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ASYMMETRIC SYNTHESIS OF ISOQUINUCLIDINE BY DIELS-ALDER REACTION OF 1,2-DIHYDROPYRIDINE AND CHIRAL DIENOPHILE UTILIZING A CHIRAL LEWIS ACID

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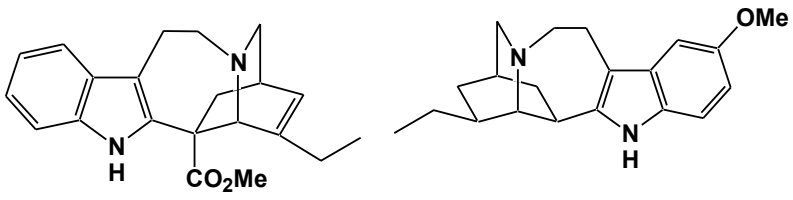
Abstract – The asymmetric Diels-Alder reaction of 1-phenoxycarbonyl-1,2-dihydropyridine **1** with 3-acryloyl (4*S*)-4-benzyl-1,3-oxazolidin-2-one (4*S*)-**2** {or (4*R*)-**2**} in the presence of Ti-TADDOLate **4** as a chiral Lewis acid afforded the chiral isoquinuclidine derivative *endo*-(4'*S*)-**3** in high yield (99%) with high diastereoselectivity (up to 92% d.e.). The reaction exhibits a strong match-mismatch effect. The stereochemistry of *endo*-(4'*S*)-**3** was established to be (1*R*, 4*S*, 7*R*) and a reaction mechanism is proposed.

The isoquinuclidines (2-azabicyclo[2.2.2]octane ring systems) are found in natural products such as iboga-type indole alkaloids which have varied and interesting biological properties (Figure 1).[1] (+)-Catharanthine is of interest because of its eminent role as a biogenetic as well as a synthetic precursor of the antitumor alkaloids, vinblastine and vincristine.[1] (–)-Ibogaine is the medicine for alcohol dependence which has bearing on the ibogamine skeleton.[2] Furthermore, isoquinuclidines are valuable intermediates in the synthesis of other alkaloids,[3] and in medicinal chemistry such as oseltamivir.[4,5] The most promising method for the synthesis of isoquinuclidine derivatives is the Diels-Alder (D-A) reaction between 1,2-dihydropyridines and dienophiles.

Dedicated with respect to Dr. Albert Padwa on the occasion of his 75th birthday.

In the asymmetric synthesis of isoquinuclidines, the diastereoselective cycloadditions using 1,2-dihydropyridines or dienophiles having a chiral auxiliary have been reported.[6] The D-A reaction of 1,2-dihydropyridines and *N*-acryloyl (1*S*)-2,10-camphorsultam in the presence of Lewis acid, such as titanium tetrachloride, zirconium tetrachloride, and hafnium tetrachloride, afforded the *endo*-cycloaddition product (chiral isoquinuclidine derivatives) in good yield with excellent diastereoselectivity (up to 98% d.e.).[6f] Recently, its catalytic enantioselective synthesis was also reported.[7] In order to synthesize the chiral isoquinuclidines, we adopted the asymmetric D-A reaction catalyzed by a chiral Lewis acid. We report the study on the synthesis of the chiral isoquinuclidines by D-A reaction of 1,2-dihydropyridine **1** with chiral dienophile **2** having a chiral auxiliary in the presence of Lewis acid. We investigated the two ways of the asymmetric D-A reactions. One is the reaction of 1-phenoxycarbonyl-1,2-dihydropyridine **1**[8] and 3-acryloyl-(4*S*)-4-benzyl-1,3-oxazolidin-2-one (4*S*)-**2** {or 3-acryloyl-(4*R*)-4-benzyl-1,3-oxazolidin-2-one (4*R*)-**2**}[9] using Lewis acid and the other is the reaction of **1** and (4*S*)-**2** {or (4*R*)-**2**} using Ti-TADDOLate **4** as a chiral Lewis acid. Though it is reported that 1,2-dihydropyridine is unstable for Lewis acid,[6d] our reaction system afforded chiral isoquinuclidines in good yields with high diastereoselectivity (up to 92% d.e.). The absolute stereochemistry of the cycloaddition product *endo*-(4'*S*)-**3** was determined to be (7*R*) by conversion of *endo*-(4'*S*)-**3** to the known benzyl ester (7*R*)-**5**.

