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# A Convenient Method for Synthesis of Optically Active Methylphenidate from *N*-Methoxycarbonylpiperidine by Utilizing Electrochemical Oxidation and Evans Aldol-type Reaction

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**Abstract**—A new method to prepare optically active methylphenidate starting from piperidine is described. The method consists of a transformation of *N*-methoxycarbonylated piperidine to the corresponding α-methoxylated carbamate utilizing electrochemical oxidation followed by the coupling reaction with optically active Evans imides to produce optically active methylphenidate derivatives with high stereoselectivity (*erythro*/*threo*=5.3/94.7, the *threo* isomer; 99.6%ee). 

Methylphenidate (methyl 2-phenyl-2-(2′-piperidyl)acetate (**1**), Fig. 1) has four stereoisomers since it possesses two asymmetric carbons. Among them, the *threo*-methylphenidate hydrochloride salt (*threo*-**1**-HCl, Ritalin®) has been used mainly for the treatment of attention deficit hyperactivity disorder (ADHD) in children in the USA,[1] and administered to patients as the racemic form. However, the most active enantiomer is the *d-threo*-isomer,[2] while *d*- and *l-erythro*-**1** were shown to possess very little therapeutic effect and the toxic hypertensive effects.[3] Accordingly, a development of efficient methods selectively producing the *d-threo* isomer is worthwhile.

Existing practical methods for the preparation of *dl-threo*-**1** consist of the attack of phenylacetonitrile on 2-halopyridine, the hydrogenation of the 2-alkylated pyridine ring, and a separation of *threo* precursor from the mixture of diastereomers.[4] Recently, there has been reported a new method for the synthesis of *dl-threo*-**1** through a β-lactam intermediate, which leads to a 6/1 *threo*/*erythro* selectivity.[5] There had been only one report of an asymmetric synthesis of *d-threo*-**1** before our study has been started. It used an expensive optically active pipecolinic acid as the starting compound together with the use of an excess of (+)-IPC·$BH_2$ at the key step of multistage reactions (8 steps).[6] More recently, there have appeared enantioselective syntheses of *d-threo*-**1**[7,8] which are based on the Evans aldol reaction[9] and a Rh-catalyzed insertion reaction of carbenoids into the α-C–H bond of *N*-Boc-piperidine.[8] We also developed a convenient method for the stereoselective synthesis of *d-threo* isomer of **1** from *N*-methoxycarbonylpiperidine (**2**) utilizing an electrochemical oxidation and the Evans aldol-type reaction (Scheme 1), and reported the preliminary result.[10] This paper describes the scope of the method.

## Results and Discussion

### The C–C bond forming reaction between α-methoxycarbamates 3 and Evans Imides 4a–c

Scheme 2 illustrates our general method for synthesis of **1**

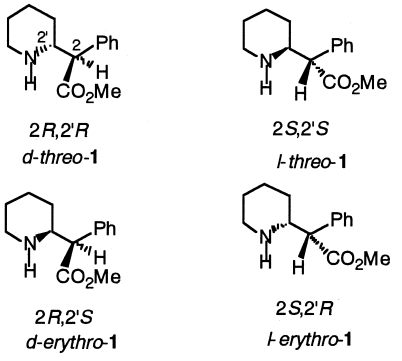
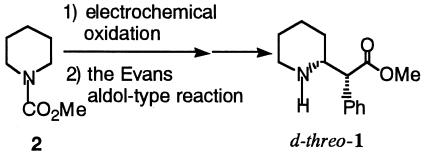



**Figure 1.** Methylphenidate (methyl 2-phenyl-2-(2′-piperidyl)acetate (**1**)).




**Scheme 1.**

*Keywords*: asymmetric synthesis; electrochemical reactions; piperidines; diastereoselection.

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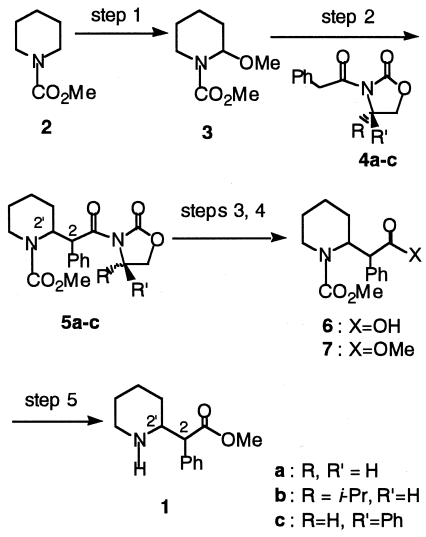
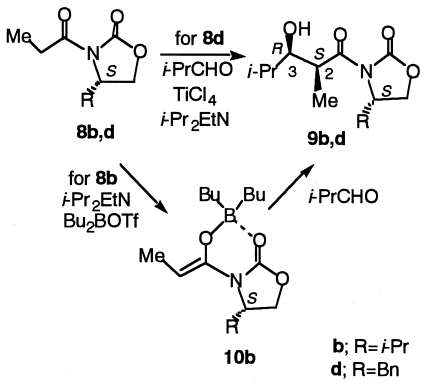



**Scheme 2.**

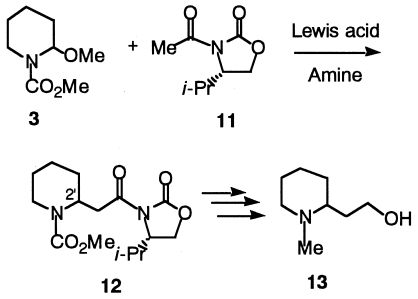
which consists of only five steps, (step 1) an electrochemical α-methoxylation of **2** to afford α-methoxypiperidine **3**, (step 2) a C–C bond formation at the α-position of **3** with Evans imides **4a**–**c**, (steps 3 and 4) a removal of the chiral auxiliary from the products **5** followed by the esterification of an acid **6**, and (step 5) the deprotection of *N*-methoxycarbonyl group of the resulting ester **7** to give **1**. A highly stereoselective synthesis of *d-threo*-**1** was achieved by using *N*-(phenylacetyl)-(4*S*)-isopropyl-2-oxazolidinone (**4b**) as the Evans imide.

Since the first step in Scheme 2 has well been established by us as a promising method for introducing nucleophiles to the α-position of carbamates,[11] the key step in the scheme is step 2. While the Ti-promoted C–C bond forming reaction of Evans imides with carbonyl compounds[9] and *O*,*O*-acetals[12] has been reported, step 2 is a hitherto unknown coupling[13] between Evans imides and *N*,*O*-acetals such as **3**.[14]

In general, the Evans aldol reaction between *N*-acyl-4-substituted-2-oxazolidinone and an aldehyde has been known to take place with high stereo- selectivity according to a general rule exemplified by the reaction of *N*-propionyl-(4*S*)-alkyl-2-oxazolidinone **8b**,**d** with isobutyraldehyde (Scheme 3). That is, **8b**,**d** gives a *syn* (*erythro*) adduct




**Scheme 3.**




**Scheme 4.**

**9b**,**d** (3-(2*S*,3*R*)-isomer) either in a direct route ($TiCl_4$, DIPEA, *i*-PrCHO)[9b] or in an indirect route through boron enolate **10b**.[9a,15]

With this background, we first examined the reaction between **3** and a simple Evans imide **11** to see whether the C–C bond forming reaction efficiently takes place to afford the coupling product **12** and also to explore the reaction conditions to obtain a stereochemical outcome suitable to our purpose (Scheme 4). The results, shown in Table 1, show that the coupling reaction proceeds smoothly under appropriate conditions. Although the diastereoselectivity for the coupling reaction was clarified at the stage of **12**, the absolute configuration of the 2′-position of **12** was difficult to determine. Thus, **12** was converted to amino alcohol **13**, which was compared with the authentic sample.

The efficiency for the C–C bond formation was found to be dependent on the kind of Lewis acid and amine. Lewis acids other than $TiCl_4$ resulted in a recovery of most of **3** (entries 1–5, Table 1), suggesting that iminium ion **2**$^*$ (Fig. 2) requisite for the C–C bond forming reaction might not be generated under the reaction conditions without using $TiCl_4$. A combination of $TiCl_4$ and diisopropylethylamine (DIPEA) gave the best result (entry 6) among the conditions examined, though it gave an unsatisfactory diastereoselectivity. Since the use of excess DIPEA also gave **12** in a good yield (entry 7), the titanium enolate generated from **11** might be responsible for the formation of iminium ion **2**$^*$ from **3**. The temperature-dependent results (entries 8 and 9) suggest that the titanium enolate generated from **11** was unstable at room temperature and the C–C bond forming reaction was slow at −78°C. Furthermore, it was found that the kind of amines affected the diastereoselectivities, though the reason was not clear (entries 10 and 11).

The major point in this coupling reaction is that the stereochemistry at the 2′-position of the major stereoisomer of **12** was opposite to that desired.

