Excellent Chiral Introduction by Diene Iron-Tricarbonyl Moiety. III $^{1}$: Asymmetric Synthesis of Hydroxyethylidene Dipeptide Isostere Using a Diastereoselective 1,2-Nucleophilic Addition of Organocerium Reagents into a 1-Azatriene Fe(CO)$_3$ Complex

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A 1-iminobutadiene-iron tricarbonyl [Fe(CO)$_3$] complex (1) reacts with various organometallic nucleophiles in a stereoselective manner, and especially, by use of organocerium reagents, only single secondary amine complexes (2) were obtained in good yields. Application of this methodology was demonstrated in the asymmetric synthesis of hydroxyethylidene dipeptide isostere from the chiral starting material N-((2R)-(2E)-tricarbonyl[2,5-naphthalene]iron) benzylamine (1b).

Key words 1,2-nucleophilic addition; 1-azatriene iron-tricarbonyl complex; organocerium reagent; 1,4-functionalization; iodocyclocarbamation; hydroxyethylidene dipeptide isostere

The diastereoselective addition of organometallic reagents to the C=O double bond of chiral imines offers an attractive approach for the asymmetric synthesis of chiral amines.$^{2,3}$ Thus far, numerous stereoselective nucleophilic additions into the chiral imines derived from 1-phenylethylamine$^{3}$ and amino acid derivatives$^{4,5}$ as a chiral auxiliary have been reported.

In connection with our program aimed at the development of a highly stereoselective reaction mediated by a diene iron tricarbonyl complex, which can be easily removed by oxidative decomplexation, converted to various functional groups, and expected to induce high stereoselectivity,$^{6}$ we investigated the diastereoselective nucleophilic addition of several organometallics to an 1-iminodienoic complex (1).

Recently, acyclic and functionalized diene-iron tricarbonyl complexes have been demonstrated to be valuable intermediates in organic synthesis to construct stereogenic centers utilizing the chirality of an iron tricarbonyl moiety.$^{6}$ Concerning the stereoselectivity of the 1,2-nucleophilic additions to the C=O double bond, it has been manifested that organometallic reagents react with diene iron tricarbonyl complexes stereoselectively,$^{7}$ but those reagents generally offer a diastereomixture of secondary alcohols in reaction with dienal complexes.$^{8}$ On the other hand, there have been no reports on the stereoselectivity of the nucleophilic addition of organometallics to the 1-imino-diene complex (1). The point of this work is to determine whether such addition to imine complexes occurs stereoselectively or not. In addition, the resulting amine complex (2) and its decomplexed product (3) seem to be versatile intermediates for the synthesis of several alkaloids bearing a diene moiety such as clavepicte B$^{9}$ and for the subsequent transformation utilizing a diene moiety such as an electrophile-mediated cyclization reaction and Diels-Alder reaction$^{10}$ (Chart 1). If stereo- and regiocontrolled $\beta$-hydroxylation of the acyclic diene moiety can be achieved by intramolecular iodocarbamation reaction, this methodology would be very effective for the synthesis of biologically active $\alpha,\beta$-amino alcohol

![Diagram](image-url)

Chart 1

*N-Morpholinopinosphosine$^{12}$  Hydroxyethylidene Isostere (4)$^{13}$  Actinobolin$^{11}$  Clavepicte B$^{9}$

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bearing a C=C double bond such as sphingosine derivatives,12 and hydroxyethyldiene dipeptide isostere13 (Chart 1). In this paper, we report the stereoselective nucleophilic addition of organocerium reagents (RCCl3 or RMgX-CeCl3) to the 1-imi-no-diene complex (1), resulting in (1R5,2SR)-amine complexes (2), as well as its application to the asymmetric synthesis of a hydroxyethyldiene dipeptide isostere (4) by the use of intramolecular iodocarbamation cyclization as a key step.14