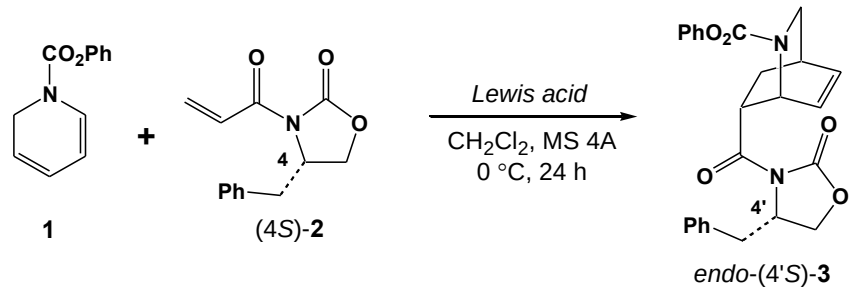


(+)-catharanthine (-)-ibogaine

Figure 1. Indole alkaloids

We first examined the D-A reaction of 1-phenoxycarbonyl-1,2-dihydropyridine **1** and 3-acryloyl-(4*S*)-4-benzyl-1,3-oxazolidin-2-one (4*S*)-**2** using Lewis acids such as dichlorotitanium diisopropoxide, zirconium tetrachloride, hafnium tetrachloride, and scandium trifluoromethane-sulfonate (Scheme 1). These D-A reactions were carried out in dichloromethane at 0 ^{o}C for 24 hours in the presence of molecular sieves 4A and the results are summarized in Table 1. The D-A reaction of 2 equiv. of 1,2-dihydropyridine **1** and 1 equiv. of (4*S*)-**2** using 2 equiv. of Ti(*i*-PrO)$_2$Cl$_2$ was carried out at 0 ^{o}C for 24 hours to afford the cycloaddition product *endo*-(4'*S*)-**3** in 99% yield with 63% d.e. and the product was only *endo* isomer (Table 1, Entry 1). In the D-A reaction of 2

equiv. of **1** and (4*S*)-**2** using 1 equiv. of $ZrCl_4$, only *endo*-(4'*S*)-**3** was obtained in 42% yield with 48% d.e. (Entry 2). Similarly, D-A reaction of 2 equiv. of **1** and (4*S*)-**2** using 1 equiv. of $HfCl_4$, only *endo*-(4'*S*)-**3** was afforded in 73% yield with 59% d.e. (Entry 4). The D-A reacton of 2 equiv. of **1** and 1 equiv. of (4*S*)-**2** using 1 equiv. of $Sc(OTf)_3$ gave only *endo*-(4'*S*)-**3** in 99% yield with 52% d.e. (Entry 6). However, in the D-A reaction of 3 equiv. of **1** and (4*S*)-**2** using 1 equiv. of $ZrCl_4$, the yield of *endo*-(4'*S*)-**3** increased to 72% yield with 57% d.e. (Entry 3). Similarly, in the D-A reaction of 3 equiv. of **1** and (4*S*)-**2** using 1 equiv. of $HfCl_4$, the yield of *endo*-(4'*S*)-**3** increased to 94% yield with 43% d.e. (Entry 5). As a result, the chemical yield of *endo*-(4'*S*)-**3** in the D-A reaction of **1** and (4*S*)-**2** was good to high, however, the diastereoselectivity of *endo*-(4'*S*)-**3** was moderate (43% d.e. to 63% d.e.).



