

(12) 特許協力条約に基づいて公開された国際出願

(19) 世界知的所有権機関

国際事務局

(43) 国際公開日

2023年3月9日(09.03.2023)



(10) 国際公開番号

WO 2023/032940 A1

(51) 国際特許分類:

*C07D 471/14* (2006.01) *A61P 9/12* (2006.01)  
*A61K 31/424* (2006.01) *A61P 11/00* (2006.01)  
*A61K 31/437* (2006.01) *A61P 21/00* (2006.01)  
*A61K 31/4985* (2006.01) *A61P 25/00* (2006.01)  
*A61K 31/5025* (2006.01) *A61P 25/02* (2006.01)  
*A61K 31/5377* (2006.01) *A61P 25/28* (2006.01)  
*A61K 31/5386* (2006.01) *A61P 27/06* (2006.01)  
*A61P 3/00* (2006.01) *A61P 35/00* (2006.01)  
*A61P 3/06* (2006.01) *A61P 43/00* (2006.01)  
*A61P 3/10* (2006.01) *C07D 487/14* (2006.01)  
*A61P 9/00* (2006.01) *C07D 498/04* (2006.01)  
*A61P 9/04* (2006.01) *C07D 498/14* (2006.01)  
*A61P 9/10* (2006.01) *C07D 519/00* (2006.01)

(21) 国際出願番号: PCT/JP2022/032483

(22) 国際出願日: 2022年8月30日(30.08.2022)

(25) 国際出願の言語: 日本語

(26) 国際公開の言語: 日本語

(30) 優先権データ:

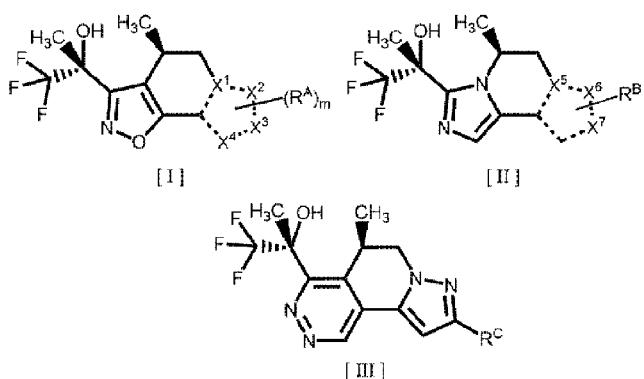
特願 2021-142742 2021年9月1日(01.09.2021) JP

(71) 出願人: 日本たばこ産業株式会社 (JAPAN TOBACCO INC.) [JP/JP]; 〒1056927 東京都港区虎ノ門四丁目1番1号 Tokyo (JP).

(72) 発明者: 山川真希 (YAMAKAWA, Maki); 〒5691125 大阪府高槻市紫町1番1号 日本たばこ産業株式会社 医薬総合研究所内 Osaka (JP). 須澤孝一 (SUZAWA, Koichi); 〒5691125 大阪府高槻市紫町1番1号 日本たばこ産業株式会社 医薬総合研究所内 Osaka (JP). 山下智也 (YAMASHITA, Tomoya); 〒5691125 大阪府高槻市紫町1番1号 日本たばこ産業株式会社 医薬総合研究所内 Osaka (JP). 上野弘資 (UENO, Hiroshi); 〒5691125 大阪府高槻市紫町1番1号 日本たばこ産業株式会社 医薬総合研究所内 Osaka (JP). 真部知幸 (MANABE, Tomoyuki);

(54) Title: NITROGEN-CONTAINING TRICYCLIC COMPOUND AND PHARMACEUTICAL USE THEREOF

(54) 発明の名称: 含窒素三環性化合物及びその医薬用途



(57) Abstract: The present invention provides a compound which has PDHK inhibitory activity and which is useful for treating or preventing diabetes (type 1 diabetes, type 2 diabetes, etc.), insulin resistance syndrome, metabolic syndrome, hyperglycemia, hyperlactatemia, diabetes complications (diabetic neuropathy, diabetic retinopathy, diabetic nephropathy, cataract, etc.), heart failure (acute heart failure, chronic heart failure), cardiomyopathy, myocardial ischemia, myocardial infarction, angina pectoris, dyslipidemia, atherosclerosis, peripheral arterial disease, intermittent claudication, chronic obstructive pulmonary disease, brain ischemia, stroke, mitochondrial disease, mitochondrial encephalomyopathy, cancer, pulmonary hypertension, Alzheimer's disease, vascular dementia, glaucoma, retinopathy of diabetes, retinopathy of prematurity, retinal vein occlusion, ischemic optic neuropathy, or chronic kidney disease. The present invention relates to a compound represented by formula [I], formula [II], or formula [III] or a pharmaceutically acceptable salt thereof. [In the formula, each symbol has the same meaning as in the description.]



〒5691125 大阪府高槻市紫町 1 番 1 号 日本たば  
こ産業株式会社 医薬総合研究所内 Osaka (JP).

(74) 代理人: 高島 一 (TAKASHIMA, Hajime);  
〒5410044 大阪府大阪市中央区伏見町  
四丁目 1 番 1 号 明治安田生命大阪  
御堂筋ビル Osaka (JP).

(81) 指定国(表示のない限り、全ての種類の国内保  
護が可能): AE, AG, AL, AM, AO, AT, AU, AZ,  
BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH,  
CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO,  
DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,  
HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP,  
KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK,  
LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW,  
MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE,  
PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD,  
SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT,  
TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) 指定国(表示のない限り、全ての種類の広域保  
護が可能): ARIPO (BW, GH, GM, KE, LR, LS,  
MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM,  
ZW), ユーラシア (AM, AZ, BY, KG, KZ, RU, TJ,  
TM), ヨーロッパ (AL, AT, BE, BG, CH, CY, CZ,  
DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT,  
LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS,  
SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM,  
GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

添付公開書類 :

- 国際調査報告 (条約第21条(3))
- 明細書の別個の部分として表した配列リスト  
(規則5.2(a))

(57) 要約 : 本発明は、PDHK阻害活性を有し、糖尿病（1型糖尿病、2型糖尿病等）、インスリン抵抗性症候群、メタボリックシンドローム、高血糖症、高乳酸血症、糖尿病合併症（糖尿病性神経障害、糖尿病性網膜症、糖尿病性腎症、白内障等）、心不全（急性心不全、慢性心不全）、心筋症、心筋虚血症、心筋梗塞、狭心症、脂質異常症、アテローム性硬化症、末梢動脈疾患、間欠性跛行、慢性閉塞性肺疾患、脳虚血症、脳卒中、ミトコンドリア病、ミトコンドリア脳筋症、癌、肺高血圧症、アルツハイマー病、血管性認知症、緑内障、糖尿病網膜症、未熟児網膜症、網膜静脈閉塞症、虚血性視神経症または慢性腎臓病の治療または予防のために有用な化合物を提供する。本発明は、式 [I]、式 [II] もしくは式 [III] の化合物、またはその製薬上許容される塩に関する。 [式中の各記号は明細書に記載のものと同義である。]

[DESCRIPTION]

[Title of Invention] NITROGEN-CONTAINING TRICYCLIC COMPOUND  
AND PHARMACEUTICAL USE THEREOF

[Technical Field]

5 [0001]

The present invention relates to a nitrogen-containing tricyclic compound and a pharmaceutical use thereof. More particularly, the present invention relates to a nitrogen-containing tricyclic compound or a pharmaceutically acceptable 10 salt thereof having a pyruvate dehydrogenase kinase (hereinafter to be abbreviated as PDHK) inhibitory activity, a pharmaceutical composition containing the same, a therapeutic or prophylactic agent containing the same for diabetes (type 1 diabetes, type 2 diabetes etc.), insulin resistance syndrome, 15 metabolic syndrome, hyperglycemia, hyperlactacidemia, diabetic complications (diabetic neuropathy, diabetic retinopathy, diabetic nephropathy, cataract etc.), cardiac failure (acute cardiac failure, chronic cardiac failure), cardiomyopathy, myocardial ischemia, myocardial infarction, angina pectoris, 20 dyslipidemia, atherosclerosis, peripheral arterial disease, intermittent claudication, chronic obstructive pulmonary disease, brain ischemia, cerebral apoplexy, mitochondrial disease, mitochondrial encephalomyopathy, cancer, pulmonary hypertension, Alzheimer disease, vascular dementia, glaucoma, 25 diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion, ischemic optic neuropathy, or chronic kidney disease, and the like.

[Background Art]

[0002]

30 In tissues, for reactions using energy such as biosynthesis, active transport, muscle contraction and the like, the energy is supplied by hydrolysis of adenosine triphosphate (ATP). ATP is produced by oxidation of metabolic fuel which yields much energy, such as glucose and free fatty

acids. In oxidative tissues such as muscle, ATP is mostly produced from acetyl-CoA that enters citric acid cycle. Acetyl-CoA is produced by oxidation of glucose via glycolytic pathway or  $\beta$  oxidation of free fatty acid. An enzyme that 5 plays a pivotal role in controlling acetyl-CoA production from glucose is pyruvate dehydrogenase (hereinafter to be abbreviated as PDH). PDH catalyzes reduction of nicotinamide adenine dinucleotide (NAD) to NADH, simultaneously with oxidation of pyruvic acid to acetyl-CoA and carbon dioxide 10 (e.g., non-patent documents 1, 2).

[0003]

PDH is a multienzyme complex consisting of three enzyme components (E1, E2 and E3) and some subunits localized in mitochondrial matrix. E1, E2 and E3 are responsible for 15 decarboxylation from pyruvic acid, production of acetyl-CoA and reduction of NAD to NADH, respectively.

Two classes of enzyme having regulatory function bind to PDH. One is PDHK, which is a protein kinase having specificity to PDH. The role thereof is to inactivate E1 $\alpha$  subunit of the 20 PDH complex by phosphorylation. The other is PDH phosphatase, which is a specific protein phosphatase that activates PDH via dephosphorylation of E1 $\alpha$  subunit. The proportion of PDH in its active (dephosphorylated) state is determined by the balance of kinase activity and phosphatase activity. The kinase 25 activity is regulated by the relative concentration of metabolic substrates. For example, the kinase activity is activated by an increase in NADH/NAD, acetyl-CoA/CoA and ATP/adenosine diphosphate (ADP) ratios, and inhibited by pyruvic acid (e.g., non-patent document 3).

30 [0004]

In the tissues of mammals, 4 kinds of PDHK isozymes are identified. Particularly, PDHK2 is expressed in a wide range of tissues including the liver, skeletal muscles and adipose tissues involved in glucose metabolism. Furthermore, since

PDHK2 shows comparatively high sensitivity to activation by increased NADH/NAD or acetyl-CoA/CoA and inhibition by pyruvic acid, involvement in a short-term regulation of glucose metabolism is suggested (e.g., non-patent document 4).

5 [0005]

In addition, PDHK1 is expressed in large amounts in cardiac muscle, skeletal muscle, pancreatic  $\beta$  cell and the like. Furthermore, since expression of PDHK1 is induced via activation of hypoxia inducible factor (HIF) 1 in ischemic 10 state, its involvement in ischemic diseases and cancerous diseases is suggested (e.g., non-patent document 5).

[0006]

In diseases such as insulin-dependent (type 1) diabetes, non-insulin-dependent (type 2) diabetes and the like, 15 oxidation of lipids is promoted with simultaneous reduction in glucose utilization. This reduction in glucose utilization is one of the factors causing hyperglycemia. When the oxidative glucose metabolism decreases in type 1 and type 2 diabetes and obesity, PDH activity also decreases. It suggests involvement 20 of reduced PDH activity in the reduced glucose utilization in type 1 and type 2 diabetes (e.g., non-patent documents 6, 7).

On the contrary, hepatic gluconeogenesis is enhanced in type 1 and type 2 diabetes, which also forms one factor causing hyperglycemia. The reduced PDH activity increases 25 pyruvic acid concentration, which in turn increases availability of lactic acid as a substrate for hepatic gluconeogenesis. It suggests possible involvement of reduced PDH activity in the enhanced gluconeogenesis in type 1 and type 2 diabetes (e.g., non-patent documents 8, 9).

30 When PDH is activated by inhibition of PDHK, the rate of glucose oxidation is considered to rise. As a result, glucose utilization in the body is promoted and hepatic gluconeogenesis is suppressed, whereby hyperglycemia in type 1 and type 2 diabetes is expected to be improved (e.g., non-

patent documents 10, 11, 12).

Another factor contributing to diabetes is impaired insulin secretion, which is known to be associated with reduced PDH activity in pancreatic  $\beta$  cells, and induction of 5 PDHK1, 2 and 4 (e.g., non-patent documents 13, 14).

In addition, sustained hyperglycemia due to diabetes is known to cause complications such as diabetic neuropathy, diabetic retinopathy, diabetic nephropathy and the like.

Thiamine and  $\alpha$ -lipoic acid contribute to activation of PDH as 10 coenzymes. Thiamine and  $\alpha$ -lipoic acid, or thiamine derivatives and  $\alpha$ -lipoic acid derivatives are shown to have a promising effect on the treatment of diabetic complications. Thus, activation of PDH is expected to improve diabetic complications (e.g., non-patent documents 15, 16).

15 [0007]

Under ischemic conditions, limited oxygen supply reduces oxidation of both glucose and fatty acid and reduces the amount of ATP produced by oxidative phosphorylation in the tissues. In the absence of sufficient oxygen, ATP level is 20 maintained by promoted anaerobic glycolysis. As a result, lactic acid increases and intracellular pH decreases. Even though the cells try to maintain homeostasis of ion by energy consumption, abnormally low ATP level and disrupted cellular osmolarity lead to cell death. In addition, adenosine 25 monophosphate-activating kinase activated in an ischemic state inactivates acetyl-CoA carboxylase by phosphorylation. The levels of total malonyl-CoA in the tissue drop, carnitine palmitoyltransferase-I activity is therefore increased and fatty acid oxidation is favored over glucose oxidation by 30 allowing the transport of acyl-CoA into mitochondria. Oxidation of glucose is capable of yielding more ATP per molecule of oxygen than is oxidation of fatty acids. Under ischemic conditions, therefore, when energy metabolism becomes glucose oxidation dominant by activation of PDH, the ability

to maintain ATP level is considered to be enhanced (e.g., non-patent document 17).

In addition, since activation of PDH causes oxidation of pyruvic acid produced by glycolysis, and reducing production 5 of lactic acid, the net proton burden is considered to be reduced in ischemic tissues. Therefore, PDH activation by inhibition of PDHK is expected to protectively act in ischemic diseases such as cardiac muscle ischemia (e.g., non-patent documents 18, 19).

10 [0008]

A drug that activates PDH by inhibition of PDHK is considered to decrease lactate production since it promotes pyruvate metabolism. Hence, such drug is expected to be useful for the treatment of hyperlactacidemia such as mitochondrial 15 disease, mitochondrial encephalomyopathy and sepsis (e.g., non-patent document 20).

[0009]

In cancer cells, the expression of PDHK1 or 2 increases. In cancer cells, moreover, ATP production by oxidative 20 phosphorylation in mitochondria decreases, and ATP production via the anaerobic glycolysis in cytoplasm increases. PDH activation by inhibition of PDHK is expected to promote oxidative phosphorylation in mitochondria, and increase production of active oxygen, which will induce apoptosis of 25 cancer cells. Therefore, the PDH activation by PDHK inhibition is useful for the treatment of cancerous diseases (e.g., non-patent document 21).

[0010]

Pulmonary hypertension is characterized by high blood 30 pressure caused by partial narrowing of the pulmonary artery due to promoted cellular proliferation therein. In pulmonary hypertension, therefore, activation of PDH in the pulmonary artery cell is expected to promote oxidative phosphorylation in mitochondria, increase production of active oxygen, and

induce apoptosis of the pulmonary artery cells. Therefore, the PDH activation by PDHK inhibition is considered to be useful for the treatment of pulmonary hypertension, for example, pulmonary arterial hypertension (e.g., non-patent document 22).

5 [0011]

Energy production and glucose metabolism in the cerebrum decrease in Alzheimer disease, and also, PDH activity declines. When the PDH activity declines, production of acetyl CoA decreases. Acetyl CoA is utilized for ATP production in the 10 electron transport system via the citric acid cycle. Acetyl CoA is also a starting material for synthesizing acetylcholine, which is one of the neurotransmitters. Therefore, reduced brain PDH activity in Alzheimer disease is considered to cause neuronal cell death due to the decreased ATP production.

15 Moreover, it is considered that synthesis of acetylcholine, which is the transmitter for cholinergic nerve, is inhibited to induce deterioration of memory and the like. Activation of PDH in the brain is expected to enhance energy production and acetylcholine synthesis in Alzheimer disease. Therefore, 20 activation of PDH by the inhibition of PDHK is considered to be useful for the treatment of Alzheimer disease (e.g., non-patent documents 23, 24).

[0012]

Vascular dementia is a disease that is roughly classified 25 into a large-vessel type and a small-vessel type. In the large-vessel type, cerebral infarction including ischemia reperfusion is a factor, and neuronal cell death is induced by an increase in pyruvic acid and lactic acid values due to a decrease in the intracerebral PDH activity, and a decrease in 30 energy production. In the small-vessel type, white matter lesion due to cerebral hypoperfusion is a factor and is considered to cause cognitive dysfunction due to a chronic decrease in glucose metabolism. When PDH in the brain is activated in vascular dementia, a decrease in the lactic acid

value and the like and an increase in the energy production are expected in the large-vessel type, and promoted glucose metabolism is expected in the small-vessel type. Therefore, activation of PDH by PDHK inhibitors is considered to be 5 useful for the treatment of vascular dementia (e.g., non-patent documents 28, 29, 30).

[0013]

It has been shown that dichloroacetic acid, which is a drug having a PDH activating action, provides promising 10 effects for the treatment of diabetes, myocardial ischemia, myocardial infarction, angina pectoris, cardiac failure, hyperlactacidemia, brain ischemia, cerebral apoplexy, peripheral arterial disease, chronic obstructive pulmonary disease, cancerous disease, and pulmonary hypertension (e.g., 15 non-patent documents 10, 18, 20, 22, 25, 26, 27).

It has been shown that a compound having a PDHK inhibitory action has a neuroprotective effect on retinal ischemia-reperfusion injury (non-patent document 31). Retinal ischemia injury is involved in diseases such as glaucoma, 20 diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion and the like.

It has also been shown that in disease model animals exhibiting chronic kidney disease-like renal disorder and decreased renal function, compounds having a PDHK inhibitory 25 action reduce the severity of the diseases (patent document 1).

[0014]

From the foregoing findings, a PDHK inhibitor is considered to be useful for the treatment or prophylaxis of diseases relating to glucose utilization disorder, for example, 30 diabetes (type 1 diabetes, type 2 diabetes etc.), insulin resistance syndrome, metabolic syndrome, hyperglycemia, hyperlactacidemia, diabetic complications (diabetic neuropathy, diabetic retinopathy, diabetic nephropathy, cataract etc.). Furthermore, a PDHK inhibitor is considered to be useful for

the treatment or prophylaxis of diseases caused by limited energy substrate supply to the tissues, for example, cardiac failure (acute cardiac failure, chronic cardiac failure), cardiomyopathy, myocardial ischemia, myocardial infarction,  
5 angina pectoris, dyslipidemia, atherosclerosis, peripheral arterial disease, intermittent claudication, chronic obstructive pulmonary disease, brain ischemia, cerebral apoplexy, Alzheimer disease, vascular dementia, glaucoma, diabetic retinopathy, retinopathy of prematurity, retinal vein  
10 occlusion, ischemic optic neuropathy and chronic kidney disease. Furthermore, a PDHK inhibitor is considered to be useful for the treatment or prophylaxis of mitochondrial disease, mitochondrial encephalomyopathy, cancer, pulmonary hypertension and the like.

15 [0015]

Therefore, a PDHK inhibitor is considered to be useful for the treatment or prophylaxis of diabetes (type 1 diabetes, type 2 diabetes etc.), insulin resistance syndrome, metabolic syndrome, hyperglycemia, hyperlactacidemia, diabetic complications (diabetic neuropathy, diabetic retinopathy, diabetic nephropathy, cataract etc.), cardiac failure (acute cardiac failure, chronic cardiac failure), cardiomyopathy, myocardial ischemia, myocardial infarction, angina pectoris, dyslipidemia, atherosclerosis, peripheral arterial disease,  
20 intermittent claudication, chronic obstructive pulmonary disease, brain ischemia, cerebral apoplexy, mitochondrial disease, mitochondrial encephalomyopathy, cancer, pulmonary hypertension, Alzheimer disease, vascular dementia, glaucoma, diabetic retinopathy, retinopathy of prematurity, retinal vein  
25 occlusion, ischemic optic neuropathy, or chronic kidney disease.

[Citation List]

[Patent Literature]

[0016]

[PTL 1]

WO 2020/054734

[Non Patent Literature]

[0017]

5 [NPL 1]

Reed LJ, Hackert ML. Structure-function relationships in dihydrolipoamide acyltransferases. *J Biol Chem.* 1990 Jun 5; 265(16):8971-4.

[NPL 2]

10 Patel MS, Roche TE. Molecular biology and biochemistry of pyruvate dehydrogenase complexes. *FASEB J.* 1990 Nov; 4(14):3224-33.

[NPL 3]

15 Sugden MC, Holness MJ. Recent advances in mechanisms regulating glucose oxidation at the level of the pyruvate dehydrogenase complex by PDKs. *Am J Physiol Endocrinol Metab.* 2003 May; 284(5):E855-62.

[NPL 4]

20 Bowker-Kinley MM, Davis WI, Wu P, Harris RA, Popov KM. Evidence for existence of tissue-specific regulation of the mammalian pyruvate dehydrogenase complex. *Biochem J.* 1998 Jan 1; 329 (Pt 1):191-6.

[NPL 5]

25 Kim JW, Tchernyshyov I, Semenza GL, Dang CV. HIF-1-mediated expression of pyruvate dehydrogenase kinase: a metabolic switch required for cellular adaptation to hypoxia. *Cell Metab.* 2006 Mar; 3(3):177-85.

[NPL 6]

30 Morino K, Petersen KF, Dufour S, Befroy D, Frattini J, Shatzkes N, et al. Reduced mitochondrial density and increased IRS-1 serine phosphorylation in muscle of insulin-resistant offspring of type 2 diabetic parents. *J Clin Invest.* 2005 Dec; 115(12):3587-93.

[NPL 7]

Caterson ID, Fuller SJ, Randle PJ. Effect of the fatty acid oxidation inhibitor 2-tetradecylglycidic acid on pyruvate dehydrogenase complex activity in starved and alloxan-diabetic rats. *Biochem J.* 1982 Oct 15; 208(1):53-60.

5 [NPL 8]

Boden G, Chen X, Stein TP. Gluconeogenesis in moderately and severely hyperglycemic patients with type 2 diabetes mellitus. *Am J Physiol Endocrinol Metab.* 2001 Jan; 280(1):E23-30.

[NPL 9]

10 Shangraw RE, Fisher DM. Pharmacokinetics and pharmacodynamics of dichloroacetate in patients with cirrhosis. *Clin Pharmacol Ther.* 1999 Oct; 66(4):380-90.

[NPL 10]

15 Stacpoole PW, Moore GW, Kornhauser DM. Metabolic effects of dichloroacetate in patients with diabetes mellitus and hyperlipoproteinemia. *NEngl J Med.* 1978 Mar 9; 298(10):526-30.

[NPL 11]

20 Mayers RM, Leighton B, Kilgour E. PDH kinase inhibitors: a novel therapy for Type II diabetes? *Biochem Soc Trans.* 2005 Apr; 33(Pt 2):367-70.

[NPL 12]

Jeoung NH, Rahimi Y, Wu P, Lee WN, Harris RA. Fasting induces ketoacidosis and hypothermia in PDHK2/PDHK4-double-knockout mice. *Biochem J.* 2012 May 1; 443(3):829-39.

25 [NPL 13]

Zhou YP, Berggren PO, Grill V. A fatty acid-induced decrease in pyruvate dehydrogenase activity is an important determinant of beta-cell dysfunction in the obese diabetic db/db mouse. *Diabetes.* 1996 May; 45(5):580-6.

30 [NPL 14]

Xu J, Han J, Epstein PN, Liu YQ. Regulation of PDK mRNA by high fatty acid and glucose in pancreatic islets. *Biochem Biophys Res Commun.* 2006 Jun 9; 344(3):827-33.

[NPL 15]

Benfotiamine. Monograph. Altern Med Rev. 2006 Sep; 11(3):238-42.

[NPL 16]

Vallianou N, Evangelopoulos A, Koutalas P. Alpha-lipoic Acid and diabetic neuropathy. Rev Diabet Stud. 2009 Winter; 6(4):230-6.

[NPL 17]

Ussher JR, Lopaschuk GD. The malonyl CoA axis as a potential target for treating ischaemic heart disease. Cardiovasc Res. 2008 Jul 15; 79(2):259-68.

[NPL 18]

Wargovich TJ, MacDonald RG, Hill JA, Feldman RL, Stacpoole PW, Pepine CJ. Myocardial metabolic and hemodynamic effects of dichloroacetate in coronary arterial disease. Am J Cardiol. 1988 Jan 1; 61(1):65-70.

[NPL 19]

Taniguchi M, Wilson C, Hunter CA, Pehowich DJ, Clanachan AS, Lopaschuk GD. Dichloroacetate improves cardiac efficiency after ischemia independent of changes in mitochondrial proton leak. Am J Physiol Heart Circ Physiol. 2001 Apr; 280(4):H1762-9.

[NPL 20]

Stacpoole PW, Nagaraja NV, Hutson AD. Efficacy of dichloroacetate as a lactate-lowering drug. J Clin Pharmacol. 2003 Jul; 43(7):683-91.

[NPL 21]

Bonnet S, Archer SL, Allalunis-Turner J, Haromy A, Beaulieu C, Thompson R, et al. A mitochondria-K<sup>+</sup> channel axis is suppressed in cancer and its normalization promotes apoptosis and inhibits cancer growth. Cancer Cell. 2007 Jan; 11(1):37-51.

[NPL 22]

McMurtry MS, Bonnet S, Wu X, Dyck JR, Haromy A, Hashimoto K, et al. Dichloroacetate prevents and reverses pulmonary hypertension by inducing pulmonary artery smooth muscle cell

apoptosis. *Circ Res.* 2004 Oct 15; 95(8):830-40.

[NPL 23]

Saxena U. Bioenergetics breakdown in Alzheimer's disease: targets for new therapies. *Int J Physiol Pathophysiol Pharmacol.* 2011; 3(2):133-9.

[NPL 24]

Stacpoole PW. The pyruvate dehydrogenase complex as a therapeutic target for age-related diseases. *Aging Cell.* 2012 Jun; 11(3):371-7.

[NPL 25]

Marangos PJ, Turkel CC, Dziewanowska ZE, Fox AW. Dichloroacetate and cerebral ischaemia therapeutics. *Expert Opin Investig Drugs.* 1999 Apr; 8(4):373-82.

[NPL 26]

Calvert LD, Shelley R, Singh SJ, Greenhaff PL, Bankart J, Morgan MD, et al. Dichloroacetate enhances performance and reduces blood lactate during maximal cycle exercise in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2008 May 15; 177(10):1090-4.

[NPL 27]

Flavin DF. Non-Hodgkin's Lymphoma Reversal with Dichloroacetate. *J Oncol.* Hindawi Publishing Corporation Journal of Oncology Volume 2010, Article ID 414726, 4 pages doi:10.1155/2010/414726.

[NPL 28]

Froelich L, Goetz ME, Weinmueller M, Youdim MB, Barth N, Dirr A, Gsell W, Jellinger K, Beckmann H, Riederer P. (r)-, but not (s)-alpha lipoic acid stimulates deficient brain pyruvate dehydrogenase complex in vascular dementia, but not in Alzheimer dementia. *J Neural Transm (Vienna).* 2004 Mar; 111(3):295-310

[NPL 29]

Parnetti L, Rebaldi GP, Gallai V. Cerebrospinal fluid pyruvate levels in Alzheimer's disease and vascular dementia. *Neurology.*

2000 Feb 8; 54(3):735-7.

[NPL 30]

Pascual B, Prieto E, Arbizu J, Marti-Climent J, Olier J, Masdeu JC. Brain glucose metabolism in vascular white matter disease with dementia: differentiation from Alzheimer disease. Stroke. 2010 Dec; 41(12):2889-93.

[NPL 31]

Sato K, Mochida S, Tomimoto D, Konuma T, Kiyota N, Tsuda S, Shiga Y, Omodaka K, Nakazawa T. A pyruvate dehydrogenase kinase inhibitor prevents retinal cell death and improves energy metabolism in rat retinas after ischemia/reperfusion injury. Experimental eye research 2020 Apr; 193: 107997.

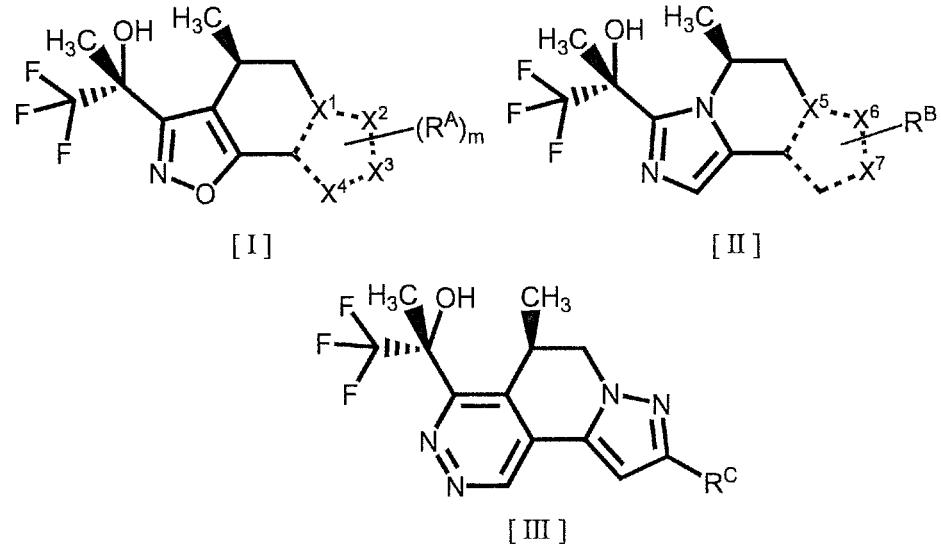
[Summary of Invention]

[0018]

15 The present invention is as follows.

[1] A compound of the formula [I], the formula [II], or the formula [III], or a pharmaceutically acceptable salt thereof:

[0019]



20 [0020]

wherein

-- is a single bond or a double bond,

$X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$ ,  $X^5$ ,  $X^6$  and  $X^7$  are each independently C or N,

$R^A$  is

(1)  $C_{1-6}$  alkyl wherein the  $C_{1-6}$  alkyl is optionally substituted by one substituent selected from the group consisting of hydroxy and cyano,

(2) halo  $C_{1-4}$  alkyl,

5 (3)  $-OR^a$  wherein  $R^a$  is

(i)  $C_{1-6}$  alkyl wherein the  $C_{1-6}$  alkyl is optionally substituted by one substituent selected from the group consisting of

10 (a) hydroxy,

(b) cyano,

(c)  $C_{1-4}$  alkoxy,

(d)  $C_{3-6}$  cycloalkyl optionally substituted by one cyano,

(e) phenyl, and

15 (f) 4- to 6-membered saturated heterocyclyl having one oxygen atom,

(ii) halo  $C_{1-4}$  alkyl,

(iii) 4- to 6-membered saturated heterocyclyl having one oxygen atom, or

20 (iv)  $C_{3-6}$  cycloalkyl wherein the  $C_{3-6}$  cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of  $C_{1-6}$  alkyl, hydroxy, and cyano,

(4) phenyl optionally substituted by one halogen,

(5)  $C_{3-6}$  cycloalkyl wherein the  $C_{3-6}$  cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

25 (i) halogen,

(ii)  $C_{1-4}$  alkyl,

(iii) halo  $C_{1-4}$  alkyl,

30 (iv) hydroxy, and

(v) cyano,

(6) 4- to 6-membered saturated heterocyclyl having one oxygen atom, or

(7) bridged  $C_{5-10}$  cycloalkyl wherein the bridged  $C_{5-10}$  cycloalkyl

is optionally substituted by one substituent selected from the group consisting of

- (i)  $C_{1-4}$  alkoxy carbonyl,
- (ii) hydroxy  $C_{1-4}$  alkyl,
- 5 (iii) halo  $C_{1-4}$  alkyl, and
- (iv) cyano,

$m$  is 0 or 1,

$R^B$  is

- (1) phenyl,
- 10 (2) 4- to 6-membered saturated heterocyclyl having 1 or 2 hetero atoms independently selected from a nitrogen atom and an oxygen atom,
- (3) 6- to 10-membered saturated fused heterocyclyl having 1 or 2 hetero atoms independently selected from a nitrogen atom and an oxygen atom wherein the saturated fused heterocyclyl is 15 optionally substituted by 1 or 2 halogens,
- (4) 6- to 10-membered spiro heterocyclyl having 1 or 2 hetero atoms independently selected from a nitrogen atom and an oxygen atom wherein the spiro heterocyclyl is optionally substituted by 1 or 2 halogens,
- 20 (5) 5- to 10-membered bridged heterocyclyl having 1 or 2 hetero atoms independently selected from a nitrogen atom and an oxygen atom wherein the bridged heterocyclyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of halogen, cyano, and hydroxy  $C_{1-4}$  alkyl,
- (6) bridged  $C_{5-10}$  cycloalkyl wherein the bridged  $C_{5-10}$  cycloalkyl is optionally substituted by one substituent selected from the group consisting of hydroxy  $C_{1-4}$  alkyl and cyano, or
- (7)  $-OCH_2Cy^1$  wherein  $Cy^1$  is bridged  $C_{5-10}$  cycloalkyl optionally substituted by one cyano, and

$R^C$  is

- (1) halo  $C_{1-4}$  alkyl,
- (2)  $C_{3-6}$  cycloalkyl optionally substituted by one halogen, or
- (3) bridged  $C_{5-10}$  cycloalkyl wherein the bridged  $C_{5-10}$  cycloalkyl

is optionally substituted by one substituent selected from the group consisting of cyano and C<sub>1-4</sub> alkoxy carbonyl.

[0021]

[2] The compound of [1] or a pharmaceutically acceptable salt 5 thereof, which is a compound of the formula [I] or a pharmaceutically acceptable salt thereof.

[3] The compound of [1] or [2], wherein R<sup>a</sup> is

(1) halo C<sub>1-4</sub> alkyl,

(2) -OR<sup>a</sup> wherein R<sup>a</sup> is

10 (i) C<sub>1-6</sub> alkyl wherein the C<sub>1-6</sub> alkyl is optionally substituted by one substituent selected from the group consisting of

(a) hydroxy,

(b) C<sub>3-6</sub> cycloalkyl optionally substituted by one cyano,

15 and

(c) 4- to 6-membered saturated heterocyclyl having one oxygen atom,

(ii) halo C<sub>1-4</sub> alkyl,

20 (iii) 4- to 6-membered saturated heterocyclyl having one oxygen atom, or

(iv) C<sub>3-6</sub> cycloalkyl wherein the C<sub>3-6</sub> cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of C<sub>1-6</sub> alkyl, hydroxy, and cyano,

25 (3) C<sub>3-6</sub> cycloalkyl wherein the C<sub>3-6</sub> cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

(i) C<sub>1-4</sub> alkyl,

(ii) hydroxy, and

30 (iii) cyano, or

(4) 4- to 6-membered saturated heterocyclyl having one oxygen atom, or a pharmaceutically acceptable salt thereof.

[0022]

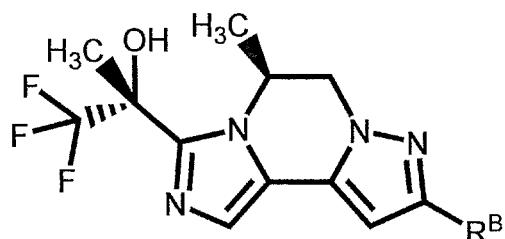
[4] The compound of [1] or [2], wherein m is 0, or a

pharmaceutically acceptable salt thereof.

[0023]

[5] The compound of [1], or a pharmaceutically acceptable salt thereof, which is a compound of the formula [II-a]:

5 [0024]



[ II -a]

[0025]

wherein R<sup>B</sup> is

(1) 6- to 10-membered spiro heterocyclyl having 1 or 2 hetero atoms independently selected from a nitrogen atom and an oxygen atom wherein the spiro heterocyclyl is optionally substituted by 1 or 2 halogens,

(2) 5- to 10-membered bridged heterocyclyl having 1 or 2 hetero atoms independently selected from a nitrogen atom and an oxygen atom wherein the bridged heterocyclyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of halogen, cyano, and hydroxy C<sub>1-4</sub> alkyl,

(3) bridged C<sub>5-10</sub> cycloalkyl wherein the bridged C<sub>5-10</sub> cycloalkyl is optionally substituted by one substituent selected from the group consisting of hydroxy C<sub>1-4</sub> alkyl and cyano, or

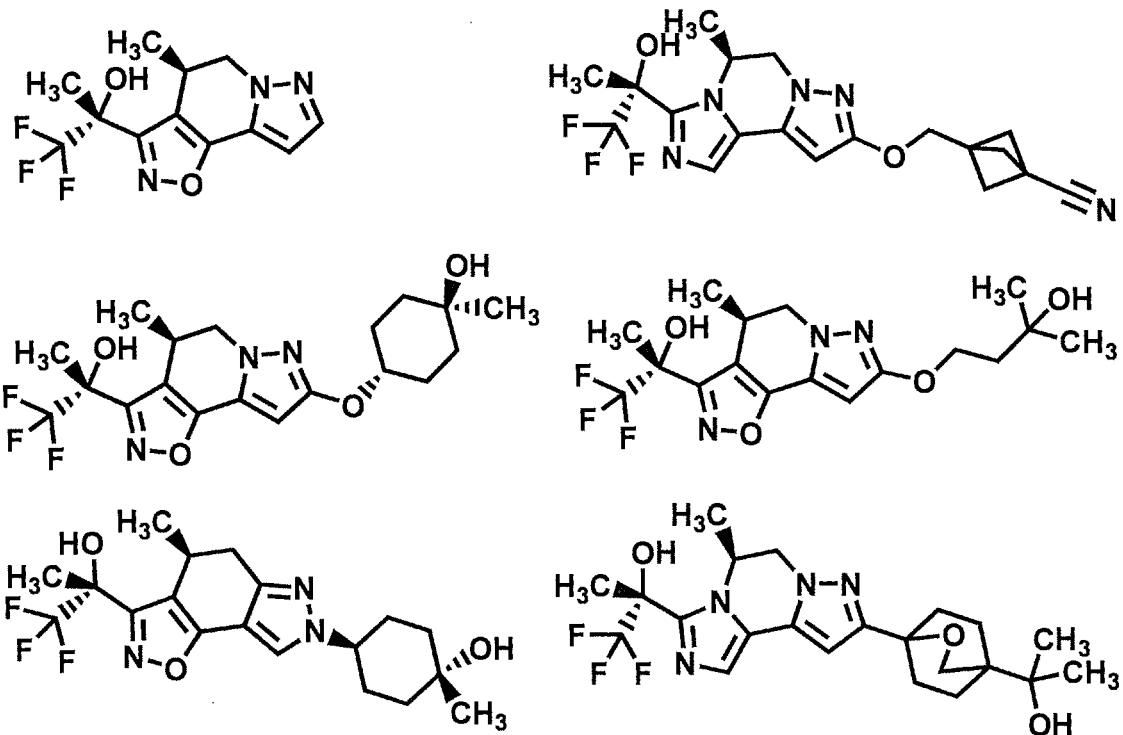
(4) -OCH<sub>2</sub>Cy<sup>1</sup> wherein Cy<sup>1</sup> is bridged C<sub>5-10</sub> cycloalkyl optionally substituted by one cyano,

or a pharmaceutically acceptable salt thereof.

[0026]

25 [6] A compound selected from the following formulas:

[0027]



[0028]

or a pharmaceutically acceptable salt thereof.

[0029]

5 [7] A pharmaceutical composition comprising the compound of any one of [1] to [6] or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[8] A PDHK inhibitor comprising the compound of any one of [1] to [6] or a pharmaceutically acceptable salt thereof.

10 [9] A PDHK2 inhibitor comprising the compound of any one of [1] to [6] or a pharmaceutically acceptable salt thereof.

[0030]

15 [10] An agent for the treatment or prophylaxis of diabetes, insulin resistance syndrome, metabolic syndrome, hyperglycemia, hyperlactacidemia, diabetic complication, cardiac failure, cardiomyopathy, myocardial ischemia, myocardial infarction, angina pectoris, dyslipidemia, atherosclerosis, peripheral arterial disease, intermittent claudication, chronic obstructive pulmonary disease, brain ischemia, cerebral 20 apoplexy, mitochondrial disease, mitochondrial encephalomyopathy, cancer, pulmonary hypertension, Alzheimer

disease, vascular dementia, glaucoma, diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion, ischemic optic neuropathy or chronic kidney disease, the agent comprising the compound of any one of [1] to [6] or a 5 pharmaceutically acceptable salt thereof.

[11] The agent of [10], wherein the diabetes is type 1 diabetes or type 2 diabetes.

[12] The agent of [10], wherein the vascular dementia is a 10 large-vessel type of vascular dementia or a small-vessel type of vascular dementia.

[13] The agent of [10], wherein the cardiac failure is acute cardiac failure or chronic cardiac failure.

[14] The agent of [10], wherein the pulmonary hypertension is pulmonary arterial hypertension.

15 [0031]

[15] A method for inhibiting PDHK, comprising administering a therapeutically effective amount of the compound of any one of [1] to [6] or a pharmaceutically acceptable salt thereof to a mammal.

20 [16] A method for treating or preventing a disease selected from the group consisting of diabetes, insulin resistance syndrome, metabolic syndrome, hyperglycemia, hyperlactacidemia, diabetic complication, cardiac failure, cardiomyopathy, myocardial ischemia, myocardial infarction, angina pectoris, 25 dyslipidemia, atherosclerosis, peripheral arterial disease, intermittent claudication, chronic obstructive pulmonary disease, brain ischemia, cerebral apoplexy, mitochondrial disease, mitochondrial encephalomyopathy, cancer, pulmonary hypertension, Alzheimer disease, vascular dementia, glaucoma, 30 diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion, ischemic optic neuropathy and chronic kidney disease, the method comprising administering a therapeutically effective amount of the compound of any one of [1] to [6] or a pharmaceutically acceptable salt thereof to a mammal.

[17] The method of [16], wherein the diabetes is type 1 diabetes or type 2 diabetes.

[18] The method of [16], wherein the vascular dementia is a large-vessel type of vascular dementia or a small-vessel type 5 of vascular dementia.

[19] The method of [16], wherein the cardiac failure is acute cardiac failure or chronic cardiac failure.

[20] The method of [16], wherein the pulmonary hypertension is pulmonary arterial hypertension.

10 [0032]

[21] Use of the compound of any one of [1] to [6] or a pharmaceutically acceptable salt thereof in the manufacture of a PDHK inhibitor.

[22] Use of the compound of any one of [1] to [6] or a 15 pharmaceutically acceptable salt thereof in the manufacture of an agent for the treatment or prophylaxis of a disease selected from the group consisting of diabetes, insulin 20 resistance syndrome, metabolic syndrome, hyperglycemia, hyperlactacidemia, diabetic complication, cardiac failure, cardiomyopathy, myocardial ischemia, myocardial infarction, angina pectoris, dyslipidemia, atherosclerosis, peripheral arterial disease, intermittent claudication, chronic 25 obstructive pulmonary disease, brain ischemia, cerebral apoplexy, mitochondrial disease, mitochondrial encephalomyopathy, cancer, pulmonary hypertension, Alzheimer disease, vascular dementia, glaucoma, diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion, ischemic optic neuropathy and chronic kidney disease.

[23] The use of [22], wherein the diabetes is type 1 diabetes 30 or type 2 diabetes.

[24] The use of [22], wherein the vascular dementia is a large-vessel type of vascular dementia or a small-vessel type of vascular dementia.

[25] The use of [22] wherein the cardiac failure is acute

cardiac failure or chronic cardiac failure.

[26] The use of [22] wherein the pulmonary hypertension is pulmonary arterial hypertension.

[0033]

5 [27] The compound of any one of [1] to [6] or a pharmaceutically acceptable salt thereof for use in the treatment or prophylaxis of a disease selected from the group consisting of diabetes, insulin resistance syndrome, metabolic syndrome, hyperglycemia, hyperlactacidemia, diabetic  
10 complication, cardiac failure, cardiomyopathy, myocardial ischemia, myocardial infarction, angina pectoris, dyslipidemia, atherosclerosis, peripheral arterial disease, intermittent claudication, chronic obstructive pulmonary disease, brain ischemia, cerebral apoplexy, mitochondrial disease,  
15 mitochondrial encephalomyopathy, cancer, pulmonary hypertension, Alzheimer disease, vascular dementia, glaucoma, diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion, ischemic optic neuropathy and chronic kidney disease.

20 [28] The compound of [27] or a pharmaceutically acceptable salt thereof, wherein the diabetes is type 1 diabetes or type 2 diabetes.

[29] The compound of [27] or a pharmaceutically acceptable salt thereof, wherein the vascular dementia is a large-vessel  
25 type of vascular dementia or a small-vessel type of vascular dementia.

[30] The compound of [27] or a pharmaceutically acceptable salt thereof, wherein the cardiac failure is acute cardiac failure or chronic cardiac failure.

30 [31] The compound of [27] or a pharmaceutically acceptable salt thereof, wherein the pulmonary hypertension is pulmonary arterial hypertension.