Results and Discussion

Racemic 1-imi-no-diene complexes (1a6a and 1b) were prepared by the condensation of known dienal complexes15 and benzylamine in the presence of molecular sieves 4A in benzene at room temperature. The results of the 1,2-nucleophilic addition of several organometallics to 1a, b are summarized in Table 1. Whereas the reaction of 1a with organolithium, Grignard reagent and aluminum complex gave ψ-endo 2a and ψ-endo 2b in a highly diastereoselective manner, respectively, these reagents are not suitable for the aimed reaction because of the low chemical yield (entries 2—4). Therefore, we next examined the reaction of 1a with none-basic organometallic reagents. Diallylcuprate reagent16 reacted with 1a smoothly in tetrahydrofuran (THF) at −78°C to afford a separable epimeric mixture of ψ-endo 2b and ψ-exo 2b in moderate yield and stereoselectivity (entry 5). On the other hand, treatment of 1a with n-butyllum reagent,17a prepared in situ from n-butyllithium and cerium(III) chloride (CeCl3) at −78°C for 30 min, provided the alkyldated secondary amine complex (ψ-endo 2a) not only in good yield (74%) but also with excellent diastereoselectivity (entry 6). Similarly, the exposure of methyl- and phenyl- cerium reagents as nucleophiles to 1a, b provided the corresponding amine complexes (2c—e) in good yields and in a highly stereoselective manner, respectively (entries 7—9). It is worthy to note that the organocerium reagents can be replaced by the mixing system17b prepared from the corresponding Grignard reagents (5 eq) and CeCl3 (5 eq) without loss of stereoselectivity (entries 10—13). However, a switch in metal species from cerium to ytterbium decreased the chemical yield (entry 14). Therefore, the most successful organometallic reagents in the nucleophilic attack to the imine complexes were usually organocerium derivatives. The diastereomeric purity of 2a—f (entries 2—4, 6—14) was determined by their 500 MHz 1H-NMR spectra. The stereochemistries of the secondary amines (ψ-endo 2b and ψ-exo 2b) were predicted from Rf values according to Lilly’s method,18a which had been applied to secondary alcohols. They proposed that since the hydroxy group of the ψ-endo isomer is sterically shielded by a Fe(CO)5 moiety, the Rf value of the ψ-endo isomer is higher than that of the ψ-exo isomer. We applied this method to the secondary amine complexes (ψ-endo 2b and ψ-exo 2b).18b We estimated that the major product (less polar) was a ψ-endo isomer from the Rf values of the products (ψ-endo 2b: Rf 0.30, ψ-exo 2b: Rf 0.15, AcOEt: hexane = 1: 10). Those of the other secondary amine complexes (2a, c—f) were estimated, as shown in Table 1, from a mechanistic analogy of 2b.

In order to definitely determine the relative configurations of the resultant secondary amines, we planned the asymmetric synthesis of the hydroxyethyldiene dipeptide isostere (4). The hydroxyethyldiene dipeptide isostere (4) first reported by Hanson and Lindberg is an interesting dipeptide analog which was designed to restrict conformational flexibility and to be susceptible to an attack of

Table 1. Diastereoselective Addition of Organometallic Reagents to 1-Imino-diene-Iron Complex (1)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R²-Metal</th>
<th>Product</th>
<th>Yield (%)</th>
<th>de (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>n-BuLi</td>
<td>2a</td>
<td>0—0</td>
<td>0—0</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>n-BuLi, BBr₃</td>
<td>2b</td>
<td>46—0</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>(allyl)MeBr</td>
<td>2b</td>
<td>40—0</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>(allyl)AIE₃ MgBr</td>
<td>2b</td>
<td>30—0</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>n-BuCeCl₂</td>
<td>2b</td>
<td>46—16</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>1a</td>
<td>n-BuCeCl₂</td>
<td>2a</td>
<td>74—0</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>1a</td>
<td>MeCeCl₂</td>
<td>2e</td>
<td>69—0</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>1a</td>
<td>MeCeCl₂</td>
<td>2e</td>
<td>62—0</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>1a</td>
<td>PhCeCl₂</td>
<td>2d</td>
<td>57—0</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>1a</td>
<td>MeMgBr, CeCl₃</td>
<td>2e</td>
<td>70—0</td>
<td>100</td>
</tr>
<tr>
<td>11</td>
<td>1a</td>
<td>PhMgBr, CeCl₃</td>
<td>2d</td>
<td>95—0</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>1a</td>
<td>PhMgBr, CeCl₃</td>
<td>2f</td>
<td>80—0</td>
<td>100</td>
</tr>
<tr>
<td>13</td>
<td>(allyl)MgBr, CeCl₃</td>
<td>2b</td>
<td>79—0</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>(allyl)MgBr, YbCl₃</td>
<td>2b</td>
<td>41—0</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

a) Isolated yields. b) Determined by 500 MHz 1H-NMR spectra. c) Recovery of the starting material (30—51%) as an aldehyde after SiO₂ column.
enzyme nucleophiles such as cysteine thiol. Moreover, it is not only incorporated in renin inhibitor but is also a key intermediate in the synthesis of trans alkene dipeptide isosteres, which are important components of peptidomimetic analogs of enkephalin, substance P and protein kinase inhibitor.\(^{19}\)

The retrosynthetic analysis is illustrated in Chart 2. In turn, the synthetic precursor (5) of (4) can be easily derived from (6) by the iodocyclocarbamation reaction, recently developed by us\(^ {20}\) for regio- and stereocontrolled 1,4-functionalization of an acyclic 1,3-diene system. Furthermore, (6) can be available from (2g) by oxidative decomplexation and protection of the amino group. Employing the stereoselective 1,2-nucleophilic addition reaction described above, (2g) would be synthesized from the chiral imine complex (1b).

