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Discovery and stereoselective synthesis of the novel isochroman neurokinin-1 receptor antagonist 'CJ-17,493'

Yuji Shishido *,‡, Hiroaki Wakabayashi ‡, Hiroki Koike, Naomi Ueno, Seiji Nukui †, Tatsuya Yamagishi ‡, Yoshinori Murata, Fumiharu Naganeo, Mayumi Mizutani ‡, Kaoru Shimada ‡, Yoshiko Fujiwara, Ayano Sakakibara ‡, Osamu Suga, Rinko Kusano, Satoko Ueda, Yoshihito Kanai, Megumi Tsuchiya, Kunio Satake ‡

Pfizer Global Research & Development, Nagoya Laboratories, 5-2 Taketoyo, Aichi 470-2394, Japan

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ABSTRACT

A novel central nervous system (CNS) selective neurokinin-1 (NK_1) receptor antagonist, (2*S*,3*S*)-3-[(1*R*)-6-methoxy-1-methyl-1-trifluoromethylisochroman-7-yl]-methylamino-2-phenylpiperidine 'CJ-17,493' (compound (+)-**1**), was synthesized stereoselectively using a kinetic resolution by lipase-PS as a key step. Compound (+)-**1** displayed high and selective affinity (K_i = 0.2 nM) for the human NK_1 receptor in IM-9 cells, potent activity in the [Sar^9, $Met(O_2)^{11}$]SP-induced gerbil tapping model (ED_{50} = 0.04 mg/kg, sc) and in the ferret cisplatin (10 mg/kg, ip)-induced anti-emetic activity model (vomiting: ED_{90} = 0.07 mg/kg, sc), all levels of activity comparable with those of CP-122,721. In addition, compound (+)-1 exhibited linear pharmacokinetics rather than the super dose-proportionality of CP-122,721 and this result provides a potential solution for the clinical issue observed with CP-122,721.

1. Introduction

The neurokinin-1 (NK_1) receptor is a member of the seven-transmembrane G-protein coupled family of receptors and is associated with sensory neurons in the peripheral and specific areas of the central nervous system. The neuropeptide 'Substance P' and its human neurokinin-1 (hNK_1) receptor have been associated with various biological disorders such as anxiety, depression, emesis, asthma and inflammatory bowel disease (IBD).[1] Recently, two selective NK_1 receptor antagonists have been approved: aprepitant (Merck; Emend®),[2] as part of a combination therapy with a corticosteroid and a 5-HT_3 receptor antagonist for the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV) in humans; and maropitant (Pfizer; Cerenia®)[3] as a veterinary medication to prevent and treat acute vomiting in dogs (Fig. 1).

The Pfizer compounds CP-99,994 and CP-96,345 were the first non-peptide neurokinin-1 receptor antagonists to be disclosed (Fig. 1).[4] Using the piperidine derivatives CP-99,994 and GR-203040 (Glaxo), it was soon demonstrated that NK_1 antagonism results in the inhibition of cisplatin-induced emesis in humans and animals and that the site of action is a part of the central nervous system.[5] Subsequently, CP-122,721, derived from CP-99,994 by the introduction of a trifluoromethoxy group, demonstrated anti-emetic activity at one-tenth the effective dose of CP-99,994. However, CP-122,721 exhibited strong competitive inhibition (K_i = 0.02 μM against metabolic oxidation of bufuralol) of the CYP2D6 enzyme. Furthermore, a comparison of half-lives of CP-122,721 upon exposure to CYP2D6-deficient human liver microsomes (HLM) with or without addition of exogenous CYP2D6 enzyme (hereinafter called the CYP2D6 +/− assay) revealed that the half-life of the compound decreased more than 3-fold upon addition of exogenous CYP2D6. The first step of the major metabolic pathway for CP-122,721 was identified as the CYP2D6 catalyzed O-demethylation on the 2-methoxy moiety.[6]

Based on the prototype NK_1 receptor antagonist 'CP-122,721', we initiated a program aimed at lowering the effective dose in the anti-emetic model and addressing the high affinity of CP-122,721 for the CYP2D6 enzyme. In order to address these major issues, our initial approach focused on the modification at the 5 (or 4, 5)-position(s) of the benzylamine moiety by introduction of fluorine atoms as in the 5-trifluoromethoxy group of

* Corresponding author.
E-mail address: yuji.shishido@raqualia.com (Y. Shishido).
† Present address: Pfizer Global Research & Development, La Jolla Laboratories, 10614 Science Center Drive, San Diego, CA 92121, USA.
‡ Present address: RaQualia Pharma Inc. 5-2 Taketoyo, Aichi, 470-2341, Japan.

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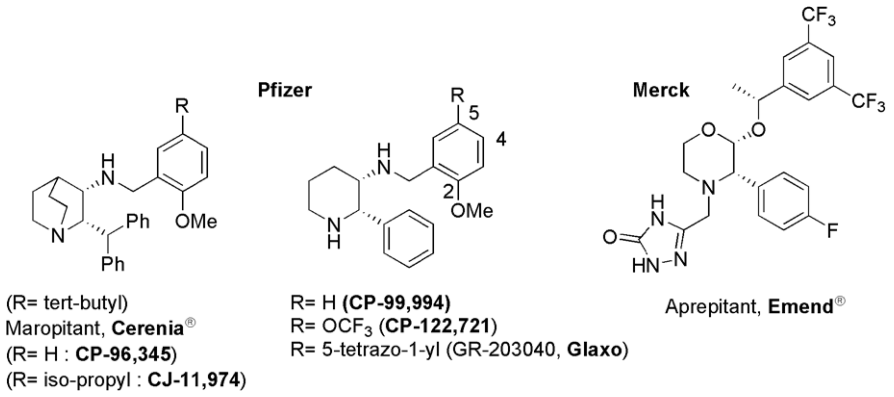


Figure 1. NK_1 receptor antagonists as anti-emetic drugs for humans and animals (dog).

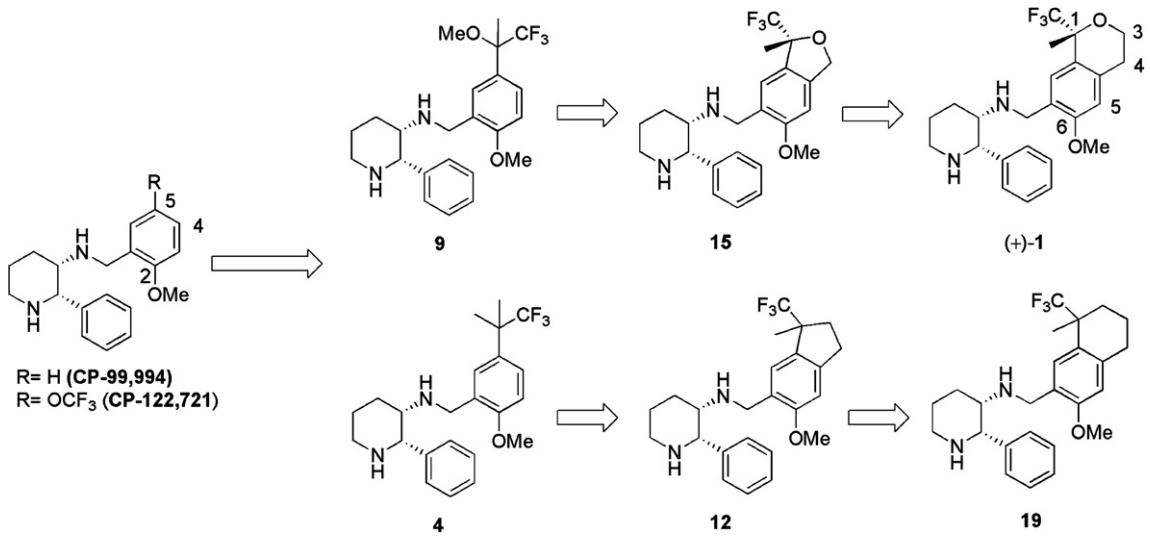


Figure 2. Approach to compound (+)-**1** starting from CP-99,994 and CP-122,721.

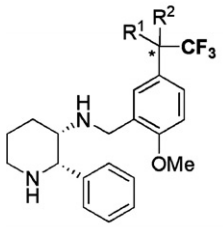
CP-122,721, while retaining the 2-methoxy moiety which plays an important role in the antagonistic activity (Fig. 2). As a result, the highly potent and metabolically stable compound (+)-**1** was found among a series of synthesized 4,5-fused derivatives containing an oxygen atom. (+)-**1** showed anti-emetic activity comparable to that of CP-122,721 in the gerbil tapping assay, known to be connected to the central NK_1 receptor site, and in the cisplatin-induced ferret emesis and vomiting model. In addition, compound **21** (5:1 diastereomer mixture of compound (+)-**1**) displayed a 6-fold lower affinity for the CYP2D6 enzyme and a 3-fold improvement in the CPY2D6 +/− assay, comparing favorably to the high affinity for CYP2D6 which had identified as a major issue for CP-122,721. This report summarizes our SAR pursuit from CP-122,721 to compound (+)-**1**, a compound with enhanced safety potential which may prove useful as an anti-emetic drug, and outlines the first synthetic method of optically active (+)-**1** using a kinetic resolution by lipase-PS.[7]

2. Discussion and results

The results of our modifications around the 5 (or 4, 5)-position(s) of the benzylamine moiety are summarized in SAR Tables 1–3, focusing in turn on non-cyclic analogs (Table 1), 5-ring membered analogs (Table 2), and 6-ring membered analogs (Table 3). The conversion of the trifluoromethoxy group of CP-122,721 to a fluoroalkyl moiety led to an improvement in the affinity for IM-9 cells and in the specific interaction to CYP2D6, while conserving the hNK_1 receptor antagonistic activity in vitro (Table 1). In particular, the introduction of geminal-methyl groups or of fluorine groups (F, CF_3) at the 5-benzylic position of CP-122,721 (compounds **4**, **6** and **7**) resulted in moderate inhibition of the metabolic oxidation of bufuralol at 5 μM substrate, while retaining the intrinsic activity in the gerbil tapping assay as shown in Table 1. Furthermore, the 5- and 6-membered cyclized trifluoromethyl derivatives (**10**–**13**, **15**–**17**, and **21**) showed comparable to or improved activity over CP-122,721 in the gerbil tapping assay, while the introduction of an oxygen atom in the 5- and 6-membered derivatives (**15** and **21**) resulted in a significant increase in inhibitory activity (ED_{90} < 0.1 mg/kg, sc) in the cisplatin-induced emesis assay, as shown in Tables 2 and 3. Compound **21** was evaluated as a 5:1 *R*/*S* mixture at the 6-position. The lower activity in vivo of these in vitro potent compounds (in the binding assay) can be explained by a lower CNS penetration, as evidenced by the ratio of free fraction concentration in brain (or CSF) versus plasma.