[0034]

[32] A commercial package comprising the pharmaceutical

composition of [7], and a written matter associated therewith, the written matter stating that the pharmaceutical composition can be used for the treatment or prophylaxis of a disease selected from the group consisting of diabetes, insulin resistance syndrome, metabolic syndrome, hyperglycemia, hyperlactacidemia, diabetic complication, cardiac failure, cardiomyopathy, myocardial ischemia, myocardial infarction, angina pectoris, dyslipidemia, atherosclerosis, peripheral arterial disease, intermittent claudication, chronic 5 obstructive pulmonary disease, brain ischemia, cerebral apoplexy, mitochondrial disease, mitochondrial encephalomyopathy, cancer, pulmonary hypertension, Alzheimer disease, vascular dementia, glaucoma, diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion, ischemic 10 optic neuropathy and chronic kidney disease.

[0035]

[33] A kit comprising the pharmaceutical composition of [7], and a written matter associated therewith, the written matter stating that the pharmaceutical composition can be used for 20 the treatment or prophylaxis of a disease selected from the group consisting of diabetes, insulin resistance syndrome, metabolic syndrome, hyperglycemia, hyperlactacidemia, diabetic complication, cardiac failure, cardiomyopathy, myocardial ischemia, myocardial infarction, angina pectoris, dyslipidemia, 25 atherosclerosis, peripheral arterial disease, intermittent claudication, chronic obstructive pulmonary disease, brain ischemia, cerebral apoplexy, mitochondrial disease, mitochondrial encephalomyopathy, cancer, pulmonary hypertension, Alzheimer disease, vascular dementia, glaucoma, diabetic retinopathy, retinopathy of prematurity, retinal vein 30 occlusion, ischemic optic neuropathy and chronic kidney disease.

[Description of Embodiments]

[0036]

The definitions of the terms used in the present invention are as follows.

[0037]

The "halogen" is fluoro, chloro, bromo, or iodo. As 5 "halogen", fluoro or chloro is preferred.

[0038]

The "C<sub>1-4</sub> alkyl" means a straight chain or branched chain alkyl having 1 to 4 carbon atoms. Examples thereof include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl 10 and tert-butyl. As "C<sub>1-4</sub> alkyl", methyl or ethyl is preferred.

[0039]

The "C<sub>1-6</sub> alkyl" means a straight chain or branched chain alkyl having 1 to 6 carbon atoms. Examples thereof include methyl, ethyl, propyl, isopropyl, 1,1-dimethylpropyl, 1-ethyl- 15 propyl, 1-methyl-1-ethyl-propyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isoheptyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 2-ethylbutyl and the like.

[0040]

20 The "halo C<sub>1-4</sub> alkyl" means straight chain or branched chain alkyl having 1 to 4 carbon atoms and substituted by 1 to 5 "halogens" defined above. When alkyl is substituted by plural halogens, the halogens may be the same or different. Examples of the "halo C<sub>1-4</sub> alkyl" include fluoromethyl, 25 difluoromethyl, trifluoromethyl, 1-fluoroethyl, 1-fluoro-1-methylethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, 2-fluoro-2-methylethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 1,1-difluoropropyl, 1,1-difluoro-2-methylpropyl and the like. As "halo C<sub>1-4</sub> alkyl", C<sub>1-4</sub> alkyl substituted by 1 to 3 fluoros is 30 preferred.

[0041]

The "hydroxy C<sub>1-4</sub> alkyl" means "C<sub>1-4</sub> alkyl" defined above which is substituted by one hydroxy group. Examples thereof include hydroxymethyl, 2-hydroxyethyl, 1-hydroxy-1-methylethyl,

3-hydroxypropyl, 4-hydroxybutyl and the like. As "hydroxy C<sub>1-4</sub> alkyl", hydroxymethyl is preferred.

[0042]

The "C<sub>1-4</sub> alkoxy" means alkyl-oxy in which the alkyl moiety is "C<sub>1-4</sub> alkyl" defined above and includes, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy and tert-butoxy. As "C<sub>1-4</sub> alkoxy", methoxy is preferred.

[0043]

The "C<sub>1-4</sub> alkoxycarbonyl" means alkyl-oxy-carbonyl in which the alkyl moiety is "C<sub>1-4</sub> alkyl" defined above and includes, for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl and tert-butoxycarbonyl.

[0044]

The "C<sub>3-6</sub> cycloalkyl" means a 3- to 6-membered monocyclic hydrocarbon ring group and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[0045]

The "bridged C<sub>5-10</sub> cycloalkyl" means a bridged cyclic saturated hydrocarbon group having 5 to 10 carbon atoms. The bridged cyclic saturated hydrocarbon group means a ring group in which two cycloalkyls share three or more atoms. Examples of the "bridged C<sub>5-10</sub> cycloalkyl" include bicyclo[1.1.1]pentyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, and bicyclo[2.2.2]octyl.

[0046]

The "4- to 6-membered saturated heterocyclyl having one oxygen atom" means a 4- to 6-membered monocyclic saturated heterocyclic group having one oxygen atom besides carbon atom. Examples of the saturated heterocyclyl include oxetanyl, tetrahydrofuranyl, and tetrahydropyranyl.

[0047]

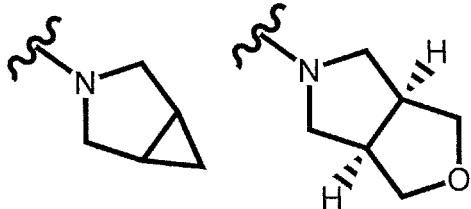
The "4- to 6-membered saturated heterocyclyl having 1 or 2 hetero atoms independently selected from a nitrogen atom and

an oxygen atom" means a 4- to 6-membered monocyclic saturated heterocyclic group having, besides carbon atom, 1 or 2 hetero atoms independently selected from the group consisting of a nitrogen atom and an oxygen atom. Examples of the saturated heterocyclyl include oxetanyl, tetrahydrofuranyl, 5 tetrahydropyranyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, and the like, and morpholinyl is preferred.

[0048]

10 The "6- to 10-membered saturated fused heterocyclyl having 1 or 2 hetero atoms independently selected from a nitrogen atom and an oxygen atom" means a 6- to 10-membered fused bicyclic saturated heterocyclic group having, besides carbon atom, 1 or 2 hetero atoms independently selected from 15 the group consisting of a nitrogen atom and an oxygen atom. The fused bicyclic saturated heterocycle means a heterocycle in which two saturated rings share two atoms. Examples of the saturated fused heterocyclyl include the following partial structures.

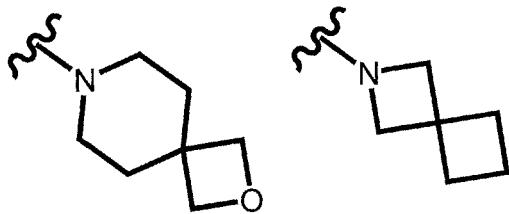
20 [0049]



[0050]

The "6- to 10-membered spiro heterocyclyl having 1 or 2 hetero atoms independently selected from a nitrogen atom and 25 an oxygen atom" means a 6- to 10-membered spirocyclic saturated heterocyclic group having, besides carbon atom, 1 or 2 hetero atoms independently selected from the group consisting of a nitrogen atom and an oxygen atom. The spirocyclic saturated heterocycle means a heterocycle in which 30 two saturated rings share one atom. Examples of the spiro heterocyclyl include the following partial structures.

[0051]

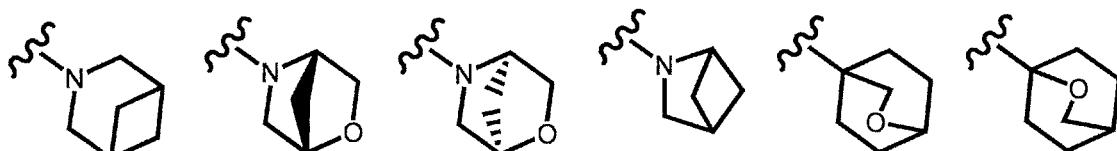


[0052]

The "5- to 10-membered bridged heterocyclyl having 1 or 2 hetero atoms independently selected from a nitrogen atom and an oxygen atom" means a heterocyclyl in which one or two carbon atoms of the "bridged C<sub>5-10</sub> cycloalkyl" defined above are replaced with hetero atoms independently selected from the group consisting of a nitrogen atom and an oxygen atom.

10 Examples of the bridged heterocyclyl include the following partial structures.

[0053]

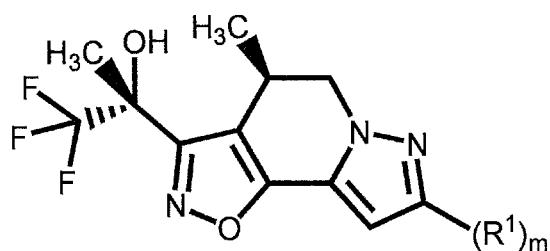


[0054]

15 Preferred embodiments of the compound of the formula [I] or the formula [II] are explained below.

One of the preferred embodiments of the formula [I] is the formula [I-a]:

[0055]



20

[I-a]

[0056]

wherein R<sup>1</sup> is

(1) -OR<sup>a</sup> wherein R<sup>a</sup> is

(i) C<sub>1-6</sub> alkyl wherein the C<sub>1-6</sub> alkyl is optionally

substituted by one substituent selected from the group consisting of

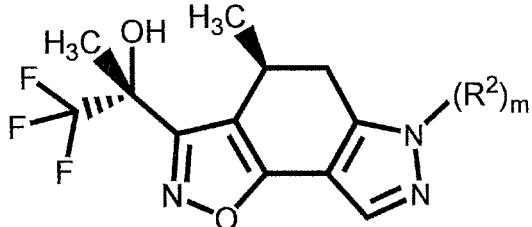
- (a) hydroxy,
- (b) cyano,
- 5 (c)  $C_{1-4}$  alkoxy,
- (d) phenyl, and
- (e) 4- to 6-membered saturated heterocyclyl having one oxygen atom,

10 (ii) halo  $C_{1-4}$  alkyl, or  
(iii)  $C_{3-6}$  cycloalkyl wherein the  $C_{3-6}$  cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of  $C_{1-6}$  alkyl, hydroxy, and cyano, or  
(2) 4- to 6-membered saturated heterocyclyl having one oxygen atom, and  
15 other symbol is as defined for the aforementioned formula [I].

[0057]

Another preferred embodiment of the formula [I] is the formula [I-b]:

20 [0058]



[I-b]

[0059]

wherein  $R^2$  is

- (1)  $C_{1-6}$  alkyl wherein the  $C_{1-6}$  alkyl is optionally substituted by one substituent selected from the group consisting of hydroxy and cyano,
- (2) halo  $C_{1-4}$  alkyl,
- (3)  $C_{3-6}$  cycloalkyl wherein the  $C_{3-6}$  cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from

the group consisting of

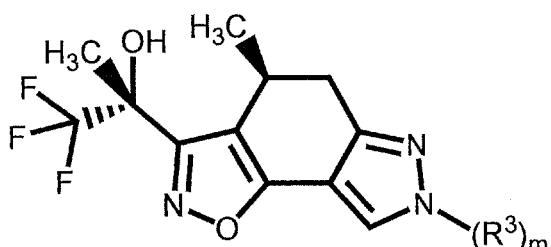
- (i)  $C_{1-4}$  alkyl,
- (ii) cyano, and
- (iii) hydroxy, or

5 (4) bridged  $C_{5-10}$  cycloalkyl wherein the bridged  $C_{5-10}$  cycloalkyl is optionally substituted by one cyano, and other symbol is as defined for the aforementioned formula [I].

[0060]

Another preferred embodiment of the formula [I] is the 10 formula [I-c]:

[0061]



[I-c]

[0062]

wherein  $R^3$  is

15 (1)  $C_{1-6}$  alkyl wherein the  $C_{1-6}$  alkyl is optionally substituted by one substituent selected from the group consisting of hydroxy and cyano,

(2) halo  $C_{1-4}$  alkyl,

(3)  $C_{3-6}$  cycloalkyl wherein the  $C_{3-6}$  cycloalkyl is optionally 20 substituted by 1 or 2 substituents independently selected from the group consisting of

- (i)  $C_{1-4}$  alkyl,
- (ii) cyano, and
- (iii) hydroxy, or

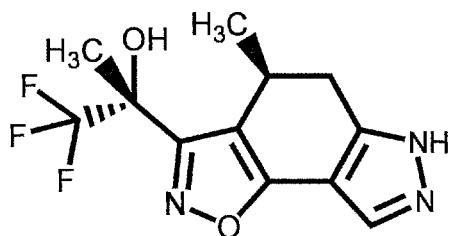
25 (4) bridged  $C_{5-10}$  cycloalkyl wherein the bridged  $C_{5-10}$  cycloalkyl is optionally substituted by one cyano, and other symbol is as defined for the aforementioned formula [I].

[0063]

A compound of the formula [I-b] or the formula [I-c],

wherein m is 0 is a compound represented by the formula [I-d].

[0064]

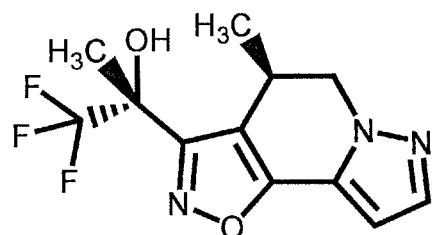


[I-d]

[0065]

5 A compound of the formula [I-a], wherein m is 0 is a compound represented by the formula [I-e].

[0066]

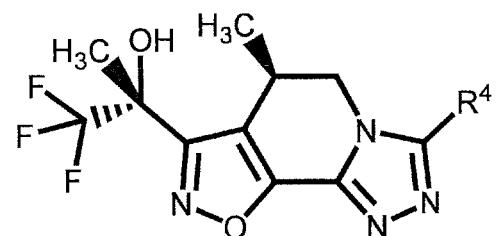


[I-e]

[0067]

10 Another preferred embodiment of the formula [I] is the formula [I-f]:

[0068]



[I-f]

[0069]

15 wherein R<sup>4</sup> is

- (1) C<sub>1-6</sub> alkyl,
- (2) halo C<sub>1-4</sub> alkyl,
- (3) C<sub>3-6</sub> cycloalkyl optionally substituted by one halogen,
- (4) phenyl optionally substituted by one halogen, or

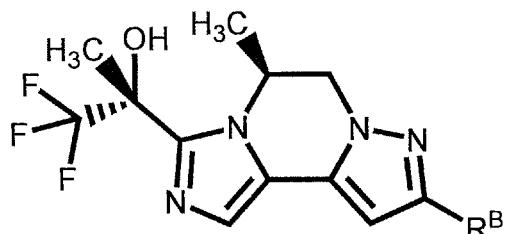
(5) bridged C<sub>5-10</sub> cycloalkyl wherein the bridged C<sub>5-10</sub> cycloalkyl is optionally substituted by one substituent selected from the group consisting of

(i) C<sub>1-4</sub> alkoxy carbonyl,  
5 (ii) hydroxy C<sub>1-4</sub> alkyl, and  
(iii) halo C<sub>1-4</sub> alkyl.

[0070]

One of the preferred embodiments of the formula [II] is the formula [II-b]:

10 [0071]



[II-b]

[0072]

wherein the symbol is as defined for the aforementioned formula [II].

15 [0073]

The "pharmaceutically acceptable salt" may be any salt without excessive toxicity known in the art. Specifically, salts with inorganic acids, salts with organic acids, salts with inorganic bases, salts with organic bases and the like can be mentioned. Various forms of pharmaceutically acceptable salts are well known in the art and for example, they are described in the following reference documents:

(a) Berge et al., J. Pharm. Sci., 66, p1-19 (1977),  
(b) Stahl et al., "Handbook of Pharmaceutical Salts:  
25 Properties, Selection, and Use" (Wiley-VCH, Weinheim, Germany,  
2002),  
(c) Paulekuhn et al., J. Med. Chem., 50, p6665-6672 (2007).

A pharmaceutically acceptable salt of a compound of the formula [I], the formula [II] or the formula [III] can be

obtained by reacting the compound with an inorganic acid, organic acid, inorganic base or organic base according to a method known per se. The compound of the formula [I], the formula [II] or the formula [III] may be formed with one half 5 molecule, one molecule or two or more molecules of an acid or base per molecule of the compound of the formula [I], the formula [II] or the formula [III].

[0074]

Examples of the salt with inorganic acid include salts 10 with hydrofluoric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, phosphoric acid and sulfuric acid.

Examples of the salt with organic acid include salts with 15 acetic acid, adipic acid, alginic acid, 4-aminosalicylic acid, anhydromethylenecitric acid, benzoic acid, benzenesulfonic acid, calcium edetate, camphoric acid, camphor-10-sulfonic acid, carbonic acid, citric acid, edetic acid, ethane-1,2-disulfonic acid, dodecylsulfuric acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, glucuronic acid, glycolylarsanilic acid, hexylresorcylic acid, hydroxynaphthoic acid, 2-hydroxy-1-ethanesulfonic acid, lactic acid, lactobionic acid, malic acid, maleic acid, mandelic acid, methanesulfonic acid, methylsulfuric acid, methylnitric acid, methylenebis(salicylic acid), galactaric acid, naphthalene-2-sulfonic acid, 2-naphthoic acid, 1,5-naphthalenedisulfonic acid, 25 oleic acid, oxalic acid, pamoic acid, pantothenic acid, pectic acid, picric acid, propionic acid, polygalacturonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, teoclic acid, thiocyanic acid, trifluoroacetic acid, p-toluenesulfonic acid, undecanoic acid, aspartic acid 30 and glutamic acid.

[0075]

Examples of the salt with inorganic base include a salt with lithium, sodium, potassium, magnesium, calcium, barium,

aluminum, zinc, bismuth or ammonium.

Examples of the salt with organic base include a salt with arecoline, betaine, choline, clemizole, ethylenediamine, N-methylglucamine, N-benzylphenethylamine,  
5 tris(hydroxymethyl)methylamine, arginine or lysine.

[0076]

A preferred embodiment of the "pharmaceutically acceptable salt" is as described below.

Examples of the salt with inorganic acid include salts  
10 with hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid and hydrobromic acid.

Examples of the salt with organic acid include salts with oxalic acid, maleic acid, citric acid, fumaric acid, lactic acid, malic acid, succinic acid, tartaric acid, acetic acid,  
15 trifluoroacetic acid, benzoic acid, glucuronic acid, oleic acid, pamoic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and 2-hydroxy-1-ethanesulfonic acid.

Examples of the salt with inorganic base include salts with sodium, potassium, calcium, magnesium and zinc.

20 Examples of the salt with organic base include salts with tris(hydroxymethyl)methylamine, N-methylglucamine and lysine.

[0077]

The compound of the formula [I], the formula [II] or the formula [III] or a pharmaceutically acceptable salt thereof  
25 may exist as a solvate. The term "solvate" refers to the compound of the formula [I], the formula [II] or the formula [III] or a pharmaceutically acceptable salt thereof with which a solvent molecule is associated, and also includes hydrates.

Such solvates are preferably pharmaceutically acceptable  
30 solvates and include, for example, hydrate, ethanol solvate, dimethyl sulfoxide-solvate and the like of the compound of the formula [I], the formula [II] or the formula [III] or a pharmaceutically acceptable salt thereof.

Specific examples include hemihydrate, monohydrate,

dihydrate or mono(ethanol)solvate of the compound of the formula [I], the formula [II] or the formula [III] or a monohydrate of hydrochloride of the compound of the formula [I], the formula [II] or the formula [III], dihydrate of 5 hydrochloride of the same and the like. Such solvates can be produced according to conventional methods.

[0078]

The compound of the formula [I], the formula [II] or the formula [III] may exist as a stereoisomer that should be 10 recognized as a cis/trans isomer. In this case, these compounds may exist as a cis isomer, a trans isomer, or a mixture of a cis isomer and a trans isomer.

The compound of the formula [I], the formula [II] or the formula [III] may exist as a tautomer. In this case, these 15 compounds may exist as an individual tautomer or a mixture of tautomers.

The compound of the formula [I], the formula [II] or the formula [III] may contain one or more asymmetric carbons. In this case, these compounds may exist as a single enantiomer, a 20 single diastereomer, a mixture of enantiomers or a mixture of diastereomers.

The compound of the formula [I], the formula [II] or the formula [III] may exist as an atropisomer. In this case, these compounds may exist as an individual atropisomer or a mixture 25 of atropisomers.

The compound of the formula [I], the formula [II] or the formula [III] may simultaneously contain plural structural characteristics that produce the above-mentioned isomers. Moreover, these compounds may contain the above-mentioned 30 isomers at any ratio.

In the absence of other reference such as annotation and the like, the formulas, chemical structures and compound names indicated in the present specification without specifying the stereochemistry thereof encompass all the above-mentioned

isomers that may exist.

[0079]

A diastereomeric mixture can be separated into each diastereomer by conventional methods such as chromatography, 5 crystallization and the like. In addition, each diastereomer can also be formed by using a stereochemically single starting material, or by a synthesis method using a stereoselective reaction.

[0080]

10 An enantiomeric mixture can be separated into each single enantiomer by a method well known in the art.

For example, a mixture of enantiomers may be reacted with a substantially pure enantiomer which is known as a chiral auxiliary to form a mixture of diastereomers, which may be 15 then isolated into a diastereomer with an enhanced isomeric ratio or a substantially pure single diastereomer by a common method such as fractionated crystallization or chromatography. The added chiral auxiliary may be removed from the isolated diastereomer by a cleavage reaction to give a desirable 20 enantiomer.

In addition, a mixture of enantiomers of a compound can also be directly separated by a chromatography method using a chiral solid phase well known in the art. Alternatively, one of the enantiomers can also be obtained by using a 25 substantially pure optically active starting material or stereoselective synthesis (asymmetric induction) of a prochiral intermediate using a chiral auxiliary or an asymmetric catalyst.

[0081]

30 The absolute steric configuration can be determined based on the X-ray crystal analysis of the resultant crystalline product or intermediate. In this case, a resultant crystalline product or intermediate derivatized with a reagent having an asymmetric center with a known steric configuration may be

used where necessary.

[0082]

The compound of the formula [I], the formula [II] or the formula [III] may be labeled with an isotope ( $^2\text{H}$ ,  $^3\text{H}$ ,  $^{14}\text{C}$ ,  $^{35}\text{S}$  and the like).

[0083]

A compound of the formula [I], the formula [II] or the formula [III] or a pharmaceutically acceptable salt thereof is preferably a substantially purified compound thereof or a pharmaceutically acceptable salt thereof. Further preferably, it is a compound thereof or a pharmaceutically acceptable salt thereof that is purified to a purity of not less than 80%.

[0084]

The pharmaceutical composition of the present invention may be produced by appropriately admixing a suitable amount of a compound of the formula [I], the formula [II] or the formula [III] or a pharmaceutically acceptable salt thereof with at least one kind of a pharmaceutically acceptable carrier according to a method known in the art of pharmaceutical preparations. The content of the compound or a pharmaceutically acceptable salt thereof in the pharmaceutical composition varies depending on the dosage form, the dose, and the like. It is, for example, 0.1 to 100 wt% of the whole composition.

[0085]

A dosage form of the compound of the formula [I], the formula [II] or the formula [III] or a pharmaceutically acceptable salt thereof includes an oral preparation such as a tablet, a capsule, a granule, a powder, a lozenge, a syrup, an emulsion, and a suspension or a parenteral preparation such as an external preparation, a suppository, an injection, an eye drop, a nasal preparation, and a pulmonary preparation.

[0086]

Examples of the "pharmaceutically acceptable carrier"

include various organic or inorganic carrier substances conventionally used as preparation materials, and include excipient, disintegrant, binder, glidant, lubricant, and the like for solid preparations, and solvent, solubilizing agent, 5 suspending agent, isotonic agent, buffering agent, soothing agent, and the like for liquid preparations and base, emulsifier, wetting agent, stabilizer, stabilizing agent, dispersing agent, plasticizer, pH adjuster, absorption promoter, gelation agent, preservative, filler, dissolving 10 agent, solubilizing agent, suspending agent, and the like for semisolid preparations. Where necessary, moreover, additives such as preservative, antioxidant, colorant, sweetening agent, and the like may also be used.

[0087]

15 Examples of the "excipient" include lactose, sucrose, D-mannitol, D-sorbitol, cornstarch, dextrin, crystalline cellulose, crystalline cellulose, carmellose, carmellose calcium, sodium carboxymethyl starch, low-substituted hydroxypropylcellulose, gum arabic, and the like.

20 Examples of the "disintegrant" include carmellose, carmellose calcium, carmellose sodium, sodium carboxymethyl starch, croscarmellose sodium, crospovidone, low-substituted hydroxypropylcellulose, hydroxypropylmethylcellulose, crystalline cellulose, and the like.

25 Examples of the "binder" include hydroxypropylcellulose, hydroxypropylmethylcellulose, povidone, crystalline cellulose, sucrose, dextrin, starch, gelatin, carmellose sodium, gum arabic, and the like.

Examples of the "glidant" include light anhydrous silicic 30 acid, magnesium stearate, and the like.

Examples of the "lubricant" include magnesium stearate, calcium stearate, talc, and the like.

Examples of the "solvent" include purified water, ethanol, propylene glycol, macrogol, sesame oil, corn oil, olive oil,

and the like.

Examples of the "solubilizing agents" include propylene glycol, D-mannitol, benzyl benzoate, ethanol, triethanolamine, sodium carbonate, sodium citrate, and the like.

5 Examples of the "suspending agent" include benzalkonium chloride, carmellose, hydroxypropylcellulose, propylene glycol, povidone, methylcellulose, glycerol monostearate, and the like.

Examples of the "isotonic agent" include glucose, D-sorbitol, sodium chloride, D-mannitol, and the like.

10 Examples of the "buffering agent" include sodium hydrogenphosphate, sodium acetate, sodium carbonate, sodium citrate, and the like.

Examples of the "soothing agent" include benzyl alcohol and the like.

15 Examples of the "base" include water, animal and vegetable oils (olive oil, corn oil, peanut oil, sesame oil, castor oil, and the like), lower alcohols (ethanol, propanol, propylene glycol, 1,3-butyleneglycol, phenol, and the like), higher fatty acid and ester thereof, waxes, higher alcohol, 20 polyhydric alcohol, hydrocarbons (white petrolatum, liquid paraffin, paraffin, and the like), hydrophilic petrolatum, purified lanolin, water absorption ointment, hydrous lanolin, hydrophilic ointment, starch, pullulan, gum arabic, gum tragacanth, gelatin, dextran, cellulose derivative 25 (methylcellulose, carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and the like), synthetic polymer (carboxyvinyl polymer, sodium polyacrylate, poly(vinyl alcohol), polyvinylpyrrolidone, and the like), propylene glycol, macrogol (macrogol 200 - 600 and the like), 30 and a combination of two or more kinds thereof.

Examples of the "preservative" include ethyl paraoxybenzoate, chlorobutanol, benzyl alcohol, sodium dehydroacetate, sorbic acid, and the like.

Examples of the "antioxidant" include sodium sulfite,

ascorbic acid and the like.

Examples of the "colorant" include food colors (e.g., Food Color Red No. 2 or 3, Food Color yellow No. 4 or 5 etc.),  $\beta$ -carotene, and the like.

5 Examples of the "sweetening agent" include saccharin sodium, dipotassium glycyrrhizinate, aspartame, and the like.  
[0088]

The pharmaceutical composition of the present invention can be administered orally or parenterally (topical, rectal, 10 intravenous administration, intramuscular, subcutaneous, and the like) to mammals other than human (e.g., mouse, rat, hamster, guinea pig, rabbit, cat, dog, swine, bovine, horse, sheep, monkey and the like) and human. The dose varies depending on the subject of administration, disease, symptom, 15 dosage form, administration route and the like. For example, the daily dose for oral administration to an adult patient is generally within the range of about 0.01 mg to 1 g, based on the compound of the formula [I], the formula [II] or the formula [III] as the active ingredient. This amount can be 20 administered in one to several portions.

[0089]

The compound of the formula [I], the formula [II] or the formula [III], or a pharmaceutically acceptable salt thereof has a PDHK inhibitory action, and is useful for the treatment 25 and/or prophylaxis of various diseases or conditions expected to be improved by controlling PDHK activity. Examples of various diseases or conditions expected to be improved by controlling PDHK activity include diseases such as diabetes (type 1 diabetes, type 2 diabetes), insulin resistance, 30 syndrome, metabolic syndrome, hyperglycemia, hyperlactacidemia, diabetic complications (diabetic neuropathy, diabetic retinopathy, diabetic nephropathy, cataract), cardiac failure (acute cardiac failure, chronic cardiac failure), cardiomyopathy, myocardial ischemia, myocardial infarction,

angina pectoris, dyslipidemia, atherosclerosis, peripheral arterial disease, intermittent claudication, chronic obstructive pulmonary diseases, brain ischemia, cerebral apoplexy, mitochondrial disease, mitochondrial 5 encephalomyopathy, cancer, pulmonary hypertension (pulmonary arterial hypertension), Alzheimer disease, vascular dementia (large-vessel type or small-vessel type vascular dementia), glaucoma, diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion, ischemic optic neuropathy, chronic 10 kidney disease, and the like.

[0090]

The symptoms of Alzheimer disease include a decline in cognitive function, mental symptoms and behavioral disorders, and the like.

15 [0091]

To "inhibit PDHK" means to eliminate or attenuate the activity of PDHK by inhibit the function thereof. For example, it means to inhibit the function as PDHK based on the conditions in the below-mentioned Experimental Example 1. To 20 "inhibit PDHK", human PDHK is preferably inhibited. To "inhibit PDHK", preferably, "PDHK2 is inhibited".

The "PDHK inhibitor" means a substance that binds to PDHK and inhibits the function of PDHK. As the "PDHK inhibitor", a "human PDHK inhibitor" is preferred. As the "PDHK inhibitor", 25 an "inhibitor of PDHK2" is preferred.

[0092]

In the present specification, the "treatment" also includes improvement of symptoms, prevention of severity, maintenance of remission, prevention of exacerbation, and 30 further, prevention of recurrence.

In the present specification, the "prevention" or "prophylaxis" means to suppress the onset of symptoms.

[0093]

In the present specification, presentation of preferred

embodiments and options of the compound, method, use and composition of the present invention also includes combinations of preferred embodiments and options as long as they can be combined and are free of inconsistency.

5 [0094]

The production methods of the compound of the formula [I], the formula [II] or the formula [III] or a pharmaceutically acceptable salt thereof are explained in the following. However, the production method of the compound or a 10 pharmaceutically acceptable salt thereof is not limited to such production methods.

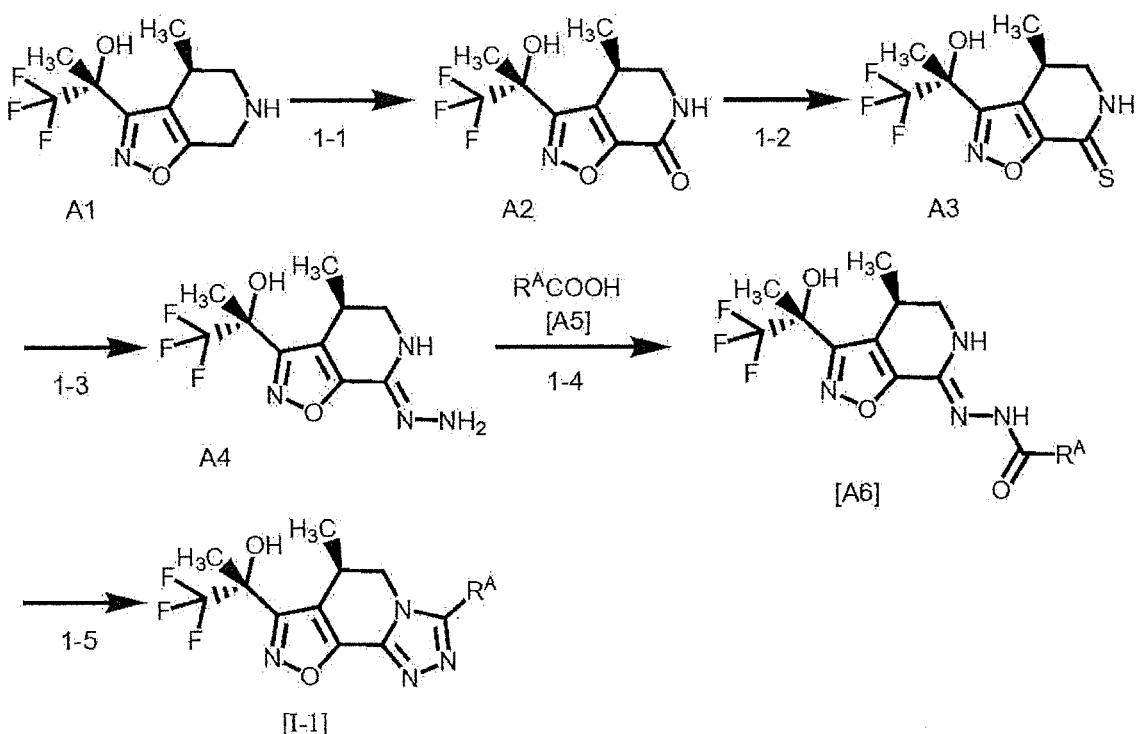
The compound obtained in each step can be isolated or purified as necessary by conventional methods such as distillation, recrystallization, column chromatography and the 15 like. In some cases, the next step may be performed without isolation or purification. When the reaction to be performed in each step is an anhydrous reaction, it is preferably performed in an inert gas atmosphere of argon, nitrogen and the like.

20 [0095]

[Production Method 1]

The compound of the formula [I-1] can be obtained by Production Method 1 shown by the following scheme.

[0096]



[0097]

wherein each symbol is as defined for the aforementioned formula [I].

5 [0098]

Step 1-1

Compound A2 can be obtained by an oxidation reaction of compound A1. For example, compound A2 can be obtained by reacting compound A1 with iodosobenzene in a solvent in the 10 presence of tetra-n-butylammonium iodide.

Examples of the solvent include a mixed solvent of acetonitrile and water.

Compound A1 can be obtained by Production Example 12 described in WO 2019/151274.

15 [0099]

Step 1-2

Compound A3 can be obtained by reacting compound A2 with a sulfur reagent. For example, compound A3 can be obtained by reacting compound A2 with a sulfur reagent in a solvent at 20 room temperature to 120°C.

Examples of the sulfur reagent include Lawesson's reagent

(2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide).

Examples of the solvent include toluene and pyridine.

[0100]

5 Steps 1-3 and 1-4

Compound [A6] can be obtained by reacting compound A3 with hydrazine to give compound A4, and then reacting compound A4 with compound [A5]. The reaction of compound A4 with hydrazine can be performed by, for example, reacting compound 10 A4 with hydrazine in a solvent at room temperature to 120°C.

Examples of the solvent include ethanol and isopropanol.

The reaction of compound A4 with compound [A5] can be performed by, for example, reacting compound A4 with compound [A5] in a solvent in the presence of a condensing agent under 15 ice-cooling to room temperature.

Examples of the condensing agent include 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole monohydrate.

Examples of the solvent include acetonitrile and N,N-dimethylformamide.

Compound [A5] may be a commercially available product, or may be obtained by appropriately converting a commercially available product by a method well known to those of ordinary skill in the art.

25 [0101]

Compound [A6] can also be obtained by reacting acid chloride of compound [A5] ( $R^A COCl$ ) with compound A4. For example, compound [A6] can be obtained by reacting  $R^A COCl$  with compound A4 in a solvent in the presence of a base under ice-30 cooling to room temperature.

Examples of the base include diisopropylethylamine and sodium hydrogen carbonate.

Examples of the solvent include tetrahydrofuran and chloroform.

[0102]

Step 1-5

Compound [I-1] can be obtained by a dehydration reaction of compound [A6]. For example, compound [I-1] can be obtained 5 by reacting compound [A6] with a dehydrating reagent in a solvent.

Examples of the dehydrating reagent include (methoxycarbonylsulfamoyl)triethylammonium hydroxide (Burgess reagent), acetic anhydride and acetic acid, trifluoroacetic 10 anhydride and trifluoroacetic acid.

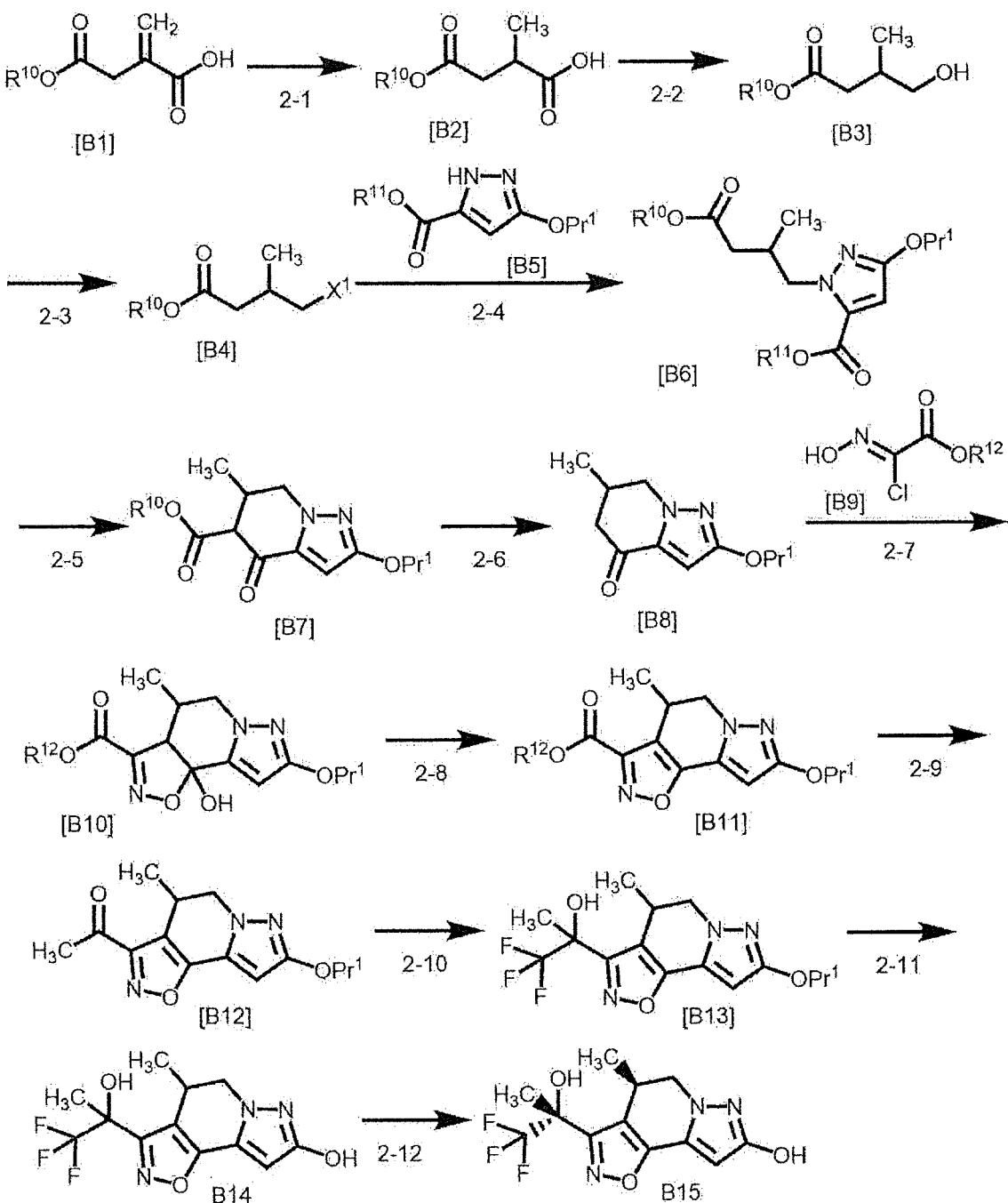
Examples of the solvent include N-methylpyrrolidone, tetrahydrofuran, dichloromethane and toluene.

[0103]

[Production Method 2]

15 A compound of the formula B15 can be obtained by Production Method 2 shown by the following scheme.

[0104]



[0105]

wherein  $\text{R}^{10}$ ,  $\text{R}^{11}$  and  $\text{R}^{12}$  are each independently  $\text{C}_{1-4}$  alkyl;

$\text{X}^1$  is a leaving group such as methanesulfonyloxy and the like;

5 and

$\text{Pr}^1$  is a hydroxy-protecting group such as benzyl and the like.

[0106]

Step 2-1

Compound [B2] can be obtained by reducing the double bond  
10 of compound [B1]. For example, compound [B2] can be obtained

by catalytic reduction of compound [B1] in a solvent under a hydrogen atmosphere in the presence of a palladium catalyst at room temperature.

Examples of the palladium catalyst include palladium 5 carbon.

Examples of the solvent include methanol, ethanol, and ethyl acetate.

Compound [B1] may be a commercially available product, or may be obtained by appropriately converting a commercially 10 available product by a method well known to those of ordinary skill in the art.

[0107]

Step 2-2

Compound [B3] can be obtained by reducing the carboxy 15 group of compound [B2]. For example, compound [B3] can be obtained by reacting compound [B2] with a reducing agent in a solvent under ice-cooling to room temperature.

Examples of the reducing agent include borane.

Examples of the solvent include tetrahydrofuran.

20 [0108]

Step 2-3

Compound [B4] can be obtained by converting the hydroxy group of compound [B3] to a leaving group. For example, when  $X^1$  is methanesulfonyloxy, compound [B4] can be obtained by 25 reacting compound [B3] with methanesulfonic anhydride in a solvent in the presence of a base.

Examples of the base include triethylamine.

Examples of the solvent include chloroform,

dichloromethane, and tetrahydrofuran.

30 [0109]

Step 2-4

Compound [B6] can be obtained by reacting compound [B4] and compound [B5]. For example, compound [B6] can be obtained by reacting compound [B4] with compound [B5] in a solvent in

the presence of a base.

Examples of the base include potassium carbonate and cesium carbonate.

Examples of the solvent include N,N-dimethylformamide.

5 [0110]

Step 2-5

Compound [B7] can be obtained by intramolecular Claisen condensation of compound [B6]. For example, compound [B7] can be obtained by treating compound [B6] with a base in a solvent 10 at room temperature to 120°C.

Examples of the base include potassium tert-butoxide.

Examples of the solvent include toluene and tetrahydrofuran.

[0111]

15 Step 2-6

Compound [B8] can be obtained by treating compound [B7] with sodium chloride or lithium chloride in a solvent at 100°C to 160°C.

Examples of the solvent include water and dimethyl 20 sulfoxide.

[0112]

Step 2-7

Compound [B10] can be obtained by reacting compound [B8] and compound [B9]. For example, compound [B10] can be obtained 25 by reacting compound [B8] treated with a base with compound [B9] treated with a base in a solvent at -78°C to room temperature.

Examples of the base include lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, and 30 potassium bis(trimethylsilyl)amide.

Examples of the solvent include tetrahydrofuran.

Compound [B9] may be a commercially available product, or may be obtained by appropriately converting a commercially available product by a method well known to those of ordinary

skill in the art.

[0113]

Step 2-8

Compound [B11] can be obtained by converting the hydroxy group of compound [B10] to a leaving group, followed by an elimination reaction. When the leaving group is methanesulfonyloxy, compound [B11] can be obtained by reacting compound [B10] with methanesulfonic anhydride in a solvent in the presence of a base under ice-cooling, followed by heating 10 at 40°C to 70°C.

Examples of the base include triethylamine.

Examples of the solvent include tetrahydrofuran and toluene.

[0114]

15 Step 2-9

Compound [B12] can be obtained by reacting compound [B11] with methylmagnesium halide. For example, compound [B12] can be obtained by reacting compound [B11] with methylmagnesium halide in a solvent in the presence of a base at -78°C to 0°C.

20 Examples of the methylmagnesium halide include methylmagnesium bromide.

Examples of the base include triethylamine.

Examples of the solvent include tetrahydrofuran, 2-methyltetrahydrofuran, toluene, and diethyl ether.

25 [0115]

Step 2-10

Compound [B13] can be obtained by reacting compound [B12] with (trifluoromethyl)trimethylsilane. For example, compound [B13] can be obtained by reacting compound [B12] with 30 (trifluoromethyl)trimethylsilane in a solvent in the presence of an additive under ice-cooling to room temperature.

Examples of the additive include tetra-n-butylammonium fluoride, lithium acetate, potassium carbonate, and cesium fluoride.

Examples of the solvent include tetrahydrofuran, N,N-dimethylformamide, and N,N-dimethylacetamide.

The methyl group of compound [B12] becomes a steric hindrance and the reaction proceeds diastereoselectively.

5 [0116]

Step 2-11

Compound B14 can be obtained by deprotecting compound [B13]. For example, when Pr<sup>1</sup> is benzyl, compound B14 can be obtained by catalytic reduction of compound [B13] in a solvent 10 under a hydrogen atmosphere in the presence of a palladium catalyst at room temperature.

Examples of the palladium catalyst include palladium carbon.

Examples of the solvent include tetrahydrofuran and 15 methanol.

[0117]

Step 2-12

Compound B15 can be obtained by purifying compound B14 by chiral column chromatography. The steric configuration of 20 compound B15 can be determined by, for example, X-ray crystal structure analysis.