A chiral imine complex (1b) was synthesized from a known chiral pentadentate complex\(^ {69}\) in the same manner as racemates (1b) (Chart 3). The exposure of (1b) on the diastereoselective nucleophilic addition of benzylmercury reagents gave rise to the desired amine complex (2g) as a single isomer in high yield. We investigated the stereoselective introduction of the β-hydroxy group into (2g) by the intramolecular iodocyclocarbamation of the methyl carbamate (6). The requisite carbamate (6) was prepared from (2g) by the following sequence: protection of the amino group with methyl chlorofomate and then decomplexation of the iron complex with ammonium cerium(IV) nitrate (CAN) in MeOH at −40°C.

The result of the intramolecular iodocyclocarbamation of (6) is shown in Table 2. The reaction of (6) with N-iodosuccinimide (NIS) and iodonium dichloride perchlorate [I\((\text{coll})_2\)ClO\(_4\)]\(^ {21}\) proceeded regioselectively, but the desired oxazolidinone (7) could not be obtained in a stereoselective manner (entries 1 and 2). On the other hand, the reaction of (6) with iodine (I\(_2\)) in CH\(_2\)Cl\(_2\) at room temperature gave rise to (7) stereoselectively (entry 3), and furthermore, the addition of potassium iodide (KI) to the reaction mixture promoted the reaction rate to afford (7) in 86% yield (entry 4). The diastereomeric ratio of (7) was estimated by 500 MHz \(^1\)H-NMR spectra (trans/cis = 97/3), and the relative stereochemistry of the major isomer (7) was determined to be trans by the nuclear Overhauser effect (NOE) enhancement between C4-H and Cl1-H.

Table 2. Iodocyclocarbamation of 6\(^ {a}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Yield (%)</th>
<th>trans-7: cis-7(^ {b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NIS</td>
<td>10</td>
<td>50:50</td>
</tr>
<tr>
<td>2</td>
<td>I((\text{coll})_2)ClO(_4)</td>
<td>20</td>
<td>60:40</td>
</tr>
<tr>
<td>3</td>
<td>I(_2)</td>
<td>43</td>
<td>92: 8</td>
</tr>
<tr>
<td>4</td>
<td>I(_2), KI</td>
<td>86</td>
<td>97: 3</td>
</tr>
</tbody>
</table>

\(a\) The reactions were carried out in CH\(_2\)Cl\(_2\) at room temperature. \(b\) Determined by 500 MHz \(^1\)H-NMR.

Chart 3

\(a\) BnNH\(_2\), MS4A, Benzene, r.t. (quant.); \(b\) BnMgCl, CeCl\(_3\), THF, −30°C (90%); \(c\) Cl\(_2\)O, CH\(_2\)Cl\(_2\), K\(_2\)CO\(_3\), CH\(_2\)Cl\(_2\), r.t., (98%); \(d\) CAN, CH\(_3\)CN, −40°C, (91%); \(e\) I\(_2\), KI, CH\(_2\)Cl\(_2\), r.t. (90%)
Moreover, as it was known that the Fe(CO), moiety can be remedied by treatment with I₂, we investigated the one-pot iodocyclcarbamation from the diene iron complex (2g). As expected, the reaction of 2g with I₂-KI proceeded smoothly to afford 7 in an improved yield without loss of stereocontrollability (Chart 3).

Subsequently, an inseparable mixture of 7 was converted to the alcohol (5), namely acetoxylation of 7 with silver acetate was followed by hydrolysis with sodium hydroxide to afford a mixture of trans- and cis-5, from which trans-5 could be separated by recrystallization from isopropyl ether (Pr₂O) (Chart 4). Birch reduction of the isolated alcohol (5) gave rise to the debenzyl compound (8) in 94% yield. Successive treatment of 8 by Jones oxidation and protection with di-tert-butyl dicarbonate gave the acid (9), which was converted to the desired hydroxyethylidene dipeptide isostere (4) in 78% yield by subjection with cesium carbonate in MeOH. The specific rotation of 4, \([\alpha]_D^{25} = -98.2^\circ\) (c = 0.185, MeOH) [lit. \([\alpha]_D^{25} = -100^\circ\) (c = 0.64, MeOH) for 4S,5S], \(^{15}N\) confirms our assignment of an (S) configuration at C5 in 4. Therefore, the stereochemistry of \(\psi\)-endo 2a–f were determined as shown in Table 1. Here we have achieved the asymmetric synthesis of the hydroxyethylidene dipeptide isostere (4) using a diastereoselective 1,2-nucleophilic addition of organocerium reagents into 1b.