CP-122,721 demonstrated super dose-proportional kinetics among poor metabolizers (PMs) of CYP2D6 in a human PK study of healthy male subjects,[6] while the quinuclidine compound CJ-11,974 showed dose-proportional pharmacokinetics in clinical data. An in vitro assay of these compounds confirmed the difference in K_m values for CP-122,721 and CJ-11,974 in human liver microsomes.[8] We therefore hypothesized that it is possible to pre-

Table 1
Non-cyclic analogs based on CP-122,721

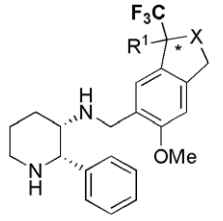


Non-cyclic analogs

$R^1 = R^2 = H$ (**2**)
$R^1 = Me, R^2 = H$ (**3**): R/S = 1:1
$R^1 = R^2 = Me$ (**4**)
$R^1 = OMe, R^2 = H$ (**5**): R/S = 1:1
$R^1 = F, R^2 = H$ (**6**): R/S = 1:1
$R^1 = CF3, R^2 = H$ (**7**)
$R^1 = F, R^2 = Me$ (**8**): R/S = 1:1
$R^1 = OMe, R^2 = Me$ (**9**): R/S = 1:1

Compound	IM-9 binding	Affinity to CYP2D6	Gerbil tapping assay	Cisplatin-induced emesis in ferrets	
	(IC_{50}, nM)	(% inh. at 5 μM)	ED_{50} (mg/kg, sc) or % inhibition (dose, mg/kg)	ED_{100} (mg/kg, sc)	ED_{90} (mg/kg, sc)
CP-122,721	0.4	95.6	0.28 ($n = 3$)	⩾0.3	0.09
2	0.9	95.9	0.03	0.1	<0.1
3	0.4	65.9	0.82	⩾1.0	0.3
4	0.2	54.8	0.12	1	0.21
5	<0.1	92.9	67% (1)	NT	NT
6	0.7	46.6	0.16	97% inh. (0.1 mg/kg)	
7	<0.1	43.1	0.33	0.90	0.48
8	<0.1	NT	57% (1), 30% (0.1)	NT	NT
9	<0.1	62.6	55% (1), 63% (0.1)	15% inh. (0.1 mg/kg)	

Table 2
5-Membered ring analogs based on CP-122,721



5-rings membered analogs

$R^1 = H, X = CH_2$ (**10**): R/S = 1:1
$R^1 = H, X = CH_2$ (**11**): R/S = 36:1
$R^1 = Me, X = CH_2$ (**12**): R/S = 1:1
$R^1 = H, X = O$ (**13**): R/S = 5:4
$R^1 = Me, X = O$ (**14**): R/S =1:9
$R^1 = Me, X = O$ (**15**): R/S =49:1
$R^1 = Me, X = O$ (**16**): R/S = 1:1

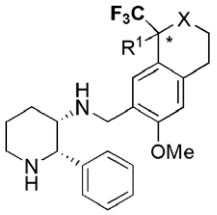
Compound	IM-9 binding	Affinity to CYP2D6	Gerbil tapping assay	Cisplatin-induced emesis in ferrets	
	(IC_{50}, nM)	(% inh. at 5 μM)	ED_{50} (mg/kg, sc) or % inhibition (dose, mg/kg)	ED_{100} (mg/kg, sc)	ED_{90} (mg/kg, sc)
10	0.9	74.2	0.11	1	0.12
11	0.4	75.9	88 (1), 79 (0.1)	100% inh. (1 mg/kg)	
12	<0.1	NT	80 (1), 68 (0.1)	NT	NT
13	<0.1	66.4	84 (0.1)	99% inh. (0.1 mg/kg)	
14	<0.1	41.8	69 (1), 15 (0.1)	NT	NT
15	<0.1	73	77 (0.1)	0.3	0.05
16	0.16	81	94 (1), 87 (0.1)	99% inh. (0.3 mg/kg)	

dict the kinetic behavior of compounds in this series by their K_i values and the ratio of their half-life in the CYP2D6 +/− assay. Thus a new screening sequence was devised, consisting of an inhibitory assay of the 1′-hydroxylation of bufuralol at 5 μM concentration of substrates, followed by a full inhibition assay to determine the inhibition constant (K_i) of the compound for the inhibition of bufuralol by CYP2D6 instead of the cumbersome measurement of K_m values. In addition to the K_i value, the $T_{1/2}$ ratio in HLM in the CPY2D6 +/− assay or HLM in the quinidine +/− was also determined.[9]

Compounds with potent anti-emetic efficacy were selected and compared for their effect on CYP2D6, as shown in Table 4. Compounds **2**, **3**, **15** and **21** showed high specific interaction (>60% inhibition at 5 μM, $K_i < 1.0$ μM) with the CYP2D6 enzyme in the 50% inhibition assay using bufuralol at 5 μM concentration of substrates, and low K_i values in the bufuralol metabolism assay by human CYP2D6, while tetrahydronaphthalene derivative **19** (a C-analog of compound **21**) showed a definite improvement over **21**. Among the compounds with inhibition constants more than 25 times greater than the K_i value for CP-122,721 ($K_i > 0.5$ μM vs 0.02 μM) in Table 4, compound **11** and **17** demonstrated hypermetabolism in CYP2D6 +/− assay. A possible explanation for the 10-fold jump for **11** in the CYP2D6 +/− assay is a rapid metabolite formation despite its low affinity for the CYP2D6 enzyme.

Finally, in order to study the relationship between pharmacological activity in vivo and affinity to CYP2D6 in vitro, the 5- and 6-membered derivatives (**15** and **21**) were selected. Since the respective K_i values of 0.66 and 0.12 μM for **15** and **21** indicate a 6- to 30-fold lower affinity compared to the K_i value (0.02 μM) for CP-122,721, we predicted that compound **21** would not demonstrate appreciable super dose-proportionality in humans at pharmacologically relevant doses. The half-life ratio in the CPY2D6 +/− of compound **21** is also 3-fold lower than the corresponding ratio (6.00) for CP-122,721. Furthermore, although the profile of compound **21** is comparable to that of the 5-membered-ring compound **15**, the pharmacokinetics of compound **21** showed a 2- to 4-fold superiority in AUC, C_{max} and half-life (dog, 5 mg/kg, po). Thus our effort shifted to the development of an efficient synthesis of optically active (+)-**1**.

Table 3
6-Membered ring analogs based on CP-122,721



6-rings membered analogs

R^1 = H, X = CH_2 (**17**): R/S = 10:1
R^1 = H, X = CH_2 (**18**)): R/S = 1: 5
R^1 = Me, X = CH_2 (**19**): R/S = 3:1
R^1 = Me, X = CH_2 (**20**): R/S = 1: 5
R^1 = Me, X = CH_2 (**21**): R/S = 5: 1
R^1 = Me, X = CH_2 (**22**): R/S = 1: 3

Compound	IM-9 Binding	Affinity to CYP2D6	Gerbil tapping assay	Cisplatin-induced emesis in ferrets (vomiting)	
	(IC_{50}, nM)	(% inh. at 5 μM)	ED_{50} (mg/kg, sc) or % inhibition (dose, mg/kg)	ED_{100} (mg/kg, sc)	ED_{90} (mg/kg, sc)
17	0.5	76.5	77% (1), 55% (0.1)	1	0.17
18	<0.1	85.4	4% (1)	NT	NT
19	0.21	42	85% (1), 21% (0.1)	NT	NT
20	<0.1	42	65% (1), 0% (0.1)	NT	NT
21	<0.1	90	91% (1), 86% (0.1)	97% inh. (0.1 mg/kg)	
22	0.34	90	87% (1), 26% (0.1)	NT	NT
(+)-**1**	0.2*	NT	0.043		0.07

*K_i value.

Table 4
Evaluation of bufuralol turnover (K_i) and CYP2D6 +/− assay among key compounds

Compound	In vitro			In vivo	
	Affinity to CYP2D6	CYP2D6 +/−[b]	Bufuralol turnover by human CYP2D6	Cisplatin-induced emesis (vomiting)	
	(% inh. at 5 μM)		(K_i μM)	ED_{90} (mg/kg, sc)	ED_{100} (mg/kg, sc)
CP-122,721	95.6	6.0–6.20	0.02	0.09	⩾0.3
2	95.9	4.25	0.07	0.09	0.1
3	65.9	2.2/1.0[a]	0.84	0.3	⩾1.0
4	54.8	1.16	1.34	0.17	1
6	46.6	1.83	cal. 1.86[c]	97% inh. (0.3 mg/kg)	
7	43.1	2.0	2.1	0.48	0.9
11	75.9	10.6	cal. 0.52	NT	NT
15	73	2.1	0.66	0.05	0.3
17	76.5	7.35	cal. 0.5	NT	NT
19	42.0	1.58	cal. 2.24	NT	NT
21	90	1.8	0.12	97% inh. (0.1 mg/kg)	
CJ-11,974	64.1	1.8–3.80	0.42–0.57	2.1	

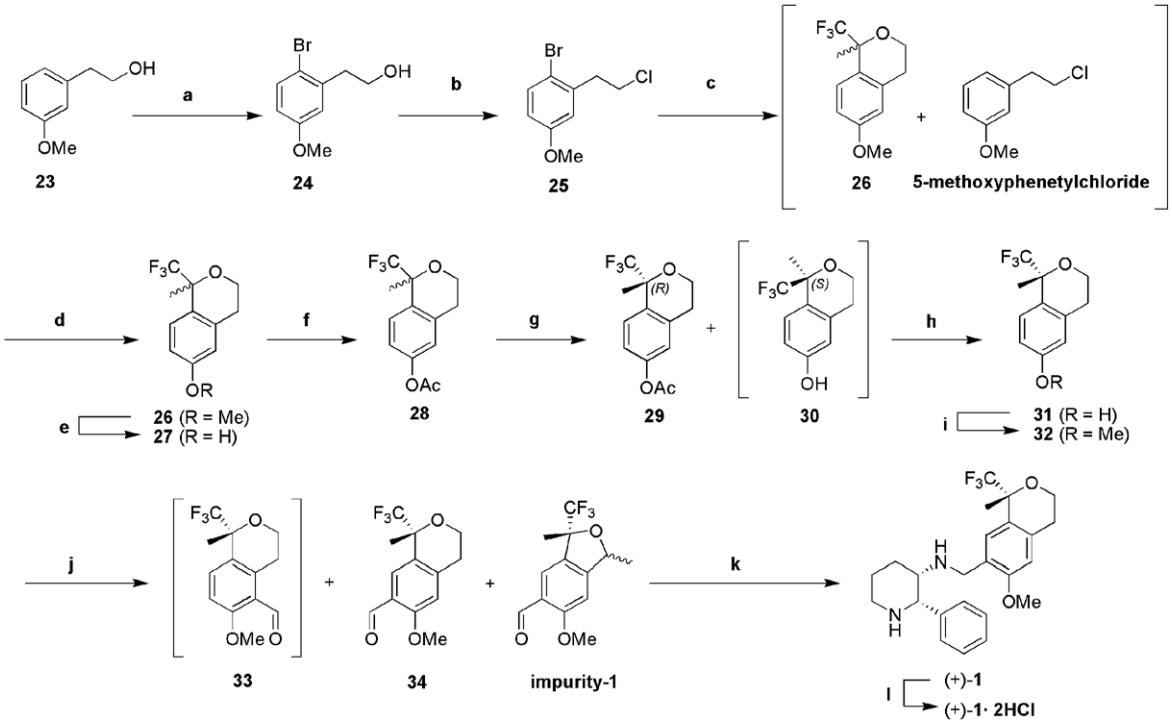
[a] Quinidine +/− assay.
[b] CYP2D6 +/− means the ratio of half-lives between CYP2D6-deficient HLM and CYP2D6-deficient HLM upon addition of exogenous CYP2D6.
[c] Calculated K_i value was estimated from the one point measurement at 5 μM substrate concentration: % inhibition (5 μM) = $5/(5 + 3.08K_i) \times 100$.

