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titled "A Convenient Method for Synthesis of Optically Active Methylphenidate from *N*-Methoxycarbonylpiperidine by Utilizing Electrochemical Oxidation "

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Preparation of 3

Electrochemical oxidation of **2** in methanol to give **3** in a good yield has been reported [8a].

Preparation of 3-Phenylacety-2-oxazolidinone (4a-c).

Those compounds were prepared according to the Evans method [7].

3-Phenylacetyl-2-oxazolidinone (4a)

colorless solid; mp 64-65˚C; IR (neat) 1771, 1698, 1497, 1476, 1456, 1387, 1109, 1037 cm^{-1}; ^{1}HNMR (300MHz) ($CDCl_3$) δ 4.03 (t, *J* =8.4Hz, 2H), 4.29 (s, 2H), 4.41 (t, *J* =8.4Hz, 2H), 7.27-7.38 (m, 5H).

3-Phenylacetyl-(4*S*)-isopropyl-2-oxazolidinone (4b)

$[\alpha]^{20}_D$ +77.6°(c=2.05, $CHCl_3$); IR (neat) 1765, 1690 cm^{-1}; ^{1}HNMR (300MHz) ($CDCl_3$) δ 0.78 (d, *J* =6.9Hz, 3H), 0.87 (d, *J* =7.0Hz, 3H), 2.23-2.37 (m, 1H), 4.11-4.38 (m, 5H), 7.20-7.38 (m, 5H).

3-Phenylacetyl-(4*R*)-phenyl-2-oxazolidinone (4c)

59% yield; colorless solid; mp 70-71˚C; $[\alpha]^{24}_D$ -87.0°(c=1.0, MeOH); IR (neat) 1779, 1705, 1613, 1512, 1387, 1329, 1248, 1200, 1179, 1105, 1042 cm^{-1}; ^{1}HNMR (300MHz) ($CDCl_3$) δ 4.23-4.30 (m, 1H), 4.29 (s, 2H), 4.69 (t, *J* =8.9, 1H), 5.42 (dd, *J* =3.9, 8.8Hz, 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.

Preparation of Methyl (2-Phenyl-2-(*N*-methoxycarbonyl-2'-piperidyl)acetate (7)

_Preparation by the reaction of **3** with **4a:** A 1M $TiCl_4$ (1.1mL, 1.1mmol) solution in CH_2Cl_2 was added into a solution of **4a** (1mmol) in CH_2Cl_2 (5 mL) at -78˚C under a nitrogen atmosphere, and DIPEA (1.2mmol) was added to the solution. After 1.5 hr, a solution of **3** (1.2mmol) in CH_2Cl_2 (1mL) was added, and the resulting solution was allowed to be stirred at rt overnight. The reaction mixture was poured in to 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 (1mL), LiOH(4mmol), and 35%H_2O_2(1mL) were successively added to **5a** dissolved in THF(4mL), The solution was stirred at rt overnight, and quenched with 1.5M$NaHSO_3$. 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%.

Similarly, **7** was obtained by the reactions of **3** with **4b**, and **3** with **4c**. The yields of **7** obtained in these reactions were 54% and 40%, respectively.

The *threo*-**7** was separable from *erythro*-**7** by column chromatography (silica gel, AcOEt/hexane=1/3), and the % ee was obtained by DAICEL Chiralcpak AD [hexane: isopropanol: methanol (150: 4:0.5) (v/v)].

Synthesis of Hydrogen Chloride Salt of Methylphenidate 1 from 7

_A solution of Me_3SiI (526mg, 2.7mmol) in CH_2Cl_2 (5mL) was dropwise added at rt into a solution of the main diastereo isomer of **7** (307mg, 1.1mmol) in CH_2Cl_2(2mL), and the solution was stirred at rt. After 12hr, MeOH(2mL) 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 alkalized 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 1M HCl-MeOH. Evaporation of MeOH from the solution gave a white solid, which was recrystallized from EtOH/ether to give hydrogen chloride salt of **1**: 60% yield from *threo*-**7**; $[\alpha]^{27}_{D}$ +83.0°(c=1.0, MeOH). [lit.[6] (2*R*,2'*R*)-**1** ; $[\alpha]^{20}_{D}$ +82.6°(c=1.09, MeOH)].