From the stereochemical outcome of the major products, the nucleophilic addition to the imine complexes (1a, b) should be explained as follows. Observation of NOE enhancement from the H₁ proton to two olefinic protons (H₂, H₃) and a benzyl proton in 1a reveals that the imine complex (1a) exists as an equilibrium mixture of both conformers (A and B) bearing an (E)-imine form, respectively. However, in cases using Lewis acidic organometallic reagents (organoaaluminium, organomagnesium, and organocerium derivatives) and also in the presence of Lewis acids such as BBr₃, CeCl₃, and YbCl₃, the coordinated complex of conformer A by Lewis acid would be more stable than that of conformer B because of the severe steric hindrance between Lewis acid and H₃ in the latter case (Fig. 1). Therefore, nucleophiles attack from the opposite side of the bulky tricarbonyl iron unit in the coordinated conformer A to yield \(\psi\)-endo 2 stereoselectively. On the other hand, diallylcuprate reagent, of which stereoselective nucleophilic addition to chiral imines proceed without coordination to the nitrogen atom, adds to the C=N double bond of both conformers (A and B) from the upper side, resulting in the diastereomixture of \(\psi\)-endo 2b and \(\psi\)-exo 2b.

In conclusion, considering the perfect diastereoselectivity, our method might be one of the best tools to synthesize optically active natural products containing a nitrogen atom. In practice, this method was applied to the asymmetric synthesis of hydroxyethylidene dipeptide isostere.
Experimental

All melting points were determined using a Yanagimoto MP-21 melting point apparatus and are uncorrected. Measurements of optical rotations were carried out using a JASCO DIP-360 digital polarimeter. IR spectral measurements were performed with a Hitachi 260-10 IR spectrometer as KBr discs. The mass spectra of the samples were recorded with a Horiba FT 210 IR spectrometer as a neat sample on KBr by the diffuse reflectance measurement method.

\(^1\)H-NMR spectra were measured with a JEOL JNM-GX200 spectrometer (500 MHz). \(^13\)C-NMR spectra were measured with a JEOL JNM-EX270 spectrometer (67.8 MHz). All signals are expressed as ppm downfield from tetramethylsilane, used as an internal standard (δ value). The following abbreviations are used: singlet (s), doublet (d), triplet (t), multiplet (m), broad (br), mL. Mass spectra of water, water and brine, and with saturated NH₄Cl solution, water and brine, and then concentrated in vacuo. The residue was purified by column chromatography (hexane:AcOEt=10:1) to give \(\phi\text{-endo} \ 2a \ (7.6 \text{mg}, 46\%) \) as a yellow oil and (2E,4E)-tricycloben[2.5-9-hexadienyl]iron (8.2 mg, 32%). \(^1\)H-NMR (CDCl₃) δ: 0.92 (d, J = 7.1 Hz, C-4H), 1.13 (m, J = 7.1 Hz, C-5H, C-9H), 1.20 – 1.47 (m, J = 7.1 Hz, C-2H, C-3H, C-3' and N), 1.48 (s, J = 7.1 Hz, C-7H, C-7'H), 2.30 (m, J = 7.1 Hz, C-1'H, C-1'H), 1.62 (J = 7.1 Hz, C-6'H, 3.47 (s, J = 7.1 Hz, C-1'H, C-1'H), 0.54 (dd, J = 5.0, 8.6 Hz, C-3'H or C-4'H), 5.12 (dd, J = 5.0, 8.6 Hz, C-3'H or C-4'H), 7.23 – 7.36 (m, 5H, Ar-H). \(^1\)C-NMR (CDCl₃) δ: 14.0 (C4), 19.1 (C6), 23.0 (C3), 27.8 (C2), 36.1 (C1), 52.0 (Ph), 58.2 (C5), 63.5 (C1'), 69.1 (C2), 82.2 (C3), 84.9 (C4), 126.9 (Ar), 128.1 (Ar), 128.4 (Ar), 140.4 (Ar-quartet), 212.5 (CO), IR (CHCl₃): 3020~3300, 2960, 2940, 2100 (CO), 1450 cm⁻¹. MS m/z (%): 383 (M⁺, 6.0), 269 (100), 186 (28). HRMS Calcd for C₂₉H₂₃FeNO₃: 383.184. Found: 383.191.