Next, we investigated the effect of an *N*-phenylthioacetyl group upon the stereochemistry of the C–C bond forming reaction (Scheme 5). It proved easy to determine the effect since the phenylthio group of the coupling product **15** was easily removed to afford **12**. The result was as expected. That is, the overall yield of **12** was 54% under the reaction conditions similar to that in entry 6 of Table 1, and the ratio of *R*/*S* at the 2′-position of **12** was 77/23, the *R*-isomer being major.

**Table 1.** Reaction of 3-acetyl-2-oxazolidinone **11** with α-methoxycarbamate **3** (the amount of **3** was 1.2 equiv. to **11**)

| Entry | Lewis acid[a] | Amine | (Equiv. to **11**) | Reaction temp (°C)[b] | Isolated yields (%) of **12** | (*R*/*S*)[c] |
|---|---|---|---|---|---|---|
| 1 | $ZnCl_2$ | DIPEA[d] | 1.2 | −78°C to rt | 0 | – |
| 2 | $SnCl_4$ | DIPEA | 1.2 | −78°C to rt | 0 | – |
| 3 | $SnCl_4$ | DIPEA | 5.0 | −78°C to rt | 0 | – |
| 4 | $Bu_2B(OTf)$ | DIPEA | 1.2 | −78°C to rt | 12 | (31/69) |
| 5 | $Bu_2B(OTf)$ | DIPEA | 5.0 | −78°C to rt | 12 | (30/70) |
| 6 | $TiCl_4$ | DIPEA | 1.2 | −78°C to rt | 81 | (30/70) |
| 7 | $TiCl_4$ | DIPEA | 5.0 | −78°C to rt | 78 | (30/70) |
| 8 | $TiCl_4$ | DIPEA | 1.2 | −78°C to rt[e] | 0 | – |
| 9 | $TiCl_4$ | DIPEA | 1.2 | −78°C | 47 | (30/70) |
| 10 | $TiCl_4$ | $Et_3N$ | 1.2 | −78°C to rt | 50 | (43/57) |
| 11 | $TiCl_4$ | *N*-Et-piperidine | 1.2 | −78°C to rt | 75 | (44/56) |

[a] The amount of Lewis acid was 1.1 equiv. to **11**.
[b] After an addition of amine to a solution of Lewis acid and **11** in $CH_2Cl_2$ at −78°C and stirring for 1.5 h at the temperature, a solution of **3** in $CH_2Cl_2$ was added to the resulting solution, and then the solution was warmed to rt, if otherwise was not noted.
[c] The ratio of diastereomers; *R* and *S* show the absolute configuration of α-position of piperidine ring.
[d] Diisopropylethylamine.
[e] The solution containing titanium enolate was warmed to rt followed by the addition of **3** at rt.

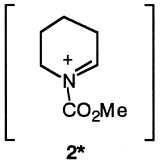



**Figure 2.** Iminium ion **2*** from **3**.

With these results in hand, we tried the reaction between **3** and **4a**–**c** (Scheme 2) with our expectation that the replacement of the *N*-acetyl group of **11** with a more bulky *N*-phenylacetyl group might bring about more remarkable effect on the stereochemistry of the coupling reaction than phenylthioacetyl group. Fortunately, the coupling reaction proceeded smoothly to give the products **5a**–**c** in 60–75% yields as a mixture of the stereoisomers. They were converted, without isolation, to *N*-methoxycarbonylmethylphenidate **7** since an analysis of the configuration of **5a**–**c** was difficult. The ratio of four stereoisomers of **7** was obtained using chiral HPLC; at this stage, the absolute configuration of each stereoisomer of **7** was determined by converting **7** to the stereoisomers of **1** followed by the comparison with authentic samples. The overall yields of **7** from **4a**–**c** were 40–54% and the stereoselectivity was high. The results are summarized in Table 2.

Expectedly, the main diastereoisomer of **7** was *threo* and the absolute configuration of the 2′-position was found to be *R*. The ratios of *erythro* to *threo* of **7** obtained in the reaction of **3** with **4a** and **4b** were 6.9/93.1 and 5.3/94.7, respectively, and the ee of *threo* product (*threo*-**7**) from **4b** was very high (99.6%) (entries 1 and 2 in Table 2). The high diastereoselectivity was also observed in the reaction of **3** with **4c** (*erythro*/*threo*=1.6/98.4, entry 3 in Table 2), whereas the ee

**Table 2.** Reaction of α-methoxycarbamate **3** with 3-(phenylacetyl)-2-oxazolidinones (**4a**–**c**)

| Entry | **4a**–**c** | Yield (%) of **7**[a] | *erythro*/*threo* | *threo*-**7** % ee[b] | Main **7**[c] |
|---|---|---|---|---|---|
| 1 | **4a** | 48 | 6.9/93.1 | – | – |
| 2 | **4b** | 54 | 5.3/94.7 | 99.6 | (2*R*,2′*R*) |
| 3 | **4c** | 40 | 1.6/98.4 | 81.8 | (2*S*,2′*S*) |

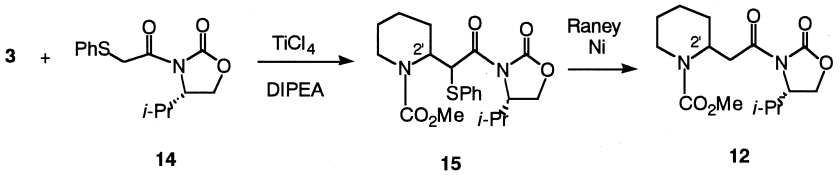
[a] Overall yield of **7** from **4a**–**c**.
[b] The % ee was determined using CSP HPLC.
[c] The absolute configuration was determined by converting **7** to methylphenidate **1** hydrochloride followed by comparison of the salts with the authentic samples [Ref. 6].

of the *threo* isomer was 81.8%, indicating that the 4-isopropyl substituent of 2-oxiazolidinone ring was superior to the 4-phenyl substituent. The product **7** obtained from the reaction of **3** with **4c** possessed an absolute configuration (2*S*,2′*S*) which was opposite to that (2*R*,2′*R*) of **7** obtained from the reaction of **3** with **4b**.

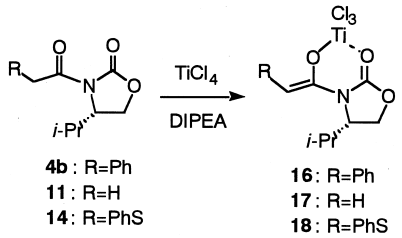
## Reaction mechanism

The observed stereochemical outcomes are explainable by taking account of the reaction intermediates. For simplicity, we discuss the cases of (4*S*)-isopropyl-2-oxazolidinone derivatives **4b**, **11** and **14**. The titanium enolates generated from **4b**, **11** and **14** may exist as *Z*-forms **16**–**18** (Scheme 6) since the formation of *Z*-enolates from Evans imides has been established.[9a,18] In addition, the *re*-face attack of an iminium ion **2*** on an *E*-enolate, if it was generated, produces a coupling product **19** as a main product which possesses a 2*S*-configuration (Scheme 7).

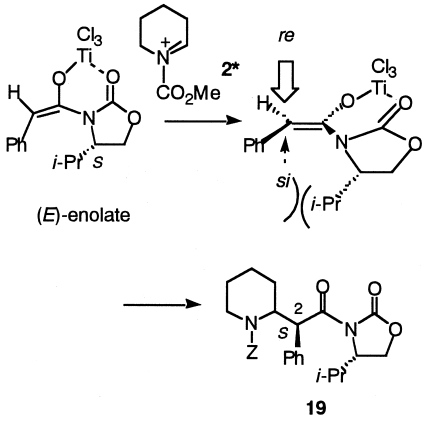
With these considerations in mind, several plausible intermediates must be examined depending upon the mode of




**Scheme 5.**



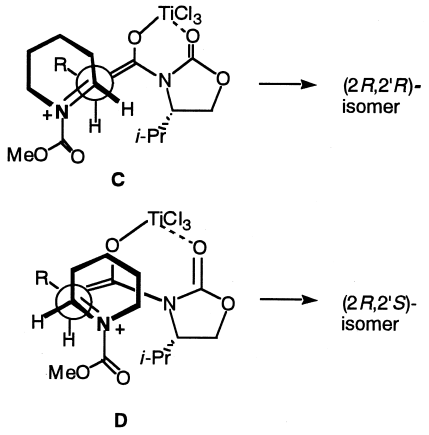

**Scheme 6.**



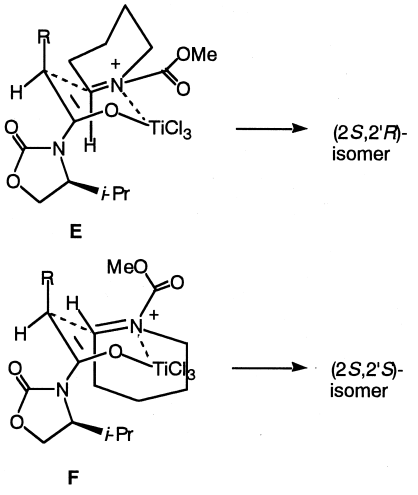

**Scheme 7.**

attack of an iminium ion **2*** on *Z*-enolates **16**–**18**. Schemes 8–10 show such intermediates **A**–**F** which are formed as (i) a coordinated species involving a chelated enolate (Scheme 8), (ii) a non-coordinated intermediate involving a chelated enolate (Scheme 9), or as (iii) a coordinated species involving a non-chelated enolate (Scheme 10). Non-chelated intermediates have been proposed to explain the stereochemistry (*syn*) observed in the Evans aldol reaction (Scheme 3).[15]