Scheme 1. D-A reaction of **1** and (4*S*)-**2** in the presence of Lewis acid

Table 1. D-A reaction of **1** and (4*S*)-**2** in the presence of Lewis acid

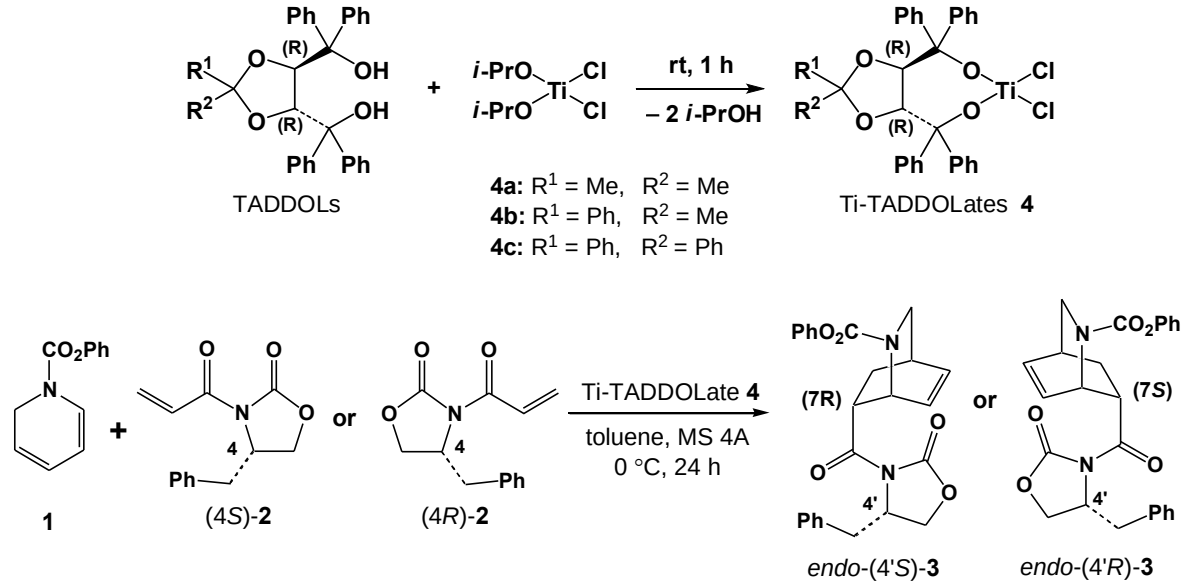
Entry	Diene (mol equiv)	Dienophile (mol equiv)	Lewis Acid (mol equiv)	Yield[a] / % *endo*-**3**	% de of *endo*-**3**[b]
1	**1** (2)	(4*S*)-**2** (1)	$Ti(i\text{-}PrO)_2Cl_2$ (2)	99	63 (4'*S*)
2	**1** (2)	(4*S*)-**2** (1)	$ZrCl_4$ (1)	42 (24)	48 (4'*S*)
3	**1** (3)	(4*S*)-**2** (1)	$ZrCl_4$ (1)	72 (10)	57 (4'*S*)
4	**1** (2)	(4*S*)-**2** (1)	$HfCl_4$ (1)	73 (21)	59 (4'*S*)
5	**1** (3)	(4*S*)-**2** (1)	$HfCl_4$ (1)	94	43 (4'*S*)
6	**1** (2)	(4*S*)-**2** (1)	$Sc(OTf)_3$ (1)	99	52 (4'*S*)

[a] Isolated yield. Recovery of (4*S*)-**2** is shown in parentheses.

[b] Diastereomeric excess (% d.e.) was determined by HPLC analysis using a TOSOH TSK-GEL Silica-60; 5% 2-propanol/*n*-hexane, flow rate 0.8 mL/min, t_R = 18 min (minor), 28 min (major).

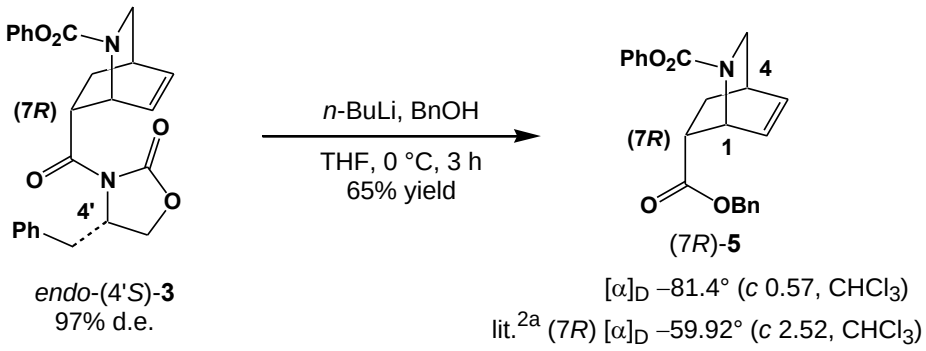
In order to investigate the additional effect of chiral Lewis acid, the chiral 1,4-diol (TADDOL)[11] {TADDOL: (2*R*,3*R*)-2,3-*O*-isopropylidene-1,1,4,4-tetraphenyl-1,2,3,4-butanetetrol, (2*R*,3*R*)-2,3-

