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A Convenient Method for Synthesis of Enantiomerically Enriched Methylphenidate from *N*-Methoxycarbonylpiperidine

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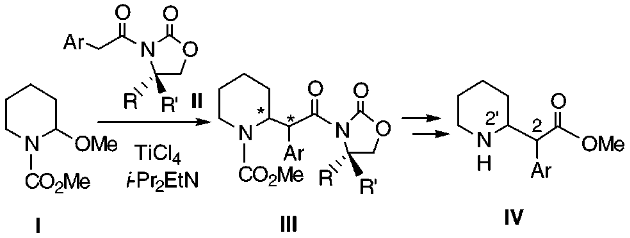
ABSTRACT



This report describes a new method to prepare optically active methylphenidate starting from piperidine. The method consists of a transformation of *N*-methoxycarbonylpiperidine to the corresponding α-methoxylated carbamate I by utilizing electrochemical oxidation followed by the coupling reaction with optically active Evans imides II to produce optically active methylphenidate derivatives III with high stereoselectivities. *threo*-(2*R*,2′*R*)-Methylphenidate (IV; Ar=Ph; Ritalin) was easily prepared from III in three steps.

threo-Methylphenidate (methyl *threo*-2-phenyl-2-(2′-piperidyl)acetate) (*threo*-**1**, Figure 1), called Ritalin on the market, has been used mainly for the treatment of attention deficit hyperactivity disorder (ADHD) in children in the USA.[1] It has been administered to patients as a racemic form despite the knowledge that the most active enantiomer is the *d-threo* isomer.[2] On the other hand, *d*- and *l*-*erythro*-**1** (Figure 1) were shown to possess very little therapeutic effect and had toxic hypertensive effects.[3] Accordingly, an exploitation of efficient methods selectively producing the *d-threo* isomer is very much worthwhile.

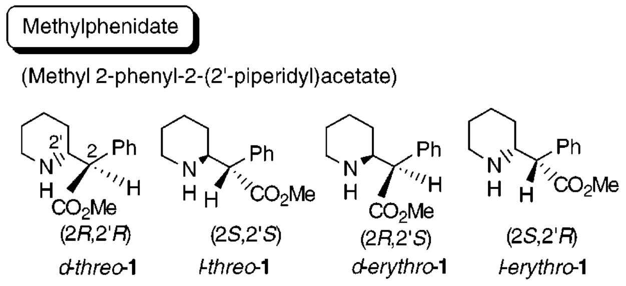


Figure 1.

Existing methods for the practical preparation of racemic *threo*-**1** involve procedures to separate its precursor from the

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[1] Barley, R. A. *J. Child Psychol. Psychiatry* **1977**, *18*, 137.

[2] Patrick, K. S.; Caldwell, R. W.; Ferris, R. M.; Breese, G. R. *J. Pharmacol. Exp. Ther.* **1987**, *241*, 152.

[3] Szporny, L.; Gorog, P. *Biochem. Pharmacol.* **1961**, *8*, 263.

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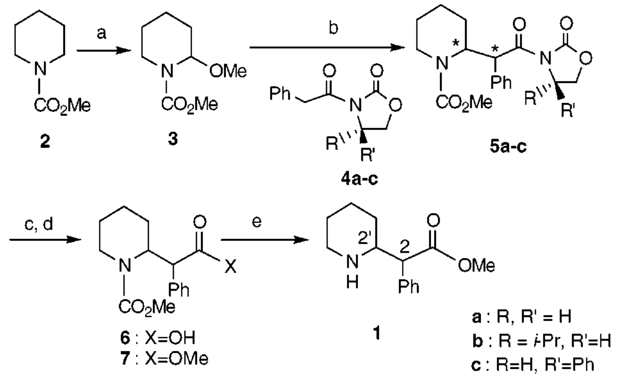
mixture of diastereomers at an appropriate stage of the synthetic scheme.[4] A new method through β-lactam intermediates for a stereoselective preparation of racemic *threo*-**1** has recently been reported.[5] Also, there has been only one report concerning on an asymmetric synthesis of *d-threo*-**1**, though the method uses expensive L-pipecolinic acid as the starting material together with an excess amount of (+)-IPC·BH$_2$ at the key step to produce the *d-threo* isomer with high diastereoselectivity, and it also requires multistage procedures.[6]

We report herein a very convenient method for the stereoselective synthesis of the *d-threo* isomer of **1** starting from easily available *N*-methoxycarbonylpiperidine **2**. Scheme 1 illustrates our method which consisits of only five steps: (a) an electrochemical α-methoxylation of **2** to afford α-methoxypiperidine **3**, (b) a C−C bond formation at the α-position of **3** with Evans imides **4a**−**c**,[7] (c) a removal of the chiral auxiliary from the products **5a**−**c**, (d) the esterification of an acid **6**, and (e) the deprotection of the *N*-methoxycarbonyl group of the resulting ester **7** to give *d-threo*-**1**.