Finally, the important K_m value for synthesized compound (+)-**1** was measured directly based on the results for the affinity to CYP2D6 enzyme for compound **21** (active-enriched 5:1 diastereomer mixture). While the major metabolite of CP-122,721 is O-demethylation in human liver microsomes, the metabolic routes for CJ-17,493 are 4-hydroxylation on the benzylamine moiety (not demethylation in 6-position as in the metabolism of CP-122,721) and N-dealkylation on the 3-carbon atom between the benzylic NH moiety and the piperidine skeleton. The K_m values in human liver microsomes were 16.6 and 2.3 μM for hydroxylation and N-dealkylation, that is, 10- to 70-fold higher than the K_m of CP-122,721 in human liver microsomes. This K_m ratio between CP-122,721 and CJ-17,493 was considered to be sufficient to predict a lack of super-proportional kinetics. In fact, the FIH study of CJ-17,493 confirmed the dose-proportionality in a PK study at doses ranging from 30 to 380 mg (individual subjects dose-adjusted $AUC_{(0-inf)s}$ were similar) and no differences between CYP2D6 EMs (n = 20) and PMs (n = 4).

3. Chemistry

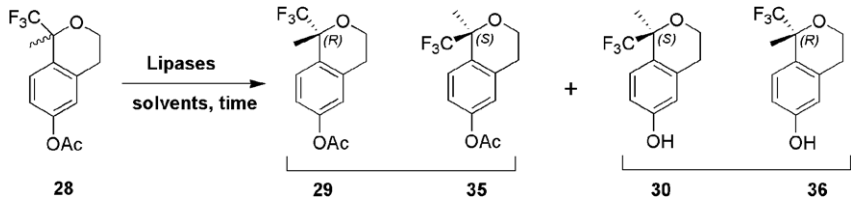
Regioselective mono-bromination of the commercially available **23** was followed by chlorination of the hydroxyl group (Scheme 1). The conversion of **25** to 3,4-dihydro-1*H*-isochromen derivative **26** was then effected by selective lithiation at the 4-position using *n*-butyl lithium at −100 °C followed by the addition of 1,1,1-trifluoroacetone, affording a 3.9:1 mixture of **26** and 3-methoxyphenetyl chloride. The by-product was converted to 1-methoxy-3-vinylbenzene using DBU, after which distillation of the crude product gave pure **26** in 77% yield. After conversion of **26** to **28**, compound **28** was subjected to kinetic resolution using lipase-PS, leading to the optically active *O*-acetyl derivative **29** with an enantiomeric excess of 94%.[10] Compound **29** was converted to the 1-methoxy derivative in two steps to furnish **32**, which was formylated regioselectively at the 7-position using a combination of aluminum(III) chloride and dichloromethyl *n*-butyl ether (ratio in 5-/7-position = 5.3:1, isolated yield 54%) (Table 7, entry 5). The reductive amination of **34** with (2*S*,3*S*)-3-amino-2-phenylpiperidine led to compound **1**, which was treated with 10% hydrochloric methanol to give (+)-**1**·dihydrochloride. The optical purity of the obtained (+)-**1**·dihydrochloride was then increased to >99% de by two successive recrystallizations.

The following Table 5 summarizes the screening of lipases for the kinetic resolution of racemic compound **28**.[11] The lipase PS series of standard and immobilized reagents produced the optically active acetate **29** in more than 60% enantiomer excess (ee). Thus the inexpensive standard lipase PS was selected, and we proceeded to study the limited solvent choices, as shown in Table 6. Although the com-



Scheme 1. Synthesis of compound (+)-**1** (CJ-17,493). Reagents and conditions: (a) bromine, pyridine (1.1 equiv), CH_2Cl_2 (100%); (b) CCl_4, triphenylphosphine, 85 °C, 75%; (c) *n*-butyllithium, THF/hexane (3:1), −100 °C then 1,1,1-trifluoroacetone, −70 °C–rt; (d) DBU, toluene, reflux, 77% from **25**; (e) 48% HBr aq AcOH, reflux, 100%; (f) AcCl, triethylamine, THF, rt, 89%; (g) lipase-PS, 10% *sec*-butanol/hexane, rt, 24 h, 45%; (h) K_2CO_3, methanol/H_2O (2.5:1), rt, 93%, 94% ee; (i) MeI, 60% NaH, DMF, rt, 98%; (j) dichloromethyl *n*-butyl ether, $AlCl_3$, CH_2Cl_2, 74%; (k) (2*S*,3*S*)-3-amino-2-phenylpiperidine, $NaBH(OAc)_3$, CH_2Cl_2, rt, 24 h, 100% (crude yield); (l) 10% HCl/methanol, methanol, 78%.

Table 5
Lipase kinetic resolution: lipase screening[a]



Entry	Lipases	Time (h)	Conversion (%)	ee (acetate **29**)	ee (phenol **30**)
1	Lipase PS	2	51.3	69.6	67.4
2	Lipase AY	1.5	52.6	3.5	2.3
3	Lipase AH	13	41.5	50.4	84.0
4	CHE	13	42.4	23.9	34.2
5	LPL-A (TOYOBO)	13	32	30.7	64.9
6	Steapsin (TCI)	4	54.3	2.5	1

[a] **28** (50 mg) and lipases (50 mg)/IPE-saturated water (2 mL)/rt.

Table 6
Lipase PS kinetic resolution: solvent screening[a]

Entry	Solvents	Time (h)	Conversion (%)	ee (**29**)	ee (**30**)
1	Phosphate buffer pH 7.0	1	32.9	33	63.5
2	20% Acetone-phosphate buffer pH 7.0	0.5	55.3	100	74.3
3	20% *t*-BuOH/phosphate buffer pH 7.0	0.5	65.7	100	50.4
4	10% *sec*-BuOH/hexane	13	41.1	61.8	100
5[b]	10% *sec*-BuOH/hexane	23	51.0	94[c]	83
6	10% MeOH-IPE	20	46.2	51.1	63.4
7	IPE saturated with H_2O	13	40.5	54.9	100

[a] **28** (30 mg) and lipase-PS (30 mg)/solvents (2 mL)/rt.
[b] **28** (38 g) and lipase-PS (35 g)/solvents (1.3 L).
[c] Ref. [10b].

binations of 10% alcohols with hexane only moderately increased the enantiomeric excess (ee) of compound **29**, this combination of solvents allowed a better control of the rate of the kinetic resolution than the combination of alcohols and buffer solution. The conversion rate (%) at ambient temperature was carefully investigated on a 15 g scale for **28** and the 50% conversion time was determined to be ca. 20–23 h. Finally, a combination of lipase-PS using 10% *sec*-butanol/hexane as the solvent gave the optical acetate **29** in 94% ee (51% conversion) on multigram scale: **28** (38.4 g)/lipase PS (35 g)/10% *sec*-BuOH/hexane (1.3 L)/rt 23 h (Table 6, entry 5).

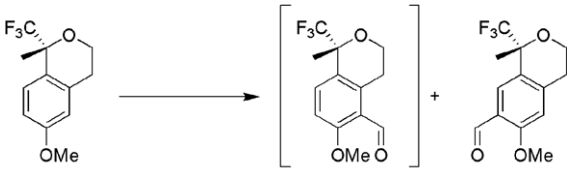
Another issue in the synthesis of compound (+)-**1** was the need to improve the regioselectivity in the formylation of compound **32** (Table 7). A **34**/**33** ratio of 1.5:1 was obtained using titanium chloride and dichloromethyl methyl ether,[12] compared with a 10–15:1 ratio when this combination of reagents was used to produce the 5-mem-

bered analog **40** in scheme 2. After testing various reagent combinations, we found that the combination of aluminum chloride (2.3 equiv) and dichloromethyl *n*-butyl ether (2.0 equiv) in dichloromethane with dry ice/methanol cooling increased the regioselectivity of the formylation to a ratio of 5–6: 1 (Table 7, entry 5).

Compound **15** was also synthesized according to the same sequence as compound **1** (Scheme 2). Cyclization of **38** to **39** afforded a 13:1 mixture of **38** and **37**, which was treated with glycine[13] to give a single compound **38** in 69% yield. The subsequent formylation of **39** using titanium chloride/dichloromethyl methyl ether gave 6-formyl derivative **40** (82% yield) in a ratio of 15:1, as compared to the 5.3:1 ratio obtained in the formylation of compound **32** under the same conditions. The reductive amination of **40** with (2*S*,3*S*)-3-amino-2-phenylpiperidine led to compound **15** as a 1:1 diastereomer mixture, which was treated with 10% hydrochloric methanol to give **15**·dihydrochloride. Finally, triple recrystallization of **15**·dihydrochloride allowed the isolation of the enriched 1*R* diastereomer as a 49:1 mixture without the need for any kinetic resolution of an intermediate.

For the synthesis of the carbocyclic analogs **12** and **19**, the following general protocol was used (Scheme 3). The ketones (**42** and **43**) were transformed into the trifluoromethyl tertiary alcohols (**44** and **45**) using Ruppert's reagent ($TMS\text{-}CF_3$) followed by acidic hydrolysis.[14] Next, chlorination of the cyclic tertiary alcohols using titanium(IV) chloride (2 equiv) at −78 °C followed by addition of dimethylzinc (2 equiv), all in one pot, afforded the desired products (**48** and **49**) in high yield.[15] These were converted to the desired formyl derivatives **52** and **53** using titanium(IV) chloride and dichloromethyl methyl ether as the first-line choice, the two compounds giving different regioselectivity results. The reductive amination of these formyl derivatives with (2*S*,3*S*)-*tert*-butyl 3-amino-2-phenylpiperidine-1-carboxylate led to compounds **12** and **19**, which were treated with 10% hydrochloric methanol to give **12**·dihydrochloride and **19**·dihydrochloride, respectively.

