5, 1 Hz), 7.26—7.42 (5H, m), 7.44 (1H, dd, *J*=2, 1 Hz). HR-MS (EI) *m/z*: 231.0893 (Calcd for $C_{13}H_{13}NO_3$ ($M^+$): 231.0895).

**Phenylmethyl (*Z*)-4,5-Dihydro-*N*-methoxy-4,4-dimethyl-2-oxazolecarboximidate (1c)** A colorless oil; IR ($CHCl_3$) $cm^{-1}$: 1649. $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 1.33 (6H, s), 3.93 (3H, s), 4.01 (2H, s), 5.43 (2H, s), 7.30—7.46 (5H, m). HR-MS (EI) *m/z*: 262.1327 (Calcd for $C_{14}H_{18}N_2O_3$ ($M^+$): 262.1316).

**General Procedure for Imino 1,2-Wittig Rearrangement** A solution of *Z*-hydroximate **1a—c** (1 mmol) in THF (5 ml) was added with stirring at temperature shown in Table 1 to a LDA solution, prepared from diisopropylamine (2 mmol or 4 mmol) and *n*-BuLi (1.65 M in hexane) (2 mmol or 4 mmol) under nitrogen atmosphere. After being stirred at the same temperature for 1 or 2 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. In the case of **1b** and **1c**, purification of the residue by MCC (hexane/AcOEt 7 : 1) afforded **2b** (217 mg, 94%) and **2c** (131 mg, 50%), respectively. On the other hand, the residue in reaction of **1a** was purified by MCC (hexane/AcOEt 3 : 1) to give the amide **10** (94 mg, 40%).

**(*E*)-1-(2-Furyl)-2-hydroxy-2-phenylethanone *O*-Methyloxime (2b)** Colorless crystals: mp 100—101 °C (hexane/$CHCl_3$); IR ($CHCl_3$) $cm^{-1}$: 3538. $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 3.79 (1H, d, *J*=8 Hz), 3.95 (3H, s), 6.12 (1H, d, *J*=8 Hz), 6.42 (1H, dd, *J*=4, 2 Hz), 6.77 (1H, dd, *J*=4, 1 Hz), 7.24—7.35 (5H, m), 7.48 (1H, dd, *J*=2, 1 Hz). HR-MS (EI) *m/z*: 231.0890 (Calcd for $C_{13}H_{13}NO_3$ ($M^+$): 231.0895. *Anal.* Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06, Found: C, 67.69; H, 5.77; N, 6.03.

**(*E*)-1-[(4,5-Dihydro-4,4-dimethyl)-2-oxazolyl]-2-hydroxy-2-phenylethanone *O*-Methyloxime (2c)** A colorless oil; IR ($CHCl_3$) $cm^{-1}$: 3316. $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 1.24 and 1.37 (each 3H, s), 4.00 (2H, s), 4.10 (3H, s), 6.35 (1H, br d, *J*=8 Hz), 6.59 (1H, br d, *J*=8 Hz), 7.40—7.65 (5H, m). HR-MS (EI) *m/z*: 262.1337 (Calcd for $C_{14}H_{18}N_2O_3$ ($M^+$): 262.1316).

**α-Hydroxy-*N*,*N*-bis(1-methylethyl)benzeneacetamide (10)**[18,19] Colorless crystals: mp 95—97 °C (hexane/$CHCl_3$) (lit.[18,19] mp 94—96 °C, 92—93 °C); IR ($CHCl_3$) $cm^{-1}$: 3433, 1645. $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 0.46, 1.15, 1.40 and 1.48 (each 3H, d, *J*=7 Hz), 3.35 and 3.80 (each 1H, sept, *J*=7 Hz), 5.11 (1H, s), 7.24—7.38 (5H, m). HR-MS (EI) *m/z*: 235.1545 (Calcd for $C_{14}H_{21}NO_2$ ($M^+$): 235.1571). These spectral data are identical with those reported.[18,19]

