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## HIGHLY ENANTIOSELECTIVE SYNTHESIS OF ISOQUINUCLIDINE BY DIELS-ALDER REACTION OF 1,2-DIHYDROPYRIDINE UTILIZING CHIRAL BISOXAZOLINE-Cu(II) COMPLEX

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**Abstract** – The enantioselective Diels-Alder (D-A) reaction between *N*-phenoxy carbonyl- or *N*-benzyloxycarbonyl-1,2-dihydropyridine (**1a** or **1b**) and *N*(2)-acryloyl-*N*(1)-(1-naphthylmethyl)-5,5-dimethylpyrazolidin-3-one (**2b**) using (*S,S*)-bisoxazoline-Cu(II) catalyst (**A**, **B**, **C** or **D**) has been investigated. Utilizing (*S,S*)-*t*-Bu-bisoxazoline-Cu(II) catalyst **C**, the D-A reaction of **1a** and **2** afforded the *endo*-(7*S*)-isoquinuclidines (**3**, **4** or **5**) in good chemical yields with high enantioselectivity (up to 99% e.e.).

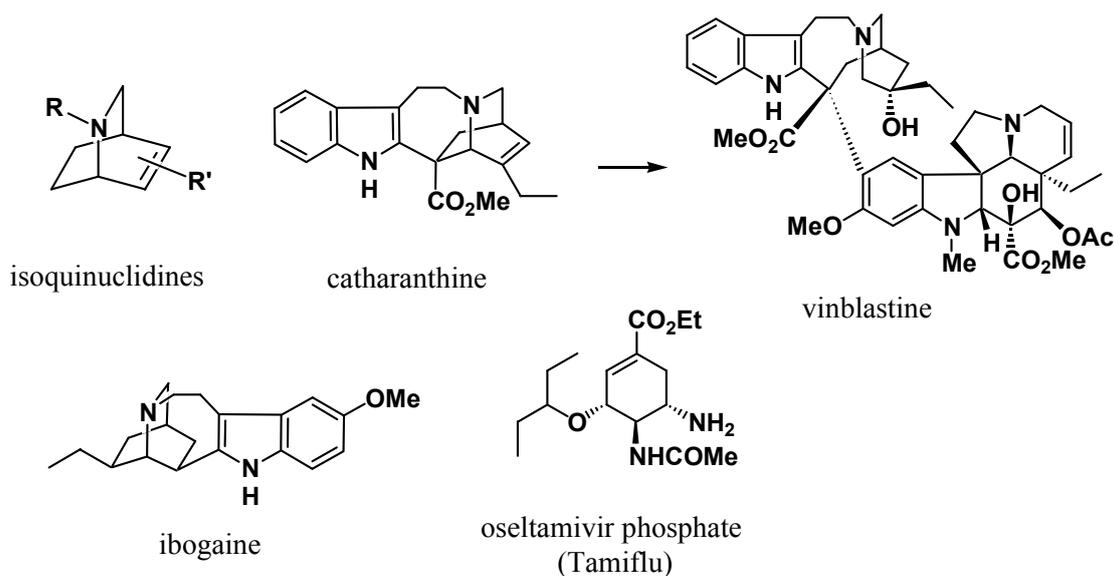
## INTRODUCTION

Syntheses of natural product-like compounds having isoquinuclidine skeleton, 2-azabicyclo[2.2.2]octane derivatives, *via* asymmetric synthesis have become one of the most important area of medicinal chemistry.<sup>1,2</sup> For example, catharanthine is the prototypical structure of iboga alkaloid which is known to be the precursor of anticancer drug, vinblastine.<sup>3</sup> Ibogaine is the medicine for alcohol or other drugs dependence.<sup>4</sup> It is also reported that isoquinuclidines are valuable intermediates in the synthesis of oseltamivir phosphate (Tamiflu) (Figure 1).<sup>5</sup> The chiral isoquinuclidine can be accomplished by the Diels-Alder (D-A) reaction of 1,2-dihydropyridines with dienophiles. In the asymmetric synthesis of isoquinuclidines, the previous reports have focused on dienophiles having a chiral auxiliary in

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Dedicated with respect to Dr. Ei-ichi Negishi on the occasion of his 77<sup>th</sup> birthday.

diastereoselective process.<sup>6</sup> In this paper, we describe the utility of (*S,S*)-bisoxazoline-Cu(II) catalyst<sup>7,8</sup> for the enantioselective Diels-Alder reaction of 1,2-dihydropyridine<sup>9</sup> **1** and achiral *N*(2)-acryloyl-*N*(1)-arylmethylsubstituted-5,5-dimethylpyrazolidin-3-one **2** to synthesize the chiral isoquinuclidines in good yields with high enantioselectivity. The R group of pyrazolidinone also can be easily varied and can be effective for providing the face selection in the D-A reaction.<sup>10</sup> We used the dienophile which has R group such as 1-benzyl, 1-naphthylmethyl or 2-naphthylmethyl group substituted at *N*(1) position of pyrazolidinone **2**. (*S,S*)-Bisoxazoline-Cu(II) catalysts (**A**, **B**, **C** and **D**) were selected because of their successful application of *C*<sub>2</sub>-symmetric bisoxazoline-Cu(II) complexes as chiral chelating Lewis acids in numerous asymmetric reactions and also due to the possibility of the controlling selectivity with their structural diversity. The usefulness of bisoxazoline ligand with mild Lewis acid such as Cu(OTf)<sub>2</sub> in the D-A reaction has been reported by Evans *et al.* in the reaction between cyclopentadiene and acrylimide in dichloromethane as a solvent and the D-A reaction afforded *endo*-cycloadduct with high stereoselectivity (*endo*/*exo* = 98:2).<sup>7b</sup>

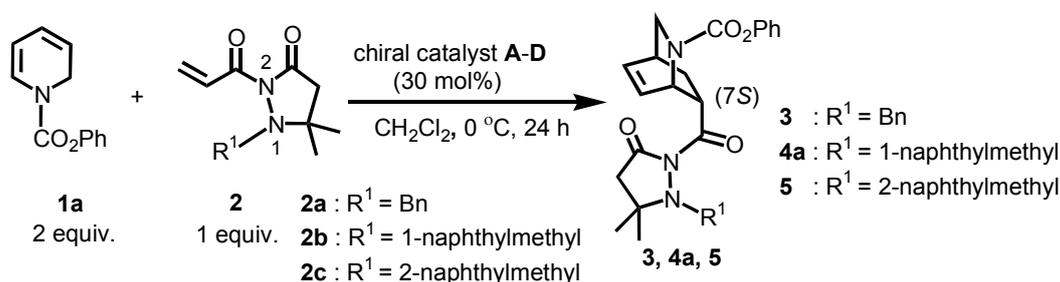


**Figure 1.** Isoquinuclidine derivatives

## RESULTS AND DISCUSSION

We investigated the asymmetric D-A reactions of *N*-phenoxy carbonyl-1,2-dihydropyridine **1a** with the dienophile, *N*(2)-acryloyl-*N*(1)-arylmethylsubstituted-5,5-dimethylpyrazolidin-3-one (**2a**, **2b** or **2c**)<sup>3</sup> at 0 °C in dichloromethane as a solvent in the presence of chiral (*S,S*)-bisoxazoline-Cu(II) catalyst (**A**, **B**, **C** or **D**). The results are summarized in Table 1. The (*S,S*)-bisoxazoline catalysts (**A**, **B** and **D**) were prepared according to the procedure reported by Evans *et al.*<sup>7b</sup> The D-A reaction of diene **1a** (2 equiv.) and *N*(2)-acryloyl-*N*(1)-benzyl-5,5-dimethylpyrazolidin-3-one **2a** (1 equiv.) was carried out at 0 °C using