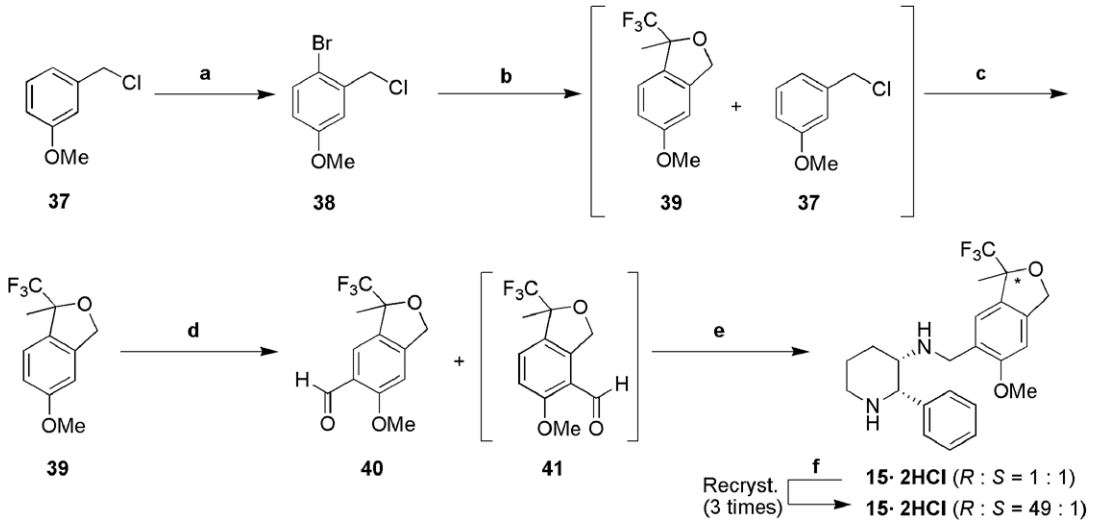
Table 7
Regioselective formylation of compound **32**



32 **33** **34**

Entry	Reagent 1	Reagent 2	Time/temp (°C)	Solvent	Regioselectivity	
					34	**33**
1	$TiCl_4$ (2.2)	Cl_2CHOMe (2.0)	1 h/−78	CH_2Cl_2	1.6–1.8	1
2	$TiCl_2$ (O-*i*-Pr)$_2$ (2.2)	Cl_2CHOMe (2.0)	4 h/−78–rt	CH_2Cl_2	NR	
3	$TiCl_4$ (2.2)	Cl_2CHO-*n*-Bu (2.0)	1 h/−78	CH_2Cl_2	1.6–1.8	1
4	$AlCl_3$ (2.2)	Cl_2CHOMe (2.0)	1 h/−78	CH_2Cl_2	2.3	1
5	$AlCl_3$ (2.3)	Cl_2CHO-*n*-Bu (2.0)	1 h/−78	CH_2Cl_2	4.7–5.5	1
6	$POCl_3$ (5.0)		6h/120–160	DMF	NR	
7	HMTA (6.0)		15 h, reflux	CF_3CO_2H	5	1

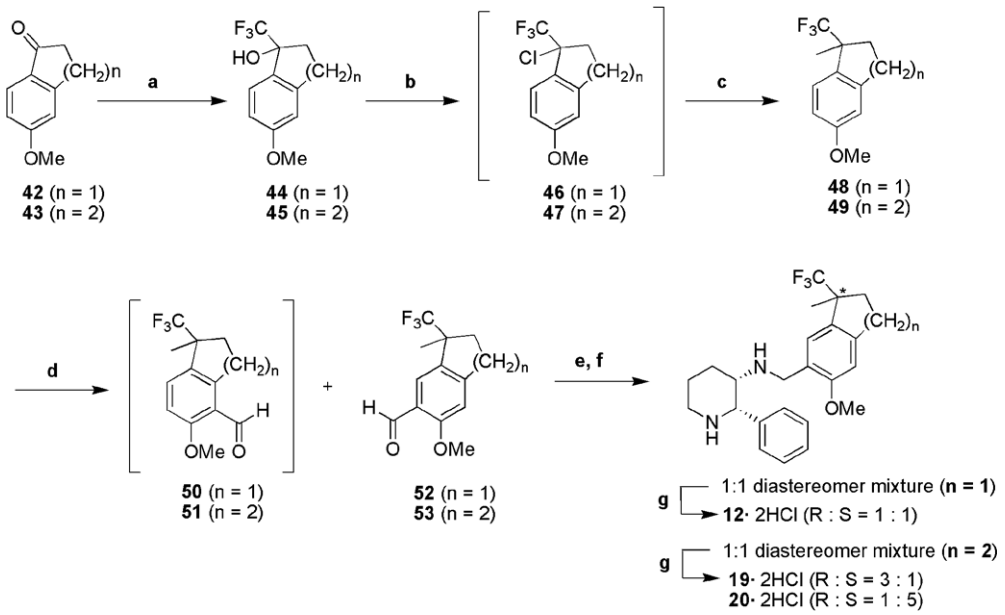
The parenthetic number means the mol ratio (equiv.) of reagent against **32**.



37 **38** **39** **37**

39 **40** **41**

Scheme 2. Synthesis of compound **15**. Reagents and conditions: (a) bromine, pyridine (1.2 equiv)/CH_2Cl_2, 0 °C–rt, 18 h; (b) *n*-butyllithium, THF/hexane (3:1), −100 °C then 1,1,1-trifluoroacetone, −70 to −30 °C (**39**/**37** = 13.2:1); (c) glycine, KOH, EtOH/H_2O (3:2), reflux, 2 h then distillation (bp 94–96 °C/1.5 mm Hg), 69% from **37**; (d) dichloromethyl methyl ether, $TiCl_4$, CH_2Cl_2, 82% (**40**/**41** = 15:1); (e) (2*S*,3*S*)-3-amino-2-phenylpiperidine, $NaBH(OAc)_3$, CH_2Cl_2, rt, 24 h, 100% (crude yield); (f) 10% HCl/methanol, ethyl acetate, 21% after three times recrystallization.



Scheme 3. Synthesis of compound **12**, **19** and **20** (indane and tetraline derivatives). Reagents and conditons: (a) $TMSCF_3$, TBAF (cat.), THF, rt, then dil HCl aq; (b) $TiCl_4$ (2.2 equiv), CH_2Cl_2, −78 °C; (c) 1.0 M Me_2Zn in hexane solution (2.0 equiv) (n = 1:87%; n = 2:92%); (d) $TiCl_4$ (2.2 equiv), Cl_2CHOMe (2.2 equiv), CH_2Cl_2, 0 °C (n = 1:85%; n = 2: 40%); (e) (2*S*,3*S*)-*tert*-butyl 3-amino-2-phenylpiperidine-1-carboxylate, $NaBH(OAc)_3$, CH_2Cl_2, rt, 24 h; (f) 2 M HCl aq/ethyl acetate (n = 1:86%; n = 2:94% from **52** and **53**); (g) 10% HCl/methanol.

4. Evaluation of compound(+)-1 (CJ-17,493)

4.1. In vitro data of compound (+)-1 (CJ-17,493)

Compound (+)-**1** binds with high affinity (K_i = 0.2 nM) to the NK_1 receptor labeled by [^{3}H]SP in the IM-9 human lymphoblastoma cell line. (The IC_{50} values in human IM-9 cell were <0.1, 0.34 and 0.79 nM for compound (+)-**1**, the 1*S* epimer of compound (+)-**1** and substance P, respectively). On the other hand, it possesses moderate affinity to the verapamil binding site at the L-type Ca^{2+} channel labeled by [^{3}H]desmethoxyverapamil (IC_{50} = 164 nM) and the sodium channel site 2 labeled by [^{3}H]batrachotoxinin (IC_{50} = 48 nM). The functional activity of compound (+)-**1** against the sodium channel was examined by whole-cell patch clamp using CHO-CNaIIA cells stably transfected with the rat Na^+-channel type IIA-subunit. The compound had no significant activity against the sodium channel at up to 1 μM concentration (13% inh.), and 88% inhibition was observed at a concentration of 10 μM.

4.2. Pharmacology of compound (+)-1 (CJ-17,493)

The activity of optically active compound (+)-**1** in the CNS was assessed by the intracelebroventricular injection of a stable NK_1 receptor agonist, that is, the gerbil [Sar^9, $Met(O_2)^{11}$]SP-induced tapping model. Compound (+)-**1**, dosed sc 30 min before the agonist injection, inhibited the tapping response in a dose-dependent manner. The ED_{50} was 0.043 ± 0.003 mg/kg, sc (mean ± SEM, n = 3). Capsaicin elicits plasma extravasation in a variety of tissues through the release of endogenous SP from sensory afferents. In the guinea pig ureter, intraperitoneally injected capsaicin (30 μM) produces a plasma protein leakage which is likely to be mediated by activation of the peripheral NK_1 receptor. In this model, (+)-**1** showed dose-dependent inhibition with an ED_{50} of 0.005 mg/kg, po. NK_1 receptor antagonists have been shown to block retching and vomiting responses induced by a wide range of centrally and peripherally acting emetogens in the ferret. Intraperitoneal injection of cisplatin (10 mg/kg ip), a chemotherapeutic agent, elicits acute emetic episodes such as retching, vomiting and gagging in the ferret. (+)-**1**, given sc 30 min before cisplatin, inhibited the emesis response in a dose-dependent manner with ED_{90} values of 0.03 and 0.07 mg/kg, sc for retching and vomiting/gagging, respectively (Fig. 3).

4.3. PK profile of compound (+)-1 (CJ-17,493)

In rats, the systemic plasma clearance (CL), volume of distribution at steady-state (V_{dss}), and half-life ($T_{1/2}$) of optically active (+)-**1** (0.3 mg/kg, iv) were 0.66 L/h/kg, 7 L/kg, and 8.8 h, respectively. After oral administration (1–30 mg/kg), exposure to compound (+)-**1** increased with dose and maximum drug concentrations (C_{max}) occurred within 0.5 h post dose. Oral bioavailability of optically active (+)-**1** administered as the hydrochloride salt dissolved in water was lower than 1% at the tested doses. In dogs, optically active (+)-**1** at 1 mg/kg, iv gave CL, V_{dss}, and $T_{1/2}$ of 1.9 L/h/kg, 11 L/kg, and 3.8 h, respectively. Exposure in dogs after oral administration was significantly higher than that in rats and the oral bioavailability at 5 mg/kg, administered p.o. as a water solution was 9.8%. Finally, the FIH study of compound (+)-**1** confirmed the dose-proportionality in PK from 30 to 380 mg doses (individual subjects dose-adjusted $AUC_{(0-inf)}$s were similar) and no differences between CYP2D6 EMs (n = 20) and PMs (n = 4).