Among those routes, route (iii) can be dismissed immediately since it affords coupling products possessing a 2*S*-configuration. Thus, the reaction proceeds through routes (i) or (ii). We prefer route (i) to route (ii) for the following reasons; In the case where R=Ph, the severe repulsion between it and the piperidinium ring may direct the reaction to pass through **A**, which gives (2′*R*)-isomer, rather than

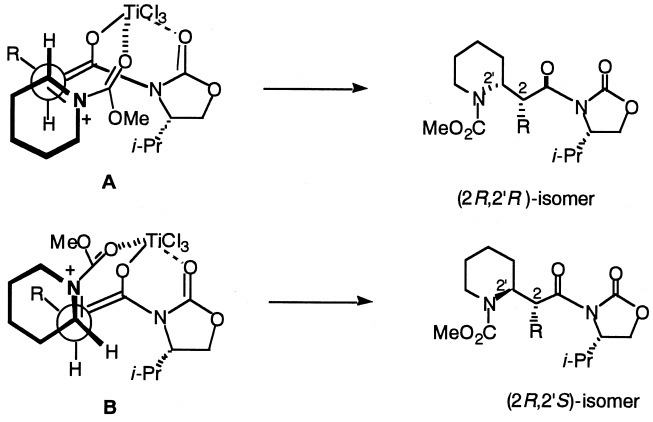



**Scheme 9.** Route (ii) via non-coordinated intermediates **C** and **D** involving a chelated enolate.




**Scheme 10.** Route (iii) via coordinated intermediates **E** and **F** involving a non-chelated enolate.

through **B** (Scheme 8), while the same repulsion in route (ii) may make the reaction to produce (2′*S*)-isomer through **D** rather than (2′*R*)-isomer through **C** (Scheme 9). The configuration of the main product obtained was 2′*R* as described above. Also, route (i) can explain the increase in the amount of a coupling product possessing a




**Scheme 8.** Route (i) via coordinated intermediates **A** and **B** involving a chelated enolate.

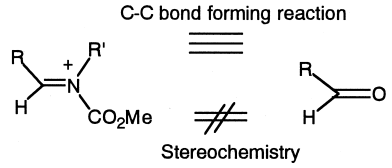



**Figure 3.** Reactivity of imminium ion and aldehyde toward Evans Imide.

2′*S*-configuration in proportion to the decrease of the bulkiness of R group (Ph>PhS>H).

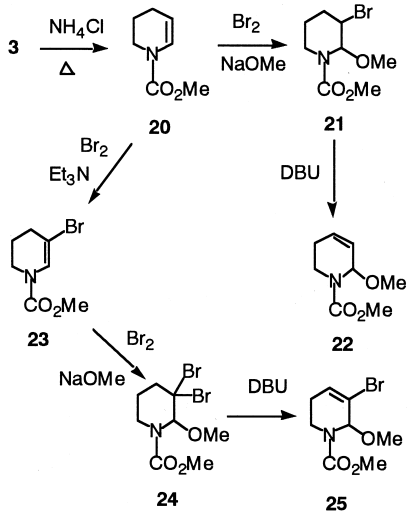
Interestingly, the stereochemistry observed in our reaction (*threo* isomer; (2*R*,2′*R*)-isomer) was largely different from that observed in the Evans aldol reaction which predominantly gives *syn* (*erythro*) products (Scheme 3). The difference may be explained in terms of the intervention of chelated intermediates for iminium ions and non-chelated intermediates for aldehydes. Accordingly, it may be concluded that iminium ion behaves equivalent to aldehyde in the C–C bond-forming reaction toward Evans imides but it shows a stereochemical result completely different from aldehydes (Fig. 3).

## Effect of the structure of iminium ions

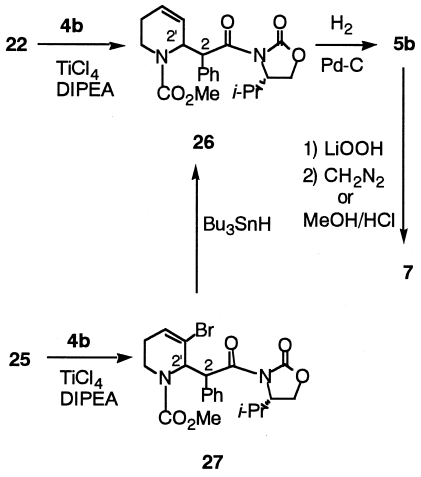
The influence of the piperidine structure upon the C–C bond forming reaction was then studied. Compounds **22** and **25** were prepared from **3** according to the routes shown in Scheme 11.

The reaction of **22** and **25** with the titanium enolate derived from **4b** gave **26** and **27**, respectively. After **27** was reduced to **26** by tributyltin hydride, **26** was transformed to **7** through **5b**. The stereochemistry of **7** was then clarified by use of the CSP HPLC method (Scheme 12). The results are shown in Table 3.

The result shows that the existence of a double bond at the β,γ-position of piperidine ring did not affect the stereochemistry in the coupling reaction (entry 1 in Table 3). Interestingly, however, a β-bromo-substituent largely




**Scheme 11.**




**Scheme 12.**

reduced the ee of *threo* isomer and the main stereoisomer was *threo*-(2*S*,2′*S*)-**7** (entry 2 in Table 3). The formation of (2*S*,2′*S*)-**7** cannot be explained in terms of intermediates similar to **A**–**D** in routes (i) and (ii) since such intermediates give (2*R*)-isomers. An intermediate similar to **F** may be responsible for a formation of (2*S*,2′*S*)-**7**.

## Synthesis of *p*-substituted methylphenidate

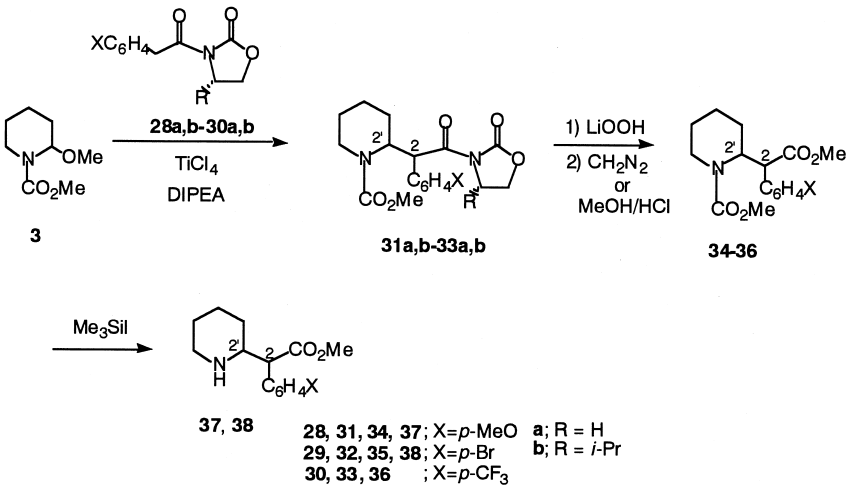
Our method was applied to the preparation of racemic and optically active *p*-substituted methylphenidates (Scheme 13). The reaction was carried out between **3** and **28a**,**b**–**30a**,**b** under the reaction conditions described above. The C–C bond forming reaction proceeded successfully and the stereoselectivity was also very high. Since the stereochemistry of the initially formed C–C bond forming products **31a**,**b**–**33a**,**b** was ambiguous, their configurations were determined at the stage of **34**–**36**. Among *p*-substituted methylphenidate derivatives **34**–**36**, the absolute configuration of *p*-methoxy- and *p*-bromo-substituted derivatives **34** and **35** were determined by their conversion to **37** and **38**, respectively, followed by comparison of **37** and **38** with authentic samples.[6] The absolute configuration of *p*-trifluoromethyl-substituted derivatives **36** was estimated as depicted one on the basis of the stereochemical results in the preparation of **7**, **34** and **35**. Those results are summarized in Table 4.

