ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D

Full Paper

Process Development for the Synthesis of a Selective M1 and M4 Muscarinic Acetylcholine Receptors Agonist

Yoshiharu Uruno, Kazuki Hashimoto, Yoichi Hiyama, and Takaaki Sumiyoshi

Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.7b00236 • Publication Date (Web): 05 Sep 2017

Just Accepted

ACS Publications

Organic Process Research & Development is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Process Development for the Synthesis of a Selective M_1 and M_4 Muscarinic Acetylcholine Receptors Agonist

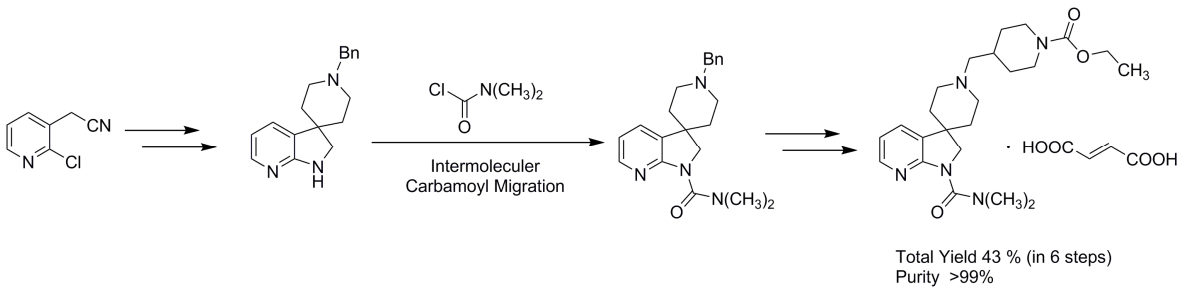
Yoshiharu Uruno,[†,*] Kazuki Hashimoto,[‡] Yoichi Hiyama,[§] and Takaaki Sumiyoshi[†,¶]

[†]Chemistry Research Laboratory, Sumitomo Dainippon Pharma Co. Ltd., 3-1-98, Kasugade-naka, Konohana-ku, Osaka 554-0022, Japan

[‡]Process Chemistry Research & Development Laboratories, Sumitomo Dainippon Pharma Co. Ltd., 3-1-98, Kasugade-naka, Konohana-ku, Osaka 554-0022, Japan

[§]Genomic Science Laboratories, Sumitomo Dainippon Pharma Co. Ltd., 3-1-98, Kasugade-naka, Konohana-ku, Osaka 554-0022, Japan

TABLE OF CONTENTS GRAPHIC



Total Yield 43 % (in 6 steps)
Purity >99%

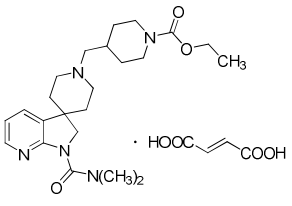
ABSTRACT

A practical and chromatography-free synthetic process to selective M_1 and M_4 muscarinic acetylcholine receptors agonist was developed and demonstrated on a several hundred grams scale. The key feature of this route is *N,N*-dimethylcarbamoylation of the anilinic nitrogen on the spiro 7-azaindoline structure via intermolecular migration of the *N,N*-dimethylcarbamoyl group. The resulting compound **1** was prepared in 43% overall yield with a chemical purity >99% via six steps starting with (2-chloropyridin-3-yl)acetonitrile.

Keywords: 7-Azaindoline, *N,N*-Dimethylcarbamoylation, Intermolecular migration, Muscarinic acetylcholine receptors agonist, X-ray crystal structure

INTRODUCTION

Many of the important central actions of acetylcholine (ACh) are mediated by the muscarinic ACh receptors (mAChRs).[1] To date, five mAChR subtypes (M_1−M_5) have been identified and are considered to play important roles in the peripheral and central nervous systems (CNS).[2] Clinical trials with xanomeline, an M_1 and M_4 preferring orthosteric agonist, demonstrated that M_1 and M_4 mAChRs are attractive therapeutic targets for Alzheimer's disease and schizophrenia.[3] During one of our drug discovery program,[4] we have found the 7-azaindoline derivative **1** as a lead candidate with selective M_1 (EC_{50} = 133 nM) and M_4 (EC_{50} = 47 nM) mAChRs agonistic activity. Further studies led to the selection of this compound as a potential therapy for CNS disorders. However, to support preclinical studies, we had to find a practical synthetic route to **1** suitable for kilogram scale. This is because the initial chemical synthesis of **1** presents not only safety concerns, but also reproducibility and purification challenges. In this report, we describe a successful synthetic route to **1** that overcomes conventional issues and provides a practical process for scale-up to several hundred grams.



