HETEROCYCLES, Vol. 89, No. 7, 2014, pp. 1632 - 1643. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 23rd April, 2014, Accepted, 23rd May, 2014, Published online, 4th June, 2014
DOI: 10.3987/COM-14-13012

A PRACTICAL SYNTHESIS OF (4-(SPIRO[CHROMANE-2,4'-PIPERIDIN]- 6-YL)PHENYL)METHANOL AS A KEY INTERMEDIATE OF NOVEL GPR119 AGONIST

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Abstract – Starting from commercially available 4'-hydroxy-[1,1'-biphenyl]-4-carboxylic acid, a practical synthesis has been established in high yield for (4-(spiro[chromane-2,4'-piperidin]-6-yl)phenyl)methanol as a key intermediate for a novel GPR119 agonist.

INTRODUCTION

GPR119 is a G protein-coupled receptor predominantly expressed in pancreatic islet β-cells and incretin-releasing cells in the gastrointestinal tract. GPR119 agonists are reported to stimulate glucose-dependent insulin secretion *in vitro* and lower elevated blood-glucose levels *in vivo*.[1] Therefore, these agents have emerged as a promising target for the treatment of type 2 diabetes and obesity by improving glucose homoeostasis.[2]

During the course of our drug discovery program, we identified (*R*)-1,1,1-trifluoropropan-2-yl 6-(4-(((pyridin-2-ylmethyl)sulfonyl)methyl)phenyl)spiro[chromane-2,4'-piperidine]-1'-carboxylate (**1**) as a highly potent GPR119 agonist (EC_{50} = 54 nM) with a hypoglycemic effect (3 mg/kg po. 30% decrease in OGTT/C57BL mice).[3] We required a large amount of **1** to conduct a safety test.

In the initial production of **1**, we performed a palladium-mediated coupling reaction between (4-(hydroxymethyl)phenyl)boronic acid (**4**) and *tert*-butyl 6-bromospiro[chromane-2,4'-piperidine]-1'-carboxylate (**5**)[4] to produce the key intermediate **3** leading to **2** as a precursor of **1** in moderate yield, as shown in Figure 1.