One of the advantages in our method is indicated by the high stereoselectivity shown in Table 4. In addition, our method can provide a route to prepare *p*-trifluoromethyl-substituted methylphenidate **36** which could not be prepared by the conventional method.[4]

**Table 3.** Reaction of α-methoxycarbamates **22** and **25** with **4b**

| Entry | **22**,**25** | Yield (%) of **7** | **7** *erythro*/*threo*[a] | *threo*-**7** % ee[a,b] |
|---|---|---|---|---|
| 1 | **22** | 54 | 10.3/89.7 | 98.1 (2*R*,2′*R*) |
| 2 | **25** | 42 | 1.9/98.1 | 26.8 (2*S*.2′*S*) |

[a] The ratio was determined at the stage of **7**.
[b] The configuration of main stereoisomer.

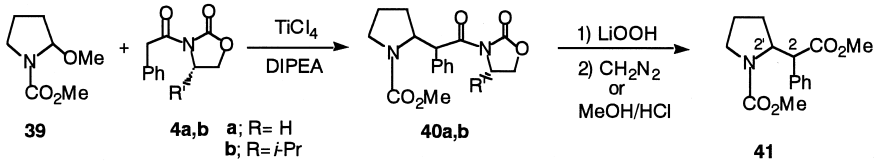



**Scheme 13.**

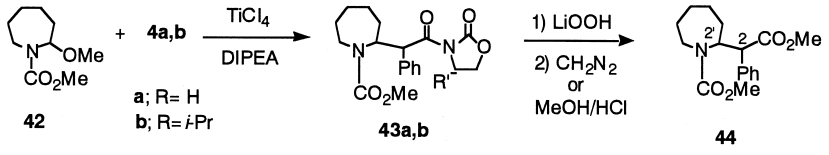
**Table 4.** Reaction of α-methoxycarbamate **3** with *p*-substituted phenylacetyl-2-oxazolidinones **28a**,**b**–**30a**,**b**

| Entry | Nucleophiles | For C–C bond formation | | Ratio[a] of *erythro*/*threo* | *threo*-**34**–**36** | |
|---|---|---|---|---|---|---|
| | | Products | Yields[b] (%) | | % ee[a] | Stereochemistry[a] |
| 1 | **28a** | **34** | 48 | 10.6/89.4 | – | – |
| 2 | **28b** | **34** | 52 | 5.9/94.1 | >99.9 | (2*R*,2′*R*) |
| 3 | **29a** | **35** | 37 | 1.2/98.8 | – | – |
| 4 | **29b** | **35** | 40 | 5.6/94.4 | 97.6 | (2*R*,2′*R*) |
| 5 | **30a** | **36** | 32 | 10.6/89.4 | – | – |
| 6 | **30b** | **36** | 30 | 5.2/94.8 | >99.9 | (2*R*,2′*R*)[c] |

[a] The ratio and absolute configuration were determined at the stage of **34**–**36** by CSP HPLC method.
[b] Overall yield from **28**–**30**.
[c] Estimated configuration.




**Scheme 14.**




**Scheme 15.**

**Table 5.** Reaction of α-methoxycarbamates **39**, **42** with phenylacetyl-2-oxazolidinones **4a**,**b**

| Entry | **39**,**42** | **4a**,**b** | For C–C bond formation | | Ratio[a] of *erythro/threo* | *threo*-**41**,**44** % ee[a] |
|---|---|---|---|---|---|---|
| | | | Products | Yields[b] (%) | | |
| 1 | **39** | **4a** | **41** | 62 | 7.0/93.0 | – |
| 2 | **39** | **4b** | **41** | 52 | 12.0/88.0 | 93.0 |
| 3 | **42** | **4a** | **44** | 61 | 3.5/96.5 | – |
| 4 | **42** | **4b** | **44** | 59 | 15.1/84.9 | 96.4 |

[a] The ratio and absolute configuration were determined at the stage of **41**, **44** by CSP HPLC method.
[b] Overall yield from **39**,**42**.

### Application to synthesis of five- and seven-membered analogues of methylphenidate

Our method was also applicable to the preparation of five- and seven-membered amino esters **41** and **44**, analogues of methylphenidate derivative **7** (Schemes 14 and 15).

In those reactions, high stereoselectivity was observed as shown in Table 5. Although the configuration of products **41** and **44** could not be identified, that of the main stereoisomer of **41** and **44** was estimated to be (2*R*,2′*R*) on the basis of the proposed reaction mechanism described above.

## Experimental

### General

Electrochemical reactions were carried out by using DC Power Supply (GP 050-2) of Takasago Seisakusho, Inc. HPLC analyses were achieved by using a LC-10AT *VP* and a SPD-10A VP of Shimadzu Seisakusho Inc. Specific rotations were measured with Jasco DIP-1000. $^1$H NMR spectra were measured on a Varian Gemini 300 spectrometer with TMS as an internal standard. IR spectra were obtained on a Shimadzu FTIR-8100A. Elemental analyses were carried out in Center for Instrumental Analysis, Nagasaki University. Mass spectra were obtained on a JEOL JMS-DX 303 instrument.

### Preparation of α-methoxycarbamates 3, 22, 25, 39 and 42

Electrochemical oxidation of *N*-methoxycarbonylpiperidine (**2**), *N*-methoxycarbonylpyrroridine, and *N*-methoxycarbonylhexamethyleneimine in methanol has been reported to give **3**,[11a,b] **39**,[11a,b] and **42**,[19] respectively, in good yields (80–89%). α-Methoxycarbamates **22** and **25** were prepared according to the reported method.[20]

**3,4-Didehydro-*N*-methoxycarbonyl-2-methoxypiperidine (22).** Colorless oil; IR (neat) 1701, 1445, 1402, 1304, 1266, 1238, 1190, 1082 cm$^{-1}$; $^1$H NMR (300 MHz) ($CDCl_3$) $\delta$ 1.90–2.38 (m, 2H), 2.88–3.21 (m, 1H), 3.4 (br s, 3H), 3.75 (s, 3H), 3.90–4.24 (m, 1H), 5.30–5.53 (m, 1H), 5.70–5.84 (m, 1H), 5.95–6.10 (m, 1H); HRMS calcd for $C_8H_{13}NO_3$: 171.0895. found: 171.0891. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.34; H, 7.90; N, 8.21.

**3-Bromo-3,4-didehydro-*N*-methoxycarbonyl-2-methoxypiperidine (25).** Colorless oil; IR (neat) 1725, 1649, 1410, 1335, 1256, 1117, 1092, 1059 cm$^{-1}$; $^1$H NMR (300 MHz) ($CDCl_3$) $\delta$ 1.98–2.40 (m, 2H), 3.02–3.31 (m, 1H), 3.4 (br s, 3H), 3.77 (s, 3H), 3.90–4.20 (m, 1H), 5.39 (br s, 0.5H), 5.54 (br s, 0.5H), 6.28 (br s, 1H); HRMS calcd for $C_8H_{12}BrNO_3$: 249.0000. found: 249.0039. Anal. Calcd for $C_8H_{12}BrNO_3$: C, 38.42; H, 4.84; N, 5.60. Found: C, 38.45; H, 4.88; N, 5.62.

### Preparation of 3-phenylacetyl-2-oxazolidinones (4a–c), 3-acetyl-2-oxazolidinone (11), and 3-phenylthioacetyl-2-oxazolidinone (14)

3-Acetyl-2-oxazolidinone (**11**) is commercially available. The other compounds were prepared according to the Evans method.[9] The typical procedure was exemplified by the preparation of **11**. Into a solution of (4*S*)-(−)-4-isopropyl-2-oxazolidinone (100 mmol) in anhydrous THF (200 mL) cooled by ice water was added NaH (150 mmol), and the solution was stirred for 2 h. Then, acetyl chloride (155 mmol) was added. After stirring for 3 h, the solution was poured into a saturated aqueous solution of $NH_4Cl$, and the organic portion was extracted with $CH_2Cl_2$ three times. The extracts were dried on $MgSO_4$, and **11** was isolated by column chromatography.

**3-Phenylacetyl-2-oxazolidinone (4a).** Colorless solid; mp 64–65°C; IR (neat) 1771, 1698, 1497, 1476, 1456, 1387, 1109, 1037 cm$^{-1}$; $^1$H NMR (300 MHz) ($CDCl_3$) $\delta$ 4.03 (t, $J$=8.4 Hz, 2H), 4.29 (s, 2H), 4.41 (t, $J$=8.4 Hz, 2H), 7.27–7.38 (m, 5H). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.35; H, 5.45; N, 6.77.

**(4*S*)-3-Phenylacetyl-4-isopropyl-2-oxazolidinone (4b).** 68% Yield; colorless oil; $[\alpha]_D^{20}$=+77.6° ($c$=2.05, $CHCl_3$); IR (neat) 1765, 1690 cm$^{-1}$; $^1$H NMR (300 MHz) ($CDCl_3$) $\delta$ 0.78 (d, $J$=6.9 Hz, 3H), 0.87 (d, $J$=7.0 Hz, 3H), 2.23–2.37 (m, 1H), 4.11–4.38 (m, 5H), 7.20–7.38 (m, 5H). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.02; H, 6.89; N, 5.59.