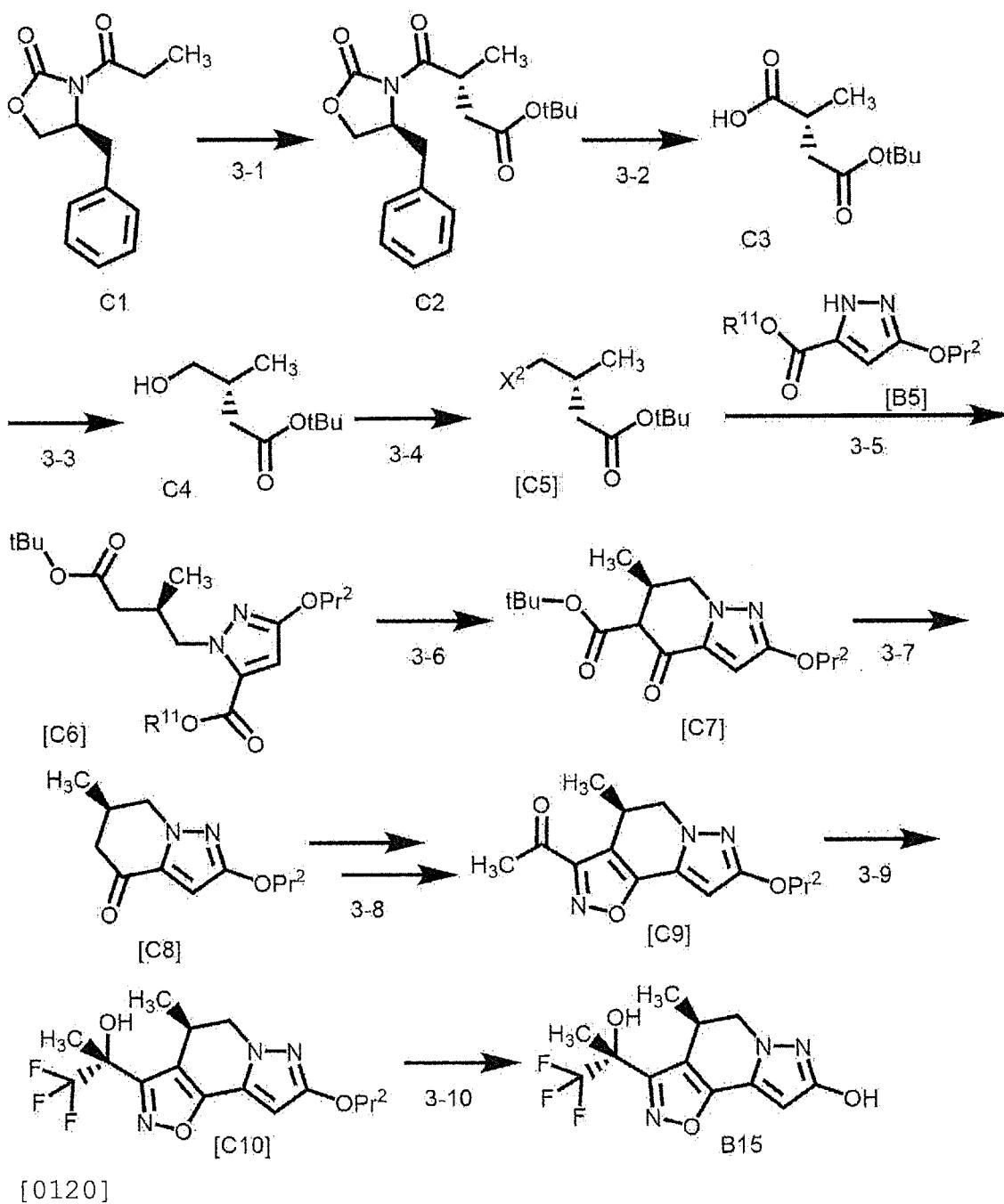
Compound B15 can also be obtained by purifying compound [B11] by chiral column chromatography, and then performing reactions similar to those in Steps 2-9 to 2-11.

25 [0118]

[Production Method 3]

A compound of the formula B15 can also be obtained by Production Method 3 shown by the following scheme.

[0119]



[0120]

wherein X<sup>2</sup> is a leaving group such as ethanesulfonyloxy and the like;

5 Pr<sup>2</sup> is a hydroxy-protecting group such as benzyl and the like; and

other each symbol is as defined above.

[0121]

Step 3-1

10 Compound C2 can be obtained by reacting compound C1 with tert-butyl bromoacetate. For example, compound C2 can be

obtained by reacting compound C1 with tert-butyl bromoacetate in a solvent at -78°C to room temperature in the presence of a base.

Examples of the base include lithium 5 bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide and potassium bis(trimethylsilyl)amide.

Examples of the solvent include tetrahydrofuran.

Compound C1 may be a commercially available product, or may be obtained by appropriately converting a commercially 10 available product by a method well known to those of ordinary skill in the art.

[0122]

Step 3-2

Compound C3 can be obtained by removing the chiral 15 auxiliary group of compound C2. For example, C3 can be obtained by reacting compound C2 with alkali and an oxidizing agent in a solvent under ice-cooling to room temperature.

Examples of the alkali include lithium hydroxide.

Examples of the oxidizing agent include hydrogen peroxide 20 water.

Examples of the solvent include tetrahydrofuran and water.

[0123]

Step 3-3

Compound C4 can be obtained by reducing the carboxy group 25 of compound C3. For example, compound C4 can be obtained by reacting compound C3 with a reducing agent in a solvent under ice-cooling to room temperature.

Examples of the reducing agent include borane.

Examples of the solvent include tetrahydrofuran.

30 [0124]

Step 3-4

Compound [C5] can be obtained by converting the hydroxy group of compound C4 to a leaving group. For example, when  $X^2$  is ethanesulfonyloxy, compound [C5] can be obtained by

reacting compound C4 with ethanesulfonyl chloride in a solvent in the presence of a base.

Examples of the base include triethylamine.

Examples of the solvent include chloroform,  
5 dichloromethane, and tetrahydrofuran.

[0125]

Step 3-5

Compound [C6] can be obtained by reacting compound [C5] with compound [B5]. For example, compound [C6] can be obtained  
10 by an operation similar to that in Step 2-4.

[0126]

Step 3-6

Compound [C7] can be obtained by intramolecular Claisen condensation of compound [C6]. For example, compound [C7] can  
15 be obtained by an operation similar to that in Step 2-5.

[0127]

Step 3-7

Compound [C8] can be obtained by treating compound [C7] with an acid in a solvent at 80°C to 110°C.

20 Examples of the acid include trifluoroacetic acid.

Examples of the solvent include toluene.

[0128]

Step 3-8

Compound [C9] can be obtained using compound [C8] by  
25 reactions similar to those in Steps 2-7, 2-8 and 2-9.

[0129]

Step 3-9

Compound [C10] can be obtained by reacting compound [C9] with (trifluoromethyl)trimethylsilane. For example, compound  
30 [C10] can be obtained by an operation similar to that in Step 2-10.

The methyl group of compound [C9] becomes a steric hindrance and the reaction proceeds diastereoselectively, whereby compound [C10] is obtained as an optically active form.

[0130]

Step 3-10

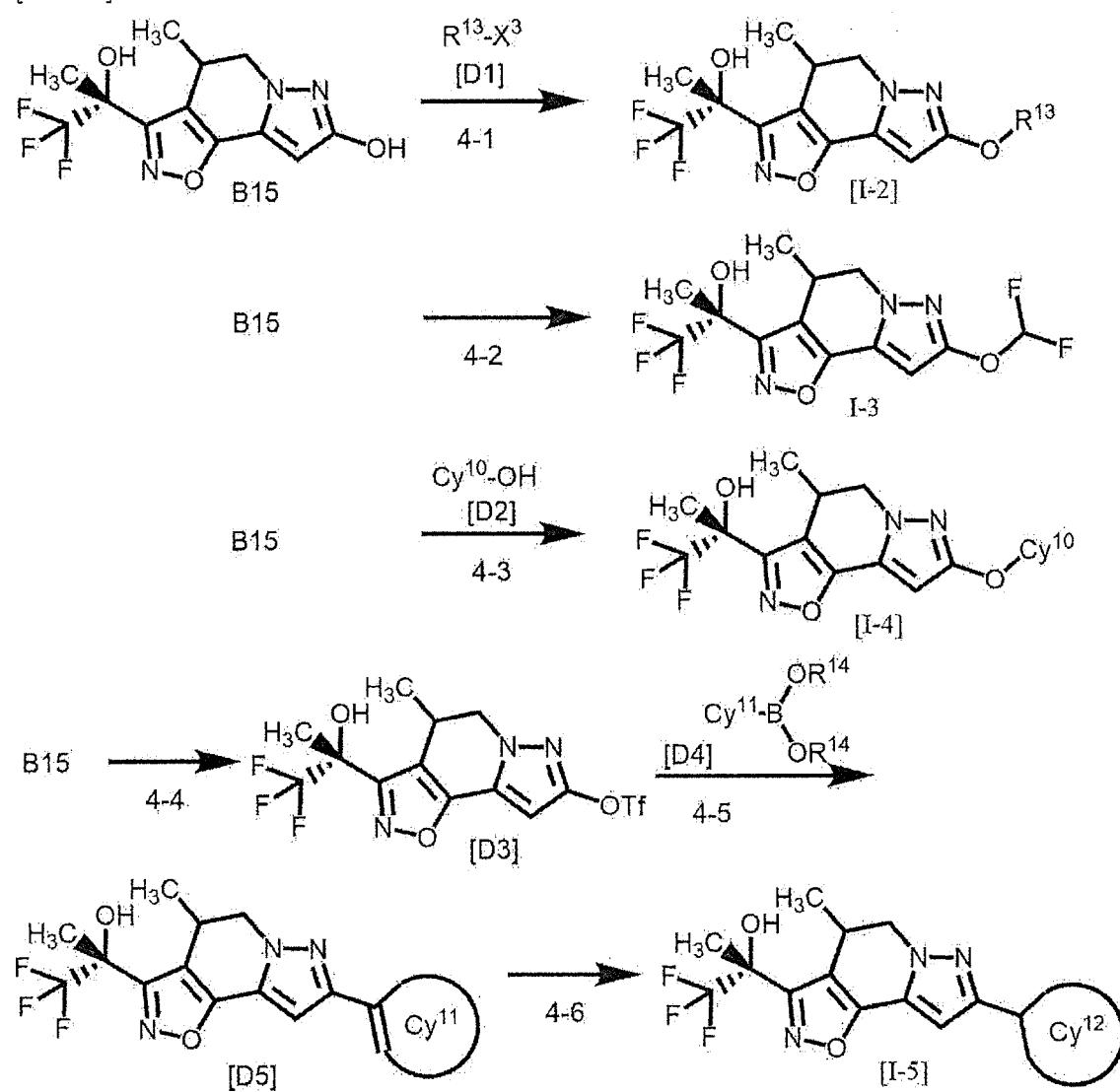
Compound B15 can be obtained by deprotection of compound [C10]. For example, when  $\text{Pr}^2$  is benzyl, compound B15 can be obtained by an operation similar to that in Step 2-11.

[0131]

[Production Method 4]

Compounds of the formulas [I-2] to [I-5] can be obtained by converting compound B15, which is obtained by Production Method 2 or 3, by Production Method 4 shown by the following scheme.

[0132]



[0133]

wherein  $\text{X}^3$  is a leaving group such as bromo, p-

toluenesulfonyloxy, and the like;

R<sup>13</sup> is

(1) C<sub>1-6</sub> alkyl wherein the C<sub>1-6</sub> alkyl is optionally substituted by one substituent selected from the group consisting of

5 (a) hydroxy,  
(b) cyano,  
(c) C<sub>1-4</sub> alkoxy,  
(d) C<sub>3-6</sub> cycloalkyl optionally substituted by one cyano,  
(e) phenyl, and  
10 (f) 4- to 6-membered saturated heterocyclyl having one oxygen atom, or

(2) halo C<sub>1-4</sub> alkyl;

Cy<sup>10</sup> is

(1) 4- to 6-membered saturated heterocyclyl having one oxygen

15 atom, or

(2) C<sub>3-6</sub> cycloalkyl wherein the C<sub>3-6</sub> cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of C<sub>1-6</sub> alkyl, hydroxy, and cyano;

Cy<sup>11</sup> is 4- to 6-membered unsaturated heterocyclyl having one oxygen atom;

Cy<sup>12</sup> is 4- to 6-membered saturated heterocyclyl having one oxygen atom; and

each R<sup>14</sup> is independently hydrogen or C<sub>1-4</sub> alkyl, and one R<sup>14</sup> may be bonded to the other R<sup>14</sup> to form a ring.

25 [0134]

Step 4-1

Compound [I-2] can be obtained by reacting compound B15 with compound [D1]. For example, compound [I-2] can be obtained by reacting compound B15 with compound [D1] in a

30 solvent in the presence of a base at room temperature to 90°C.

Examples of the base include potassium carbonate and cesium carbonate.

Examples of the solvent include N,N-dimethylformamide.

[0135]

Step 4-2

Compound I-3 can be obtained by reacting compound B15 with sodium chlorodifluoroacetate in a solvent in the presence of a base at room temperature to 100°C.

5 Examples of the base include potassium carbonate.

Examples of the solvent include N,N-dimethylformamide.

[0136]

Step 4-3

Compound [I-4] can be obtained by a Mitsunobu reaction of 10 compound B15 and compound [D2]. For example, compound [I-4] can be obtained by reacting compound B15 with phosphine and azodicarboxylic acid diester in a solvent at room temperature to 100°C.

15 Examples of the phosphine include trioctylphosphine, tributylphosphine and triphenylphosphine.

Examples of the azodicarboxylic acid diester include diisopropyl azodicarboxylate and di-tert-butyl azodicarboxylate.

20 Examples of the solvent include toluene, tetrahydrofuran, and 2-methyltetrahydrofuran.

[0137]

Step 4-4

Compound [D3] can be obtained by reacting compound B15 with trifluoromethanesulfonic anhydride in a solvent in the 25 presence of a base at 0°C to room temperature.

Examples of the base include triethylamine.

Examples of the solvent include dichloromethane and chloroform.

[0138]

30 Step 4-5

Compound [D5] can be obtained by Suzuki coupling of compound [D3] and compound [D4]. For example, compound [D5] can be obtained by reacting compound [D3] with compound [D4] in a solvent in the presence of a base and a palladium

catalyst at room temperature to 100°C.

Examples of the base include potassium carbonate and tripotassium phosphate.

Examples of the palladium catalyst include XPhos Pd G4.

5 Examples of the solvent include 1,4-dioxane, water, and toluene.

10 Compound [D4] may be a commercially available product, or may be obtained by appropriately converting a commercially available product by a method well known to those of ordinary skill in the art.

[0139]

Step 4-6

15 Compound [I-5] can be obtained by reducing the double bond of compound [D5]. For example, compound [I-5] can be obtained by catalytic reduction of compound [D5] in a solvent under a hydrogen atmosphere in the presence of a palladium catalyst at room temperature.

Examples of the palladium catalyst include palladium carbon.

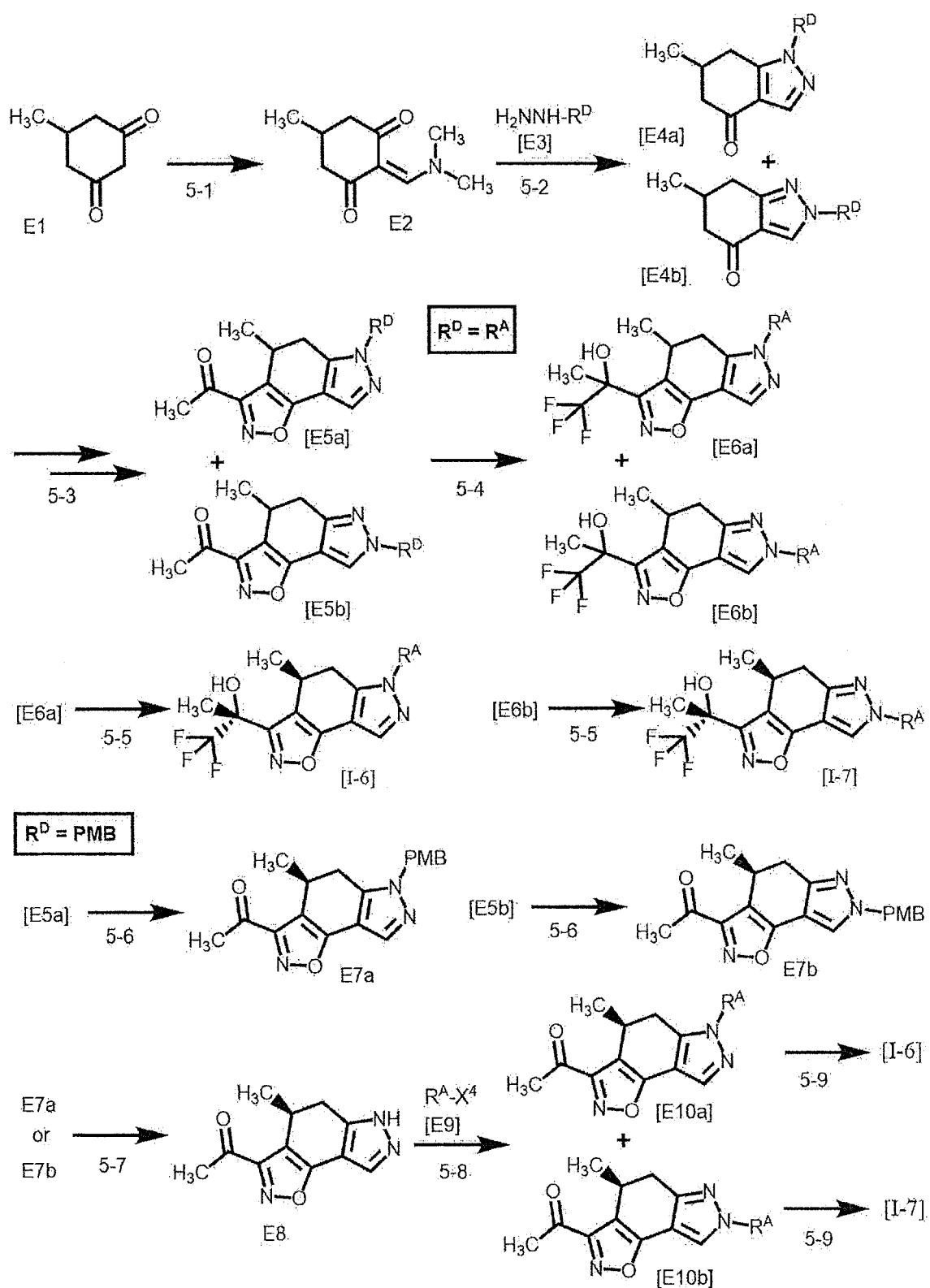
20 Examples of the solvent include methanol, ethanol, tetrahydrofuran, and ethyl acetate.

[0140]

[Production Method 5]

25 Compounds of the formulas [I-6] and [I-7] can be obtained by Production Method 5 shown by the following scheme.

[0141]



wherein  $R^D$  is  $R^A$  or p-methoxybenzyl (PMB);  
 $X^4$  is a leaving group such as p-toluenesulfonyloxy,  
 5 methanesulfonyloxy, and the like; and  
 other each symbol is as defined for the aforementioned formula

[I].

[0143]

Steps 5-1 and 5-2

Compounds [E4a] and [E4b] can be obtained by a pyrazole cyclization reaction using compound E1 and compound [E3]. For example, compounds [E4a] and [E4b] can be obtained by reacting compound E1 with N,N-dimethylformamide dimethyl acetal in a solvent at 100°C to 120°C, and reacting the obtained compound with compound [E3] in the presence of an acid at 100°C to 200°C. After isolating the intermediate compound E2, the intermediate may be reacted with compound [E3]. A microwave device may also be used as necessary. The reaction may be performed without using a solvent.

Examples of the acid include acetic acid.

Examples of the solvent include ethanol and water.

Compounds E1 and [E3] may be commercially available products, or may be obtained by appropriately converting a commercially available product by a method well known to those of ordinary skill in the art.

[0144]

Step 5-3

Compounds [E5a] and [E5b] can be obtained using compounds [E4a] and [E4b] by reactions similar to those in Steps 2-7 to 2-9.

[0145]

Step 5-4

When R<sup>D</sup> is R<sup>A</sup>, compounds [E6a] and [E6b] can be obtained by reacting compounds [E5a] and [E5b] with (trifluoromethyl)trimethylsilane, and purifying the obtained compounds by column chromatography. For example, the reaction with (trifluoromethyl)trimethylsilane can be performed by an operation similar to that in Step 2-10.

[0146]

Step 5-5

Compounds [I-6] and [I-7] can be obtained by purifying compounds [E6a] and [E6b] by chiral column chromatography. The steric configuration of compounds [I-6] and [I-7] can be determined, for example, by X-ray crystal structure analysis.

5 [0147]

When R<sup>D</sup> is p-methoxybenzyl (PMB), the compounds [I-6] and [I-7] can also be obtained by Steps 5-6 to 5-9.

[0148]

Step 5-6

10 Compounds E7a and E7b can be obtained by respectively purifying compounds [E5a] and [E5b] by chiral column chromatography. The steric configuration of compounds E7a and E7b can be determined, for example, by X-ray crystal structure analysis.

15 [0149]

Step 5-7

Compound E8 can be obtained by deprotection of compound E7a or E7b. For example, compound E8 can be obtained by treating compounds E7a and E7b with an acid at room 20 temperature to 100°C. Where necessary, a microwave device may also be used. Where necessary, a cation scavenger may also be used.

Examples of the acid include trifluoroacetic acid.

Examples of the cation scavenger include anisole.

25 [0150]

Step 5-8

Compounds [E10a] and [E10b] can be obtained by reacting compound E8 with compound [E9]. For example, compounds [E10a] and [E10b] can be obtained by reacting compound E8 with 30 compound [E9] in a solvent in the presence of a base at 80°C to 100°C. Where necessary, an additive may be added.

Examples of the base include potassium carbonate and cesium carbonate.

Examples of the solvent include N,N-dimethylformamide.

Examples of the additive include sodium iodide.

Compound [E9] may be a commercially available product, or may be obtained by appropriately converting a commercially available product by a method well known to those of ordinary skill in the art.

[0151]

Step 5-9

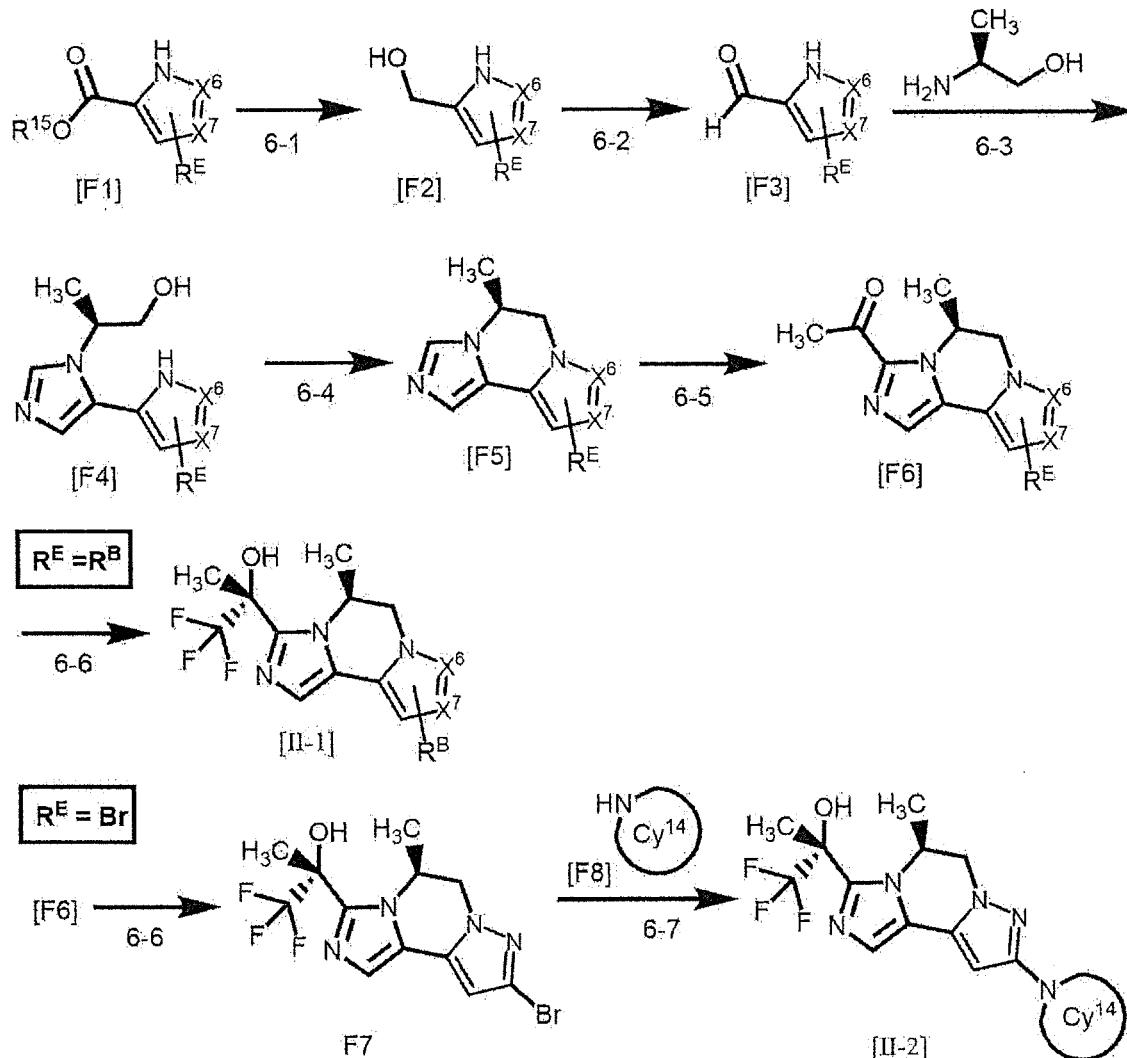
Compounds [I-6] and [I-7] can be obtained using compounds [E10a] or [E10b] and by the reaction of Step 5-4.

[0152]

[Production Method 6]

Compounds of the formulas [II-1] and [II-2] can be obtained by Production Method 6 shown by the following scheme.

[0153]



[0154]

wherein R<sup>E</sup> is R<sup>B</sup> or bromo;

R<sup>15</sup> is C<sub>1-4</sub> alkyl; and

Cy<sup>14</sup> is

5 (1) 4- to 6-membered saturated heterocyclyl having 1 or 2 nitrogen atoms or having one nitrogen atom and one oxygen atom,

(2) 6- to 10-membered saturated fused heterocyclyl having 1 or 2 nitrogen atoms or having one nitrogen atom and one oxygen atom wherein the saturated fused heterocyclyl is optionally substituted by 1 or 2 halogens,

10 (3) 6- to 10-membered spiro heterocyclyl having 1 or 2 nitrogen atoms or having one nitrogen atom and one oxygen atom wherein the spiro heterocyclyl is optionally substituted by 1 or 2 halogens, or

15 (4) 5- to 10-membered bridged heterocyclyl having 1 or 2 nitrogen atoms or having one nitrogen atom and one oxygen atom wherein the bridged heterocyclyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of halogen, cyano, and hydroxy C<sub>1-4</sub> alkyl.

20 [0155]

Step 6-1

Compound [F2] can be obtained by reducing the ester group of compound [F1]. For example, compound [F2] can be obtained by reacting compound [F1] with a reducing agent in a solvent 25 at -40°C to room temperature.

Examples of the reducing agent include lithium aluminum hydride, diisobutylaluminum hydride, and lithium borohydride.

Examples of the solvent include tetrahydrofuran, diethyl ether, and cyclopentyl methyl ether.

30 Compound [F1] may be a commercially available product, or may be obtained by appropriately converting a commercially available product by a method well known to those of ordinary skill in the art.

[0156]

Step 6-2

Compound [F3] can be obtained by oxidation of the hydroxy group of compound [F2]. For example, compound [F3] can be obtained by reacting compound [F2] with an oxidizing agent in 5 a solvent under ice-cooling to room temperature.

Examples of the oxidizing agent include manganese dioxide, Dess-Martin periodinane, and sulfur trioxide-pyridine complex.

Examples of the solvent include tetrahydrofuran, 1,2-dimethoxyethane, toluene, dimethyl sulfoxide, chloroform, and dichloromethane.

[0157]

Step 6-3

Compound [F4] can be obtained by an imination reaction of 15 compound [F3] and (S)-2-aminopropan-1-ol, and a cyclization reaction using p-toluenesulfonylmethyl isocyanide. For example, an imination reaction is performed by reacting compound [F3] and (S)-2-aminopropan-1-ol in a solvent at room temperature to 20 60°C. Then, the resultant product is reacted with p-toluenesulfonylmethyl isocyanide in a solvent in the presence of a base under ice-cooling to room temperature, whereby compound [F4] can be obtained.

Examples of the solvent of the imination reaction include methanol, 1,2-dimethoxyethane, and N,N-dimethylformamide.

25 Examples of the base include potassium carbonate.

Examples of the solvent of the cyclization reaction include methanol, 1,2-dimethoxyethane, and N,N-dimethylformamide.

[0158]

30 Step 6-4

Compound [F5] can be obtained by an intramolecular Mitsunobu reaction of compound [F4]. For example, compound [F5] can be obtained by reacting compound [F4] with phosphine and azodicarboxylic acid diester in a solvent at room

temperature to 100°C.

Examples of the phosphine include trioctylphosphine, tributylphosphine, and triphenylphosphine.

Examples of the azodicarboxylic acid diester include  
5 diisopropyl azodicarboxylate and di-*tert*-butyl azodicarboxylate.

Examples of the solvent include toluene, tetrahydrofuran, and 2-methyltetrahydrofuran.

[0159]

10 Step 6-5

Compound [F6] can be obtained by reacting compound [F5] with N-methoxy-N-methylacetamide. For example, compound [F6] can be obtained by reacting compound [F5] with N-methoxy-N-methylacetamide in a solvent at -78°C to room temperature in  
15 the presence of a base.

Examples of the base include *n*-butyllithium and lithium diisopropylamide.

Examples of the solvent include cyclopentyl methyl ether, tetrahydrofuran, and toluene.

20 [0160]

Step 6-6

When R<sup>E</sup> is R<sup>B</sup>, compound [II-1] can be obtained by reacting compound [F6] with (trifluoromethyl)trimethylsilane. For example, compound [II-1] can be obtained by an operation  
25 similar to that in Step 2-10.

The methyl group of compound [F6] becomes a steric hindrance and the reaction proceeds diastereoselectively, whereby compound [II-1] is obtained as an optically active form.

30 [0161]

Step 6-7

When X<sup>6</sup> is nitrogen, X<sup>7</sup> is carbon, and R<sup>E</sup> is bromo bonded to X<sup>7</sup>, compound F7 is obtained by Step 6-6. Compound [II-2] can be obtained by reacting compound F7 with compound [F8].

For example, Compound [II-2] can be obtained by reacting compound F7 with compound [F8] in a solvent in the presence of a base and a palladium catalyst at room temperature to 120°C.

Examples of the base include sodium tert-butoxide.

5 Examples of the palladium catalyst include XPhos Pd G4 and RuPhos Pd G4.

Examples of the solvent include 1,4-dioxane and toluene.

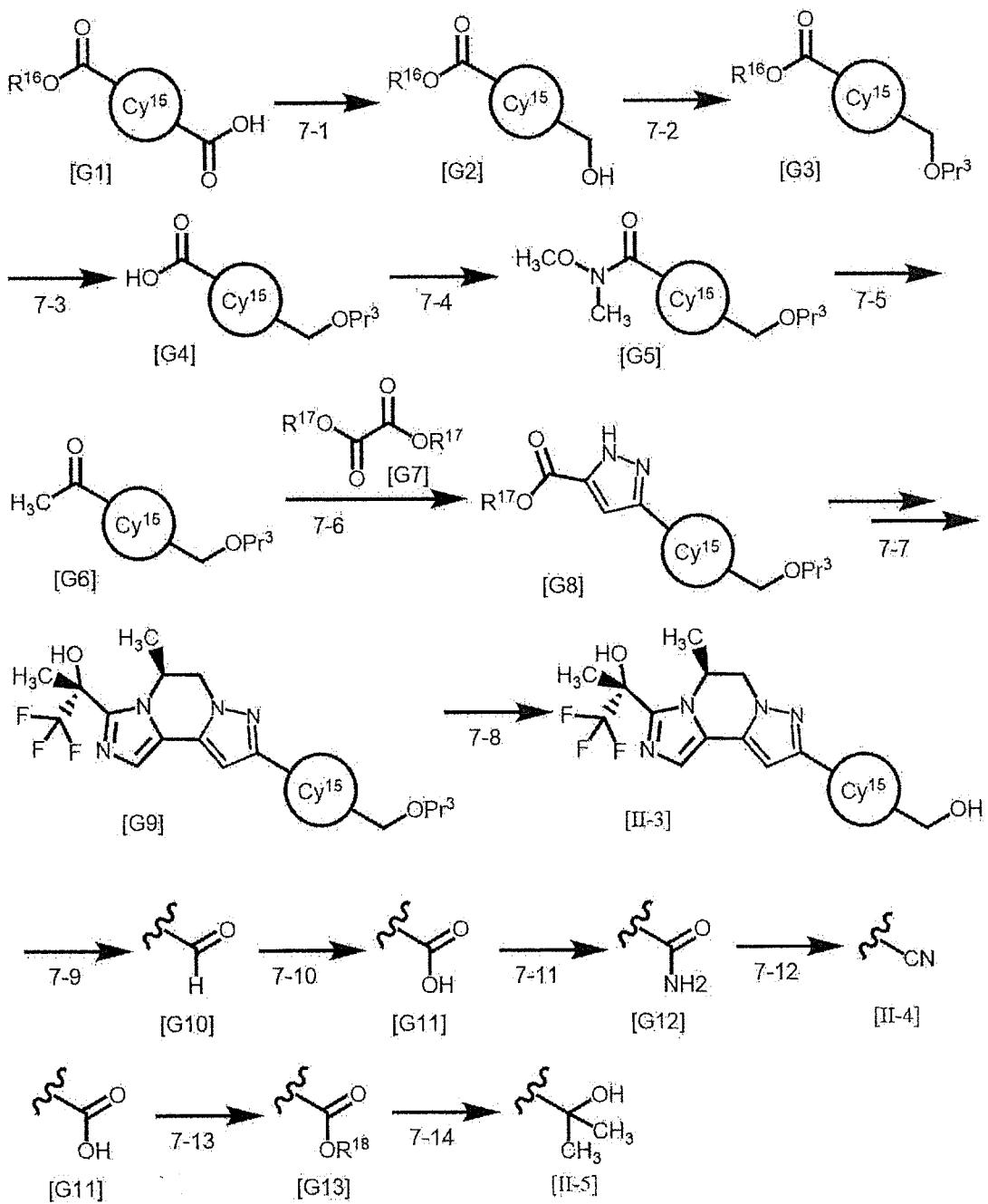
Compound [F8] may be a commercially available product, or may be obtained by appropriately converting a commercially 10 available product by a method well known to those of ordinary skill in the art. Compound [F8] may also be a salt with an acid.

[0162]

[Production Method 7]

15 Compounds of the formulas [II-3] to [II-5] can be obtained by Production Method 7 shown by the following scheme.

[0163]



[0164]

wherein  $\text{R}^{16}$ ,  $\text{R}^{17}$  and  $\text{R}^{18}$  are each independently  $\text{C}_{1-4}$  alkyl;  $\text{Cy}^{15}$  is bridged  $\text{C}_{5-10}$  cycloalkylene or 5- to 10-membered bridged heterocyclylene having 1 or 2 hetero atoms independently selected from a nitrogen atom and an oxygen atom; and  $\text{Pr}^3$  is a hydroxy-protecting group such as 2-tetrahydropyranyl and the like.

[0165]

10 Step 7-1

Compound [G2] can be obtained by reducing the carboxy group of compound [G1]. For example, compound [G2] can be obtained by an operation similar to that in Step 2-2.

Compound [G1] may be a commercially available product, or 5 may be obtained by appropriately converting a commercially available product by a method well known to those of ordinary skill in the art.

[0166]

Step 7-2

10 Compound [G3] can be obtained by protecting the hydroxy group of compound [G2]. For example, when  $\text{Pr}^3$  is 2-tetrahydropyranyl, compound [G3] can be obtained by reacting compound [G2] with 3,4-dihydro-2H-pyran in a solvent in the presence of an acid under ice-cooling to room temperature.

15 Examples of the acid include pyridinium p-toluenesulfonate.

Examples of the solvent include acetonitrile.

[0167]

Step 7-3

20 Compound [G4] can be obtained by hydrolysis of the ester of compound [G3]. For example, compound [G4] can be obtained by treating compound [G3] with an alkali in a solvent under ice-cooling to 80°C.

25 Examples of the alkali include lithium hydroxide and sodium hydroxide.

Examples of the solvent include methanol, ethanol, and water.

[0168]

Step 7-4

30 Compound [G5] can be obtained by an amidation reaction of compound [G4] and N,O-dimethylhydroxylamine. For example, compound [G5] can be obtained by reacting compound [G4] with N,O-dimethylhydroxylamine in a solvent in the presence of a base and a condensing agent under ice-cooling to room

temperature.

Examples of the base include diisopropylethylamine and triethylamine.

Examples of the condensing agent include 1-  
5 [bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-  
b]pyridinium 3-oxide hexafluorophosphate (HATU) and 1-ethyl-3-  
(3-dimethylaminopropyl) carbodiimide hydrochloride (WSC·HCl).

Examples of the solvent include pyridine and N,N-  
dimethylformamide.

10 [0169]

Step 7-5

Compound [G6] can be obtained by reacting compound [G5] with methylmagnesium halide. For example, compound [G5] can be obtained by the same operation as in Step 2-9.

15 [0170]

Step 7-6

Compound [G8] can be obtained by a pyrazole cyclization reaction using compound [G6] and compound [G7]. For example, compound [G8] can be obtained by reacting compound [G6] with 20 compound [G7] in a solvent in the presence of a base under ice-cooling to room temperature, and then reacting the obtained compound with hydrazine under ice-cooling to room temperature. The intermediate resulting from the reaction with compound [G7] may be isolated and the intermediate may be 25 reacted with hydrazine.

Examples of the base include potassium tert-butoxide.

Examples of the solvent include tetrahydrofuran.

Compound [G7] may be a commercially available product, or may be obtained by appropriately converting a commercially 30 available product by a method well known to those of ordinary skill in the art.

[0171]

Step 7-7

Compound [G9] can be obtained using compound [G8] by

reactions similar to those in Steps 6-1 to 6-6.

[0172]

Step 7-8

Compound [II-3] can be obtained by deprotection of  
5 compound [G9]. For example, when  $\text{Pr}^3$  is 2-tetrahydropyranyl,  
compound [II-3] can be obtained by treating compound [G9] with  
an acid in a solvent at room temperature to 70°C.

Examples of the acid include 10-camphorsulfonic acid.

Examples of the solvent include methanol.

10 [0173]

Step 7-9

Compound [G10] can be obtained by oxidation of a hydroxy  
group of compound [II-3]. For example, compound [G10] can be  
obtained by an operation similar to that in Step 6-2.

15 [0174]

Step 7-10

Compound [G11] can be obtained by reacting compound [G10]  
with an oxidizing agent in a solvent in the presence of an  
additive and a scavenger under ice-cooling to room temperature.

20 Examples of the oxidizing agent include sodium chlorite.

Examples of the additive include sodium dihydrogen  
phosphate dihydrate and disodium hydrogen phosphate.

Examples of the scavenger include 2-methyl-2-butene.

Examples of the solvent include tert-butanol and water.

25 [0175]

Step 7-11

Compound [G12] can be obtained by an amidation reaction  
of compound [G11] and ammonia. For example, compound [G12] can  
be obtained by an operation similar to that in Step 7-4.

30 [0176]

Step 7-12

Compound [II-4] can be obtained by a cyanation reaction  
of compound [G12]. For example, compound [II-4] can be  
obtained by reacting compound [G12] with an acid anhydride in

a solvent in the presence of a base under ice-cooling to room temperature.

Examples of the base include triethylamine.

Examples of the acid anhydride include trifluoroacetic 5 anhydride.

Examples of the solvent include 1,4-dioxane and tetrahydrofuran.

[0177]

Step 7-13

10 Compound [G13] can be obtained by an esterification reaction of compound [G11]. For example, compound [G13] can be obtained by reacting compound [G11] with trimethylsilyldiazomethane in a solvent under ice-cooling to room temperature.

15 Examples of the solvent include toluene and methanol.

[0178]

Step 7-14

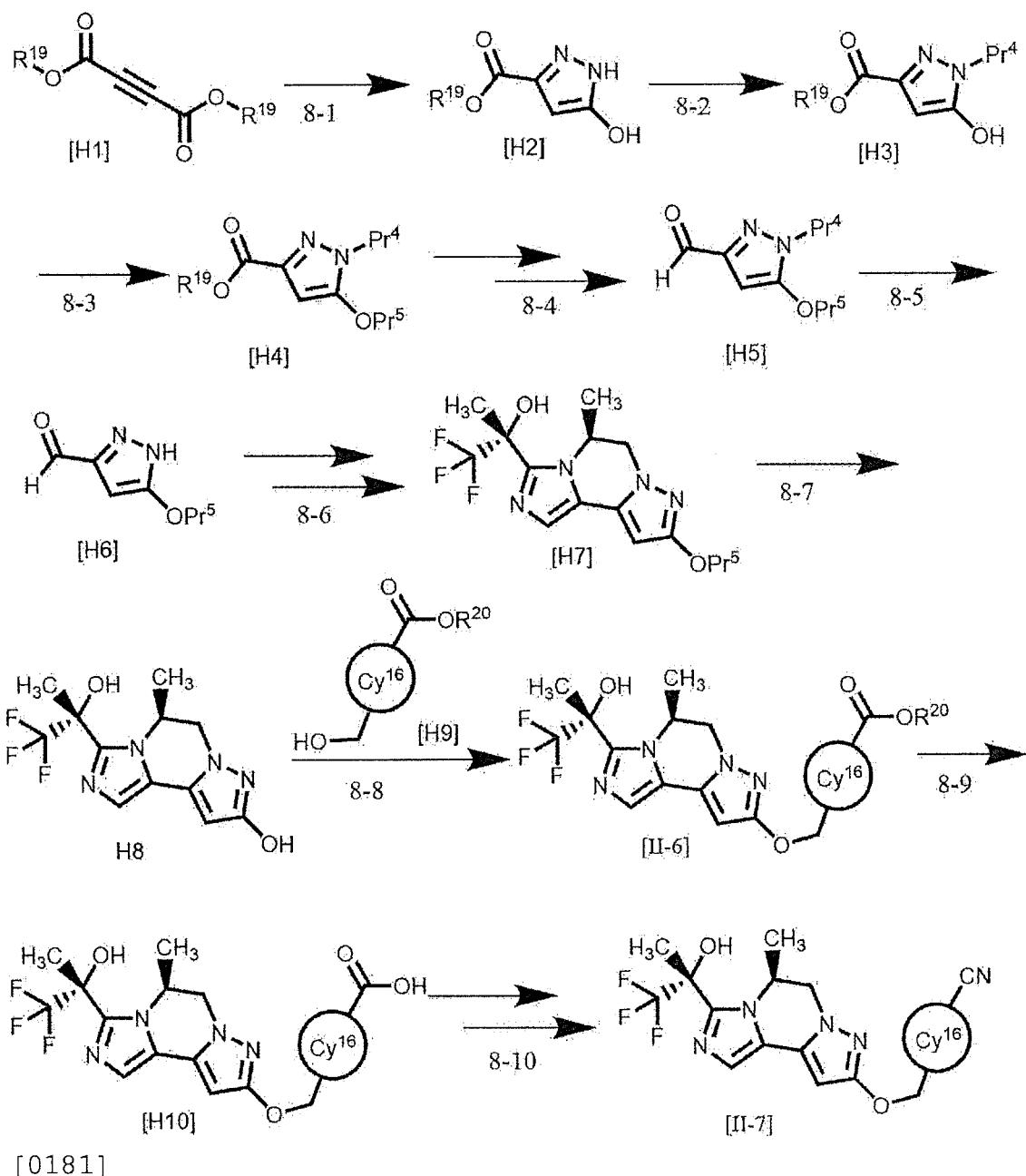
Compound [II-5] can be obtained by reacting compound [G13] with two equivalents of methylmagnesium halide. For 20 example, compound [II-5] can be obtained by an operation similar to that in Step 2-9.

[0179]

[Production Method 8]

The compounds of the formulas [II-6] and [II-7] can be 25 obtained by Production Method 8 shown by the following scheme.

[0180]



wherein R<sup>19</sup> and R<sup>20</sup> are each independently C<sub>1-4</sub> alkyl;

<sup>4</sup> Pr is a pyrazole-protecting group such as 2-tetrahydropyranyl and the like;

$\text{Pr}^5$  is a hydroxy-protecting group such as benzyl and the like; and

Cy<sup>16</sup> is bridged C<sub>5-10</sub> cycloalkylene.

[0182]

10 Step 8-1

Compound [H2] can be obtained by reacting compound [H1] with hydrazine. For example, compound [H2] can be obtained by

reacting compound [H1] with hydrazine in a solvent at room temperature. Where necessary, the reaction may be performed in the presence of an acid.

Examples of the solvent include acetonitrile, toluene and 5 ethanol.

Examples of the acid include acetic acid.

Compound [H1] may be a commercially available product, or may be obtained by appropriately converting a commercially available product by a method well known to those of ordinary 10 skill in the art.

[0183]

Step 8-2

Compound [H3] can be obtained by introduction of a protecting group into pyrazole of compound [H2]. For example, 15 when  $Pr^4$  is 2-tetrahydropyranyl, compound [H3] can be obtained by reacting compound [H2] with 3,4-dihydro-2H-pyran in a solvent in the presence of an acid at room temperature.

Examples of the solvent include acetonitrile and N,N-dimethylformamide.

20 Examples of the acid include pyridinium p-toluenesulfonate and p-toluenesulfonic acid.

[0184]

Step 8-3

Compound [H4] can be obtained by protecting the hydroxy 25 group of compound [H3]. For example, when  $Pr^5$  is benzyl, compound [H4] can be obtained by reacting compound [H3] with benzyl halide in a solvent in the presence of a base at room temperature.

Examples of the benzyl halide include benzyl chloride and 30 benzyl bromide.

Examples of the solvent include N-methylpyrrolidone, N,N-dimethylformamide, acetonitrile, toluene, isopropyl acetate, tetrahydrofuran, and dimethyl sulfoxide.

Examples of the base include potassium carbonate, sodium

carbonate, cesium carbonate, lithium carbonate, potassium tert-butoxide, potassium acetate, potassium phosphate, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and N,N-diisopropylethylamine.

5 [0185]

Step 8-4

Compound [H5] can be obtained using compound [H4] by reactions similar to those in Steps 6-1 and 6-2.