Scheme 1[a]



[a] (a) 85%, 2.3*F*/mol of electricity in MeOH containing Et$_4$NBF$_4$; (b) TiCl$_4$ (1.1 equiv to **4**) and DIPEA (1.2 equiv to **4**) at −78 °C for 1.5 h in CH$_2$Cl$_2$, then **3** (1.2 equiv to **4**) at −78 °C, and overnight at room temperature; (c) LiOOH (4.0 equiv to **4**) in H$_2$O/THF overnight at room temperature; (d) CH$_2$N$_2$ for 2 h at room temperature in ether; (e) Me$_3$SiI (2.5 equiv to **7**) in CH$_2$Cl$_2$ at room temperature overnight; 75%.

Since the first step has been well established by us as a promising method for introducing nucleophiles to the α-position of carbamates,[8] the key step in this scheme is a C−C bond forming reaction (step 2) between Evans imides and *N*,*O*-acetals such as **3**,[9] whereas the Ti-promoted C−C bond forming reaction of Evans imides with carbonyl compounds[10] and *O*,*O*-acetals[11] has been reported.[12]

We found that the C−C bond forming reaction between **3** and **4a**−**c** was successfully achieved by using a combination[10] of TiCl$_4$ and diisopropylethylamine (DIPEA) to give the coupling products **5a**−**c** with high stereoselectivity. The configuration of **5a**−**c** was determined at the stage of **7** and **1**. Namely, the diastereoselectivity of **5a**−**c** was determined by HPLC analysis of **7** which was derived from **5a**−**c** through **6**, and the absolute configuration of a main stereoisomer of **7** was identified by converting a main diastereoisomer of **7** to **1**, of which absolute stereochemistry is known.[6] The results, shown in Table 1, which indicates that the C−C bond forming reaction proceeds with very high diastereo- and enantioselectivities.

Table 1. Reaction of α-Methoxycarbamate **3** with Phenylacetyloxazolidinones (**4a**−**c**)

entry	4a-c	yield (%) of 7$^{a)}$	*erythro*/*threo*$^{b)}$ of 7	%ee$^{b)}$ of *threo*-7	configuration of main product of *threo*-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] **3a** was not recovered. Overall yield of **7** from **4a**−**c**. [b] Determined by CSP HPLC analysis. [c] The absolute configuration was determined by converting **7** to hydrochloride salts of each stereoisomer of methyl phenidate **1** followed by comparison of the salts with the authentic samples.[6]

The ratios of *erythro*-**7** to *threo*-**7** obtained in the reaction of **3** with **4a** and **4b** were 6.9/93.1 and 5.3/94.7, respectively (entries 1 and 2), and the ee of *threo* isomer from **4b** was excellent (99.6%) (entry 2). Also, the high stereoselectivities (*erthro*/*threo* = 1.6/98.4, the ee of *threo* isomer = 81.8%) were observed in the reaction of **3** with **4c** (entry 3), of which product **7** possessed the absolute configuration (2*S*,2′*S*) opposite to that (2*R*,2′*R*) of **7** obtained by the reaction of **3** with **4b**.

These stereoselectivities can be explained by considering the reaction intermediates as exemplified by the mechanism of the reaction of **3** with **4b**. Two routes, (a) coordinated route (Scheme 2) and (b) noncoordinated route (Scheme 3), are conceivable for the mode of the attack of a titanium enolate generated from **4b** on an acyliminium ion generated

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[4] (a) Panizzon, L. *Helv. Chim. Acta* **1944**, *27*, 1748. (b) Deutsch, H. M.; Shi, Q.; Gruszecka-Kowalik, E.; Schweri, M. M. *J. Med. Chem.* **1996**, *39*, 1201.

[5] Axten, J. M.; Krim, L.; Kung, H. F.; Winkler, J. D. *J. Org. Chem.* **1998**, *63*, 9628.

[6] Thai, D. L.; Sapko, M. T.; Reiter, C. T.; Bierer, D. E.; Perel, J. M. *J. Med. Chem.* **1998**, *41*, 591.

[7] (a) Evans, D. A.; Bartroli, J.; Shih, T. L.*J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Nerz-Stormes, M.; Thornton, E. R. *J. Org. Chem.* **1991**, *56*, 2489.