1

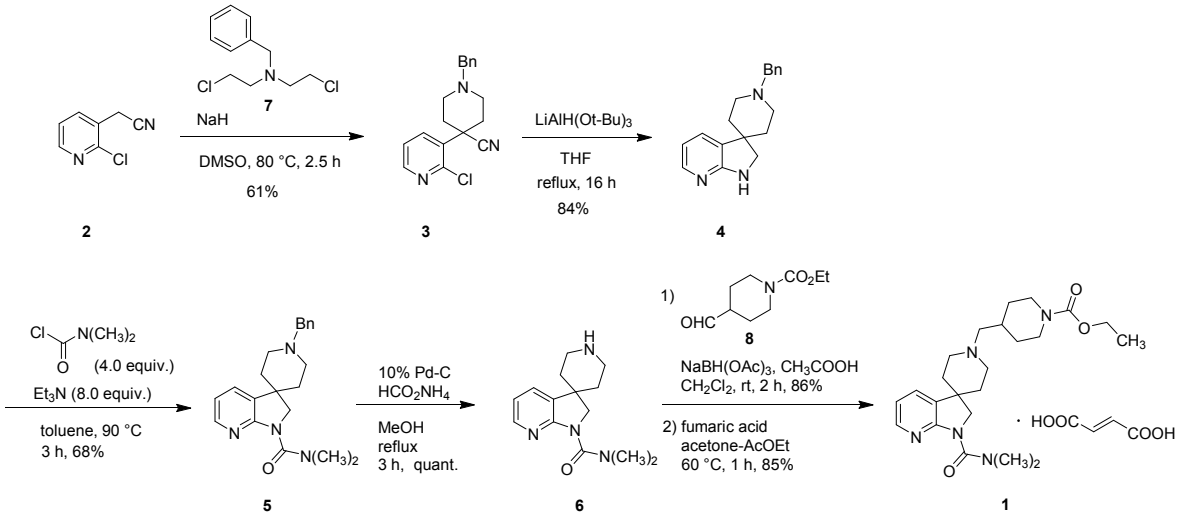
Figure 1. Structure of a selective M_1 and M_4 mAChRs agonist **1**

RESULTS AND DISCUSSION

Initial Chemical Synthesis of 1.

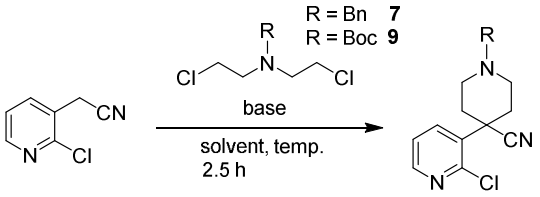
Various effective synthetic approaches of azaspiroindoline[5] or spiroindoline[6] derivatives were reported. However, there are few examples about 7-azaspiroindoline.[7] Based on these literatures, we chose the synthetic route in scheme 1 for construction of 7-azaspiroindoline derivative **1** in terms of short synthetic process. Compound **1** was first prepared from the commercially available (2-Chloropyridin-3-yl) acetonitrile **2** in six steps and 30 % yield (Scheme 1). Deprotection at the benzylic position of compound **2** by NaH followed by reaction with **7** in DMSO gave the spiro compound **3** in 61% yield. Reduction of **3** with $LiAlH(O\textit{t}\text{-}Bu)_3$ and subsequent cyclization provided the 7-azaindoline derivative **4** in 84 % yield. Next, *N,N*-dimethylcarbamoylation of the anilinic nitrogen of **4** was accomplished in 68% yield by use of excess amounts of *N,N*-dimethylcarbamoyl chloride (4.0 equiv.) and triethylamine (8.0 equiv.). Deprotection of the benzyl group of **5** with $HCOONH_4$ in MeOH, followed by reductive amination with the aldehyde **8** afforded the free form of **1** in 86% yield. Finally, salt formation with fumaric acid and re-crystallization using acetone-ethyl acetate gave the desired product **1** in 85% yield. The initial synthesis enabled the production of gram quantities of **1**. However, further development was necessary to address large-scale safety concerns and multiple chromatography purification. The initial synthesis of **1** presented three majors issues. Namely, 1) the potential of explosion in the steps that transform compound **2** to **3** and compound **5** to **6**, 2) the poor reproducibly in the step that provides compound **5** from **4**, and 3) the need for column chromatography purification in the preparation of compounds **3** and **5**.

Scheme 1. Initial Synthesis of the Selective M_1 and M_4 mAChRs Agonist 1



The preparation of compound **3** required the use of NaH, compound **7** in DMSO, and a temperature of 80 °C. These reaction conditions can cause explosion at scale-up.[8] In addition, the commercially available **7**·HCl had to be desalted with 10% K_2CO_3 solution before use and, as such, could not be stored for long time. Furthermore, compound **3** could not be purified without column chromatography due to the production of multi undesired by-products. To overcome these challenges, we considered optimization of the reaction conditions.