According to the method described above, *erythro*-**1** was obtained from minor stereoisomer of **7**;$[\alpha]^{20}_{D}$ +106.6°(c=0.7, MeOH). [lit.[6] (2*R*,2'*S*)-**1** ; $[\alpha]^{20}_{D}$ +92.3°(c=1.11, MeOH)].

Methyl *threo*-(2-Phenyl-2-(*N*-methoxycarbonyl-2'-piperidyl)acetate (*threo*-7)

colorless oil; IR (neat) 1736, 1698, 1447, 1271, 1248, 1192 cm-1; 1HNMR (300MHz) ($CDCl_3$) δ 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.

Methyl *erythro*-(2-phenyl-2-(*N*-methoxycarbonyl-2'-piperidyl)acetate (*erythro*-**7**)

colorless oil; IR (neat) 1734, 1698, 1447, 1266, 1250, 1172 cm-1; 1HNMR (300MHz) ($CDCl_3$) δ 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.

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Synthesis and Identification of *p*-Substituted Mehtylphenidate 14-16

Preparation of 3-(*p*-Substituted phenylacetyl)-2-oxazolidinones 8a,b-10a,b.

3-(*p*-Methoxyphenyl)acetyl-2-oxazolidinone (8a)

79% yield; colorless solid; mp 112-115_; IR (neat) 1786, 1705, 1612, 1514, 1478, 1391, 1368, 1267, 1181, 1113, 1036 cm^{-1}; ^{1}HNMR (300MHz) ($CDCl_3$) δ 3.79 (s, 3H), 4.01 (t, *J* =7.5Hz, 2H), 4.22 (s, 2H), 4.40 (t, *J* =8.1Hz, 2H), 6.68 (d, *J* =8.8Hz, 2H), 7.74 (d, *J* =8.5Hz, 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 (8b)

60% yield; colorless solid; mp 89-90_; $[\alpha]^{24}_{D}$ +73.7°(c=0.6, MeOH); IR (neat) 1792, 1709, 1613, 1586, 1518, 1466, 1393, 1375, 1302, 1256, 1213, 1183, 1121, 1034 cm^{-1}; ^{1}HNMR (300MHz) ($CDCl_3$) δ 0.79 (d, *J* =6.9Hz, 3H), 0.88 (d, *J* =7.0Hz, 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 (9a)

50% yield; colorless solid; mp 119-121_; IR (neat) 1763, 1698, 1476, 1404, 1389, 1370, 1273, 1238, 1113, 1009 cm^{-1}; ^{1}HNMR (300MHz) ($CDCl_3$) δ 4.03 (t, *J* =7.9Hz, 2H), 4.24 (s, 2H), 4.43 (t, *J* =8.1Hz, 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 (9b)

49% yield; colorless solid; mp 70-74_; $[\alpha]^{23}_{D}$ +56.3°(c=0.6, MeOH); IR (neat) 1790, 1701, 1489, 1389, 1374, 1306, 1254, 1211, 1121, 1013 cm^{-1}; ^{1}HNMR (300MHz) ($CDCl_3$) d 0.84 (dd, *J* =7.0, 17.0Hz, 6H), 2.23-2.43 (m, 1H), 4.12-4.39 (m, 4H), 4.40-4.49 (m, 1H), 7.19 (d, *J* =8.1Hz, 2H), 7.45 (d, *J* =8.4Hz, 2H); HRMS calcd for $C_{14}H_{16}BrNO$ 325.0313 found 325.0324.

3-(*p*-Trifluoromethylphenyl)acetyl-2-oxazolidinone (10a)

43% yield; colorless solid; mp 144-146_; IR (neat) 1761, 1694, 1477, 1414, 1333, 1279, 1240, 1111, 1017, 1071 cm^{-1}; ^{1}HNMR (300MHz) ($CDCl_3$) δ 4.04 (t, *J* =8.1Hz, 2H), 4.35 (s, 2H), 4.44 (t, *J* =8.2Hz, 2H), 7.43 (d, *J* =8.1Hz, 2H), 7.59 (d, *J* =8.1Hz, 2H); HRMS calcd for $C_{12}H_{10}F_3NO$ 273.0613 found 273.0605.