**(4*R*)-3-Phenylacetyl-4-phenyl-2-oxazolidinone (4c).** 59% Yield; colorless solid; mp 70–71°C; $[\alpha]_D^{24}$=−87.0° ($c$=1.0, MeOH); IR (neat) 1779, 1705, 1613, 1512, 1387, 1329, 1248, 1200, 1179, 1105, 1042 cm$^{-1}$; $^1$H NMR (300 MHz) ($CDCl_3$) $\delta$ 4.23–4.30 (m, 1H), 4.29 (s, 2H), 4.69 (t, $J$=8.9 Hz, 1H), 5.42 (dd, $J$=3.9, 8.8 Hz, 1H), 7.18–7.40 (m, 10H); Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.55; H, 5.45; N, 4.87.

**(4*S*)-3-Phenylthioacetyl-4-isopropyl-2-oxazolidinone (14).** 48% Yield; yellow oil: $[\alpha]_D^{24}$=+167.1° ($c$=1.00, MeOH); IR (neat) 1784, 1700, 1483, 1389, 1368, 1323, 1210, 1171 cm$^{-1}$; $^1$H NMR (300 MHz) ($CDCl_3$) $\delta$ 0.88 (dd, $J$=3.8, 6.9 Hz, 6H), 2.22–2.42 (m, 1H), 4.09–4.47 (m, 5H), 7.18–7.35 (m, 3H), 7.39–7.48 (m, 2H); HRMS calcd for $C_{14}H_{17}NO_3S$: 279.0929. found: 279.0952. Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01; S, 11.48. Found: C, 59.84; H, 5.92; N, 4.72; S, 11.32.

### Coupling reaction of 3 with 11

A solution of 1.0 M $TiCl_4$ in $CH_2Cl_2$ (1.1 mL, 1.1 mmol) was added into a solution of **11** (1.0 mmol) in $CH_2Cl_2$ (5 mL) at −78°C under a nitrogen atmosphere; DIPEA (0.21 mL, 1.2 mmol) was also added to the solution. After 1.5 h, a solution of **3** (1.2 mmol) in $CH_2Cl_2$ (1 mL) was added, and the resulting solution was allowed to be stirred at rt overnight. The reaction mixture was poured into aqueous ammonium chloride. The organic portion was extracted $CH_2Cl_2$ to afford a crude **12**, which was subjected on silica gel chromatography to afford a pure sample of **12**.

The yield of **12** was 81%, consisting of stereoisomers (30/70). The ratio of (2′*S*)-**12** to (2′*R*)-**12** was determined by DAICEL Chiralcel OD (4.6 mm∅, 25 cm) [hexane/ethanol (20/1)(v/v), 1.0 mL/min, detection at 210 nm]; 9 min for (2′*R*)-**12**, 16 min for (2′*S*)-**12**. The main isomer was separated by column chromatography and was found to possess a (2′*S*)-configuration after it was converted to **13**, whose stereochemistry is known.

**(2′*S*,4*S*)-3-(*N*′-Methoxycarbonyl-2′-piperidyl)acetyl-4-isopropyl-2-oxazolidinone ((2′*S*)-12).** Colorless oil: $[\alpha]_D^{15}=+41.1°$ (*c*=0.88, MeOH); IR (neat) 1786, 1709, 1451, 1408, 1389, 1316, 1269, 1210 $cm^{-1}$; $^1H$ NMR (300 MHz) ($CDCl_3$) $\delta$ 0.90 (dd, *J*=3.9, 7.0 Hz, 6H), 1.35–1.75 (m, 5H), 2.20–2.45 (m, 1H), 2.39–3.03 (m, 1H), 3.11 (dd, *J*=16.4, 7.9 Hz, 6H), 3.66 (s, 3H), 3.94–4.15 (m, 1H), 4.20–4.35 (m, 2H), 4.38–4.48 (m, 1H), 4.80–4.93 (m, 1H); HRMS calcd for $C_{15}H_{24}N_2O_5$: 312.1685. found: 312.1699. Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.68; H, 7.74; N, 8.97. Found: C, 57.38; H, 7.40; N, 8.59.

**(2′*R*,4*S*)-3-(*N*′-Methoxycarbonyl-2′-piperidyl)acetyl-4-isopropyl-2-oxazolidinone ((2′*R*)-12).** Colorless oil: $[\alpha]_D^{15}=+53.4°$ (*c*=1.75, MeOH); IR (neat) 1784, 1705, 1449, 1408, 1387, 1339, 1269, 1211 $cm^{-1}$; $^1H$ NMR (300 MHz) ($CDCl_3$) $\delta$ 0.89 (t, *J*=7.1 Hz, 6H), 1.30–1.75 (m, 5H), 2.25–2.45 (m, 1H), 2.87–3.20 (m, 2H), 3.28–3.45 (m, 1H), 3.65 (s, 3H), 3.90–4.39 (m, 4H), 4.75–4.90 (m, 1H); HRMS calcd for $C_{15}H_{24}N_2O_5$: 312.1685. found: 312.1647. Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.68; H, 7.74; N, 8.97. Found: C, 57.30; H, 7.50; N, 8.67.

**Transformation of (2′*S*)-12 to (2*S*)-*N*-methyl-2-piperidineethanol ((2*S*)-13).** Water (1.5 mL), LiOH (6 mmol), and 35%$H_2O_2$ (1.5 mL) were successively added to a solution of (2′*S*)-**12** (486 mg, 1.6 mmol) in THF (6 mL), and the resulting solution was stirred at rt overnight and quenched with an aqueous 1.5 M $NaHSO_3$ solution. Then an aqueous 5%NaOH solution was added and the organic portion was extracted with $CH_2Cl_2$. The aqueous solution was acidified with 5%HCl and the extraction with $CH_2Cl_2$ gave a crude carboxylic acid, which was subjected to column chromatography to afford (2*S*)-*N*-methoxycarbonyl-2-piperidineacetic acid. 76% yield; colorless solid: mp 94–95°C: $[\alpha]_D^{23}=-9.7°$ (*c*=3.1, MeOH); IR (neat) 3450, 3200, 1447, 1408, 1370, 1264, 1193, 1173 $cm^{-1}$; $^1H$ NMR (300 MHz) ($CDCl_3$) $\delta$ 1.25–1.75 (m, 6H), 2.63 (d, *J*=7.7 Hz, 2H), 2.75–2.95 (m, 1H), 3.69 (s, 3H), 3.92–4.10 (m, 1H), 4.68–4.81 (m, 1H), 6.5 (br s, 1H); HRMS calcd for $C_9H_{15}NO_4$: 201.1002. found: 201.1001. Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.53; H, 7.49; N, 6.72.

Into a solution of (2*S*)-*N*-methoxycarbonyl-2-piperidineacetic acid (63 mg, 0.31 mmol) in THF (10 mL), $LiAlH_4$ (35 mg, 0.93 mmol) was added, and the solution was refluxed for 4 h. After water was added, the solution was acidified with dilute HCl and extracted with $CH_2Cl_2$. The aqueous solution was treated with an aqueous NaOH, and extracted with $CH_2Cl_2$. The conventional procedures for the extract gave (2*S*)-*N*-methyl-2-piperidineethanol ((2*S*)-**13**). 43% yield; colorless oil: $[\alpha]_D^{23}=-42.1°$ (*c*=0.4, EtOH) (lit.[21] $[\alpha]_D^{27}=-43.8°$ (*c*=1.0, EtOH)); IR (neat) 3360, 1445, 1374, 1264, 1271, 1055 $cm^{-1}$; $^1H$ NMR (300 MHz) ($CDCl_3$) $\delta$ 1.23–1.82 (m, 6H), 1.94–2.14 (m, 2H), 2.19–2.31 (m, 1H), 2.36 (s, 3H), 2.84–2.96 (m, 1H), 3.35 (br s, 1H), 3.64–3.89 (m, 2H), 3.89–4.03 (m, 1H); HRMS calcd for $C_8H_{17}NO$: 143.1310. Found: 143.1309.

**Coupling reaction of 3 with 14**

According to a procedure similar to the coupling reaction of **3** with **11**, the reaction of **3** with **14** was carried out to give **15**, which was treated with Raney Ni without purification. The Raney Ni reduction was achieved under hydrogen gas atmosphere using MeOH as a solvent suspended with a catalytic amount of Raney-Ni overnight. The overall yield of **12** from **14** was 54%. The ratio of (2′*R*)-**12**/(2′*S*)-**12** was 77/23.