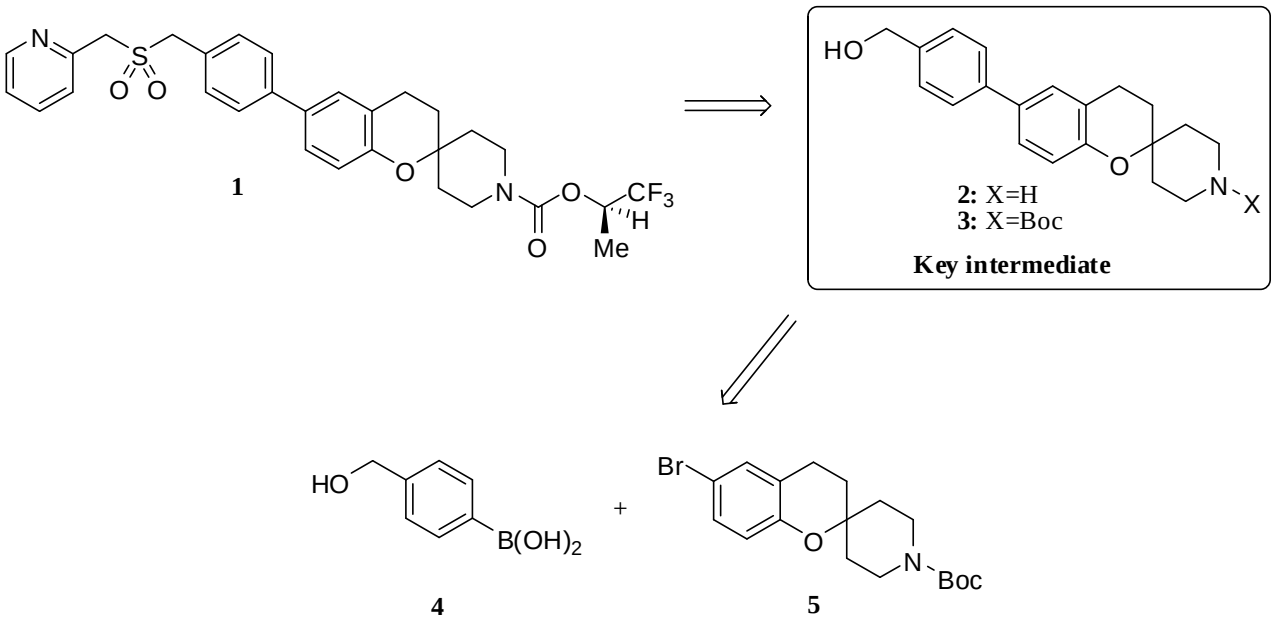


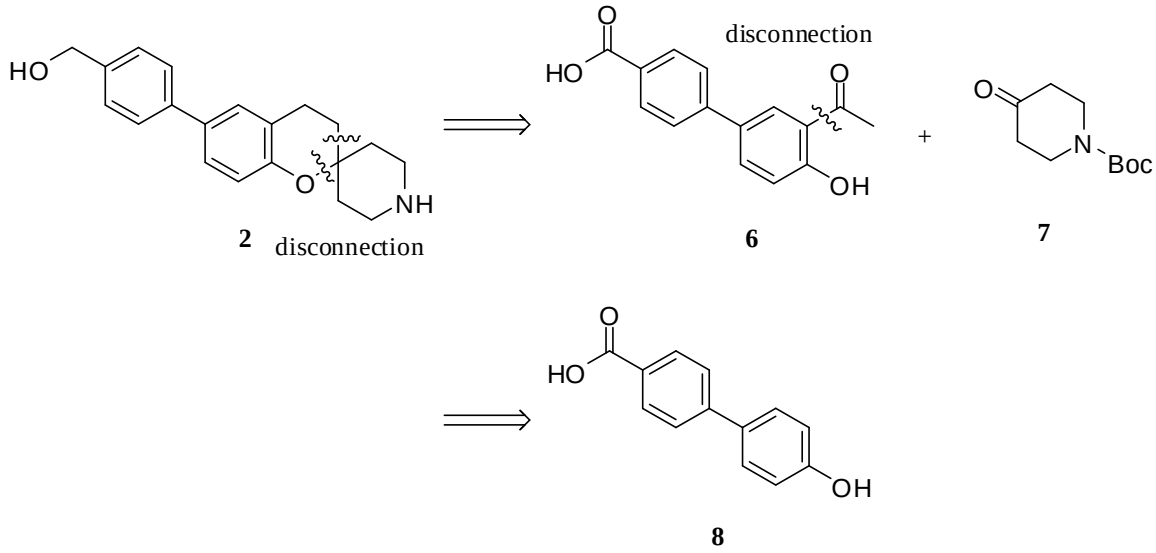
Figure 1. Structure of the GPR119 agonist (**1**) and a retrosynthetic analysis in the initial synthesis

To date, the Suzuki-Miyaura coupling reaction has been widely demonstrated for industrial applications as a convenient and useful method for the construction of biaryl compounds.[5] However, when applying it to the production of an active pharmaceutical ingredient (API), we encountered several potential drawbacks. a) The cost: the Pd catalyst and arylboronic acid are expensive. b) Genotoxicity concerns: arylboronic acids have been recently indicated as structure alerts for mutagenicity or carcinogenicity according to a structure-based assessment using the *in silico* tool DEREK (Deductive Estimation of Risk from Existing Knowledge).[6,7] c) Residual-Pd issue: the content of Pd should be controlled to less than 10 ppm in orally administered drug substances according to API regulations.[8,9] d) Process control: attention should be paid to the suitable selection of the Pd ligands and base, ligand-particle size, and moisture and oxygen content for the optimization of the reaction procedure when converting to large-scale production.[10] To avoid these problems, we must develop an alternative synthetic method for the production of **2** without using a metal-catalyzed cross coupling reaction. Here, we report a facile and powerful synthetic route to the key intermediate **2** from readily available and affordable starting materials.