3-(*p*-Trifluoromethylphenyl)acetyl-(4*S*)-isopropyl-2-oxazolidinone (10b)

35% yield; yellow oil; $[\alpha]^{19}_{D}$ +44.7°(c=1.6, MeOH); IR (neat) 1779, 1701, 1619, 1323, 1165, 1119, 1067, 1021 cm^{-1}; ^{1}HNMR (300MHz) ($CDCl_3$) δ 0.85 (dd, *J* =5.3, 14.,9Hz, 6H), 2.27-2.45 (m, 1H), 4.19-4.50 (m, 5H), 7.43 (d, *J* =8.1Hz, 2H), 7.59 (d, *J* =8.5Hz, 2H); HRMS calcd for $C_{15}H_{16}F_3NO$ 315.1082 found 315.1079.

Reaction of 3 with 8a,b-10a,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 **14-16** were obtained from **8a,b-10a,b**. The yields of **14-16** were calculated based on the amount of **8a,b-10a,b**. The diastereoselectivity at the stage of the reaction of **3** with **8a,b-10a,b** was determined by the analysis of the stereochemistry of **14-16** using HPLC. The enantioselectivity of **14** and **15** was determined by the transformation of **14** and **15** to *p*-MeO- and *p*-bromo-substituted methylphenidates followed by the comparison with authentic samples [6].

The enantioselectivity of **16** was estimated on the basis of the proposed mechanism.

The yield of **14** by the reaction of **3** with **8a;** 48% yield; *erythro/threo* =10.6/89.4.

The yield of **14** by the reaction of **3** with **8b;** 52%yield; *erythro/threo* =5.9/94.1; the %ee of the main stereo isomer of *threo* is >99.9%.

The yield of **15** by the reaction of **3** with **9a;** 37% yield; *erythro/threo* =1.2/98.9.

The yield of **15** by the reaction of **3** with **9b;** 40% yield; *erythro/threo* =5.6/94.4; the %ee of the main stereo isomer of *threo* is 97.6%.

The yield of **16**by the reaction of **3** with **10a;** 32% yield; *erythro/threo* =10.6/89.4.

The yield of **16** by the reaction of **3** with **10b;** 30% yield; *erythro/threo* =5.2/94.8; the %ee of the main stereo isomer of *threo* is >99.9%.

The ratio of *threo*-**14** to *erythro*-**14** was determined by DAICEL Chiralpak AD [hexane: isopropanol (11: 1 (v/v))].

Methyl *threo*-2-(*p*-Methoxyphenyl)-2-(*N*'-methoxycarbonyl-2'-piperidyl)acetate (*threo*-14)

colorless oil; IR (neat) 1744, 1701, 1611, 1514, 1449, 1408, 1260, 1173, 1088, 1034 cm^{-1}; ^{1}HNMR (300MHz) ($CDCl_3$) δ 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.

Methyl *erythro*-2-(*p*-Methoxyphenyl)-2-(*N*'-methoxycarbonyl-2'-piperidyl)acetate (*erythro*-14)

colorless oil; IR (neat) 1738, 1698, 1613, 1512, 1447, 1410, 1250, 1177, 1086, 1032 cm^{-1}; ^{1}HNMR (300MHz) ($CDCl_3$) δ 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.

_The ratio of *threo*-**15** to *erythro*-**15** was determined by DAICEL Chiralpak AD [hexane: isopropanol (15: 1 (v/v))].

Methyl *threo*-2-(*p*-Bromophenyl)-2-(*N*'-methoxycarbonyl-2'-piperidyl)acetate (*threo*-15)

IR (neat) 1748, 1709, 1451, 1408, 1370, 1314, 1275, 1246, 1173, 1075, 1013 cm^{-1}; ^{1}HNMR (300MHz) (CDCl3) δ 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.