5. Conclusion

As a result of our search for a new anti-emetic drug based on prototype 'CP-122,721', we have found a compound with high potency and selectivity (K_i = 0.2 nM) for the NK_1 receptor in IM-9 cells and potent anti-emetic activity in the cisplatin (10 mg/kg, ip)-induced anti-emetic ferret assay (vomiting: ED_{90} = 0.07 mg/kg, sc) comparable with CP-122,721, while lowering the affinity for the CYP2D6 enzyme. Thus compound (+)-**1**′ CJ-17,493′ was identified as an anti-emetic candidate that addresses the PK issue of CP-122,721 in poor metabolizers (PMs).

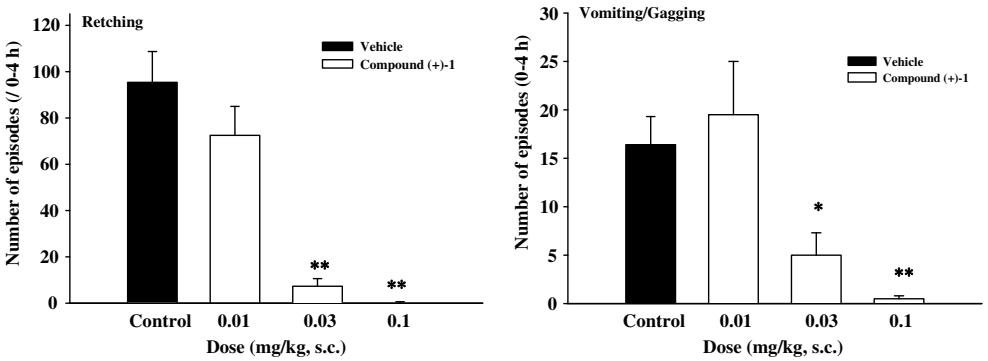


Figure 3. Activity of optically active (+)-**1** on retching and vomiting/gagging induced by cisplatin (10 mg/kg, ip) in ferrets. $^{*}P < 0.05$ and $^{**}P < 0.01$ versus control by Student's-test. Data are mean ± SEM, $n = 4–5$.

6. Experimental

6.1. General

Proton nuclear magnetic resonance (^{1}H NMR) spectra were measured on a JEOL FX270 by using deuterochloroform or dimethylsulfoxide-d_6, and proton chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane as an internal standard. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), m (multiplet), and br s (broad singlet). Gas chromatography analysis was determined using Column: J&DB-1 30 m × 0.25 mm (Film thickness 0.25 mm), Carrier gas: He, 20 psi (138 kPa), Injector: split (ca. 100:1), $T = 250$ °C, Detector: FID: $T = 250$ °C, Oven 170 °C (10 min). The electron spray ionization mass spectra (ESI-MS) were obtained with Quattro-II triplequadrupole mass spectrometer (micromass, UK). Melting points were determined on a Yanagimoto micro-melting-point apparatus and were uncorrected. The results of elemental analyses were within ±0.4% of the theoretical values and reported only with symbols. Reactions were followed by TLC on Silica-gel 60 F_{254} precoated TLC plates (E. Merck) or NH_2 HPTLC F_{254}s plates (E. Merck). Chromatographic separations were carried out on silica-gel (E. Merck, 70–230 mesh) using the indicated eluents. The color fixing agent of TLC plates was used Dragendorf's reagent in the case of the basic compounds.

6.1.1. (2*S*,3*S*)-3-[(1*R*)-6-Methoxy-1-methyl-1-trifluoromethylisochroman-7-yl]methylamino-2-phenylpiperidine ((+)-1)·dihydrochloride

6.1.1.1. 2-Bromo-5-methoxyphenethyl alcohol (24). To a stirred mixture of 3-methoxyphenethyl alcohol (50.0 g, 0.33 mol) and pyridine (29 mL, 0.36 mol) in anhydrous dichloromethane (560 mL) was added bromine (20 mL, 0.39 mol) dropwise under nitrogen at 0 °C. The organic solution was stirred at ambient temperature for 2 h. To the mixture was added additional bromine (0.85 mL, 17.0 mmol) at the same temperature to complete the reaction and the solution was stirred for 1.5 h. The resultant mixture was quenched by addition of 10% aqueous sodium bisulfite (100 mL), and extracted with dichloromethane. The organic extracts were washed with brine (100 mL), dried over magnesium sulfate, and concentrated to give crude product **24** (76.0 g, quant.).

^{1}H NMR ($CDCl_3$): δ 7.43 (d, $J = 8.8$ Hz, 1H), 6.83 (d, $J = 3.3$ Hz, 1H), 6.67 (dd, $J = 8.8$, 3.3 Hz, 1H), 3.91–3.81 (m, 2H), 3.78 (s, 3H), 2.99 (t, $J = 6.6$ Hz, 2H). $^{*}OH$ (1 proton, not observed) GC retention time: 5.98 min (compound **24**), 3.05 min (3-methoxyphenethyl alcohol).

6.1.1.2. 2-Bromo-5-methoxyphenethyl chloride (25). To a stirred solution of compound **24** (150.0 g, 0.66 mol) in carbon tetrachloride (940 mL) was added triphenylphosphine (190.0 g, 0.72 mol) portionwise at ambient temperature and the organic solution was stirred at 84 °C for 4 h. After cooling the mixture to room temperature, additional triphenylphosphine (8.5 g, 32.0 mmol) was added to the solution and the reaction mixture was stirred at 84 °C for 10 h. The reaction mixture was filtered through Celite, and the filter cake was washed with carbon tetrachloride (5× 50 mL). The combined filtrate and washings were washed with saturated aqueous sodium bicarbonate (100 mL), brine (100 mL), dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography (Silica-gel, 12 × 9 cm, 2–3% ethyl acetate in hexane) to afford the compound **25** (281.0 g, 85%), which was distilled (bp 133 °C/1.9 mm Hg), to provide the compound **25** (247.0 g, 75%).

^{1}H NMR ($CDCl_3$): δ 7.43 (d, $J = 8.7$ Hz, 1H), 6.83 (d, $J = 3.0$ Hz, 1H), 6.69 (dd, $J = 8.7$, 3.0 Hz, 1H), 3.79 (s, 3H), 3.73 (t, $J = 7.1$ Hz, 2H), 3.16 (t, $J = 7.1$ Hz, 2H).

GC retention time: 5.64 min (compound **25**).

6.1.1.3. 6-Methoxy-1-methyl-1-trifluoromethylisochroman (26). To a stirred solution of compound **25** (80.0 g, 0.32 mol) in anhydrous tetrahydrofuran (1300 mL)/hexane (450 mL) was added *n*-butyllithium (230 mL, 0.35 mol) dropwise under nitrogen at −100 °C (internal temperature). The reaction mixture was stirred at −93 °C for 2 h. To the reaction mixture was added a solution of 1,1,1-trifluoroacetone (37 mL, 0.42 mol) in anhydrous tetrahydrofuran (120 mL)/hexane (40 mL) dropwise at −105 °C to −70 °C (internal temperature) for 40 min using a dropping funnel and stirred overnight at −70 °C to room temperature (The temperature was gradually raised to room temperature overnight). This was quenched by water (100 mL), and extracted with dichloromethane. The combined organic extracts were dried over magnesium sulfate, and concentrated in vacuo to give a crude product. The ratio of desired compound and 3-methoxyphenethyl chloride was 3.9:1 as determined by ^{1}H NMR and GC. To remove the by-product (3-methoxyphenethyl chloride), the residue was diluted with toluene (530 mL) and to the mixture was added 1,8-diazabicyclo[5.4.0]undec-7ene (DBU) (37 mL, 0.24 mol). After the solution was stirred at 110 °C for 16 h, aqueous 2 M hydrochloric acid (200 mL) was added to the stirred solution mixture at 0 °C. The organic layer was extracted with ethyl acetate (500 mL), washed with aqueous 2 M hydrochloric acid (100 mL), saturated aqueous sodium bicarbonate (100 mL), brine (100 mL), dried over magnesium sulfate, and concentrated in vacuo. The residue was passed through a short column (Silica-gel, 12 × 9 cm, 5% ethyl acetate in hexane) to remove the baseline compound. The mixture was distilled to provide compound **26** (61.0 g, 77%) (bp 106 °C/0.9 mm Hg) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 7.26 (d, J = 8.9 Hz, 1H), 6.81 (dd, J = 8.9, 2.6 Hz, 1H), 6.68 (d, J = 2.6 Hz, 1H), 4.14 (dt, J = 11, 5.8 Hz, 1H), 3.90 (dt, J = 11, 5.8 Hz, 1H), 3.81 (s, 3H), 2.87-2.81 (m, 2H), 1.64 (s, 3H).

GC retention time: 3.71 min (compound **26**), 3.07 min (3-methoxyphenethyl chloride), 2.21 min (3-vinylanisole).

6.1.1.4. 6-Hydroxy-1-methyl-1-trifluoromethylisochroman (27). To a stirred solution of compound **26** (71.0 g, 0.29 mol) in acetic acid (600 mL) was added aqueous 48% HBr (300 mL) and the mixture was stirred at 130 °C for 13 h. After the removal of solvent in vacuo, the reaction mixture was treated with aqueous 8 M sodium hydroxide until the pH became 5 to 6. The resultant solution was extracted with ethyl acetate (2× 400 mL) and the combined extracts were washed with brine (100 mL), dried over magnesium sulfate, and concentrated in vacuo, followed by flash chromatography (Silica-gel, 15 × 20 cm, 17% ethyl acetate in hexane) to afford the compound **27** (67.0 g, quant.) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 7.22 (d, J = 9.1 Hz, 1H), 6.73 (dd, J = 9.1, 2.6 Hz, 1H), 6.63 (d, J = 2.6 Hz, 1H), 5.00 (s, 1H), 4.17–4.07 (m, 1H), 3.90 (dt, J = 11, 5.8 Hz, 1H), 2.84–2.74 (m, 2H), 1.64 (s, 3H).

GC retention time: 4.26 min (compound **27**).

6.1.1.5. 6-Acetoxy-1-methyl-1-trifluoromethylisochroman (28). To a stirred solution of compound **27** (79.0 g, 0.34 mol) and triethylamine (120 mL, 0.88 mol) in tetrahydrofuran (680 mL) was added acetyl chloride (31 mL, 0.44 mol) at 0 °C, and the mixture was stirred at ambient temperature for 1 h. The reaction mixture was quenched by adding aqueous 1 M hydrochloric acid (400 mL), and the organic solution was extracted with ethyl acetate (500 mL). The extracts were washed with aqueous saturated sodium bicarbonate (100 mL) and brine (100 mL), dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by flash chromatography (Silica-gel, 15 × 20 cm, 6% ethyl acetate in hexane) to afford the compound **28** (83.0 g, 89%) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 7.36 (d, J = 7.2 Hz, 1H), 6.98 (dd, J = 7.2, 2.5 Hz, 1H), 6.91 (d, J = 2.5 Hz, 1H), 4.18–4.08 (m, 1H), 3.92 (dt, J = 11, 5.4 Hz, 1H), 2.86 (t, J = 5.4 Hz, 2H), 2.30 (s, 3H), 1.66 (s, 3H).