**(*Z*)-1-(2-Furyl)-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-phenylethanone *O*-Methyloxime (11)** To a solution of **2b** (462 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 20 : 1) afforded **11** (690 mg, quant.) as colorless crystals mp 86—88 °C (hexane/$CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: −0.08 and 0.00 (each 3H, s), 0.80 (9H, s), 3.98 (3H, s), 6.18 (1H, dd, *J*=3.5, 2 Hz), 6.52 (1H, s), 6.62 (1H, dd, *J*=3.5, 1 Hz), 7.06—7.22 (3H, m), 7.25 (1H, dd, *J*=2, 1 Hz), 7.30—7.37 (2H, m). HR-MS (EI) *m/z*: 345.1758 (Calcd for $C_{19}H_{27}NO_3Si$ ($M^+$): 345.1760). *Anal.* Calcd for $C_{19}H_{27}NO_3Si$: C, 66.05; H, 7.88; N, 4.05, Found: C, 66.02; H, 7.71; N, 4.03.

**Conversion of *Z*-2-Hydroxyoxime Ethers 2b and 11 into Oxazolidinones 13** (Table 2, Entry 1): To a solution of **2b** (300 mg, 1.3 mmol) in THF (30 ml) was added SMEAH (65% in toluene) (7.74 ml, 5.72 mmol) under a nitrogen atmosphere at −30 °C. The reaction mixture was stirred at the same temperature for 2 h. After being heated at 60 °C for 3 h, the reaction mixture was cooled to room temperature. 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 afford the crude amino alcohols **12** (*threo* : *erythro*=>99 : <1). To a solution of the crude amino alcohols in MeCN (20 ml) were added DMAP (190 mg, 1.3 mmol) and $(Boc)_2O$ (672 mg, 2.86 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 *trans*-**13** (280 mg, 67%). The ratio of *trans*- to *cis*-adducts was determined by $^1$H-NMR spectrum.

(Table 2, Entry 2): To a suspension of $LiAlH_4$ (985 mg, 25.6 mmol) in $Et_2O$ (20 ml) was added a solution of **11** (220 mg, 0.64 mmol) in $Et_2O$ (5 ml) with stirring under a nitrogen atmosphere at 0 °C. After being stirred at the same temperature for 12 h, usual work-up afforded the crude amino alcohols **12** (*threo* : *erythro*=3 : 97). To a solution of the crude amino alcohols in MeCN (10 ml) were added DMAP (94 mg, 0.64 mmol) and $(Boc)_2O$ (331 mg, 1.41 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*- and *trans*-**13** (97 : 3) (124 mg, 59%). The ratio of *trans*- to *cis*-adducts **13** was determined by $^1$H-NMR spectrum.

**1,1-Dimethylethyl *trans*-4-(2-Furyl)-2-oxo-5-phenyl-3-oxazolidinecarboxylate (*trans*-13)** A colorless oil; IR ($CHCl_3$) $cm^{-1}$: 1815. $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 1.39 (9H, s), 5.10 (1H, d, *J*=5.5 Hz), 5.47 (1H, d, *J*=5.5 Hz), 6.37 (1H, dd, *J*=3.5, 1 Hz), 6.42 (1H, dd, *J*=3.5, 2 Hz), 7.30—7.34 (2H, m), 7.38—7.44 (3H, m), 7.48 (1H, dd, *J*=2, 1 Hz). HR-MS (EI) *m/z*: 329.1270 (Calcd for $C_{18}H_{19}NO_5$ ($M^+$): 329.1262).

**1,1-Dimethylethyl *cis*-4-(2-Furyl)-2-oxo-5-phenyl-3-oxazolidinecarboxylate (*cis*-13)** A colorless oil; IR ($CHCl_3$) $cm^{-1}$: 1815. $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 1.41 (9H, s), 5.50 (1H, d, *J*=7.5 Hz), 5.74 (1H, d, *J*=7.5 Hz), 6.03 (1H, br d, *J*=3.5 Hz), 6.11 (1H, dd, *J*=3.5, 2 Hz), 7.10—7.16 (3H, m), 7.20—7.24 (3H, m). HR-MS (EI) *m/z*: 329.1281 (Calcd for $C_{18}H_{19}NO_5$ ($M^+$): 329.1262).

