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An efficient synthesis of chiral isoquinuclidines by Diels–Alder reaction using Lewis acid catalyst

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ABSTRACT

The Diels–Alder reaction of 1,2-dihydropyridine derivatives (1-phenoxycarbonyl-1,2-dihydropyridine **1** or 1-methoxycarbonyl-1,2-dihydropyridine **4**) with *N*-acryloyl (1*S*)-2,10-camphorsultam (1*S*)-**2** {or *N*-acryloyl (1*R*)-2,10-camphorsultam (1*R*)-**2**} in the presence of Lewis acid, such as titanium tetrachloride, zirconium tetrachloride, and hafnium tetrachloride afforded the *endo*-cycloaddition product, 2-azabicyclo[2.2.2]octane derivatives in good yields with excellent diastereoselectivity. The absolute stereochemistry assignment of the *endo*-cycloaddition product (1*S*)-**5a** starting from *N*-acryloyl (1*S*)-2,10-camphorsultam (1*S*)-**2** has been established to be (1*S*,4*R*,7*S*) and the reaction mechanism was proposed.

1. Introduction

The isoquinuclidine ring system, 2-azabicyclo[2.2.2]octane ring is common to *Iboga*-type indole alkaloids of which (+)-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] (−)-Ibogamine and (+)-catharanthine are prototypical structures of *Iboga* alkaloids (Fig. 1). It is known that Ibogaine, which is the medicine for alcohol dependence is bearing the ibogamine skeleton.[2] Furthermore, isoquinuclidines are valuable intermediates in the synthesis of other alkaloid,[3] such as oseltamivir[4] and in medicinal chemistry.[5] The Diels–Alder (D–A) reaction between 1,2-dihydropyridines and chiral dienophiles may be the most promising method for this purpose. In the asymmetric synthesis of the 2-azabicyclo[2.2.2]octane ring system, diastereoselective cycloadditions using 1,2-dihydropyridines or dienophiles attached to a chiral auxiliary have been reported.[6] Recently, its catalytic enantioselective synthesis was also reported.[7]

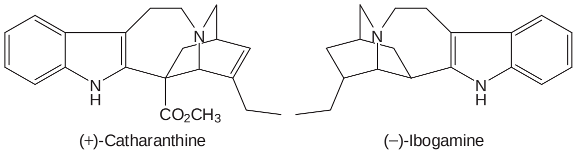
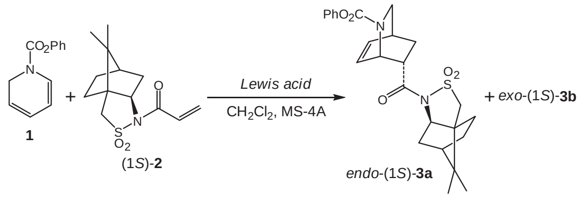


Figure 1. Iboga alkaloids.

We investigated the D–A cycloaddition of 1,2-dihydropyridine derivatives[8] (1-phenoxycarbonyl-1,2-dihydropyridine **1** or 1-methoxycarbonyl-1,2-dihydropyridine **4**) with *N*-acryloyl-(1*S*)-2,10-camphorsultam (1*S*)-**2** {or *N*-acryloyl-(1*R*)-2,10-camphorsultam (1*R*)-**2**}[6c,9] in the presence of a Lewis acid (Schemes 1, 3 and 4).[10] Though it is reported that 1,2-dihydropyridine is unstable for Lewis acid, our reaction system afforded chiral



Scheme 1. Cycloaddition reaction of 1-phenoxycarbonyl-1,2-dihydropyridine **1** with *N*-acryloyl (1*S*)-2,10-camphorsultam **2** in the presence of Lewis acid.

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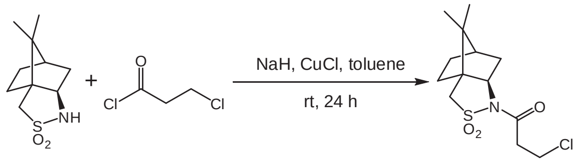
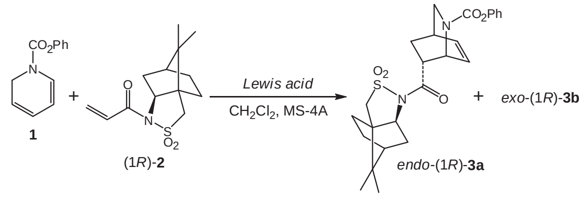
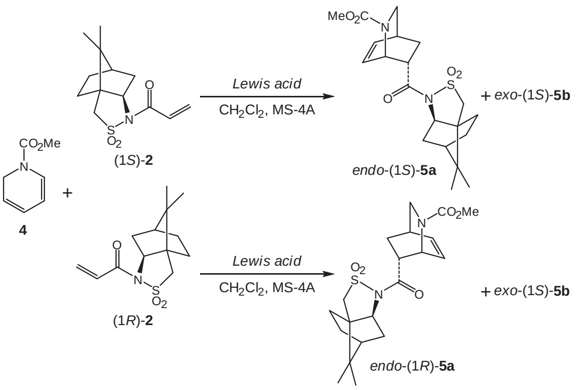


Scheme 2. Preparation of *N*-3-chloropropanoyl (1*S*)-2,10-camphorsultam.



Scheme 3. Cycloaddition reaction of 1-phenoxycarbonyl-1,2-dihydropyridine **1** with *N*-acryloyl (1*R*)-2,10-camphorsultam **2** in the presence of Lewis acid.



Scheme 4. Cycloaddition of 1,2-dihydropyridine **4** with (1*S*)-**2** or (1*R*)-**2** in the presence of Lewis acid.

isoquinuclidines in good yields with high diastereoselectivity. The absolute stereochemistry of the *endo*-cycloaddition products was determined by conversion of (1*S*)-**5a** to the known product (7*S*)-**6**.[11] We describe the detail of the very useful method for synthesis of the chiral isoquinuclidines.

2. Results and discussion

2.1. Diels–Alder reaction of 1-phenoxycarbonyl-1,2-dihydropyridine 1 with 1*S*-2 (or 1*R*-2)

We initially tested the cycloaddition of 1-phenoxycarbonyl 1,2-dihydropyridine **1** with *N*-acryloyl-(1*S*)-2,10-camphorsultam **2**. The reaction was carried out under reflux conditions in toluene to give the corresponding cycloaddition products **3** (*endo* **3a**:*exo* **3b**=57:43) in 82% yield with 38% de of *endo* adduct **3a** (Table 1, entry 15).

Thus, the cycloaddition of **1** with (1*S*)-**2** under reflux conditions showed low diastereoselectivity. Next, the cycloadditions of **1** with (1*S*)-**2** in the presence of various Lewis acids, such as titanium tetrachloride ($TiCl_4$), zirconium tetrachloride ($ZrCl_4$), and hafnium tetrachloride ($HfCl_4$) as a catalyst were investigated.