GC retention time: 4.95 min (compound **28**).

6.1.2. (1*R*)-6-Acetoxy-1-methyl-1-trifluoromethylisochroman (29) and (1*S*)-6-hydroxy-1-methyl-1-trifluoromethylisochroman (30)

A mixture of racemic compound **28** (38.4 g, 0.14 mol), 10% *sec*-butanol solution in hexane (1.3 L), and lipase PS (Amano enzyme: lot LPSAV09512, 35 g) was stirred vigorously at ambient temperature for 23 h. After the filtration, the filtrate was concentrated under reduced pressure to give a mixture. This was purified by silica-gel column chromatography eluted with a gradient of hexane and ethyl acetate (15:1–5:1–2:1) to give compound **29** (first fraction, 17.3 g, 45%) as a colorless oil. The second fraction gave compound **30**[(1*S*)-6-hydroxy-1-methyl-1-trifluoromethylisochroman] (16.9 g, 52%, 83% ee).

The ^{1}H NMR ($CDCl_3$) spectra of these compounds was identical with those of racemates **28** and **30**.

6.1.3. (1*R*)-6-Hydroxy-1-methyl-1-trifluoromethylisochroman (31)

To a stirred mixture of compound **29** (35.5 g, 0.129 mol), methanol (860 mL), and water (340 mL) was added potassium carbonate (35.7 g, 0.258 mol) at 0 °C, then the mixture was stirred at room temperature for 1 h. The resultant mixture was acidified with 2 M hydrochloric acid to pH 3 and evaporated in vacuo to remove the methanol. The residue was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over magnesium sulfate. After filtration, the filtrate was concentrated in vacuo to afford the compound **31** (28.0 g, 93%, 94% ee) as a colorless oil.

The ^{1}H NMR ($CDCl_3$) spectra of this compound was identical with that of racemate **27**.

6.1.4. (1*R*)-6-Methoxy-1-methyl-1-trifluoromethylisochroman (32)

To a stirred mixture of 60% sodium hydride (3.47 g, 0.145 mol) in *N*,*N*-dimethylformamide (50 mL) was added a solution of compound **31** (28.0 g, 0.121 mol) in DMF (370 mL) at 0 °C and the mixture was stirred at the same temperature for 1 h. Methyl iodide (25.8 g, 0.182 mol) was added dropwise to the resulting mixture at 0 °C and the mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with water and diluted with saturated aqueous ammonium chloride. This was extracted with ethyl acetate/toluene (4:1) and the combined solution was washed with water, brine and dried over magnesium sulfate. After the solvent was removed in vacuo, the residue was purified by column chromatography on silica-gel eluted with hexane/ethyl acetate (40:1) to give the compound **32** (29.1 g, 98%) as a colorless oil.

The ^{1}H NMR ($CDCl_3$) spectra of this compound was identical with that of racemate **26**.

6.1.5. (1*R*)-6-Methoxy-1-methyl-1-trifluoromethylisochroman-7-carbaldehyde (34)

To a stirred solution of compound **32** (33.2 g, 0.135 mol) in anhydrous dichloromethane (1 L) was added powdered aluminum chloride (41.4 g, 0.31 mol) portionwise at −78 °C and stirred for 20 min. To the yellow solution was added a solution of dichloromethyl *n*-butyl ether (42.3 g, 0.27 mol) in anhydrous dichloromethane (100 mL) dropwise and the mixture was stirred at −78 °C for 2.5 h. This was poured into ice-water and stirred at room temperature for 1 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3× 300 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo to afford a slightly yellow crystalline solid (40.3 g) as a mixture of compound **34** (7-formyl) and compound **33** (5-formyl) in a ratio of ca. 5.3:1, as determined by ^{1}H NMR. The solid (40.3 g) was recrystallized from a mixed solvent of ethyl acetate (35 mL) and hexane (400 mL) to give the compound **34** (19.8 g, 54%) in a pure form.

^{1}H NMR ($CDCl_3$): 10.41 (s, 1H), 7.82 (s, 1H), 6.77 (s, 1H), 4.24–3.82 (m, 2H), 3.94 (s, 3H), 3.02–2.80 (m, 2H), 1.68 (d, J = 1.2 Hz, 3H).

The filtrate was concentrated in vacuo, and the residual solid was purified by column chromatography on silica-gel with hexane/ethyl acetate (10:1–3:1). The first fraction afforded the compound **33** (5.24 g, 14.2%) as a yellow crystalline solid.

^{1}H NMR ($CDCl_3$): 10.63 (s, 1H), 7.55 (d, J = 8.9 Hz, 1H), 6.94 (d, J = 8.9 Hz, 1H), 4.13–3.80 (m, 2H), 3.94 (s, 3H), 3.28–3.19 (m, 2H), 1.66 (s, 3H).

The second fraction afforded a mixture containing 1-methyl-1-trifluoromethyl-3-methyl-5-methoxy-1,3-dihydroisobenzofuran-aldehyde (impurity-1) eluting with hexane/ethyl acetate (10:1–7:1) as a pale yellow crystalline solid (total 2 g, maximum 5.4% yield as impurity-1).

^{1}H NMR ($CDCl_3$): 10.44 (s, 1H), 7.77 (s, 1H), 6.88 (s, 1H), 5.44 (q, J = 6.4 Hz, 1H), 3.98 (s, 3H), 1.69 (d, J = 1.0 Hz, 3H), 1.56 (d, J = 6.4 Hz, 3H).

The third fraction, eluting with hexane/ethyl acetate (7:1–3:1), afforded the desired compound **34** (7.44 g, 20%) as a yellow crystalline solid, which was recrystallized from ethyl acetate/hexane (1:10) to give the pure compound (6.00 g, 16.2%) as a yellow crystalline solid.

6.1.6. (2*S*,3*S*)-3-[(1*R*)-6-Methoxy-1-methyl-1-trifluoromethylisochroman-7-yl]methylamino-2-phenylpiperidine ((+)-1)·dihydrochloride

To a stirred solution of (2*S*,3*S*)-3-amino-2-phenylpiperidine (16.0 g, 90.8 mmol) and compound **34** (24.9 g, 90.8 mmol) in anhydrous dichloromethane (850 mL) was added sodium triacetoxyborohydride (38.5 g, 181.5 mmol) portionwise under nitrogen at ambient temperature. The reaction mixture was stirred at the same temperature for 20 h. The reaction mixture was made basic to pH > 10 with 2 M sodium hydroxide aqueous solution with ice-cooling and stirred at room temperature for 30 min. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3× 300 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give crude product (40.2 g) as a white viscous oil. H NMR of the crude mixture indicated contamination with dialkylated compound at N-1 on the piperidine ring of compound (+)-**1** in a ratio of compound-**1**/dialkyl derivative = ca. 20:1 as determined by ^{1}H NMR. To a solution of the crude oil (40.2 g) in methanol (250 mL) was added 10% HCl/methanol (1000 mL). The solvent was removed, and the residue was diluted with dry methanol (800 mL) and heated at 110 °C (bath temperature) for 13 h. The solvent was concentrated to a volume of ca. 500 mL, and cooled to room temperature. The white crystalline solid was filtered to give the compound (+)-**1**·dihydrochloride (35.5 g, 77.7%).

Mp 257–258 °C.

MS (ESI): *m*/*z* 435 $(M+H)^+$ [Quattro-II triplequadrupole mass spectrometer].

^{1}H NMR (free base, $CDCl_3$): δ 7.35–7.17 (m, 5H), 6.95 (s, 1H), 6.44 (s, 1H), 4.17–4.05 (m, 1H), 3.95–3.82 (m, 2H), 3.62 (d, *J* = 14.0 Hz, 1H), 3.51 (s, 3H), 3.34 (d, *J* = 14.0 Hz, 1H), 3.34–3.22 (m, 1H), 2.88–2.72 (m, 4H), 2.15–1.80 (m, 4H), 1.70–1.52 (m, 1H), 1.59 (d, *J* = 0.8 Hz, 3H), 1.48–1.35 (m, 1H).

^{13}C NMR (free base, $CDCl_3$): 157.1, 142.3, 134.7, 128.2 (2 carbons), 127.7, 127.1, 126.7, 126.4 (2carbons), 126.0, 124.0, 109.9, 76.0, 64.1, 61.4, 55.0, 54.9, 47.7, 46.6, 29.2, 28.5, 23.3, 20.2.

X-ray crystallography: the stereochemistry at 1-position on the isochroman (Me, CF_3) was determined by X-ray crystallography to be as shown in the chemical structure.

Optical rotation: $[\alpha]_D^{27}$ +75.44° (*c* 0.424, methanol).

Elementary Anal. Calcd for $C_{24}H_{29}F_3N_2O_2 \cdot 2HCl$: C, 56.81%; H, 6.16%; N, 5.22%; F, 11.23%; Cl, 13.97%. Found: C, 56.76%; H, 6.16%; N, 5.63%; F, 11.35%; Cl, 13.93%.

6.1.7. (2*S*,3*S*)-3-(6-Methoxy-3-methyl-3-trifluoromethyl-1,3-dihydroisobenzofuran-5-yl)methylamino-2-phenylpiperidine (15)·dihydrochloride

6.1.7.1. 2-Bromo-5-methoxybenzyl chloride (38). To a stirred solution of 3-methoxybenzyl chloride (37.2 g, 0.238 mol) and pyridine (23.1 mL, 0.286 mol) dissolved in dry dichloromethane (400 mL) was added bromine (23.1 mL, 0.88 mol) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h, then at ambient temperature for 18 h. This was diluted with a saturated aqueous solution of sodium thiosulfate, and extracted with dichloromethane. The combined extracts were washed with brine, sequentially. The extracts were dried over magnesium sulfate, and concentrated to give a crude product as a slightly yellow crystalline solid. This solid was taken up in ethyl acetate, and the precipitate was filtered. The filtrate was washed, and concentrated to give a slightly yellow crystalline solid, which was washed with hexane to afford the title compound **38** (43 g, 77%) as a white solid.

^{1}H NMR ($CDCl_3$): δ 7.44 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 3.3 Hz, 1H), 6.74 (dd, *J* = 8.8, 3.3 Hz, 1H), 4.64 (s, 2H), 3.79 (s, 3H).