[0186]

10 Step 8-5

Compound [H6] can be obtained by deprotection of the protecting group of pyrazole of compound [H5]. For example, when  $\text{Pr}^4$  is 2-tetrahydropyranyl, compound [H6] can be obtained by treating compound [H5] with an acid in a solvent at room 15 temperature.

Examples of the acid include hydrochloric acid, methanesulfonic acid, sulfuric acid, and phosphoric acid.

Examples of the solvent include 1,2-dimethoxyethane.

[0187]

20 Step 8-6

Compound [H7] can be obtained using compound [H6] by reactions similar to those in Step s 6-3 to 6-6.

[0188]

Step 8-7

25 Compound H8 can be obtained by deprotection of compound [H7]. For example, compound H8 can be obtained by treating compound [H7] with an acid at room temperature to 50°C. Compound H8 may be obtained as a salt with an acid used.

Examples of the acid include concentrated hydrochloric 30 acid.

[0189]

Step 8-8

Compound [II-6] can be obtained by a Mitsunobu reaction of compound H8 and compound [H9]. For example, compound [II-6]

can be obtained by an operation similar to that in Step 4-3.

Compound [H9] may be a commercially available product, or may be obtained by appropriately converting a commercially available product by a method well known to those of ordinary skill in the art.

[0190]

Step 8-9

Compound [H10] can be obtained by hydrolysis of the ester of compound [II-6]. For example, compound [H10] can be obtained by an operation similar to that in Step 7-3.

[0191]

Step 8-10

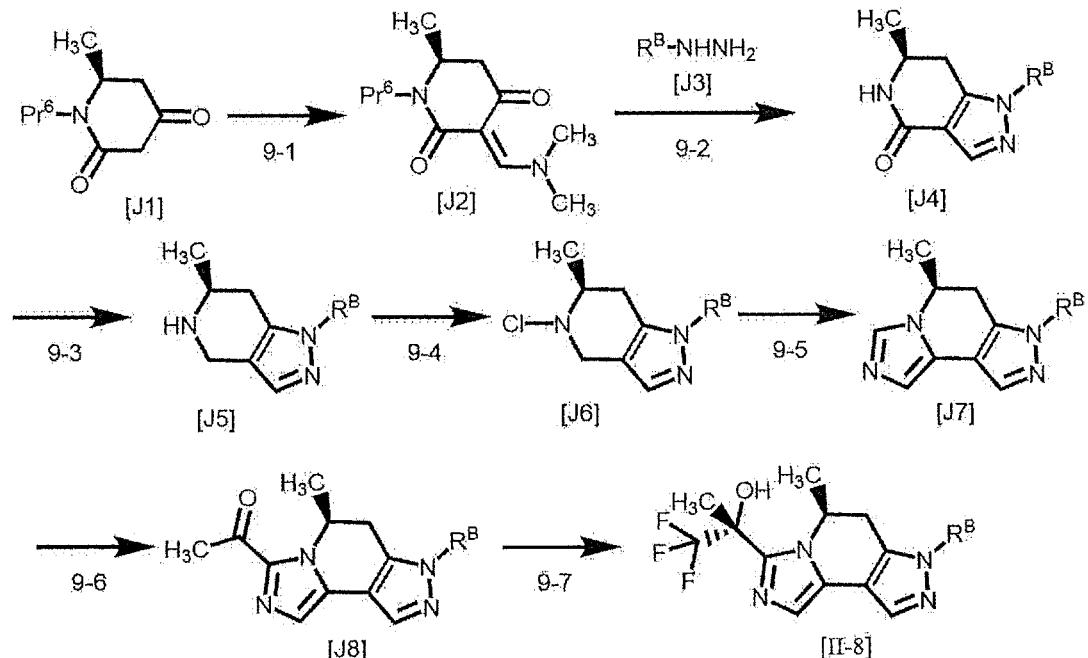
Compound [III-7] can be obtained using compound [H10] by reactions similar to those in Steps 7-11 and 7-12.

[0192]

[Production Method 9]

The compound of the formula [III-8] can be obtained by Production Method 9 shown by the following scheme.

[0193]



[0194]

wherein  $\text{Pr}^6$  is an amino-protecting group such as tert-butoxycarbonyl and the like; and

other each symbol is as defined for the formula [II].

[0195]

Steps 9-1 and 9-2

Compound [J4] can be obtained by a pyrazole cyclization reaction using compound [J1] and compound [J3]. For example, compound [J2] can be obtained by reacting compound [J1] with N,N-dimethylformamide dimethyl acetal in a solvent at room temperature. Thereafter, compound [J4] can be obtained by reacting compound [J2] with compound [J3] in a solvent in the presence of an acid at 100°C to 200°C. When Pr<sup>6</sup> is tert-butoxycarbonyl, deprotection also proceeds.

Examples of the solvent of the reaction with N,N-dimethylformamide dimethyl acetal include toluene.

Examples of the solvent of the cyclization reaction include ethanol, isopropanol, and water.

Examples of the acid include acetic acid.

Compound [J1] and compound [J3] may be commercially available products, or may be obtained by appropriately converting a commercially available product by a method well known to those of ordinary skill in the art.

[0196]

Step 9-3

Compound [J5] can be obtained by reducing compound [J4]. For example, compound [J5] can be obtained by reacting compound [J4] with a reducing agent in a solvent at room temperature to 90°C.

Examples of the reducing agent include borane and lithium aluminum hydride.

Examples of the solvent include tetrahydrofuran.

[0197]

Step 9-4

Compound [J6] can be obtained by chlorination of compound [J5]. For example, compound [J6] can be obtained by reacting compound [J5] with a chlorinating agent in a solvent in the

presence of a base under ice-cooling to room temperature.

Examples of the base include 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Examples of the chlorinating agent include N-5 chlorosuccinimide.

Examples of the solvent include dichloromethane.

[0198]

Step 9-5

Compound [J7] can be obtained by an imination reaction of 10 compound [J6] and a cyclization reaction using p-toluenesulfonylmethyl isocyanide. For example, the imination reaction is performed by reacting compound [J6] with a base in a solvent at room temperature. Then the resultant product is reacted with p-toluenesulfonylmethyl isocyanide in a solvent 15 in the presence of a base under ice-cooling to room temperature, whereby compound [J7] can be obtained.

Examples of the solvent of the imination reaction include methanol and 1,2-dimethoxyethane.

Examples of the base of the imination reaction include 20 sodium hydroxide.

Examples of the base of the cyclization reaction include potassium carbonate.

Examples of the solvent of the cyclization reaction include tetrahydrofuran and 1,2-dimethoxyethane.

25 [0199]

Step 9-6

Compound [J8] can be obtained by an acylation reaction of compound [J7]. For example, compound [J8] can be obtained by reacting compound [J7] with N-methoxy-N-methylacetamide in a 30 solvent in the presence of a base.

Examples of the base include lithium diisopropylamide.

Examples of the solvent include tetrahydrofuran.

[0200]

Step 9-7

Compound [II-8] can be obtained by reacting compound [J8] with (trifluoromethyl)trimethylsilane. For example, compound [II-8] can be obtained by an operation similar to that in Step 2-10.

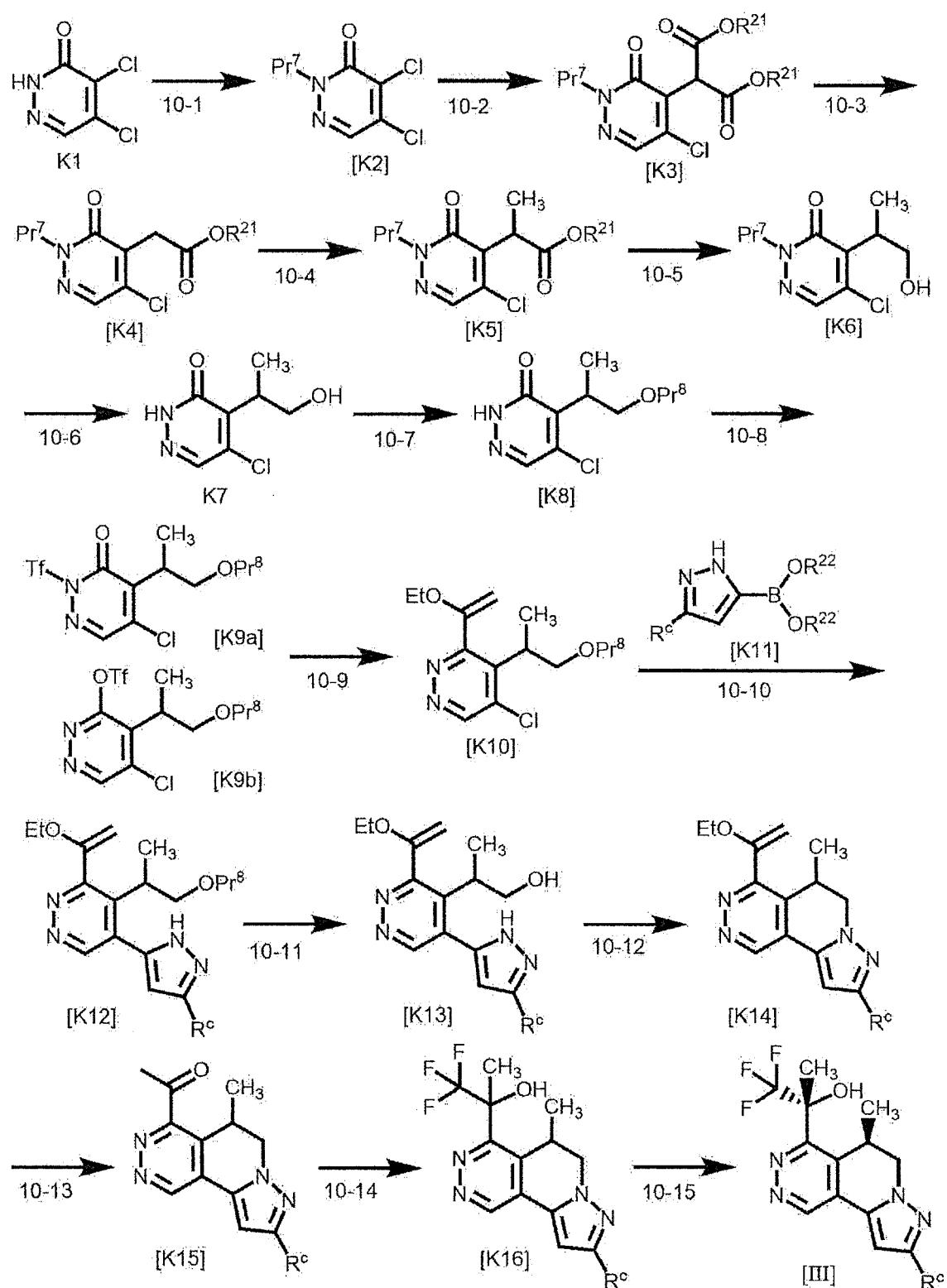
5 The methyl group of compound [J8] becomes a steric hindrance and the reaction proceeds diastereoselectively, whereby compound [II-8] is obtained as an optically active form.

[0201]

10 [Production Method 10]

The compound of the formulas [III] can be obtained by Production Method 10 shown by the following scheme.

[0202]



[0203]

wherein  $\text{Pr}^7$  is a protecting group such as p-methoxybenzyl and the like;

<sup>5</sup>  $\text{Pr}^8$  is a hydroxy-protecting group such as tert-butyldimethylsilyl and the like;

R<sup>21</sup> is C<sub>1-4</sub> alkyl;  
each R<sup>22</sup> is independently hydrogen or C<sub>1-4</sub> alkyl, and one R<sup>22</sup> may  
be bonded to the other R<sup>22</sup> to form a ring; and  
other each symbol is as defined for the aforementioned formula  
5 [III].

[0204]

Step 10-1

Compound [K2] can be obtained by protection of compound K1. For example, when Pr<sup>7</sup> is p-methoxybenzyl, compound [K2] 10 can be obtained by reacting compound K1 with p-methoxybenzyl halide in a solvent in the presence of a base. Where necessary, an additive may also be used.

Examples of the p-methoxybenzyl halide include p-methoxybenzyl chloride.

15 Examples of the base include potassium hydroxide and cesium carbonate.

Examples of the additive include tetrabutylammonium bromide.

20 Examples of the solvent include toluene and N,N-dimethylformamide.

Compound [K1] may be a commercially available product, or may be obtained by appropriately converting a commercially available product by a method well known to those of ordinary skill in the art.

25 [0205]

Step 10-2

Compound [K3] can be obtained by reacting compound [K2] with malonic acid diester. For example, compound [K3] can be obtained by reacting compound [K2] with malonic acid diester 30 in a solvent in the presence of a base.

Examples of the malonic acid diester include diethyl malonate.

Examples of the base include sodium tert-pentoxide.

Examples of the solvent include tetrahydrofuran.

[0206]

Step 10-3

Compound [K4] can be obtained by heating compound [K3] in a solvent at 100°C to 140°C.

5 Examples of the solvent include water and dimethyl sulfoxide.

[0207]

Step 10-4

Compound [K5] can be obtained by methylation of compound 10 [K4]. For example, compound [K5] can be obtained by reacting compound [K4] with a methylating agent in a solvent in the presence of a base at -78°C to room temperature.

Examples of the base include lithium bis(trimethylsilyl)amide.

15 Examples of the methylating agent include methyl iodide.

Examples of the solvent include tetrahydrofuran.

[0208]

Step 10-5

Compound [K6] can be obtained by reduction of the ester 20 group of compound [K5]. For example, compound [K6] can be obtained by reacting compound [K5] with a reducing agent in a solvent under ice-cooling.

Examples of the reducing agent include lithium aluminum hydride.

25 Examples of the solvent include tetrahydrofuran, diethyl ether, and cyclopentyl methyl ether.

[0209]

Step 10-6

Compound K7 can be obtained by deprotection of compound 30 [K6]. For example, when Pr<sup>7</sup> is p-methoxybenzyl, compound K7 can be obtained by reacting compound [K6] with cerium(IV) ammonium nitrate in a solvent under ice-cooling to room temperature.

Examples of the solvent include acetonitrile and water.

[0210]

Step 10-7

Compound [K8] can be obtained by protection of the hydroxy group of compound K7. For example, when  $\text{Pr}^8$  is tert-butyldimethylsilyl, compound [K8] can be obtained by reacting compound K7 with tert-butyldimethylsilyl chloride in a solvent in the presence of a base under ice-cooling to room temperature.

Examples of the base include imidazole and 4-dimethylaminopyridine.

Examples of the solvent include  $\text{N},\text{N}$ -dimethylformamide.

[0211]

Step 10-8

Compounds [K9a] and [K9b] can be obtained by reacting compound [K8] with trifluoromethanesulfonic anhydride in a solvent in the presence of a base under ice-cooling.

Examples of the base include pyridine.

Examples of the solvent include dichloromethane.

[0212]

Step 10-9

Compound [K10] can be obtained by a coupling reaction using compounds [K9a] and [K9b] and an organotin reagent. For example, compound [K10] can be obtained by reacting compounds [K9a] and [K9b] with an organotin reagent in a solvent in the presence of a palladium catalyst and an additive at 100°C to 130°C.

Examples of the palladium catalyst include tetrakis(triphenylphosphine)palladium.

Examples of the additive include lithium chloride and copper iodide.

Examples of the organotin reagent include tributyl(1-ethoxyvinyl)stannane.

Examples of the solvent include 1,4-dioxane.

[0213]

Step 10-10

Compound [K12] can be obtained by Suzuki coupling of compound [K10] and compound [K11]. For example, compound [K12] can be obtained by an operation similar to that in Step 4-5.

5 Compound [K11] may be a commercially available product, or may be obtained by appropriately converting a commercially available product by a method well known to those of ordinary skill in the art.

[0214]

10 Step 10-11

Compound [K13] can be obtained by deprotection of compound [K12]. For example, when  $\text{Pr}^8$  is tert-butyldimethylsilyl, compound [K13] can be obtained by reacting compound [K12] with a fluorine reagent in a solvent under ice-15 cooling to room temperature.

Examples of the fluorine reagent include tetrabutylammonium fluoride.

Examples of the solvent include tetrahydrofuran.

[0215]

20 Step 10-12

Compound [K14] can be obtained by an intramolecular Mitsunobu reaction of compound [K13]. For example, compound [K14] can be obtained by an operation similar to that in Step 6-4.

25 [0216]

Step 10-13

Compound [K15] can be obtained by treating compound [K14] with an acid in a solvent at room temperature to 60°C.

Examples of the acid include hydrochloric acid.

30 Examples of the solvent include methanol and tetrahydrofuran.

[0217]

Step 10-14

Compound [K16] can be obtained by reacting compound [K15]

with (trifluoromethyl)trimethylsilane. For example, compound [K16] can be obtained by an operation similar to that in Step 2-10.

[0218]

5 Step 10-15

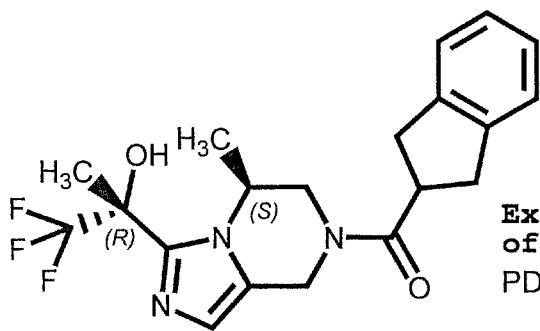
Compound [III] can be obtained by purifying compound [K16] by chiral column chromatography. The steric configuration of compound [III] can be determined, for example, by X-ray crystal structure analysis.

10 [0219]

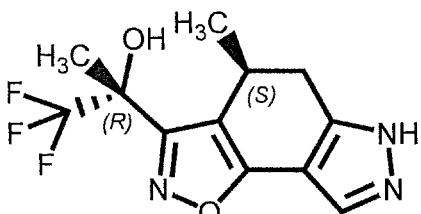
Estimation of steric configuration

WO 2019/151274 discloses PDHK inhibitors of Example 3 and the like, in which the absolute configuration of the ring carbon substituted by the methyl group is S and the absolute 15 configuration of the carbon substituted by the hydroxy group is R. Example 20 (racemate) of the present invention showed an hPDHK2 inhibitory activity of  $IC_{50} = 22.6$  nM. Example 28, which is an optically active form of Example 20, showed an activity of  $IC_{50} = 8.5$  nM, whereas the inhibitory activity of 20 its enantiomer was low. From these results, the steric configuration of Example 28 could be estimated. In this way, the steric configuration can be estimated from the inhibitory activity of each enantiomer.

[0220]

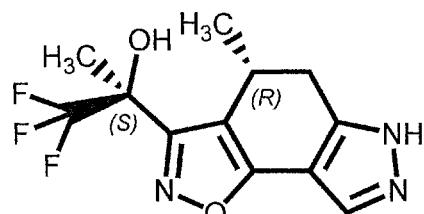


Example 3 (optically active form)  
of WO 2019/151274A  
PDHK2 IC<sub>50</sub> = 14 nM



Example 28 (optically active form)

PDHK2 IC<sub>50</sub> = 8.5 nM



Example 20 (racemate)

PDHK2 IC<sub>50</sub> = 22.6 nM

enantiomer of Example 28

PDHK2 IC<sub>50</sub> > 100 nM

[Example]

[0221]

The production method of the compound of the formula [I],  
5 the formula [II] or the formula [III] or a pharmaceutically  
acceptable salt thereof of the present invention is  
specifically explained by way of the following Production  
Examples. However, the production method of the compound or a  
pharmaceutically acceptable salt thereof is not limited by the  
10 Production Examples.

Unless otherwise specified, % shows wt%. Unless  
otherwise specified, the ratio of a mixed solvent is a volume  
mixing ratio.

In the Examples, abbreviations mean the following.

15 DMSO: dimethyl sulfoxide

DMF: N,N-dimethylformamide

THF: tetrahydrofuran

M: mol/L

N: normality

20 HATU: 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate

WSC-HCl: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride

HOBt-H<sub>2</sub>O: 1-hydroxybenzotriazole monohydrate

The measurement results of <sup>1</sup>H-NMR are indicated using the  
5 following abbreviations.

s: singlet, d: doublet, dd: double doublet, dt: double triplet,  
t: triplet, q: quartet, dq: double quartet, m: multiplet, brs:  
broad singlet, brm: broad multiplet, J: coupling constant, Hz:  
Hertz

10 <sup>1</sup>H-NMR spectrum was measured in CDCl<sub>3</sub> or DMSO-D<sub>6</sub> using tetramethylsilane as an internal standard, and all  $\delta$  values are shown in ppm.

[0222]

Production Example 1

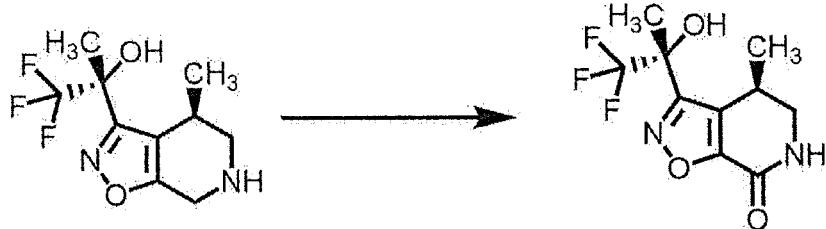
15 Synthesis of (R)-1,1,1-trifluoro-2-((R)-6-methyl-3-(trifluoromethyl)-5,6-dihydroisoxazolo[5,4-c][1,2,4]triazolo[4,3-a]pyridin-7-yl)propan-2-ol (Example 1)

[0223]

Step 1

20 (R)-4-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroisoxazolo[5,4-c]pyridin-7(4H)-one

[0224]



[0225]

25 (R)-1,1,1-Trifluoro-2-((R)-4-methyl-4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-yl)propan-2-ol (1.5 g) was mixed with acetonitrile (27 ml) and water (3 ml). Under ice-cooling, tetrabutylammonium iodide (0.221 g) and iodosobenzene (1.978 g) were added, and the mixture was stirred at room  
30 temperature for 1 hr. Under ice-cooling, tetrabutylammonium

iodide (0.221 g) and iodosobenzene (1.978 g) were added, and the mixture was stirred at room temperature for 100 min. To the reaction mixture was added saturated sodium thiosulfate aqueous solution, and the mixture was stirred for 1 hr. The 5 mixture was extracted with ethyl acetate. The organic layer was washed twice with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel 10 column chromatography (hexane:ethyl acetate=100:0 to 0:100) to give the title compound (1.19 g).

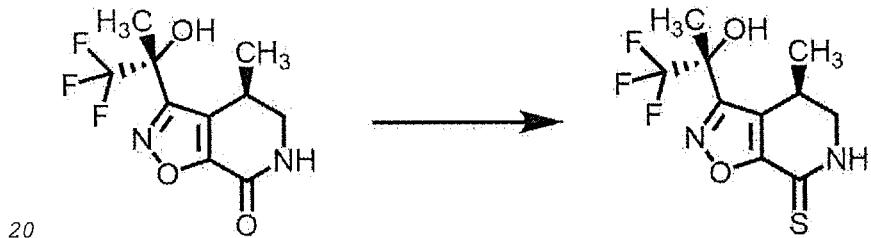
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.21 (d, J=6.95Hz, 3H), 1.76 (s, 3H), 3.03 - 3.22 (m, 2H), 3.60 - 3.68 (m, 1H), 7.28 (s, 1H), 8.20 - 8.13 (m, 1H)

15 [0226]

Step 2

(R)-4-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroisoxazolo[5,4-c]pyridin-7(4H)-thione

[0227]



[0228]

(R)-4-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroisoxazolo[5,4-c]pyridin-7(4H)-one (1.76 g) was mixed with toluene (35.2 ml). At room temperature, pyridine 25 (2.68 ml) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (1.886 g), and the mixture was stirred at 120°C for 3 hr. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (hexane:ethyl 30 acetate=100:0 to 0:100) to give the title compound (0.648 g).

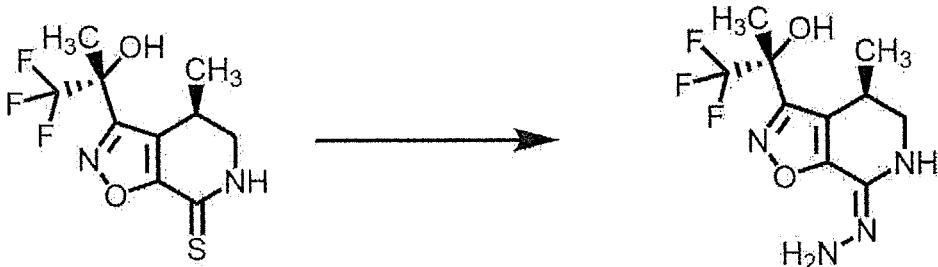
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.16 (d, J=6.94Hz, 3H), 1.76 (s, 3H), 3.13 – 3.21 (m, 1H), 3.27 – 3.35 (m, 1H), 3.56 – 3.66 (m, 1H), 7.30 (s, 1H), 10.49 (brs, 1H)

[0229]

5 Step 3

(R)-1,1,1-trifluoro-2-((R)-7-hydrazinylidene-4-methyl-4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-yl)propan-2-ol

[0230]



10 [0231]

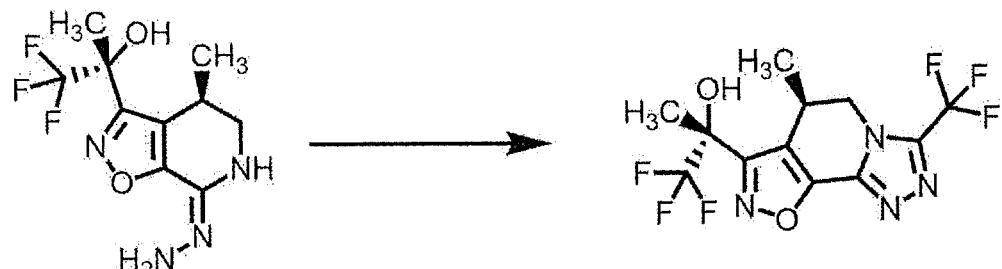
(R)-4-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroisoxazolo[5,4-c]pyridin-7(4H)-thione (0.075 g) obtained in the previous step was mixed with 2-propanol (0.75 ml). At room temperature, hydrazine monohydrate (0.067 g) was 15 added, and the mixture was stirred at 120°C for 40 min. The reaction mixture was concentrated under reduced pressure to give a crude product (0.075 g) of the title compound.

[0232]

Step 4

20 (R)-1,1,1-trifluoro-2-((R)-6-methyl-3-(trifluoromethyl)-5,6-dihydroisoxazolo[5,4-c][1,2,4]triazolo[4,3-a]pyridin-7-yl)propan-2-ol

[0233]



25 [0234]

(R)-1,1,1-Trifluoro-2-((R)-7-hydrazinylidene-4-methyl-

4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-yl)propan-2-ol (0.075 g) obtained in the previous step was mixed with chloroform (0.15 ml). At room temperature, trifluoroacetic acid (0.45 ml) and trifluoroacetic anhydride (0.113 ml) were 5 added, and the mixture was stirred overnight. The mixture was stirred at 70°C for 2 hr. At room temperature, saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was extracted with ethyl acetate and the organic layer was washed with water and saturated aqueous sodium chloride 10 solution. After filtration through a phase separator, the residue was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=80:20 to 50:50) to give the title compound (0.066 g).

15  $^1\text{H-NMR}$  (400 MHz, DMSO- $\text{D}_6$ ) 1.21 (d,  $J=6.94\text{Hz}$ , 3H), 1.82 (s, 3H), 3.56 – 3.60 (m, 1H), 4.40 (d,  $J=3.24\text{Hz}$ , 2H), 7.49 (s, 1H) [0235]

#### Production Example 2-1

Synthesis of (R)-1,1,1-trifluoro-2-((R)-8-(2-hydroxy-2-methylpropoxy)-4-methyl-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-3-yl)propan-2-ol (Example 31)

20 [0236]

#### Step 1

25 4-ethoxy-2-methyl-4-oxobutyric acid

[0237]



20 [0238]

4-Ethoxy-2-methylene-4-oxobutyric acid (25.0 g) and 10 w/w% palladium carbon (2.5 g) were mixed with methanol (200 ml). Under hydrogen atmosphere, the mixture was stirred at room temperature overnight. The reaction mixture was filtered 30 through celite, and the filtrate was concentrated under

reduced pressure. The obtained residue was azeotroped with toluene. The obtained residue was filtered through celite again, and the filtrate was concentrated under reduced pressure to give a crude product (25.0 g) of the title  
5 compound.

[0239]

Step 2

ethyl 4-hydroxy-3-methylbutyrate

[0240]



[0241]

The crude product (21.7 g) of 4-ethoxy-2-methyl-4-oxobutyric acid obtained in the previous step was dissolved in tetrahydrofuran (217 ml). Under ice-cooling, to this solution  
15 was added dropwise 0.89 M borane/tetrahydrofuran solution (168 ml). The reaction mixture was stirred at room temperature for 3 hr. Under ice-cooling, methanol (43.5 ml) was added dropwise to the reaction mixture, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated  
20 under reduced pressure, water was added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution and dried over magnesium sulfate. Magnesium sulfate was filtered off, and the filtrate was concentrated under  
25 reduced pressure to give a crude product (18.4 g) of the title compound.

[0242]

Step 3

ethyl 3-methyl-4-((methylsulfonyl)oxy)butanoate

30 [0243]



[0244]

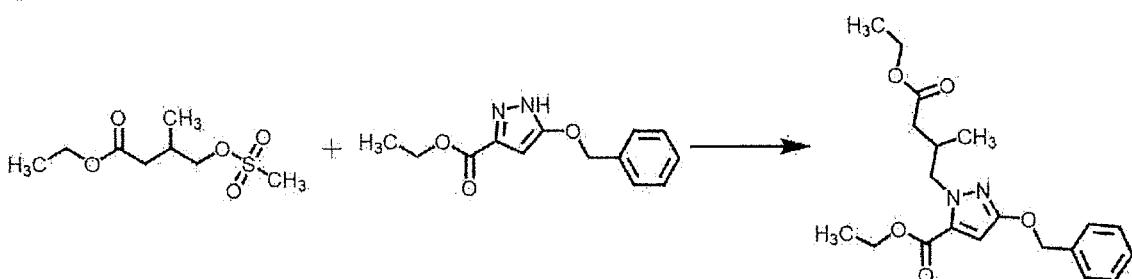
The crude product (18.4 g) of ethyl 4-hydroxy-3-methylbutyrate obtained in the previous step was mixed with 5 dichloromethane (147 ml). Under ice-cooling, triethylamine (26.3 ml) was added to the reaction mixture, and then methanesulfonic anhydride (24.1 g) was added in 3 portions. The reaction mixture was stirred at 0°C for 1 hr. To the reaction mixture was added saturated aqueous sodium hydrogen 10 carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with 1N hydrochloric acid and saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced 15 pressure to give a crude product (27.4 g) of the title compound.

[0245]

Step 4

ethyl 3-(benzyloxy)-1-(4-ethoxy-2-methyl-4-oxobutyl)-1H-20 pyrazole-5-carboxylate

[0246]



[0247]

The crude product (27.4 g) of ethyl 3-methyl-4-((methylsulfonyl)oxy)butanoate obtained in the previous step 25 was mixed with dimethylformamide (219 ml). At room temperature, to the reaction mixture were added a crude product (27.4 g) of ethyl 3-(benzyloxy)-1H-pyrazole-5-carboxylate obtained in

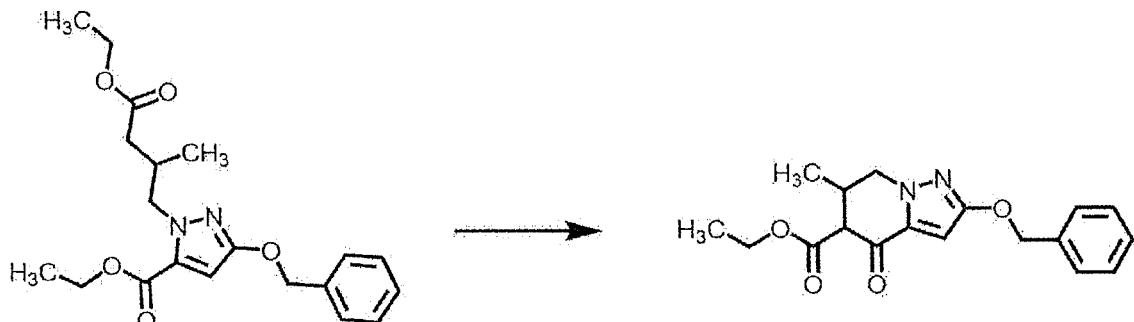
Auxiliary Step 1 and cesium carbonate (54.3 g). After heating at 80°C for 2 hr, the mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted with toluene. The organic layer was 5 washed successively with saturated ammonium chloride aqueous solution and saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give a crude product (45 g) of the title compound.

10 [0248]

Step 5

ethyl 2-(benzyloxy)-6-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carboxylate

[0249]



15

[0250]

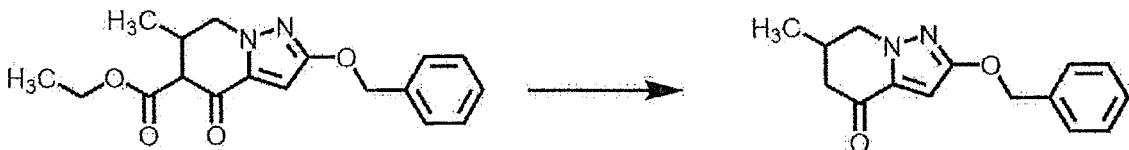
The crude product (45.0 g) of ethyl 3-(benzyloxy)-1-(4-ethoxy-2-methyl-4-oxobutyl)-1H-pyrazole-5-carboxylate obtained in the previous step was mixed with toluene (319 ml). Under 20 water cooling, to the reaction mixture was added potassium tert-butoxide (13.1 g), and the mixture was heated under reflux at 120°C for 2 hr. Saturated ammonium chloride aqueous solution was added to the reaction mixture at room temperature, and the mixture was extracted with ethyl acetate. The organic 25 layer was washed successively with water and saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give a crude product (37.2 g) of the title compound.

[0251]

Step 6

2-(benzyloxy)-6-methyl-6,7-dihydropyrazolo[1,5-a]pyridin-4(5H)-one

5 [0252]



[0253]

The crude product (37.2 g) of ethyl 2-(benzyloxy)-6-methyl-4-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-5-carboxylate obtained in the previous step was mixed with dimethyl sulfoxide (372 ml) and water (74 ml). At room temperature, to the reaction mixture was added lithium chloride (11.1 g), and the mixture was heated under reflux at 150°C for 8 hr. Water was added to the reaction mixture at room temperature, and the mixture was extracted with toluene. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=95:5 to 50:50) to give the title compound (21.0 g).

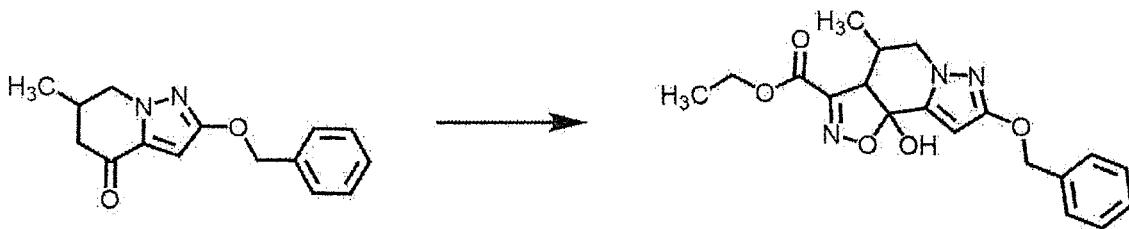
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.07 (d, J=6.47Hz, 3H), 2.41 - 2.63 (m, 3H), 3.86 (dd, J=12.72, 9.25Hz, 1H), 4.22 - 4.27 (m, 1H), 5.17 (s, 2H), 6.25 (s, 1H), 7.31 - 7.45 (m, 5H)

25 [0254]

Step 7

30 ethyl 8-(benzyloxy)-9b-hydroxy-4-methyl-3a,4,5,9b-tetrahydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridine-3-carboxylate

[0255]



[0256]

Ethyl 2-chloro-2-(hydroxyimino)acetate (8.73 g) was mixed with tetrahydrofuran (123 ml). To this solution was added 5 dropwise 1.3 M lithium bis(trimethylsilyl)amide/tetrahydrofuran solution (44.3 ml) at -78°C to prepare nitrile oxide solution. In a separate reaction vessel, 2-(benzyloxy)-6-methyl-6,7-dihydropyrazolo[1,5-a]pyridin-4(5H)-one (12.3 g) obtained in the previous step was mixed with tetrahydrofuran (123 ml). To this solution was added dropwise 1.3 M lithium bis(trimethylsilyl)amide/tetrahydrofuran solution (40.6 ml) at -78°C. This reaction mixture was added dropwise through a cannula to the aforementioned nitrile oxide solution cooled to -78°C. The reaction mixture was stirred at -78°C for 30 min, and allowed to warm to room temperature over 1 hr. To the reaction mixture was added dropwise 2N hydrochloric acid (120 ml) at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and filtered through a phase separator. The above-mentioned operation was also performed on 2-(benzyloxy)-6-methyl-6,7-dihydropyrazolo[1,5-a]pyridin-4(5H)-one (10.0 g). The filtrates were combined and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=10:90 to 43:57) to give a crude product (12.5 g) of the title compound.

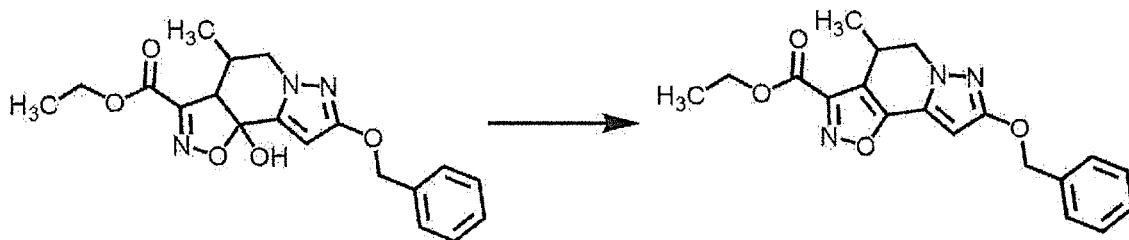
[0257]

Step 8

30 ethyl 8-(benzyloxy)-4-methyl-4,5-dihydroisoxazolo[5,4-

c]pyrazolo[1,5-a]pyridine-3-carboxylate

[0258]



[0259]

5 The crude product (12.5 g) of ethyl 8-(benzyloxy)-9b-hydroxy-4-methyl-3a,4,5,9b-tetrahydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridine-3-carboxylate obtained in the previous step was dissolved in tetrahydrofuran (125 ml). Under ice-cooling, to the reaction mixture were successively added 10 methanesulfonic anhydride (10.2 g) and triethylamine (14 ml). The mixture was stirred at 0°C for 30 min, after which stirred at 45°C for 30 min. The reaction mixture was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=5:95 to 15 ethyl acetate:hexane=50:50) to give the title compound (9.7 g).

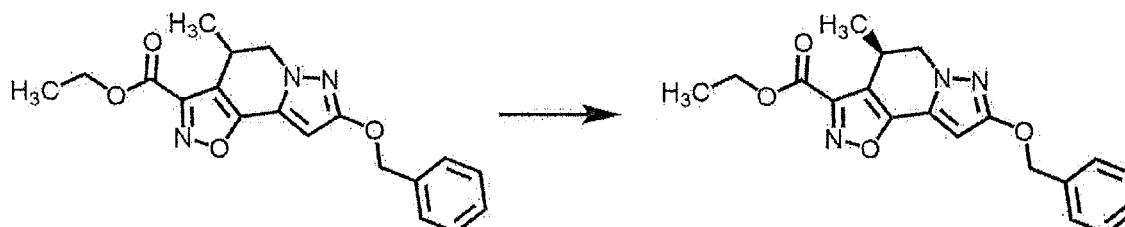
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.21 (d, J=7.48Hz, 3H), 1.35 (t, J=7.11Hz, 3H), 3.51 - 3.55 (m, 1H), 4.13 - 4.23 (m, 2H), 4.38 - 4.44 (m, 2H), 5.21 (s, 2H), 6.39 (s, 1H), 7.35 - 7.50 (m, 5H)

20 [0260]

Step 9

ethyl (R)-8-(benzyloxy)-4-methyl-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridine-3-carboxylate

[0261]



25

[0262]

Ethyl 8-(benzyloxy)-4-methyl-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridine-3-carboxylate (2.0 g) obtained in the previous step was optically resolved using Japan Analytical Industry Co., Ltd. automatic recycling preparative 5 HPLC (apparatus name: LaboACE LC-7080, column: Daicel CHIRALPAK IA, 20 mm(I.D.) x 250 mm(L), 5  $\mu$ m, mobile phase flow rate: 20 ml/min, mobile phase mixing ratio: isocratic, hexane:ethanol=85:15) to give the title compound (0.93 g) as the second peak fraction.

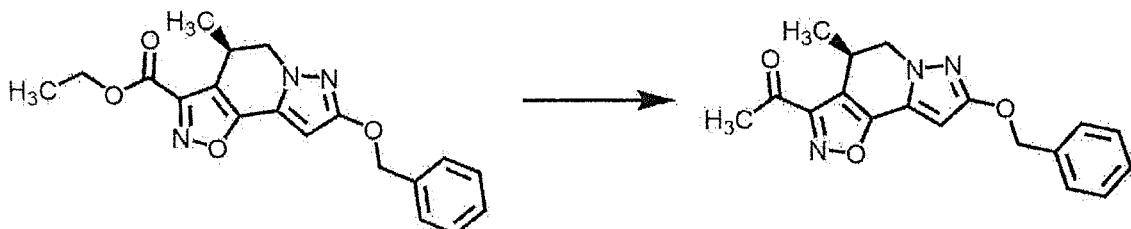
10  $^1$ H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.21 (d, J=7.17Hz, 3H), 1.35 (t, J=7.05Hz, 3H), 3.52 - 3.54 (m, 1H), 4.15 - 4.21 (m, 2H), 4.37 - 4.45 (m, 2H), 5.21 (s, 2H), 6.39 (s, 1H), 7.36 - 7.48 (m, 5H)

[0263]

15 Step 10

(R)-1-(8-(benzyloxy)-4-methyl-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-3-yl)ethan-1-one

[0264]



20 [0265]

Ethyl (R)-8-(benzyloxy)-4-methyl-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridine-3-carboxylate (0.93 g) obtained in the previous step was dissolved in 2-methyltetrahydrofuran (18.6 ml). Under ice-cooling, a mixture 25 of triethylamine (2.2 ml) and 1.08 M methylmagnesium bromide/tetrahydrofuran solution (5.3 ml) was added dropwise, and the mixture was stirred at 0°C for 1 hr. To the reaction mixture was added saturated ammonium chloride aqueous solution, and the mixture was extracted with ethyl acetate. The organic 30 layer was washed successively with water and saturated aqueous

sodium chloride solution, and filtered through a phase separator. the filtrate was concentrated under reduced pressure. To the obtained residue were added ethyl acetate (8 ml) and hexane (42 ml), and the mixture was stirred at room 5 temperature. The precipitated solid was collected by filtration to give the title compound (0.64 g).

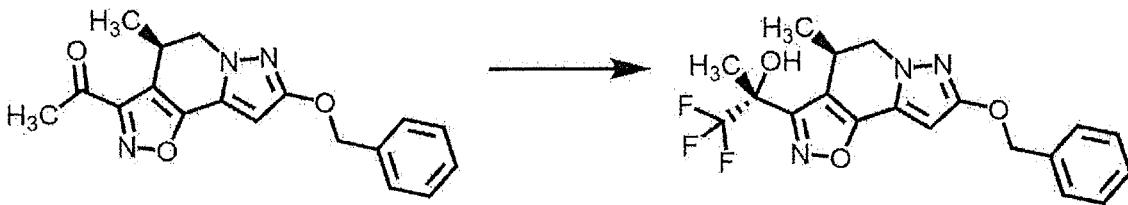
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.18 (d, J=6.73Hz, 3H), 2.63 (s, 3H), 3.53 - 3.55 (m, 1H), 4.12 - 4.18 (m, 2H), 5.21 (s, 2H), 6.39 (s, 1H), 7.36 - 7.44 (m, 5H)  
10 [0266]

Step 11

(R)-2-((R)-8-(benzyloxy)-4-methyl-4,5-dihydroisoxazolo[5,4-

c]pyrazolo[1,5-a]pyridin-3-yl)-1,1,1-trifluoropropan-2-ol

[0267]



15

[0268]

(R)-1-(8-(Benzylxy)-4-methyl-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-3-yl)ethan-1-one (0.63 g) obtained in the previous step was mixed with tetrahydrofuran (12.6 ml).

20 Under ice-cooling, to the mixture was added cesium fluoride (0.059 g), and then (trifluoromethyl)trimethylsilane (0.42 ml) was added dropwise. The reaction mixture was stirred at room temperature for 3 hr, methanol (12.6 ml) and potassium carbonate (0.54 g) were added at room temperature, and the 25 mixture was stirred at room temperature for 2 hr. To the reaction mixture was added saturated ammonium chloride aqueous solution, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, filtered through a phase separator, and the filtrate was concentrated under 30 reduced pressure. The obtained residue was purified by silica

gel column chromatography (ethyl acetate:hexane=2:98 to 35:65) to give the title compound (0.4 g).