O-(1-phenylethylidene)-1,1,4,4-tetraphenyl-1,2,3,4-butanetetrol, and (4*R*,5*R*)-α,α,α',α',2,2-hexaphenyl-4,5-dimethanol-1,3-dioxalone[12]} was employed as a chiral auxiliary (Scheme 2).[10,11] Chiral titanium complex Ti-TADDOLates **4** {**4a** (R^1= R^2= CH_3), **4b** (R^1= Ph, R^2= CH_3), and **4c** (R^1= R^2= Ph)} was prepared from TADDOL and dichlorotitanium diisopropoxide (ratio, 1 : 1) in the presence of molecular sieves 4A at room temperature (Scheme 2).[11] In order to test the possibility of match-mismatch effect on the diastereoselectivity of D-A cycloaddition product *endo*-**3**, the reaction of 1,2-dihydropyridine **1** and (4*S*)-**2** {or (4*R*)-**2**} in the presence of Ti-(2*R*,3*R*)-TADDOLate **4** was carried out in toluene at 0 °C for 24 h and the results are summarized in Table 2. In the D-A reaction of 2 equiv. of **1** and 1 equiv. of (4*S*)-**2** using 0.3 equiv. of **4a**, only *endo*-(4'*S*)-**3** was obtained in 96% yield with 87% d.e. (Table 2, Entry 1). In the D-A reaction of 2 equiv. of **1** and (4*S*)-**2** using 0.3 equiv. of **4b**, only *endo*-(4'*S*)-**3** was obtained in 99% yield with 92% d.e. (Entry 2).[13] The D-A reaction of 2 equiv. of **1** and (4*S*)-**2** using 0.3 equiv. of **4c** afforded only *endo*-(4'*S*)-**3** in 99% yield with 88% d.e. (Entry 3). However, in the D-A reactions of 2 equiv. of **1** and 1 equiv. of (4*R*)-**2** using 0.3 equiv. of **4a-c**, both the chemical yield (51% to 73%) and the diastereoselectivity (68% d.e. to 70% d.e.) of *endo*-(4'*R*)-**3** are lower than those of *endo*-(4'*S*)-**3** produced from the D-A reaction of **1** and (4*S*)-**2** using **4** (Entries 4, 5, and 6). As a result, the combination of Ti-(2*R*,3*R*)-TADDOLate **4** and (4*S*)-**2** was a matched pair to give (7*R*)-**3** in 96% to 99% yield (up to 92% d.e.) (Table 2, Entries 1, 2, and 3), while the combination of Ti-(2*R*,3*R*)-TADDOLate **4** and (4*R*)-**2** was a mismatched pair to afford (7*S*)-**3** in 51% to 73% yield (up to 70% d.e.) (Entries 4, 5, and 6).



Scheme 2. The D-A reaction of **1** and (4*S*)-**2**{or (4*R*)-**2**} in the presence of Ti-TADDOLate **4**

The absolute stereochemistry of the *endo*-(4'*S*)-**3** was established to be (1*R*, 4*S*, 7*R*) by comparing the sign of the optical rotation with the literature value of (7*R*)-benzyl ester **5** {lit.,[2a] $[\alpha]_D$ -59.92° (*c* 2.52, $CHCl_3$), 97% e.e.} as follows: the reaction of the *endo*-(4'*S*)-**3** (97% d.e.) with benzyl alcohol using *n*-BuLi as a base ($PhCH_2OLi$) in THF afforded the corresponding (7*R*)-benzyl ester **5** {$[\alpha]_D$ -81.4° (*c* 0.57, $CHCl_3$), 97% e.e.} in 65% yield (Scheme 3).[14]



Scheme 3. Determination of absolute configuration of (4'*S*)-**3**

On the other hand, the absolute stereochemistry of isoquinuclidine derivative *endo*-(4'*R*)-**3**, which was obtained from the reaction of **1** and (4*R*)-**2** in the presence of Ti-TADDOLate **4b**, has been established to be (1*S*, 4*R*, 7*S*).

Table 2. Match-mismatch effect on diastereoselectivity of **3** in the asymmetric D-A reaction of **1** and (4*S*)-**2** {or (4*R*)-**2**} using Ti-TADDOLate **4**

Entry	Diene (mol equiv)	Dienophile (mol equiv)	Ti-TADDOLate **4** (mol equiv)	Product	Yield[a] / % *endo*-**3**	% de of *endo*-**3**[b]
1	**1** (2)	(4*S*)-**2** (1)	**4a** (0.3)	(7*R*)-**3**	96	87 (4'*S*)
2	**1** (2)	(4*S*)-**2** (1)	**4b** (0.3)	(7*R*)-**3**	99	92 (4'*S*)
3	**1** (2)	(4*S*)-**2** (1)	**4c** (0.3)	(7*R*)-**3**	99	88 (4'*S*)
4	**1** (2)	(4*R*)-**2** (1)	**4a** (0.3)	(7*S*)-**3**	55 (22)	70 (4'*R*)
5	**1** (2)	(4*R*)-**2** (1)	**4b** (0.3)	(7*S*)-**3**	73 (15)	68 (4'*R*)
6	**1** (2)	(4*R*)-**2** (1)	**4c** (0.3)	(7*S*)-**3**	51 (36)	68 (4'*R*)

[a] Isolated yield. Recovery of (4*R*)-**2** is shown in parentheses.