(1R,S,2R,5S)-(2E,4E)-Tricycloben[2.5-9-phenyl-1-benzyl-2,4-hexadienyl]iron (\(\phi\text{-endo} \ 2a\)) Table 1. Entry 2: Boron tribromide (29.9 μL, 0.177 mmol) was added to a solution of 1a (34.3 mg, 0.155 mmol) in toluene (1 mL) at 0°C under a nitrogen atmosphere. The mixture was stirred for 30 min. The mixture was allowed to cool to –78°C. A solution of n-butyllithium (0.328 mL, 1.60 M) in hexane was added to the mixture at –78°C. The mixture was stirred at –78°C for 15 min, and then the reaction was quenched with 10% NaOH solution. The resulting mixture was extracted with AcOEt. The extract was washed with water and brine, dried, and then concentrated in vacuo.

The residue was purified by column chromatography (hexane:AcOEt=10:1) to give \(\phi\text{-endo} \ 2b \ (14.4 \text{mg}, 46\%) \) as a yellow oil. \(\phi\text{-exo} \ 2b \ (4.9 \text{mg}, 16\%) \) as a yellow oil. \(\phi\text{-exo} \ 2b \ (7.4 \text{mg}, 33\%) \) as an orange oil. \(\phi\text{-exo} \ 2b \ (6.5 \text{mg}, 23\%) \) as a yellow oil. \(\phi\text{-exo} \ 2b \ (4.6 \text{mg}, 16\%) \) as a yellow oil. \(\phi\text{-exo} \ 2b \ (7.4 \text{mg}, 33\%) \) as an orange oil. \(\phi\text{-exo} \ 2b \ (6.5 \text{mg}, 23\%) \) as a yellow oil. \(\phi\text{-exo} \ 2b \ (4.6 \text{mg}, 16\%) \) as a yellow oil. \(\phi\text{-exo} \ 2b \ (7.4 \text{mg}, 33\%) \) as an orange oil. 

General Procedure for the Reaction of 1a, b with Organocerium Reagents (1R,S,2R,5S)-(2E,4E)-Tricycloben[2.5-9-phenyl-1-benzyl-2,4-hexadienyl]iron (\(\phi\text{-endo} \ 2a\)) as Example Method A

Table 1, entry 7: Anhydrous cerium chloride (113 mg, 0.458 mmol) was placed in a two-necked flask and heated at 140°C under 0.1 mmHg for 4 h. While the flask was still hot, argon gas was introduced. The flask was cooled in an ice-bath, and THF (2 mL) was introduced via syringe. The flask was then placed in an ultrasonic bath (Branson B2000) at room temperature for 1 h. The resulting white slurry was then cooled to –78°C, a solution of methyltributyltin in Et₂O (0.380 mL, 1.2 mmol) was added to the mixture at –78°C, and then the mixture was stirred at –78°C for 30 min. A solution of 1a (29.8 mg, 0.0917 mmol) in THF (0.5 mL) was added to the mixture at –78°C, and then the mixture was stirred at –78°C for 1 h. The reaction was quenched with water. The resulting mixture was extracted with AcOEt. The extract was washed with water and brine, dried, and then concentrated in vacuo. The residue was purified by column chromatography (hexane:AcOEt=10:1) to give \(\phi\text{-endo} \ 2e \ (21.5 \text{mg}, 69\%) \) as a yellow oil. 

Method B: Table 1, entry 10: The white slurry prepared from anhydrous CeCl₃ (116 mg, 0.473 mmol) was then cooled to –30°C. A solution of dimethyldimethylsilane in THF (0.473 mL, 1.0 mg) was added to the mixture at –30°C, and then the mixture was stirred at –30°C for 30 min. A solution of 1a (30.8 mg, 0.0948 mmol) in THF (0.5 mL) was added to the mixture at –30°C, and then the mixture was stirred at –30°C for 1 h. The reaction was quenched with water. The resulting mixture was extracted with AcOEt. The extract was washed with water and brine, dried, and then concentrated in vacuo. The residue was purified by column chromatography (hexane:AcOEt=10:1) to give \(\phi\text{-endo} \ 2e \ (22.8 \text{mg}, 70\%) \) as a yellow oil.
C₂H₂ and Cs₂H₅), 1.24 (d, 3H, J = 6.0 Hz, C5-Me), 1.39 (d, 3H, J = 6.0 Hz, C5-H), 2.51 (qd, 1H, J = 6.0, 8.3 Hz, C₁-H), 3.69 (d, 1H, J = 13.0 Hz, PhCH₃), 3.85 (d, 1H, J = 13.0 Hz, PhCH₃), 5.04 (dd, 1H, J = 5.1, 8.5 Hz, C₃-H or C₄-H), 5.08 (dd, 1H, J = 5.1, 8.6 Hz, C₃-H or C₄-H), 7.24−7.33 (m, 3H), 7.44−7.48 (m, 1H, IR(CDCl₃), 2.21 (C), 51.9 (PhCH₃), 56.8 (C₁), 58.2 (C₅), 70.0 (C₂), 81.4 (C₄), 85.5 (C₆), 127.0 (C₈), 128.0 (Ar), 128.5 (Ar), 140.1 (Ar-quinonoid), 212.3 (CO). IR (CHCl₃): 3200−3000 (OH), 2900−3000 (2000), 1990 (CO), 1290 cm⁻¹. MS m/z (%): 341 (M⁺, 0.40), 257 (100). HRMS Calcd for C₁₅H₁₃NO₂: 341.071. Found: 341.0706.