30 mol% of catalyst **A** ( $R^2 = \text{Me}$ ) to give the cycloaddition product *endo*-**3** in 89% yield with moderate enantioselectivity (72% e.e., Table 1, entry 1). The 2 equiv. (or 3 equiv.) of 1,2-dihydropyridine **1a** (or **1b**) was used in the D-A reaction because it is reported that 1,2-dihydropyridines (**1a** and **1b**) were unstable in the presence of Lewis acids.<sup>68</sup> The D-A reaction of **1a** with *N*(2)-acryloyl-*N*(1)-(1-naphthylmethyl)-5,5-dimethylpyrazolidin-3-one **2b** using 30 mol% of catalyst **A** gave *endo*-**4a** in 99% yield with 85% e.e. (entry 2). The D-A reaction of **1a** with *N*(2)-acryloyl-*N*(1)-2-naphthylmethyl-5,5-dimethylpyrazolidin-3-one **2c** using catalyst **A** afforded *endo*-**5** in 96% yield (67% e.e., entry 3). The result of the D-A reaction of **1a** and **2b** shows that the stereoselectivity of *endo*-**3**, **4a** and **5** increased according to the bulkiness of the group  $R^2$  of chiral ligand (**A**, **B** or **C**) as follows ( $\text{Me} < i\text{-Pr} < t\text{-Bu}$ ); Table 1, entry 2, chiral catalyst **A** ( $R^2 = \text{Me}$ ) 85% e.e.; entry 5, **B** ( $R^2 = i\text{-Pr}$ ) 91% e.e.; entry 8, **C** ( $R^2 = t\text{-Bu}$ ) 96% e.e. However, despite our expectations, the D-A reaction of **1a** and **2** using benzyl-bisoxazoline **D** ( $R^2 = \text{Bn}$ ) did not produce better stereoselectivity of *endo*-**4a** (entry 11, **D**,  $R^2 = \text{Bn}$ , 83% e.e.). From these enantioselectivities, we found that chiral ligand **C** (*t*-Bu-bisoxazoline) was suitable for this reaction as the catalyst. Among three types of dienophiles (**2a**, **2b**, and **2c**), **2b** was found to be effective for providing higher enantioselectivity of the D-A cycloadduct.

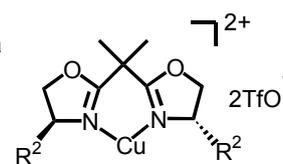


**Table 1.** Effect of catalyst (**A**, **B**, **C** or **D**) in cycloaddition of 1,2-dihydropyridine **1a** with pyrazolidinone (**2a**, **2b** or **2c**)

Entry	<b>2</b>	Catalyst	Product	Yield <sup>a)</sup> / %	% e.e. of <i>endo</i> - <b>3,4a,5</b> <sup>b)</sup>
1	<b>2a</b>	<b>A</b>	<b>3</b>	89	72
2	<b>2b</b>	<b>A</b>	<b>4a</b>	99	85
3	<b>2c</b>	<b>A</b>	<b>5</b>	96	67
4	<b>2a</b>	<b>B</b>	<b>3</b>	99	78
5	<b>2b</b>	<b>B</b>	<b>4a</b>	93	91
6	<b>2c</b>	<b>B</b>	<b>5</b>	91	81
7	<b>2a</b>	<b>C</b>	<b>3</b>	76	98
8	<b>2b</b>	<b>C</b>	<b>4a</b>	71 (24)	96
9	<b>2c</b>	<b>C</b>	<b>5</b>	58 (8)	89
10	<b>2a</b>	<b>D</b>	<b>3</b>	82	66
11	<b>2b</b>	<b>D</b>	<b>4a</b>	95	83
12	<b>2c</b>	<b>D</b>	<b>5</b>	84	62

<sup>a)</sup> Isolated yields. Recovery of dienophile is shown in parentheses.

<sup>b)</sup> Enantiomeric excess (% e.e.) was determined by HPLC analysis using a Daicel Chiralpak AD-H column; eluent, 50% 2-propanol/*n*-hexane, flow rate 0.5 mL/min,  $t_{\text{R}} = 14$  min (major, 7*S*),  $t_{\text{R}} = 17$  min (minor, 7*R*).



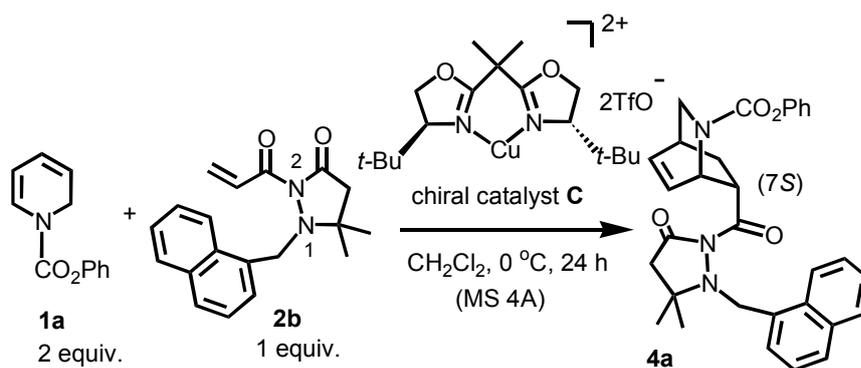
**A:**  $R^2 = \text{Me}$

**B:**  $R^2 = i\text{-Pr}$

**C:**  $R^2 = t\text{-Bu}$

**D:**  $R^2 = \text{Bn}$

We investigated the D-A reaction of **1a** and **2b** by decreasing the amount of catalyst **C** ( $R^2 = t\text{-Bu}$ ) from 30 mol% to 20 mol%, 15 mol% or 10 mol% and the results were summarized in Table 2. Because the coordination between the copper and the chiral ligand was sensitive to moisture, the addition of activated molecular sieves 4A may be effective in enhancing the chemical yield and stereoselectivity in the D-A reaction. The D-A reaction of **1a** and **2b** using 30 mol% of catalyst **C** in the presence of MS-4A showed higher chemical yield and enantioselectivity of *endo*-**4a** (Table 2, entry 1, 91% yield with 98% e.e.) than that in the absence of MS-4A (Table 1, entry 8, 71% yield with 96% e.e.). In the D-A reaction of **1a** and **2b** using 15 mol% of catalyst **C** without MS-4A still afforded *endo*-**4a** with high stereoselectivity but in low yield (Table 2, entry 3, 46% yield with 92% e.e.). In the D-A reaction with MS-4A, the chemical yield and enantioselectivity of *endo*-**4a** increased to 78% yield with 98% e.e. (Table 2, entry 3). However, when the amount of catalyst **C** was reduced to 10 mol% in the presence of MS-4A, the chemical yield and stereoselectivity of *endo*-**4a** was only 44% yield with 90% e.e. (entry 4).