RESULTS AND DISCUSSION

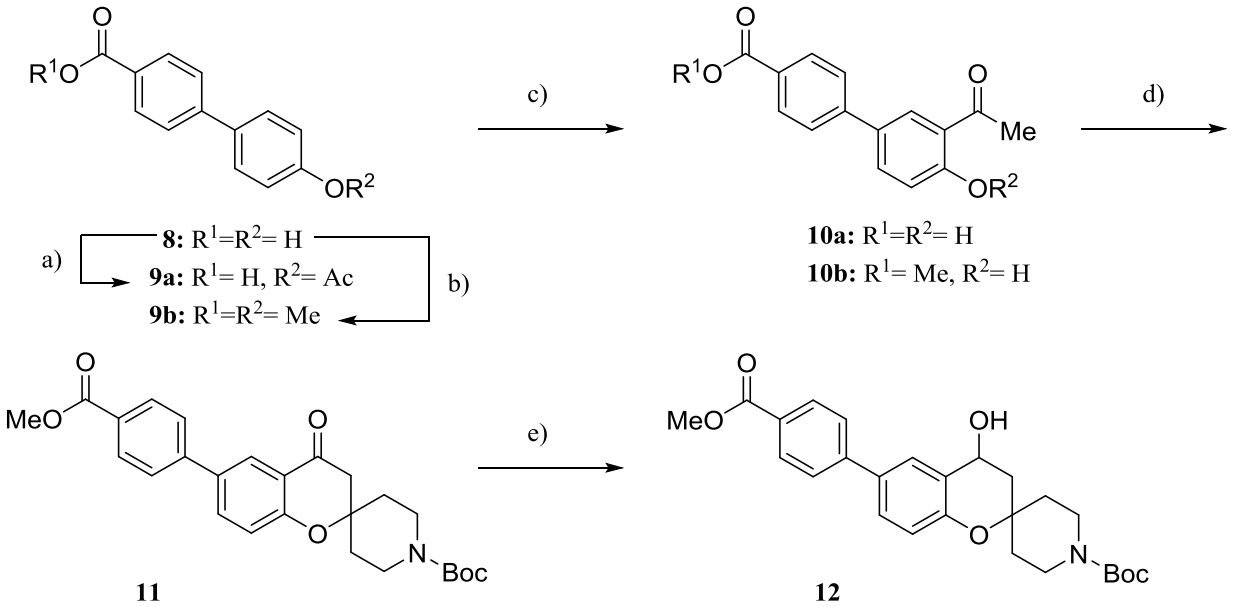
In the retrosynthetic analysis (Scheme 1), our attention was focused on avoiding C-C bond formation of the biaryl compound by the unfavorable Suzuki-Miyaura coupling reaction and on constructing the requisite skeleton starting from a commercially available biphenyl material. The key intermediate **2** that possesses a 6-phenylspiro[chromane-2,4'-piperidine] skeleton would be dismantled into the

biphenylethanone unit **6** and the 4-oxopiperidine unit **7** via spirocyclization. The required compound **6** could be prepared by a regioselective acylation of 4'-hydroxy-[1,1'-biphenyl]-4-carboxylic acid (**8**), which was chosen as an inexpensive starting material.[11]



Scheme 1. Retrosynthetic analysis of the key intermediate **2**

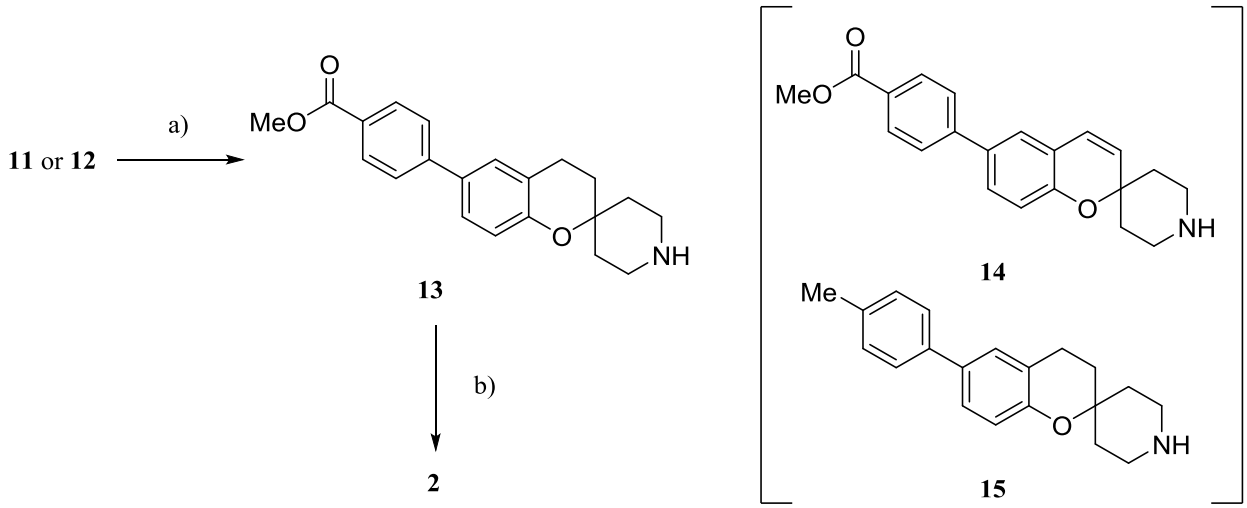
At first, we attempted to transform 4'-acetoxy-[1,1'-biphenyl]-4-carboxylic acid (**9a**) into **10a** via a Fries-rearrangement reaction with $AlCl_3$ (Scheme 2), but we did not obtain a satisfactory result because of the difficult separation between the deacetylated compound **8** and the desired compound **10a** in a simple workup.