Table 1. Optimization of the Reaction Conditions



2 **3**

entry	reagent	base (equiv.)	solvent	temp.	yield
1	**7**	NaH (2.0)	DMSO	80 °C	61%
2	**7**	KOH (2.0)	DMSO	80 °C	67%
3	**7**	KOH (2.0)	DMSO	30 °C	70%
4	**7**·HCl	KOH (3.0)	DMSO	30 °C	82%
5	**7**·HCl	NaOH (3.0)	DMSO	30 °C	65%
6	**7**·HCl	K_2CO_3 (3.0)	DMSO	30 °C	14%
7	**7**·HCl	KOH (3.0)	DMF	30 °C	trace
8	**9**·HCl	KOH (3.0)	DMSO	30 °C	trace

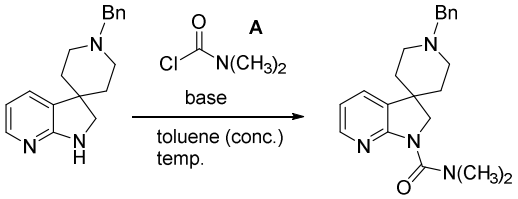
Construction of spiro ring structure at the benzylic position of compound **2** is usually conducted by NaH in DMSO condition at high temperature. In previous literatures, spiro structure at benzylic position was constructed by hexadecyltributylphosphonium bromide in 50% NaOH solution at reflux condition.[9] We tried to adapt and simplify this reaction condition. First, we changed the base used for deprotonation of compound **2** from NaH to KOH (entry 2, Table 1). This change allowed the preparation of compound **3** in 67% yield as compared to 61% with NaH. Lowering the temperature from 80 °C to 30 °C (entry 3) resulted in 70% yield. Next, we tried to use the commercially available **7**·HCl without pre-desaltation and instead used KOH at 3 equiv. to achieve in-situ desaltation. This modification afforded **3** in 82% yield (entry 4). Using NaOH or K_2CO_3 as a base provided **3** in 65% or 14%, respectably (entries 5 and 6). When the solvent was changed to DMF, **3** was obtained only in trace amount (entry 7). In case of the Boc protected reagent **9**·HCl, multi products were afforded (entry 8). Based on these findings, we selected the conditions of entry 4 for a safe reaction at ambient temperature.

Preparation of the 7-Azaindoline Derivative 4 and *N,N*-Dimetylcarbamoylation of Anilinic

Nitrogen.

Compound **4** was synthesized in acceptable yield from compound **3** using $LiAlH(O\textit{t}\text{-}Bu)_3$ as a reductive agent.[10] However *N,N*-dimethylcarbamoylation of the anilinic nitrogen of **4** required the use of excess amounts of *N,N*-dimethylcarbamoyl chloride (4.0 equiv.) and triethylamine (8.0 equiv.), giving **5** in 68% yield (entry 2, Table 2). Without these excess amounts (entry 1, Table 2), compound **5** was obtained in only 28% isolated yield. Although the excess conditions provide **5** in 68% yield (entry 2), the reproducibility of this yield is poor, especially in case of large scale production (>10 g). Furthermore, some of the starting material **4** remained after the reaction (entries 1 and 2), necessitating column chromatography for separation of **5**. Thus, perfect conversion will be needed to avoid column chromatography. To avoid chromatography, we conducted further investigation and found that this reaction proceeds in two steps via intermolecular migration of the *N,N*-dimethycarbamoly group[11] as depicted in Scheme 2. Details of an experimental and theoretical study of this reaction indicate that the concentration, temperature and procedure are important to accomplish complete conversion of **4** to **5**.[12] Therefore, optimized reaction conditions as described in entry 3 afforded the desired compound **5** in 99% yield (entry 3). Details of the procedure are described in the experimental section.

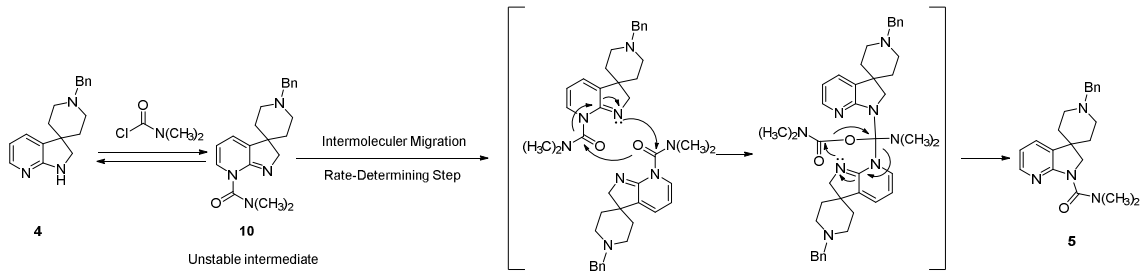
Table 2. Effects of Base, Concentration and Temperature on *N,N*-Dimethylcarbamoylation of 4