**Table 2.** Effect of molecular sieves 4A

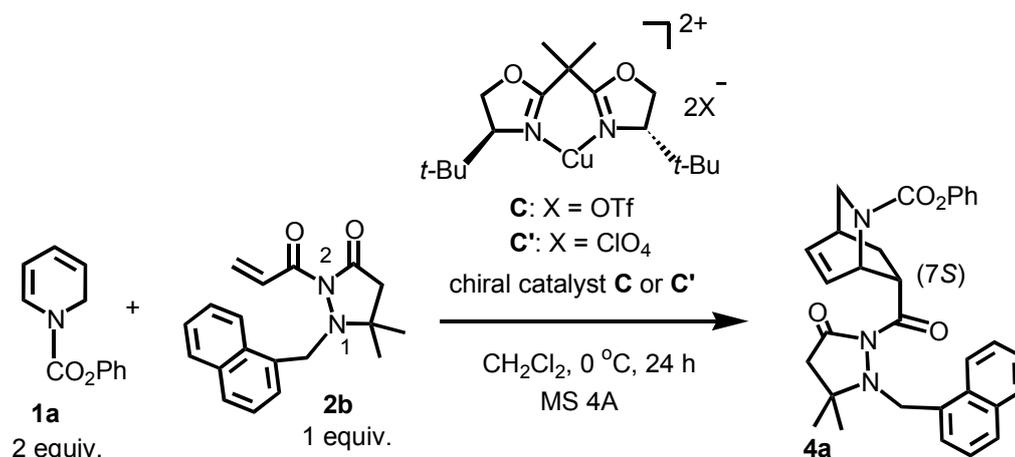
Entry	Catalyst <b>C</b> / mol%	Without MS-4A		With MS-4A	
		Yield/% <i>endo</i> - <b>4a</b> <sup>a)</sup>	% e.e. of <i>endo</i> - <b>4a</b> <sup>b)</sup>	Yield/% <i>endo</i> - <b>4a</b> <sup>a)</sup>	% e.e. of <i>endo</i> - <b>4a</b> <sup>b)</sup>
1	30	71 (24)	96	91 (4)	98
2	20	43 (27)	95	82 (10)	97
3	15	46 (30)	92	78 (10)	98
4	10	10 (40)	40	44 (33)	90

<sup>a)</sup> Isolated yields. Recovery of dienophile is shown in parentheses.

<sup>b)</sup> Enantiomeric excess (% e.e.) was determined by HPLC analysis using a Daicel Chiralpak AD-H column; eluent, 50% 2-propanol/*n*-hexane, flow rate 0.5 mL/min,  $t_{\text{R}} = 14$  min (major, 7*S*),  $t_{\text{R}} = 17$  min (minor, 7*R*).

In the D-A reaction of **1a** and **2b** using 15 mol% of  $\text{Cu}(\text{OTf})_2$  without (*S,S*)-*t*-Bu-bisoxazoline, *endo*-**4a** was obtained in 87% yield (Table 3, entry 1). From this result, we considered that the complete formation of Cu(II)-complex with (*S,S*)-*t*-Bu-bisoxazoline is very important. When the excess amount

of chiral ligand (*S,S*)-*t*-Bu-bisoxazoline than the amount of Cu(OTf)<sub>2</sub> was used in the presence of MS-4A, the enantioselectivity of the D-A adduct *endo*-**4a** was increased (Table 3). The D-A reaction of **1a** and **2b** in the presence of 17 mol% of (*S,S*)-*t*-Bu-bisoxazoline and 15 mol% of Cu(OTf)<sub>2</sub> gave *endo*-**4a** in 76% yield with 99% e.e. (Table 3, entry 2). This result gave slightly higher stereoselectivity than that in the presence of 15 mol% of *t*-Bu-bisoxazoline and 15 mol% of Cu(OTf)<sub>2</sub>, which *endo*-**4a** was obtained in 78% yield with 98% e.e. (Table 2, entry 3). Furthermore, the reaction in the presence of 18 mol% of *t*-Bu-bisoxazoline and 15 mol% of Cu(OTf)<sub>2</sub> gave *endo*-**4a** in better yield (Table 3, entry 3, 82% yield with 99% e.e.). Similarly, in the reaction using 12 mol% of (*S,S*)-*t*-Bu-bisoxazoline and 10 mol% of Cu(OTf)<sub>2</sub>, the enantiomeric excess of *endo*-**4a** was increased to 98% e.e. (Table 3, entry 4), though the reaction in the presence of 10 mol% of *t*-Bu-bisoxazoline and 10 mol% of Cu(OTf)<sub>2</sub> gave *endo*-**4a** in 44% yield with 90% e.e. (Table 2, entry 4). Next, we examined the effect of counter ion of catalyst in the D-A reaction. In the reaction using 18 mol% of *t*-Bu-bisoxazoline and 15 mol% of Cu(ClO<sub>4</sub>)<sub>2</sub>, *endo*-**4a** was obtained in 61% yield with 97% e.e. (Table 3, entry 6). Though the reaction was continued for 48 h, the chemical yield and stereoselectivity of *endo*-**4a** was 65% yield with 96% e.e. (Table 3, entry 7).



**Table 3.** Effect of excess amount of bisoxazoline and counter ions of catalyst

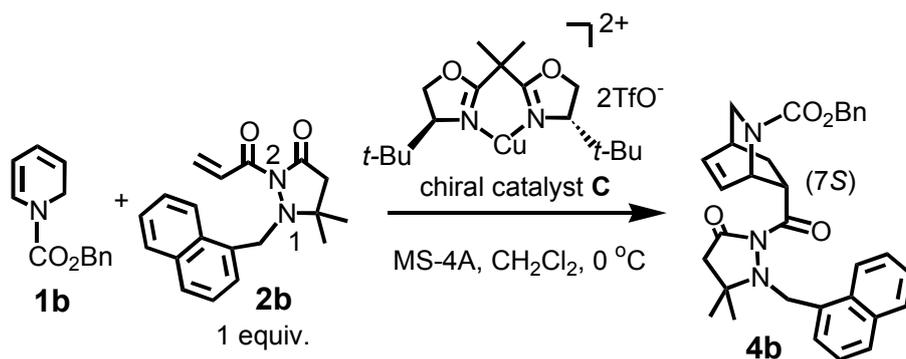
Entry	<b>1</b>	Counter ion X	Bisoxazoline / mol%	Lewis Acid / mol%	Yield <sup>a)</sup> / %	% e.e. of <i>endo</i> - <b>4a</b> <sup>b)</sup>
1	<b>1a</b>	OTf	-	15	87	0
2	<b>1a</b>	OTf	17	15	76 (16)	99
3	<b>1a</b>	OTf	18	15	82 (14)	99
4	<b>1a</b>	OTf	12	10	69 (17)	98
5	<b>1a</b>	ClO <sub>4</sub>	17	15	45 (34)	97
6	<b>1a</b>	ClO <sub>4</sub>	18	15	61 (23)	97
7 <sup>c)</sup>	<b>1a</b>	ClO <sub>4</sub>	18	15	65 (14)	96

<sup>a)</sup> Isolated yield. Recovery of dienophile is shown in parentheses.

<sup>b)</sup> Enantiomeric excess (% e.e.) was determined by HPLC analysis using a Daicel Chiralpak AD-H column; eluent, 50% 2-propanol/*n*-hexane, flow rate 0.5 mL/min, *t*<sub>R</sub> = 14 min (major, 7*S*), *t*<sub>R</sub> = 17 min (minor, 7*R*).

<sup>c)</sup> Reaction time is 48 h.