**4-Methyl 3-(1,1-Dimethylethyl) *trans*-2-Oxo-5-phenyl-3,4-oxazolidinedicarboxylate (15)**[21] To a solution of *trans*-**13** (280 mg, 0.85 mmol) in $CCl_4$–MeCN–$H_2O$ (2 : 2 : 3) (9.1 ml) was added $NaIO_4$ (1.48 g, 6.9 mmol) and $RuCl_3 \cdot xH_2O$ (5.3 mg, 0.025 mmol) at room temperature. After being stirred at the same 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 to afford the crude *trans*-carboxylic acid. To a solution of the crude *trans*-carboxylic acid in MeOH (20 ml) was added a solution of $CH_2N_2$ (2.1 mmol) in $Et_2O$, prepared according to a usual method, at 0 °C. 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 3 : 1) afforded *trans*-**15** (251 mg, 92%) as colorless crystals mp 123—125 °C (hexane/$CHCl_3$); IR ($CHCl_3$) $cm^{-1}$: 1815, 1757. $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 1.51 (9H, s),

3.90 (3H, s), 4.65 (1H, d, $J$=4.5 Hz), 5.39 (1H, d, $J$=4.5 Hz), 7.36—7.48 (5H, m). HR-MS (CI) $m/z$: 322.1289 (Calcd for $C_{16}H_{19}NO_6$+1 ($QM^+$): 322.1290). *Anal.* Calcd for $C_{19}H_{27}NO_3Si : C_{16}H_{19}NO_6 \cdot 1/5H_2O$: C, 59.14; H, 6.01; N, 4.31, Found: C, 59.14; H, 5.96; N, 4.36.

**Oxidative Cleavage of Furan Ring in *cis*-13** (Table 3, Entry 1): According to the procedure given for *trans*-**15**, *cis*-**13** was treated with $NaIO_4$ and $RuCl_3 \cdot xH_2O$ at room temperature to give the crude *cis*-carboxylic acid which was subjected to methylation with $CH_2N_2$ at 0 °C to give the *cis*-methyl ester **15** and methoxyoxazolidinone **16** as shown in Table 3, entry 1.

(Table 3, Entry 2): According to the procedure given for *trans*-**15**, *cis*-**13** was treated with $NaIO_4$ and $RuCl_3 \cdot xH_2O$ at 0 °C to give the crude *cis*-carboxylic acid which was subjected to methylation with $CH_2N_2$ at 0 °C to give the *cis*-methyl ester **15** as shown in Table 3, entry 2.

**4-Methyl 3-(1,1-Dimethylethyl) *cis*-2-Oxo-5-phenyl-3,4-oxazolidinedicarboxylate (15)** Colorless crystals mp 114—115 °C (hexane/$CHCl_3$); IR ($CHCl_3$) $cm^{-1}$: 1827, 1755. $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 1.51 (9H, s), 3.25 (3H, s), 4.97 (1H, d, $J$=9 Hz), 5.72 (1H, d, $J$=9 Hz), 7.26—7.44 (5H, m). HR-MS (EI) $m/z$: 321.1225 (Calcd for $C_{16}H_{19}NO_6$ ($M^+$): 321.1212).

**1,1-Dimethylethyl 4-Methoxy-2-oxo-5-phenyl-3-oxazolidinecarboxylate (16)** A colorless oil; IR ($CHCl_3$) $cm^{-1}$: 1828. $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 1.49 (9H, s), 3.50 (3H, s), 5.82 (1H, d, $J$=9 Hz), 5.94 (1H, d, $J$=9 Hz), 7.22—7.40 (5H, m). HR-MS (EI) $m/z$: 293.1248 (Calcd for $C_{15}H_{19}NO_5$ ($M^+$): 293.1262).