The results of the cycloaddition in the presence of a Lewis acid are summarized in Table 1. The cycloaddition of **1** with (1*S*)-**2** in the presence of 1.3 equiv of $TiCl_4$ was carried out at −78 °C in dichloromethane to afford the *endo*-cycloaddition product **3a** in 99% yield with 94% de (Table 1, entry 1). The cycloaddition of **1** with (1*S*)-**2** using 2 equiv of $TiCl_4$ was carried out at −78 °C for 24 h, followed by reaction at room temperature for 24 h to give the *endo*-cycloaddition product **3a** in 66% yield with 96% de (entry 2). When the cycloaddition of **1** with (1*S*)-**2** in the presence of $TiCl_4$ (1 equiv) was run at 0 °C or at room temperature, the reaction did not proceed well and the unknown compound, the chlorinated camphorsultam as shown in Scheme 2 (5% yield at 0 °C, 44% yield at room temperature), was obtained. The yield of **3a** was 30% and (1*S*)-**2** (46% yield) was recovered at 0 °C (entry 3). In order to determine the unknown compound, *N*-3-chloropropanoyl (1*S*)-2,10-camphorsultam[12] was prepared (Scheme 2) and the ^1H NMR spectra of the authentic compound and the by-product were identical. Therefore, in a case of using $TiCl_4$, it is necessary to keep the low reaction temperature (−78 °C).

The reactivity of several Lewis acids for the asymmetric cycloaddition of 1-phenoxycarbonyl 1,2-dihydropyridine **1** with (1*S*)-**2** was also investigated. Lewis acids of the group IV metals such as $TiCl_4$, $ZrCl_4$, and $HfCl_4$ have been found to be effective catalysts for this cycloaddition system. In the presence of these catalysts, the cycloadditions of **1** with (1*S*)-**2** produced the *endo*-cycloaddition product (1*S*)-**3a** in good yields, and the diastereoselectivity of the *endo*-cycloaddition product was excellent as shown in Table 1; for

Table 1
Cycloaddition of 1,2-dihydropyridine **1** with dienophile (1*S*)-**2** or (1*R*)-**2** in the presence of Lewis acid

Entry	Diene (mol equiv)	Dienophile (mol equiv)	Lewis acid (mol equiv)	Temp/°C	Time/h	Yield[a]/%	*endo*:*exo* **3a**:**3b**	% de of *endo* **3a**[b]
1	**1** (2)	(1*S*)-**2** (1)	$TiCl_4$ (1.3)	−78	24	99	96:4	94 (1*S*)
2[c]	**1** (2)	(1*S*)-**2** (1)	$TiCl_4$ (2)	−78 then rt	48	66 (28)	98:2	96 (1*S*)
3	**1** (2)	(1*S*)-**2** (1)	$TiCl_4$ (1)	0	24	30 (46)	94:6	93 (1*S*)
4[d]	**1** (2)	(1*S*)-**2** (1)	$ZrCl_4$ (2)	rt	24	78 (15)	98:2	96 (1*S*)
5	**1** (2)	(1*S*)-**2** (1)	$HfCl_4$ (2)	−78	24	45(34)	98:2	98 (1*S*)
6	**1** (2)	(1*S*)-**2** (1)	$HfCl_4$ (2)	rt	24	89 (6)	99:1	97 (1*S*)
7	**1** (2)	(1*S*)-**2** (1)	$SnCl_4$ (1.3)	−78	24	12 (69)	99:1	82 (1*S*)
8	**1** (2)	(1*S*)-**2** (1)	$Sc(OTf)_3$ (1)	−78	24	60 (18)	99:1	68 (1*S*)
9	**1** (2)	(1*S*)-**2** (1)	$Ti(i\text{-}PrO)_2Cl_2$ (2)	rt	24	34 (60)	100:0	94 (1*S*)
10	**1** (2)	(1*R*)-**2** (1)	$TiCl_4$ (1)	−78	24	98	99:1	96 (1*R*)
11	**1** (2)	(1*R*)-**2** (1)	$TiCl_4$ (1)	0	24	19	97:3	89 (1*R*)
12[d]	**1** (2.5)	(1*R*)-**2** (1)	$ZrCl_4$ (2)	rt	24	78 (15)	99:1	92 (1*R*)
13	**1** (2.5)	(1*R*)-**2** (1)	$HfCl_4$ (2)	rt	24	97	99:1	94 (1*R*)
14[c]	**1** (2)	(1*R*)-**2** (1)	$Ti(i\text{-}PrO)_2Cl_2$ (1.5)	−78 then rt	48	30 (54)	100:0	98 (1*R*)
15[e]	**1** (2)	(1*R*)-**2** (1)	No catalyst	Reflux	48	82 (5)	57:43	38 (1*S*)
16[e]	**1** (3)	(1*R*)-**2** (1)	No catalyst	Reflux	48	>99	78:22	33 (1*R*)

[a] Isolated yield. Recovery of **2** is shown in parentheses.

[b] Diastereomeric excess (% de) was determined by HPLC analysis using a TOSOH TSK-GEL Silica-60; 1% ethanol/*n*-hexane, flow rate 1.0 mL/min, t_R=45 min (major), 49 min (minor).

[c] At −78 °C for 24 h then at rt for 24 h.

[d] Dropwise addition of **1**.

[e] Refluxing in toluene.

example, $\mathrm{TiCl_4}$ (94% de) (Table 1, entry 1), $\mathrm{ZrCl_4}$ (96% de) (entry 4), and $\mathrm{HfCl_4}$ (97% de) (entry 6). When $\mathrm{ZrCl_4}$ was employed, dropwise addition of diene **1** gave better result (78% yield) (entry 4). $\mathrm{HfCl_4}$ was the most useful Lewis acid and the cycloaddition reaction smoothly proceeded at room temperature. (entry 6). When the Lewis acid except for the described above was used as a catalyst, the cycloaddition did not proceed well. The cycloaddition of **1** with (1*S*)-**2** using tin tetrachloride ($\mathrm{SnCl_4}$) as a Lewis acid was carried out at −78 °C to give the *endo*-cycloaddition product (1*S*)-**3a** in 12% yield with 82% de (entry 7). The reactivity of $\mathrm{SnCl_4}$ was very low, but the diastereoselectivity of (1*S*)-**3a** was relatively high. The cycloaddition of **1** with (1*S*)-**2** using scandium trifluoromethanesulfonate [$\mathrm{Sc(OTf)_3}$] as a Lewis acid proceeded and gave *endo*-cycloaddition product **3a** in moderate yield (60%), but the diastereoselectivity was low (68% de) (entry 8). The cycloaddition of **1** with (1*S*)-**2** using Ti(*i*-PrO)$_2$Cl$_2$ gave low yield of (1*S*)-**3a** at room temperature (34% yield), but the diastereoselectivity was high (94% de) (entry 9).

The cycloaddition reaction of 1-phenoxycarbonyl 1,2-dihydropyridine **1** with (1*R*)-**2**, which is an enantiomer of (1*S*)-**2**, was carried out and the results are summarized in Table 1. In the presence of $\mathrm{TiCl_4}$, $\mathrm{ZrCl_4}$, and $\mathrm{HfCl_4}$, the cycloadditions of **1** with (1*R*)-**2** produced the *endo*-cycloaddition product (1*R*)-**3a** in good yields, and the diastereoselectivity of the *endo*-cycloaddition product (1*R*)-**3a** was excellent as shown in Table 1; for example, $\mathrm{TiCl_4}$ (96% de) (Table 1, entry 10), $\mathrm{ZrCl_4}$ (92% de) (Table 1, entry 12), and $\mathrm{HfCl_4}$ (94% de) (Table 1, entry 13). On the other hand, the cycloaddition of **1** with (1*R*)-**2** using Ti(*i*-PrO)$_2$Cl$_2$ was undergone at −78 °C for 24 h, followed by reaction at room temperature for 24 h to afford the *endo*-cycloaddition product (1*R*)-**3a** in 30% yield with 98% de. Though the reactivity of Ti(*i*-PrO)$_2$Cl$_2$ was low under the conditions, the stereoselectivity of *endo* (1*R*)-**3a** was high (98% de) (Table 1, entry 14).