We also investigated the D-A reaction of *N*-benzyloxycarbonyl-1,2-dihydropyridine **1b** with **2b**. In the D-A reaction of **1b** (2 equiv.) with *N*(2)-acryloyl-*N*(1)-(1-naphthylmethyl)-5,5-dimethylpyrazolidin-3-one **2b** (1 equiv.) was carried out in the presence of 30 mol% of catalyst **C** gave *endo*-**4b** in 42% yield with 99% e.e. (Table 4, entry 1). In the D-A reaction of **1b** with **2b**, the dropwise addition of **1b** (2 equiv.) to **2b** (1 equiv.) was carried out in the presence of MS-4A using 30 mol% of catalyst **C**, and *endo*-**4b** was obtained in better yield (entry 2, 78% yield with 99% e.e.). We also investigated the D-A reaction by dropwise addition of **1b** (3 equiv.) to **2b** (1 equiv.) and the *endo*-**4b** was obtained in 75% yield with 99% e.e. (entry 3). The D-A reaction of **1b** with **2b** for 48 h, afforded *endo*-**4b** in 73% yield with 99% e.e. (entry 4). Since the presence of a small excess amount of (*S,S*)-*t*-Bu-bisoxazoline to Cu salt in the reaction between **1a** and **2b** improved the chemical yield and stereoselectivity of the cycloadduct *endo*-**4a** as shown in Table 3, we have examined the D-A reaction of **1b** (3 equiv.) with **2b** (1 equiv.) using 36 mol% of (*S,S*)-*t*-Bu-bisoxazoline and 30 mol% of Cu(OTf)<sub>2</sub>, however, the chemical yield with stereoselectivity of *endo*-**4b** was 72% yield with 99% e.e. (entry 5).



**Table 4.** Cycloaddition of diene **1b** with **2b**

Entry	<b>1</b> (equiv.)	Time	Bisoxazoline / mol%	Lewis Acid / mol%	Yield <sup>a)</sup> / %	% e.e. of <i>endo</i> - <b>4b</b> <sup>b)</sup>
1 <sup>c)</sup>	<b>1b</b> (2)	24	30	30	42 (26)	99
2	<b>1b</b> (2)	24	30	30	78	99
3	<b>1b</b> (3)	24	30	30	75	99
4	<b>1b</b> (3)	48	30	30	73	99
5	<b>1b</b> (3)	24	36	30	72	99

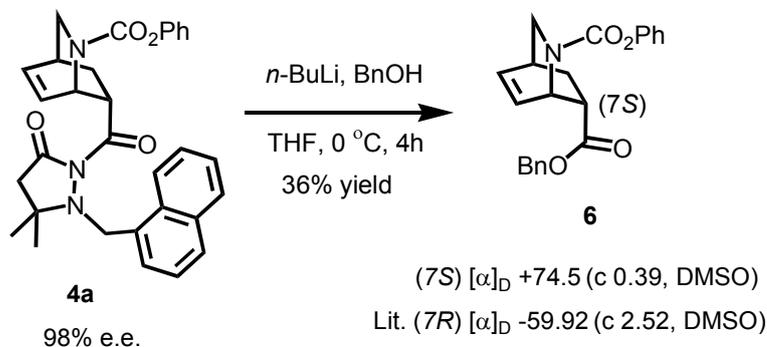
<sup>a)</sup> Isolated yield. Recovery of dienophile is shown in parentheses.

<sup>b)</sup> Enantiomeric excess (% e.e.) was determined by HPLC analysis using a Daicel Chiralpak AD-H column; eluent, 50% 2-propanol/hexane, flow rate 0.5 mL/min,  $t_R = 20$  min (major, 7*S*),  $t_R = 24$  min (minor, 7*R*).

<sup>c)</sup> Without MS-4A.

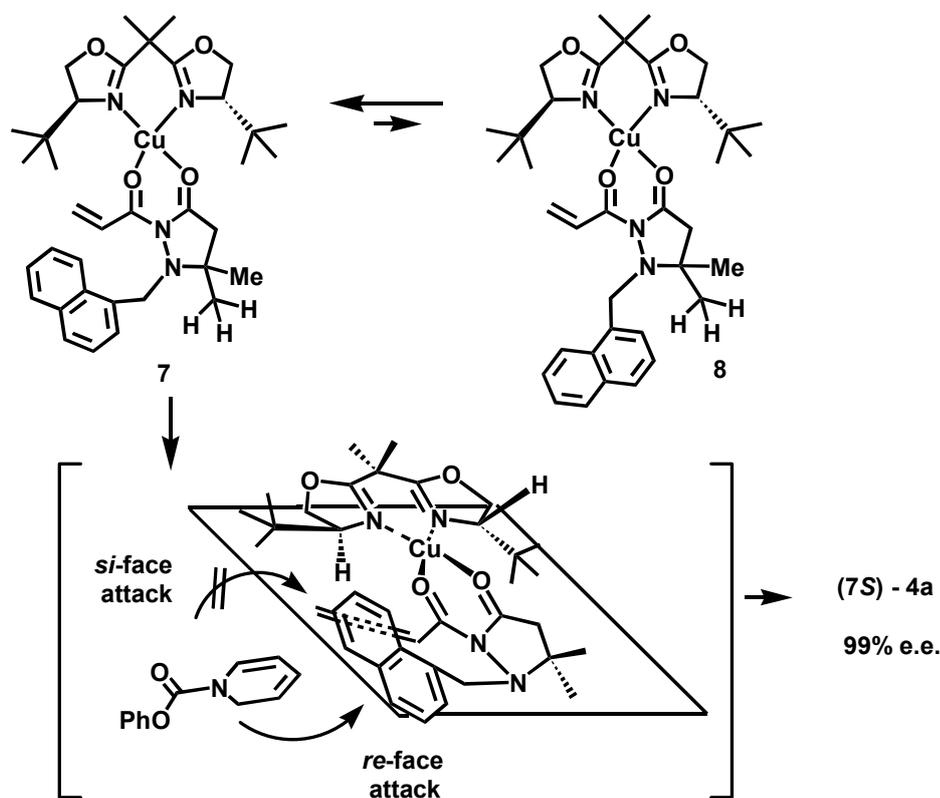
The absolute stereochemistry of D-A adduct **4a** was established to be (1*S*,4*R*,7*S*) by comparing the sign of the optical rotation with the literature value of (7*R*)-benzyl ester **6**, {lit.,<sup>3a</sup> [ $\alpha$ ]<sub>D</sub> -59.92 (*c* 2.52, DMSO)} as follows: the reaction of the *endo*-**4a** (98% e.e.) with benzyl alcohol using *n*-BuLi as a base (PhCH<sub>2</sub>OLi)

in THF afforded the corresponding (7*S*)-benzyl ester **6**  $\{[\alpha]_D +74.5$  (*c* 0.39, DMSO), 98% e.e. $\}$  in 36% yield (Scheme 1).



**Scheme 1.** Determination of absolute configuration of Diels-Alder adduct **4a**

From the absolute stereochemistry and high enantioselectivity (up to 99% e.e.) of (7*S*)-**4a**, we considered the plausible reaction mechanism of the asymmetric D-A reaction of **1a** and **2b** as shown in Figure 2. It is well established that the complex of (4*S*,4'*S*)-bisoxazoline-Cu(II) catalyst react via distorted square planar geometries upon complexation to bidentate substrates.<sup>7b</sup> Sibi *et al.* have reported the x-ray structures of pyrazolidinones and possibility of  $\pi$ - $\pi$  interactions between aromatic relay groups and the olefin of the dienophile.<sup>10c</sup>



**Figure 2.** Plausible reaction mechanism of D-A reaction of **1a** and **2b** using catalyst **C**

The role of the flunctional *N*(1) substituent with the bulky 1-naphthylmethyl group of achiral pyrazolidinone template in conjugation with chiral Lew acid, (*4S,4'S*)-*t*-Bu-bisoxazoline catalyst **C** ( $R^2 = t\text{-Bu}$ ), provided enantioselectivities up to 99% e.e. Some chiral Lewis acids might induce chirality such that the pyrazolidinone chirality works in concert with the chiral Lewis acid (matched case) and amplify enantioselectivity. In other cases, the induced chirality might display a mismatched, dissonant effect.