Scheme 2. Reagents and conditions: (a) Ac_2O, pyridine, 25 °C; (b) MeI, K_2CO_3, DMF, 25 °C; (c) AcCl, $AlCl_3$, 1,2-dichloroethane, 70 °C; (d) **7**, pyrrolidine, MeOH, reflux; (e) $NaBH_4$, MeOH, THF, 0 °C.

Then, we followed a reported procedure[12] to prepare methyl 4'-methoxy-[1,1'-biphenyl]-4-carboxylate (**9b**) and conducted a Friedel-Crafts reaction of **9b** with acetyl chloride and $AlCl_3$ in 1,2-dichloroethane. The regioselective acylation, subsequently followed by demethylation of methyl ether, proceeded smoothly to produce the desired compound **10b** in 89% yield. Thus, the obtained compound **10b** was treated with *tert*-butyl 4-oxopiperidine-1-carboxylate (**7**) and pyrrolidine[13] in MeOH at reflux temperature to give the cyclized product **11** in 86% yield. The reduction of the spirochromanone-piperidine compound **11** with $NaBH_4$ produced the spirochromanol-piperidine compound **12** in 93% yield.

To convert **11** or **12** into the desired spirochroman-piperidine **13**, we investigated a variety of reaction conditions to identify a high-yield and efficient procedure (Scheme 3, Table 1).



Scheme 3. Reagents and conditions: (a) see Table 1; (b) $NaBH_4$, pyridine, 100 °C.

Upon exposure of the spirochromanol-piperidine compound **12** to Et_3SiH and CF_3CO_2H in CH_2Cl_2,[4] deoxygenation occurred (entry 1). The desired product **13** was successfully obtained along with the deprotection of the *N*-Boc group in 89% yield. Having obtained a satisfactory yield, we next sought to avoid expensive and erosive solvent such as CF_3CO_2H. Similarly, the deprotection product **13** was obtained in 95% yield when conducting the hydrogenolysis of **12** in the presence of Pd-C in AcOH at 80 °C (entry 2). To avoid stepwise reduction, we investigated an alternative reaction, treating **11** with a combination of Et_3SiH and $InCl_3$ or $InBr_3$,[14] but these conditions resulted in no reaction (entries 3 and 4). The conversion of **11** into **13** by a conventional method such as the Clemmensen reduction could be performed in 68% yield, but it also resulted in a small amount of subproduct **14** (entry 5).

Table 1. Results of the reduction of chromanol **12** and chromanone **11**

Entry	Substrate	Reagents (eq.)	Temp. (°C)	Time (h)	Yield (%)
1	**12**	Et_3SiH (10.7), CF_3CO_2H / CH_2Cl_2	rt	12	89[a]
2	**12**	H_2, Pd-C / AcOH	80	9	95[a]
3	**11**	Et_3SiH (2.4), $InCl_3$ (0.05) / CH_2Cl_2	rt	5	no reaction
4	**11**	Et_3SiH (4), $InBr_3$ (0.05) / $CHCl_3$	60	5	no reaction
5	**11**	Zn (25) / AcOH	100	5	**13** : 64, **14** : 4[b]
6	**11**	$TiCl_4$ (1.4), $Me_2NH{\cdot}BH_3$ (1.4) / CH_2Cl_2	0 to rt	3	**13** : 83, **15** :8[c]
7	**11**	$TiCl_4$ (1.2), $Me_2NH{\cdot}BH_3$ (1.2) / CH_2Cl_2	-20 to rt	3.5	79[a,d]

[a] Isolated yield.

[b] Each yield was calculated on the basis of ^{1}H-NMR analysis for an inseparable mixture of **13** and **14**.

[c] Each yield was calculated on the basis of ^{1}H-NMR analysis for a mixture of **13** and **15** as hydrochloride salts.

[d] A mixture of **13** and **15** (^{1}H-NMR analytical ratio of 50:1) hydrochloride salts was crystallized from MeOH to give the pure hydrochloride salt of **13**.