**Preparation of methyl (2-phenyl-2-(*n*-methoxycarbonyl-2′-piperidyl)acetate (7). Preparation of 7 by the reaction of 3 with 4a**

A solution of 1.0 M $TiCl_4$ (1.1 mL, 1.1 mmol) in $CH_2Cl_2$ was added into a solution of **4a** (1 mmol) in $CH_2Cl_2$ (5 mL) at −78°C under a nitrogen atmosphere, and DIPEA (1.2 mmol) was added to the solution. After 1.5 h, a solution of **3** (1.2 mmol) in $CH_2Cl_2$ (1 mL) was added, and the resulting solution was allowed to be stirred at rt overnight. The reaction mixture was poured into aqueous ammonium chloride. The organic portion was extracted $CH_2Cl_2$ to afford a crude **5a**, which was subjected without isolation to further hydrolysis. That is, $H_2O$ (1 mL), LiOH (4 mmol), and 35%$H_2O_2$ (1 mL) were successively added to **5a** dissolved in THF (4 mL). The solution was stirred at rt overnight, and quenched with 1.5 M $NaHSO_3$. Then an aqueous 5% NaOH solution was added and the organic portion was extracted with $CH_2Cl_2$. The aqueous solution was acidified with 5%HCl and the extraction with $CH_2Cl_2$ gave a crude carboxylic acid **6**, which was subjected with diazomethane in ether to give **7**. The yield of **7** from **4a** was 48%. The overall yield of **7** from **4a** was 32% in a case that esterification was carried out by 1 M HCl–MeOH method (at rt, overnight). The *threo*-**7** was separable from *erythro*-**7** by column chromatography (silica gel, AcOEt/hexane=1/3). The ratio of *erythro*-**7**/*threo*-**7** was 6.9/93.1.

**Preparation of 7 by the reaction of 3 with 4b and 4c**

According to a similar procedure described above, **7** was obtained by the reactions of **3** with **4b**, and **4c**. The yields of **7** obtained in these reactions were 54 and 40%, respectively, using diazomethane. The ratios of *erythro*-**7**/*threo*-**7** were 5.3/94.7 in the reaction of **3** with **4b** and 1.6/98.4 in the reaction of **3** with **4c**. The ee was obtained by DAICEL Chiralpak AD (4.6 mm∅, 25 cm) [hexane/isopropanol/methanol (150:4:0.5) (v/v/v), 0.8 mL/min, detection at 210 nm, 17 min for (2*R*, 2′*R*)-**7**, 22 min for (2*S*, 2′*S*)-**7**, 25 min for (2*R*, 2′*S*)-**7**, 28 min for (2*S*,2′*R*)-**7**. The ratios of (2*R*,2′*R*)-**7**/(2*S*,2′*S*)-**7** were 99.8/0.2 in the reaction of **3** with **4b** and 90.9/9.1 in the reaction of **3** with **4c**.

**Methyl *threo*-(2-phenyl-2-(*N*-methoxycarbonyl-2′-piperidyl)acetate (*threo*-7).** Colorless oil; IR (neat) 1736, 1698,

1447, 1271, 1248, 1192 $cm^{-1}$; $^1H$ NMR (300 MHz) ($CDCl_3$) $\delta$ 1.18–1.78 (m, 6H), 2.96–3.20 (m, 1H), 3.61 (s, 3H), 3.74 (br s, 3H), 3.86–4.28 (m, 2H), 4.80–5.10 (m, 1H), 7.22–7.50 (m, 4H); HRMS calcd for $C_{16}H_{21}NO_4$: 291.1470. found: 291.1485. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81. Found: C, 66.13; H, 7.22; N, 4.71.

**Methyl *erythro*-(2-phenyl-2-(*N*-methoxycarbonyl-2′-piperidyl)acetate (*erythro*-7).** Colorless oil; IR (neat) 1734, 1698, 1447, 1266, 1250, 1172 $cm^{-1}$; $^1H$ NMR (300 MHz) ($CDCl_3$) $\delta$ 1.18–1.83 (m, 6H), 2.65–2.83 (m, 1H), 3.67 (s, 3H), 3.77 (s, 3H), 3.87–4.20 (m, 2H), 4.77–5.03 (m, 1H), 7.15–7.49 (m, 4H); HRMS calcd for $C_{16}H_{21}NO_4$: 291.1470. found: 291.1466. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81. Found: C, 66.20; H, 7.21; N, 4.65.

### Synthesis of hydrochloride salt of methylphenidate (1) from 7

Each stereo isomer of the compound **7** derived from the coupling product **5b** in the reaction of **3** with **4b** was isolated by column chromatography (silica gel, hexane/AcOEt), and they were subjected to deprotection procedures described below. That is, a solution of $Me_3SiI$ (526 mg, 2.7 mmol) in $CH_2Cl_2$ (5 mL) was dropwise added at rt into a solution of the main diastereoisomer (polar isomer) of **7** (307 mg, 1.1 mmol) in $CH_2Cl_2$ (2 mL), and the solution was stirred at rt. After 12 h, MeOH(2 mL) was added, and the solvents were evaporated in vacuo to give a residue, which was then dissolved in ether. The ethereal solution was washed with an aqueous 5% HCl solution three times. The combined aqueous solution was made alkaline by adding a 5% NaOH solution, and then organic portion was extracted with ether. The removal of ether in vacuo gave a yellow residue, which was dissolved 1 M HCl–MeOH. Evaporation of MeOH from the solution gave a white solid, which was recrystallized from EtOH/ether to give hydrochloride salt of *threo*-**1**: 60% yield from *threo*-**7**; $[\alpha]_D^{27}=+83.0°$ ($c$=1.0, MeOH). [lit.[6] (2*R*,2′*R*)-**1**; $[\alpha]_D^{20}=+82.6°$ ($c$=1.09, MeOH)]. On the bases of this result, the main stereoisomer in the reaction of **3** with **4b** was found to have a (2*R*,2′*R*)-configuration.

Also, according to the method described above, hydrochloride salt of *erythro*-**1** was obtained from minor stereoisomer (less polar isomer) of **7**; $[\alpha]_D^{20}=+106.6°$ ($c$=0.7, MeOH). [lit.[6] (2*R*,2′*S*)-**1**; $[\alpha]_D^{20}=+92.3°$ ($c$=1.11, MeOH)]. On the basis of this result, the minor stereoisomer in the reaction of **3** with **4b** was determined to have a (2*R*,2′*S*)-configuration.

### Coupling reaction of 22 with 4b

According to a similar procedure to the reaction of **3** with **4a**, the coupling reaction of **22** with **4b** was carried out to yield **26**, which was hydrogenated without purification (an atmospheric pressure of hydrogen gas in MeOH with Pd/C catalyst). Further, the crude product **5b** was converted to **7** by procedures described above. The overall yield of **7** from **4b** was 54%. The ratio of *erythro*-**7**/*threo*-**7** was 10.3/89.7, and the ratio of (2*R*,2′*R*)-**7**/(2*S*,2′*S*)-**7** was 99.1/0.9.

### Coupling reaction of 25 with 4b

According to a similar procedure to the reaction of **3** with **4a**, the coupling reaction of **25** with **4b** was carried out to yield **27**, which was reduced without purification ($n$-$Bu_3SnH$ (2.5 mmol), AIBN (0.25 mmol) in benzene solvent (5 mL), refluxing for 4 h, then, washed with 10% KF, extracted with benzene). The resulting compound **26** was converted to **7** via **5b** by procedures described above. The overall yield of **7** from **4b** was 42%. The ratio of *erythro*-**7**/*threo*-**7** was 1.9/98.1, and the ratio of (2*R*,2′*R*)-**7**/(2*S*,2′*S*)-**7** was 36.6/63.4.

### Preparation of 3-(*p*-substituted phenylacetyl)-2-oxazolidinones 28a,b–30a,b

Those compounds were prepared according to a procedure of the preparation of **4a**–**c**.

**3-(*p*-Methoxyphenyl)acetyl-2-oxazolidinone (28a).** 79% Yield; colorless solid; mp 112–115°C; IR (neat) 1786, 1705, 1612, 1514, 1478, 1391, 1368, 1267, 1181, 1113, 1036 $cm^{-1}$; $^1H$ NMR (300 MHz) ($CDCl_3$) $\delta$ 3.79 (s, 3H), 4.01 (t, $J$=7.5 Hz, 2H), 4.22 (s, 2H), 4.40 (t, $J$=8.1 Hz, 2H), 6.68 (d, $J$=8.8 Hz, 2H), 7.74 (d, $J$=8.5 Hz, 2H); Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.14; H, 5.57; N, 5.78.

**3-(*p*-Methoxyphenyl)acetyl-(4*S*)-isopropyl-2-oxazolidinone (28b).** 60% Yield; colorless solid; mp 89–90°C; $[\alpha]_D^{24}=+73.7°$ ($c$=0.6, MeOH); IR (neat) 1792, 1709, 1613, 1586, 1518, 1466, 1393, 1375, 1302, 1256, 1213, 1183, 1121, 1034 $cm^{-1}$; $^1H$ NMR (300 MHz) ($CDCl_3$) $\delta$ 0.79 (d, $J$=6.9 Hz, 3H), 0.88 (d, $J$=7.0 Hz, 3H), 2.22–2.35 (m, 1H), 3.79 (s, 3H), 4.07–4.38 (m, 2H), 4.38–4.49 (m, 1H), 6.83–6.90 (m, 2H), 7.20–7.29 (m, 2H); Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.17; H, 6.90; N, 4.93.