2.2. Diels–Alder reaction of 1-methoxycarbonyl-1,2-dihydropyridine 4 with 1*S*-2 (or 1*R*-2)

Next, we investigated the reaction of 1-methoxycarbonyl-1,2-dihydropyridine **4** and *N*-acryloyl 2,10-camphorsultams **2**.[13]

Firstly, the cycloaddition of 1-methoxycarbonyl-1,2-dihydropyridine **4** with *N*-acryloyl (1*S*)-2,10-camphorsultam **2** [or *N*-acryloyl (1*R*)-2,10-camphorsultam **2**] was carried out under reflux in toluene. As the results are shown in Table 2, the reactions of **4** with **2** proceeded smoothly to give cycloaddition products *endo*-(1*S*)-**5a** and *exo*-(1*S*)-**5b** (*endo*-**5a**:*exo*-**5b**=60:40), but the diastereoselectivity of the cycloaddition products (1*S*)-**5** was not high (63% de) (Table 2, entry 10). Next, Lewis acids, such as $\mathrm{TiCl_4}$, $\mathrm{ZrCl_4}$, and $\mathrm{HfCl_4}$ were employed in the cycloaddition reaction of 1-methoxycarbonyl-1,2-dihydro-pyridine **4** with **2**. The results are summarized in Table 2. Although 1-methoxycarbonyl-1,2-dihydropyridine **4** is unstable for Lewis acid than 1-phenoxycarbonyl-1,2-dihydropyridine **1**, the cycloaddition reaction in the presence of Lewis acid proceeded smoothly. The cycloaddition of 2.2 equiv of 1-methoxycarbony-1,2-dihydropyridine **4** and *N*-acryloyl (1*S*)-camphorsultam **2** in the presence of 1.5 equiv of $\mathrm{TiCl_4}$ was carried out at −78 °C to give the *endo*-cycloaddition product (1*S*)-**5** (*endo*-**5a**:*exo*-**5b**=100:0) in 63% yield with 95% de (entry 1). In the presence of 2 equiv of $\mathrm{TiCl_4}$, the D–A reaction of 4 equiv of **4** with (1*S*)-**2** were carried out at −78 °C to give the *endo*-cycloaddition product (1*S*)-**5a** in 71% yield with 99% de (entry 2). On the other hand, the cycloaddition of **4** with (1*S*)-**2** using $\mathrm{ZrCl_4}$ as a Lewis acid could hardly undergo, and *N*-acryloyl (1*S*)-camphorsultam **2** was recovered (81%) (entry 3). The cycloaddition in the presence of $\mathrm{HfCl_4}$ was subsequently investigated at 0 °C or room temperature. In the D–A reaction of **4** with (1*S*)-**2** at 0 °C, the yield of **5a** was 17% and 63% of the *N*-acryloyl (1*S*)-camphorsultam (1*S*)-**2** was recovered (entry 4). In the presence of 2 equiv of $\mathrm{HfCl_4}$, the D–A reaction of **4** with (1*S*)-**2** was carried out at room temperature to give the *endo*-cycloaddition product (1*S*)-**5a** in 87% yield with 98% de (entry 5). The D–A reaction of 1-methoxycarbonyl-1,2-dihydropyridine **4** with *N*-acryloyl (1*R*)-2,10-camphorsultam **2**, which is enantiomer of *N*-acryloyl (1*S*)-2,10-camphorsultam (1*S*)-**2**, was also carried out in the presence of $\mathrm{TiCl_4}$, $\mathrm{ZrCl_4}$, and $\mathrm{HfCl_4}$. In the presence of 1 equiv of $\mathrm{TiCl_4}$, the D–A reaction was carried out at −78 °C to give the *endo*-cycloaddition product (1*R*)-**5a** in 26% yield and the diastereomeric excess was high (97% de), and 73% of the camphorsultam **2** was recovered (entry 6). In the presence of 2 equiv of $\mathrm{TiCl_4}$, the D–A reaction of **4** with (1*R*)-**2** proceeded smoothly and *endo* (1*R*)-**5a** was obtained in 91% yield with 99% de (entry 7). In the presence of 2 equiv of $\mathrm{HfCl_4}$, the D–A reaction of **4** with (1*R*)-**2** was carried out at room temperature to give the *endo*-cycloaddition product (1*R*)-**5a** in 52% yield with 98% de (entry 9). However, when $\mathrm{ZrCl_4}$ as a Lewis acid was employed, the D–A reaction of **4** with (1*R*)-**2** did not proceed smoothly (entry 8).

2.3. Determination of absolute stereochemistry of isoquinuclidine: estimation of plausible reaction mechanism

The absolute stereochemistry of the *endo*-cycloaddition products (1*S*)-**5a** and (1*R*)-**5a** were determined as follows. For the assignment of the *endo*-cycloaddition product (1*S*)-**5a**, the product was converted to the known (1*S*,4*R*,7*S*)-methyl ester **6**.[11] Thus, the reaction of the product (1*S*)-**5a** with lithium methoxide as a base in MeOH–THF afforded (7*S*)-methyl ester **6** in moderate yield (54%). Similarly, the product (1*R*)-**5a** was converted to the known (1*R*,4*S*,7*R*)-methyl ester **6** in 49% yield (Scheme 5).[11] According to the stereochemistry of (7*S*)-**6**, the absolute configuration of azabicyclo[2.2.2]octane derivative (1*S*)-**3a**, which was obtained from the reaction of *N*-acryloyl (1*S*)-2,10-camphorsultam **2** with 1-phenoxycarbonyl-1,2-dihydro-pyridine **1**, has been also established to be (1*S*,4*R*,7*S*). On the other hand, the

Table 2

Cycloaddition of 1,2-dihydropyridine **4** with dienophile (1*S*)-**2** or (1*R*)-**2** in the presence of Lewis acid