In the complex of dienophile **2b** and (*4S,4'S*)-*t*-Bu-bisoxazoline catalyst **C** ( $R^2 = t\text{-Bu}$ ), the reaction might be through the intermediate **7** that has less steric interaction between *N*(1)-1-naphthylmethyl group and C-5 methyl hydrogen atoms of dienophile than that of the intermediate **8**. Thus, 1,2-dihydropyridine **1a** can approach from the *re*-face to give (*7S*)-**4a** (up to 99% e.e.) since the *si*-face of the *N*(2)-acryloyl group of dienophile **2b** is shielded by the *N*(1)-1-naphthylmethyl group of dienophile **2b** and C4-*tert*-butyl group of (*4S,4'S*)-*t*-Bu-bis(oxazoline) catalyst **C**.

In conclusion, we have developed the highly enantioselective Diels-Alder reaction of 1,2-dihydropyridine derivatives (**1a** and **1b**) with achiral dienophile *N*(2)-acryloyl-*N*(1)-(1-naphthylmethyl)-5,5-dimethylpyrazolidin-3-one **2b** using (*S,S*)-*tert*-Bu-substituted bisoxazoline-Cu(II) catalyst **C**, which provides an efficient methodology for obtaining the pharmacologically important chiral isoquinuclidine derivatives in good yield with high enantioselectivity (up to 99% e.e.).

## EXPERIMENTAL

**General.** Melting points were measured using AS ONE ATM-01 melting point apparatus.  $^1\text{H}$  NMR spectra and  $^{13}\text{C}$  NMR spectra were recorded at 270 MHz on JEOL JNM-EX 270 FT NMR SYSTEM and 500 MHz and 125 MHz on a JEOL JNM-ECA. Chemical shifts of  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR are reported in parts per million downfield from tetramethylsilane ( $\delta$ ) as the internal standard and coupling constants are in hertz (Hz). Specific rotations were recorded at the sodium D line with a polarimeter. Purification of reaction product was carried out by flash chromatography on silica gel 60 (KANTO CHEMICALS, 40-100  $\mu\text{m}$ ). The enantiomeric excess (e.e.) of the cycloaddition products was determined by high performance liquid chromatography (HPLC) using the Chiralpak AD-H (25 cm). Bisoxazoline ligands ( $R^2 = \text{Me}$ , *i*-Pr, and Bn) were prepared according to the reported methods.<sup>10b</sup> (*S,S*)-*t*-Butyl-bisoxazoline ligand was purchased from Tokyo Chemical Ind. Co. Commercially available compounds were used without further purification.

**1.1 Preparation of 1-(phenoxycarbonyl)-1,2-dihydropyridine (**1a**)<sup>9</sup>:** The compound **1a** has been previously prepared.<sup>6b</sup> A solution of pyridine (8.00 g, 65 mmol) and  $\text{NaBH}_4$  (2.06 g, 55 mmol) in 60 mL of absolute EtOH was stirred together at  $-78\text{ }^\circ\text{C}$  and phenyl chloroformate (10.6 g, 65 mmol) was added

slowly for 1 h. The reaction mixture was stirred for 24 h at  $-78\text{ }^{\circ}\text{C}$  and then quenched with ice-water and the mixture was stirred until the  $\text{H}_2$  bubble stopped. The product was extracted with  $\text{Et}_2\text{O}$  (100 mL x 3). The organic layer was dried over sodium sulfate, filtered, and concentrated. The product **1a** was recrystallized from EtOH to give a white solid product in 50% yield (6.60 g, 32.8 mmol). The ratio of 1,2-dihydropyridine and 1,4-dihydropyridine (95:5) was measured by  $^1\text{H}$  NMR ( $\delta$  4.45-4.59 ppm for 1,2-dihydropyridine and  $\delta$  2.89 ppm for 1,4-dihydropyridine): white solid; mp  $64\text{-}66\text{ }^{\circ}\text{C}$ ;  $^1\text{H}$  NMR [ppm] (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.45 (q,  $J = 4.0, 1.9$  Hz, 1.2H), 4.59 (br s, 0.8H), 5.23-5.29 (m, 1H), 5.55-5.61 (m, 1H), 5.89-5.92 (m, 1H), 6.81 (d,  $J = 7.4$  Hz, 0.6 H), 6.88 (d,  $J = 8.0$  Hz, 0.4 H), 7.13 (d,  $J = 8.0$  Hz, 2H), 7.23 (t,  $J = 7.4$  Hz, 1H), 7.38 (t,  $J = 7.7$  Hz, 2H);  $^{13}\text{C}$  NMR [ppm] (125 MHz,  $\text{CDCl}_3$ )  $\delta$  43.82, 105.85, 119.51, 121.57 (2C), 121.84, 125.37, 125.71, 126.06, 129.40 (2C), 150.92.

**1.2 Preparation of 1-(benzyloxycarbonyl)-1,2-dihydropyridine (1b)<sup>9</sup>:** To absolute EtOH (8 mL) solution of pyridine (1.89 g, 24 mmol) and  $\text{NaBH}_4$  (0.39 g, 10 mmol) was slowly added benzyl chloroformate (3.41 g, 20 mmol for **1a**) for 1 h at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred for 24 h at  $-78\text{ }^{\circ}\text{C}$  and then quenched with ice-water and extract with  $\text{Et}_2\text{O}$ . The organic layer was dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (eluent, *n*-hexane/AcOEt = 20:1) to afford **1b** as pale yellow oil in 54% yield (2.30 g, 10.0 mmol). The ratio of 1,2-dihydropyridine and 1,4-dihydropyridine (99:1) was measured by  $^1\text{H}$  NMR ( $\delta$  4.38 ppm for 1,2-dihydropyridine and  $\delta$  2.89 ppm for 1,4-dihydropyridine): oil;  $^1\text{H}$  NMR [ppm] (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.38 (s, 2H), 5.10 (t,  $J = 6.3$  Hz, 1H), 5.18 (br s, 2H), 5.51-5.53 (m, 1H), 5.80-5.83 (m, 1H), 6.70 (d,  $J = 8.0$  Hz, 0.6H), 6.78 (d,  $J = 7.4$  Hz, 0.4H), 7.32-7.36 (m, 5H);  $^{13}\text{C}$  NMR [ppm] (125 MHz,  $\text{CDCl}_3$ )  $\delta$  43.6, 43.85, 67.77, 105.02, 119.18, 121.86, 125.52, 128.10, 128.27, 128.47, 128.54, 153.00.