We additionally attempted this conversion with a combination of a reducing reagent and a Lewis acid such as $Me_2NH{\cdot}BH_3/TiCl_4$.[15] Our initial attempt gave a mixture of **13** and the over-reduced compound **15** when performing the reaction at 0 °C (entry 6). Then, we optimized the reaction conditions for the quantity of reducing agent and the reaction temperature to minimize the over-reduction of **13**, leading to the subproduct **15** by way of **2**. Finally, we were able to control well the reduction of the ketone accompanied by the deprotection of the *N*-Boc in **11** to produce the intermediate **13** in 79% yield when treated with a small surplus amount (1.2 eq.) of reducing reagent in the temperature range from -20 °C to room temperature (entry 7). After workup, the remaining ester could be smoothly reduced by $NaBH_4$ in pyridine at 100 °C in 75% yield.

In conclusion, we established a practical synthesis of a key intermediate **2** of a novel GPR119 agonist staring from 4'-hydroxy-[1,1'-biphenyl]-4-carboxylic acid (**8**) without troublesome intermediates or a tedious protocol. Furthermore, we developed a feasible, convenient reduction system to convert a ketone into a methylene and an ester into an alcohol with deprotection. Further process development and toxicological study are currently in progress.

EXPERIMENTAL

General. All reactions were performed under an argon atmosphere unless otherwise noted. The IR spectra were recorded on a Thermo Nicolet 370 FTIR spectrometer. The ^{1}H-NMR spectra and ^{13}C-NMR spectra were obtained on a JEOL JNM-AL 400 MHz spectrometer using the solvents $CDCl_3$ or CD_3OD with tetramethylsilane as an internal standard, unless otherwise noted. The mass spectra were obtained on a JEOL MS-BU20 mass spectrometer. The elemental analyses (C, H, and N) were performed by Yanaco MT-5. The melting points were determined in open glass capillaries on a Buchi B-545 melting point apparatus.

tert-Butyl 6-bromospiro[chromane-2,4'-piperidine]-1'-carboxylate (5)

The target compound **5** was prepared according to the patent literature.[4]

tert-Butyl 6-(4-(hydroxymethyl)phenyl)spiro[chroman-2,4'-piperidine]-1'-carboxylate (3)

Na_2CO_3 (55.0 g, 520 mmol) and $Pd(PPh_3)_4$ (2.40 g, 2.10 mmol) were added at room temperature under an argon atmosphere to a stirred solution of **4** (21.0 g, 140 mmol) and **5** (40.0 g, 100 mmol) in a mixture of DME (500 mL) and water (500 mL). The reaction mixture was stirred at 90 °C for 18 h and then allowed to cool to room temperature. The reaction mixture was extracted with AcOEt (3 x 300 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was crystallized from AcOEt to give **3** (31.0 g, 72%) as a colorless, crystalline powder.

mp 173 °C; IR (KBr): 3462, 2942, 1679, 1488, 1432, 1366, 1234, 1165, 1149, 819;
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.47 (9H, s), 1.54-1.67 (2H, m), 1.79-1.87 (4H, m), 2.84 (2H, t, J = 6.8 Hz), 3.14-3.36 (2H, m), 3.75-4.02 (2H, m), 4.69-4.75 (2H, br), 6.90 (1H, d, J = 8.3 Hz), 7.29 (1H, d, J = 2.2 Hz), 7.34 (1H, dd, J = 8.3, 2.2 Hz), 7.40 (2H, d, J = 8.0 Hz), 7.53 (2H, d, J = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 23.0, 29.9, 33.4, 35.8, 40.9, 66.3, 74.3, 81.0, 119.1, 122.9, 127.6, 128.2, 128.9, 129.5, 134.3, 140.8, 141.6, 154.3, 156.4; MS (EI) *m/z* 409 [M^+]; Anal. Calcd for $C_{25}H_{31}NO_4$: C, 73.32; H, 7.63; N, 3.42. Found: C, 73.46; H, 7.69; N, 3.48.

Methyl 4'-methoxy-[1,1'-biphenyl]-4-carboxylate (9b)

The target compound was prepared from 4'-hydroxy-[1,1'-biphenyl]-4-carboxylic acid **(8)** according to the patent literature.[12]

Methyl 3'-acetyl-4'-hydroxy-[1,1'-biphenyl]-4-carboxylate (10b)

Acetyl chloride (30.0 mL, 420 mmol) was added at 0 °C under an argon atmosphere to a suspension of $AlCl_3$ (112 g, 839 mmol) in dry 1,2-dichloroethane (210 mL). After stirring for 10 min, **9b** (50.8 g, 210 mmol) was added to this mixture dropwise. The resulting mixture was stirred at 70 °C for 1 h. After completing the reaction, the reaction mixture was poured onto ice (1000 g) and then diluted with AcOEt (1.7 L). The organic layer was washed with water (600 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was dissolved in $CHCl_3$ (130 mL) and diluted with hexane (500 mL). The precipitate was filtered off and washed with hexane (200 mL) to give **10b** (50.3 g, 89%) as a yellow solid. A sample was crystallized from $CHCl_3$ and hexane to give colorless prisms for analysis.