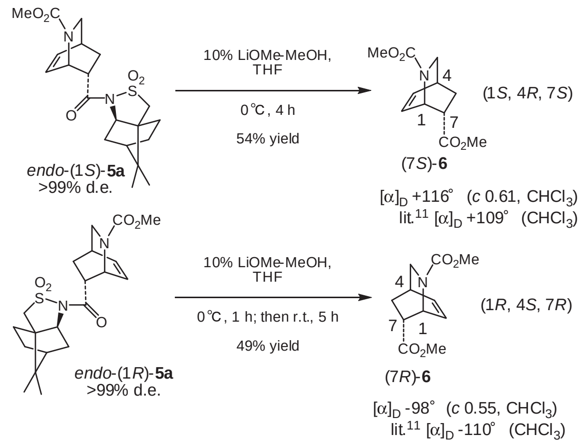
Entry	Diene (mol equiv)	Dienophile (mol equiv)	Lewis acid (mol equiv)	Temp/°C	Time/h	Yield/%[a]	*endo*:*exo* **5a**:**5b**	% de of *endo* **5a**[b]
1	**4** (2.2)	(1*S*)-**2** (1)	$\mathrm{TiCl_4}$ (1.5)	−78	24	63 (31)	100:0	95 (1*S*)
2	**4** (4)	(1*S*)-**2** (1)	$\mathrm{TiCl_4}$ (2)	−78	24	71 (27)	100:0	>99 (1*S*)
3	**4** (2)	(1*S*)-**2** (1)	$\mathrm{ZrCl_4}$ (1)	rt	24	5 (81)	Nd[d]	Nd[d]
4	**4** (2)	(1*S*)-**2** (1)	$\mathrm{HfCl_4}$ (1.5)	0	24	17 (63)	100:0	98 (1*S*)
5	**4** (2)	(1*S*)-**2** (1)	$\mathrm{HfCl_4}$ (2)	rt	24	87 (12)	100:0	98 (1*S*)
6	**4** (2)	(1*R*)-**2** (1)	$\mathrm{TiCl_4}$ (1)	−78	24	26 (73)	97:3	97 (1*R*)
7	**4** (4)	(1*R*)-**2** (1)	$\mathrm{TiCl_4}$ (2)	−78	24	91 (9)	100:0	>99 (1*R*)
8	**4** (2)	(1*R*)-**2** (1)	$\mathrm{ZrCl_4}$ (2)	rt	24	11 (41)	Nd[d]	Nd[d]
9	**4** (2)	(1*R*)-**2** (1)	$\mathrm{HfCl_4}$ (2)	rt	24	52 (36)	100:0	98 (1*R*)
10[c]	**4** (3)	(1*S*)-**2** (1)	No catalyst	Reflux	24	89 (9)	60:40	63 (1*S*)
11[c]	**4** (3)	(1*R*)-**2** (1)	No catalyst	Reflux	24	95	67:33	65 (1*R*)

[a] Isolated yield. Recovery of **2** is shown in parentheses.

[b] Diastereomeric excess (% de) was determined by HPLC analysis using a TOSOH TSK-GEL Silica-60; 1% ethanol/*n*-hexane, flow rate 1.0 mL/min, t_R=60 min (major), 63 min (minor).

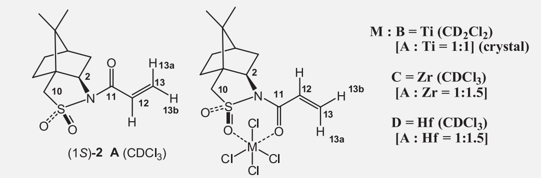
[c] Refluxing in toluene.

[d] Not determined.



Scheme 5. Determination of absolute configuration of D–A adduct **5a**.

Table 3
Comparison of NMR chemical shifts: (1*S*)-**2** (**A**) and (1*S*)-**2** coordinated with Lewis acid (**B**, **C**, **D**)



compound	^{1}H-NMR [ppm] (270 MHz, 25 °C)					^{13}C-NMR [ppm] (67.8 MHz, 25 °C)				
	(10)	(2)	(13a)	(13b)	(12)	(10)	(2)	(12)	(13)	(11)
A [a]	3.50	3.95	5.86	6.51	6.78	53.04	65.05	127.69	131.31	163.75
B (TiCl$_4$) [b]	3.70	4.14	6.25	6.85	6.70	53.26	66.26	125.31	—	—
(Δ : B-A)	(+0.20)	(+0.19)	(+0.39)	(+0.34)	(-0.08)	(+0.22)	(+1.21)	(-2.38)		
C (ZrCl$_4$) [c]	3.67	4.57	6.53	7.54	7.06	53.31	66.44	123.53	143.25	171.33
(Δ : C-A)	(+0.17)	(+0.62)	(+0.67)	(+1.03)	(+0.28)	(+0.27)	(+1.39)	(-4.16)	(+11.94)	(+7.58)
D (HfCl$_4$) [c]	3.70	4.58	6.54	7.63	7.07	53.40	66.55	123.26	143.80	171.72
(Δ : D-A)	(+0.20)	(+0.63)	(+0.68)	(+1.12)	(+0.29)	(+0.36)	(+1.50)	(-4.43)	(+12.49)	(+7.97)

[a] **A** is (1*S*)-**2**.

[b] (1*S*)-**2**-TiCl$_4$ complex (**B**) was prepared according to the Opporzer's procedure.[14] The signals of C(13) and C(11) of **B** were not observed.

[c] Mixture of (1*S*)-**2** and Lewis acid in CDCl$_3$.

absolute configuration of azabicyclo[2.2.2]octane derivative (1*R*)-**3a**, which was obtained from the reaction of *N*-acryloyl (1*R*)-2,10-camphorsultam **2** with 1-phenoxycarbonyl-1,2-dihydropyridine **1**, has been established to be (1*R*,4*S*,7*R*).

Based on the X-ray structure of the complex of *N*-crotonoyl (1*S*)-2,10-camphorsultam with TiCl$_4$ reported by Oppolzer et al.[14] and the high diastereopurity (up to 99% de) of the chiral D–A adduct (1*S*)-**5a**, a model of the π-facial selective reaction course was proposed as follows (Fig. 2). Because of the complex formation of *N*-acryloyl (1*S*)-2,10-camphorsultam (1*S*)-**2** with Lewis acid, such as TiCl$_4$, the complex structure may be fixed tightly. Attack of the diene to the (1*S*)-**2**-metal complex was then postulated to occur π-facial selectivity to give (1*S*)-**3a** {or (1*S*)-**5a**}. Due to the bulky camphorsultam group in (1*S*)-**2**-metal complex, the diene **1** (or **4**) may attack from the *re* face of the acryloyl group on the dienophiles (1*S*)-**2**. The regioselective D–A reaction of diene **1** (or **4**) with (1*S*)-**2** gave 7-substituted compound (1*S*)-**3a** {or (1*S*)-**5a**}.[2]

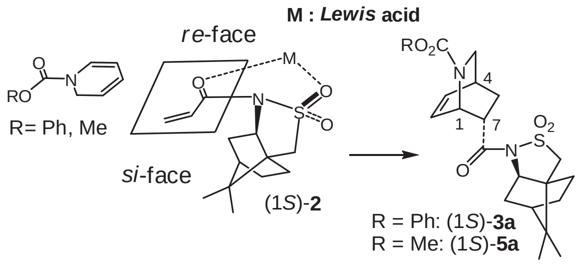


Figure 2. Plausible reaction course of 1,2-dihydropyridine with (1*S*)-**2** in the presence of Lewis acid.