4 **5**

entry	**A** (equiv.)	base (equiv.)	conc.	temp.	yield
1	1.5	Et_3N (2.0)	0.2 M	90 °C	28%
2	4.0	DIPEA (8.0)	0.2 M	90 °C	68%
3	1.5 + 0.2	DIPEA (2.0 + 0.6)	2.0 M	reflux	99%

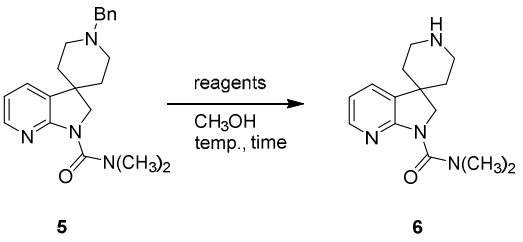
Scheme 2. Reaction Mechanism of *N,N*-Dimethylcarbamoylation of 4



Deprotection of the benzyl group of 5, giving compound 6.

In initial synthesis of **1**, deprotection of benzyl group of **5** was achieved by 10%Pd/C and $HCOONH_4$ in methanol under reflux condition, affording **6** in quantitative yield (Table 3, entry 1). However, at kilogram scale, it is possible that $HCOONH_4$ decomposition material clogs the reflux condenser. To avoid such risk, hydrogen was used as reducing agent and 10% Pd/C as catalyst (entry 2). Using 20% $Pd(OH)_2/C$ (entry 3) reduced the reaction time by half to 8 h (entry 3).

Table 3. Optimization of Deprotection of the Benzyl Group of 5



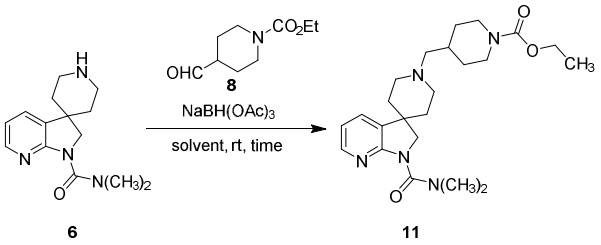
entry	reagents		temp.	time	conversion
1	$HCOONH_4$	10%Pd/C	reflux	3 h	>99%
2	H_2	10%Pd/C	40 °C	16 h	70%
3	H_2	20%$Pd(OH)_2$/C	40 °C	8 h	>99%

Reductive Amination of 6 with 8.

In the initial synthesis of **11**, compound **6** was reacted with the aldehyde **8** and $NaBH(OAc)_3$ in CH_2Cl_2 to afford compound **11** in 86% yield (entry 1, Table 4). In this reaction, the isolated yield was acceptable, however, a halogenated solvent (dichloromethane) was used. Generally, a replacement for this solvent is desired for pharmaceutical manufacturing. We found that this reaction could be conducted in THF with the desired compound **11** obtained in >99% yield (entry 2, Table 4). By using toluene, the yield of compound **11** decreased to 91%. Furthermore compound **11** was obtained in >99% yield without

addition of acetic acid (entry 3, Table 4). These optimization steps allowed the preparation of compound **11** in 99% yield without the use of a halogenated solvent, which is suitable pharmaceutical manufacturing. Single crystal X-ray structure of the obtained compound **11** is depicted in Figure 2, and the details are described in the supporting information.[13]

Table 4. Reductive Amination of compound 6



entry	AcOH	solvent	time	yield
1	1.0 equiv.	CH_2Cl_2	2 h	86%
2	1.0 equiv.	THF	2 h	>99%
3	1.0 equiv.	toluene	2 h	91%
4	-	THF	2 h	>99%

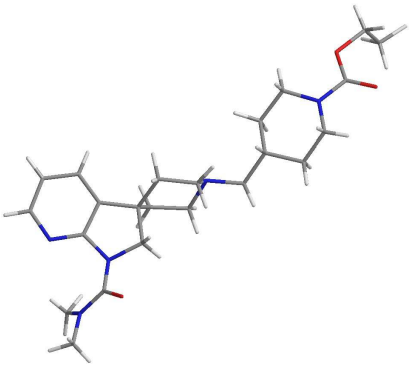
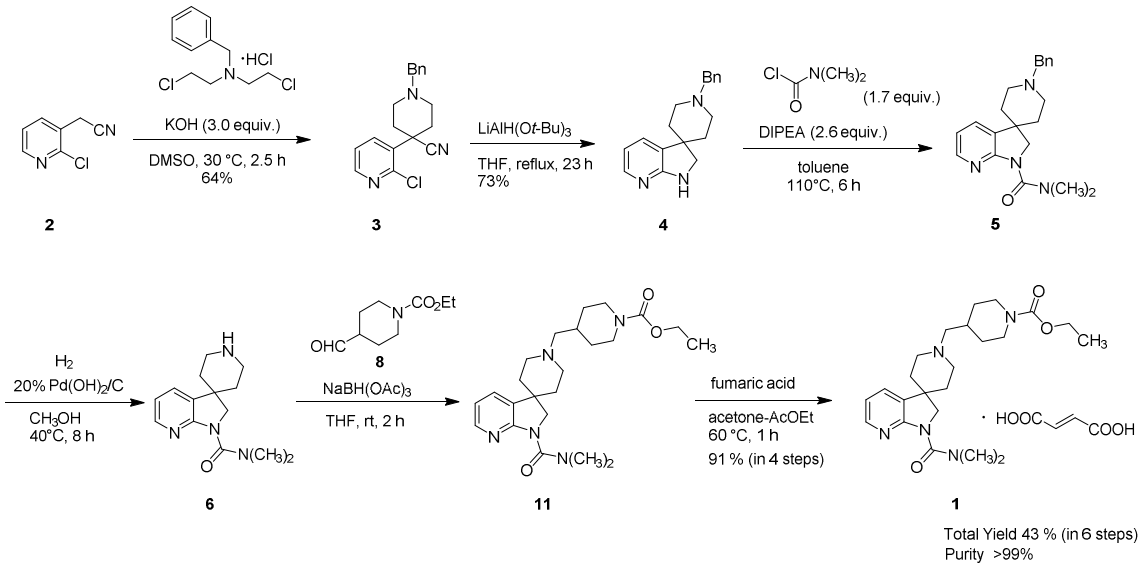