mp 150-152 °C; IR (KBr): 3017, 1709, 1641, 1606, 1520, 1433, 1304, 1288, 1216, 1109;

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.74 (3H, s), 3.97 (3H, s), 7.11 (1H, d, J = 8.8 Hz), 7.63 (2H, d, J = 8.0 Hz), 7.77 (1H, dd, J = 8.8, 2.0 Hz), 7.98 (1H, d, J = 2.0 Hz), 8.14 (2H, d, J = 8.0 Hz), 12.36 (1H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 26.7, 52.2, 119.2, 119.9, 126.9, 128.9, 129.2, 130.3, 131.1, 135.3, 144.3, 162.5, 166.8, 204.5; MS (EI) *m/z* 270 [M^+]; Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.12; H, 5.29.

tert-Butyl 6-(4-(methoxycarbonyl)phenyl)-4-oxospiro[chromane-2,4'-piperidine]-1'-carboxylate (11)

At room temperature, **10b** (74.8 g, 277 mmol) was added to a solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (55.2 g, 277 mmol) and pyrrolidine (11.4 mL, 138 mmol) in MeOH (277 mL). The reaction mixture was stirred at reflux temperature for 12 h. After completing the reaction, the reaction mixture was cooled to 0 °C. The precipitate was filtered off and washed with cold MeOH to give **11** (107.8 g, 86%) as a yellow solid. A sample was crystallized from AcOEt and hexane to give yellow prisms for analysis.

mp 159-160 °C; IR (KBr): 1722, 1688, 1607, 1433, 1397, 1303, 1249, 1147, 1115, 770;

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.49 (9H, s), 1.63-1.71 (2H, m), 2.04-2.12 (2H, br m), 2.79 (2H, s), 3.22-3.34 (2H, br m), 3.80-3.99 (2H, m), 3.96 (3H, s), 7.12 (1H, d, J = 8.8 Hz), 7.67 (2H, d, J = 8.0 Hz), 7.81 (1H, dd, J = 8.8, 2.0 Hz), 8.13 (2H, d, J = 8.0 Hz), 8.17 (1H, d, J = 2.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 28.3, 33.9, 39.1, 47.9, 52.0, 78.2, 79.8, 119.0, 120.1, 125.0, 126.4, 128.9, 130.1, 133.9, 134.9, 143.8, 154.6, 158.9, 166.7, 191.2; MS (EI) *m/z* 451 [M^+]; Anal. Calcd for $C_{26}H_{29}NO_6$: C, 69.16; H, 6.47; N, 3.10. Found: C, 69.24; H, 6.53; N, 3.06.

tert-Butyl 4-hydroxy-6-(4-(methoxycarbonyl)phenyl)spiro[chromane-2,4'-piperidine]-1'-carboxylate (12)

$NaBH_4$ (4.40 g, 116 mmol) was added portionwise at 0 °C to a solution of **11** (52.6 g, 116 mmol) in a mixture of MeOH (50 mL) and THF (200 mL). The reaction mixture was stirred at room temperature for

1 h. After completing the reaction, the solvent was removed under reduced pressure. The residue was dissolved in AcOEt (300 mL) and quenched with a saturated aqueous solution of NH_4Cl (100 mL). The aqueous layer was extracted with AcOEt (100 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was dissolved in AcOEt (50 mL) and diluted with hexane (150 mL). The precipitate was filtered off and washed with hexane to give **12** (48.9 g, 93%) as a white solid. A sample was crystallized from AcOEt and hexane to give colorless prisms for analysis.

mp 168-170 °C; IR (KBr): 3476, 2957, 1713, 1674, 1607, 1488, 1427, 1284, 1236, 1170;
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.47 (9H, s), 1.63-2.00 (5H, m), 2.20 (1H, dd, J = 13.4, 6.1 Hz), 3.12-3.34 (2H, br m), 3.86-3.94 (2H, m), 3.94 (3H, s), 4.99-4.92 (1H, br m), 6.96 (1H, d, J = 8.4 Hz), 7.50 (1H, dd, J = 8.4, 2.0 Hz), 7.63 (2H, d, J = 8.3 Hz), 7.74 (1H, d, J = 2.0 Hz), 8.08 (2H, d, J = 8.3 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 28.4, 33.7, 35.9, 41.8, 52.1, 62.8, 74.2, 79.6, 117.9, 125.1, 126.4, 126.9, 128.2, 128.3, 130.1, 132.5, 145.1, 152.8, 154.8, 167.1; MS (EI) *m/z* 453 [M^+]; Anal. Calcd for $C_{26}H_{31}NO_6$: C, 68.86; H, 6.89; N, 3.09. Found: C, 68.91; H, 6.94; N, 3.07.