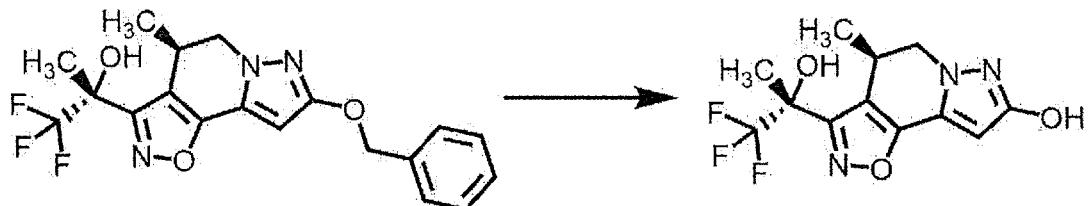
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.20 (d, J=6.94Hz, 3H), 1.78 (s, 3H), 3.41 - 3.42 (m, 1H), 4.12 (d, J=3.24Hz, 2H), 5.20 (s, 2H), 6.32 (s, 1H), 7.30 - 7.48 (m, 6H)

5 [0269]

Step 12

(R)-4-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-8-ol

10 [0270]



11 [0271]

(R)-2-((R)-8-(Benzylxy)-4-methyl-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-3-yl)-1,1,1-trifluoropropan-2-ol (1.35 g) obtained in the previous step and 10 w/w% palladium carbon (0.27 g) were mixed with methanol (13.5 ml) and tetrahydrofuran (27 ml). Under hydrogen atmosphere, the mixture was stirred overnight at room temperature. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure to give the title compound (1.1 g).

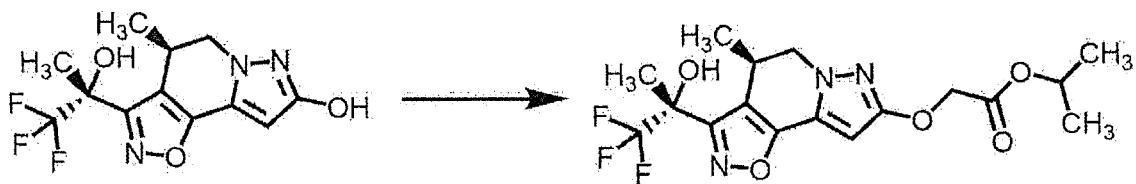
12 <sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.19 (d, J=6.94Hz, 3H), 1.77 (s, 3H), 3.36 - 3.39 (m, 1H), 4.01 - 4.02 (m, 2H), 5.96 (s, 1H), 7.26 (s, 1H), 10.17 (s, 1H)

13 [0272]

Step 13

isopropyl 2-((R)-4-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-8-yl)oxy)acetate

14 [0273]



[0274]

(R)-4-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-8-ol  
 5 (0.07 g) obtained in the previous step was mixed with dimethylformamide (1.4 ml). At room temperature, potassium carbonate (0.064 g) and isopropyl bromoacetate (0.063 ml) were added, and the mixture was stirred at 80°C for 1 hr. The reaction mixture was purified by reversed-phase silica gel chromatography (acetonitrile:water=5:95 to 100:0) to give the title compound (0.072 g).

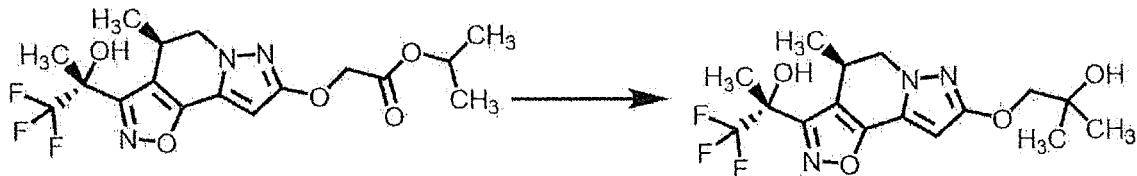
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.17 - 1.19 (m, 9H), 1.78 (s, 3H), 3.38 - 3.42 (m, 1H), 4.03 - 4.09 (m, 2H), 4.77 (s, 2H), 4.96 - 5.02 (m, 1H), 6.30 (s, 1H), 7.29 (s, 1H)

15 [0275]

Step 14

(R)-1,1,1-trifluoro-2-((R)-8-(2-hydroxy-2-methylpropoxy)-4-methyl-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-3-yl)propan-2-ol

20 [0276]



[0277]

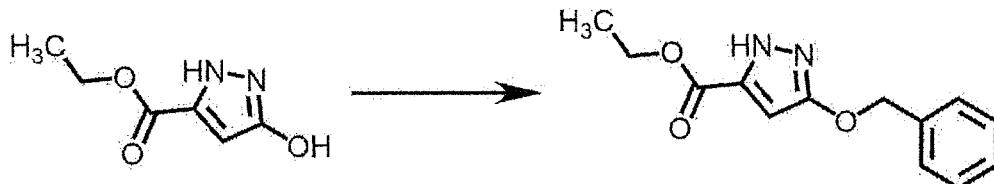
Isopropyl 2-((R)-4-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-8-yl)oxy)acetate (0.063 g) obtained in the previous step was mixed with toluene (1.3 ml). Under ice-cooling, 1.08 M methylmagnesium bromide/tetrahydrofuran solution (0.6 ml) was added, and the mixture was stirred at room temperature for

1 hr. To the reaction mixture was added saturated ammonium chloride aqueous solution, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and 5 filtered through a phase separator. The filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (hexane:ethyl acetate=67:33 to ethyl acetate) to give the title compound (0.056 g).

10  $^1\text{H-NMR}$  (400 MHz, DMSO- $\text{D}_6$ ) 1.18 - 1.21 (m, 9H), 1.78 (s, 3H), 3.39 - 3.41 (m, 1H), 3.87 (s, 2H), 4.08 - 4.10 (m, 2H), 4.62 (s, 1H), 6.25 (s, 1H), 7.29 (s, 1H)  
[0278]

#### Auxiliary Step 1

15 ethyl 3-(benzyloxy)-1H-pyrazole-5-carboxylate  
[0279]



[0280]

Ethyl 3-hydroxy-1H-pyrazole-5-carboxylate (10 g) was 20 mixed with tetrahydrofuran (100 ml). To the mixture were added benzyl alcohol (8.0 ml) and triphenylphosphine (18.5 g). Under ice-cooling, diisopropyl azodicarboxylate (13.7 ml) was added dropwise, and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced 25 pressure, ethyl acetate (70 ml) and hexane (140 ml) were added, and the mixture was stirred at room temperature. The precipitated solid was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=92:8 to hexane:ethyl acetate=47:53) to give a crude product (20 g) of the title compound.

[0281]

Production Example 2-2

Synthesis of (R)-1,1,1-trifluoro-2-((R)-4-methyl-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-3-yl)propan-2-ol

5 (Example 60)

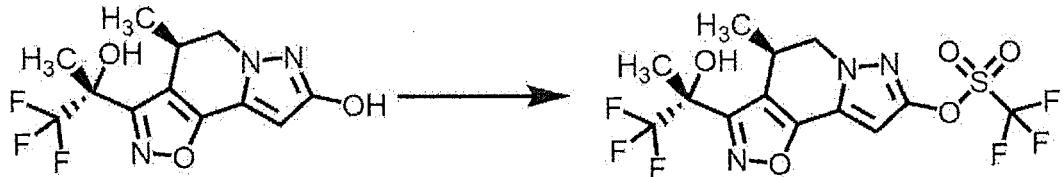
[0282]

Step 1

(R)-4-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-8-yl

10 trifluoromethanesulfonate

[0283]



[0284]

(R)-4-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-8-ol  
15 (0.15 g) was mixed with chloroform (1.5 ml). Under ice-cooling, triethylamine (0.138 ml) and trifluoromethanesulfonic anhydride (0.10 ml) were added, and the mixture was stirred for 1 hr. The reaction mixture was purified by silica gel column chromatography (ethyl acetate:hexane=8:92 to 66:34) to give the title compound (0.2006 g).

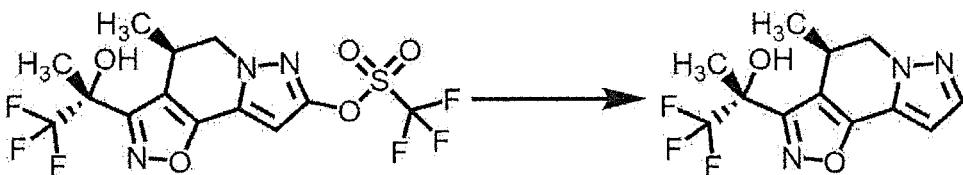
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.17 (d, J=7.40Hz, 3H), 1.77 (s, 3H), 3.46 - 3.47 (m, 1H), 4.29 - 4.31 (m, 2H), 7.07 (s, 1H), 7.35 (s, 1H)

25 [0285]

Step 2

(R)-1,1,1-trifluoro-2-((R)-4-methyl-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-3-yl)propan-2-ol

[0286]



[0287]

(R)-4-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-8-yl trifluoromethanesulfonate (0.10 g) obtained in the previous step, 10 w/w% palladium carbon (0.05 g), and sodium acetate (0.094 g) were mixed with methanol (1.0 ml). Under hydrogen atmosphere, the mixture was stirred at room temperature for 4 hr. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by reversed-phase silica gel column chromatography (acetonitrile:water=5:95 to acetonitrile) to give the title compound (0.0594 g).

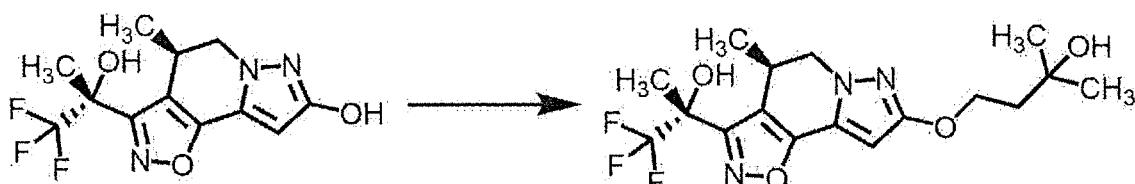
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.16 (d, J=6.94Hz, 3H), 1.78 (s, 3H), 3.44 - 3.46 (m, 1H), 4.25 (dd, J=13.00, 5.20Hz, 1H), 4.34 (d, J=13.00Hz, 1H), 6.79 (d, J=1.85Hz, 1H), 7.29 (s, 1H), 7.64 (d, J=2.08Hz, 1H)

[0288]

Production Example 2-3

Synthesis of 2-methyl-4-(((R)-4-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-8-yl)oxy)butan-2-ol (Example 62)

[0289]



25 [0290]

(R)-4-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-8-ol (0.06 g) was mixed with dimethylformamide (1 ml). Potassium

carbonate (0.041 g) and 4-bromo-2-methylbutan-2-ol (0.036 g) were added at room temperature, and the mixture was stirred at 80°C for 3 hr. Water was added to the reaction mixture at room temperature, and the mixture was extracted with ethyl acetate. 5 The organic layer was washed with water and saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=12:88 to ethyl acetate) and reversed-phase 10 silica gel chromatography (acetonitrile:water=5:95 to 100:0) to give the title compound (0.052 g).

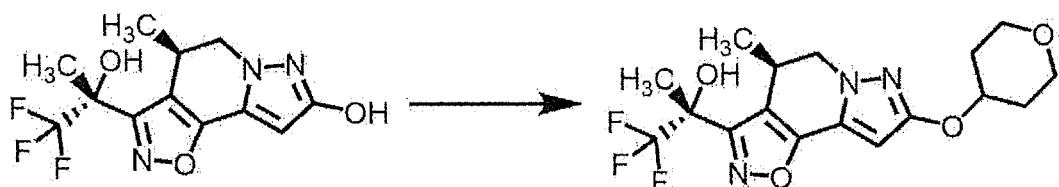
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.15 (s, 6H), 1.19 (d, J=7.17Hz, 3H), 1.77 (s, 3H), 1.83 (t, J=7.23Hz, 2H), 3.38 - 3.40 (m, 1H), 15 4.09 (d, J=3.01Hz, 2H), 4.21 (t, J=7.23Hz, 2H), 4.35 (s, 1H), 6.23 (s, 1H), 7.29 (s, 1H)

[0291]

#### Production Example 2-4

Synthesis of (R)-1,1,1-trifluoro-2-((R)-4-methyl-8-20 ((tetrahydro-2H-pyran-4-yl)oxy)-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-3-yl)propan-2-ol (Example 59)

[0292]



[0293]

25 (R)-4-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-8-ol (0.05 g) was mixed with tetrahydrofuran (0.5 ml). At room temperature, to the reaction mixture were added triphenylphosphine (0.065 g), di-tert-butyl azodicarboxylate 30 (0.057 g) and tetrahydro-2H-pyran-4-ol (0.016 g), and the mixture was stirred at room temperature for 1 hr. The reaction

mixture was purified by reversed-phase silica gel chromatography (acetonitrile:water=5:95 to 100:0), and then purified by silica gel column chromatography (ethyl acetate:hexane=20:80 to 55:45) to give the title compound 5 (0.047 g).

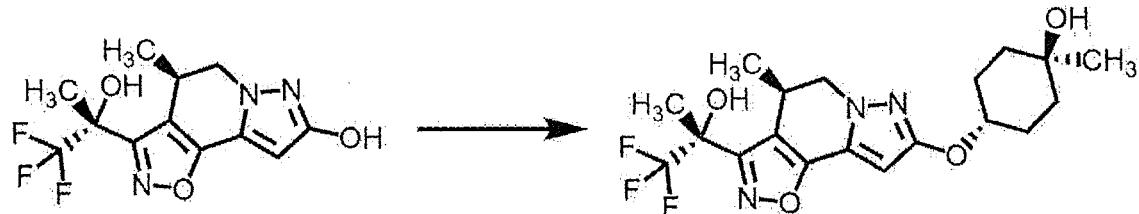
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.19 (d, J=6.94Hz, 3H), 1.60 - 1.63 (m, 2H), 1.77 (s, 3H), 2.00 - 2.02 (m, 2H), 3.41 - 3.47 (m, 3H), 3.84 - 3.86 (m, 2H), 4.09 (d, J=3.24Hz, 2H), 4.66 - 4.67 (m, 1H), 6.28 (s, 1H), 7.27 (s, 1H)

10 [0294]

Production Example 2-5

Synthesis of (1R,4r)-1-methyl-4-((R)-4-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-8-yl)oxy)cyclohexan-1-ol (Example 65)

15 [0295]



[0296]

(R)-4-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-8-ol

20 (0.07 g) was mixed with tetrahydrofuran (0.7 ml). At room temperature, to the reaction mixture were added triphenylphosphine (0.091 g), di-tert-butyl azodicarboxylate (0.036 g) and cis-1-methylcyclohexane-1,4-diol (0.036 g), and the mixture was stirred at room temperature for 1 hr. The 25 reaction mixture was purified by reversed-phase silica gel chromatography (acetonitrile:water=5:95 to 100:0), and then purified by silica gel column chromatography (ethyl acetate:hexane=20:80 to 65:35) to give the title compound (0.045 g). The steric configuration of the title compound was 30 determined by X-ray crystal structure analysis.

<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.16 (d, J=17.11Hz, 3H), 1.19 (q,

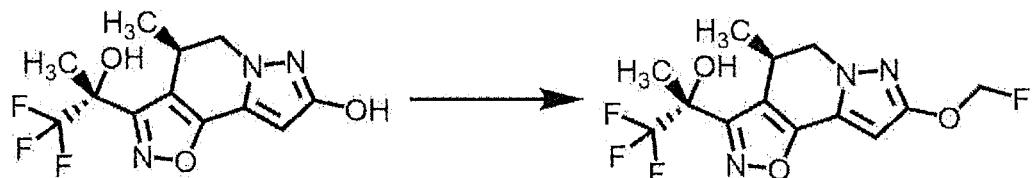
J=6.94Hz, 3H), 1.38 - 1.41 (m, 2H), 1.57 - 1.66 (m, 4H), 1.77 (s, 3H), 1.89 - 1.93 (m, 2H), 3.37 - 3.41 (m, 1H), 4.08 (d, J=3.24Hz, 2H), 4.16 (s, 1H), 4.56 - 4.61 (m, 1H), 6.24 (s, 1H), 7.27 (s, 1H)

5 [0297]

Production Example 2-6

Synthesis of (R)-1,1,1-trifluoro-2-((R)-8-(fluoromethoxy)-4-methyl-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-3-yl)propan-2-ol (Example 64)

10 [0298]



[0299]

(R)-4-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-8-ol

15 (0.2 g) was mixed with dimethylformamide (2 ml). At room temperature, potassium carbonate (0.182 g) and fluoromethyl 4-methoxybenzenesulfonate (0.162 g) were added, and the mixture was stirred at 80°C for 3 hr. Water was added to the reaction mixture at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=12:88 to ethyl acetate), reversed-phase silica gel chromatography (acetonitrile:water=5:95 to 100:0), and amino silica gel column chromatography (ethyl acetate:hexane=8:92 to 88:12) to give the title compound (0.099 g).

20

25

30  $^1\text{H-NMR}$  (400 MHz, DMSO- $\text{D}_6$ ) 1.20 (d, J=6.94Hz, 3H), 1.78 (s, 3H), 3.42 - 3.44 (m, 1H), 4.16 (s, 2H), 5.81 (q, J=2.39Hz, 1H),

5.95 (q,  $J=2.39\text{Hz}$ , 1H), 6.47 (s, 1H), 7.30 (s, 1H)

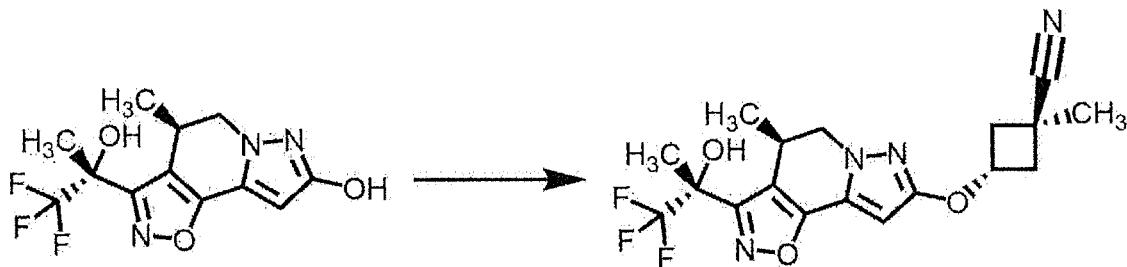
[0300]

Production Example 2-7

Synthesis of (1*R*,3*r*)-1-methyl-3-((*(R)*-4-methyl-3-((*R*)-1,1,1-

5 trifluoro-2-hydroxypropan-2-yl)-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-8-yl)oxy)cyclobutane-1-carbonitrile  
(Example 63)

[0301]



10 [0302]

(*R*)-4-Methyl-3-((*R*)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-8-ol

(0.1 g) was mixed with tetrahydrofuran (2 ml). At room

temperature, to the reaction mixture were added

15 triphenylphosphine (0.13 g) and 3-hydroxy-1-methylcyclobutane-1-carbonitrile (0.044 g). Under heating at 70°C, di-*tert*-butyl azodicarboxylate (0.114 g) was added, and the mixture was

stirred for 45 min. To the reaction mixture were added

triphenylphosphine (0.065 g), 3-hydroxy-1-methylcyclobutane-1-

20 carbonitrile (0.022 g), and di-*tert*-butyl azodicarboxylate

(0.057 g), and the mixture was stirred for 75 min. The

reaction mixture was purified by silica gel column

chromatography (ethyl acetate:hexane=6:94 to 50:50), and then

purified by reversed-phase silica gel chromatography

25 (acetonitrile:water=5:95 to 100:0) to give the title compound

(0.073 g).

$^1\text{H-NMR}$  (400 MHz, DMSO- $\text{D}_6$ ) 1.19 (d,  $J=7.17\text{Hz}$ , 3H), 1.54 (s, 3H),  
1.77 (s, 3H), 2.26 - 2.27 (m, 2H), 2.95 - 3.01 (m, 2H), 3.38 -  
3.41 (m, 1H), 4.10 - 4.10 (m, 2H), 4.97 (t,  $J=7.28\text{Hz}$ , 1H),

30 6.28 (s, 1H), 7.28 (s, 1H)

[0303]

Production Example 2-8

Synthesis of (R)-1,1,1-trifluoro-2-((R)-4-methyl-8-(tetrahydro-2H-pyran-4-yl)-4,5-dihydroisoxazolo[5,4-

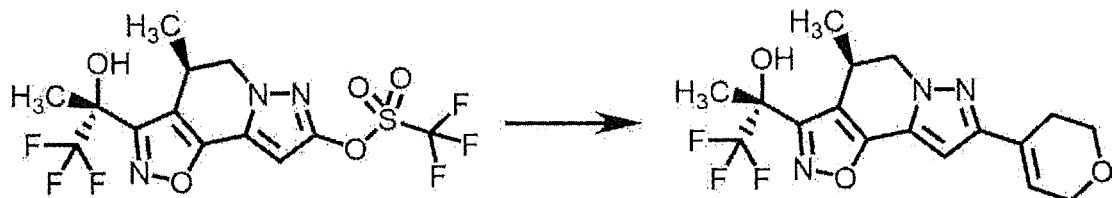
5 c]pyrazolo[1,5-a]pyridin-3-yl)propan-2-ol (Example 61)

[0304]

Step 1

(R)-2-((R)-8-(3,6-dihydro-2H-pyran-4-yl)-4-methyl-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-3-yl)-1,1,1-10 trifluoropropan-2-ol

[0305]



[0306]

(R)-4-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-8-yl trifluoromethanesulfonate (100 mg) obtained in the previous step, methanesulfonato(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)(2'-methylamino-1,1'-biphenyl-2-yl)palladium(II) (59.4 mg), 3,6-dihydro-2H-pyran-4-boronic acid pinacol ester (72.4 mg), and tripotassium phosphate (146 mg) were mixed with 1,4-dioxane (1.2 ml)-water (0.6 ml). Under an argon atmosphere, the reaction mixture was stirred at 70°C for 1 hr. At room temperature, water was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=12:88 to ethyl acetate) to give the title compound (54.5 mg).

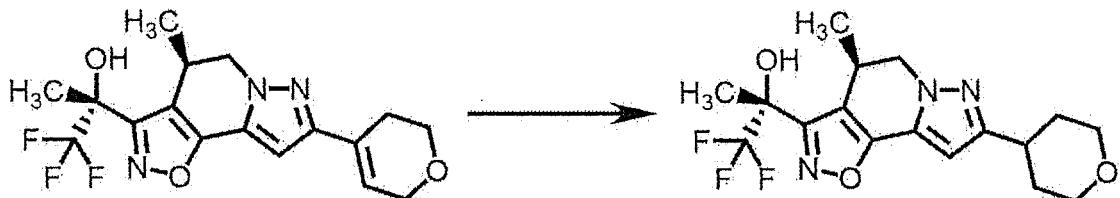
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.21 - 1.28 (m, 3H), 1.91 (s, 3H), 2.55 - 2.62 (m, 2H), 2.91 (s, 1H), 3.41 - 3.51 (m, 1H), 3.91 (t, J=5.55Hz, 2H), 4.19 - 4.35 (m, 4H), 6.28 - 6.32 (m, 1H), 6.66 (s, 1H)

5 [0307]

Step 2

(R)-1,1,1-trifluoro-2-((R)-4-methyl-8-(tetrahydro-2H-pyran-4-yl)-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-3-yl)propan-2-ol

10 [0308]



[0309]

(R)-2-((R)-8-(3,6-Dihydro-2H-pyran-4-yl)-4-methyl-4,5-dihydroisoxazolo[5,4-c]pyrazolo[1,5-a]pyridin-3-yl)-1,1,1-trifluoropropan-2-ol (54.5 mg) obtained in the previous step and palladium carbon (27.3 mg) were mixed with ethanol (1 ml). Under hydrogen atmosphere, the mixture was stirred at room temperature for 4 hr. Palladium carbon was filtered off from the reaction mixture by using celite as an aid, and the 20 filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=12:88 to ethyl acetate) to give the title compound (36.2 mg).

<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.15 (d, J=6.94Hz, 3H), 1.58 - 1.71 (m, 2H), 1.76 (s, 3H), 1.79 - 1.88 (m, 2H), 2.80 - 2.93 (m, 1H), 3.36 - 3.49 (m, 3H), 3.83 - 3.93 (m, 2H), 4.17 (dd, J=13.41, 5.09Hz, 1H), 4.24 (d, J=12.02Hz, 1H), 6.65 (s, 1H), 7.25 (s, 1H)

30 [0310]

Production Example 3-1

Synthesis of (1S,4r)-1-methyl-4-((S)-4-methyl-3-((R)-1,1,1-

trifluoro-2-hydroxypropan-2-yl)-4,5-dihydro-7H-isoxazolo[5,4-e]indazol-7-yl) cyclohexan-1-ol and enantiomer thereof (Example 55) and

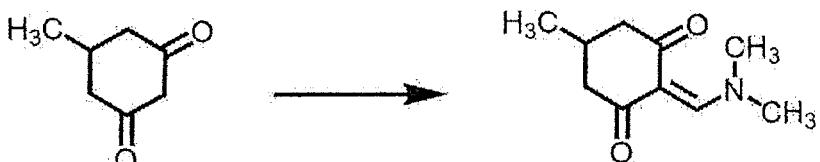
5 (1S,4r)-1-methyl-4-((S)-4-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydro-6H-isoxazolo[5,4-e]indazol-6-yl)cyclohexan-1-ol and enantiomer thereof (Example 56)

[0311]

Step 1

2-((dimethylamino)methylene)-5-methylcyclohexane-1,3-dione

10 [0312]



[0313]

5-Methylcyclohexane-1,3-dione (5.4 g) was mixed with N,N-dimethylformamide dimethyl acetal (10.2 g). The reaction

15 mixture was heated under reflux at 110°C for 1 hr. The reaction mixture was concentrated under reduced pressure, and azeotroped with toluene. To the obtained residue was added a mixed solution of hexane:ethyl acetate=90:10, and the mixture was stirred at room temperature. The precipitated solid was 20 collected by filtration to give the title compound (7.5 g).

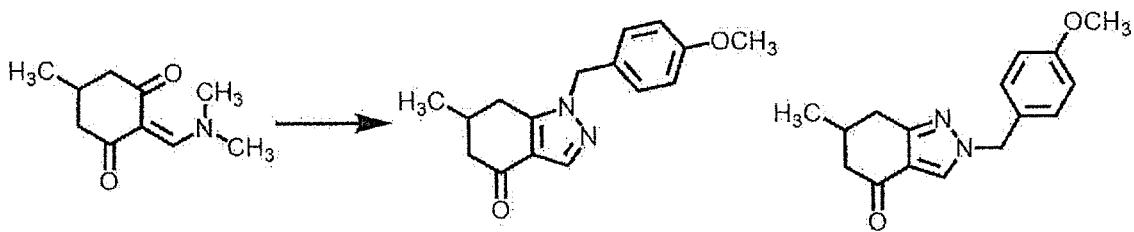
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 0.96 (d, J=5.78Hz, 3H), 2.05 - 2.08 (m, 3H), 2.30 - 2.38 (m, 2H), 3.04 (s, 3H), 3.38 (s, 3H), 7.96 (s, 1H)

[0314]

25 Step 2

mixture of 1-(4-methoxybenzyl)-6-methyl-1,5,6,7-tetrahydro-4H-indazol-4-one and 2-(4-methoxybenzyl)-6-methyl-2,5,6,7-tetrahydro-4H-indazol-4-one

[0315]



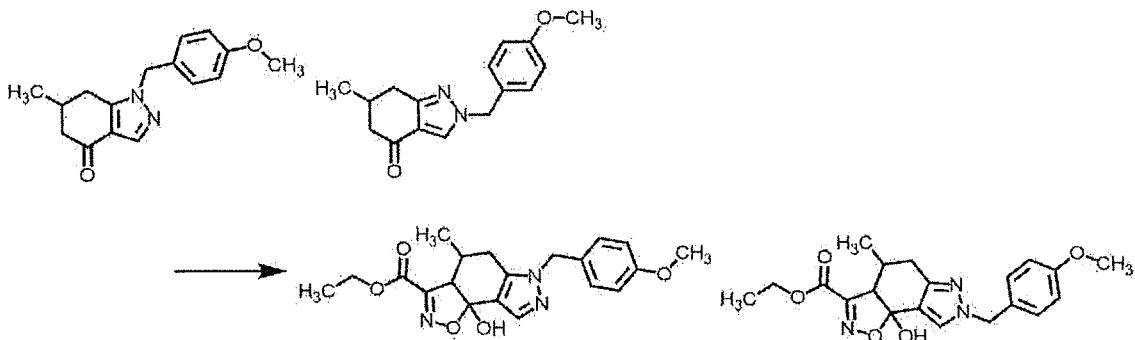
[0316]

2-((Dimethylamino)methylene)-5-methylcyclohexane-1,3-dione (5.0 g) obtained in the previous step was dissolved in 5 ethanol (50 ml) and acetic acid (25 ml). At room temperature, to the reaction mixture was added (4-methoxybenzyl)hydrazine hydrochloride (5.5 g), and the mixture was heated under reflux at 125°C for 2 hr. The reaction mixture was concentrated under reduced pressure, 1 M sodium hydroxide aqueous solution was 10 added to the residue, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with sodium hydrogen carbonate aqueous solution and saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was 15 concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=80:20 to 20:80), and azeotroped with toluene to give a crude product (7.4 g) of the title compound.

[0317]

20 Step 3  
 mixture of ethyl 8b-hydroxy-6-(4-methoxybenzyl)-4-methyl-3a,5,6,8b-tetrahydro-4H-isoxazolo[5,4-e]indazole-3-carboxylate and ethyl 8b-hydroxy-7-(4-methoxybenzyl)-4-methyl-3a,5,7,8b-tetrahydro-4H-isoxazolo[5,4-e]indazole-3-carboxylate

25 [0318]



[0319]

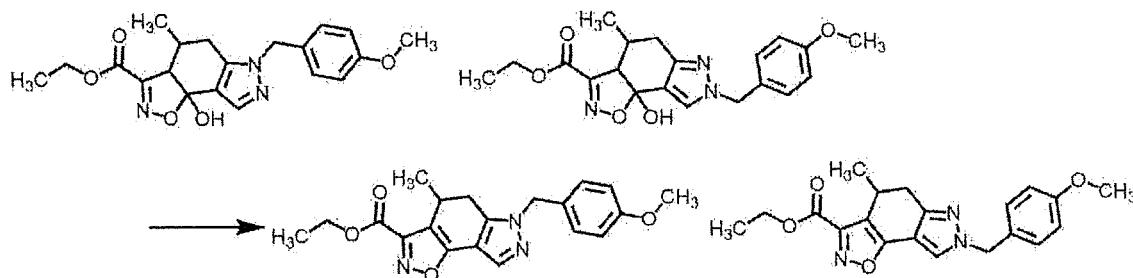
Ethyl 2-chloro-2-(hydroxyimino)acetate (4.7 g) was mixed with tetrahydrofuran (70 ml). To this solution was added 5 dropwise 1.3 M lithium bis(trimethylsilyl)amide/tetrahydrofuran solution (25.9 ml) at -78°C to prepare a nitrile oxide solution. In a separate reaction vessel, the mixture (7.0 g) of 1-(4-methoxybenzyl)-6-methyl-1,5,6,7-tetrahydro-4H-indazol-4-one and 2-(4-methoxybenzyl)-6-methyl-2,5,6,7-tetrahydro-4H-indazol-4-one obtained in the previous step was mixed with tetrahydrofuran (70 ml). To this solution was added dropwise 1.3 M lithium bis(trimethylsilyl)amide/tetrahydrofuran solution (29.9 ml) at -78°C. The reaction mixture was added dropwise through a cannula to the aforementioned nitrile oxide solution cooled to -78°C. The reaction mixture was allowed to warm to 0°C over 1 hr. To the reaction mixture was added dropwise 2N hydrochloric acid (51.8 ml) at room temperature, then saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=40:60 to 90:10) to give a crude product (12.5 g) of the title compound.

[0320]

Step 4

mixture of ethyl 6-(4-methoxybenzyl)-4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazole-3-carboxylate and ethyl 7-(4-methoxybenzyl)-4-methyl-5,7-dihydro-4H-isoxazolo[5,4-e]indazole-3-carboxylate

5 [0321]



[0322]

The mixture (9.65 g) of ethyl 8b-hydroxy-6-(4-methoxybenzyl)-4-methyl-3a,5,6,8b-tetrahydro-4H-isoxazolo[5,4-e]indazole-3-carboxylate and ethyl 8b-hydroxy-7-(4-methoxybenzyl)-4-methyl-3a,5,7,8b-tetrahydro-4H-isoxazolo[5,4-e]indazole-3-carboxylate obtained in the previous step was dissolved in tetrahydrofuran (77 ml). Under ice-cooling, to the reaction mixture were successively added methanesulfonic anhydride (5.68 g) and triethylamine (10.5 ml). The reaction mixture was stirred at 0°C for 30 min. At room temperature, to the reaction mixture was added triethylamine (10.5 ml), and the mixture was heated under reflux at 70°C overnight. To the reaction mixture was added water at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated ammonium chloride aqueous solution and saturated aqueous sodium chloride solution, and dried over magnesium sulfate. Magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=20:80 to 60:40) to give a crude product (6.7 g) of the title compound.

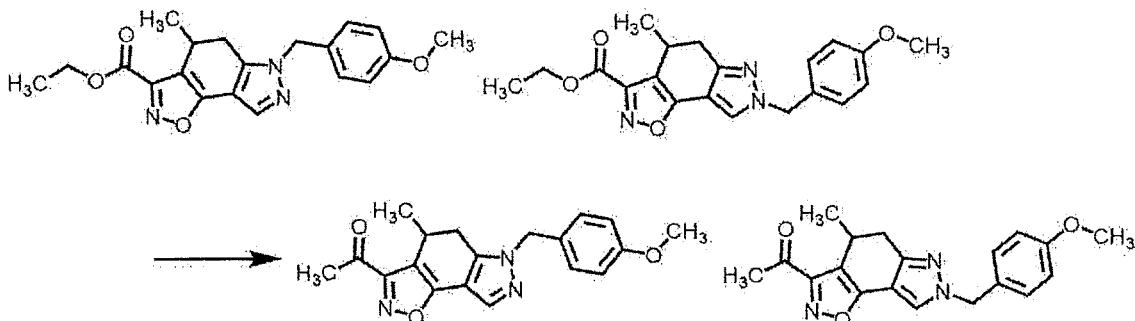
[0323]

Step 5

30 mixture of 1-(6-(4-methoxybenzyl)-4-methyl-5,6-dihydro-4H-

isoxazolo[5,4-e]indazol-3-yl)ethan-1-one and 1-(7-(4-methoxybenzyl)-4-methyl-5,7-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)ethan-1-one

[0324]



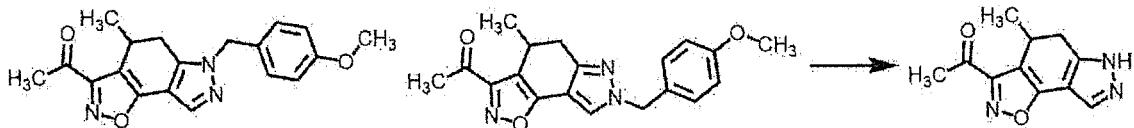
[0325]

The mixture (6.7 g) of ethyl 6-(4-methoxybenzyl)-4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazole-3-carboxylate and ethyl 7-(4-methoxybenzyl)-4-methyl-5,7-dihydro-4H-isoxazolo[5,4-e]indazole-3-carboxylate obtained in the previous step was dissolved in toluene (66.8 ml). Under ice-cooling, a mixture of triethylamine (12.7 ml) and 1.08 M methylmagnesium bromide/tetrahydrofuran solution (23.6 ml) was added dropwise, and the mixture was stirred at 0°C for 1 hr. Under ice-cooling, a mixture of triethylamine (1.27 ml) and 1.08 M methylmagnesium bromide/tetrahydrofuran solution (2.4 ml) was further added dropwise, and the mixture was stirred at 0°C for 1 hr. To the reaction mixture was added 2N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium hydrogen carbonate solution and saturated aqueous sodium chloride solution, and dried over magnesium sulfate. Magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=30:70 to 60:40) to give a crude product (5.0 g) of the title compound.

[0326]

Step 6

1-(4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)ethan-1-one  
[0327]



5 [0328]

The mixture (1.2 g) of 1-(6-(4-methoxybenzyl)-4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)ethan-1-one and 1-(7-(4-methoxybenzyl)-4-methyl-5,7-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)ethan-1-one obtained in the previous step was 10 mixed with trifluoroacetic acid (11.6 ml). To the reaction mixture was added anisole (0.75 ml), and the mixture was stirred at 130°C for 1 hr under microwave (Biotage (registered trademark) Initiator+) radiation. To the reaction mixture was added toluene, and the mixture was concentrated under reduced 15 pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=20:80 to 85:15) to give the title compound (0.71 g).

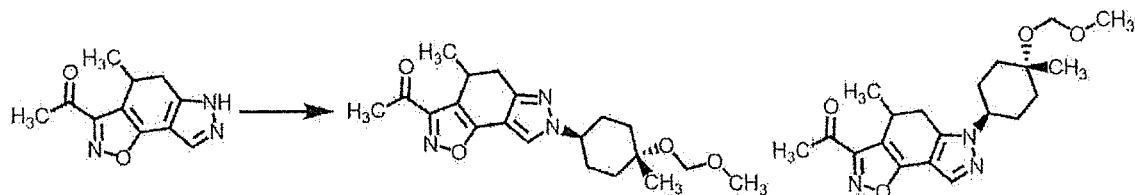
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.00 (d, J=6.73Hz, 3H), 2.59 (s, 3H), 2.75 - 2.79 (m, 1H), 2.94 - 3.00 (m, 1H), 3.48 - 3.50 (m, 1H), 20 8.22 (s, 1H), 13.09 (s, 1H)

[0329]

Step 7

mixture of 1-(7-((1r,4r)-4-(methoxymethoxy)-4-methylcyclohexyl)-4-methyl-5,7-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)ethan-1-one and 1-(6-((1r,4r)-4-(methoxymethoxy)-4-methylcyclohexyl)-4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)ethan-1-one  
25

[0330]



[0331]

1-(4-Methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)ethan-1-one (0.050 g) obtained in the previous step was mixed with dimethylformamide (0.75 ml). To the reaction mixture were added cesium carbonate (0.23 g) and cis-4-(methoxymethoxy)-4-methylcyclohexyl methanesulfonate (0.15 g) obtained in Auxiliary Step 3, and the mixture was stirred at 80°C for 4 hr. The reaction mixture was purified by reversed-phase silica gel chromatography (acetonitrile:water=0:100 to 100:0), and the crude product was purified by silica gel column chromatography (ethyl acetate:hexane=2:98 to 30:70) to give a crude product (0.043 g) of the title compound.

[0332]

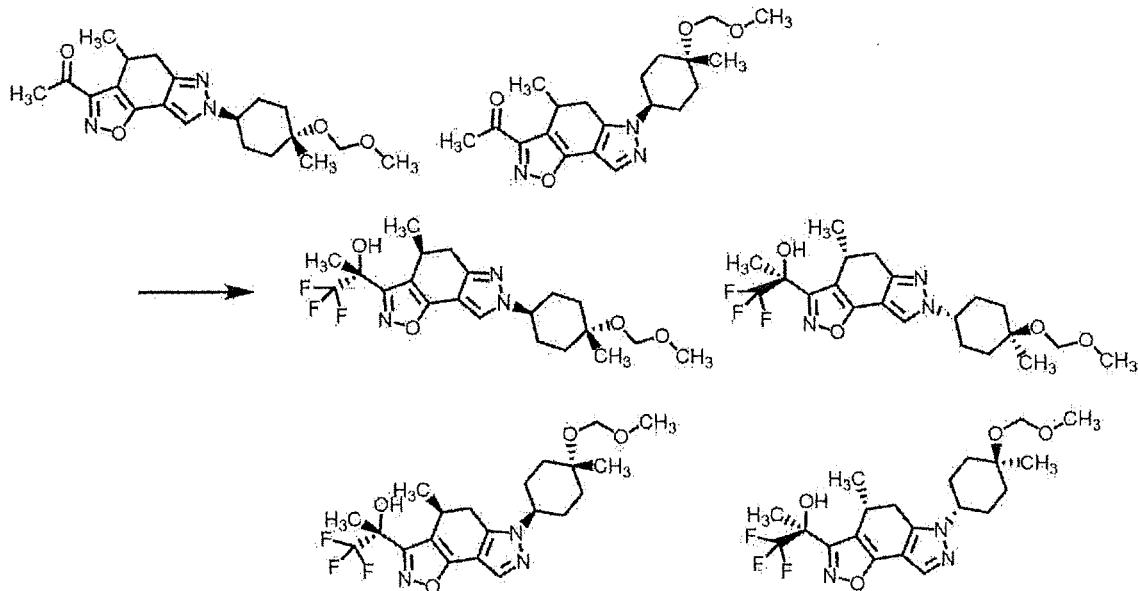
Step 8

15 mixture of (R)-1,1,1-trifluoro-2-((S)-7-((1r,4S)-4-(methoxymethoxy)-4-methylcyclohexyl)-4-methyl-5,7-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)propan-2-ol and (S)-1,1,1-trifluoro-2-((R)-7-((1r,4R)-4-(methoxymethoxy)-4-methylcyclohexyl)-4-methyl-5,7-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)propan-2-ol, and mixture of (R)-1,1,1-trifluoro-2-((S)-6-((1r,4S)-4-(methoxymethoxy)-4-methylcyclohexyl)-4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)propan-2-ol and (S)-1,1,1-trifluoro-2-((R)-6-((1r,4R)-4-(methoxymethoxy)-4-methylcyclohexyl)-4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)propan-2-ol

20

25

[0333]



[0334]

The mixture (0.043 g) of 1-(7-((1*r*,4*r*)-4-(methoxymethoxy)-4-methylcyclohexyl)-4-methyl-5,7-dihydro-4*H*-5 isoxazolo[5,4-*e*]indazol-3-yl)ethan-1-one and 1-(6-((1*r*,4*r*)-4-(methoxymethoxy)-4-methylcyclohexyl)-4-methyl-5,6-dihydro-4*H*-5 isoxazolo[5,4-*e*]indazol-3-yl)ethan-1-one obtained in the previous step was mixed with tetrahydrofuran (0.86 ml). Under ice-cooling, to the mixture was added cesium fluoride (0.004 g), and then (trifluoromethyl)trimethylsilane (0.033 ml) was added dropwise. The reaction mixture was stirred for 1 hr while raising the temperature to room temperature. Methanol (0.86 ml) and potassium carbonate (0.095 g) were added at room temperature, and the mixture was stirred at room temperature for 30 min. To the reaction mixture was added saturated ammonium chloride aqueous solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, filtered through a phase separator, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by preparative thin layer silica gel chromatography (dichloromethane:ethyl acetate=6:1, developed 3 times) to give the title compound (0.009 g) and a diastereomer (0.004 g) thereof each as a racemate.

<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.03 (d, J=6.94Hz, 3H), 1.28 (s, 3H), 1.62 - 1.75 (m, 7H), 1.90 - 2.01 (m, 4H), 2.71 (d, J=16.35Hz, 1H), 2.85 (dd, J=16.30, 6.82Hz, 1H), 3.27 (s, 3H), 3.36 - 3.37 (m, 1H), 4.23 - 4.24 (m, 1H), 4.70 (s, 2H), 7.03 (s, 1H), 8.23 (s, 1H)

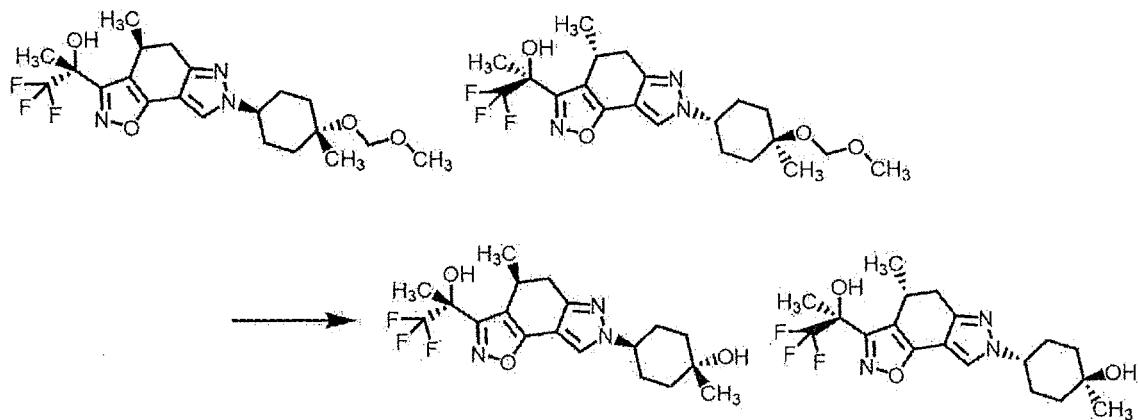
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.05 (d, J=6.73Hz, 3H), 1.29 (s, 3H), 1.67 - 2.03 (m, 11H), 2.89 - 3.05 (m, 2H), 3.27 (s, 3H), 3.38 - 3.44 (m, 1H), 4.32 - 4.35 (m, 1H), 4.71 (s, 2H), 7.04 (s, 1H), 7.78 (s, 1H)

10 [0335]

Step 9

mixture of (1*S*,4*r*)-1-methyl-4-((*S*)-4-methyl-3-((*R*)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydro-7*H*-isoxazolo[5,4-*e*]indazol-7-yl)cyclohexan-1-ol and (1*R*,4*r*)-1-methyl-4-((*R*)-4-methyl-3-((*S*)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydro-7*H*-isoxazolo[5,4-*e*]indazol-7-yl)cyclohexan-1-ol

15 [0336]



20 [0337]

The mixture (0.009 g) of (*R*)-1,1,1-trifluoro-2-((*S*)-7-((1*r*,4*S*)-4-(methoxymethoxy)-4-methylcyclohexyl)-4-methyl-5,7-dihydro-4*H*-isoxazolo[5,4-*e*]indazol-3-yl)propan-2-ol and (*S*)-1,1,1-trifluoro-2-((*R*)-7-((1*r*,4*R*)-4-(methoxymethoxy)-4-methylcyclohexyl)-4-methyl-5,7-dihydro-4*H*-isoxazolo[5,4-*e*]indazol-3-yl)propan-2-ol obtained in the previous step was mixed with tetrahydrofuran (0.09 ml). At room temperature, to the reaction mixture was added 6*N* hydrochloric acid (0.033 ml),

and the mixture was stirred for 1 hr. The reaction mixture was further stirred at 45°C for 30 min. Under ice-cooling, to the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. 5 Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give the title compound (0.008 g) as a racemate.