Figure 2. X-ray crystal structure of 11

Improved Process for Preparation of 1.

Based on all the optimizations described above, we attempted the synthesis of **1** at several hundred grams scale. Starting with 477 g of compound **2**, we were able to generate compound **11** (free form of **1**) in good yield (Scheme 3). Finally, transformation into a salt using fumaric acid in ethanol and re-crystallization with acetone-ethyl acetate at 60 °C afforded the target compound **1** in 43% over all yield and >99% HPLC area purity.

Scheme 3. Improved Process for the Preparation of 1



CONCLUSION

In conclusion, we described in this study the initial synthesis of compound **1**, a selective M_1 and M_4 mAChRs agonist, and carried various optimizations to suit production at several hundred grams scale. Our work addressed safety and methodology concerns and simplified the original synthesis. We also accomplished a higher yield than the initial synthetic route.

EXPERIMENTAL SECTION

General. All reagents and solvents were purchased from commercial suppliers and used without further purification. Nuclear Magnetic Resonance (NMR) spectra were recorded at ambient temperature on a JEOL JNM-AL400 FT NMR spectrometer, operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. ESI mass spectra were measured on a SHIMADZU LCMS-2010EV. ESI mass spectra (for HRMS) were measured on a Thermo Fischer Science LTQ Orbitrap Discovery MS equipment. Infrared (IR) spectra were measured on a SHIMADZU IRAffinity-1 equipped with Smiths Detection DuraScope. Melting points were determined on a YANACO MP-J3 without correction. Elemental analysis was performed on a CE Instruments EA1110 and a Yokokawa analytical system IC7000. HPLC analysis was performed on Agilent 1100 Series. NMR spectra of unknown compounds are included within the supporting information. Characterization of compound **4**, **5**, **10** and **11** have been described in our previous paper (*Tetrahedron* **2013**, *69*, 9675-9681).

1-Benzyl-4-(2-chloropyridin-3-yl)piperidine-4-carbonitrile (3). To a solution of **2** (477 g, 3.13 mol) in DMSO (9.5 L) was added KOH pellet (544 g, 9.69 mol) portion wise at room temperature. *N*-Benzyl-bis(2-chloroethyl)amine hydrochloride (840 g, 3.13 mol) was added to reaction mixture

portion wise and reaction was continued at 30 °C for 2.5 h. The reaction mixture was cooled to 20 °C and poured on water and extracted with ethyl acetate. The organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give brown solid (959 g). Ethyl acetate (190 mL) was added to the brown solid and stirred at 65 °C for 3 h. The reaction mixture was cooled to 5 °C and stirred for 2 h. The reaction mixture was filtrated to give pale brown solid and the solid was washed by *n*-hexane to afford **3** (627 g, 64%). Brown solid; mp 144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (dt, *J* = 12.9, 3.7 Hz, 2H), 2.51 (dd, *J* = 12.9, 2.4 Hz, 2H), 2.61 (dt, *J* = 12.9, 2.0 Hz, 2H), 3.05 (d, *J* = 12.9 Hz, 2H), 3.62 (s, 2H), 7.26−7.34 (m, 6H), 7.75 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.40 (dd, *J* = 4.6, 1.7 Hz, 1H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 33.8, 40.4, 50.0, 62.7, 119.7, 122.9, 127.3, 128.4, 129.1, 133.4, 136.0, 138.0, 149.0, 150.5; IR 702, 741, 795, 991, 1400, 1562 cm^{-1}; MS (ESI, positive) *m/z* 312 $(M+H)^+$; HRMS (ESI, positive) *m/z* calcd for $C_{18}H_{19}N_3Cl$ $(M+H)^+$ 312.1262, found 312.1270.