2.4. Complex formation of dienophiles with Lewis acid

The X-ray diffraction analysis of the crystalline complex of *N*-crotonoyl (1*S*)-2,10-camphorsultam with TiCl$_4$ is reported by Oppolzer et al.[14] The complex shows a chelation structure of the carbonyl oxygen-atom and the SO$_2$ oxygen-atom with TiCl$_4$. In order to study the complex formation of *N*-acryloyl (1*S*)-2,10-camphorsultam with a Lewis acid, ^{1}H NMR spectra and ^{13}C NMR spectra of the mixture of *N*-acryloyl (1*S*)-2,10-camphorsultam **2** and Lewis acids, such as TiCl$_4$, ZrCl$_4$, and HfCl$_4$ were measured and the results are summarized in Table 3. Firstly, ^{1}H NMR spectrum and ^{13}C NMR spectrum of the non-coordinated *N*-acryloyl (1*S*)-2,10-camphorsultam (1*S*)-**2** (**A**) were measured in CDCl$_3$ (Table 3, compound **A**) The crystalline complex of *N*-acryloyl (1*S*)-2,10-camphorsultam **2** with TiCl$_4$ (1 mol equiv) was also prepared according to the Oppolzer's procedure,[14] and its ^{1}H NMR spectrum and ^{13}C NMR spectrum were measured in CD$_2$Cl$_2$ (Table 3, compound **A**). In the ^{13}C NMR spectrum of **B** the signals of C(13) and C(11) were not observed. However, the signals of C(13) and C(11) of the complex of *N*-crotonoyl (1*S*)-2,10-camphorsultam and TiCl$_4$, which was prepared by Oppolzer were observed and assigned.[14] The chemical shifts of the Oppolzer's complex are as follows: C(10) 53.07, C(2) 66.14, C(12) 119.93, C(13) 159.80, and C(11) 172.04 ppm. The complex **B** was unstable in the air and in the solution. As time went by, the complex was decomposed and HCl was generated. The ^{1}H NMR of the complex was measured every few hours. Then the signals of the chlorinated camphorsultam (Scheme 2) were appeared in the spectrum of the crystalline complex. In the case of ZrCl$_4$ or HfCl$_4$, the NMR of mixtures of *N*-acryloyl (1*S*)-2,10-camphorsultam **2** with 1.5 equiv of ZrCl$_4$ or HfCl$_4$ were measured in CDCl$_3$. The ^{1}H NMR spectra of compound **C** or **D** revealed downfield shifts of 0.1–1.1 ppm for the neighboring protons of the chelation atoms (Table 3, compound **C** or **D**). The ^{13}C NMR spectra of compound **C** or **D** also revealed downfield shifts of 0.2 to 12.5 ppm for C(10), C(2), C(11), and C(13), whereas C(12) exhibited upfield shifts. Consequently, we concluded that *N*-acryloyl (1*S*)-2,10-camphorsultam **2** formed metal complex with Lewis acids in solution.

3. Conclusion

In conclusion, we have developed the highly diastereoselective Diels–Alder reaction of 1,2-dihydropyridine derivatives (**1** and **4**) with chiral dienophiles **2**, which provide an efficient methodology for obtaining pharmacologically important chiral isoquinuclidines. Starting from *N*-acryloyl (1*S*)-2,10-camphorsultam (1*S*)-**2**, (1*S*,4*R*,7*S*)-isoquinuclidines {(1*S*)-**3** and (1*S*)-**5**} were obtained in good yield with excellent selectivity (up to 99% de). On the other hand, starting from *N*-acryloyl (1*R*)-2,10-camphorsultam (1*R*)-**2**, (1*R*,4*S*,7*R*)-isoquinuclidines {(1*R*)-**3** and (1*R*)-**5**} were obtained (up to 99% de). In the reaction, the chelation of Lewis acid with *N*-acryloyl (1*S*)-2,10-camphorsultam **2** {or *N*-acryloyl (1*R*)-2,10-camphorsultam **2**} is effective for affording the corresponding cycloaddition products.

4. Experimental section

4.1. General information

(1*S*)-2,10-Camphorsultam and (1*R*)-2,10-camphorsultam were purchased from Aldrich Chemical Co. Dichloromethane, tetrahydrofuran, methanol, ethanol, diethyl ether, toluene, pyridine, triethylamine, sodium hydride, sodium borohydride, and copper chloride were purchased from Kanto Kagaku Reagent Division. Titanium tetrachloride, hafnium tetrachloride, tin tetrachloride, scandium trifluoromethanesulfonate, phenyl chloroformate, methyl chloroformate, 10% lithium methoxide in methanol solution, hexane, ethyl acetate, and chloroform were purchased from Wako Pure Chemical Ind. Dichlorotitanium diisopropoxide, acrylic acid, acryloyl chloride, 3-chloropropionyl chloride were purchased from Tokyo Chemical Ind. Co. Zirconium tetrachloride and molecular sieve 4 Å were purchased from Merck Co. IR spectra were recorded as thin films (liquids). ^{1}H NMR spectra and ^{13}C NMR spectra were recorded at 270 MHz and 67.8 MHz on a JEOL JNM-EX 270 FT NMR SYSTEM in $CDCl_3$ and DMSO-d_6 using tetramethylsilane as an internal standard. Specific rotations were recorded at the sodium D line with a polarimeter at room temperature. The diastereomeric excess (de) of the cycloaddition products was determined by HPLC.

4.2. General procedure

*4.2.1. Method A. General procedure for the cycloaddition of 1,2-dyhydropyridines (**1** or **4**) and N-acryloyl 2,10-camphor-sultams (**2**) with $TiCl_4$.* To the solution of *N*-acryloyl 2,10-camphorsultam **2** (0.2 M, 269 mg, 1 mmol), molecular sieves 4 Å (100 mg) in dry CH_2Cl_2 (5 mL) was added $TiCl_4$ (1.3 equiv) at room temperature, and the yellow solution was stirred for 30 min under nitrogen. The solution was then cooled to −78 °C by acetone/dry ice bath. When to the solution was added the solution of 1,2-dihydropyridine (**1** or **4**) (0.4 M, 2 equiv) in dry CH_2Cl_2 (5 mL) at −78 °C, the color of the solution changed from yellow to dark red. The solution was stirred at −78 °C for 24 h. The reaction was quenched by addition of 1 M NaOH (10 equiv) and water and the product was extracted with chloroform. The organic solution was dried over sodium sulfate and filtered. After column chromatography of products on silica gel (20% ethyl acetate in hexane), the *endo*-**3a** and *exo*-**3b** were obtained. The ratio of *endo*-(1*S*)-**3a** and *exo*-(1*S*)-**3b** was determined by HPLC analysis using a TOSOH TSK-GEL Silica-60; 1% EtOH/hexane; flow rate, 1.0 ml/min: retention time, *exo*-(1*S*)-**3b** 25 min, *endo*-(1*S*)-**3a** 45 min.

*4.2.2. Method B. General procedure for the cycloaddition of 1,2-dyhydropyridines (**1** or **4**) and N-acryloyl 2,10-camphor-sultams (**2**) with $ZrCl_4$.* To the solution of *N*-acryloyl 2,10-camphorsultam **2** (0.2 M, 1 equiv), molecular sieves 4 Å (100 mg) in dry CH_2Cl_2 (5 mL) was added $ZrCl_4$ (2 equiv) at room temperature and the solution was stirred for 20 min under nitrogen. Then the solution of 1,2-dihydropyridiene (**1** or **4**) (0.5 M, 2.5 equiv) in CH_2Cl_2 (5 mL) was slowly added by a dropping funnel and the solution was stirred for 24 h under nitrogen at room temperature. The reaction was quenched by addition of 1 M NaOH (8 equiv) and water and the product was extracted with chloroform. The organic solution was dried over sodium sulfate and filtered. After column chromatography of products on silica gel (20% ethyl acetate in hexane), the *endo*-**3a** and *exo*-**3b** were obtained. The ratio of *endo*-(1*S*)-**3a** and *exo*-(1*S*)-**3b** was determined by HPLC analysis using a TOSOH TSK-GEL Silica-60; 1% EtOH/hexane; flow rate, 1.0 ml/min: retention time, *exo*-(1*S*)-**3b** 25 min, *endo*-(1*S*)-**3a** 45 min.