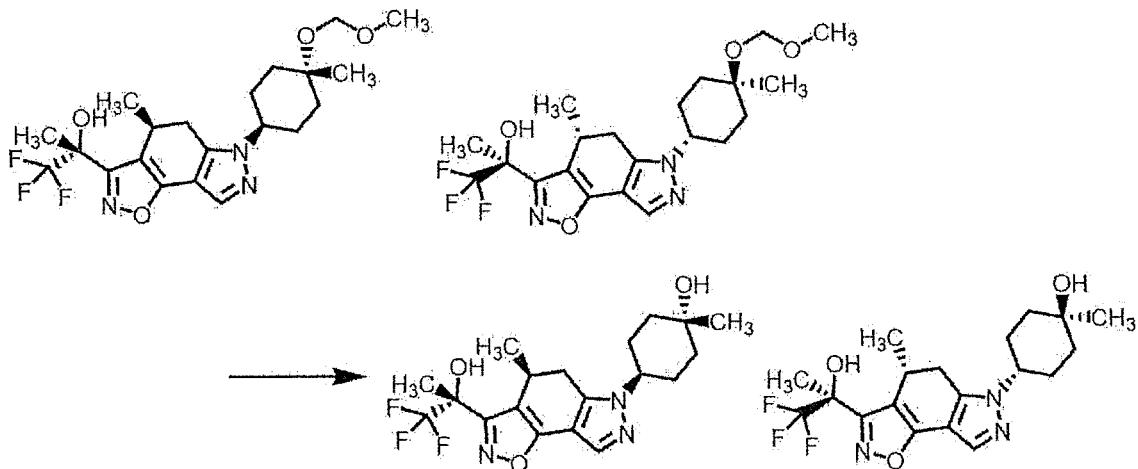
10  $^1\text{H-NMR}$  (400 MHz, DMSO- $\text{D}_6$ ) 1.05 (d,  $J=6.73\text{Hz}$ , 3H), 1.20 (s, 3H), 1.56 - 1.64 (m, 4H), 1.74 (s, 3H), 1.83 - 1.96 (m, 4H), 2.94 - 3.01 (m, 2H), 3.39 - 3.40 (m, 1H), 4.25 - 4.26 (m, 1H), 4.43 (s, 1H), 7.03 (s, 1H), 7.77 (s, 1H)

[0338]

15 Step 10

mixture of (1*S*,4*r*)-1-methyl-4-((*S*)-4-methyl-3-((*R*)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydro-6*H*-isoxazolo[5,4-*e*]indazol-6-yl)cyclohexan-1-ol and (1*R*,4*r*)-1-methyl-4-((*R*)-4-methyl-3-((*S*)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-20 dihydro-6*H*-isoxazolo[5,4-*e*]indazol-6-yl)cyclohexan-1-ol

[0339]



[0340]

25 The mixture (0.004 g) of (R)-1,1,1-trifluoro-2-((S)-6-((1*r*,4*S*)-4-(methoxymethoxy)-4-methylcyclohexyl)-4-methyl-5,6-dihydro-4*H*-isoxazolo[5,4-*e*]indazol-3-yl)propan-2-ol and (S)-

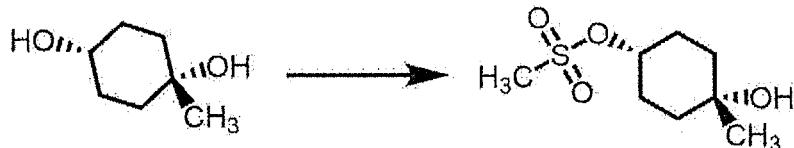
1,1,1-trifluoro-2-((R)-6-((1*r*,4*R*)-4-(methoxymethoxy)-4-methylcyclohexyl)-4-methyl-5,6-dihydro-4*H*-isoxazolo[5,4-e]indazol-3-yl)propan-2-ol obtained in the previous step was mixed with tetrahydrofuran (0.04 ml). At room temperature, to 5 the reaction mixture was added 6*N* hydrochloric acid (0.015 ml), and the mixture was stirred for 1 hr. The reaction mixture was further stirred at 45°C for 30 min. Under ice-cooling, to the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl 10 acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give the title compound (0.036 g) as a racemate.

15  $^1\text{H-NMR}$  (400 MHz, DMSO- $\text{D}_6$ ) 1.05 (d,  $J=6.73\text{Hz}$ , 3H), 1.20 (s, 3H), 1.56 - 1.64 (m, 4H), 1.74 (s, 3H), 1.83 - 1.96 (m, 4H), 2.94 - 3.01 (m, 2H), 3.39 - 3.40 (m, 1H), 4.25 - 4.26 (m, 1H), 4.43 (s, 1H), 7.03 (s, 1H), 7.77 (s, 1H)  
[0341]

20 Auxiliary Step 2

cis-4-hydroxy-4-methylcyclohexyl methanesulfonate

[0342]



[0343]

25 cis-1-Methylcyclohexane-1,4-diol (1.0 g) was mixed with dichloromethane (10 ml). Under ice-cooling, triethylamine (2.1 ml), methanesulfonic anhydride (2.0 g), and 4-dimethylaminopyridine (0.094 g) were added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture 30 was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=50:50 to ethyl acetate) to give the title

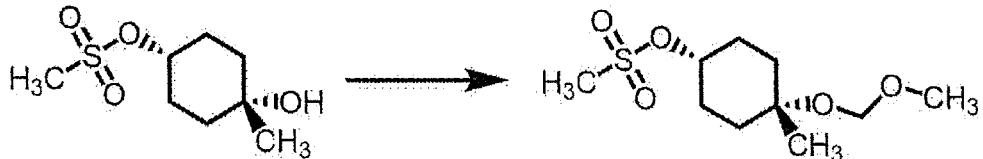
compound (0.37 g).

<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.09 (s, 3H), 1.34 - 1.44 (m, 2H), 1.56 - 1.59 (m, 2H), 1.70 - 1.84 (m, 4H), 3.14 (s, 3H), 4.21 (brs, 1H), 4.51 - 4.58 (m, 1H)

5 [0344]

Auxiliary Step 3

cis-4-(methoxymethoxy)-4-methylcyclohexyl methanesulfonate  
[0345]



10 [0346]

cis-4-Hydroxy-4-methylcyclohexyl methanesulfonate (1.1 g) obtained in the previous step was mixed with dichloromethane (20 ml). Under ice-cooling, chloromethyl methyl ether (0.74 ml) and N,N-diisopropylethylamine (2.1 ml) were added, and the 15 mixture was stirred at room temperature overnight. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and filtered through a phase separator. The filtrate 20 was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=10:90 to 55:45) to give the title compound (1.0 g).

<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.13 (s, 3H), 1.38 - 1.45 (m, 2H), 1.71 - 1.85 (m, 6H), 3.14 (s, 3H), 3.27 (s, 3H), 4.55 - 4.60 (m, 1H), 4.64 (s, 2H)

25 [0347]

Using (R)-1,1,1-trifluoro-2-((S)-4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)propan-2-ol obtained in the 30 below-mentioned Production Example 3-2, Step 3, the reactions of Production Example 3-1, Step 7 to Step 10, are performed, whereby (1S,4r)-1-methyl-4-((S)-4-methyl-3-((R)-1,1,1-

trifluoro-2-hydroxypropan-2-yl)-4,5-dihydro-7H-isoxazolo[5,4-e]indazol-7-yl)cyclohexan-1-ol (Example 105 which is an optically active form of Example 55) and (1S,4r)-1-methyl-4-((S)-4-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydro-6H-isoxazolo[5,4-e]indazol-6-yl)cyclohexan-1-ol (optically active form of Example 56) can be obtained.

5 [0348]

Production Example 3-2

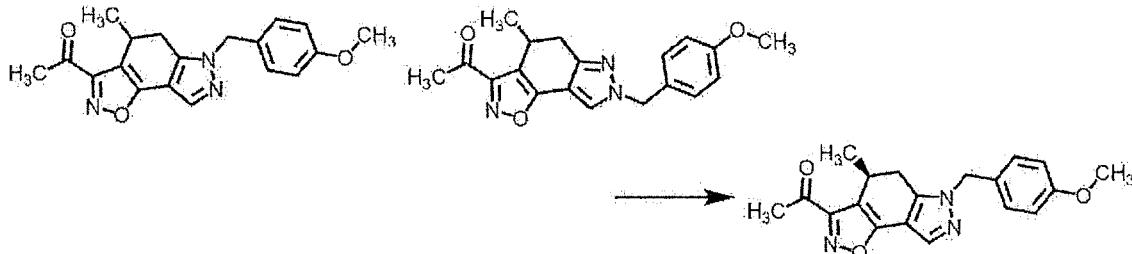
Synthesis of (R)-1,1,1-trifluoro-2-((S)-4-methyl-5,6-dihydro-10 4H-isoxazolo[5,4-e]indazol-3-yl)propan-2-ol (Example 28)

[0349]

Step 1

(S)-1-(6-(4-methoxybenzyl)-4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)ethan-1-one

15 [0350]



[0351]

The mixture (0.85 g) of 1-(6-(4-methoxybenzyl)-4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)ethan-1-one and 1-20 (7-(4-methoxybenzyl)-4-methyl-5,7-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)ethan-1-one was subjected to optical resolution using recycling preparative HPLC (apparatus name: Japan Analytical Industry Co., Ltd. LaboACE LC-7080, column: Daicel CHIRALPAK IG, 20 mm(I.D.) x 250 mm(L), 5 µm, mobile phase flow rate: 20 ml/min, mobile phase mixing ratio: isocratic, hexane:ethanol=40:60). The third peak fraction and the fourth peak fraction were recycled once and then fractionated to give the title compound (0.35 g) as the third peak fraction.

<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 0.97 (d, J=7.48Hz, 3H), 2.58 (s, 3H), 30 2.96 - 3.02 (m, 2H), 3.47 - 3.53 (m, 1H), 3.72 (s, 3H), 5.33

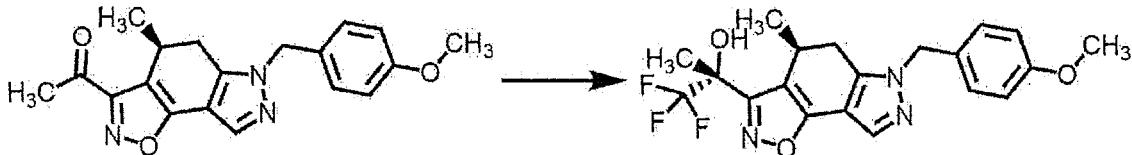
(d,  $J=2.99\text{Hz}$ , 2H), 6.90 (d,  $J=8.23\text{Hz}$ , 2H), 7.15 (d,  $J=8.23\text{Hz}$ , 2H), 7.87 (s, 1H)

[0352]

Step 2

5 (R)-1,1,1-trifluoro-2-((S)-6-(4-methoxybenzyl)-4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)propan-2-ol

[0353]



[0354]

10 (S)-1-(6-(4-Methoxybenzyl)-4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)ethan-1-one (0.025 g) obtained in the previous step was mixed with tetrahydrofuran (0.5 ml). Under ice-cooling, to the mixture was added cesium fluoride (0.002 g), and then (trifluoromethyl)trimethylsilane (0.016 ml) was added dropwise. The reaction mixture was stirred for 1 hr while raising the temperature to room temperature. At room temperature, methanol (0.5 ml) and potassium carbonate (0.02 g) were added, and the mixture was stirred at room temperature for 30 min. To the reaction mixture was added saturated 15 ammonium chloride aqueous solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, filtered through a phase separator, and the filtrate was concentrated under reduced pressure. The obtained residue was 20 purified by preparative thin layer silica gel chromatography (hexane:ethyl acetate=3:2) to give a crude product (0.015 g) of the title compound.

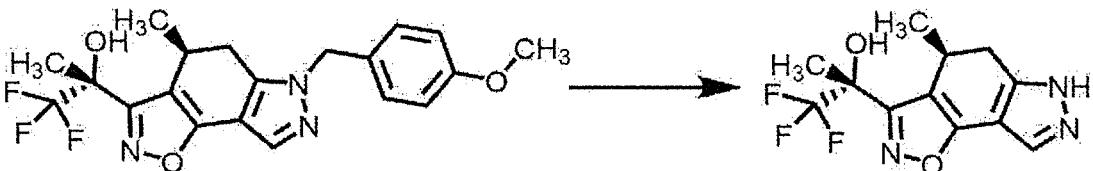
$^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-D}_6$ ) 1.00 (d,  $J=6.73\text{Hz}$ , 3H), 1.74 (s, 3H), 2.84 (dd,  $J=16.83$ , 7.48Hz, 1H), 3.02 (d,  $J=16.83\text{Hz}$ , 1H), 3.37 25 - 3.38 (m, 1H), 3.72 (s, 3H), 5.32 (d,  $J=2.99\text{Hz}$ , 2H), 6.89 (d,  $J=8.23\text{Hz}$ , 2H), 7.03 (s, 1H), 7.14 (d,  $J=8.23\text{Hz}$ , 2H), 7.81 (s, 1H)

[0355]

Step 3

(R)-1,1,1-trifluoro-2-((S)-4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)propan-2-ol

5 [0356]



[0357]

(R)-1,1,1-Trifluoro-2-((S)-6-(4-methoxybenzyl)-4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)propan-2-ol (0.015 g) obtained in the previous step and anisole (0.008 ml) were mixed with trifluoroacetic acid (0.75 ml). The reaction mixture was stirred at 130°C for 30 min under microwave (Biotage (registered trademark) Initiator+) radiation. To the reaction mixture was added toluene, and the mixture 15 concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=30:70 to ethyl acetate) to give the title compound (0.009 g).

<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.01 (d, J=6.94Hz, 3H), 1.73 (s, 3H), 20 2.62 - 2.92 (m, 2H), 3.32 - 3.41 (m, 1H), 7.02 (s, 1H), 8.13 (s, 1H), 12.98 (s, 1H)

[0358]

Production Example 3-3

Synthesis of (1S,3r)-1-methyl-3-((S)-4-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydro-6H-isoxazolo[5,4-e]indazol-6-yl)cyclobutane-1-carbonitrile and enantiomer thereof (Example 53),

(1S,3r)-1-methyl-3-((S)-4-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydro-7H-isoxazolo[5,4-e]indazol-7-yl)cyclobutane-1-carbonitrile and enantiomer thereof (Example 54),

(1*R*,3*s*)-1-methyl-3-((*S*)-4-methyl-3-((*R*)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydro-6*H*-isoxazolo[5,4-*e*]indazol-6-yl)cyclobutane-1-carbonitrile and enantiomer thereof (Example 57), and

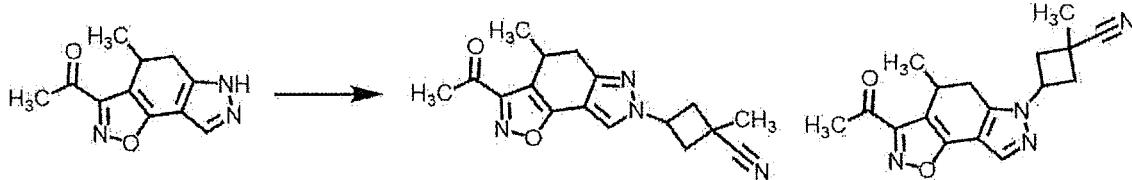
5 (1*R*,3*s*)-1-methyl-3-((*S*)-4-methyl-3-((*R*)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydro-7*H*-isoxazolo[5,4-*e*]indazol-7-yl)cyclobutane-1-carbonitrile and enantiomer thereof (Example 58)

[0359]

10 Step 1

mixture of 3-(3-acetyl-4-methyl-4,5-dihydro-7*H*-isoxazolo[5,4-*e*]indazol-7-yl)-1-methylcyclobutane-1-carbonitrile and 3-(3-acetyl-4-methyl-4,5-dihydro-6*H*-isoxazolo[5,4-*e*]indazol-6-yl)-1-methylcyclobutane-1-carbonitrile

15 [0360]



[0361]

(1-(4-Methyl-5,6-dihydro-4*H*-isoxazolo[5,4-*e*]indazol-3-yl)ethan-1-one (0.1 g) obtained in the previous step was mixed 20 with dimethylformamide (1.5 ml). To the reaction mixture were added cesium carbonate (0.45 g), sodium iodide (0.14 g), and 3-cyano-3-methylcyclobutyl 4-methylbenzenesulfonate (0.24 g) obtained in Auxiliary Step 5, and the mixture was stirred at 80°C for 2 hr. The reaction mixture was purified by reversed- 25 phase silica gel chromatography (acetonitrile:water=0:100 to 100:0) to give a crude product (0.16 g) of the title compound.

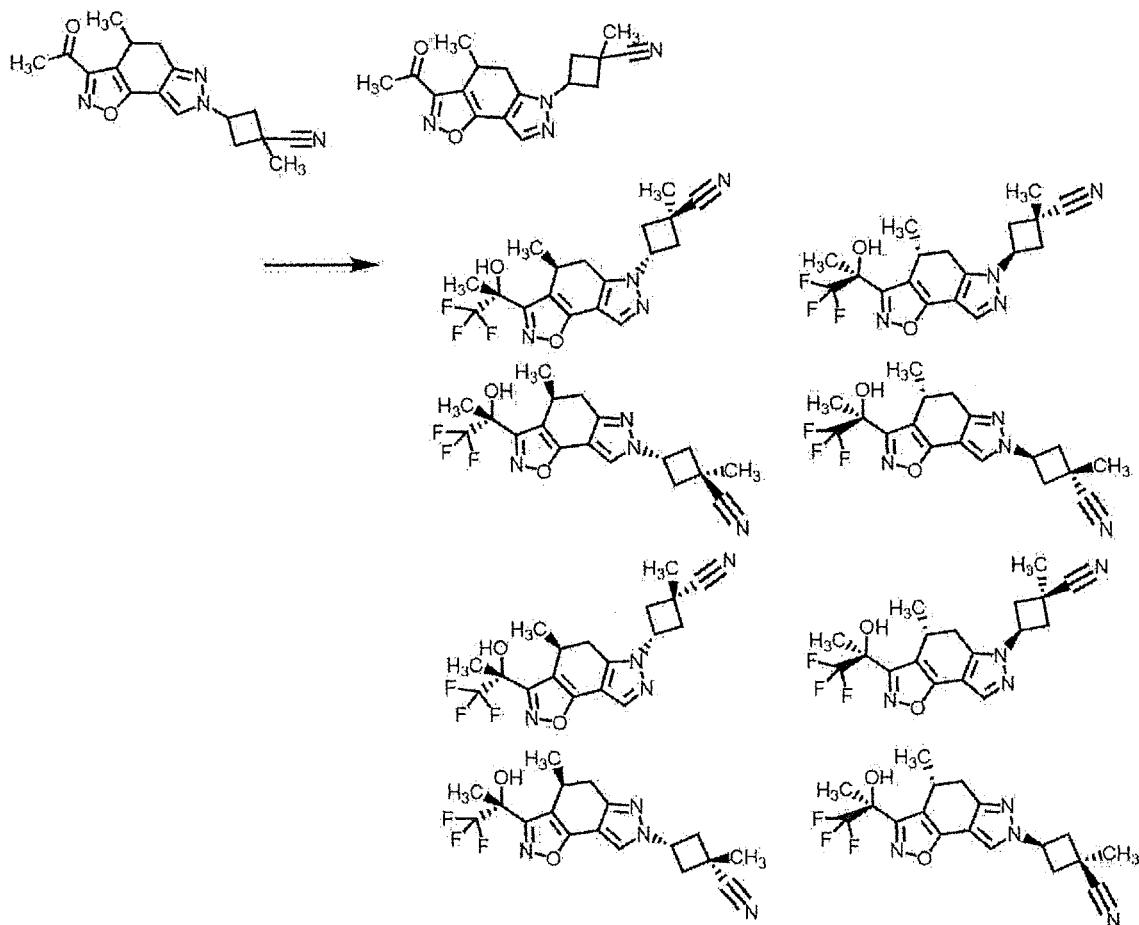
[0362]

Step 2

mixture of (1*S*,3*r*)-1-methyl-3-((*S*)-4-methyl-3-((*R*)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydro-6*H*-isoxazolo[5,4-*e*]indazol-6-yl)cyclobutane-1-carbonitrile and (1*R*,3*r*)-1-

methyl-3-((R)-4-methyl-3-((S)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydro-6H-isoxazolo[5,4-e]indazol-6-yl)cyclobutane-1-carbonitrile,  
mixture of (1S,3r)-1-methyl-3-((S)-4-methyl-3-((R)-1,1,1-  
5 trifluoro-2-hydroxypropan-2-yl)-4,5-dihydro-7H-isoxazolo[5,4-  
e]indazol-7-yl)cyclobutane-1-carbonitrile and (1R,3r)-1-  
methyl-3-((R)-4-methyl-3-((S)-1,1,1-trifluoro-2-hydroxypropan-  
2-yl)-4,5-dihydro-7H-isoxazolo[5,4-e]indazol-7-yl)cyclobutane-  
1-carbonitrile,  
10 mixture of (1R,3s)-1-methyl-3-((S)-4-methyl-3-((R)-1,1,1-  
trifluoro-2-hydroxypropan-2-yl)-4,5-dihydro-6H-isoxazolo[5,4-  
e]indazol-6-yl)cyclobutane-1-carbonitrile and (1S,3s)-1-  
methyl-3-((R)-4-methyl-3-((S)-1,1,1-trifluoro-2-hydroxypropan-  
2-yl)-4,5-dihydro-6H-isoxazolo[5,4-e]indazol-6-yl)cyclobutane-  
15 1-carbonitrile, and  
mixture of (1R,3s)-1-methyl-3-((S)-4-methyl-3-((R)-1,1,1-  
trifluoro-2-hydroxypropan-2-yl)-4,5-dihydro-7H-isoxazolo[5,4-  
e]indazol-7-yl)cyclobutane-1-carbonitrile and (1S,3s)-1-  
methyl-3-((R)-4-methyl-3-((S)-1,1,1-trifluoro-2-hydroxypropan-  
20 2-yl)-4,5-dihydro-7H-isoxazolo[5,4-e]indazol-7-yl)cyclobutane-  
1-carbonitrile

[0363]



[0364]

The mixture (0.16 g) of 3-(3-acetyl-4-methyl-4,5-dihydro-7H-isoxazolo[5,4-e]indazol-7-yl)-1-methylcyclobutane-1-carbonitrile and 3-(3-acetyl-4-methyl-4,5-dihydro-6H-isoxazolo[5,4-e]indazol-6-yl)-1-methylcyclobutane-1-carbonitrile obtained in the previous step was mixed with tetrahydrofuran (3.3 ml). Under ice-cooling, to the mixture was added cesium fluoride (0.016 g), and then (trifluoromethyl)trimethylsilane (0.15 ml) was added dropwise. The reaction mixture was stirred for 1 hr while raising the temperature to room temperature. At room temperature, methanol (3.3 ml) and potassium carbonate (0.44 g) were added, and the mixture was stirred at room temperature for 30 min. To the reaction mixture was added saturated ammonium chloride aqueous solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, filtered through a phase separator,

and the filtrate was concentrated under reduced pressure. The obtained residue was purified by preparative thin layer silica gel chromatography (hexane:ethyl acetate=2:1). The crude product was purified by preparative thin layer silica gel chromatography (dichloromethane:ethyl acetate=10:1, developed three times) to give the title compounds (0.007 g), (0.003 g), (0.003 g), and (0.009 g) in the order from lowest polarity, each as a racemate.

[0365]

10  $^1\text{H-NMR}$  (400 MHz, DMSO- $\text{D}_6$ ) 1.03 (d,  $J=6.94\text{Hz}$ , 3H), 1.56 (s, 3H), 1.73 (s, 3H), 2.59 (dd,  $J=11.97$ ,  $9.02\text{Hz}$ , 1H), 2.73 (dd,  $J=11.97$ ,  $8.67\text{Hz}$ , 1H), 2.91 - 3.03 (m, 4H), 3.37 - 3.39 (m, 1H), 5.13 - 5.15 (m, 1H), 7.03 (s, 1H), 7.88 (s, 1H)

[0366]

15  $^1\text{H-NMR}$  (400 MHz, DMSO- $\text{D}_6$ ) 1.03 (d,  $J=6.94\text{Hz}$ , 3H), 1.57 (s, 3H), 1.74 (s, 3H), 2.64 - 2.67 (m, 2H), 2.75 (d,  $J=15.95\text{Hz}$ , 1H), 2.87 (dd,  $J=15.95$ ,  $6.47\text{Hz}$ , 1H), 2.96 - 2.98 (m, 2H), 3.37 - 3.38 (m, 1H), 5.06 - 5.11 (m, 1H), 7.06 (s, 1H), 8.27 (s, 1H)

[0367]

20  $^1\text{H-NMR}$  (400 MHz, DMSO- $\text{D}_6$ ) 1.04 (d,  $J=6.73\text{Hz}$ , 3H), 1.62 (s, 3H), 1.74 (s, 3H), 2.58 - 2.64 (m, 2H), 2.88 - 3.14 (m, 4H), 3.39 - 3.41 (m, 1H), 5.20 - 5.22 (m, 1H), 7.05 (s, 1H), 7.92 (s, 1H)

[0368]

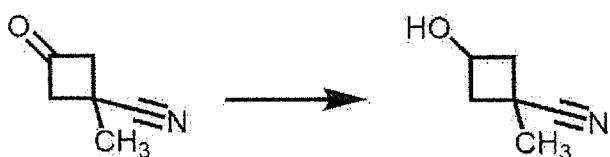
25  $^1\text{H-NMR}$  (400 MHz, DMSO- $\text{D}_6$ ) 1.04 (d,  $J=6.73\text{Hz}$ , 3H), 1.59 (s, 3H), 1.74 (s, 3H), 2.61 - 2.63 (m, 2H), 2.77 (d,  $J=15.71\text{Hz}$ , 1H), 2.88 (dd,  $J=15.71$ ,  $6.73\text{Hz}$ , 1H), 2.96 - 3.02 (m, 2H), 3.36 - 3.39 (m, 1H), 5.11 - 5.13 (m, 1H), 7.05 (d,  $J=3.74\text{Hz}$ , 1H), 8.24 (s, 1H)

[0369]

30 Auxiliary Step 4

3-hydroxy-1-methylcyclobutane-1-carbonitrile

[0370]



[0371]

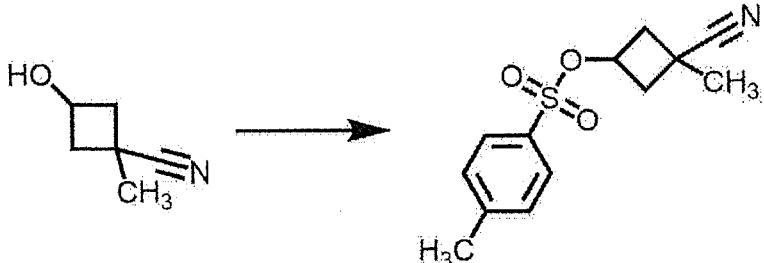
1-Methyl-3-oxocyclobutane-1-carbonitrile (0.76 g) was mixed with methanol (7.6 ml). To the reaction mixture was 5 added sodium borohydride (0.079 g), and the mixture was stirred at room temperature for 2 hr. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, filtered through a phase 10 separator, and the filtrate was concentrated under reduced pressure to give a crude product (0.75 g) of the title compound.

[0372]

Auxiliary Step 5

15 3-cyano-3-methylcyclobutyl 4-methylbenzenesulfonate

[0373]



[0374]

The crude product (0.34 g) of 3-hydroxy-1- 20 methylcyclobutane-1-carbonitrile obtained in the previous step was mixed with dichloromethane (3.4 ml). To the reaction mixture were added p-toluenesulfonyl chloride (0.7 g), 4-dimethylaminopyridine (0.14 g), and triethylamine (0.46 g), and the mixture was stirred at room temperature overnight. To 25 the reaction mixture was added saturated ammonium chloride aqueous solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, and filtered through a phase

separator. The filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=20:80 to 60:40) to give a crude product (0.47 g) of the title compound.

5 [0375]

Using (R)-1,1,1-trifluoro-2-((S)-4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)propan-2-ol obtained in Production Example 3-2, Step 3, the reactions of Production Example 3-3, Step 1 and Step 2, are performed, whereby 10 (1S,3r)-1-methyl-3-((S)-4-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydro-6H-isoxazolo[5,4-e]indazol-6-yl)cyclobutane-1-carbonitrile (optically active form of Example 53), (1S,3r)-1-methyl-3-((S)-4-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydro-7H-isoxazolo[5,4-e]indazol-7-yl)cyclobutane-1-carbonitrile (optically active 15 form of Example 54), (1R,3s)-1-methyl-3-((S)-4-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydro-6H-isoxazolo[5,4-e]indazol-6-yl)cyclobutane-1-carbonitrile (optically active form of Example 57), and (1R,3s)-1-methyl-3-((S)-4-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydro-6H-isoxazolo[5,4-e]indazol-6-yl)cyclobutane-1-carbonitrile (optically active form of Example 58) can be obtained.

[0376]

25 Production Example 4

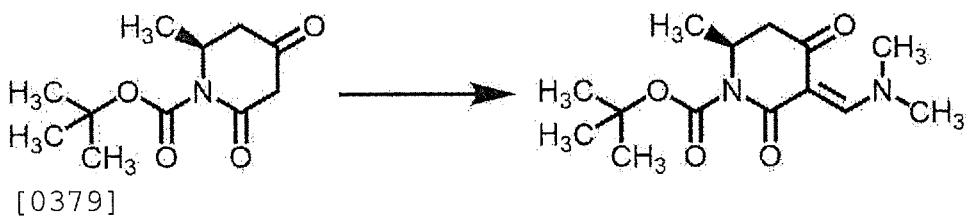
Synthesis of (S)-1,1,1-trifluoro-2-((S)-5-methyl-3-phenyl-4,5-dihydro-3H-imidazo[1,5-a]pyrazolo[4,3-c]pyridin-7-yl)propan-2-ol (Example 73)

[0377]

30 Step 1

tert-butyl (S,E)-3-((dimethylamino)methylene)-6-methyl-2,4-dioxopiperidine-1-carboxylate

[0378]



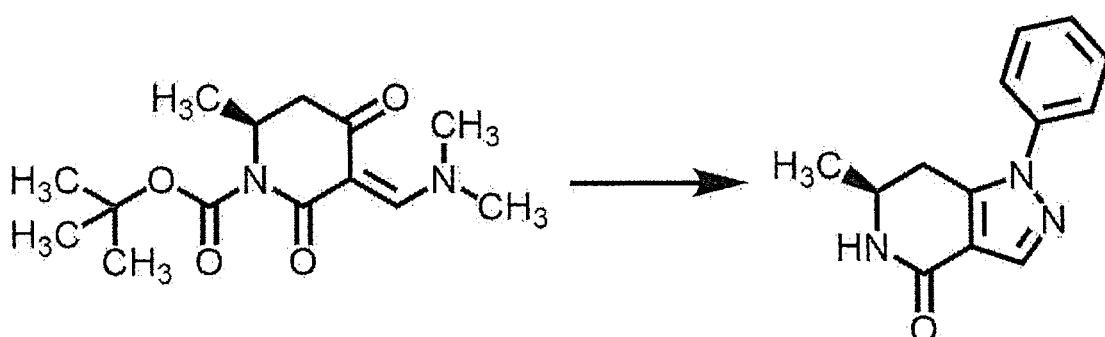
tert-Butyl (S)-2-methyl-4,6-dioxopiperidine-1-carboxylate (1.5 g) was mixed with toluene (7.5 ml). To the reaction mixture was added N,N-dimethylformamide dimethyl acetal (1.8 ml), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure to give the title compound (1.5 g).

<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.20 (d, J=6.35Hz, 3H), 1.45 (s, 9H), 2.14 (dd, J=16.41, 2.08Hz, 1H), 2.78 (dd, J=16.41, 6.35Hz, 1H), 3.04 (s, 3H), 3.38 (s, 3H), 4.31 - 4.35 (m, 1H), 7.99 (s, 1H)

[0380]

Step 2

(S)-6-methyl-1-phenyl-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-c]pyridin-4-one  
[0381]

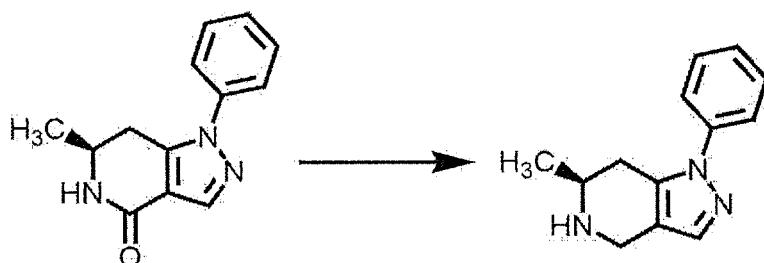


tert-Butyl (S,E)-3-((dimethylamino)methylene)-6-methyl-2,4-dioxopiperidine-1-carboxylate (1.0 g) obtained in the previous step was dissolved in isopropanol (5.0 ml), acetic acid (0.53 ml), and water (7.0 ml). To the reaction mixture was added phenylhydrazine (0.38 g), and the mixture was heated under reflux for 2 hr. To the reaction mixture was added toluene (5.0 ml), and the mixture was further heated under reflux for 2 hr. Water was added to the reaction mixture, and

the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and filtered through a phase separator. The filtrate was concentrated under reduced pressure. The obtained residue 5 was purified by silica gel column chromatography (ethyl acetate:hexane=40:60 to ethyl acetate, thereafter ethyl acetate:methanol=85:15) to give the title compound (0.54 g).  
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.22 (d, J=5.78Hz, 3H), 2.88 (dd, J=16.24, 10.52Hz, 1H), 3.06 (dd, J=16.24, 5.78Hz, 1H), 3.74 - 10 3.77 (m, 1H), 7.39 (s, 1H), 7.45 (tt, J=7.05, 1.73Hz, 1H), 7.54 - 7.61 (m, 4H), 7.94 (s, 1H)  
[0383]

Step 3

(S)-6-methyl-1-phenyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-  
15 c]pyridine  
[0384]



[0385]

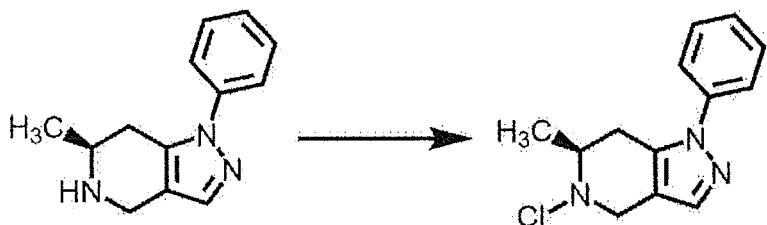
Lithium aluminum hydride (0.27 g) was dissolved in  
20 tetrahydrofuran (10 ml). To the reaction mixture was added  
(S)-6-methyl-1-phenyl-1,5,6,7-tetrahydro-4H-pyrazolo[4,3-  
c]pyridin-4-one (0.53 g) obtained in the previous step, and  
the mixture was heated under reflux at 90°C for 1 hr. To the  
reaction mixture was added lithium aluminum hydride (0.27 g),  
25 and the mixture was further heated under reflux at 90°C for 1  
hr. At room temperature, to the reaction mixture were  
successively added water (0.53 ml), 4 M sodium hydroxide  
aqueous solution (0.53 ml), and water (1.5 ml). Insoluble  
material was filtered off through celite, and the filtrate was  
30 concentrated under reduced pressure. The obtained residue was

purified by SCX column chromatography (methanol to 1N ammonia/methanol solution) to give the title compound (0.47 g).  
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.29 (d, J=6.24Hz, 3H), 2.52 (dd, J=16.07, 9.83Hz, 1H), 2.74 - 2.78 (m, 1H), 2.94 - 2.99 (m, 1H),  
5 3.96 - 4.01 (m, 2H), 7.31 - 7.34 (m, 1H), 7.43 - 7.51 (m, 5H)  
[0386]

Step 4

(S)-5-chloro-6-methyl-1-phenyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine

10 [0387]



[0388]

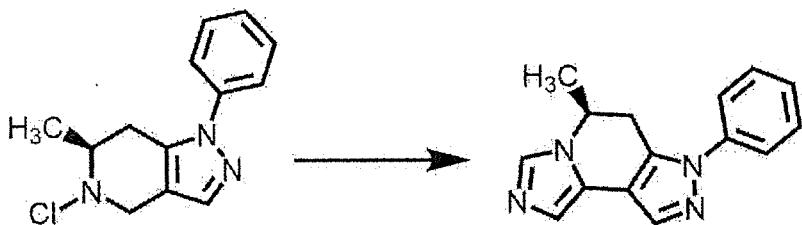
(S)-6-Methyl-1-phenyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine (0.28 g) obtained in the previous step was dissolved in dichloromethane (2.7 ml). At room temperature, to the reaction mixture was added N-chlorosuccinimide (5.68 g), and the mixture was stirred for 30 min. At room temperature, to the reaction mixture was added 1,8-diazabicyclo[5.4.0]-7-undecene (0.21 ml), and the mixture was further stirred for 30 min. To the reaction mixture was added water at room temperature, and the mixture was filtered through silica gel (10 g). The filtrate was concentrated under reduced pressure to give a crude product (0.12 g) of the title compound.

[0389]

25 Step 5

(S)-5-methyl-3-phenyl-4,5-dihydro-3H-imidazo[1,5-a]pyrazolo[4,3-c]pyridine

[0390]



[0391]

The crude product (0.12 g) of (S)-5-chloro-6-methyl-1-phenyl-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine obtained in the previous step was dissolved in 1,2-dimethoxyethane (3.6 ml) and methanol (0.9 ml). At room temperature, potassium hydroxide (0.03 g) was added, and the mixture was stirred for 30 min. At room temperature, 2 M sodium hydroxide aqueous solution (0.097 ml) was added and the mixture was further stirred for 30 min. After confirming the disappearance of the starting material, to the mixture were added potassium carbonate (0.4 g) and p-toluenesulfonylmethyl isocyanide (0.42 g), and the mixture was stirred at room temperature for 2 days. The reaction mixture was purified by reversed-phase silica gel chromatography (acetonitrile:water=0:100 to 100:0) to give the title compound (0.036 g).

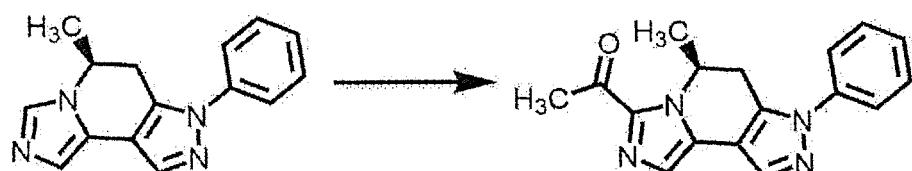
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.59 (d, J=5.90Hz, 3H), 2.98 (dd, J=15.95, 8.55Hz, 1H), 3.28 (dd, J=15.95, 5.90Hz, 1H), 4.37 - 4.40 (m, 1H), 7.17 (s, 1H), 7.38 - 7.43 (m, 1H), 7.48 - 7.54 (m, 4H), 7.59 (s, 1H), 7.85 (s, 1H)

[0392]

Step 6

(S)-1-(5-methyl-3-phenyl-4,5-dihydro-3H-imidazo[1,5-a]pyrazolo[4,3-c]pyridin-7-yl)ethan-1-one

[0393]



[0394]

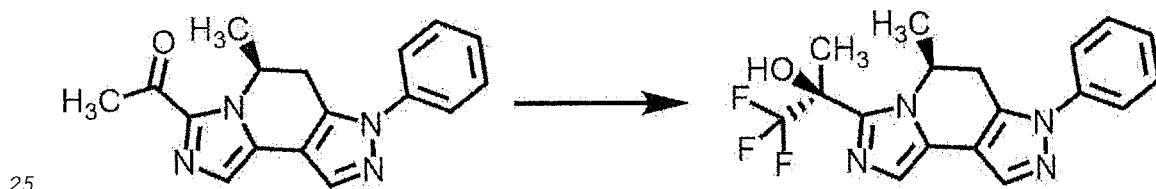
(S)-5-Methyl-3-phenyl-4,5-dihydro-3H-imidazo[1,5-a]pyrazolo[4,3-c]pyridine (0.034 g) obtained in the previous step was dissolved in tetrahydrofuran (1.0 ml). 2 M Lithium diisopropylamide/tetrahydrofuran-heptane-ethylbenzene solution (0.065 ml) was added dropwise to the reaction mixture at -78°C, and the mixture was stirred for 30 min. To the mixture was added N-methoxy-N-methylacetamide (0.033 ml), and the mixture was stirred at -78°C for 1 hr. To the mixture was added dropwise 1 M lithium diisopropylamide/tetrahydrofuran-heptane-ethylbenzene solution (0.068 ml), and the mixture was stirred at -78°C for 1 hr. At room temperature, to the reaction mixture was added saturated ammonium chloride aqueous solution, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and filtered through a phase separator. The filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane to ethyl acetate:hexane=33:67) to give a crude product (0.018 g) of the title compound.

20 [0395]

Step 7

(S)-1,1,1-trifluoro-2-((S)-5-methyl-3-phenyl-4,5-dihydro-3H-imidazo[1,5-a]pyrazolo[4,3-c]pyridin-7-yl)propan-2-ol

[0396]



[0397]

The crude product (0.018 g) of (S)-1-(5-methyl-3-phenyl-4,5-dihydro-3H-imidazo[1,5-a]pyrazolo[4,3-c]pyridin-7-yl)ethan-1-one obtained in the previous step was mixed with tetrahydrofuran (1 ml). Under ice-cooling, to the mixture was added cesium fluoride (0.005 g), and then

(trifluoromethyl)trimethylsilane (0.018 ml) was added dropwise. The reaction mixture was stirred for 1 hr while raising the temperature to room temperature. At room temperature, methanol (0.5 ml) and potassium carbonate (0.026 g) were added, and the 5 mixture was stirred at room temperature for 1 hr. To the reaction mixture was added saturated ammonium chloride aqueous solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, filtered through a phase separator, 10 and the filtrate was concentrated under reduced pressure. The obtained residue was purified by reversed-phase silica gel chromatography (acetonitrile:water=5:95 to 100:0) to give the title compound (0.017 g).

<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.09 (d, J=6.24Hz, 3H), 1.81 (s, 3H), 2.99 (d, J=16.93Hz, 1H), 3.46 (dd, J=16.93, 7.28Hz, 1H), 5.33 15 - 5.35 (m, 1H), 7.05 (s, 1H), 7.08 (s, 1H), 7.42 - 7.43 (m, 1H), 7.53 - 7.59 (m, 4H), 7.97 (s, 1H)

[0398]

#### Production Example 5

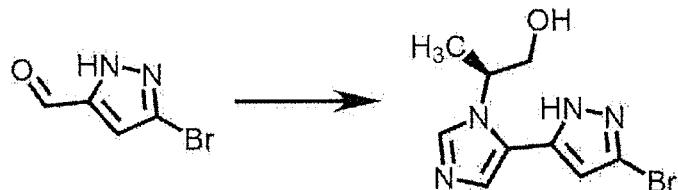
20 Synthesis of (R)-2-((S)-9-((6,6-difluoro-2-azaspiro[3.3]heptan-2-yl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)-1,1,1-trifluoropropan-2-ol (Example 84)

[0399]

#### Step 1

25 (S)-2-(5-(3-bromo-1H-pyrazol-5-yl)-1H-imidazol-1-yl)propan-1-ol

[0400]



[0401]

30 3-Bromo-1H-pyrazole-5-carbaldehyde (2.41 g) and (S)-2-aminopropan-1-ol (1.034 g) were mixed with methanol (24.1 ml),

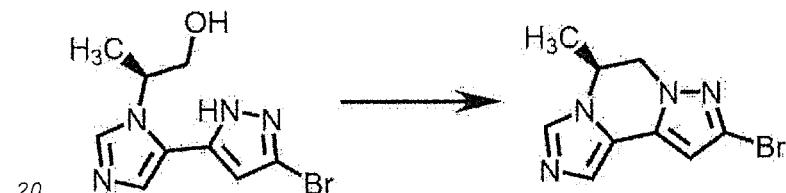
and the mixture was stirred at room temperature overnight. To the mixture was added 1,2-dimethoxyethane (48.2 ml). Under ice-cooling, p-toluenesulfonylmethyl isocyanide (4.03 g) and potassium carbonate (5.71 g) were added, and the mixture was 5 stirred at room temperature overnight. Water was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate. The organic layer was washed twice with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the 10 filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=25:75 to ethyl acetate, thereafter ethyl acetate:methanol=50:50), and azeotroped twice with THF to give a crude product (3.12 g) of the title compound.

15 [0402]

Step 2

(S)-9-bromo-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazine

[0403]



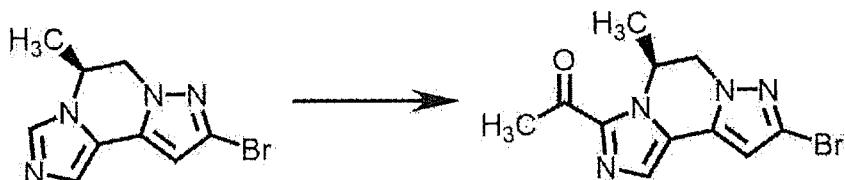
[0404]

The crude product (2.91 g) of (S)-2-(5-(3-bromo-1H-pyrazol-5-yl)-1H-imidazol-1-yl)propan-1-ol obtained in the previous step was mixed with tetrahydrofuran (58.2 ml). Under 25 ice-cooling, triphenylphosphine (3.38 g) and diisopropyl azodicarboxylate (2.60 g) were added, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure, and purified by silica gel column chromatography (ethyl acetate:hexane=25:75 to ethyl acetate, thereafter ethyl acetate:methanol=50:50) to give the 30 title compound (2.23 g).