1-Benzyl-1',2'-dihydrospiro[piperidine-4,3'-pyrrolo[2,3-b]pyridine] (4). To a solution of $LiAlH(O\textit{t}\text{-}Bu)_3$ (2.55 kg, 10.0 mol) in THF (3.1 L) was added to a THF solution of **3** (625 g, 2.00 mol) in THF solution (4.4 L) portion wise at 65 °C. The mixture was stirred under reflux for 23 h. The resulting mixture was cooled to 0 ºC and ice water was poured on ice water. The reaction mixture was extracted with ethyl acetate and washed with 20% NaCl aqueous solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give brown solid (551 g). The brown solid was dissolved in ethyl acetate (1.1 L) at 75 °C and the reaction mixture was cooled to 25 °C and stirred for 1.5 h. n-Hexane was added the mixture and filtrated to give pale brown solid. The pale brown solid was washed by n-hexane to afford **4** (406 g, 73%).

1-Benzyl-*N*,*N*-dimethylspiro[piperidine-4,3'-pyrrolo[2,3-b]pyridine]-1'(2'H)-carboxamide (5). *N, N*-Diisopripylethylamine (105 mL, 752 mmol) was added to a stirred solution of **4** (105 g, 376 mmol) in toluene (247 mL) at room temperature. *N, N*-Dimetylcarbamoyl chloride (52 mL, 564 mmol) was added to the reaction mixture and reaction was continued at reflux condition. After 3 h, *N,N*-diisopripylethylamine (32 mL, 226 mmol) and *N,N*-dimetylcarbamoyl chloride (10 mL, 113 mmol) were added to reaction mixture. Additional 3 h, the reaction mixture was cooled to room temperature and quenched by water and separated. The water layer was extracted with AcOEt and combined. The organic extracts were washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give **5** (132 g).

***N, N*-Dimethylspiro[piperidine-4,3'-pyrrolo[2,3-b]pyridine]-1'(2'H)-carboxamide (6).** A mixture of **5** (132 g, 376 mmol), 20% $Pd(OH)_2$ on carbon (23.8 g) and MeOH (1.1 L) was stirred and stirred at 40 °C under H_2 atmosphere for 8 h. Filtrated Pd on carbon and concentrated under reduced pressure to give **6** (96 g). White solid; mp 104 °C; ^{1}H NMR(400 MHz, $CDCl_3$) δ 1.68−1.71 (m, 2H),

1.79−1.86 (m, 2H), 2.76−2.83 (m, 2H), 3.01 (s, 6H), 3.03−3.10 (m, 2H), 3.80 (s, 2H), 6.74 (dd, J = 7.3, 5.1 Hz, 1H), 7.35 (dd, J = 7.3, 1.7 Hz, 1H), 8.03 (dd, J = 5.1, 1.7 Hz, 1H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 36.2, 38.1, 40.3, 43.1, 57.7, 116.2, 130.3, 132.3, 146.5, 157.2, 57.6; IR 771, 1219, 1366, 1381,1419, 1651 cm^{-1}; MS (ESI, positive) *m/z* 260 $(M+H)^+$; HRMS (ESI, positive) *m/z* calcd for $C_{14}H_{21}ON_4$ $(M+H)^+$ 261.1710, found 261.1718.