**Methyl *threo*-(±)-*N*-[(1,1-Dimethylethyloxy)carbonyl]-β-hydroxyphenylalaninate (17)**[21] To a solution of *trans*-**15** (80 mg, 0.25 mmol) in MeOH (2.5 ml) was added $Cs_2CO_3$ (16 mg, 0.05 mmol) at room temperature. 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 *threo*-**17** (64 mg, 87%) as colorless crystals mp 100—102 °C (hexane/$CHCl_3$) (lit.[21] 101—102 °C (2*S*,3*R*-**17**)); IR ($CHCl_3$) $cm^{-1}$: 3444, 1743, 1715. $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 1.33 (9H, br s), 2.72 (1H, br s), 3.76 (3H, s), 4.53 (1H, m), 5.23 (1H, br, t, $J$=3.5 Hz), 5.26—5.38 (1H, m), 7.28—7.40 (5H, m). HR-MS (EI) $m/z$): 295.1411 (Calcd for $C_{15}H_{21}NO_5$ ($M^+$): 295.1419).

The spectral and physical data of *threo*-**17** are identical with those reported.[21]

**Methyl *erythro*-(±)-*N*-[(1,1-Dimethylethyloxy)carbonyl]-β-hydroxyphenylalaninate (17)**[21] To a solution of *cis*-**15** (25 mg, 0.08 mmol) in MeOH (1 ml) was added $Cs_2CO_3$ (5 mg, 0.02 mmol) at 0 °C. After being stirred at 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 *erythro*-**17** (21 mg, 91%) as colorless crystals mp 100—102 °C (hexane/$CHCl_3$) (lit.[21] 101—102 °C (2*S*,3*S*-**17**)); IR ($CHCl_3$) $cm^{-1}$: 3433, 1742, 1715. $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 1.44 (9H, br s), 3.70 (3H, s), 3.90 (1H, br s), 4.73 (1H, m), 5.19 (1H, m), 5.26 (1H, m), 7.28—7.40 (5H, m). HR-MS (EI) $m/z$: 295.1409 (Calcd for $C_{15}H_{21}NO_5$ ($M^+$): 295.1419).

The spectral and physical data of *erythro*-**17** are identical with those reported.[21]

**Methyl *threo*-(±)-β-Hydroxyphenylalaninate (18)**[23—25] To a solution of *threo*-**17** (16 mg, 0.054 mmol) in $CH_2Cl_2$ (0.5 ml) was added TFA (7.4 mg, 0.065 mmol) at room temperature. After being stirred at the same temperature for 3 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. Purification of the residue by MCC (hexane/AcOEt 1 : 1) afforded *threo*-**18** (10 mg, 99%) as colorless crystals mp 58—60 °C (hexane/$CHCl_3$) (lit.[24] 59.3 °C (2*R*,3*S*-**18**); lit.[25] an oil ((±)-**18**)); IR ($CHCl_3$) $cm^{-1}$: 3409, 1736. $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 2.00 (3H, br s), 3.66 (1H, d, $J$=4.5 Hz), 3.69 (3H, s), 4.91 (1H, d, $J$=4.5 Hz), 7.26—7.40 (5H, m); HR-MS (EI) $m/z$: 195.0893 (Calcd for $C_{10}H_{13}NO_3$ ($M^+$): 195.0895).

The spectral and physical data of *threo*-**18** are identical with those reported.[23—25]

According to the usual procedure, the methylation of commercially available *threo*-(±)-β-phenylserine (271 mg, 1.5 mmol) with $CH_2N_2$ gave the ester **18** (180 mg, 62%), which is identical with *threo*-**18** prepared from *threo*-**17**.