Methyl *erythro*-2-(*p*-Bromophenyl)-2-(*N*'-methoxycarbonyl-2'-piperidyl)acetate (*erythro*-15)

IR (neat) 1736, 1698, 1449, 1408, 1368, 1312, 1277, 1266, 1175, 1075, 1013 cm^{-1}; ^{1}HNMR (300MHz) ($CDCl_3$) δ 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.

The ratio of *threo*-**16** to *erythro*-**16** was determined by DAICEL Chiralpak AD [hexane: isopropanol (15: 1 (v/v))].

Methyl *threo*-2-(*p*-Trifluoromethyl)-2-(*N*'-methoxycarbonyl-2'-piperidyl)acetate (*threo*-16)

IR (neat) 1744, 1701, 1449, 1410, 1327, 1260, 1167, 1127, 1069, 1021 cm^{-1}; ^{1}HNMR (300MHz) ($CDCl_3$) δ 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.

Methyl *erythro*-2-(*p*-Trifluoromethyl)-2-(*N*'-methoxycarbonyl-2'-piperidyl)acetate (*erythro*-16)

IR (neat) 1736, 1701, 1449, 1410, 1325, 1266, 1163, 1122, 1069, 1021 cm^{-1}; ^{1}HNMR (300MHz) ($CDCl_3$) δ 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.

Hydrogen Chloride Salt of Methyl (2*R*,2'*R*)-2-(*p*-Methoxyphenyl)-2-(2'-piperidyl)acetate

After diastereo isomers of **14** were separated by column chromatography, the main stereo isomer was converted to hydrogen chloride salt of the corresponding amine in a similar way to the procedure for the conversion of **7** to hydrogen chloride salt of **1**.

Hydrogen chloride salt of methyl (2*R*,2'*R*)-2-(4'-methoxyphenyl)-2-(2'-piperidyl) acetate: $[\alpha]^{22}_D$ +87.4°(c=1.0, MeOH). [lit.[6]; $[\alpha]^{20}_D$ +86.6°(c=1.98, MeOH)].

Hydrogen Chloride Salt of Methyl (2*R*,2'*R*)-2-(*p*-Bromophenyl)-2-(2'-piperidyl)acetate

This salt was obtained from **15**. $[\alpha]^{22}_D$ +83.5°(c=1.0, CH_2Cl_2)[lit.[6]; $[\alpha]^{20}_D$ +69.1°(c=3.09, CH_2Cl_2)].

Preparation of 19,22 by the Reaction of 4a,b with 17,20

The C-C bond forming reaction between **4a,b** and **17,20** followed by the conversion of the coupling products **18a,b** and **21a,b** to **19** and **22** was carried out in a similar way to the method described above.

_The yields of **19, 22** were calculated based on the amount of **4a,b**. The stereoselectivity at the reaction of **4a,b** and **17**,**20** was determined on the basis of the diastereomeric ratio of **19, 22** which was analyzed by chiral HPLC. The diastereo- and enantio-selectivities of **19, 22** were estimated on the basis of the proposed reaction mechanism. These results are shown in Table 3.

The ratio of *threo*-**19** to *erythro*-**19** and the % ee of *threo*-**19** were determined by DAICEL Chiralpak AS [hexane: isopropanol (20: 1 (v/v))].

Methyl *threo* -(2-Phenyl-2-(*N*'-methoxycarbonyl-2'-pyrrolidyl)acetate (*threo*-19)

colorless oil; IR (neat) 1734, 1705, 1453, 1385, 1200, 1163, 1121 cm^{-1}; ^{1}HNMR (300MHz) ($CDCl_3$) δ 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.

The ratio of *threo*-**22** to *erythro*-**22** and the % ee of *threo*-**22** were determined by DAICEL Chiralpak AD [hexane: isopropanol (15: 1 (v/v))].

Methyl *threo*-(2-Phenyl-2-(*N*'-methoxycarbonyl-2'-hexamethyleneimidyl)acetate (*threo*-22)

colorless oil; IR (neat) 1734, 1700, 1455, 1437, 1406, 1208, 1167, 1105 cm^{-1}; ^{1}HNMR (300MHz) ($CDCl_3$) δ 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 calcd for $C_{17}H_{23}NO_4$-OMe found 274.1420.