**1.3 General procedure for the preparation of bisoxazoline ligand<sup>10b</sup>:** Zinc chloride (5 mmol), dimethylmalononitrile (10 mmol) and (*S*)-2-aminopropanol (22 mmol) {for Me-bisoxazoline ligand ( $\text{R}^2 = \text{Me}$ ) or L-valinol (22 mol) for *i*-Pr-bisoxazoline ligand ( $\text{R}^2 = i\text{-Pr}$ ) or L-alaninol (22 mmol) for Bn-bisoxazoline ligand ( $\text{R}^2 = \text{Bn}$ )} in chlorobenzene (20 mL) was heated at reflux for 72 h. The reaction solution was cooled to room temperature and the solvent was evaporated. The residue was dissolved with  $\text{CH}_2\text{Cl}_2$  (40 mL) and ammonium hydroxide (5 mL) and then the organic layer was washed with water (5 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residual oil was purified by column chromatography (eluent, MeOH/AcOEt = 1:9).

**1.3.1 2,2-Bis[2-(4*S*)-methyl-1,3-oxazolinyl]propane:** 31% yield; colorless oil,  $[\alpha]_{\text{D}}^{25} -119.0$  (*c* 1.02,

CH<sub>2</sub>Cl<sub>2</sub>) (Lit.,<sup>7b</sup> [ $\alpha$ ]<sub>D</sub><sup>25</sup> -67.7 (*c* 1.0, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were identified with the literature values.<sup>10b</sup> <sup>1</sup>H NMR [ppm] (270 MHz, CDCl<sub>3</sub>)  $\delta$  1.25 (d, *J* = 6.4 Hz, 6H), 1.51 (s, 6H), 3.80 (t, *J* = 7.5 Hz, 2H), 4.19 (dd, *J* = 15.7, 6.8 Hz, 2H), 4.36 (t, *J* = 8.6 Hz, 2H); <sup>13</sup>C NMR [ppm] (125 MHz, CDCl<sub>3</sub>)  $\delta$  21.20, 24.26, 38.30, 61.27, 74.35, 168.83.

**1.3.2 2,2-Bis[2-(4*S*)-isopropyl-1,3-oxazolinyl]propane:** 30% yield; colorless oil, [ $\alpha$ ]<sub>D</sub><sup>25</sup> -126.9 (*c* 1.02, CH<sub>2</sub>Cl<sub>2</sub>) (Lit.,<sup>10</sup> [ $\alpha$ ]<sub>D</sub><sup>25</sup> -107.5 (*c* 1.0, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were identified with the literature values.<sup>11</sup> <sup>1</sup>H NMR [ppm] (270 MHz, CDCl<sub>3</sub>)  $\delta$  0.85 (d, *J* = 6.7 Hz, 6H), 0.91 (d, *J* = 6.7, 6H), 1.51 (s, 6H), 1.77-1.84 (m, 2H), 3.92-4.02 (m, 4H), 4.15-4.22 (m, 2H); <sup>13</sup>C NMR [ppm] (125 MHz, CDCl<sub>3</sub>)  $\delta$  17.29, 18.50, 24.41, 32.14, 38.52, 69.88, 71.43, 168.74.

**1.3.3 2,2-Bis[2-(4*S*)-benzyl-1,3-oxazolinyl]propane:** 24% yield; pale yellow oil, [ $\alpha$ ]<sub>D</sub><sup>28</sup> -76.6 (*c* 0.89, CH<sub>2</sub>Cl<sub>2</sub>); <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were identified with the literature values.<sup>11b</sup> <sup>1</sup>H NMR [ppm] (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.45 (s, 6H), 2.63-2.68 (dd, *J* = 13.7, 8.6 Hz, 2H), 3.09 (dd, *J* = 13.7, 4.5 Hz, 2H), 3.99-4.02 (m, 2H), 4.17 (t, *J* = 8.8 Hz, 2H), 4.37-4.42 (m, 4H), 7.18-7.30 (m, 10H); <sup>13</sup>C NMR [ppm] (125 MHz, CDCl<sub>3</sub>)  $\delta$  24.14, 38.49, 41.26, 66.89, 71.97, 126.43, 128.40, 129.42, 137.61, 169.40.

**1.4 General procedure for the preparation of pyrazolidin-3-ones 2a-c<sup>3</sup>:** To a solution of acrylic acid (13 mmol) in THF (50 mL) using a 100 mL flask, triethylamine (25 mmol) was added. The mixture was stirred at -20 °C and acryloyl chloride (12 mmol) was added. The mixture was stirred for 1 h. LiCl (12.5 mmol) and 1-(1-naphthylmethyl)-5,5-dimethylpyrazolidin-3-one (10 mmol) **2a**, 1-(2-naphthylmethyl)-5,5-dimethylpyrazolidin-3-one (10 mmol) **2b** or 1-benzyl-5,5-dimethylpyrazolidin-3-one **2c** was added and the mixture was stirred for 10 min, followed by stirring at room temperature for 24 h. The reaction was quenched with 0.2 M HCl aq. and THF was removed under a reduced pressure. The reaction product was extracted with ethyl acetate, and the organic layer was washed with 0.2 M HCl aq., brine, and 1.0 M NaHCO<sub>3</sub> aq. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtrated, and concentrated under reduced pressure. The residual oil was purified by dry silica gel column chromatography (eluent, toluene). *n*-Hexane was added for crystallization of pyrazolidin-3-one and the solid was filtered to afford **2a**, **2b** or **2c**, respectively.

**1.4.1 N(2)-Acryloyl-N(1)-benzyl-5,5-dimethylpyrazolidin-3-one (2a):** 33% yield, white solid; mp 81-82 °C (Lit.,<sup>10b</sup> mp 82-83 °C); <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were identified with the literature values.<sup>10b</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.29 (s, 6H), 2.57 (s, 2H), 4.07 (s, 2H), 5.67 (d, *J* = 10.9 Hz, 1H), 6.35 (dd, *J* = 17.2, 1.1 Hz, 1H), 7.07 (dd, *J* = 16.6, 10.3 Hz, 1H), 7.23-7.30 (m, 3H), 7.38 (d, *J* = 6.9

Hz, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  26.04, 43.48, 56.96, 60.98, 127.62, 128.13, 128.39, 129.59, 130.72, 136.85, 162.97, 174.38.

**1.4.2 *N*(2)-Acryloyl-*N*(1)-(1-naphthylmethyl)-5,5-dimethylpyrazolidin-3-one (2b):** 39% yield, white solid; mp 129-132 °C (Lit.,<sup>10b</sup> mp 107-109 °C);  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were identified with the literature values.<sup>10b</sup>  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.42 (s, 6H), 2.75 (s, 2H), 4.44 (s, 2H), 4.99 (d,  $J$  = 9.1 Hz, 1H), 5.82 (d,  $J$  = 17.4 Hz, 1H), 6.32 (m, 1H), 7.34-7.37 (m, 1H), 7.45-7.50 (m, 2H), 7.55-7.58 (m, 1H), 7.77 (d,  $J$  = 8.0 Hz, 1H), 7.81 (d,  $J$  = 8.0 Hz, 1H), 8.17 (d,  $J$  = 8.6 Hz, 1H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  25.90, 42.94, 55.21, 61.45, 123.19, 125.32, 125.59, 126.29, 127.44, 128.72, 129.37, 129.42, 131.49, 132.30, 133.59, 163.43, 173.99.