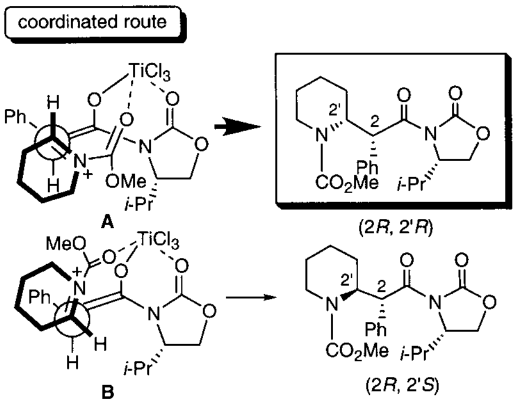
[8] (a) Shono, T.; Matsumura, Y.; Tsubata, K. *Org. Synth.* **1984**, *63*, 206. (b) Shono, T.; Matsumura, Y.; Fujita, T. *Chem. Lett.* **1991**, 81. (c) Matsumura, Y.; Terauchi, J.; Yamamoto, T.; Konno, T.; Shono, T. *Tetrahedron* **1993**, *49*, 8503.

[9] The C−C bond forming reaction of Sn-enolates of 1,3-thiazololidine-2-thiones with cyclic acyl imines derived from lactams has been reported: (a) Nagao, Y.; Kumagai, T.; Tamai, S.; Abe, T.; Kuramoto, Y.; Taga, T.; Aoyagi, S.; Nagase, Y.; Ochiai, M.; Inoue, Y.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 4673. (b) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Am. Chem. Soc.* **1988**, *110*, 289.

[10] Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047.

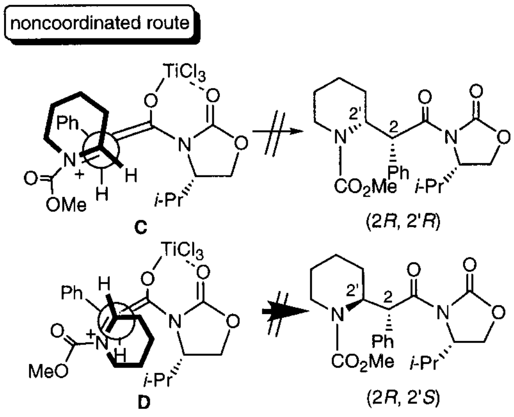
[11] Kanno, H.; Osanai, K. *Tetraheron: Asymmetry* **1995**, *6*, 1503.

Scheme 2



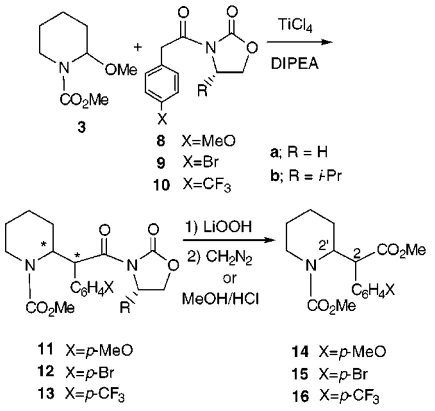
from **3**. Those routes may involve intermediates **A**−**D**, in which the acyliminium ion approaches the thermodynamically stable *Z*-form[13] of the titanium enolate from the *Si* face. The fact that (2*R*,2′*R*)-isomer was predominantly formed strongly suggests the participation of **A** or **C** among **A**−**D**. Large steric repulsion between the acyliminium ion and the substituents (especially, phenyl group) of the titanium enolate can be envisioned in **B** and **C**, while **A** and **D** may be less crowded than **B** and **C**. Thus, we suppose that the reaction might proceed through **A** via the coordinated intermediates.

Scheme 3



Our method was successfully applied to the preparation of *p*-substituted methylphenidates **14**−**16** by using *p*-substituted phenylacetyloxazolidinones **8a**,**b**−**10a**,**b** (Scheme 4). Among these products, *p*-trifluoromethyl-substituted methylphenidate derivative **16** was a new compound which could not be prepared by the conventional method.[4b]

Scheme 4



Since the determination of the configuration of the initially formed C−C bond forming products **11a**,**b**−**13a**,**b** was difficult, it was achieved at the stage of **14**−**16**. The reaction was also found to possess very high stereoselectivities as shown in Table 2.

Table 2. Reaction of α-Methoxycarbamate **3** with a Variety of *p*-Substituted Phenylacetyloxazolidinones **8a,b**−**10a,b**

entry	8a,b-10a,b	Products	yields[a] (%)	*erythro*/*threo*[b] of **14-16**	% ee[b] of *threo*-**14-16**	configuration of main product of *threo*-**14-16**
1	**8a**	**14**	48	10.6 / 89.4	−	−
2	**8b**	**14**	52	5.9 / 94.1	>99.9	(2*R*,2′*R*)
3	**9a**	**15**	37	1.2 / 98.8	−	−
4	**9b**	**15**	40	5.6 / 94.4	97.6	(2*R*,2′*R*)
5	**10a**	**16**	32	10.6 / 89.4	−	−
6	**10b**	**16**	30	5.2 / 94.8	>99.9	(2*R*,2′*R*)

[a] Overall yields from **8a,b**−**10a,b**. [b] Determined by CSP HPLC analysis.