Ethyl4-{[1'-(dimethylcarbamoyl)-1',2'-dihydro-1H-spiro[piperidine-4,3'-pyrrolo[2,3-b]pyridin]-1-yl]methyl}piperidine-1-carboxylate fumarate (1). To a solution of **6** (96 g, 370 mmol) and 4-formylpiperidine-1-carboxylate **8** (69 g, 370 mmol) in THF (542 mL) was added sodium triacetoxyborohydride (118 g, 555 mmol) at room temperature. After 2 h, 10% aqueous K_2CO_3 solution (963 mL) was added to the mixture drop wise at 0 ºC. The mixture was extracted with toluene. Organic layer was separated and concentrated under reduced pressure to afford **11** as white solid (164 g). The white solid **11** (130 g, 301 mmol) was dissolved in ethanol (1.2 L) and fumaric acid (35 g, 301 mmol) was added to the solution. The mixture was stirred for 1 h and solvent was evaporated under reduced pressure to give colorless amorphous (119 g, 99%). The colorless amorphous was dissolved in acetone (1.2 L), ethyl acetate (1.0 L) was added to the solution and wormed up to 60 °C. After 1 h, reaction mixture was cooled to 25 °C and white precipitate was collected by suction filtration. The white precipitate was washed by ethyl acetate (431 mL) and dried to give **1** (150 g, 91% in four steps, 99.7 % HPLC area purity). White solid; ^{1}H NMR (400 MHz, DMSO−d_6) δ 0.94−1.06 (m, 2H), 1.15 (t, J = 7.1 Hz, 3H), 1.65−1.78 (m, 5H), 1.88−1.98 (m, 2H), 2.30-2.42 (m, 4H), 2.70−2.89 (m, 4H), 2.90 (s, 6H), 3.65 (s, 2H), 3.89-3.99 (m, 2H), 4.00 (q, J = 7.1 Hz, 2H), 6.58 (dd, J = 7.3, 5.1 Hz, 1H), 7.54 (d, J = 6.6 Hz, 1H), 7.99 (d, J = 5.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO−d_6) δ 14.6, 30.2 (×2), 32.1, 33.9 (×2), 37.3 (×2), 43.2 (×2), 49.7 (×2), 57.0, 60.5, 63.0, 116.3, 130.7, 131.4, 134.4 (×3), 146.2, 154.6, 156.6, 157.2, 166.7 (×2); IR 1273, 1377, 1423, 1663, 1680 cm^{-1}; MS (ESI, positive) *m/z* 430 $(M+H)^+$; HRMS (ESI, positive) *m/z* calcd for $C_{23}H_{36}O_3N_5$ $(M+H)^+$ 430.2813, found 430.2824; Anal. calcd for $C_{23}H_{35}N_5O_3 \cdot C_4H_4O_4 \cdot 1/2\ H_2O$: C, 58.47; H, 7.27; N, 12.63. Found: C, 58.28; H, 7.25, N, 12.63.; HPLC analysis conditions (Column: Eclipse Plus C_{18} 4.6 × 100 mm, 3.5 μm; flow 1.0 mL/min; Eluent: Gradient 10−90% methanol in water containing 0.01% TFA).

ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR of compounds **1**, **3** and **6**. Detail data of a single crystal X-ray structure analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

* Corresponding author. Tel.: +81-6-6466-3104; fax: +81-6-6337-5287;
E-mail: yoshiharu-uruno@ds-pharma.co.jp

Present Adresses

¶ Current address: Faculty of Chemistry, Materials and Bioengineering, Department of Life Science and Biotechnology, Kansai University, 3-3-35 Yamate-cho, Suita, Osaka 564-8680, Japan.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We really thank Keiko Bando for carrying out elemental analyses, Naohiro Nishimura and Sayo Takayama for HRMS analyses and Kenjiro Hira for crystallization of compound **11**.

REFERENCES

1. Smythies, J. *Int. Rev. Neurobiol.* **2005**, *64*, 1−122.

2. (a) Caulfield, M. P.; Birdsall, N. J. *Pharmacol. Rev.* **1998**, *50*, 279–290. (b) Eglen, R. M. *Prog. Med. Chem.* **2005**, *43*, 105–136. (c) Hulme, E. C.; Birdsall, N. J.; Buckley, N. J. *Annu. Rev. Pharmacol. Toxicol.* **1990**, *30*, 633–673.

3. (a) Bodick, N.C.; Offen, W. W.; Levey, A. I.; Cutler, N.R.; Gauthier, S.G.; Satlin, A.; Shannon, H. E.; Tollefson, G. D.; Rasmussen, K.; Bymaster, F. P.; Hurley, D. J.; Potter, W. Z.; Paul, S. M. *Arch. Neurol.* **1997**, *54*, 465– 473. (b) Shekhar, A.; Potter, W. Z.; Lightfoot, J.; Lienemann, J.; Dube´, S. Mallinckrodt, C.; Bymaster, F. P.; McKinzie, D. L.; Felder, C. C. S. *Am. J. Psychiatry* **2008**, *165*, 1033–1039.

4. (a) Sumiyoshi, T.; Enomoto, T.; Takai, K.; Takahashi, Y.; Konishi, Y.; Uruno, Y.; Tojo, K.; Suwa, A.; Matsuda, H.; Nakako, T.; Sakai, M.; Kitamura, A.; Uematsu Y.; Kiyoshi, A. *ACS Med. Chem. Lett*. **2013**, *4*, 244−248. (b) Takai, K.; Inoue, Y.; Konishi, Y.; Suwa, A.; Uruno, Y.; Matsuda, H.; Nakako, T.; Sakai, M.; Nishikawa, H.; Hashimoto, G.; Enomoto, T.; Kitamura, A.; Uematsu, Y.; Kiyoshi, A.; Sumiyoshi, T. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4644–4647. (c) Suwa, A.; Konishi, Y.; Uruno, Y.; Takai, K.; Nakako, T.; Sakai, M.; Enomoto, T.; Ochi, Y.; Matsuda, H.; Kitamura, A.; Uematsu, Y.; Kiyoshi, A.; Sumiyoshi, T. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2909–2912. (d) Uruno, Y.; Konishi, Y.; Suwa, A.; Takai, K.; Tojo, K.; Nakako, T.; Sakai, M.; Enomoto, T.; Matsuda, H.; Kitamura, A.; Sumiyoshi, T. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5357–5361.