Methyl 4-(spiro[chromane-2,4'-piperidin]-6-yl)benzoate (13) (Entry 1)

CF_3CO_2H (441 mL) and subsequently Et_3SiH (75.0 mL, 470 mmol) were added at 0 °C to a stirred solution of **12** (20.0 g, 44.1 mmol) in CH_2Cl_2 (66 mL). The reaction mixture was stirred at room temperature for 12 h. After completing the reaction, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in AcOEt (50 mL) and diluted with hexane (50 mL). The precipitate was filtered off to give the CF_3CO_2H salt of **13** (19.3 g) as a white solid. A saturated aqueous solution of $NaHCO_3$ (300 mL) was added to a stirred suspension of the CF_3CO_2H salt in MeOH (200 mL). The reaction mixture was stirred at room temperature for 30 min. MeOH was evaporated from the reaction solvent under reduced pressure. The precipitate was filtered off and washed with THF (60 mL) and hexane (60 mL) to give **13** (14.4 g, 96%) as a white solid.

A sample was recrystallized from $CHCl_3$ and hexane to give a colorless, crystalline powder for analysis.
mp 148-149 °C; IR (KBr): 3340, 2934, 1711, 1605, 1486, 1436, 1284, 1245, 1184, 1110;
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.52-1.62 (2H, br m), 1.78-1.87 (4H, br m), 2.93-2.78 (4H, br m), 3.06 (2H, t, J = 10.5 Hz), 3.92 (3H, s), 6.92 (1H, d, J = 8.3 Hz), 7.33 (1H, s), 7.37 (1H, d, J = 8.3 Hz), 7.59 (2H, d, J = 8.3 Hz), 8.05 (2H, d, J = 8.3 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.1, 31.7, 35.3, 41.6, 51.6, 73.1, 117.5, 121.4, 125.8, 125.9, 127.6, 127.9, 129.6, 131.1, 145.0, 153.5, 166.7; MS (EI) *m/z* 337 [M^+]; Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.77; H, 6.92; N, 4.19.

Hydrogenolysis of 12 (Entry 2)

Under an argon atmosphere, 5% Pd-C (60 mg) was added to a solution of **12** (200 mg, 0.442 mmol) in AcOH (3 mL). The reaction mixture was stirred at room temperature for 4 h and heated at 60 °C for 15 h and at 80 °C for 9 h under a hydrogen atmosphere. After completing the reaction, 4N HCl/AcOEt (9 mL) was added to the reaction mixture. The resulting mixture was stirred overnight at room temperature. MeOH (10 mL) was added to this mixture to dissolve the precipitate that appeared. The insoluble material (Pd-C) from the reaction mixture was filtered off. The filtrate was concentrated *in vacuo* and diluted with AcOEt (30 mL). The organic solution was washed with a saturated aqueous solution of $NaHCO_3$ (30 mL) and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (20% sat. NH_3/MeOH in $CHCl_3$) to give **13** (141 mg, 95%) as a white solid.

Clemmensen reduction (Entry 5)

Zinc powder (3.60 g, 552 mmol) was added at room temperature to a stirred solution of **11** (1.00 g, 22.1 mmol) in AcOH (10 mL). The reaction mixture was stirred at 100 °C for 5 h. After completing the reaction, the insoluble material was filtered off and washed with a mixed solvent of THF and MeOH (40 mL/10 mL). To cleave the *N*-Boc group, 4N HCl/AcOEt (20 mL) was added at room temperature to the filtrate. The resulting mixture was stirred overnight at room temperature and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (100 mL). The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (30 mL) and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (20% sat. NH_3/MeOH-$CHCl_3$) to give an inseparable mixture of **13** and **14** (517 mg) as a white solid. The yield of **13** and **14** were calculated on the basis of ^{1}H-NMR analysis to show 64% and 4%, respectively.