[b] Diastereomeric excess (% d.e.) was determined by HPLC analysis using a TOSOH TSK-GEL Silica-60; 5% 2-propanol/*n*-hexane, flow rate 0.8 mL/min, t_R = 18 min (minor), 28 min (major).

Based on the X-ray structure of complex of Ti-(2*R*,3*R*)-TADDOLate **4a** with 3-[(*E*)-cinnamoyl]-1,3-oxazolidin-2-one reported by Jϕrgensen *et al.*[14], we considered the reaction mechanism of the asymmetric D-A reaction of 1,2-dihydropyridine **1** and (4*S*)-**2** in the presence of Ti-(2*R*,3*R*)-TADDOLate **4b** (Figure 2). As shown in Figure 2, in the complex of matched pair {**4b** and (4*S*)-**2**} 1,2-dihydropyridine **1** can approach predominantly from the *si* face to give (7*R*)-**3** (up to 92% d.e.) since the *re* face of the acryloyl group on the dienophile is shielded by the benzyl group of dienophile (4*S*)-**2** and the phenyl group at pseudoequatorial position of Ti-(2*R*,3*R*)-TADDOLate **4b**. On the other hand, in the complex of mismatched pair {**4b** and (4*R*)-**2**} 1,2-dihydropyridine **1** can approach from the *re* face to give (7*S*)-**3** (up to 70% d.e.) since the *si* face of the acryloyl group on the dienophile is shielded by the benzyl group of dienophile (4*R*)-**2** in the complex of Ti-(2*R*,3*R*)-TADDOLate **4b**. In the complex of mismatched pair {**4b** and (4*R*)-**2**}, the *re* face of the acryloyl group on the dienophile is also shielded by phenyl group at pseudoequatorial position of Ti-(2*R*,3*R*)-TADDOLate **4b**. Consequently, it is assumed that both the chemical yield and the diastereoselectivity of (7*S*)-**3** are lower than those of (7*R*)-**3** produced from the matched pair {**4b** and (4*S*)-**2**}.

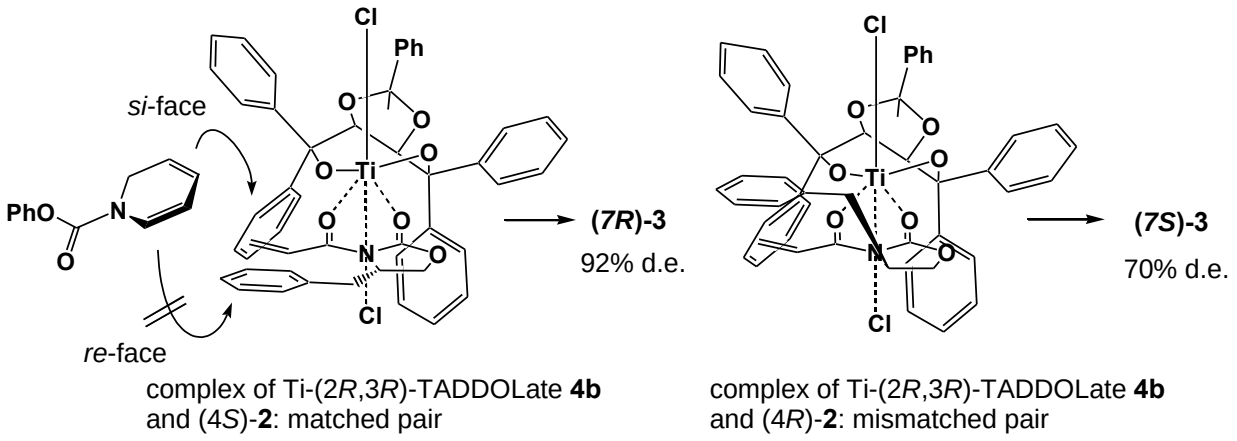


Figure 2. Plausible complex formation of Ti-(2*R*,3*R*)-TADDOLate **4b** and (4*S*)-**2** {or (4*R*)-**2**}