(1S,SR,SRS)-(2E,4E)-Tricarballyl[2-5-q-N-benzyl-1-buty-2,4-hexadienylamine]-iron (2g) This was prepared by adding the chiral imine (1b) (890 mg, 2.86 mmol) to benzylferrocenyl reagent using method B to give 2g (1.04 g, 90%) as a yellow oil. [3]⁺ = +40° (c = 1.01, CHCl₃). 1H-NMR (CD₂Cl₂): −0.13 (d, 1H, J = 8.6 Hz, Cs₂H₅), 0.78 (dd, 1H, J = 8.6, 8.6 Hz, Cs₂H₅), 1.15 (brs, 1H, NH, J = 2.4 Hz), 1.24 (d, 1H, J = 6.0 Hz, Cs₂H₅), 2.42 (dd, 1H, J = 7.7, 12.8 Hz, PhCH₂C₂), 2.52 (d, 1H, J = 5.1, 7.7 Hz, C₁-H), 2.84 (dd, 1H, J = 5.1, 12.8 Hz, PhCH₂C₂), 3.73 (d, 1H, J = 12.8 Hz, PhCH₂C₃), 3.76 (d, 1H, J = 12.8 Hz, PhCH₂C₃), 4.40 (m, 2H, C₃-H and C₄-H), 6.95 (d, 2H, J = 6.8 Hz, Ar-H), 7.06−7.16 (m, 4H, Ar-H), 7.22 (dd, 2H, J = 7.7, 7.7 Hz, Ar-H), 7.37 (d, 2H, J = 7.7 Hz, Ar-H). 13C-NMR (CD₂Cl₂): δ = 40.2 (C₅), 43.2 (PhCH₂C₂), 52.1 (PhCH₂C₃), 63.5 (C₁), 68.7 (C₂-H), 120.4 (C₄), 86.4 (Cₒ₆), 126.3 (C₉), 127.0 (Ar), 128.0 (Ar), 128.3 (Ar), 128.4 (Ar), 129.7 (Ar), 138.4 (Ar-quinonoid), 140.0 (Ar-quinonoid), 211.5 (CO). IR (KBr): 3336, 3028, 2926, 2042 (CO), 1797 (CO) cm⁻¹. MS m/z (%): 347 (M⁺ − 2CO, 14), 320 (C₃), 319 (100), 228 (39). Anal. Calcd for C₃₁H₂₃FeN₂O: C, 75.53; H, 5.25; N, 4.37. Found: C, 75.68; H, 5.35; N, 3.44.

(2E)-1-N-Benzyl-N-carboxymethyl-2,4-pentadienylamine (6) Methyl chloroformate (0.51 mL, 6.65 mmol) was added to a solution of 2g (1.03 g, 2.56 mmol) and K₂CO₃ (1.32 g, 9.58 mmol) in CH₂Cl₂ (35 mL) at 0°C under a nitrogen atmosphere. The mixture was allowed to warm to room temperature and stirred at room temperature for 3 h. The reaction was quenched with water. The resulting mixture was extracted with CH₂Cl₂. The extract was washed with water and brine, dried, and concentrated in vacuo. The residue was purified by column chromatography (hexane:AcOEt = 1:15) to give the carbamate (115 g, 98%). CAN (260 mg, 1.13 mmol) was added to a solution of the carbamates (174 mg, 0.377 mmol) in CH₂CN (5 mL) at −40°C under a nitrogen atmosphere. The mixture was stirred at −40°C for 1 h. The reaction was quenched with saturated NaHCO₃ solution. The resulting mixture was extracted with CH₂Cl₂. The extract was washed with saturated NaHCO₃ solution, water and brine, and then concentrated in vacuo. The residue was purified by column chromatography (hexane:AcOEt = 0:10) to give 6 (110 mg, 91%) as a colorless oil. [3]⁺ = +21° (c = 1.53, CHCl₃). 1H-NMR (CD₂Cl₂): δ = 2.86−3.08 (m, 2H), 3.68 (s, 3H, COOMe), 4.19−4.49 (m, 3H), 5.04 (d, 1H, J = 10.3 Hz, Cs₂H₅), 5.10 (d, 1H, J = 17.1 Hz, Cs₂H₅), 5.81 (m, 1H, C₃-H), 5.94 (dd, 1H, J = 10.3, 15.4 Hz, C₄-H), 6.22 (dd, 1H, J = 10.3, 15.4 Hz, C₄-H), 7.21−7.26 (m, 1H, Ar-H). 13C-NMR (CD₂Cl₂): δ = 40.5 (C₄), 51.6 (PhCH₃), 66.7 (C₁), 70.2 (C₂), 82.2 (C₄), 85.8 (C₅), 126.9 (Ar), 127.0 (Ar), 127.5 (Ar), 128.0 (Ar), 128.4 (Ar), 140.1 (Ar-quinonoid), 144.3 (Ar-quinonoid), 211.4 (CO). IR (KBr): 3028, 2963, 2796, 2044, 1940 (CO), 1660 cm⁻¹. MS m/z (%): 322 (M⁺ + 1, 100), 231 (100). Anal. Calcd for C₂₃H₁₄N₂O: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.47; H, 7.20; N, 4.37.