6.1.7.2. 5-Methoxy-1-methyl-1-trifluoromethyl-1,3-dihydroisobenzofuran (39). To a stirred solution of compound **38** (13.8 g, 59 mmol) in a mixture of dry tetrahydrofuran (330 mL) and hexane (110 mL) was added *n*-butyllithium (37.2 mL, 62 mmol) in hexane dropwise over 30 min at −100 °C under nitrogen, and the reaction mixture was stirred at −100 °C for 2.5 h. Then, to the mixture was added a solution of 1,1,1-trifluoroacetone (6.3 mL, 71 mmol) dissolved in dry tetrahydrofuran (15 mL) and hexane (5 mL) dropwise at the same temperature, and the resulting mixture was allowed to elevate to −30 °C. This was quenched with water, and the solvent was removed by evaporation. The residue was extracted with hexane. The organic extracts were dried over magnesium sulfate, and concentrated to give the crude product as a light yellow oil (13.6 g). The crude product (13.6 g), glycine (575 mg, 7.66 mmol) and potassium hydroxide (703 mg, 12.5 mmol) were dissolved in a mixture of ethanol (30 mL) and water (20 mL), and stirred at reflux for 2 h. After cooling, the reaction mixture was diluted with brine, and extracted with hexane. The organic extracts were dried over magnesium sulfate, and concentrated by evaporation to afford a light yellow oil (12.6 g), which was purified by distillation (bp 94–98 °C/1.5 mm Hg) to give the title compound **39** as a colorless oil (10.8 g, 78.7%).

^{1}H NMR ($CDCl_3$): δ 7.20 (d, *J* = 8.4 Hz, 1H), 6.87 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.76 (d, *J* = 2.6 Hz, 1H), 5.21–5.09 (m, 2H), 3.82 (s, 3H), 1.65 (d, *J* = 1.1 Hz, 3H).

6.1.7.3. 3-Methyl-3-trifluoromethyl-6-methoxy-1,3-dihydroisobenzofuran-5-carbaldehyde (40). To a stirred solution of compound **38** (10.8 g, 46 mmol) in dry dichloromethane (280 mL) was added titanium(IV) chloride (11.2 mL, 102 mol) dropwise under nitrogen at −78 °C, and the resulting solution was stirred for 15 min. A solution of dichloromethyl methyl ether (8.4 mL, 0.093 mol) in dry dichloromethane (20 mL) was added to the resulting brown solution at −78 °C, and stirred for 1.5 h. This mixture was poured into ice-water, and stirred at ambient temperature for 30 min. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic extracts were washed with brine, dried over magnesium sulfate, and concentrated to afford the title compound **40** as a light yellow crystalline solid (12.1 g, quant.).

^{1}H NMR ($CDCl_3$): δ 10.45 (s, 1H), 7.79 (s, 1H), 6.88 (s, 1H), 5.25–5.13 (m, 2H), 3.97 (s, 3H), 1.68 (m, 3H).

6.1.8. (2*S*,3*S*)-3-(6-Methoxy-3-methyl-3-trifluoromethyl-1,3-dihydroisobenzofuran-5-yl)methylamino-2-phenylpiperidine (15)·dihydrochloride

To a stirred solution of (2*S*,3*S*)-2-phenyl-3-aminopiperidine (4.1 g, 23.1 mmol) which was prepared by a method described in WO 92/17,449 and compound **40** (6.1 g, 23.3 mmol) in dry dichloromethane (200 mL) was added sodium triacetoxyborohydride (7.8 g, 36.9 mmol) portionwise under nitrogen at ambient temperature, and the resultant mixture was stirred at the same temperature for 16 h. The pH was adjusted to below 10 with a saturated aqueous sodium bicarbonate solution, and extracted with dichloromethane. The extracts were dried over magnesium sulfate, and concentrated to afford to a light yellow amorphous solid (10.1 g). A methanolic HCl solution was added to the crude products dissolved in ethyl acetate. Formed solids were collected by filtration, dried under vacuum, and purified by crystallization from methanol to afford the title compound as a white crystalline solid; mp 200–207 °C.

^{1}H NMR (major isomer, free amine, $CDCl_3$): δ 7.31–7.21 (m, 5H), 6.89 (s, 1H), 6.54 (s, 1H), 5.16–5.04 (m, 2H), 3.90 (d, *J* = 2.3 Hz, 1H), 3.68 (d, *J* = 14.3 Hz, 1H), 3.52 (s, 3H), 3.40 (d, *J* = 14.3 Hz, 1H), 3.29–3.26 (m, 1H), 2.85–2.75 (m, 2H), 2.14–2.09 (m, 1H), 1.95–1.86 (m,

1H), 1.66–1.54 (m, 1H), 1.60 (s, 3H), 1.44–1.40 (m, 1H). *N*H (2 proton, not observed).

Analysis by ^{1}H NMR indicated a diastereomeric ratio at the 3-position of the dihydroisobenzofuran ring of 98:2 (3*R*/3*S*). The absolute stereochemistry of the title compound **15** was determined by X-ray crystallography to be that of the (3*R*) isomer after further purification by recrystallization.

6.1.9. (2*S*,3*S*)-3-(5-Methoxy-1-methyl-1-(trifluoromethyl)indane-6-yl)methylamino-2-phenylpiperidine (12)·dihydrochloride

6.1.9.1. 5-Methoxy-1-methyl-1-(trifluoromethyl)indane (48). To a stirred solution of alcohol **44** (980 mg, 4.22 mmol) in dry dichloromethane (16 mL) was added titanium chloride (8.44 mmol, 926 μL) via a syringe at −78 °C. After 1.5 h at the same temperature, to the mixture was added a 1.0 M hexane solution of dimethylzinc (16.9 mmol, 16.9 mL) at −78 °C. The reaction mixture was stirred for 40 min at −78 °C, then warmed to ambient temperature and stirred for 5 h. The reaction mixture was poured into ice-water and filtered through a pad of Celite. The filtrate and washings were washed with brine, dried over sodium sulfate and concentrated in vacuo to give the crude product as a yellow oil. The crude product was purified by column chromatography on silica-gel (30 g) eluting with hexane/ethyl acetate (80:1) to give compound **48** (847 mg, 87%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.22 (d, J = 9.2 Hz, 1H), 6.80–6.75 (m, 2H), 3.79 (s, 3H), 3.08–2.83 (m, 2H), 2.57–2.46 (m, 1H), 2.02–1.88 (m, 1H), 1.47 (s, 3H).

6.1.9.2. 5-Methoxy-1-methyl-1-(trifluoromethyl)indane-6-carboxaldehyde (52). To a stirred solution of compound **48** (1.19 g, 5.16 mmol) in dry dichloromethane (30 mL) was added titanium(IV) chloride (2.15 g ~ 1.25 mL, 11.35 mmol) via a syringe at −78 °C with dry ice/methanol cooling. After 10 min, to this was added a solution of dichloromethyl methyl ether (1.19 g, 10.32 mmol) in dry dichloromethane (5 mL) dropwise at the same temperature and the reaction mixture was stirred at −78 °C for 5 h. The mixture was poured into ice-water and stirred at ambient temperature for 10 min. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×). The combined solution was washed with brine, dried over magnesium sulfate and concentrated in vacuo to give the crude product as a yellow solid. The crude product was purified by column chromatography on silica-gel with hexane/ethyl acetate (9:1–5:1–3:1) to give the title compound **52** (1.13 g, 85%) as a white solid.

^{1}H NMR ($CDCl_3$, 270 MHz) δ 10.41 (s, 1H), 7.79 (s, 1H), 6.87 (s, 1H), 3.93 (s, 3H), 3.19–2.88 (m, 2H), 2.63–2.50 (m, 1H), 2.06–1.90 (m, 1H), 1.50 (s, 3H).

6.1.10. (2*S*,3*S*)-3-(5-Methoxy-1-methyl-1-(trifluoromethyl)-indane-6-yl)methylamino-2-phenylpiperidine (12)

To a stirred solution of (2*S*,3*S*)-*tert*-butyl 3-amino-2-phenylpiperidine-1-carboxylate (800 mg, 2.89 mmol) in dry dichloromethane (60 mL) added compound **52** (897 mg, 3.47 mol) and sodium triacetoxyborohydride (1.23 g, 5.78 mmol) in one portion at ambient temperature. After 2 h at ambient temperature, the reaction mixture was made basic to pH > 10 with 2 M sodium hydroxide solution with ice-cooling. The aqueous layer was extracted with dichloromethane and the combined organic phases were washed with brine, dried over magnesium sulfate and concentrated in vacuo to give the crude product (1.60 g) as a white viscous oil. Then, to a solution of the crude product (1.60 g) in ethyl acetate (45 mL) was added conc. hydrochloric acid solution (4.5 mL) at room temperature. After 1.5 h, the mixture was made basic to pH > 10 with 2 M sodium hydroxide solution with ice-cooling. The organic layer was separated and the aqueous solution was extracted with ethyl acetate (2×). The combined extracts were washed with brine, dried over magnesium sulfate and concentrated in vacuo to give the crude product as a yellow oil, which was purified by column chromatography on silica-gel (40 g) with dichloromethane/methanol (10:1–6:1) to give the title compound **12** (1.04 g, 86%) as a pale yellow viscous oil.

^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.33–7.17 (m, 5H), 6.95 and 6.90 (each s, total 1H), 6.56 and 6.53 (each s, total 1H), 3.89 (d, J = 2.2 Hz, 1H), 3.66 and 3.64 (each d, J = 13.8 Hz, total 1H), 3.48 and 3.43 (each s, total 3H), 3.38 and 3.36 (each d, J = 13.8 Hz, total 1H), 3.33–3.22 (m, 1H), 3.05–2.72 (m, 4H), 2.55–2.42 (m, 1H), 2.20–1.80 (m, 5H), 1.70–1.52 (m, 1H), 1.42 (s, 3H), 1.43–1.35 (m, 1H).

6.1.11. (2*S*,3*S*)-3-(5-Methoxy-1-methyl-1-(trifluoromethyl) indane-6-yl)methylamino-2-phenylpiperidine (12)·dihydrochloride

The compound **12** (1.04 g) was treated with 10% hydrochloric methanol solution (40 mL) at ambient temperature. After the solvent was evaporated in vacuo, the residue was washed with hot ethanol (two times) to give the title compound **12**·2HCl (560 mg, 46%) as a white solid; mp 236–238 °C.

Elementary Anal. Calcd for $C_{24}H_{29}F_3N_2O$·2HCl: C, 58.66%; H, 6.36%; N, 5.70%. Found: C, 58.66%; H, 6.68%; N, 5.69%.

MS (ESI): m/z 419.4 $(M+H)^+$.