<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.48 (d, J=6.47Hz, 3H), 4.14 (dd, J=13.29, 7.74Hz, 1H), 4.48 (dd, J=13.29, 4.51Hz, 1H), 4.67 - 4.78 (m, 1H), 6.67 (s, 1H), 7.31 (s, 1H), 7.93 (s, 1H)  
[0405]

5 Step 3

(S)-1-(9-bromo-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)ethan-1-one  
[0406]



10 [0407]

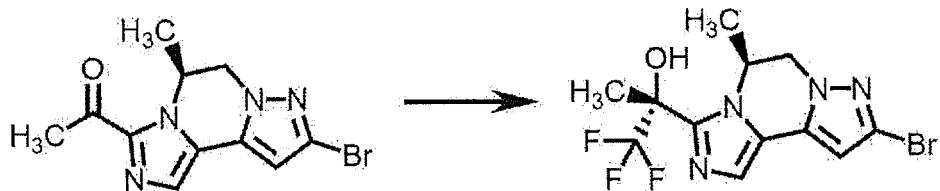
(S)-9-Bromo-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazine (1.5 g) obtained in the previous step was mixed with tetrahydrofuran (15 ml). The mixture was cooled to -78°C, and 2 M lithium diisopropylamide/tetrahydrofuran-heptane-ethylbenzene solution (2.96 ml) was added dropwise. The mixture was stirred at -78°C for 1 hr. To the mixture was added N-methoxy-N-methylacetamide (1.452 ml), and the mixture was stirred at -78°C for 1 hr. To the mixture was added dropwise 2 M lithium diisopropylamide/tetrahydrofuran-heptane-ethylbenzene solution (2.96 ml), and the mixture was stirred at -78°C for 1 hr. To the reaction mixture was added saturated ammonium chloride aqueous solution, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. To the obtained residue was added ethanol/water=1/2 (4.5 ml), and the mixture was stirred at room temperature. The precipitated solid was collected by filtration to give a crude product (1.373 g) of the title compound.  
15  
20  
25  
30

[0408]

Step 4

(R)-2-((S)-9-bromo-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)-1,1,1-trifluoropropan-2-ol

5 [0409]



[0410]

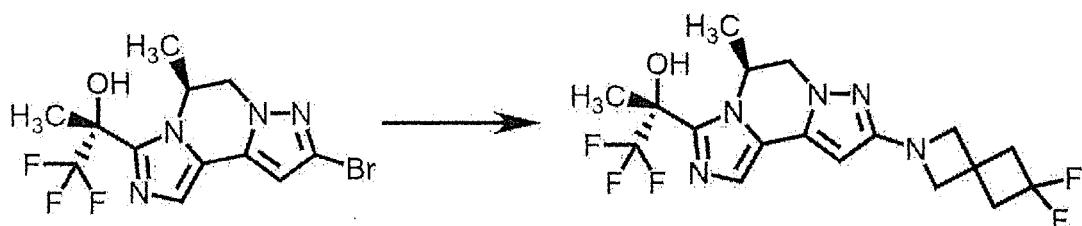
(S)-1-(9-Bromo-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)ethan-1-one crude product (1.373 g) obtained in the previous step was mixed with N,N-dimethylacetamide (6.42 ml). Under ice-cooling, to the mixture was added lithium acetate (0.086 g), and then trifluoromethyltrimethylsilane (0.966 ml) was added dropwise. The mixture was stirred under ice-cooling for 25 min. Under ice-cooling, methanol (0.642 ml) and potassium carbonate (0.721 g) were added, and the mixture was stirred at room temperature for 1 hr. To the reaction mixture was added water, and the mixture was extracted twice with ethyl acetate. The organic layer was washed successively with 1N aqueous hydrochloric acid solution, water, and saturated aqueous sodium chloride solution. The aqueous layers were combined and extracted again with ethyl acetate, and the organic layer was washed with 1N potassium hydrogen sulfate aqueous solution. The 1N potassium hydrogen sulfate aqueous solution layer was extracted again with ethyl acetate. All organic layers were combined, washed with saturated aqueous sodium hydrogen carbonate solution and saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give a crude product (1.669 g) containing the title compound. The crude product (1.421 g) was mixed with

acetonitrile (11.37 ml). To the mixture was added phosphoric acid (0.673 g), and the mixture was stirred at room temperature for 1 hr. Under ice-cooling, the mixture was stirred for 1 hr, and the precipitated solid was collected by 5 filtration to give a phosphate (1.533 g) of the title compound. Using the crude product (0.1 g) containing the title compound and by a similar method, a phosphate (0.1057 g) of the title compound was obtained. The phosphate (1.6387 g) of the title compound was mixed with ethyl acetate (16.22 ml). To the 10 mixture was added saturated aqueous sodium hydrogen carbonate solution (16.22 ml), and the mixture was stirred at room temperature for 1 hr. After layer separation, the aqueous layer was extracted with ethyl acetate. The organic layers were combined and washed successively with water and saturated 15 aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give the title compound (1.264 g).

<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.24 (d, J=6.47Hz, 3H), 1.81 (s, 3H), 20 4.30 (dd, J=13.52, 4.05Hz, 1H), 4.39 (d, J=13.52Hz, 1H), 5.28 - 5.41 (m, 1H), 6.71 (s, 1H), 7.31 (s, 2H)  
[0411]

#### Step 5

(R)-2-((S)-9-(6,6-difluoro-2-azaspiro[3.3]heptan-2-yl)-5- 25 methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)-1,1,1-trifluoropropan-2-ol  
[0412]



[0413]

30 (R)-2-((S)-9-Bromo-5-methyl-5,6-dihydroimidazo[1,5-

a]pyrazolo[5,1-c]pyrazin-3-yl)-1,1,1-trifluoropropan-2-ol (200 mg) obtained in the previous step, 6,6-difluoro-2-azaspiro[3.3]heptane 2,2,2-trifluoroacetate (382 mg), sodium tert-butoxide (346 mg), and methanesulfonato(2-5 dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl) (2'-methylamino-1,1'-biphenyl-2-yl)palladium(II) (89 mg) were mixed with toluene (1.88 ml). Under an argon atmosphere, the reaction mixture was stirred at 120°C for 1.5 hr. At room temperature, water was added to the reaction mixture, and the 10 mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was successively purified by 15 silica gel column chromatography (ethyl acetate:hexane=12:88 to ethyl acetate) and reversed-phase silica gel chromatography (acetonitrile:water=5:95 to acetonitrile) to give the title compound (154.8 mg).

<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.26 (d, J=6.47Hz, 3H), 1.81 (s, 3H), 2.83 (t, J=12.60Hz, 4H), 3.87 (s, 4H), 4.10 - 4.16 (m, 2H), 5.28 - 5.30 (m, 1H), 5.80 (s, 1H), 7.20 (s, 1H), 7.26 (s, 1H) [0414]

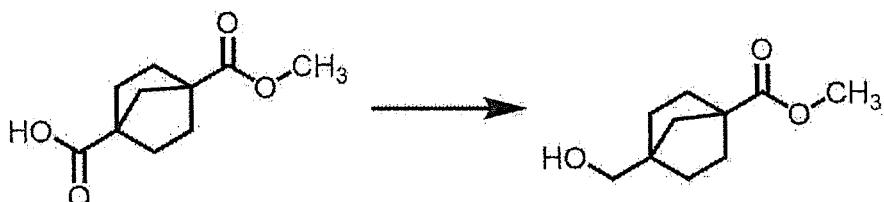
#### Production Example 6

Synthesis of 4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)bicyclo[2.2.1]heptane-1-carbonitrile (Example 86)

[0415]

#### Step 1

30 methyl 4-(hydroxymethyl)bicyclo[2.2.1]heptane-1-carboxylate [0416]



[0417]

4-(Methoxycarbonyl)bicyclo[2.2.1]heptane-1-carboxylic acid (5 g) was mixed with THF (50 ml). Under ice-cooling, to 5 the mixture was added dropwise 0.89 M borane-THF complex/THF solution (31.2 ml), and the mixture was stirred for 10 min. The reaction mixture was warmed to room temperature and stirred for 2 hr. Under ice-cooling, to the reaction mixture was added dropwise saturated aqueous sodium hydrogen carbonate 10 solution, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was 15 purified by silica gel column chromatography (ethyl acetate:hexane=12:88 to ethyl acetate) to give the title compound (4.57 g).

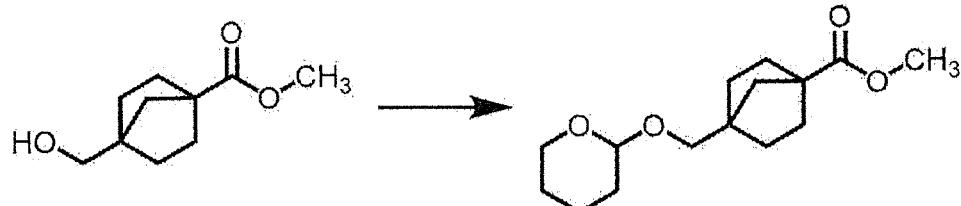
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.29 - 1.43 (m, 3H), 1.55 (s, 2H), 1.60 - 1.74 (m, 4H), 1.93 - 2.06 (m, 2H), 3.65 - 3.72 (m, 2H), 3.66 20 (s, 3H)

[0418]

Step 2

methyl 4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptane-1-carboxylate

25 [0419]



[0420]

Methyl 4-(hydroxymethyl)bicyclo[2.2.1]heptane-1-

carboxylate (4.57 g) obtained in the previous step was mixed with acetonitrile (42.3 ml). At room temperature, pyridinium p-toluenesulfonate (1.153 g) and 3,4-dihydro-2H-pyran (2.316 g) were added, and the mixture was stirred at room temperature 5 overnight. The reaction mixture was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=2:98 to 18:82) to give the title compound (6.254 g).

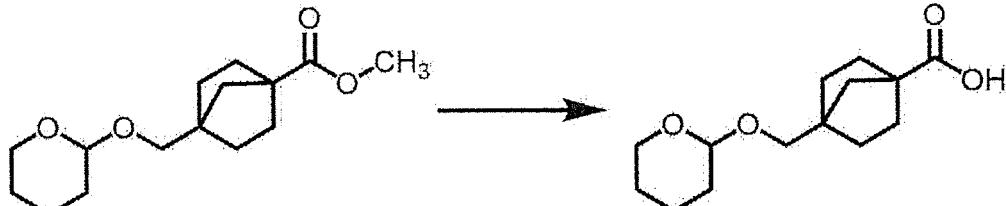
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.31 - 1.43 (m, 2H), 1.43 - 1.89 (m, 10 12H), 1.91 - 2.05 (m, 2H), 3.36 (d, J=9.94Hz, 1H), 3.44 - 3.53 (m, 1H), 3.66 (s, 3H), 3.75 - 3.87 (m, 2H), 4.53 - 4.60 (m, 1H)

[0421]

Step 3

15 4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptane-1-carboxylic acid

[0422]



[0423]

20 Methyl 4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptane-1-carboxylate (6.254 g) obtained in the previous step was mixed with ethanol (30 ml). To the reaction mixture was added 4N sodium hydroxide aqueous solution (13.98 ml), and the mixture was stirred at 80°C for 2 25 hr and allowed to stand at room temperature for 3 days. The reaction mixture was stirred at 80°C for 6 hr. After cooling to room temperature, 2N aqueous hydrochloric acid solution (28 ml) was added, and the mixture was concentrated under reduced pressure. The obtained residue was extracted twice with ethyl acetate, washed with saturated aqueous sodium chloride 30 solution, and dried over sodium sulfate. Sodium sulfate was

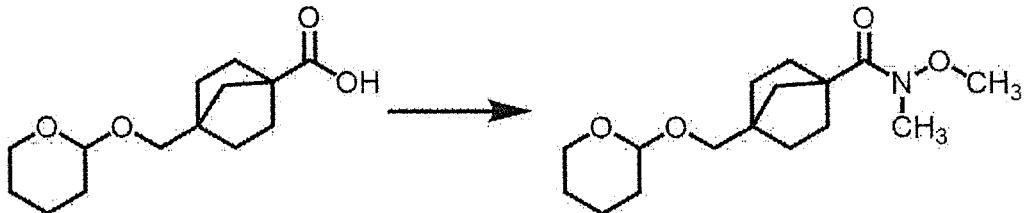
filtered off, and the filtrate was concentrated under reduced pressure to give a crude product (5.69 g) of the title compound.

[0424]

5 Step 4

N-methoxy-N-methyl-4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptane-1-carboxamide

[0425]



10 [0426]

The crude product (5.69 g) of 4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptane-1-carboxylic acid obtained in the previous step and N,O-dimethylhydroxylamine hydrochloride (2.62 g) were mixed with pyridine (28.4 ml). To 15 the mixture was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (5.15 g), and the mixture was stirred at room temperature overnight. To the reaction mixture were added N,O-dimethylhydroxylamine hydrochloride (2.62 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (5.15 g), and the mixture was stirred at room temperature for 2 hr. To the reaction mixture was added 1N aqueous hydrochloric acid solution, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with 1N aqueous 25 hydrochloric acid solution, water, and saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=5:95 to 50:50) to give the title compound (6.18 g).

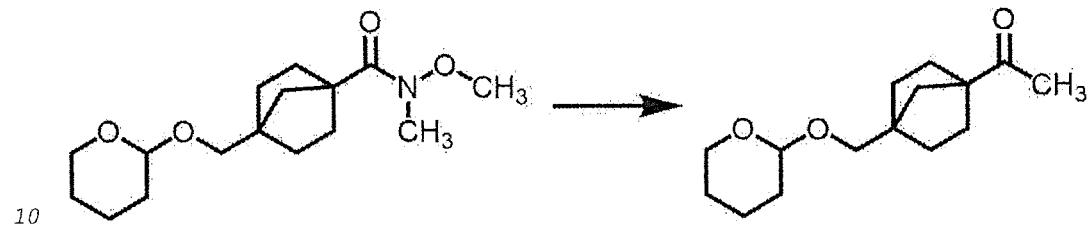
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.34 - 1.62 (m, 6H), 1.62 - 1.74 (m, 5H), 1.75 - 1.92 (m, 5H), 3.17 (s, 3H), 3.37 (d, J=9.94Hz, 1H), 3.43 - 3.52 (m, 1H), 3.65 (s, 3H), 3.79 (d, J=9.94Hz, 1H), 3.79 - 3.88 (m, 1H), 4.55 - 4.59 (m, 1H)

5 [0427]

Step 5

1-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptan-1-yl)ethan-1-one

[0428]



[0429]

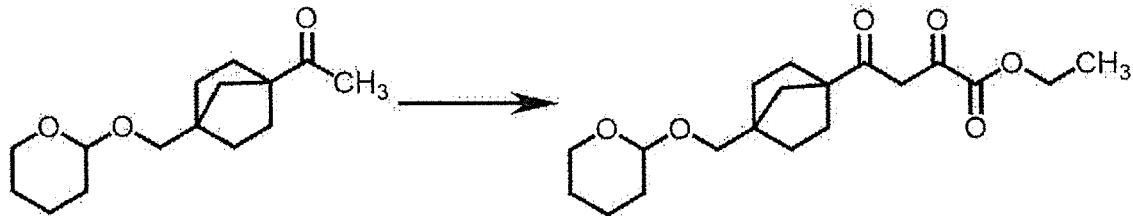
Under an argon atmosphere, N-methoxy-N-methyl-4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptane-1-carboxamide (6.18 g) obtained in the previous step was mixed with toluene (57.8 ml). Under ice-cooling, 1.04 M methylmagnesium bromide/tetrahydrofuran solution (22.42 ml) was added dropwise, and the mixture was stirred for 30 min. At room temperature, saturated ammonium chloride aqueous solution and water were added, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=8:92 to 66:34) to give the title compound (4.59 g).

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.33 - 1.97 (m, 16H), 2.15 (s, 3H), 3.37 (d, J=9.71Hz, 1H), 3.43 - 3.55 (m, 1H), 3.76 - 3.88 (m, 2H), 4.52 - 4.60 (m, 1H)

30 [0430]

Step 6

ethyl 2,4-dioxo-4-((4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptan-1-yl)butanoate  
[0431]



5 [0432]

1-(4-((4-tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptan-1-one (4.59 g) obtained in the previous step was mixed with tetrahydrofuran (45.9 ml). Under ice-cooling, to the mixture was added diethyl oxalate (489 mg), 1 M potassium tert-butoxide/tetrahydrofuran solution (21.83 ml) was added dropwise, and the mixture was stirred for 30 min. To the reaction mixture were added 1 M aqueous hydrochloric acid solution (21.3 ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure, and azeotroped with ethanol to give a crude product (6.41 g).

[0433]

20 Step 7

ethyl 3-(4-((4-tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptan-1-yl)-1H-pyrazole-5-carboxylate

[0434]

25

[0435]

The crude product (6.41 g) of ethyl 2,4-dioxo-4-(4-

((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptan-1-yl)butanoate obtained in the previous step was mixed with ethanol (64.1 ml). Under ice-cooling, hydrazine monohydrate (0.926 ml) was added dropwise, and the mixture was stirred at 5 room temperature overnight. The reaction mixture was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=8:92 to 63:37) to give the title compound (7.148 g).

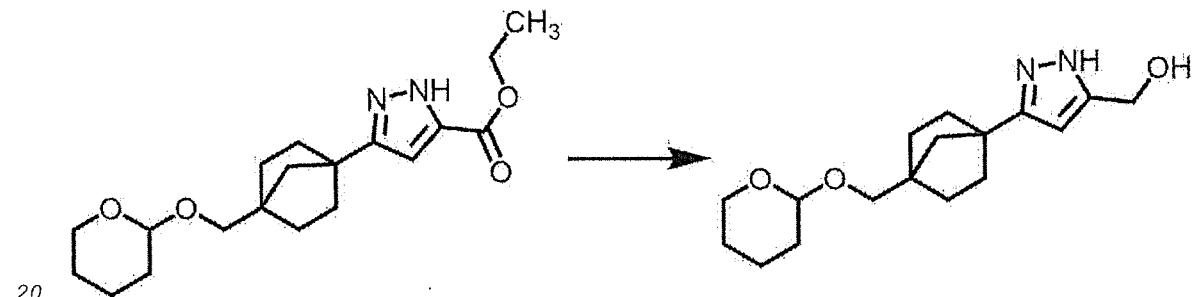
10  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 1.37 (t,  $J=7.17\text{Hz}$ , 3H), 1.41 - 1.99 (m, 16H), 3.41 (d,  $J=9.71\text{Hz}$ , 1H), 3.44 - 3.55 (m, 1H), 3.79 - 3.88 (m, 2H), 4.37 (q,  $J=7.17\text{Hz}$ , 2H), 4.56 - 4.61 (m, 1H), 6.64 (s, 1H), 10.26 (brs, 1H)

[0436]

15 Step 8

(3-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptan-1-yl)-1H-pyrazol-5-yl)methanol

[0437]



[0438]

Ethyl 3-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptan-1-yl)-1H-pyrazole-5-carboxylate (7.148 g) obtained in the previous step was mixed 25 with tetrahydrofuran (100 ml). Under ice-cooling, to the mixture was added dropwise 2 M lithium aluminum hydride/tetrahydrofuran solution (16.94 ml), and the mixture was stirred for 50 min. Under ice-cooling, to the reaction mixture was added saturated Rochelle salt aqueous solution,

and the mixture was stirred at room temperature for 1 hr and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the 5 filtrate was concentrated under reduced pressure. To the obtained residue was added ethyl acetate/hexane=1/2, and the mixture was stirred at room temperature. The precipitated solid was collected by filtration to give the title compound (4.94 g).

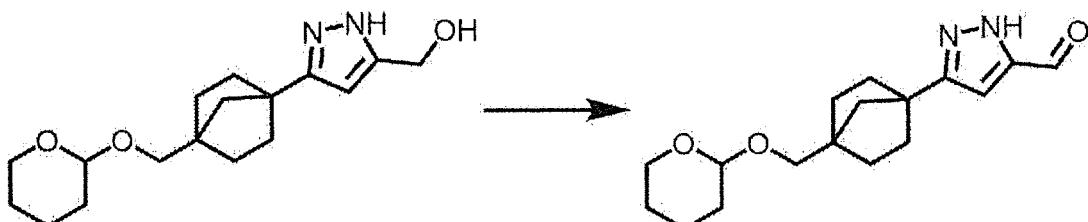
10  $^1\text{H-NMR}$  (400 MHz, DMSO- $\text{D}_6$ ) 1.30 - 1.91 (m, 16H), 3.33 - 3.45 (m, 2H), 3.65 - 3.78 (m, 2H), 4.28 - 4.41 (m, 2H), 4.52 - 4.57 (m, 1H), 4.88 (s, 1H), 5.94 (brs, 1H), 12.17 (brs, 1H)

[0439]

Step 9

15 3-((4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptan-1-yl)-1H-pyrazole-5-carbaldehyde

[0440]



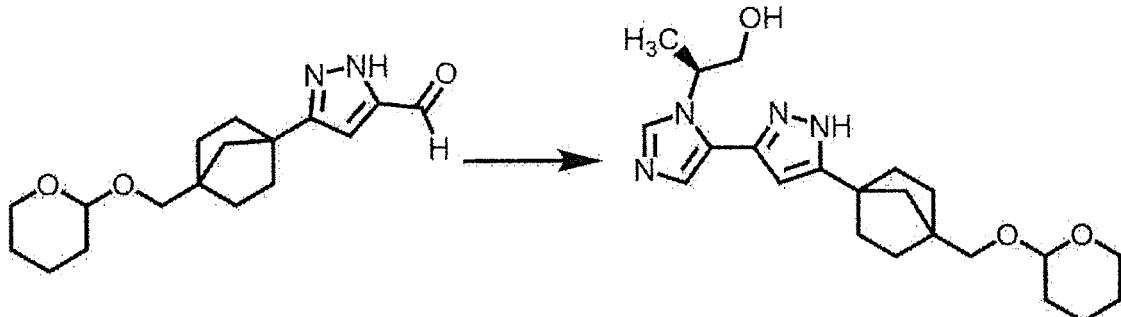
20 [0441]

(3-((4-((Tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptan-1-yl)-1H-pyrazol-5-yl)methanol (2.5 g) obtained in the previous step was mixed with 1,2-dimethoxyethane (100 ml). Manganese dioxide (7.5 g) was added, and the mixture was stirred at room temperature overnight. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (2.4 g) of the title compound.

[0442]

30 Step 10

(2S)-2-(5-(4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptan-1-yl)-1H-pyrazol-3-yl)-1H-imidazol-1-yl)propan-1-ol  
[0443]



5

[0444]

The crude product (2.4 g) of 3-(4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptan-1-yl)-1H-pyrazole-5-carbaldehyde obtained in the previous step and (S)-2-aminopropan-1-ol (0.574 g) were mixed with 1,2-dimethoxyethane (32.2 ml) and methanol (11.08 ml), and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure. To the obtained residue were successively added DMF (22.15 ml), potassium carbonate (2.012 g), and p-toluenesulfonylmethyl isocyanide (1.705 g), and the mixture was stirred at room temperature for 3 days. At room temperature, water was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:methanol=2:98 to 50:50) to give the title compound (2.11 g).

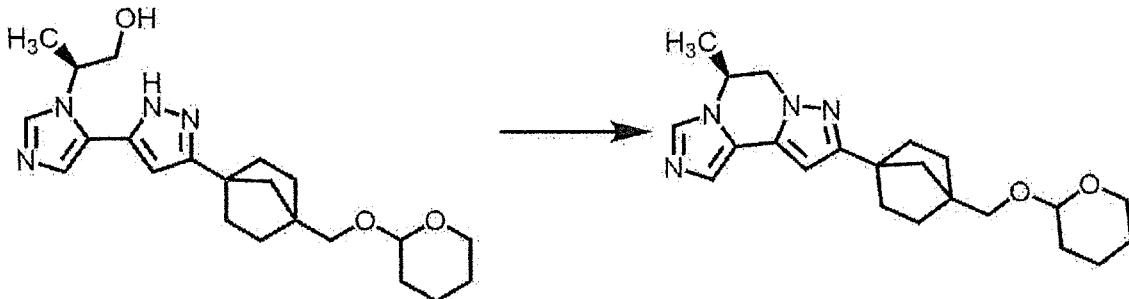
25  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 1.39 - 2.12 (m, 20H), 3.42 (d,  $J=9.71\text{Hz}$ , 1H), 3.47 - 3.54 (m, 1H), 3.68 - 3.77 (m, 1H), 3.80 - 3.89 (m, 2H), 3.95 (dd,  $J=11.44$ , 3.58Hz, 1H), 4.56 - 4.62 (m, 1H), 4.87 - 4.99 (m, 1H), 6.22 (s, 1H), 7.15 (d,  $J=0.92\text{Hz}$ , 1H), 7.66 (d,  $J=0.92\text{Hz}$ , 1H)

[0445]

Step 11

(5S)-5-methyl-9-((4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptan-1-yl)-5,6-  
5 dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazine

[0446]



[0447]

(2S)-2-(5-(5-(4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptan-1-yl)-1H-pyrazol-3-yl)-1H-imidazol-1-yl propan-1-ol (2.11 g) obtained in the previous step and triphenylphosphine (1.492 g) were mixed with tetrahydrofuran (38 ml). Under ice-cooling, diisopropyl azodicarboxylate (1.224 g) was added dropwise, and the mixture 15 was stirred at room temperature for 1 hr. The reaction mixture was purified by silica gel column chromatography (ethyl acetate:methanol=2:98 to 60:40) to give the title compound (1.74 g).

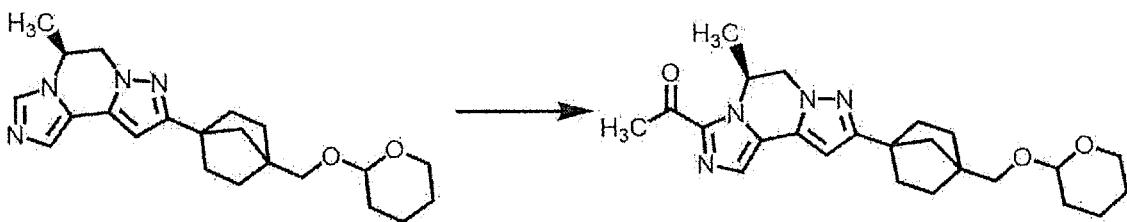
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.39 - 2.06 (m, 19H), 3.42 (d, J=9.94Hz, 1H), 3.45 - 3.53 (m, 1H), 3.80 - 3.91 (m, 2H), 4.08 (dd, J=12.95, 8.21Hz, 1H), 4.44 (dd, J=12.95, 4.39Hz, 1H), 4.53 - 4.64 (m, 2H), 6.27 (s, 1H), 7.25 (s, 1H), 7.59 (s, 1H)

[0448]

Step 12

25 1-((5S)-5-methyl-9-((4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptan-1-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)ethan-1-one

[0449]



[0450]

(5S)-5-Methyl-9-((4-tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptan-1-yl)-5,6-

5 dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazine (1.74 g) obtained in the previous step was mixed with tetrahydrofuran (17.4 ml). The mixture was cooled to -78°C, and 2 M lithium diisopropylamide/tetrahydrofuran-heptane-ethylbenzene solution (2.274 ml) was added dropwise. The mixture was stirred at - 10 78°C for 30 min. To the mixture was added N-methoxy-N-methylacetamide (1.115 ml), and the mixture was stirred at - 78°C for 30 min. To the mixture was added dropwise 2 M lithium diisopropylamide/tetrahydrofuran-heptane-ethylbenzene solution (2.274 ml), and the mixture was stirred at -78°C for 1 hr. To 15 the reaction mixture was added saturated ammonium chloride aqueous solution, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was 20 concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=12:88 to ethyl acetate, thereafter ethyl acetate:methanol=60:40) to give the title compound (1.4 g).

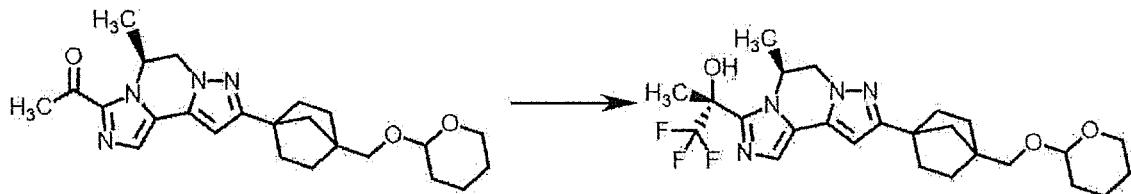
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.38 (d, J=6.70Hz, 3H), 1.41 - 1.92 (m, 14H), 1.92 - 2.05 (m, 2H), 2.67 (s, 3H), 3.42 (d, J=9.94Hz, 1H), 3.46 - 3.54 (m, 1H), 3.80 - 3.91 (m, 2H), 4.34 (d, J=3.01Hz, 2H), 4.57 - 4.64 (m, 1H), 5.74 - 5.86 (m, 1H), 6.39 (s, 1H), 7.33 (s, 1H)

[0451]

30 Step 13

(2R)-1,1,1-trifluoro-2-((5S)-5-methyl-9-((4-tetrahydro-2H-

pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptan-1-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)propan-2-ol  
[0452]



5 [0453]

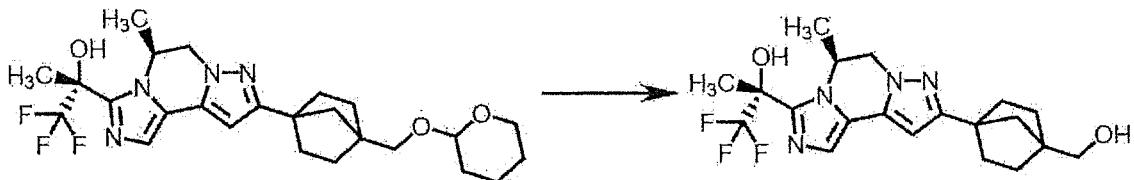
1-((5S)-5-Methyl-9-(4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptan-1-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)ethan-1-one (1.4 g) obtained in the previous step was azeotroped with toluene, and mixed with N,N-dimethylacetamide (6.55 ml). Under ice-cooling, to the mixture were added lithium acetate (0.061 g) and trifluoromethyltrimethylsilane (0.686 ml), and the mixture was stirred for 30 min. Under ice-cooling, methanol (0.655 ml) and potassium carbonate (0.512 g) were added, and the mixture was stirred at room temperature for 1 hr. To the reaction mixture was added water, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=12:88 to ethyl acetate) to give the title compound (1.32 g).

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.36 (d, J=6.70Hz, 3H), 1.41 - 2.04 (m, 19H), 3.15 (s, 1H), 3.42 (d, J=9.94Hz, 1H), 3.45 - 3.53 (m, 1H), 3.80 - 3.90 (m, 2H), 4.25 - 4.36 (m, 2H), 4.57 - 4.64 (m, 1H), 5.26 - 5.37 (m, 1H), 6.28 (s, 1H), 7.20 (s, 1H)

[0454]

Step 14  
30 (R)-1,1,1-trifluoro-2-((S)-9-(4-(hydroxymethyl)bicyclo[2.2.1]heptan-1-yl)-5-methyl-5,

dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)propan-2-ol  
[0455]



[0456]

5 (2R)-1,1,1-Trifluoro-2-((5S)-5-methyl-9-(4-((tetrahydro-  
2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.1]heptan-1-yl)-5,6-  
dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)propan-2-ol  
(650 mg) obtained in the previous step was mixed with methanol  
(6.5 ml). To the mixture was added 10-camphorsulfonic acid  
10 (153 mg), and the mixture was stirred at room temperature for  
3 hr. To the reaction mixture was added saturated aqueous  
sodium hydrogen carbonate solution, and the mixture was  
extracted twice with ethyl acetate. The organic layer was  
washed with saturated aqueous sodium chloride solution, and  
15 dried over sodium sulfate. Sodium sulfate was filtered off,  
and the filtrate was concentrated under reduced pressure. The  
obtained residue was purified by silica gel column  
chromatography (ethyl acetate:hexane=24:76 to ethyl acetate,  
thereafter ethyl acetate:methanol=90:10) to give the title  
20 compound (520 mg).

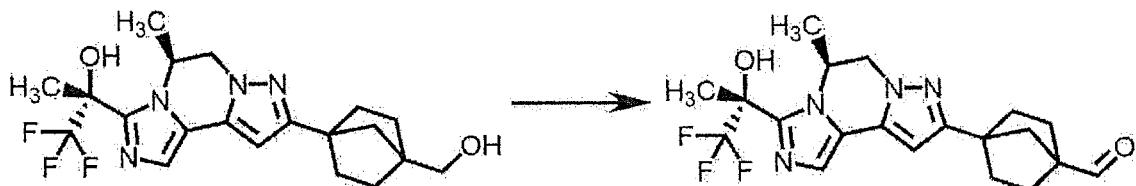
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.23 (d, J=6.47Hz, 3H), 1.25 - 1.36  
(m, 2H), 1.46 (s, 2H), 1.57 - 1.72 (m, 4H), 1.80 (s, 3H), 1.83  
- 1.95 (m, 2H), 3.47 (d, J=5.32Hz, 2H), 4.21 (dd, J=13.52,  
4.05Hz, 1H), 4.33 (d, J=13.52Hz, 1H), 4.42 (t, J=5.32Hz, 1H),  
25 5.24 - 5.38 (m, 1H), 6.37 (s, 1H), 7.21 (s, 1H), 7.23 (s, 1H)

[0457]

Step 15

4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-  
5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-  
30 yl)bicyclo[2.2.1]heptane-1-carbaldehyde

[0458]



[0459]

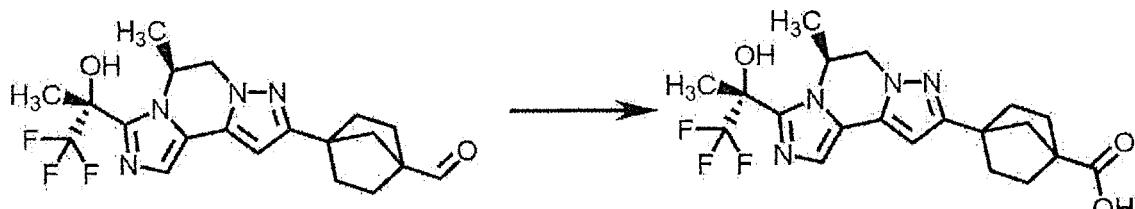
(R)-1,1,1-Trifluoro-2-((S)-9-(4-hydroxymethyl)bicyclo[2.2.1]heptan-1-yl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)propan-2-ol (250 mg) obtained in the previous step was mixed with chloroform (2.363 ml)-acetonitrile (2.363 ml). Under ice-cooling, Dess-Martin periodinane (293 mg) was added, and the mixture was stirred at room temperature overnight. To the reaction mixture were added 5% sodium thiosulfate aqueous solution and saturated aqueous sodium hydrogen carbonate solution, and the mixture was stirred at room temperature for 1 hr, and extracted twice with ethyl acetate. The organic layer was washed successively with 10% potassium carbonate aqueous solution, saturated aqueous sodium hydrogen carbonate solution, and saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give a crude product (239 mg) of the title compound.

[0460]

Step 16

4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)bicyclo[2.2.1]heptane-1-carboxylic acid

[0461]



[0462]

The crude product (239 mg) of 4-((S)-5-methyl-3-((R)-

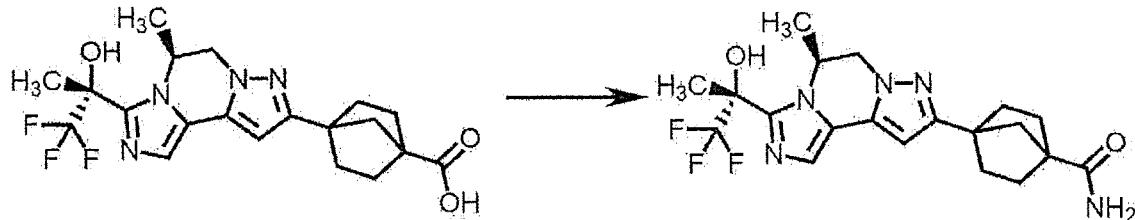
1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)bicyclo[2.2.1]heptane-1-carbaldehyde obtained in the previous step was mixed with tert-butanol (1.882 ml) and water (0.941 ml). To the mixture 5 were added 2-methyl-2-butene (0.61 ml), sodium dihydrogen phosphate (449 mg), and sodium chlorite (195 mg), and the mixture was stirred at room temperature for 2 hr. To the reaction mixture was added 5% sodium thiosulfate aqueous solution, and the mixture was stirred at room temperature for 10 30 min. The mixture was purified by reversed-phase silica gel chromatography (acetonitrile:water=5:95 to acetonitrile). To the obtained crude product was added water, the pH was adjusted to 6 to 7 with 1N aqueous hydrochloric acid solution, and the mixture was extracted three times with ethyl acetate. 15 The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give a crude product (295 mg) of the title compound.

20 [0463]

Step 17

4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)bicyclo[2.2.1]heptane-1-carboxamide

25 [0464]



[0465]

The crude product (295 mg) of 4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)bicyclo[2.2.1]heptane-1-

carboxylic acid obtained in the previous step was mixed with DMF (2.445 ml). Under ice-cooling, 7 M ammonia/methanol solution (0.247 ml) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (329 mg) were added, and the mixture was stirred at room temperature for 3 hr. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. Sodium chloride was added to the aqueous layer, and the mixture was extracted three times with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:methanol=99:1 to 60:40) to give the title compound (302.1 mg).

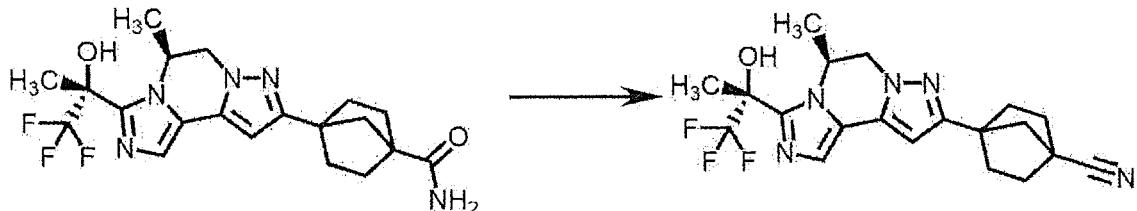
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.36 (d, J=6.70Hz, 3H), 1.76 - 1.89 (m, 4H), 1.95 - 2.00 (m, 5H), 2.04 - 2.10 (m, 4H), 3.71 - 3.82 (m, 1H), 4.26 - 4.37 (m, 2H), 5.29 - 5.43 (m, 2H), 5.59 (brs, 1H), 6.27 (s, 1H), 7.22 (s, 1H)

20 [0466]

Step 18

4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)bicyclo[2.2.1]heptane-1-carbonitrile

25 [0467]



[0468]

4-((S)-5-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)bicyclo[2.2.1]heptane-1-carboxamide (100 mg) obtained in the previous step was mixed with tetrahydrofuran (0.75 ml).

Under ice-cooling, triethylamine (0.123 ml) and trifluoroacetic anhydride (0.0375 ml) were added, and the mixture was stirred for 1 hr. Under ice-cooling, to the reaction mixture was added trifluoroacetic anhydride (0.025 ml), and the mixture was stirred for 30 min. At room temperature, to the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted twice with ethyl acetate. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=12:88 to ethyl acetate) to give the title compound (61.6 mg).

<sup>15</sup> <sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.22 (d, J=6.47Hz, 3H), 1.64 - 1.74 (m, 2H), 1.80 (s, 3H), 1.83 - 1.92 (m, 2H), 1.92 - 2.10 (m, 6H), 4.23 (dd, J=13.41, 3.93Hz, 1H), 4.35 (d, J=13.41Hz, 1H), 5.27 - 5.39 (m, 1H), 6.45 (s, 1H), 7.23 (s, 1H), 7.25 (s, 1H)  
[0469]

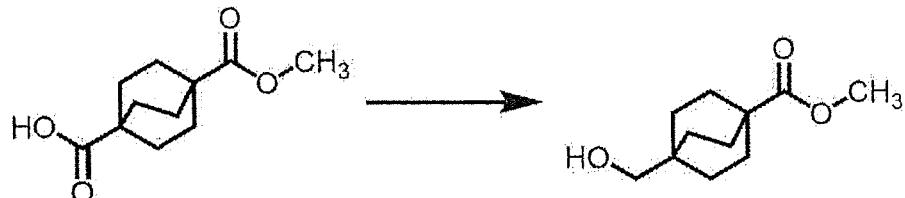
<sup>20</sup> Production Example 7

Synthesis of 4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)bicyclo[2.2.2]octane-1-carbonitrile (Example 71)

<sup>25</sup> [0470]

Step 1

methyl 4-(hydroxymethyl)bicyclo[2.2.2]octane-1-carboxylate  
[0471]



<sup>30</sup> [0472]

4-(Methoxycarbonyl)bicyclo[2.2.2]octane-1-carboxylic acid

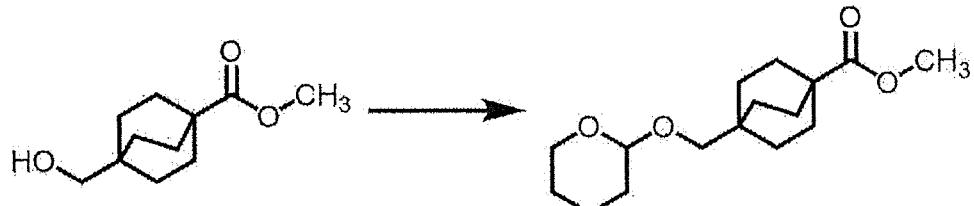
(3 g) was mixed with THF (45 ml). The reaction solution was cooled at 0°C, and 0.89 M borane-THF complex THF solution (15.88 ml) was added dropwise. The reaction mixture was stirred at room temperature for 2 hr. The reaction solution 5 was cooled to 0°C, and saturated aqueous sodium hydrogen carbonate solution was added dropwise. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and sodium sulfate was added. Sodium sulfate was filtered off, and the 10 filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0 to 0:100) to give the title compound (2.8 g).

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.23 (t, J=5.60Hz, 1H), 1.41 - 1.48 (m, 6H), 1.76 - 1.83 (m, 6H), 3.29 (d, J=5.60Hz, 2H), 3.64 (s, 3H) [0473]

Step 2

methyl 4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.2]octane-1-carboxylate

20 [0474]



21 [0475]

Methyl 4-(hydroxymethyl)bicyclo[2.2.2]octane-1-carboxylate (2.12 g) obtained in the previous step was mixed 25 with acetonitrile (30 ml). At room temperature, 3,4-dihydro-2H-pyran (1.075 ml) and pyridinium p-toluenesulfonate (0.537 g) were added, and the mixture was stirred at room temperature for 18 hr. The reaction mixture was added to silica gel (10 g) and eluted with ethyl acetate. The obtained residue was 30 purified by silica gel column chromatography (hexane:ethyl acetate=100:0 to 0:100) to give the title compound (2.86 g).

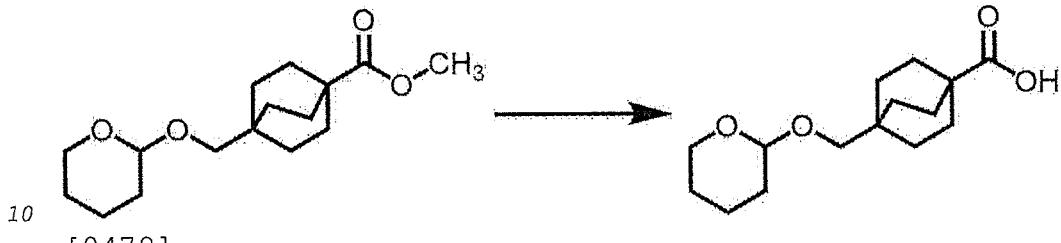
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.38 - 1.45 (m, 10H), 1.54 - 1.61 (m, 1H), 1.64 - 1.71 (m, 7H), 2.89 - 2.93 (m, 1H), 3.26 - 3.29 (m, 1H), 3.36 - 3.41 (m, 1H), 3.55 (s, 3H), 3.64 - 3.70 (m, 1H), 4.48 - 4.45 (m, 1H)

5 [0476]

Step 3

4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.2]octane-1-carboxylic acid

[0477]



[0478]

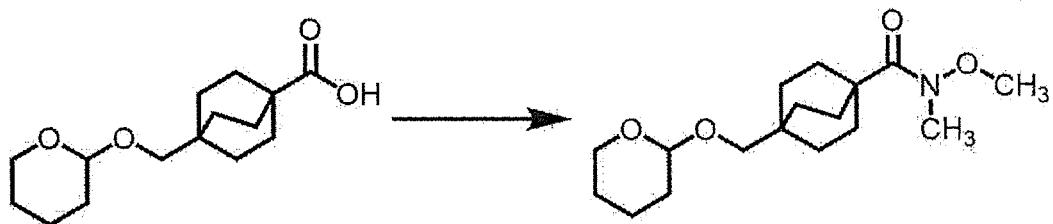
Methyl 4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.2]octane-1-carboxylate (3.28 g) was mixed with ethanol (32.8 ml). 2N Sodium hydroxide aqueous solution (6.97 ml) was added, and the mixture was stirred at 60°C for 18 hr. The reaction mixture was stirred at 70°C for 2 hr. To the reaction mixture was added 2N sodium hydroxide aqueous solution (3 ml), and the mixture was stirred at 70°C for 3 hr. The reaction mixture was stirred at 80°C for 5 hr. At room temperature, 2N hydrogen chloride solution (9.97 ml) was added, and the mixture was concentrated under reduced pressure. The obtained residue was extracted with ethyl acetate, and the organic layer was washed with saturated aqueous sodium chloride solution, and sodium sulfate was added. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give a crude product (3.12 g) of the title compound.