**3-(*p*-Bromophenyl)acetyl-2-oxazolidinone (29a).** 50% Yield; colorless solid; mp 119–121°C; IR (neat) 1763, 1698, 1476, 1404, 1389, 1370, 1273, 1238, 1113, 1009 $cm^{-1}$; $^1H$ NMR (300 MHz) ($CDCl_3$) $\delta$ 4.03 (t, $J$=7.9 Hz, 2H), 4.24 (s, 2H), 4.43 (t, $J$=8.1 Hz, 2H), 7.15–7.24 (m, 2H), 7.42–7.50 (m, 2H); Anal. Calcd for $C_{11}H_{10}BrNO_3$: C, 46.50; H, 3.55; N, 4.93. Found: C, 46.50; H, 3.50; N, 4.85.

**3-(*p*-Bromophenyl)acetyl-(4*S*)-isopropyl-2-oxazolidinone (29b).** 49% Yield; colorless solid; mp 70–74°C; $[\alpha]_D^{23}=+56.3°$ ($c$=0.6, MeOH); IR (neat) 1790, 1701, 1489, 1389, 1374, 1306, 1254, 1211, 1121, 1013 $cm^{-1}$; $^1H$ NMR (300 MHz) ($CDCl_3$) $\delta$ 0.84 (dd, $J$=7.0, 17.0 Hz, 6H), 2.23–2.43 (m, 1H), 4.12–4.39 (m, 4H), 4.40–4.49 (m, 1H), 7.19 (d, $J$=8.1 Hz, 2H), 7.45 (d, $J$=8.4 Hz, 2H); HRMS calcd for $C_{14}H_{16}BrNO$: 325.0313. found: 325.0324. Anal. Calcd for $C_{14}H_{16}BrNO$: C, 51.55; H, 4.94; N, 4.29. Found: C, 51.19; H, 4.76; N, 3.99.

**3-(*p*-Trifluoromethylphenyl)acetyl-2-oxazolidinone (30a).** 43% Yield; colorless solid; mp 144–146°C; IR (neat) 1761, 1694, 1477, 1414, 1333, 1279, 1240, 1111, 1017, 1071 $cm^{-1}$; $^1H$ NMR (300 MHz) ($CDCl_3$) $\delta$ 4.04 (t,

$J$=8.1 Hz, 2H), 4.35 (s, 2H), 4.44 (t, $J$=8.2 Hz, 2H), 7.43 (d, $J$=8.1 Hz, 2H), 7.59 (d, $J$=8.1 Hz, 2H); HRMS calcd for $C_{12}H_{10}F_3NO$: 273.0613. found: 273.0605. Anal. Calcd for $C_{12}H_{10}FNO$: C, 52.75; H, 3.69; N, 5.13. Found: C, 53.10; H, 3.64; N, 5.43.

**3-(*p*-Trifluoromethylphenyl)acetyl-(4*S*)-isopropyl-2-oxazolidinone (30b).** 35% Yield; colorless solid; mp 73–75°C; $[\alpha]_D^{19}$=+44.7° ($c$=1.6, MeOH); IR (neat) 1779, 1701, 1619, 1323, 1165, 1119, 1067, 1021 $cm^{-1}$; $^1H$ NMR (300 MHz) ($CDCl_3$) $\delta$ 0.85 (dd, $J$=5.3, 14.9 Hz, 6H), 2.27–2.45 (m, 1H), 4.19–4.50 (m, 5H), 7.43 (d, $J$=8.1 Hz, 2H), 7.59 (d, $J$=8.5 Hz, 2H); HRMS calcd for $C_{15}H_{16}F_3NO$: 315.1082. found: 315.1079. Anal. Calcd for $C_{15}H_{16}F_3NO$: C, 57.14; H, 5.11; N, 4.44. Found: C, 57.35; H, 4.86; N, 4.12.

**Reaction of 3 with 28a,b–30a,b**

In a similar way to the preparation of **7** by the reaction of **3** with **4a–c** and to the transformation of the coupling products **5a–c** to **7**, *p*-substituted methylphenidate derivatives **34–36** were obtained from **28a**,**b**–**30a**,**b**. The yields of **34–36** were calculated based on the amount of **28a**,**b**–**30a**,**b**. The diastereo- and enantiostereo-selectivities at the stage of the reaction of **3** with **28a**,**b**–**30a**,**b** were determined by the analysis of the stereochemistry of **34–36** using CSP HPLC. The absolute configuration of main stereoisomers of **34** and **35** was determined by their transformation to *p*-MeO- and *p*-bromo-substituted methylphenidates followed by the comparison with authentic samples.[6] That of **36** was estimated on the basis of the proposed mechanism.

The yield of **34** from the reaction of **3** with **28a**; 48%; *erythro*/*threo*=10.6/89.4.

The yield of **34** from the reaction of **3** with **28b**; 52%; *erythro*/*threo*=5.9/94.1; the %ee of the main stereoisomer of *threo* is >99.9.

The yield of **35** from the reaction of **3** with **29a**; 37%; *erythro*/*threo*=1.2/98.8.

The yield of **35** from the reaction of **3** with **29b**; 40%; *erythro*/*threo*=5.6/94.4; the %ee of the main stereoisomer of *threo* is 97.6.

The yield of **36** from the reaction of **3** with **30a**; 32%; *erythro*/*threo*=10.6/89.4.

The yield of **36** from the reaction of **3** with **30b**; 30%; *erythro*/*threo*=5.2/94.8; the %ee of the main stereoisomer of *threo* is >99.9.

The ratio of *threo*-**34** to *erythro*-**34** was determined by DAICEL Chiralpak AD (4.6 mm∅, 25 cm) [hexane/isopropanol (11:1 (v/v)), 0.5 mL/min, detection at 210 nm]; 23 min for (2*R*, 2′*R*)-**34**, 30 min for (2*S*, 2′*R*)- or (2*R*, 2′*S*)-**34**, 32 min for (2*R*, 2′*S*) or (2*S*, 2′*R*)-26, 35 min for (2*S*, 2′*S*)-**34**.

**Methyl *threo*-2-(*p*-methoxyphenyl)-2-(*N*′-methoxycarbonyl-2′-piperidyl)acetate (*threo*-34).** Colorless oil; IR (neat) 1744, 1701, 1611, 1514, 1449, 1408, 1260, 1173, 1088, 1034 $cm^{-1}$; $^1H$ NMR (300 MHz) ($CDCl_3$) $\delta$ 1.19–1.75 (m, 6H), 2.95–3.18 (m, 1H), 3.61 (s, 3H), 3.73 (s, 3H), 3.80 (s, 3H), 3.90–4.25 (m, 2H), 4.74–5.03 (m, 1H), 6.80–6.91 (m, 2H), 7.30–7.41 (m, 2H); HRMS calcd for $C_{17}H_{23}NO_5$: 321.1576. found: 321.1561. Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.41; H, 7.29; N, 4.27.

**Methyl *erythro*-2-(*p*-methoxyphenyl)-2-(*N*′-methoxycarbonyl-2′-piperidyl)-acetate (*erythro*-34).** Colorless oil; IR (neat) 1738, 1698, 1613, 1512, 1447, 1410, 1250, 1177, 1086, 1032 $cm^{-1}$; $^1H$ NMR (300 MHz) ($CDCl_3$) $\delta$ 1.19–1.75 (m, 6H), 2.30–3.49 (m, 1H), 3.67 (s, 3H), 3.76 (s, 3H), 3.81 (s, 3H), 3.90–4.17 (m, 2H), 4.80–4.50 (m, 1H), 6.78–6.88 (m, 2H), 7.30–7.41 (m, 2H); HRMS calcd for $C_{17}H_{23}NO_5$: 321.1576. found: 321.1587. Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.45; H, 7.24; N, 4.18.

The ratio of *threo*-**35** to *erythro*-**35** was determined by DAICEL Chiralpak AS (4.6 mm∅, 25 cm) [hexane/isopropanol/methanol (150:11:0.8 (v/v/v). 0.4 mL/min, detection at 210 nm]; 18 min for (2*S*, 2′*R*)- or (2*R*, 2′*S*)-**35**, 20 min for (2*S*, 2′*S*)-**35**, 21.5 min for (2*R*, 2′*R*)-**35**, 23 min for (2*R*, 2′*S*)- or (2*S*, 2′*R*)-**35**.