6.1.12. (2*S*,3*S*)-3-[((6-Methoxy-1-methyl-1-(trifluoromethyl)-1, 2,3,4-tetrahydronaphthalene)-7-yl)]methylamino-2-phenylpiperidine (19)·dihydrochloride

6.1.12.1. 6-Methoxy-1-methyl-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene (49). To a stirred solution of compound **45** (2.25 g, 9.16 mmol) in anhydrous dichloromethane (35 mL) was added titanium(IV) chloride (2.0 mL, 18.3 mmol) via a syringe at −78 °C. After 2 h at same temperature, to this was added 1.0 M dimethylzinc solution in hexane (36.4 mL, 36.4 mmol) via a syringe at −78 °C. The mixture was stirred at −78 °C for 40 min then allowed to warm to ambient temperature (additional 4 h). The mixture was poured into ice-water and stirred for 10 min and extracted with dichloromethane (3×). The combined extracts were washed with brine, dried over magnesium sulfate and concentrated in vacuo to give the crude product, which was purified by column chromatography on silica-gel (250 g) eluting with hexane only to give compound **49** (2.07 g, 92%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.41 (d, J = 9.2 Hz, 1H), 6.76 (dd, J = 9.2, 2.7 Hz, 1H), 6.63 (d, J = 2.7 Hz, 1H), 3.78 (s, 3H), 2.82–2.72 (m, 2H), 2.21–2.08 (m, 1H), 2.04–1.87 (m, 1H), 1.80–1.64 (m, 2H), 1.48 (s, 3H).

6.1.12.2. 6-Methoxy-1-methyl-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene-7-carbaldehyde (53). To a stirred solution of compound **49** (1.61 g, 6.58 mmol) in anhydrous dichloromethane (50 mL) was added titanium(IV) chloride (1.59 mL, 14.48 mmol) via a syringe at −78 °C. After 10 min to this was added dichloromethyl methyl ether (1.51 g, 13.2 mmol) at the same temperature. After 3 h at −78 °C, the mixture was diluted with water and stirred at ambient temperature for 15 min. The mixture was extracted with dichloromethane (3×) and the combined solution was washed with brine, dried over magnesium sulfate and concentrated in vacuo to give the crude product, which was purified by column chromatography on silica-gel (120 g) eluting with hexane/ethyl acetate (5:1–3:1) to give compound**53** (713 mg, 40%) as a white solid.

^{1}H NMR ($CDCl_3$, 270 MHz) δ 10.38 (s, 1H), 7.97 (s, 1H), 6.71 (s, 1H), 3.91 (s, 3H), 2.96–2.72 (m, 2H), 2.27–2.10 (m, 1H), 2.09–1.90 (m, 1H), 1.83–1.65 (m, 2H), 1.51 (s, 3H).

6.1.13. (2*S*,3*S*)-3-[((6-Methoxy-1-methyl-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene)-7-yl)]methylamino-2-phenylpiperidine (19)

To a stirred solution of (2*S*,3*S*)-*tert*-butyl 3-amino-2-phenylpiperidine-1-carboxylate (250 mg, 0.91 mmol) in dry dichloromethane (20 mL) and compound **53** (296 mg, 1.09 mol) was added sodium triacetoxyborohydride (384 mg, 1.81 mmol) in one portion at ambient temperature. The same procedure as described in compound **12** was performed to give the compound **19** (367 mg, 94%) as a pale yellow viscous oil.

^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.35–7.15 (m, 5H), 7.13 and 7.09 (each s, total 1H), 6.39 and 6.36 (each s, total 1H), 3.89 (d, J = 2.2 Hz, 1H), 3.70 and 3.61 (each d, J = 13.6 Hz, total 1H), 3.46 and 3.40 (each s, total 3H), 3.35 (d, J = 13.6 Hz, 1H), 3.35–3.22 (m, 1H), 2.90–2.65 (m, 4H), 2.35–1.82 (m, 6H), 1.80–1.52 (m, 3H), 1.43 (s, 3H), 1.50–1.35 (m, 1H).

6.1.14. (2*S*,3*S*)-3-[((6-Methoxy-1-methyl-1-(trifluoromethyl)-1,2,3,4-tetrahydronaphthalene)-7-yl)]methylamino-2-phenylpiperidine (19)·dihydrochloride

Compound **19** (360 mg) was treated with 10% hydrochloric methanol solution (40 mL) at ambient temperature. After the solvent was evaporated in vacuo, the residue was recrystallized from ethanol to give compound **19**·2HCl (220 mg, 52.3%) as a white solid; mp 235–237 °C.

Diastereomer ratio: *R*/*S* = 3:1.

Anal. Calcd for $C_{25}H_{31}F_3N_2O$·2HCl: C, 59.41%, H, 6.58%; N, 5.54%. Found: C, 59.17%; H, 6.88%; N, 5.50%. MS (API): *m*/*z* 433.2 $(M+H)^+$.

The filtrate was evaporated in vacuo and the residue was recrystallized from ethanol/ether to give compound **20**·2HCl (150 mg, 35.7%) as a white solid; mp 221–223 °C.

Diastereomer ratio: *R*/*S* = 1:5.

Anal. Calcd for $C_{25}H_{31}F_3N_2O$·2HCl·$2H_2O$: C, 58.99%; H, 6.61%; N, 5.50%. Found: C, 58.73%; H, 6.50%; N, 5.38%. MS (API): *m*/*z* 433.2 $(M+H)^+$.

6.1.15. (*S*,3*S*)-3-[5-(1,1-Dimethyl-2,2,2-trifluoroethyl)-2-methoxybenzylamino]-2-phenylpiperidine (4)·dihydrochloride

6.1.15.1. 5-(1,1-Dimethyl-2,2,2-trifluoroethyl)-2-methoxybenzaldehyde. 1-Methoxy-4-(2,2,2-trifluoro-1,1-dimethylethyl)benzene[11] (1.45 g, 6.64 mmol) was converted to the aldehyde derivative using the same procedure as with compound **52**. The product was purified by column chromatography on silica-gel with hexane/ethyl acetate (40:1–20:1) to give the title compound (1.49 g, 81%) as a pale yellow solid.

^{1}H NMR ($CDCl_3$, 270 MHz) δ 10.47 (s, 1H), 7.95 (d, J = 2.6 Hz, 1H), 7.75–7.65 (m, 1H), 6.99 (d, J = 8.8 Hz, 1H), 3.94 (s, 3H), 1.57 (s, 6H).

6.1.15.2. (2*S*,3*S*)-3-[5-(1,1-Dimethyl-2,2,2-trifluoroethyl)-2-methoxybenzylamino]-2-phenylpiperidine (4). To a stirred solution of (2*S*,3*S*)-*tert*-butyl 3-amino-2-phenylpiperidine-1-carboxylate (71 mg, 0.256 mmol) in dry dichloromethane (6 mL) and 5-(1,1-dimethyl-2,2,2-trifluoroethyl)-2-methoxybenzaldehyde (75 mg, 0.31 mol) was added sodium triacetoxyborohydride (109 mg, 0.51 mmol) in one portion at ambient temperature. The same procedure as described in compound **19** was performed to give the *N*-Boc derivative (128 mg, 94%) as a pale yellow viscous oil. To a stirred solution of *N*-Boc derivative (128 mg) in ethyl acetate (5 mL) was added concd HCl (0.7 mL) at ambient temperature. The reaction mixture was stirred at ambient temperature for 1 h and the mixture was made basic to pH > 10 with 10% sodium hydroxide aqueous solution with ice-cooling. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×). The combined solution was washed with brine, dried over magnesium sulfate and concentrated in vacuo to give crude product as a yellow oil, which was purified by column chromatography on silica-gel with dichloromethane/methanol (20:1–10:1) to give the compound **4** (83 mg, 80% in two steps).

^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.32–7.16 (m, 6H), 7.15–7.09 (m, 1H), 6.65 (d, J = 8.8 Hz, 1H), 3.88 (d, J = 2.2 Hz, 1H), 3.67 (d, J = 13.9 Hz, 1H), 3.48 (s, 3H), 3.39 (d, J = 13.9 Hz, 1H), 3.32–3.22 (m, 1H), 2.86–2.72 (m, 2H), 2.18–2.06 (m, 1H), 2.00–1.80 (m, 3H), 1.69–1.36 (m, 2H), 1.49 (s, 6H).

6.1.16. (2*S*,3*S*)-3-[5-(1,1-Dimethyl-2,2,2-trifluoroethyl)-2-methoxybenzylamino]-2-phenylpiperidine (4)·dihydrochloride

Compound **4** (80 mg) was treated with 10% hydrochloric methanol solution (30 mL). After the solvent was evaporated in vacuo, the residue was recrystallized from ethanol/diethyl ether to give compound **4**·2HCl (73 mg, 77%) as a white solid; mp 225–226 °C.

Anal. Calcd for $C_{23}H_{29}F_3N_2O$·2HCl: C, 57.62%; H, 6.52%; N, 5.84%. Found: C, 57.65%; H, 6.86%; N, 5.72%.

MS (API): *m*/*z* 407.0 $(M+H)^+$.

6.1.17. (2*S*,3*S*)-3-[2-Methoxy-5-(2,2,2-trifluoroethyl)benzylamino]-2-phenylpiperidine (2)

^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.35–7.20 (m, 5H), 7.06 (dd, J = 8.4, 1.8 Hz, 1H), 6.84 (d, J = 1.8 Hz, 1H), 6.65 (d, J = 8.4 Hz, 1H), 3.90 (d, J = 2.2 Hz, 1H), 3.68 (d, J = 14.3 Hz, 1H), 3.49 (s, 3H), 3.42 (d, J = 14.3 Hz, 1H), 3.35–3.24 (m, 1H), 3.20 (q, J = 11.0 Hz, 2H), 2.88–2.73 (m, 2H), 2.20–1.85 (m, 4H), 1.68–1.52 (m, 1H), 1.50–1.37 (m, 1H).

Compound **2**·2HCl: mp 209–210 °C.

Anal. Calcd for $C_{21}H_{25}F_3N_2O$·2HCl: C, 55.88%; H, 6.03%; N, 6.21%. Found: C, 55.52%; H, 6.21%; N, 6.10%.

MS (EI): *m*/*z* 378 (M^+).

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10. (a) Enzymes were kindly supplied by Amano enzyme. Lipase AY (*Candida rugosa*), CHE (*Cholesterol esterase*), lipase AH (*Pseudomonas*, sp.), lipase PS (*Pseudomonas* sp.).; (b) It was difficult to obtain the exact enantiomeric excess of compound **29**. After deacetylation, the enantiomeric excess of optical phenol **31** was analyzed by HPLC using a DICEL CHIRALCEL OJ column (4.6 × 250 mm), No. 45-04-90412, eluent; hexane/isopropanol (95:5), flow rate: 1 mL/min, temperature; 40 °C, injection; 10 μL, retention time; acetate = 7.55, 8.73 min, phenol = 15.88, 24.35 min.
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