**1.4.3 *N*(2)-Acryloyl-*N*(1)-(2-naphthylmethyl)-5,5-dimethylpyrazolidin-3-one (2c):** 64% yield, white solid; mp 115-116 °C. IR (Nujol) 1507, 1682, 1743  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ )  $\delta$  1.30 (s, 6H), 2.61 (s, 2H), 4.23 (s, 2H), 5.65 (d,  $J$  = 10.3 Hz, 1H), 6.29 (d,  $J$  = 16.6 Hz, 1H), 7.10-7.15 (m, 1H), 7.43-7.47 (m, 2H), 7.62 (d,  $J$  = 8.6 Hz, 1H), 7.78-7.80 (m, 4H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  26.14, 43.54, 57.17, 61.02, 125.91, 126.04, 127.33, 127.62, 127.79, 128.10, 128.17, 128.23, 130.83, 132.78, 133.16, 134.72, 162.91, 174.33. MS  $m/z$  309.15 [ $\text{M}^+ + 1$ ]. Anal. Calcd for: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.00; H, 6.60; N, 9.17.

**1.5 General procedure for D-A reaction of 1,2-dihydropyridine (1a or 1b) with *N*(2)-acryloyl-*N*(1)-arylmethyl-5,5-dimethylpyrazolidinone 2a-c using (*S,S*)-bisoxazoline-Cu(II) (A, B, C, or D):** To the appropriate chiral ligand (0.15 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (2 mL),  $\text{Cu}(\text{OTf})_2$  (0.15 mmol) was added. The reaction mixture was stirred for 2 h at room temperature under nitrogen atmosphere. Dienophile **2** (0.50 mol) dissolved in anhydrous  $\text{CH}_2\text{Cl}_2$  (2 mL) was added to the above solution and then diene **1** (1.0 mmol) was added. The reaction mixture was stirred for 24 h at 0 °C. The reaction was quenched with saturated  $\text{K}_2\text{CO}_3$  aq. (2 mL) and the product was extracted with  $\text{CHCl}_3$ . The organic layer was dried over sodium sulfate, filtered, and concentrated under a reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent, from *n*-hexane/AcOEt = 4:1 to *n*-hexane/AcOEt = 2:1). The reaction conditions, chemical yields and enantioselectivity are shown in Table 1. In the D-A reaction with molecular sieves 4A, the catalyst and molecular sieves 4A (230 mg) were stirred together for 2 h in anhydrous  $\text{CH}_2\text{Cl}_2$  (2 mL), followed by the addition of dienophile **2** and then 1,2-dihydropyridine **1**. The reaction conditions, chemical yields and enantioselectivity are shown in Table 2. In the reaction using  $\text{Cu}(\text{ClO}_4)_2$  as a Lewis acid, a mixture of chiral *t*-Bu-oxazoline (0.090 mmol),  $\text{CuCl}_2$  (0.075 mmol) and  $\text{AgClO}_4$  (0.15 mmol) was stirred in

anhydrous  $\text{CH}_2\text{Cl}_2$  (2 mL) for 2 h under the dark conditions. The mixture was then filtered through a syringe filter and the filtrate containing chiral catalyst **C'** was added to a solution of dienophile **2**. The reaction conditions, chemical yields and enantioselectivity are shown in Table 3. The enantiomeric excess (% e.e.) of *endo*-**3**, **4a**, or **5** was determined by HPLC analysis using a DAICEL Chiralpak AD-H column; eluent, 50% 2-propanol/*n*-hexane; flow rate, 0.5 mL/min, detection at 254 nm; retention time,  $t_{\text{R}} = 14$  min (major, *7S*),  $t_{\text{R}} = 17$  min (minor, *7R*). The enantiomeric excess (% e.e.) of *endo*-**4b** was determined by HPLC analysis using a DAICEL Chiralpak AD-H column; eluent, 50% 2-propanol/*n*-hexane; flow rate, 0.5 mL/min, detection at 254 nm; retention time,  $t_{\text{R}} = 20$  min (major, *7S*),  $t_{\text{R}} = 24$  min (minor, *7R*).

**1.5.1 Diels-Alder adduct (7S)-3:** White solid (recrystallized from AcOEt/*n*-hexane), mp 166-169 °C. (Lit.,<sup>3b</sup> mp 165-168 °C),  $[\alpha]_{\text{D}}^{20} +79.0$  (*c* 0.25,  $\text{CHCl}_3$ , 98% e.e.).  $^1\text{H}$  NMR [ppm] (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.12-1.27 (m, 6H), 1.53-1.64 (m, 1H), 2.04-2.10 (m, 1H), 2.53-2.59 (m, 1H), 2.64-2.69 (m, 1H), 2.84 (br s, 1H), 3.05 (d,  $J = 10.3$  Hz, 0.5H), 3.18 (d,  $J = 10.3$  Hz, 0.5H), 3.35 (d,  $J = 9.6$  Hz, 0.5H), 3.50 (d,  $J = 8.6$  Hz, 0.5H), 3.99 (br s, 1H), 4.04 (br s, 2H), 5.06 (br s, 1H), 6.33-6.44 (m, 2H), 7.12 (d,  $J = 7.4$  Hz, 1H), 7.16-7.24 (m, 3H), 7.28-7.31 (m, 2H), 7.33-7.38 (m, 2H), 7.43-7.44 (m, 2H);  $^{13}\text{C}$  NMR [ppm] (125 MHz,  $\text{CDCl}_3$ )  $\delta$  25.77, 26.64, 27.48, 30.72, 43.47, 45.52, 46.75, 47.22, 57.08, 60.91, 121.77, 121.82, 125.17, 127.43, 127.48, 128.35, 128.85, 128.96, 129.17, 129.22, 130.80, 133.66, 137.56, 151.32, 153.37, 169.67, 173.91.

**1.5.2 Diels-Alder adduct (7S)-4a:** White solid (recrystallized from AcOEt/*n*-hexane), mp 134-138 °C. (Lit.,<sup>3b</sup> mp 170-172 °C),  $[\alpha]_{\text{D}}^{20} +92.9$  (*c* 0.25,  $\text{CHCl}_3$ , 99% e.e.).  $^1\text{H}$  NMR [ppm] (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.28-1.41 (m, 6H), 1.61 (s, 2H), 2.68-2.70 (m, 2H), 2.84 (d,  $J = 17.2$  Hz, 1H), 2.90-3.01 (m, 2H), 3.58 (m, 1H), 4.31 (m, 1H), 4.58 (m, 1H), 4.84-4.88 (m, 1H), 6.10 (t,  $J = 6.6$  Hz, 0.5H), 6.17 (t,  $J = 6.6$  Hz, 0.5H), 6.28 (t,  $J = 7.1$  Hz, 1H), 7.12 (d,  $J = 8.0$  Hz, 1H), 7.17-7.26 (m, 2H), 7.35-7.42 (m, 3H), 7.48-7.57 (m, 2H), 7.64 (m, 1H), 7.78 (t,  $J = 8.0$  Hz, 1H), 7.86 (t,  $J = 8.6$  Hz, 1H), 8.18-8.22 (m, 1H);  $^{13}\text{C}$  NMR [ppm] (125 MHz,  $\text{CDCl}_3$ )  $\delta$  25.44, 26.74, 30.25, 30.50, 43.15, 46.43, 46.84, 47.36, 54.96, 61.26, 121.70, 123.25, 123.38, 125.13, 125.15, 125.33, 125.42, 125.73, 125.84, 126.38, 128.48, 128.74, 129.23, 129.26, 131.75, 133.65, 134.32, 151.40, 151.35, 153.13, 173.87.