Methyl 4-(spiro[chromene-2,4'-piperidin]-6-yl)benzoate (14)

The authentic sample **14** was synthesized after mesylation of **12** and elimination under basic conditions.
mp 144-145 °C; IR (KBr): 3351, 2940, 2809, 1705, 1604, 1488, 1429, 1292, 1180, 1106;
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.55-1.68 (2H, m), 1.90-2.03 (2H, m), 2.78-2.87 (2H, m), 3.04-3.14 (2H, m), 3.90 (3H, s), 5.65 (1H, d, *J* = 9.6 Hz), 6.39 (1H, d, *J* = 9.6 Hz), 6.90 (1H, d, *J* = 8.0 Hz), 7.22 (1H, d, *J* = 2.0 Hz), 7.36 (1H, dd, *J* = 8.0, 2.0 Hz), 7.56 (2H, d, *J* = 8.0 Hz), 8.04 (2H, d, *J* = 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 36.3, 41.5, 51.8, 75.5, 116.7, 122.0, 122.7, 124.9, 126.1, 127.7, 128.0, 129.8, 130.2, 132.4, 144.8, 152.7, 166.7; MS (EI) *m/z* 309 [M^+]; Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.16; H, 6.38; N, 4.05.

Reduction of 11 by $Me_2NH{\cdot}BH_3$ and $TiCl_4$ (Entry 6)

A solution of **11** (10.0 g, 22.1 mmol) in dry CH_2Cl_2 (70 mL) was added dropwise at 0 °C under an argon atmosphere to a stirred solution of $TiCl_4$ in dry CH_2Cl_2 (1.0 M solution, 26.5 mL) and $Me_2NH{\cdot}BH_3$ (1.60 g, 26.5 mmol) in dry CH_2Cl_2 (30 mL). After stirring at this temperature for 30 min, the reaction mixture was allowed to warm to room temperature and was stirred for 3 h. After completing the reaction, the reaction mixture was quenched with H_2O (100 mL) at 0 °C. The resulting mixture was stirred overnight at room temperature. The precipitate was filtered off to give a mixture of **13** and **15** as hydrochloride salts (7.54 g). The yield of **13** and **15** were calculated on the basis of ^{1}H-NMR analysis (CD_3OD) to show 83% and 8%, respectively.

Reduction of 11 by $Me_2NH{\cdot}BH_3$ and $TiCl_4$ (Entry 7)

This procedure was the same as that in Entry 6 except for the reaction temperature at -20 °C. The ratio of each compound of hydrochloride salts (**13**:**15** = 50:1) was determined by ^{1}H-NMR analysis (CD_3OD). A mixture of products was crystallized from MeOH to give the hydrochloride salt of **13** (6.54 g, 79%).

(4-(Spiro[chromane-2,4'-piperidin]-6-yl)phenyl)methanol (2)

$NaBH_4$ (1.52 g, 40.0 mmol) at 0 °C under an argon atmosphere was added to a stirred solution of **13**·HCl (6.00 g, 16.0 mmol) in dry pyridine (100 mL). The stirring reaction mixture was allowed to warm to room temperature and heated at 100 °C for 14 h. After completing the reaction, the reaction mixture was quenched with MeOH (50 mL) at 0 °C and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (200 mL) and H_2O (200 mL). The aqueous layer was extracted with $CHCl_3$ (200 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was dissolved in MeOH (20 mL) and AcOEt (80 mL). At 0 °C, 4N HCl/AcOEt (20 mL) was added to this solution. The resulting mixture was stirred at 0 °C for 30 min and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (200 mL). The organic layer was washed with 1N NaOH (30 mL), and the aqueous layer was extracted with $CHCl_3$ (200 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The solid product was crystallized from THF (100 mL) and hexane (50 mL) to give **2** (2.88 g, 58%) as a colorless, crystalline powder. The mother liquid was concentrated *in vacuo* and crystallized from THF (40 mL) and hexane (15 mL) to give **2** (0.83 g, 17%) as a colorless, crystalline powder.

A sample was recrystallized from THF to give a colorless needle for analysis.

mp 190-191 °C; IR (KBr): 3260, 3066, 2924, 1490, 1250, 1160, 1142, 1036, 972, 841;

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.61-1.72 (2H, m), 1.81-1.90 (4H, m), 2.71-2.96 (4H, m), 3.08 (2H, t, J = 11.7 Hz), 4.62 (2H, s), 6.82-6.88 (1H, m), 7.32-7.39 (4H, m), 7.53 (2H, d, J = 8.3 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.9, 31.8, 34.4, 40.9, 63.6, 72.8, 117.2, 121.6, 125.4, 126.0, 127.1, 127.5, 132.7, 139.4,

139.9, 152.8; MS (EI) *m/z* 309 [M^+]; Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.46; H, 7.55; N, 4.54.

ACKNOWLEDGEMENTS

We thank Dr. S. Tanabe, Director, for his encouragement and support at Tokyo New Drug Research Laboratories, Kowa Co., Ltd.

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