*4.2.3. Method C. General procedure for the cycloaddition of 1,2-dyhydropyridines (**1** or **4**) and N-acryloyl 2,10-camphor-sultams (**2**) with $HfCl_4$.* To the solution of *N*-acryloyl 2,10-camphorsultam **2** (0.2 M, 1 equiv), molecular sieves 4 Å (100 mg) in dry CH_2Cl_2 (5 mL) was added $HfCl_4$ (2 equiv) at room temperature and the solution was stirred for 20 min under nitrogen. Then the solution of 1,2-dihydropyridiene (**1** or **4**) (0.5 M, 2.5 equiv) in CH_2Cl_2 (5 mL) was added and the solution was stirred for 24 h under nitrogen at room temperature. The reaction was quenched by addition of 1 M NaOH (8 equiv) and water and the product was extracted with chloroform. The organic solution was dried over sodium sulfate and filtered. After column chromatography of products on silica gel (20% ethyl acetate in hexane), the *endo*-**3a** and *exo*-**3b** were obtained. The ratio of *endo*-(1*S*)-**3a** and *exo*-(1*S*)-**3b** was determined by HPLC analysis using a TOSOH TSK-GEL Silica-60; 1% EtOH/hexane; flow rate, 1.0 ml/min: retention time, *exo*-(1*S*)-**3b** 25 min, *endo*-(1*S*)-**3a** 45 min.

*4.2.4. Method D. General procedure for the cycloaddition of 1,2-dyhydropyridines (**1** or **4**) and N-acryloyl 2,10-camphorsultams (**2**) under reflux.* The mixture of *N*-acryloyl (1*S*)-2,10-camphorsultam **2** (0.1 M, 1 mmol) and 1-phenoxycarbpnyl 1,2-dihydropyridine **1** (3 mmol) was refluxed with stirring for 48 h in toluene (10 mL). The progress of the reaction was followed by TLC (33% ethyl acetate in hexane). Once the reaction was completed, the solution was concentrated. The residue was purified by silica gel column chromatography (20% ethyl acetate in hexane), and *endo*-**3a** and *exo*-**3b** were obtained.

*4.2.4.1. (1S,4R,7S)-7-((1′S)-2,10-Camphorsultam-4′-carbonyl)-2-aza-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid phenyl ester (1S)-**3a**.* The de of *endo*-(1*S*)-**3a** was determined by HPLC analysis using a TOSOH TSK-GEL Silica-60; 1% EtOH/hexane; flow rate, 1.0 ml/min: retention time, major (1*S*)-**3a** 45 min, minor diastereomer-**3a** 49 min. White solid, mp: 92–93 °C. ^{1}H NMR (DMSO-d_6, 270 MHz, 100 °C): δ 0.94 (3H, s), 1.12 (3H, s), 1.16–1.28 (1H, m), 1.35–1.47 (1H, m), 1.75–1.94 (7H, m), 2.93–2.96 (2H, m), 3.35 (1H, br s), 3.56–3.83 (4H, m), 5.12 (1H, br s), 6.21–6.26 (1H, m), 6.44–6.55 (1H, m), 7.09–7.19 (3H, m), 7.30–7.38 (2H, m); ^{13}C NMR (DMSO-d_6, 67.8 MHz, 100 °C): δ 18.97 (CH_3), 19.89 (CH_3), 24.83, 25.44, 29.77, 31.51, 37.47, 43.91, 44.32, 46.39, 46.85, 47.82, 52.03, 64.19, 78.58, 120.93 (2C), 124.28, 128.11, 128.47 (2C), 135.27, 150.96, 151.70, 170.21. IR (NaCl) 3020, 2962, 1215, 1691, 1454, 1398, 1338 cm^{-1}. $[\alpha]_D^{23}$ +14.2 (*c* 1.0, $CHCl_3$) (94% de). EIMS *m*/*z* 470 (M^+), 377, 334, 201, 162, 135, 107, 79, 69, 55, 41. HRMS calcd for $C_{25}H_{30}N_2O_5S$ (M^+) 470.1875, found 470.1875. Anal. Calcd for: C, 58.80; H, 6.91; N, 6.86. Found: C, 58.74; H, 7.14; N, 6.85.

*4.2.4.2. (1R,4S,7R)-7-((1′R)-2,10-Camphorsultam-4′-carbonyl)-2-aza-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid phenyl ester (1R)-**3a**.* The de of *endo*-(1*R*)-**3a** was determined by HPLC analysis using a TOSOH TSK-GEL Silica-60; 1% EtOH/hexane; flow rate, 1.0 ml/min: retention time, major (1*R*)-**3a** 45 min, minor diastereomer-**3a** 49 min. White solid, mp: 91–93 °C. ^{1}H NMR (DMSO-d_6, 270 MHz, 100 °C): δ 0.94 (3H, s), 1.12 (3H, s), 1.16–1.28 (1H, m), 1.35–1.47 (1H, m), 1.75–1.94 (7H, m), 2.93–2.96 (2H, m), 3.35 (1H, br s), 3.56–3.83 (4H, m), 5.12 (1H, br s), 6.21–6.26 (1H, m), 6.44–6.55 (1H, m), 7.09–7.19 (3H, m), 7.30–7.38 (2H, m); ^{13}C NMR (DMSO-d_6, 67.8 MHz, 100 °C): δ 18.97 (CH_3), 19.89 (CH_3), 24.83, 25.44, 29.77, 31.51, 37.47, 43.91, 44.32, 46.39, 46.85, 47.82, 52.03, 64.19, 78.58, 120.93 (2C), 124.28, 128.11, 128.47 (2C), 135.27, 150.96, 151.70, 170.21. IR (NaCl) 3020, 2962, 1215, 1691, 1454, 1398, 1338 cm^{-1}. $[\alpha]_D^{23}$ −12.7 (*c* 1.0, $CHCl_3$) (96% de).

*4.2.4.3. (1S,4R,7S)-7-((1′S)-2,10-Camphorsultam-4′-carbonyl)-2-aza-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid methyl ester (1S)-**5a**.* The de of *endo*-(1*S*)-**5a** was determined by HPLC analysis using a TOSOH TSK-GEL Silica-60; 1% EtOH/hexane; flow rate, 1.0 ml/min: retention time, major (1*S*)-**5a** 60 min, minor diastereomer-**5a** 63 min. White solid, mp: 204–205 °C. ^{1}H NMR ($CDCl_3$, 270 MHz, 25 °C): δ 0.97 (3H, s) 1.21 (3H, s), 1.30–1.45 (2H, m), 1.84–2.06 (7H, m), 2.86–2.94 (2H, m), 3.24–3.28 (1H, m), 3.38–3.54 (2H, m), 3.67–3.75 (4H, m), 3.82 (1H, br s), 5.03–5.17 (1H, m), 6.18–6.29 (1H, m), 6.44–6.50 (1H, m); ^{13}C NMR ($CDCl_3$, 67.8 MHz, 25 °C): δ 19.77 (CH_3), 20.65 (CH_3), 25.82, 26.42, 30.82, 32.60, 38.30, 44.35, 45.10, 46.50, 46.95, 47.76, 48.39, 52.31, 52.81, 65.08, 129.76, 134.77, 155.43, 171.49. IR (NaCl) 3020, 2962, 1215, 1691, 1454, 1398, 1338 cm^{-1}. $[\alpha]_D^{23}$ −38.8 (*c* 1.0, $CHCl_3$) (99% de). EIMS *m*/*z* 408 (M^+), 377, 334, 270, 194, 165, 139, 124, 94, 55, 41. HRMS calcd for

$C_{20}H_{28}N_2O_5S$ (M^+) 408.1719, found 408.1703. Anal. Calcd for: C, 63.81; H, 6.43; N, 5.95. Found: C, 63.61; H, 6.71; N, 5.78.