**1.5.3 Diels-Alder adduct (7S)-4b:** White solid (recrystallized from AcOEt/*n*-hexane), mp 70-72 °C,  $[\alpha]_{\text{D}}^{20} +62.7$  (*c* 0.50,  $\text{CHCl}_3$ , 99% e.e.). IR (Nujol) 1225, 1497, 1688, 1743, 2963  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR [ppm] (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.19-1.39 (m, 6H), 1.65 (s, 3H), 2.58 (s, 1H), 2.67 (d,  $J = 16.6$  Hz, 1H), 2.76-2.98 (m, 3H), 4.28-4.29 (m, 0.5H), 4.49-4.56 (m, 1H), 4.64 (s, 1H), 4.87 (s, 1H), 5.10-5.26 (m, 2H),

6.04 (t,  $J = 6.87\text{Hz}$ , 0.5H), 6.14 (t,  $J = 6.8\text{Hz}$ , 0.5H), 6.20-6.24 (m, 1H), 7.31-7.42 (m, 6H), 7.43-7.55 (m, 2H), 7.67-7.72 (m, 1H), 7.80 (dd,  $J = 31.8, 8.3\text{ Hz}$ , 2H), 8.16 (dd,  $J = 23.7, 8.30\text{ Hz}$ , 1H);  $^{13}\text{C}$  NMR [ppm] (125 MHz,  $\text{CDCl}_3$ )  $\delta$  25.47, 26.72, 30.27, 30.52, 43.13, 46.35, 46.42, 46.67, 55.07, 61.24, 66.71, 123.14, 123.24, 125.31, 125.41, 125.68, 125.84, 126.28, 126.38, 127.74, 127.90, 128.07, 128.21, 128.39, 128.71, 131.63, 133.64, 136.78, 136.89, 154.39, 154.75, 173.80. MS  $m/z$  524.25 [ $\text{M}^+ + 1$ ]. Anal. Calcd for: C, 73.40; H, 6.35; N, 8.02. Found: C, 73.34; H, 6.11; N, 7.96.

**1.5.4 Diels-Alder adduct (7S)-5:** White solid (recrystallized from AcOEt/*n*-hexane), mp 154-156 °C.  $[\alpha]_{\text{D}}^{20} +72.1$  ( $c$  0.25,  $\text{CHCl}_3$ , 89% e.e.). IR (Nujol) 1205, 1595, 1716, 2969  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR [ppm] (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.12-1.29 (m, 6H), 1.47-1.49 (m, 1H), 2.04 (m, 1H), 2.69 (d,  $J = 24.6\text{ Hz}$ , 3H), 2.99 (d,  $J = 10.8\text{ Hz}$ , 0.5H), 3.12 (d,  $J = 10.3\text{ Hz}$ , 0.5H), 3.31 (d,  $J = 10.3\text{ Hz}$ , 0.5H), 3.46 (d,  $J = 9.74\text{ Hz}$ , 0.5H), 3.98 (br s, 1H), 4.13-4.22 (m, 2H), 5.06 (d,  $J = 23.7\text{ Hz}$ , 1H), 6.09 (t,  $J = 7.4\text{ Hz}$ , 1H), 6.17 (t,  $J = 6.9\text{ Hz}$ , 0.5H), 6.27 (t,  $J = 6.6\text{ Hz}$ , 0.5H), 7.11 (d,  $J = 8.0\text{ Hz}$ , 1H), 7.14-7.20 (m, 2H), 7.32-7.37 (m, 2H), 7.44-7.46 (m, 2H), 7.64-7.67 (m, 1H), 7.77-7.82 (m, 4H);  $^{13}\text{C}$  NMR [ppm] (125 MHz,  $\text{CDCl}_3$ )  $\delta$  25.97, 27.49, 30.31, 30.61, 43.49, 45.70, 46.64, 47.19, 57.30, 60.01, 121.74, 121.80, 125.12, 125.79, 125.96, 127.08, 127.23, 127.44, 127.58, 127.65, 127.73, 127.94, 129.12, 129.16, 132.28, 134.09, 135.00, 151.27, 153.32, 169.68, 173.86. MS  $m/z$  510.23 [ $\text{M}^+ + 1$ ]. Anal. Calcd for: C, 73.06; H, 6.13; N, 8.25. Found: C, 73.24; H, 6.15; N, 8.14.

**1.6 Conversion from Diels-Alder adduct 4a to benzyl ester (7S)-6:** *n*-BuLi (0.29 mL, 1.65 M in *n*-hexane, 0.48 mmol) was added to a cooled (-78 °C) solution of benzyl alcohol (0.064 mL, 0.62 mmol) in 5 mL of THF. The resulting solution was stirred for 5 min and a solution of adduct **4a** (0.30 mmol, 98% e.e.) in THF (1 mL) was added. The solution was warmed to 0 °C and stirred for 4 h. The mixture was then quenched with saturated  $\text{NaHCO}_3$  aq. and the solvent was concentrated under reduced pressure. Water was added to the residue and extracted with  $\text{CHCl}_3$ . The combined organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The residue was purified by column chromatography on silica gel (eluent, 25% AcOEt in *n*-hexane) and benzyl ester (7S)-**6** was obtained in 36% yield (39 mg, 0.11 mmol). The enantiomeric excess (98% e.e.) of benzyl ester (7S)-**6**  $\{[\alpha]_{\text{D}}^{27} +74.5$  ( $c$  0.39, DMSO) $\}$  as shown in Scheme 1 was determined by HPLC analysis using a DAICEL Chiralpak AD-H column; eluent, 5% 2-propanol/*n*-hexane; flow rate, 0.8 mL/min, detection at 254 nm; retention time,  $t_{\text{R}} = 33.1$  min (major, 7S),  $t_{\text{R}} = 38.5$  min (minor, 7R). The absolute stereochemistry of Diels-Alder adduct **4a** was established to be (1*S*,4*R*,7*S*) by comparing the sign of the optical rotation with the literature value of (7*R*)-benzyl ester **6**,  $\{ \text{lit.},^{3a} [\alpha]_{\text{D}} -59.92$  ( $c$  2.52, DMSO) $\}$ .

**1.6.1 Benzyl ester (7S)-6:** yield 39 mg, oil, 36%;  $[\alpha]_{\text{D}}^{27} +74.5$  ( $c$  0.39, DMSO; 98% e.e.); {Lit.,<sup>3a</sup> benzyl ester (7R)  $[\alpha]_{\text{D}}^{25} -59.92$  ( $c$  2.52, DMSO)}; The  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra of (7S)-6 were identified with the literature values.<sup>3a</sup>  $^1\text{H}$  NMR (270 MHz,  $\text{CDCl}_3$ )  $\delta$  1.93-1.95 (m, 2H), 2.89 (br s, 1H), 3.04 (d,  $J = 10.5$  Hz, 0.5H), 3.15 (d,  $J = 10.0$  Hz, 0.5H), 3.22-3.25 (m, 1H), 3.34 (d,  $J = 10.5$  Hz, 0.5H), 3.48 (d,  $J = 10.2$  Hz, 0.5H), 5.04-5.12 (m, 2H), 5.15-5.24 (m, 1H), 6.31-6.36 (m, 1H), 6.45-6.50 (m, 1H), 7.07-7.12 (m, 2H), 7.16-7.19 (m, 1H), 7.24-7.32 (m, 7H);  $^{13}\text{C}$  NMR [ppm] (125 MHz,  $\text{CDCl}_3$ )  $\delta$  25.93, 30.60, 44.81, 46.91, 47.52, 66.56, 121.65, 122.72, 125.25, 128.07, 128.16, 128.21, 128.51, 128.55, 129.17, 129.21, 130.54, 135.69, 151.22, 153.58, 153.61, 172.33.

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