**Methyl *erythro*-(±)-β-Hydroxyphenylalaninate (18)**[25,26] To a solution of *erythro*-**17** (16 mg, 0.054 mmol) in $CH_2Cl_2$ (0.5 ml) was added TFA (7.4 mg, 0.065 mmol) at room temperature. After being stirred at same temperature for 3 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. Purification of the residue by MCC (hexane/AcOEt 1 : 1) afforded *erythro*-**18** (10 mg, 99%) as colorless crystals mp 60—61 °C (hexane/$CHCl_3$) (lit.[26] a colorless oil (2*S*,3*S*-**18**); lit.[25] 105.5—106 °C ((±)-**18**)); IR ($CHCl_3$) $cm^{-1}$: 3407, 1740. $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 1.94 (3H, br s), 3.70 (3H, s), 3.84 (1H, d, $J$=6 Hz), 4.96 (1H, d, $J$=6 Hz), 7.24—7.40 (5H, m); HR-MS (EI) $m/z$: 195.0893 (Calcd for $C_{10}H_{13}NO_3$ ($M^+$): 195.0895).

The spectral and physical data of *erythro*-**18** are identical with those reported.[25,26]

**Methyl (*Z*)-3-Hydroxy-2-methoxyimino-3-phenylpropionate (19)** To a solution of **2c** (55 mg, 0.21 mmol) in MeOH (2 ml) was added 5% $H_2SO_4$ in MeOH (1.05 ml) at room temperature. After being heated at reflux for 5 h, the reaction mixture was cooled at room temperature, 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 PTLC (hexane/AcOEt 2 : 1) afforded **19** (11 mg, 24%) as a colorless oil; IR ($CHCl_3$) $cm^{-1}$: 3536, 1734. $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 3.70, 4.12 (each 3H, s), 3.84 (1H, d, $J$=6 Hz), 4.96 (1H, d, $J$=6 Hz), 7.24—7.40 (5H, m). HR-MS (EI) $m/z$: 195.0893 (Calcd for $C_{11}H_{13}NO_4$ ($M^+$): 195.0895).

**Reduction of Ester 19 with $Bu_3SnH$** To a solution of ester **19** (53 mg, 0.24 mmol) in $CH_2Cl_2$ (1 ml) was added $Bu_3SnH$ (0.16 ml, 0.6 mmol) and $BF_3 \cdot Et_2O$ (0.061 ml, 0.48 mmol) at −78 °C. 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. Purification of the residue by PTLC (hexane/AcOEt 1 : 1) afforded a 4 : 1 mixture of *threo*- and *erythro*-methoxyamino alcohols **14** (15 mg, 28%) as a colorless oil and recovered **19** (18 mg, 33%). To a solution of a mixture of methoxyamino alcohols **14** (15 mg, 0.07 mmol) in $H_2O$–MeCN (1 : 15) (3.2 ml) was added $Mo(CO)_6$ (12.8 mg, 0.6 mmol) at room temperature. After being heated at reflux for 2 h, the reaction mixture was concentrated at reduced pressure. Purification of the residue by PTLC (hexane/AcOEt 1 : 1) afforded *threo*- and *erythro*-**18** (1.6 mg, 12%) (1.2 : 1) as a colorless oil. *threo*- and *erythro*-**18** are identical with authentic samples, prepared from *threo*- and *erythro*-**17**, respectively, by comparison of their spectral data. The ratio (1.2 : 1) of *threo*- to *erythro*-adducts **18** was determined by $^1$H-NMR spectrum.

**Methyl *threo*- and *erythro*-(±)-β-Hydroxy-*N*-methoxyphenylalaninate (14)** $^1$H-NMR (300 MHz, $CDCl_3$) $\delta$: 3.19 (1/5H, br s), 3.22 (4/5H, br s), 3.51 and 3.68 (each 12/15H, s), 3.52 and 3.55 (each 3/15H, s), 3.86 (4/5H, br d, $J$=7 Hz), 3.97 (1/5H, m), 4.78 (4/5H, dd, $J$=7, 2.5 Hz), 5.05 (1/5H, t, $J$=6 Hz), 6.01 (1/5H, br s), 6.30 (4/5H, br s), 7.25—7.40 (5H, m).

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