(4S,5S,3-Dibenzylidene,5-(E)-3-isodopropenyl)[oxazolidin-2-one and (4S,5S,3-Dibenzylidene,5-(E)-3-isodopropenyl)[oxazolidin-2-one (7) Method A: A mixture of 6 (104 mg, 0.325 mmol), I₂ (248 mg, 0.976 mmol), KI (80.9 mg, 0.488 mmol), and CH₂Cl₂ (5 mL) was stirred at room temperature for 12 h. The resulting mixture was extracted with AcOEt. The extract was washed with saturated Na₂SO₄ solution, water and brine, and then concentrated in vacuo. The residue was purified by column chromatography (hexane:AcOEt = 5:1) to give 7 (818 mg, 84%). Method B: A mixture of the carbamate iron complex of 2g (2g, 1.00 mg, 2.1 mmol), I₂ (2.29 g, 8.68 mmol), KI (0.720 g, 4.34 mmol) and CH₂Cl₂ (35 mL) was stirred at room temperature for 36 h. The resulting mixture was extracted with AcOEt. The extract was washed with saturated Na₂SO₄ solution, water and brine, and then concentrated in vacuo. The residue was purified by column chromatography (hexane:AcOEt = 3:1) to give 7 (848 mg, 90%) as a yellow oil. [3]⁺ = −80° (c = 0.905, CHCl₃). 1H-NMR (CD₂Cl₂): δ = 2.68 (dd, 97/100 × 100, J = 8.8, 13.8 Hz, PhCH₃), 2.75 (dd, 3/100 × 100, J = 7.9, 14.4 Hz, PhCH₂C₂), 2.94 (dd, 3/100 × 100, J = 6.4, 14.4 Hz, PhCH₂C₂), 3.09 (dd, 97/100 × 100, J = 4.7, 13.8 Hz, PhCH₃), 3.34 (dd, 97/100 × 100, J = 4.7, 5.6, 8.8 Hz, C₄-H).
3.64 (dd, 97, 100 Hz, J = 9.4, 15.4 Hz, C3′-H3′), 3.66 (dd, 97, 100 Hz, J = 9.4, 15.4 Hz, C3′-H3′), 3.77 (dd, 97, 100 Hz, J = 15.4 Hz, PhCH2N), 3.84 (d, 3, 100 Hz, J = 8.1 Hz, C3′-H3′), 3.96 (dd, 3, 100 Hz, J = 6.4, 7.8 Hz, C9′-H9′), 4.07 (d, 97, 100 Hz, J = 15.2 Hz, PhCH2N), 4.58 (dd, 97, 100 Hz, J = 5.4, 1.2 Hz, C6′-H6′), 4.78 (br, 1H, 1H-CH; C6′-H6′), 5.14 (dd, 3, 100 Hz, J = 6.8, 6.5 Hz, C5′-H5′), 5.26 (dd, 97, 100 Hz, J = 5.6, 15.0 Hz, C1′-H1′), 5.67 (dd, 3, 100 Hz, J = 6.8, 15.0 Hz, C1′-H1′), 5.74 (dd, 97, 100 Hz, J = 9.4, 15.0 Hz, C2′-H2′), 6.04 (dd, 3, 100 Hz, J = 8.1, 15.0 Hz, C2′-H2′), 7.03−7.07 (m, 10H, Ar-H).

13C-NMR (CDCl3) major: 2.62 (C3), 38.1 (PhCH2C6), 46.1 (PhCH2N), 60.4 (C4), 77.0 (C5), 127.2 (Ar), 127.8 (Ar), 129.8 (C5′), 131.1 (C2′), 136.1 (C3′), 136.4 (Ar-quinonae), 135.4 (Ar-quinonae), 157.1 (C=O), IR (KBr): 3030, 2971, 1510 (C=O), 1495 cm−1. MS (%) m/z: 433 (M+1) 342 (M+2), 280, 217, 161, 138, 125, 119, 104, 91, 77, 76, 75, 74. Anal. Calcd for C22H16N03: C, 55.44; H, 4.65; N, 3.23. Found: C, 55.50; H, 4.71; N, 3.20.