*4.2.4.4. (1R,4S,7R)-7-((1′R)-2,10-Camphorsultam-4′-carbonyl)-2-aza-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid methyl ester (1R)-**5a**.* The de of *endo*-(1*R*)-**5a** was determined by HPLC analysis using a TOSOH TSK-GEL Silica-60; 1% EtOH/hexane; flow rate, 1.0 ml/min: retention time, major (1*R*)-**5a** 60 min, minor (1*S*)-**5a** 63 min. White solid, mp: 203–204 °C. ^{1}H NMR ($CDCl_3$, 270 MHz, 25 °C): δ 0.97 (3H, s) 1.21 (3H, s), 1.30–1.45 (2H, m), 1.84–2.06 (7H, m), 2.86–2.94 (2H, m), 3.24–3.28 (1H, m), 3.38–3.54 (2H, m), 3.67–3.75 (4H, m), 3.82 (1H, br s), 5.03–5.17 (1H, m), 6.18–6.29 (1H, m), 6.44–6.50 (1H, m); ^{13}C NMR ($CDCl_3$, 67.8 MHz, 25 °C): δ 19.77 (CH_3), 20.65 (CH_3), 25.82, 26.42, 30.82, 32.60, 38.30, 44.35, 45.10, 46.50, 46.95, 47.76, 48.39, 52.31, 52.81, 65.08, 129.76, 134.77, 155.43, 171.49. IR (NaCl) 3020, 2962, 1215, 1691, 1454, 1398, 1338 cm^{-1}. $[\alpha]_D^{23}$ +39.8 (*c* 1.0, $CHCl_3$) (99% de).

*4.2.5. Ester exchange reaction of **5a**.* The solution of 10% LiOMe–MeOH (570 mg, 1.5 mmol) in MeOH (5 mL) was cooled at 0 °C. To the solution was added the solution of *endo* (1*S*)-**5a** (204 mg, 0.5 mmol) in THF (2 mL), and the mixture was stirred at 0 °C for 4 h. The reaction was quenched by addition of saturated ammonium chloride, and the product was extracted with chloroform. The organic solution was dried over sodium sulfate and filtered. After removal of solvent, the residue was purified by column chromatography on silica gel (10% MeOH in chloroform) to give product (1*S*,4*R*,7*S*)-**6** as colorless oil.

*4.2.5.1. (1S,4R,7S)-2-Methoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene-7-methyl carboxylate (7S)-**6**.* Ester exchange reaction was carried out to give (7*S*)-**6** as colorless oil in 54% yield. ^{1}H NMR ($CDCl_3$, 270 MHz, 25 °C): δ 1.85–1.87 (2H, m), 2.83 (1H, br s), 2.90–2.98 (1H, m) 3.06–3.12 (1H, m), 3.24–3.39 (1H, m), 3.64–3.72 (6H, m), 4.90–5.17 (1H, m), 6.28–6.48 (2H, m); ^{13}C NMR ($CDCl_3$, 67.8 MHz, 25 °C): δ 25.85, 30.46, 43.58, 46.89, 47.19, 51.85, 52.40, 130.45, 135.00, 155.83, 173.10. $[\alpha]_D^{23}$ +116 (*c* 0.6, $CHCl_3$); lit.[11] $[\alpha]_D^{23}$ +109 (*c* 1, $CHCl_3$).

*4.2.5.2. (1R,4S,7R)-2-Methoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene-7-methyl carboxylate (7R)-**6**.* Ester exchange reaction of (1*R*)-**5a** was carried out to give (7*R*)-**6** as colorless oil in 49% yield. ^{1}H NMR ($CDCl_3$, 270 MHz, 25 °C): δ 1.85–1.87 (2H, m), 2.83 (1H, br s), 2.90–2.98 (1H, m) 3.06–3.12 (1H, m), 3.24–3.39 (1H, m), 3.64–3.72 (6H, m), 4.90–5.17 (1H, m), 6.28–6.48 (2H, m); ^{13}C NMR ($CDCl_3$, 67.8 MHz, 25 °C): δ 25.85, 30.46, 43.58, 46.89, 47.19, 51.85, 52.40, 130.45, 135.00, 155.83, 173.10. $[\alpha]_D^{23}$ −98 (*c* 0.6, $CHCl_3$); lit.[11] $[\alpha]_D^{23}$ −110 (*c* 1, $CHCl_3$).

*4.2.6. Preparation of N-acryloyl 2,10-camphorsultam **2**[6c,9].* To the solution of acrylic acid (1.3 equiv) and triethylamine (2.5 equiv) in THF (volume corresponded to 0.2 M of 2,10-camphorsultam) was added acryloyl chloride (1.2 equiv) at −20 °C. A white solid was formed instantaneously. The mixture was stirred at −20 °C for 1 h. Lithium chloride (1.1 equiv) was added, followed by 2,10-camphorsultam (5.0 g, 23.2 mmol). The mixture was allowed to warm to room temperature and stirred for 48 h. The reaction was quenched by addition of 0.2 M HCl (2 equiv), and THF was removed in vacuo. The residue was partitioned between ethyl acetate and 0.2 M HCl (0.5 equiv). The organic layer was washed subsequently with 0.2 M HCl, brine, 1 M sodium bicarbonate (two times), and brine. The organic solution was then dried over sodium sulfate and filtered. Ethyl acetate was removed in vacuo, and the residue was dissolved in toluene. The toluene solution was filtered through a silica gel bed, and the cake was washed with toluene. Concentration of toluene solution to dryness afforded the *N*-acryloyl 2,10-camphorsultam **2**, which was crystallized from hexane as a white crystalline solid.

*4.2.6.1. N-Acryloyl (1S)-2,10-camphorsultam **2**.* White solid (recrystallized from hexane), 84% yield, mp: 192–195 °C; lit.[12a] mp: 191–193 °C. $[\alpha]_D^{23}$ −102 (*c* 1.0, $CHCl_3$); lit.[6c] $[\alpha]_D^{23}$ −100.9 (*c* 0.983, $CHCl_3$). ^{1}H NMR [ppm] (270 MHz, $CDCl_3$, 25 °C): δ 0.98 (3H, s), 1.18 (3H, s), 1.47–1.33 (2H, m), 1.99–1.89 (3H, m), 2.14–2.06 (2H, m), 3.49 (2H, q, *J*=21.6, 13.8 Hz), 3.94 (1H, t, *J*=6.4 Hz), 5.86 (1H, dd, *J*=10.9, 1.5 Hz), 6.50 (1H, dd, *J*=16.7, 1.5 Hz), 6.87 (1H, dd, *J*=16.7, 10.4 Hz); ^{13}C NMR [ppm] (67.8 MHz, $CDCl_3$, 25 °C): δ 19.86, 20.85, 26.47, 32.86, 38.40, 44.67, 47.80, 48.56, 53.10, 65.11, 127.74, 131.39, 163.82.