In conclusion, we have accomplished the synthesis of the chiral isoquinuclidine derivative *endo*-(7*R*)-**3** {or *endo*-(7*S*)-**3}** by D-A reaction of 1,2-dihydropyridine **1** with chiral dienophile (4*S*)-**2** {or (4*R*)-**2**} using Ti-TADDOLate **4** as a chiral Lewis acid, respectively. In the D-A reaction, the combination of Ti-TADDOLate **4** and chiral dienophile (4*S*)-**2** {or (4*R*)-**2**} affected the chemical yield and the diastereoselectivity of the chiral isoquinuclidine derivative *endo*-(7*R*)-**3** {or *endo*-(7*S*)-**3**}.

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13. Cycloaddition of 1-phenoxycarbonyl-1,2-dihydropyridine **1** with dienophile (4*S*)-**2** in the presence of Ti-TADDOLate **4b**: To the toluene (3 mL) solution of TADDOL (R^1 = Ph, R^2 = Me) (79 mg, 0.15 mmol) and molecular sieves 4A (200 mg) was added Ti(*i*-PrO)$_2$Cl$_2$ (36 mg, 0.15 mmol) at room temperature and the solution was stirred for 1 h under nitrogen. Then (4*S*)-**2** (116 mg, 0.50 mmol) was added and the solution was stirred at room temperature for 30 min, and the solution was cooled to 0 °C. To this solution was added the toluene (2 mL) solution of 1-phenoxycarbonyl-1,2-dihydropyridine **1** (201 mg, 1.00 mmol) and the solution was stirred at 0 °C for 24 h. Then saturated NaHCO$_3$ and water were added and the product was extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate and filtered. After purification of crude product by column chromatography on silica gel (20% ethyl acetate in hexane), the *endo*-(4'*S*)-**3** was obtained in 99% yield (214 mg, 0.495 mmol) with 92% d.e. *endo*-(4'*S*)-**3**: $[\alpha]_D$ –58.3° (*c* 0.50, CHCl$_3$). ^{1}H NMR [ppm] (500 MHz, CDCl$_3$, 20 °C): δ 1.54-1.59 (0.5H, m), 1.72-1.77 (0.5H, m), 2.14-2.19 (0.5H, m), 2.31-2.36 (0.5H, m), 2.71 (1H, dd, *J*=13.3, 9.8 Hz), 2.89-2.93 (1H, m), 3.09 (0.5H, td, *J*=10.6, 2.6 Hz), 3.22 (0.5H, td, *J*=10.4, 2.5 Hz), 3.29 (1H, d, *J*=13.3 Hz), 3.40 (0.5H, dd, *J*=10.6, 1.9 Hz), 3.56 (0.5H, dd, *J*=10.3, 1.9 Hz), 4.13-4.16 (2H, m), 4.21-4.29 (1H, m), 4.52-4.60 (1H, m), 5.17-5.19 (0.5H, m), 5.24-5.26 (0.5H, m), 6.48-6.51 (1H, m), 6.54-6.62 (1H, m), 7.12-7.14 (1H, m), 7.16-7.21 (4H, m), 7.24-7.28 (1H, m), 7.30-7.37 (4H, m); ^{13}C NMR [ppm] (125 MHz, CDCl$_3$, 20 °C): δ 28.58, 30.84, 37.79, 45.17, 46.66, 47.75, 55.60, 66.32, 121.81, 125.22, 127.42, 129.04, 129.23, 129.26, 129.38, 129.42, 130.73, 132.45, 133.57, 134.86, 135.20, 151.32, 152.65, 153.44, 173.01.

14. (7*R*)-benzyl ester **5** (97% e.e.): The enantiomeric excess (97% e.e.) of (7*R*)-benzyl ester **5** {$[\alpha]_D$ -81.4° (*c* 0.57, CHCl$_3$)} as shown in Scheme 3 was determined by HPLC analysis using a DAICEL chiralcel AD-H column; eluent 5% 2-propanol/hexane, flow rate 0.8 mL/min, t_R = 28.7 min (minor), 32.0 min (major). (7*S*)-benzyl ester **5** (99% e.e.): $[\alpha]_D$ +90.4° (*c* 0.71, CHCl$_3$); $[\alpha]_D$ +74.46° (*c* 0.39, DMSO); (7*R*)-benzyl ester **5** (97% e.e.): lit.[2b] $[\alpha]_D$ -59.92° (*c* 2.52, DMSO).

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