**Methyl *threo*-2-(*p*-bromophenyl)-2-(*N*′-methoxycarbonyl-2′-piperidyl)acetate (*threo*-35).** IR (neat) 1748, 1709, 1451, 1408, 1370, 1314, 1275, 1246, 1173, 1075, 1013 $cm^{-1}$; $^1H$ NMR (300 MHz) ($CDCl_3$) $\delta$ 1.18–1.75 (m, 6H), 2.95–3.17 (m, 1H), 3.62 (s, 3H), 3.73 (s, 3H), 3.95–4.28 (m, 2H), 4.75–5.03 (m, 1H), 7.30–7.40 (m, 2H), 7.45–7.53 (m, 2H); HRMS calcd for $C_{16}H_{20}BrNO_4$: 369.0575. found: 369.0574. Anal. Calcd for $C_{16}H_{20}BrNO_4$: C, 51.91; H, 5.44; N, 3.78. Found: C, 51.53; H, 5.11; N, 4.01.

**Methyl *erythro*-2-(*p*-bromophenyl)-2-(*N*′-methoxycarbonyl-2′-piperidyl)acetate (*erythro*-35).** IR (neat) 1736, 1698, 1449, 1408, 1368, 1312, 1277, 1266, 1175, 1075, 1013 $cm^{-1}$; $^1H$ NMR (300 MHz) ($CDCl_3$) $\delta$ 1.18–1.80 (m, 6H), 2.59–2.75 (m, 1H), 3.67 (s, 3H), 3.77 (s, 3H), 3.95–4.15 (m, 2H), 4.85–4.95 (m, 1H), 7.30–7.45 (m, 4H); HRMS calcd for $C_{16}H_{20}BrNO_4$: 369.0575. found: 369.0575. Anal. Calcd for $C_{16}H_{20}BrNO_4$: C, 51.91; H, 5.44; N, 3.78. Found: C, 51.89; H, 5.48; N, 3.89.

The ratio of *threo*-**36** to *erythro*-**36** was determined by DAICEL Chiralpak AD (4.6 mm∅, 25 cm) [hexane/isopropanol (15:1 (v/v)), 0.5 mL/min, detection at 210 nm]; 18 min for (2*R*, 2′*R*)-**36**, 24 min for (2*S*, 2′*R*)- or (2*R*, 2′*S*)-**36**, 27 min for (2*R*, 2′*S*)- or (2*S*, 2′*R*)-**36**, 34 min for (2*S*, 2′*S*)-**36**.

**Methyl *threo*-2-(*p*-trifluoromethyl)-2-(*N*′-methoxycarbonyl-2′-piperidyl)acetate (*threo*-36).** IR (neat) 1744, 1701, 1449, 1410, 1327, 1260, 1167, 1127, 1069, 1021 $cm^{-1}$; $^1H$ NMR (300 MHz) ($CDCl_3$) $\delta$ 1.14–1.80 (m, 6H), 2.95–3.20 (m, 1H), 3.63 (s, 3H), 3.74 (br s, 3H), 3.95–4.30 (m, 2H), 4.79–5.10 (m, 1H), 7.61 (br s, 4H); HRMS calcd for $C_{17}H_{20}F_3NO_4$: 359.1344. found: 359.1263. Anal. Calcd for $C_{17}H_{20}F_3NO_4$: C, 56.82; H, 5.61; N, 3.90. Found: C, 56.43; H, 5.55; N, 4.23.

**Methyl *erythro*-2-(*p*-trifluoromethyl)-2-(*N*′-methoxycarbonyl-2′-piperidyl)-acetate (*erythro*-36).** IR (neat) 1736, 1701, 1449, 1410, 1325, 1266, 1163, 1122, 1069, 1021 $cm^{-1}$; $^1H$ NMR (300 MHz) ($CDCl_3$) $\delta$ 1.19–1.98 (m, 6H), 3.30–3.45 (m, 1H), 3.63 (s, 3H), 3.69 (s, 3H), 3.95–4.30 (m, 2H), 4.88–5.25 (m, 1H), 7.41–7.68 (m, 4H); HRMS calcd for $C_{17}H_{20}F_3NO_4$: 359.1344. found: 359.1313. Anal. Calcd for $C_{17}H_{20}F_3NO_4$: C, 56.82; H, 5.61; N, 3.90. Found: C, 56.48; H, 5.60; N, 4.21.

**Hydrochloride salt of methyl (2*R*,2′*R*)-2-(*p*-methoxyphenyl)-2-(2′-piperidyl)acetate (37).** After diastereomers of **34** were separated by column chromatography, the main stereoisomer was converted in 41% yield to the hydrochloride salt of the corresponding amine in a similar way to the procedure for the conversion of **7** to the salt of **1**. Hydrochloride salt of methyl (2*R*,2′*R*)-2-(*p*-methoxyphenyl)-2-(2′-piperidyl)acetate (**37**): $[\alpha]_D^{22}=+87.4°$ ($c$=1.0, MeOH). [lit.[6] $[\alpha]_D^{20}=+86.6°$ ($c$=1.98, MeOH)].

**Hydrochloride salt of methyl (2*R*,2′*R*)-2-(*p*-bromophenyl)-2-(2′-piperidyl)acetate (38).** This salt was obtained from **35** in a 34% yield. $[\alpha]_D^{22}=+83.5°$ ($c$=1.0, $CH_2Cl_2$)[lit.[6] $[\alpha]_D^{20}=+69.1°$ ($c$=3.09, $CH_2Cl_2$)].

**Preparation of 41,44 by the reaction of 4a,b with 39, 42**

The C–C bond forming reaction between **4a**,**b** and **39**, **42** followed by the conversion of the coupling products **40a**,**b** and **43a**,**b** to **41** and **44** was carried out in a similar way to the method described above. The yields of **41**, **44** were calculated based on the amount of **4a**,**b**. The stereoselectivity at the reaction of **4a**,**b** and **39**, **42** was determined on the basis of the diastereomeric ratio of **41**, **44** which was analyzed by chiral HPLC. The diastereo- and enantio-selectivities of **41**, **44** were estimated on the basis of the proposed reaction mechanism. These results are shown in Table 5.

The ratio of *threo*-**41** to *erythro*-**41** and the ee of *threo*-**41** were determined by DAICEL Chiralpak AS (4.6 mm∅, 25 cm) [hexane/isopropanol (20:1) (v/v), 0.8 mL/min, detection at 210 nm]; 14 min for (2*R*, 2′*S*)- or (2*S*, 2′*R*)-**41**. 16 min for (2*S*, 2′*S*)-**41**, 18 min for (2*S*, 2′*R*)- or (2*R*, 2′*S*)-**41**, 24 min for (2*R*, 2′*R*)-**41**.

**Methyl *threo*-(2-phenyl-2-(*N*′-methoxycarbonyl-2′-pyrrolidyl)acetate (*threo*-41).** Colorless oil; $[\alpha]_D^{23}=+118.3°$ ($c$=0.7, MeOH) for a sample with 93.0% ee; IR (neat) 1734, 1705, 1453, 1385, 1200, 1163, 1121 $cm^{-1}$; $^1H$ NMR (300 MHz) ($CDCl_3$) $\delta$ 0.83–1.30 (m, 1H), 1.43–1.70 (m, 1H), 1.75–2.07 (m, 2H), 2.88–3.13 (m, 1H), 3.13–3.50 (m, 1H), 3.69 (s, 3H), 3.76 (s, 3H), 3.93–4.39 (m, 1H), 4.40–4.59 (m, 1H), 7.13–7.45 (m, 5H); HRMS calcd for $C_{15}H_{19}NO_4$: 277.1314. found: 277.1322. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.69; H, 6.95; N, 4.95.

The ratio of *threo*-**44** to *erythro*-**44** and the ee of *threo*-**44** were determined by DAICEL Chiralpak AD (4.6 mm∅, 25 cm)[hexane/isopropanol (15:1) (v/v), 0.5 mL/min, detection at 210 nm]; 16 min for (2*R*, 2′*R*)-**44**, 20 min for (2*S*, 2′*S*)-**44**, 21 min for (2*S*, 2′*R*)- or (2*R*, 2′*S*)-**44**, 28 min for (2*R*, 2′*S*)- or (2*S*, 2′*R*)-**44**.

**Methyl *threo*-(2-phenyl-2-(*N*′-methoxycarbonyl-2′-hexamethyleneiminyl)acetate (*threo*-44).** Colorless oil; $[\alpha]_D^{23}=+15.5°$ ($c$=1.5, MeOH) for a sample with 96.4% ee; IR (neat) 1734, 1700, 1455, 1437, 1406, 1208, 1167, 1105 $cm^{-1}$; $^1H$ NMR (300 MHz) ($CDCl_3$) $\delta$ 1.05–1.90 (m, 8H), 2.58–2.78 (m, 1H), 3.45–3.92 (m, 2H), 3.64 (s, 3H), 3.73 (s, 1.5H), 3.76 (s, 1.5H), 4.49–4.74 (m, 1H), 7.23–7.44 (m, 5H); HRMS calcd for $C_{17}H_{23}NO_4$: 305.1627. found: 274.1420. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 67.06; H, 7.61; N, 4.27.

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