5. (a) Genin, M. J., Chidester C. G., Rohrer, D. C.; Romero, D. L. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1875–1880. (b) Danneman, M. W.; Hong, K. B.; Johnston, J. N. *Org. Lett.* **2015**, *17*, 3806–3809. (c) Nardi, A.; Jakob, F.; Konetzki, I.; Craan, T.; Hesslinger, C.; Doodeman, R. *PCT Int. Appl.* WO 2016008593 , 2016. (d) Schempp, T. T.; Daniels, B. E.; Staben, S. T.; Stivala, C. E. *Org. Lett.* **2017**, *19*, 3616-3619. (e) Gonzalez-Lopez de Turiso, F.; Shin, Y.; Brown, M.; Cardozo, M.; Chen, Y.; Fong, D.; Hao, X.; He, X.; Henne, K.; Hu, Y.-L.; Johnson, M. G.; Kohn, T.; Lohman, J.; McBride, H. J.; McGee, L. R.; Medina, J. C.; Metz, D.; Miner, K.; Mohn, D.; Pattaropong, V.; Seganish, J.; Simard, J. L.; Wannberg, S.; Whittington, D. A.; Yu, G.; Cushing, T. D. *J. Med. Chem.* **2012**, *55*, 7667-7685.

6. (a) Maligres, P. E.; Houpis, I.; Rossen, K.; Molina, A. Sager, J. Upadhyay V. Wells, K. M.; Reamer, R. A.; Lynch, J. E.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron* **1997**, *53*, 10983–10992. (b) Xie, J.-S.; Huang, C. Q.; Fang, Y.-Y.; Zhu, Y.-F, F. *Tetrahedron* **2004**, *60*, 4875-4878. (c) Ong, H. H.; Profitt, J. A.; Fortunato, J.; Glamkowski, E. J.; Ellis, D. B.; Geyer, H. M. III; Wilker, J. C.; Burghard, H. *J. Med. Chem.* **1983**, *26*, 981-6.

7. (a) Qiao, J. X.; Wang, T. C.; Ruel, R.; Thibeault, C.; L'Heureux, A.; Schumacher, W. A.; Spronk, S. A.; Hiebert, S.; Bouthillier, G.; Lloyd, J.; Pi, Z.; Schnur, D. M.; Abell, L. M.; Hua, J.; Price, L. A.; Liu, E.; Wu, Q.; Steinbacher, T. E.; Bostwick, J. S.; Chang, M.; Zheng, J.; Gao, Q.; Ma, B.; McDonnell, P. A.; Huang, C. S.; Rehfuss, R.; Wexler, R. R.; Lam, P. Y. S. *J. Med. Chem.* **2013**, *56*, 9275−9295. (b) Gao, Y.-D.; Macneil, D. J.; Yang, L.; Morin, N. R.; Fukami, T.; Kanatani, A.; Fukuroda, T.; Ishii, Y.; Morin, M. *PCT Int. Appl.* WO 2000027845, 2000. (c) Ito, F.; Hayashi, S.; Hayashi, S.; Hashizume, Y.; Mihara, S. *PCT Int. Appl.* WO 2005016913, 2005.

8. (a) The Material Safety Data Sheet for DMSO suggests that possibility of explosive reaction. (b) Bassan,E.; Ruck, R. T.; Dienemann, E.; Emerson, K. M.; Humphrey, R. G.; Raheem, I. T.; Tschaen, D. M.;Vickery, T. P.; Wood, H. B.; Yasuda, N. *Org. Process Res. Dev.* **2013**, *17*, 1611-1616.

9. (a) Burkholder, T. P.; Kudlacz, E. M.; Le, T.-b; Maynard, D. US 5824690, 1998. (b) Alvaro, G.; Cardullo, F.; Di, F. R.; Giovannini, R.; Piga, E.; Tranquillini, M. E. *PCT Int. Appl.* WO 2004005256, 2004.

10. Cassayre, J.; Molleyres, L.-P.; Maienfisch, P.; Cederbaum, F. *PCT Int. Appl.* WO 2005061512, 2005.

11. (a) Pathirana, C.; Sfouggatakis, C.; Palaniswamy, V. *Magn. Reson. Chem.* **2013**, *51*, 184–187. (b) Zhao, Z.; Jaworski, A.; Piel, I.; Snieckus, V. *Org. Lett.* **2008**, *10*, 2617–2620.

12. Uruno, Y.; Tanaka, A.; Hashimoto, K.; Usui, S.; Inoue, Y.; Konishi, Y.; Suwa, A.; Takai, K.; Katoda, W.; Fujiwara, N.; Sumiyoshi, T. *Tetrahedron* **2013**, *69*, 9675–9681.

13. Recrystallzation of **11**. **11** (5 mg) was dissolved in DMSO (25 μL) at 70°C. The solution was leaved

at room temperature for 1 day. Single crystal of **11** was formed.