*4.2.6.2. N-Acryloyl (1R)-2,10-camphorsultam **2**.* White solid (recrystallized from h^{23}exane), 74% yield, mp: 196–198 °C. $[\alpha]_D^{23}$ +104 (*c* 1.0, $CHCl_3$) lit.[9] $[\alpha]_D^{23}$ +102 (*c* 1.7, $CHCl_3$). ^{1}H NMR [ppm] (270 MHz, $CDCl_3$, 25 °C): δ 0.98 (3H, s), 1.18 (3H, s), 1.47–1.33 (2H, m), 1.99–1.89 (3H, m), 2.14–2.06 (2H, m), 3.49 (2H, q, *J*=21.6, 13.8 Hz), 3.94 (1H, t, *J*=6.4 Hz), 5.86 (1H, dd, *J*=10.9, 1.5 Hz), 6.50 (1H, dd, *J*=16.7, 1.5 Hz), 6.87 (1H, dd, *J*=16.7, 10.4 Hz); ^{13}C NMR [ppm] (67.8 MHz, $CDCl_3$, 25 °C): δ 19.86, 20.85, 26.47, 32.86, 38.40, 44.67, 47.80, 48.56, 53.10, 65.11, 127.74, 131.39, 163.82.

*4.2.7. Preparation of 1-phenoxycarbonyl-1,2-dihydropyridine **1**[8].* Pyridine (24.0 g, 303 mmol) and $NaBH_4$ (6.0 g, 159 mmol) were stirred together at −78 °C in ethanol (180 mL), and then phenyl chloroformate (32.0 g, 204 mmol) was added slowly to the solution by a dropping funnel for 1 h. The mixture was stirred at −78 °C for 24 h. The solution was poured into ice-water, and the mixture was stirred until the H_2 bubble stopped. The mixture was extracted with diethyl ether (100 mL×3) and the ether solution was dried over sodium sulfate. The organic layer was filtered and the diethyl ether removed in vacuo. The residue was recrystallized from ethanol to give the product **1** as a white solid in 67% yield (27.50 g, 136.7 mmol). The ratio of 1,2-dihydropyridine and 1,4-dihydropyridine was 93 to 7. Mp: 64–66 °C. ^{1}H NMR [ppm] (270 MHz, $CDCl_3$, 25 °C): δ 4.45 (1H, q, *J*=3.8, 2.0 Hz), 4.59 (1H, br s), 5.31–5.22 (1H, m), 5.62–5.59 (1H, m), 5.93–5.88 (1H, m), 6.84 (1H, dd, *J*=20.0, 7.7 Hz), 7.13 (2H, d, *J*=7.6), 7.22 (1H, t, *J*=8.2 Hz), 7.38 (2H, t, *J*=7.8 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz, 25 °C): δ 43.78, 105.82, 119.47, 121.54 (2C), 121.82, 125.35, 125.67, 126.06, 129.36 (2C), 150.81.

*4.2.8. Preparation of 1-methoxycarbonyl-1,2-dihydropyridine **4**[8].* Pyridine (4.74 g, 60 mmol) and $NaBH_4$ (2.60 g, 68 mmol) were stirred in ethanol (50 mL) at −78 °C, and then methyl chloroformate (5.68 g, 60 mmol) was added slowly to the solution by a dropping funnel for 1 h. The mixture was stirred at −78 °C for 24 h. The solution was poured into ice-water, and the mixture was stirred until the H_2 bubble stopped. The mixture was extracted with diethyl ether (100 mL×3) and the ether solution was dried over sodium sulfate. The organic layer was filtered and the diethyl ether removed in vacuo. The product was purified by column chromatography on silica gel (10% ethyl acetate in hexane) to give the product **1** as a colorless oil in 98% (8.18 g, 58.8 mmol). The ratio of 1,2-dihydropyridine and 1,4-dihydropyridine was 94 to 6. ^{1}H NMR [ppm] (270 MHz, $CDCl_3$, 25 °C): δ 3.78 (3H, s), 4.27–4.16(1H, m), 4.36 (1H, br s), 5.14–5.12 (1H, m), 5.52–5.51 (1H, m), 5.86–5.81 (1H, m), 6.66–6.63 (1H, m); ^{13}C NMR ($CDCl_3$, 67.8 MHz, 25 °C) δ 43.35, 52.91, 104.61, 118.91, 121.73, 125.41, 149.57.

4.2.9. Preparation of N-3-chloropropanoyl (1S)-2,10-camphor sultam[12]. To a suspension of NaH (38.5 mg, 1.6 mmol) and toluene (5 mL) was added (1*S*)-2,10-camphorsultam (215 mg, 1 mmol). After 1 h at room temperature, CuCl (13 mg, 0.13 mmol) was added. The mixture was added to a solution of 3-chloropropionyl chloride in toluene (2 mL). After 30 min, the reaction mixture was quenched with water and extracted with EtOAc. The extract was passed through silica gel, concentrated under reduced pressure, and purified by column chromatography on silica gel (20% ethyl acetate in hexane) to yield *N*-3-chloropropanoyl (1*S*)-2,10-camphorsultam in 53% yield (161 mg, 0.53 mmol). Mp: 134–135 °C. $[\alpha]_D^{23}$ −98.7 (*c* 1.0, $CHCl_3$). ^1H NMR [ppm] (270 MHz, $CDCl_3$, 25 °C): δ 0.98 (3H, s), 1.16 (3H, s), 1.32–1.46 (2H, m), 1.89 (4H, br s), 2.04–2.14 (2H, m), 3.10–3.31 (2H, m), 3.49 (2H, q, *J*=21.8, 13.9), 3.74–3.97 (2H, m); ^{13}C NMR ($CDCl_3$, 67.8 MHz, 25 °C) δ 19.80, 20.70, 26.35, 32.71, 38.24, 38.34, 44.54, 47.74, 48.56, 52.80, 53.02, 65.11, 168.37.

*4.2.10. Preparation of the crystalline complex of (1S)-**2** with $TiCl_4$*[14]. *N*-Acryloyl (1*S*)-2,10-camphorsultam **2** (269 mg, 1 mmol) was dissolved in CH_2Cl_2 (10 mL) in one of two two-necked flasks, which were linked by glass tube. Addition of $TiCl_4$ (0.12 mL, 1 mmol) to the solution at room temperature gave a clear yellow solution. Hexane (10 mL) was placed in the other flask, which was then closed with septum and allowed to stand at room temperature for several days. Slow diffusion of the solvents resulted in the formation of fine yellow crystals of the complex of (1*S*)-**2** with $TiCl_4$. The crystal is very moisture sensitive and easily decomposed for few minutes in the air. The ^1H and ^{13}C NMR spectra were measured and the results were listed in Table 3. ^1H NMR [ppm] (270 MHz, CD_2Cl_2, 25 °C): δ 1.01 (3H, s), 1.16 (3H, s), 1.36–1.56 (2H, m), 1.99 (3H, br s), 2.23–2.26 (2H, m), 3.70 (2H, br s), 4.14 (1H, br s), 6.25 (1H, br s), 6.64–6.73(1H, m), 6.82–6.87 (1H, m); ^{13}C NMR (CD_2Cl_2, 67.8 MHz, 25 °C) δ 19.93, 21.17, 26.41, 33.15, 38.85, 45.40, 48.34, 48.61, 53.26, 66.26, 125.31 (two signals of C(13) and C(11) were not observed).

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.07.026.

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