The configuration of **14** and **15** (entries 1−4, Table 2) was determined by the deprotection of **14** and **15** followed by the comparison of hydrochloride salts of the resulting amino compounds with authentic samples.[6] The configuration of **16** was estimated on the basis of the proposed reaction mechanism described above (entries 5 and 6, Table 2).

Furthermore, our method was applied to the preparation of five- and seven-membered analogues[5] (**19**, **22**) of methylphenidate derivative **7** from pyrrolidine and hexamethyleneimine derivatives **17** and **20** (Schemes 5 and 6). The coupling products **18a**,**b** and **21a**,**b** were converted without isolation to **19** and **22**, and the configuration of the main stereoisomer of **19** and **22** was assigned by analogy to be (2*R*,2*R*′) on the basis of the proposed reaction mechanism. In those reactions, high diastereo- and enantioselectivities were also observed (Table 3).

In conclusion, this paper describes a new efficient method to prepare optically active methylphenidate **1** and its

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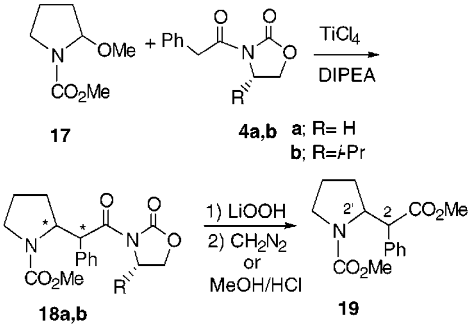
(12) A variety of the Evans aldol reactions with other electrophiles have been reported: (a) Fuentes, L. M.; Shinkai, I.; Salzmann, T. N. *J. Am. Chem. Soc.* **1986**, *108*, 4675. (b) D'Souza, A.; Motevalli, M.; Robinson, A. J.; Wyatt, P. B. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1. (c) Arvanitis, E.; Ernst, H.; Ludxig, A. A.; Robinson, A. J.; Wyatt, P. B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 521.

(13) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

Scheme 5



analogues **19** and **22** starting from easily available *N*-protected piperidine, pyrrolidine, and hexamethyleneimine. The key step was the coupling of Evans imides with electrochemically prepared α-methoxylated carbamates. It also shows the preparation of *p*-substituted methylphenidates including the first synthesis of trifluoromethyl-substituted derivative **16**. Further study on the mechanistic aspect and the optimization of yields are currently under investigation.

Scheme 6

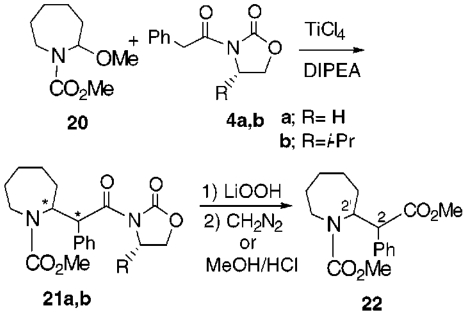


Table 3. Reaction of a Variety of α-Methoxycarbamates **17** and **20** with Phenylacetyloxazolidinone **4a,b**

entry	**17**,**20**[a)]	**4a,b**	products	yields (%)[b)]	*erythro*/*threo*[c)] of **19**, **22**	% ee[c)] of *threo*-**19**, **22**
1	**17**	**4a**	**19**	62	7.0 / 93.0	–
2	**17**	**4b**	**19**	52	12.0 / 88.0	93.0
3	**20**	**4a**	**22**	61	3.5 / 96.5	–
4	**20**	**4b**	**22**	59	15.1 / 84.9	96.4

[a] See ref 14. [b] Overall yields from **4a,b**. [c] Determined by CSP HPLC analysis.

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Supporting Information Available: Full experimental and analytical data for all new compounds; the conditions of HPLC analysis for **7**, **14**–**16**, **19**, and **22**; the specific rotations of **4b**,**c**, **8b**, **9b**, **10b**, *threo*-**19**, *threo*-**22**, and HCl salts of *threo*-**1** and its *p*-methoxy and *p*-bromo derivitives. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Those α-methoxylated carbamates were easily obtained in around 85% yields by the electrochemical oxidation of the corresponding carbamates in methanol.[8]