(4S,5S)-3-Dibenzyl-5-(E)-3-hydroxy-1-propenyl)-oxazolidin-2-one (5) Silver acetate (392 mg, 2.35 mmol) was added to a solution of 7 (484 mg, 1.96 mmol) in DMSO−AcOH (1 : 2, 20 ml) at room temperature. The mixture was stirred at room temperature for 1.5 h. The mixture was diluted with water and the resulting mixture was extracted with AcOEt. The extract was washed with water and brine, dried, and then concentrated in vacuo. The residue was purified by preparative TLC (HeOH−CHCl3 = 1 : 1) to give 9 (17.9 mg, 74%) as colorless crystals. mp 89.0−91.5°C (AcOEt−hexane), [7]d20 −28.9° (c = 1.56, MeOH).

1H-NMR (CDCl3): 0.15 (6H, s, CH3), 0.35 (dd, 1H, J = 7.9, 13.4 Hz, PhCH2), 3.26 (dd, 1H, J = 3.9, 13.4 Hz, PhCH2), 4.36 (m, 1H, C4-H), 4.96 (m, 1H, C5-H), 5.83 (d, 1H, J = 15.5 Hz, C2′-H2′), 6.63 (dd, 1H, J = 5.3, 15.5 Hz, C1′-H1′), 7.25−7.35 (m, 6H, Ar-H).

13C-NMR (CDCl3): 28.2 (C2′), 39.4 (PhCH2C6), 62.0 (C4), 77.0 (C5), 85.8 (C2′), 125.7 (C2′), 128.5 (Ar), 130.0 (Ar), 131.1 (C2′), 134.6 (C3′), 135.0 (C4), 142.0 (C5), 153.6 (C5′), 163.8 (COO). IR (KBr): 3301, 2915, 1801 (C=O), 1722 (C=O), 1731 cm−1. MS (%) m/z: 347 (M+, 0.5), 186 (17), 156 (42), 155 (41), 92 (100). HRMS Calcd for C19H18N2O4: 347.3639. Found: 347.3713.

(4S,5S)-3-(E)-5-Amino-[1-(tert-butylxonyl)]carbonyl-4-hydroxy-6-phe- nol-2-hexenoic Acid (4) (36.9 mg, 0.103 mmol) was added to a solution of 9 (17.9 mg, 0.057 mmol) in 180 ml of THF, added to the resulting solution, and the whole was stirred for 10 min. The reaction was quenched with NH4Cl solution and then the mixture was filtered at room temperature, and then the mixture was stirred at room temperature for 24 h. The reaction was quenched with 0.1M HCl solution. The resulting mixture was extracted with AcOEt. The extract was washed with water and brine, dried, and then concentrated in vacuo. The residue was purified by prep TLC (MeOH−CHCl3 = 1 : 1) to give 7 (17.2 mg, 57%) as colorless crystals. mp 94.5−96.5°C (AcOEt−hexane), [7]d20 +94.5° (c = 0.068, MeOH).

1H-NMR (CDCl3): 0.15 (6H, s, CH3), 0.35 (dd, 1H, J = 7.9, 13.4 Hz, PhCH2), 3.26 (dd, 1H, J = 3.9, 13.4 Hz, PhCH2), 4.36 (m, 1H, C4-H), 4.96 (m, 1H, C5-H), 5.83 (d, 1H, J = 15.5 Hz, C2′-H2′), 6.63 (dd, 1H, J = 5.3, 15.5 Hz, C1′-H1′), 7.25−7.35 (m, 6H, Ar-H).

13C-NMR (CDCl3): 28.2 (C2′), 39.4 (PhCH2C6), 62.0 (C4), 77.0 (C5), 85.8 (C2′), 125.7 (C2′), 128.5 (Ar), 130.0 (Ar), 131.1 (C2′), 134.6 (C3′), 135.0 (C4), 142.0 (C5), 153.6 (C5′), 163.8 (COO). IR (KBr): 3301, 2915, 1801 (C=O), 1722 (C=O), 1731 cm−1. MS (%) m/z: 347 (M+, 0.5), 186 (17), 156 (42), 155 (41), 92 (100). HRMS Calcd for C19H18N2O4: 347.3639. Found: 347.3713.

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14) A part of this work has been published in a preliminary communication; Takemoto Y., Takeuchi J., Iwata C., Tetrahedron Lett., 34, 6069—6072 (1993).