[0479]

Step 4

30 N-methoxy-N-methyl-4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.2]octane-1-carboxamide

[0480]



[0481]

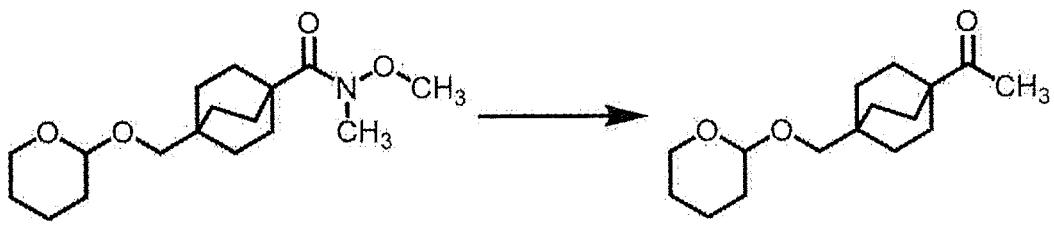
4-(((Tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.2]octane-1-carboxylic acid (3.02 g) obtained in the previous step was mixed with pyridine (30.2 ml). To the mixture were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.59 g) and N,O-dimethylhydroxylamine hydrochloride (1.317 g). The reaction mixture was stirred at room temperature for 18 hr. To the mixture were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (2.59 g) and N,O-dimethylhydroxylamine hydrochloride (1.317 g), and the mixture was stirred at 60°C for 2 hr. At room temperature, silica gel (50 g) and ethyl acetate were added to the reaction mixture, and silica gel was filtered off. The filtrate was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0 to 0:100) to give the title compound (3.2 g).  
1H-NMR (400 MHz, CDCl<sub>3</sub>) 1.42 - 1.57 (m, 10H), 1.62 - 1.73 (m, 1H), 1.78 - 1.92 (m, 7H), 2.92 - 2.97 (m, 1H), 3.14 (s, 3H), 3.39 - 3.43 (m, 1H), 3.44 - 3.50 (m, 1H), 3.64 (s, 3H), 3.77 - 3.86 (m, 1H), 4.53 - 4.49 (m, 1H)

[0482]

Step 5

1-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.2]octan-1-yl)ethan-1-one

[0483]



[0484]

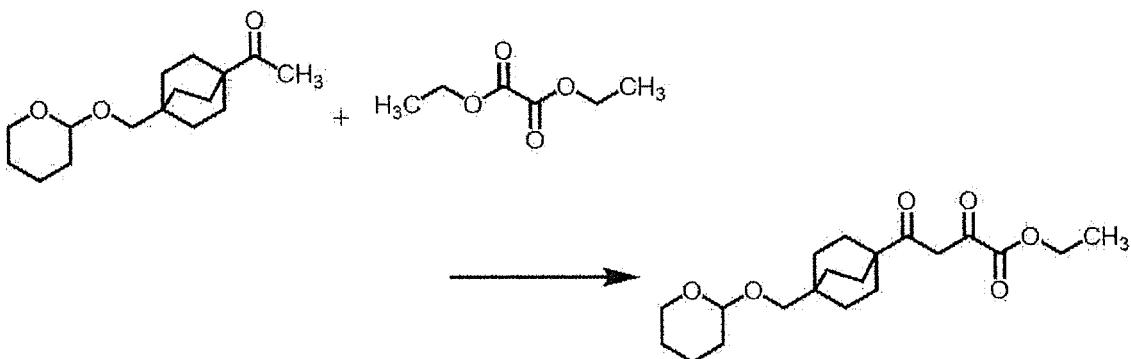
Under an argon atmosphere, N-methoxy-N-methyl-4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.2]octane-1-carboxamide (3.2 g) obtained in the previous step was mixed with tetrahydrofuran (32 ml). The mixture was ice-cooled, 1.04 M methylmagnesium bromide/tetrahydrofuran solution (11.86 ml) was added dropwise, and the mixture was stirred for 1 hr. To the reaction mixture was added saturated ammonium chloride aqueous solution. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and sodium sulfate was added. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0 to 0:100) to give the title compound (1.26 g).  
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.47 - 1.56 (m, 10H), 1.64 - 1.74 (m, 7H), 1.77 - 1.84 (m, 1H), 2.07 (s, 3H), 2.92 - 2.98 (m, 1H), 3.40 - 3.44 (m, 1H), 3.44 - 3.51 (m, 1H), 3.78 - 3.83 (m, 1H), 4.52 - 4.49 (m, 1H)

[0485]

Step 6

ethyl 2,4-dioxo-4-((4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.2]octan-1-yl)butanoate

25 [0486]



[0487]

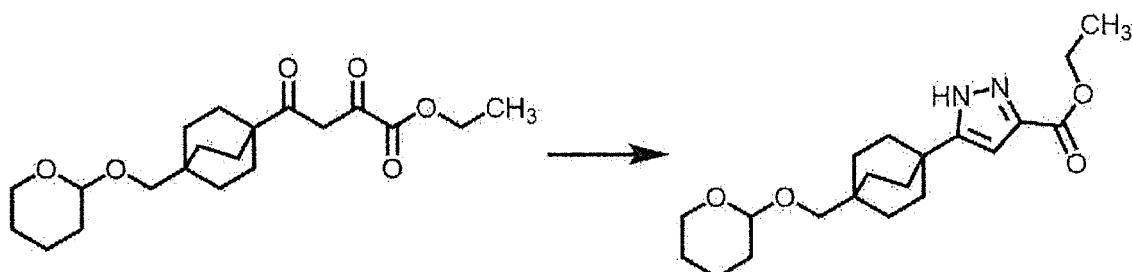
1-(4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.2]octan-1-one (1.26 g) obtained in the previous step was mixed with tetrahydrofuran (12.6 ml). To the mixture was added diethyl oxalate (0.768 ml). The mixture was ice-cooled, 1 M potassium-tert-butoxide/tetrahydrofuran solution (5.68 ml) was added dropwise, and the mixture was stirred for 2 hr. To the reaction mixture was added 1N hydrogen chloride solution (5.68 ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and sodium sulfate was added. Sodium sulfate was filtered off. The filtrate was concentrated under reduced pressure to give a crude product (1.733 g) of the title compound.

[0488]

Step 7

ethyl 5-((4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.2]octan-1-yl)-1H-pyrazole-3-carboxylate

[0489]



[0490]

Ethyl 2,4-dioxo-4-((4-((tetrahydro-2H-pyran-2-

yl)oxy)methyl)bicyclo[2.2.2]octan-1-yl)butanoate (1.73 g) obtained in the previous step was mixed with ethanol (17.3 ml). Under ice-cooling, hydrazine monohydrate (0.241 ml) was added. The mixture was stirred at room temperature for 15 hr. The 5 reaction mixture was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0 to 0:100) to give the title compound (1.53 g).

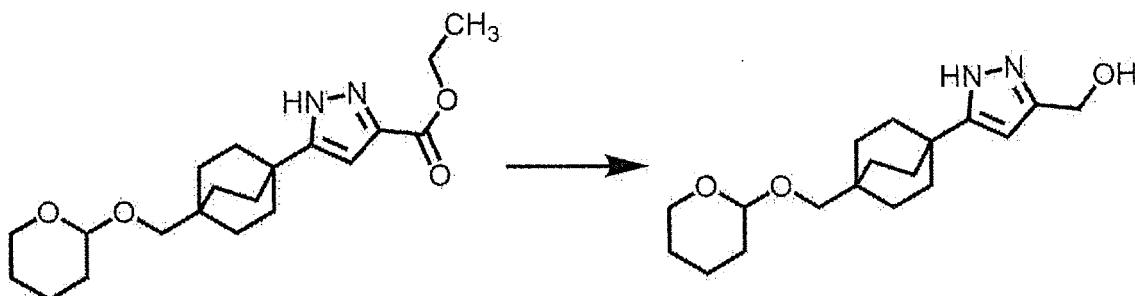
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.25 (t, J=7.05Hz, 3H), 1.41 - 1.79 10 (m, 18H), 2.92 - 2.97 (m, 1H), 3.31 - 3.34 (m, 1H), 3.37 - 3.43 (m, 1H), 3.65 - 3.73 (m, 1H), 4.22 (q, J=7.05Hz, 2H), 4.49 (s, 1H), 6.39 (s, 1H), 13.12 (brs, 1H)

[0491]

Step 8

15 (5-((4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.2]octan-1-yl)-1H-pyrazol-3-yl)methanol

[0492]



20 [0493]

Under an argon atmosphere, lithium aluminum hydride (0.129 g) was mixed with tetrahydrofuran (12.45 ml). The mixture was ice-cooled, and a solution of ethyl 5-((4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.2]octan-1-yl)-1H-pyrazole-3-carboxylate (0.615 g) obtained in the 25 previous step in tetrahydrofuran (6 ml) was added dropwise. The mixture was stirred for 150 min, and saturated potassium sodium tartrate aqueous solution was added dropwise to the reaction mixture. After stirring at room temperature for 1 hr,

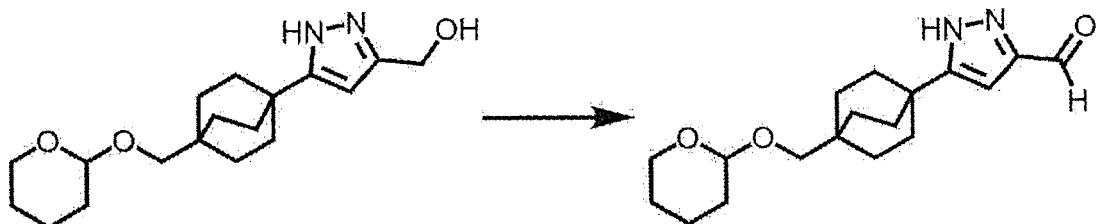
the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and sodium sulfate was added. Sodium sulfate was filtered off, and the filtrate was concentrated 5 under reduced pressure to give a crude product (0.544 g) of the title compound.

[0494]

Step 9

5-(4-(((tetrahydro-2H-pyran-2-  
10 yl)oxy)methyl)bicyclo[2.2.2]octan-1-yl)-1H-pyrazole-3-  
carbaldehyde

[0495]



[0496]

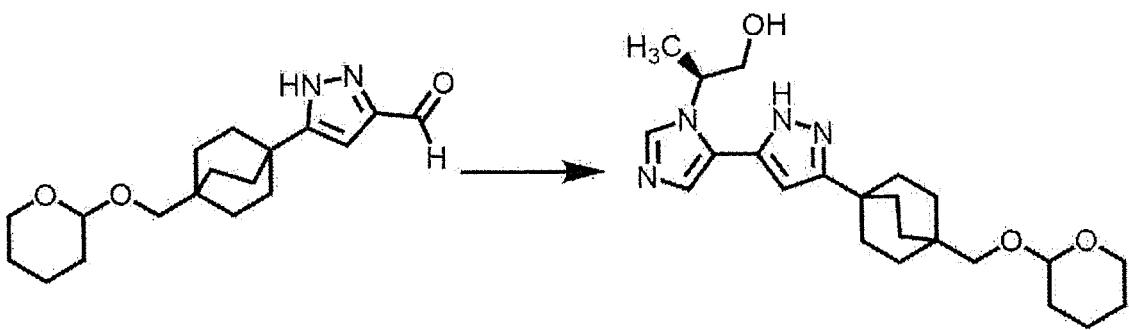
15 (5-(4-(((Tetrahydro-2H-pyran-2-  
yl)oxy)methyl)bicyclo[2.2.2]octan-1-yl)-1H-pyrazol-3-  
yl)methanol (0.632 g) was mixed with 1,2-dimethoxyethane (20  
ml). Manganese dioxide (1.58 g) was added, and the mixture was  
stirred at room temperature for 16 hr. The reaction mixture  
20 was filtered through celite, and the filtrate was concentrated  
under reduced pressure to give a crude product (0.582 g) of  
the title compound.

[0497]

Step 10

25 (2S)-2-(5-(3-(4-(((tetrahydro-2H-pyran-2-  
yl)oxy)methyl)bicyclo[2.2.2]octan-1-yl)-1H-pyrazol-5-yl)-1H-  
imidazol-1-yl)propan-1-ol

[0498]



[0499]

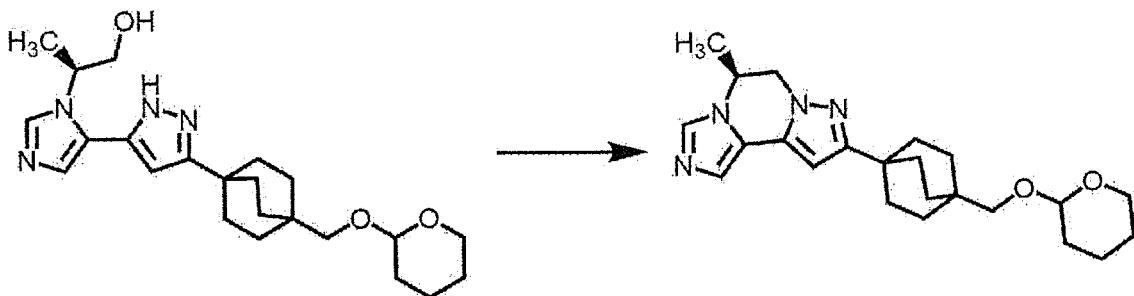
5-((4-((4-tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.2]octan-1-yl)-1H-pyrazole-3-carbaldehyde (0.582 g) obtained in the previous step was mixed with DMF (5 ml). At room temperature, (S)-2-aminopropan-1-ol (0.144 g) was added, and the mixture was stirred at room temperature for 20 hr. p-Toluenesulfonylmethyl isocyanide (0.430 g) and potassium carbonate (0.505 g) were added, and the mixture was stirred at room temperature for 43 hr. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure. To the obtained residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=25:75 to ethyl acetate, thereafter ethyl acetate:methanol=60:40) to give a crude product (0.458 g) of the title compound.

[0500]

Step 11

(5S)-5-methyl-9-((4-((4-tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.2]octan-1-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazine

[0501]



[0502]

(2S)-2-(5-(3-(4-((Tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.2]octan-1-yl)-1H-pyrazol-5-yl)-1H-imidazol-1-yl propan-1-ol (0.458 g) obtained in the previous step was mixed with tetrahydrofuran (9.16 ml). At room temperature, triphenylphosphine (0.348 g) and diisopropyl azodicarboxylate (0.285 ml) were added, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=25:75 to ethyl acetate, thereafter ethyl acetate:methanol=60:40) to give the title compound (0.43 g).

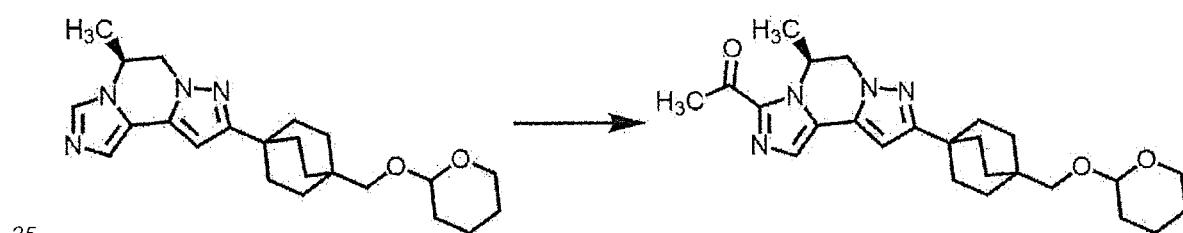
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.39 - 1.53 (m, 13H), 1.56 - 1.66 (m, 1H), 1.69 - 1.81 (m, 7H), 2.92 - 2.97 (m, 1H), 3.30 - 3.34 (m, 1H), 3.37 - 3.46 (m, 1H), 3.65 - 3.75 (m, 1H), 4.00 - 4.07 (m, 1H), 4.37 - 4.44 (m, 1H), 4.47 - 4.50 (m, 1H), 4.64 (s, 1H), 6.29 (s, 1H), 7.21 (s, 1H), 7.85 (s, 1H)

[0503]

20 Step 12

1-((5S)-5-methyl-9-(4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.2]octan-1-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)ethan-1-one

[0504]



[0505]

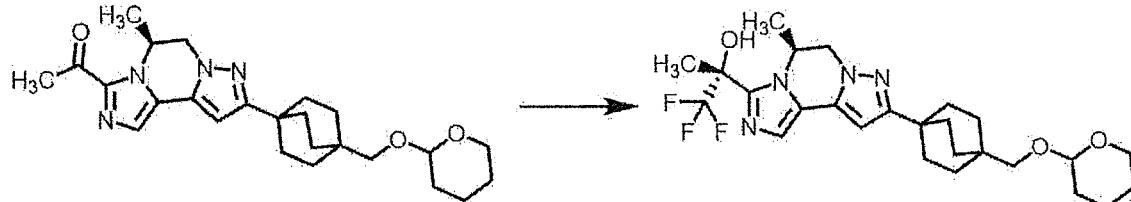
(5S)-5-Methyl-9-((4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.2]octan-1-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazine (0.43 g) obtained in the previous step was mixed with tetrahydrofuran (8.66 ml). Under cooling in an acetone-dry ice bath, 2 M lithium diisopropylamide/tetrahydrofuran solution (0.515 ml) was added dropwise, and the mixture was stirred for 1 hr. To the mixture was added N-methoxy-N-methylacetamide (0.286 ml), and the mixture was stirred for 1 hr. To the mixture was added dropwise 2 M lithium diisopropylamide/tetrahydrofuran solution (0.596 ml), and the mixture was stirred for 1 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and sodium sulfate was added. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0 to 0:100) to give the title compound (0.338 g).  
1H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.22 (d, J=6.70Hz, 3H), 1.41 - 1.53 (m, 10H), 1.56 - 1.62 (m, 1H), 1.68 - 1.83 (m, 7H), 2.56 (s, 3H), 2.92 - 2.98 (m, 1H), 3.30 - 3.35 (m, 1H), 3.38 - 3.44 (m, 1H), 3.66 - 3.73 (m, 1H), 4.34 - 4.37 (m, 2H), 4.52 - 4.48 (m, 1H), 5.59 - 5.62 (m, 1H), 6.52 (s, 1H), 7.47 (s, 1H)

[0506]

Step 13

(2R)-1,1,1-trifluoro-2-((5S)-5-methyl-9-((4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.2]octan-1-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)propan-2-ol

[0507]



[0508]

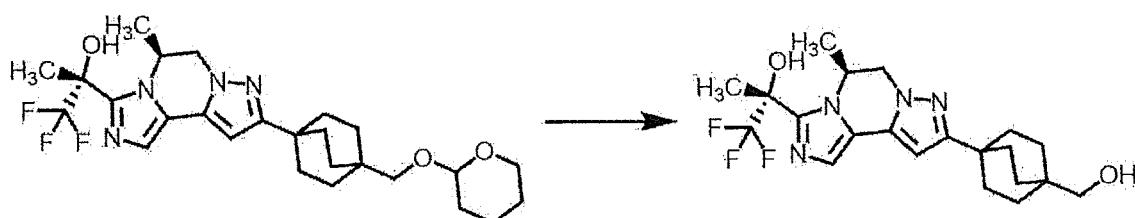
1-((5S)-5-Methyl-9-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.2]octan-1-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)ethan-1-one (0.43 g) was mixed with tetrahydrofuran (4 ml). Under ice-cooling, to the mixture was added cesium fluoride (0.023 g), and (trifluoromethyl)trimethylsilane (0.228 ml) was added dropwise. The reaction mixture was stirred at room temperature for 1 hr. Under ice-cooling, methanol (2 ml) and potassium carbonate (0.138 g) were added, and the mixture was stirred at room temperature for 16 hr. Water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0 to 0:100) to give a crude product (0.287 g) of the title compound.

[0509]

20 Step 14

(R)-1,1,1-trifluoro-2-((S)-9-(4-(hydroxymethyl)bicyclo[2.2.2]octan-1-yl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)propan-2-ol

[0510]



25

[0511]

(2R)-1,1,1-Trifluoro-2-((5S)-5-methyl-9-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.2.2]octan-1-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)propan-2-ol (0.287 g) obtained in the previous step was mixed with methanol (5 ml). 10-Camphorsulfonic acid (0.065 g) was added,

and the mixture was stirred at 70°C for 1 hr. The reaction mixture was added to silica gel (10 g), and eluted with ethyl acetate. The obtained solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0 to 0:100) to give the title compound (0.23 g).

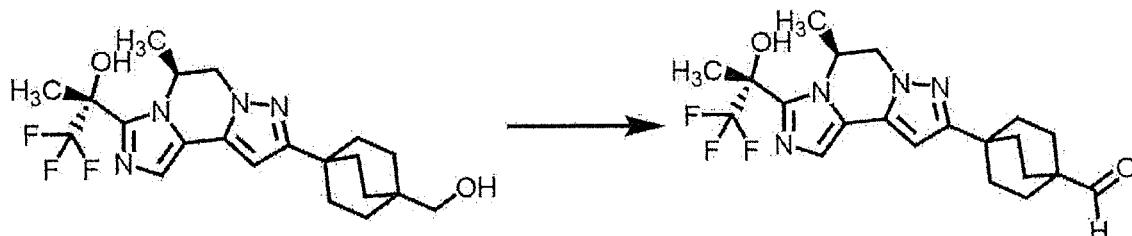
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.21 (d, J=6.47Hz, 3H), 1.37 - 1.44 (m, 6H), 1.72 - 1.78 (m, 7H), 1.80 (s, 3H), 3.05 (d, J=5.55Hz, 2H), 4.16 - 4.23 (m, 1H), 4.29 - 4.34 (m, 2H), 5.34 - 5.27 (m, 1H), 6.33 (s, 1H), 7.20 (s, 1H), 7.24 (s, 1H)

[0512]

Step 15

4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)bicyclo[2.2.2]octane-1-carbaldehyde

[0513]



[0514]

(R)-1,1,1-Trifluoro-2-((S)-9-(4-hydroxymethyl)bicyclo[2.2.2]octan-1-yl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)propan-2-ol (0.21 g) obtained in the previous step was mixed with chloroform (6 ml). Under ice-cooling, Dess-Martin periodinane (0.252 g) were added, and the mixture was stirred at room temperature for 16 hr. At room temperature, Dess-Martin periodinane (0.150 g) was added, and the mixture was stirred for 2 hr. Saturated sodium thiosulfate aqueous solution and saturated aqueous sodium hydrogen carbonate solution were added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium

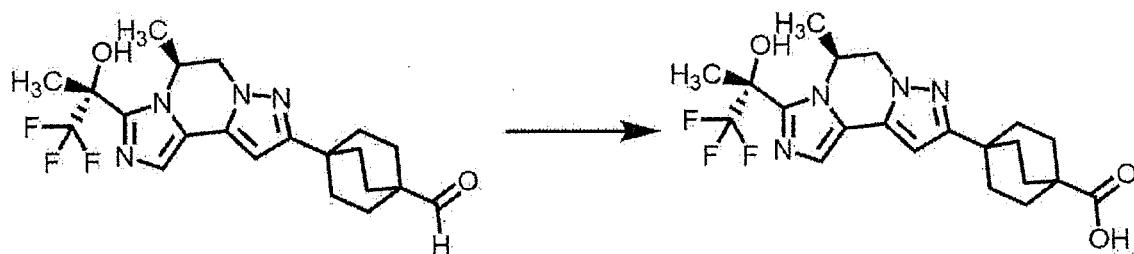
chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give a crude product (0.20 g) of the title compound.

5 [0515]

Step 16

4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)bicyclo[2.2.2]octane-1-carboxylic acid

10 [0516]



[0517]

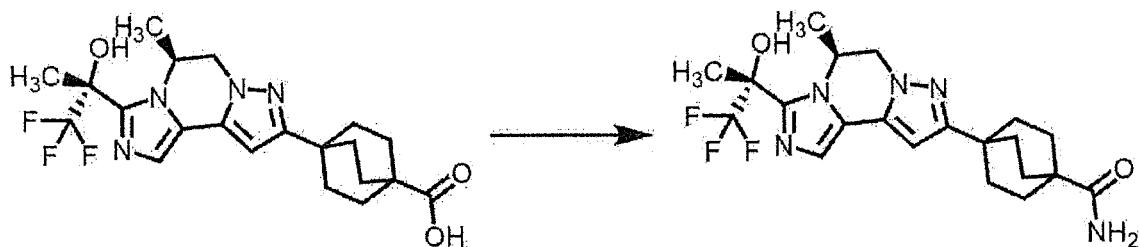
4-((S)-5-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)bicyclo[2.2.2]octane-1-carbaldehyde (0.2 g) obtained in the previous step was mixed with tert-butanol (6 ml) and water (3 ml). At room temperature, 2-methyl-2-butene (0.502 ml), disodium hydrogen phosphate (0.336 g), and sodium chlorite (0.128 g) were added, and the mixture was stirred for 17 hr. The reaction mixture was extracted with ethyl acetate. The aqueous layer was extracted twice with ethyl acetate. The organic layers were combined and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give a crude product (0.118 g) of the title compound.

[0518]

Step 17

4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)bicyclo[2.2.2]octane-1-carboxamide

[0519]



[0520]

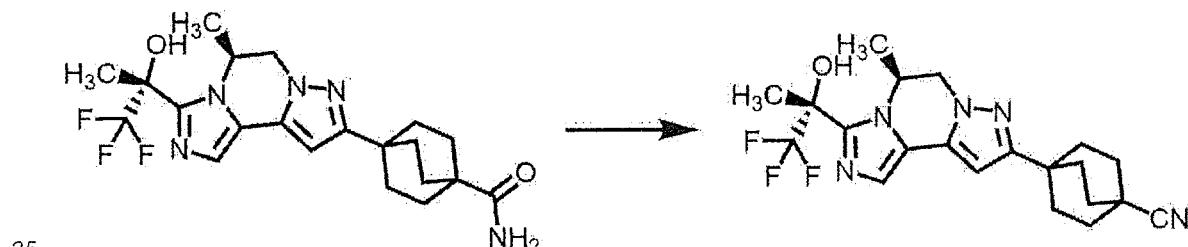
4-((S)-5-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)bicyclo[2.2.2]octane-1-carboxylic acid (0.03 g) obtained in the previous step was mixed with DMF (2 ml). At room temperature, 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (0.039 g) and 7 M ammonia/methanol solution (0.029 ml) were added, and the mixture was stirred for 3 hr. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed twice with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0 to 0:100) to give a crude product (0.026 g).

[0521]

20 Step 18

4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)bicyclo[2.2.2]octane-1-carbonitrile

[0522]



25

[0523]

4-((S)-5-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)bicyclo[2.2.2]octane-1-carboxamide (0.026 g) obtained in the previous step was mixed with tetrahydrofuran (2 ml). Under 5 ice-cooling, triethylamine (0.041 ml) and trifluoroacetic anhydride (0.013 ml) were added, and the mixture was stirred for 1 hr. The reaction mixture was added to silica gel (10 g), and eluted with ethyl acetate. The obtained solution was concentrated under reduced pressure, and the residue was 10 purified by silica gel column chromatography (hexane:ethyl acetate=100:0 to 0:100) to give the title compound (0.018 g).  
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.22 (d, J=6.73Hz, 3H), 1.80 - 1.86 (m, 9H), 1.94 - 1.99 (m, 6H), 4.19 - 4.25 (m, 1H), 4.30 - 4.36 (m, 1H), 5.36 - 5.28 (m, 1H), 6.37 (s, 1H), 7.23 (s, 1H), 7.27 (s, 1H)

[0524]

#### Production Example 8

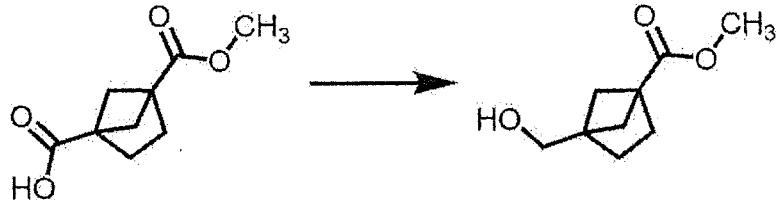
Synthesis of 4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)bicyclo[2.1.1]hexane-1-carbonitrile (Example 20 91)

[0525]

#### Step 1

methyl 4-(hydroxymethyl)bicyclo[2.1.1]hexane-1-carboxylate

25 [0526]



[0527]

4-(Methoxycarbonyl)bicyclo[2.1.1]hexane-1-carboxylic acid (1.1 g) was mixed with THF (11 ml). Under ice-cooling, to the 30 mixture was added dropwise 0.89 M borane-THF complex/THF solution (7.38 ml), and the mixture was stirred for 10 min.

The reaction mixture was warmed to room temperature and stirred for 2 hr. Under ice-cooling, to the reaction mixture was added dropwise saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=24:76 to ethyl acetate) to give the title compound (835.8 mg).

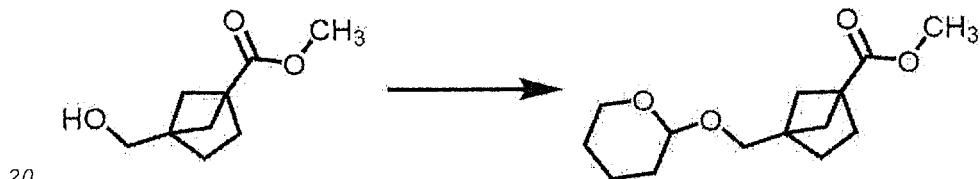
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.29 (t, J=5.09Hz, 1H), 1.37 - 1.45 (m, 2H), 1.62 - 1.69 (m, 2H), 1.75 - 1.84 (m, 2H), 1.93 - 2.00 (m, 2H), 3.68 (s, 3H), 3.71 (d, J=5.09Hz, 2H)

15 [0528]

Step 2

methyl 4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexane-1-carboxylate

[0529]



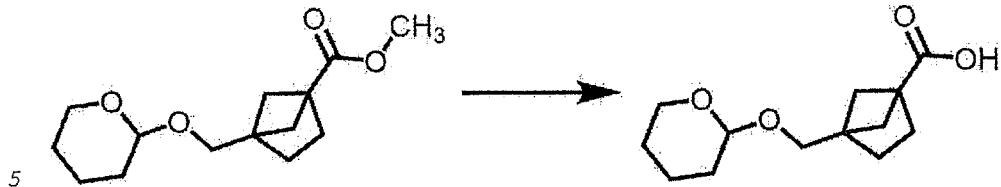
[0530]

Methyl 4-(hydroxymethyl)bicyclo[2.1.1]hexane-1-carboxylate (835.8 mg) obtained in the previous step was mixed with acetonitrile (7.857 ml). At room temperature, pyridinium 25 p-toluenesulfonate (232 mg) and 3,4-dihydro-2H-pyran (466 mg) were added, and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=5:95 to 36:64) to give a mixture (1.2375 g) containing the title compound.

30 [0531]

Step 3

4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexane-1-carboxylic acid  
[0532]



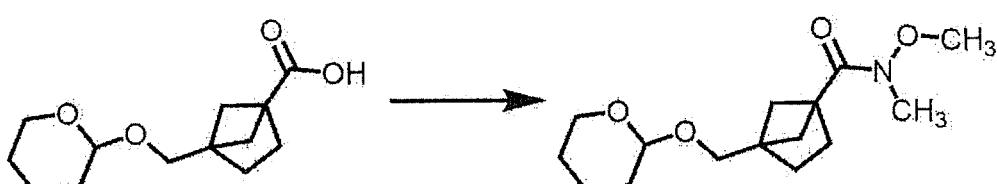
[0533]

The mixture (1.2375 g) containing methyl 4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexane-1-carboxylate obtained in the previous step was mixed with methanol (5.87 ml)-tetrahydrofuran (5.87 ml). 2N Sodium hydroxide aqueous solution (2.77 ml) was added, and the mixture was stirred at room temperature for 1.5 hr. To the reaction mixture was added 2N sodium hydroxide aqueous solution (2.77 ml), and the mixture was stirred at 80°C for 3 hr. After cooling to room temperature, 2N aqueous hydrochloric acid solution (5.54 ml) was added, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give a crude product (1.25 g) of the title compound.

[0534]

Step 4

N-methoxy-N-methyl-4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexane-1-carboxamide  
[0535]



[0536]

The crude product (1.25 g) of 4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexane-1-carboxylic acid obtained in the previous step and N,O-dimethylhydroxylamine hydrochloride (0.676 g) were mixed with pyridine (11.1 ml). To 5 the mixture was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.329 g), and the mixture was stirred at room temperature overnight. To the reaction mixture were added N,O-dimethylhydroxylamine hydrochloride (0.676 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.329 g), and 10 the mixture was stirred at room temperature for 3 hr. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with 1N aqueous hydrochloric acid solution, 15 saturated aqueous sodium hydrogen carbonate solution, and saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography 20 (ethyl acetate:hexane=12:88 to ethyl acetate) to give the title compound (1.17 g).

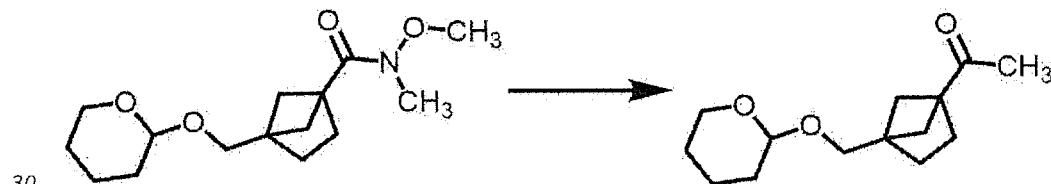
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.45 - 1.63 (m, 6H), 1.63 - 1.88 (m, 6H), 1.93 - 2.00 (m, 2H), 3.17 (s, 3H), 3.42 - 3.52 (m, 2H), 3.63 (s, 3H), 3.79 - 3.87 (m, 2H), 4.54 - 4.59 (m, 1H)

25 [0537]

Step 5

1-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexan-1-yl)ethan-1-one

[0538]



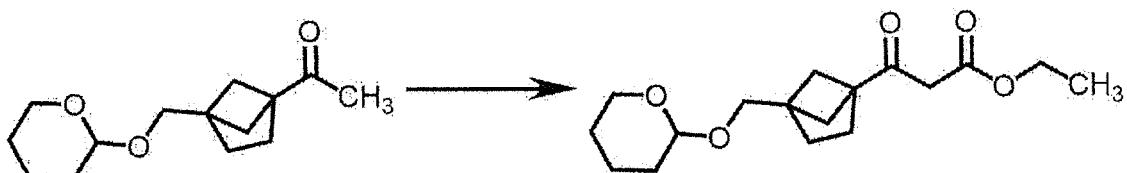
[0539]

N-Methoxy-N-methyl-4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexane-1-carboxamide (1.17 g) obtained in the previous step was mixed with toluene (57.8 ml). Under ice-cooling, 1.04 M methylmagnesium bromide/tetrahydrofuran solution (4.57 ml) was added dropwise, and the mixture was stirred for 30 min. Under ice-cooling, saturated ammonium chloride aqueous solution and water were added, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=12:88 to ethyl acetate) to give the title compound (0.741 g).

<sup>15</sup> <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.36 – 1.44 (m, 2H), 1.45 – 1.63 (m, 4H), 1.63 – 1.87 (m, 6H), 1.87 – 1.94 (m, 2H), 2.13 (s, 3H), 3.39 – 3.52 (m, 2H), 3.77 – 3.88 (m, 2H), 4.53 – 4.58 (m, 1H) [0540]

Step 6

<sup>20</sup> ethyl 2,4-dioxo-4-((4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexan-1-yl)butanoate [0541]



[0542]

<sup>25</sup> 1-(4-(((Tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexan-1-yl)ethan-1-one (741 mg) obtained in the previous step was mixed with tetrahydrofuran (7.41 ml). Under ice-cooling, to the mixture was added diethyl oxalate (500 mg), 1 M potassium tert-butoxide/tetrahydrofuran solution (3.731 ml) was added dropwise, and the mixture was stirred for 1 hr. To the reaction mixture were added 1 M

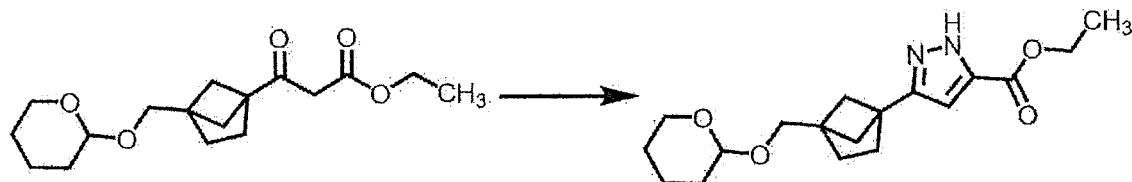
aqueous hydrochloric acid solution (3.731 ml), and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the 5 filtrate was concentrated under reduced pressure, and azeotroped with ethanol to give a crude product (1.069 g) of the title compound.

[0543]

Step 7

10 ethyl 3-((4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexan-1-yl)-1H-pyrazole-5-carboxylate

[0544]



15 [0545]

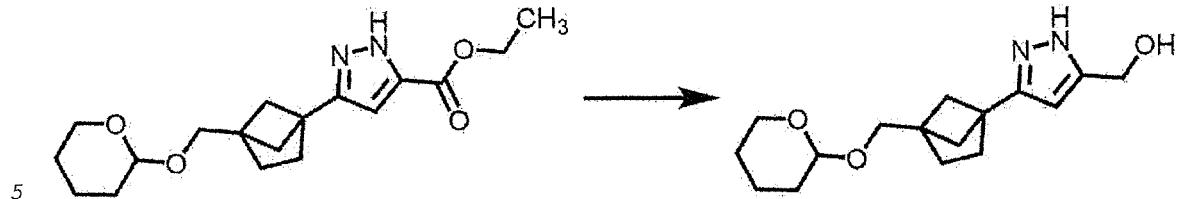
The crude product (1.069 g) of ethyl 2,4-dioxo-4-((4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexan-1-yl)butanoate obtained in the previous step and ethanol (10.52 ml) were mixed. Under ice-cooling, hydrazine monohydrate 20 (0.158 ml) was added dropwise, and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=12:88 to ethyl acetate) to give the title 25 compound (1.03 g).

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.37 (t, J=7.05Hz, 3H), 1.43 - 1.91 (m, 12H), 1.95 - 2.05 (m, 2H), 3.44 - 3.53 (m, 2H), 3.79 - 3.92 (m, 2H), 4.37 (q, J=7.05Hz, 2H), 4.56 - 4.61 (m, 1H), 6.65 (s, 1H), 10.23 (brs, 1H)

30 [0546]

Step 8

(3-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexan-1-yl)-1H-pyrazol-5-yl)methanol  
[0547]



[0548]

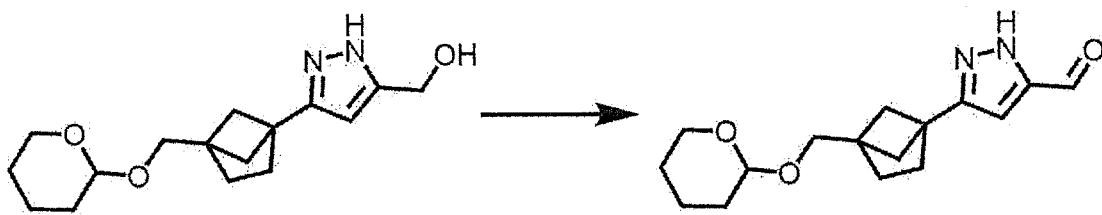
Ethyl 3-((4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexan-1-yl)-1H-pyrazole-5-carboxylate (1.03 g) obtained in the previous step was mixed with tetrahydrofuran (15.93 ml). Under ice-cooling, to the mixture was added dropwise 2 M lithium aluminum hydride/tetrahydrofuran solution (2.8 ml), and the mixture was stirred for 50 min. Under ice-cooling, to the reaction mixture was added saturated Rochelle salt aqueous solution, and the mixture was stirred at room temperature for 1 hr and extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give a crude product (0.819 g) of the title compound.

[0549]

Step 9

3-((4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexan-1-yl)-1H-pyrazole-5-carbaldehyde

[0550]



[0551]

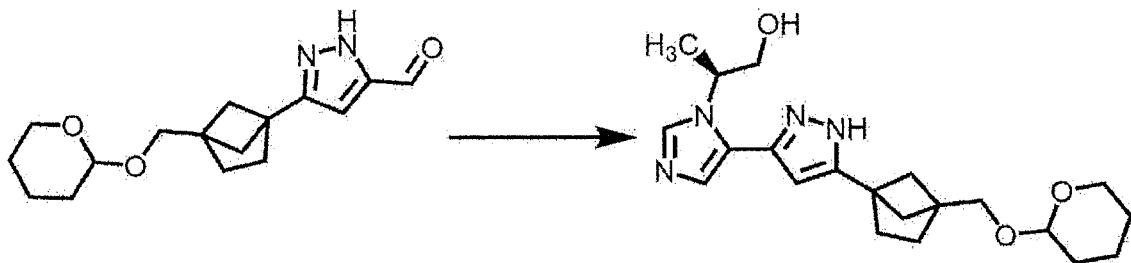
The crude product (0.819 g) of (3-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexan-1-yl)-1H-pyrazol-5-yl)methanol obtained in the previous step was mixed with 1,2-dimethoxyethane (24.56 ml). Manganese dioxide (2.456 g) was 5 added, and the mixture was stirred at room temperature overnight. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (0.7343 g) of the title compound.

[0552]

10 Step 10

(2S)-2-(5-(5-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexan-1-yl)-1H-pyrazol-3-yl)-1H-imidazol-1-yl)propan-1-ol

[0553]



[0554]

The crude product (734.3 mg) of 3-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexan-1-yl)-1H-pyrazole-5-carbaldehyde obtained in the previous step and (S)-2-aminopropan-1-ol (199 mg) were mixed with 1,2-dimethoxyethane (14.7 ml), and the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was concentrated under reduced pressure. To the obtained residue were successively added DMF (7.343 ml), potassium carbonate (1.049 g), and p-toluenesulfonylmethyl isocyanide (0.741 g), and the mixture 20 was stirred at room temperature for 4 days. At room temperature, water was added to the reaction mixture, and the mixture was extracted three times with ethyl acetate. The 25 organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium 30 chloride solution, and dried over sodium sulfate. Sodium

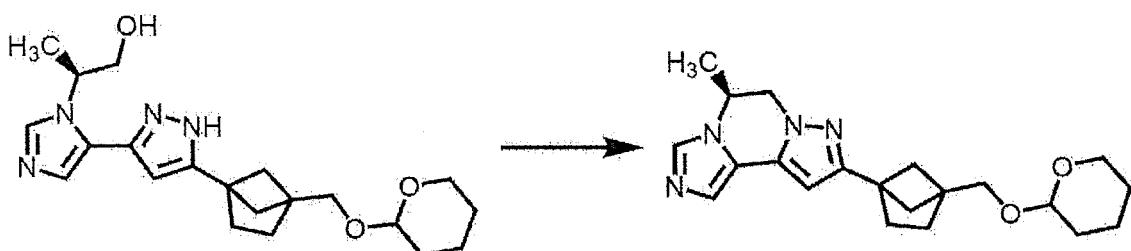
sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:methanol=2:98 to 50:50) to give a crude product (767.6 mg) of the title  
5 compound.

[0555]

Step 11

(5S)-5-methyl-9-((4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexan-1-yl)-5,6-  
10 dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazine

[0556]



[0557]

The crude product (767.6 mg) of (2S)-2-(5-(4-  
15 ((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexan-1-  
yl)-1H-pyrazol-3-yl)-1H-imidazol-1-yl)propan-1-ol obtained in  
the previous step and triphenylphosphine (569 mg) were mixed  
with tetrahydrofuran (15.352 ml). Under ice-cooling,  
diisopropyl azodicarboxylate (439 mg) was added dropwise, and  
20 the mixture was stirred at room temperature for 1 hr. Under  
ice-cooling, to the reaction mixture were added  
triphenylphosphine (142 mg) and diisopropyl azodicarboxylate  
(110 mg), and the mixture was stirred at room temperature for  
1 hr. The reaction mixture was purified by silica gel column  
25 chromatography (ethyl acetate:methanol=2:98 to 60:40) to give  
the title compound (620.1 mg).

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.43 - 1.78 (m, 12H), 1.78 - 1.91 (m,  
3H), 1.97 - 2.06 (m, 2H), 3.44 - 3.55 (m, 2H), 3.80 - 3.91 (m,  
2H), 4.09 (dd, J=13.06, 7.98Hz, 1H), 4.45 (dd, J=13.06, 4.51Hz,  
30 1H), 4.52 - 4.64 (m, 2H), 6.28 (s, 1H), 7.26 (s, 1H), 7.59 (s,

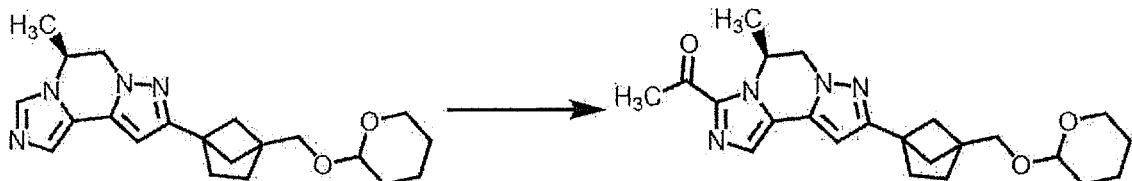
1H)

[0558]

Step 12

1-((5S)-5-methyl-9-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexan-1-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)ethan-1-one

[0559]



[0560]

10 (5S)-5-Methyl-9-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexan-1-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazine (620.1 mg) obtained in the previous step was mixed with tetrahydrofuran (12.402 ml). The mixture was cooled to -78°C, and 2 M lithium diisopropylamide/tetrahydrofuran-heptane-ethylbenzene solution (0.841 ml) was added dropwise. The reaction mixture was stirred at -78°C for 30 min. To the mixture was added N-methoxy-N-methylacetamide (0.412 ml), and the mixture was stirred at -78°C for 30 min. To the mixture was added dropwise 15 2 M lithium diisopropylamide/tetrahydrofuran-heptane-ethylbenzene solution (0.841 ml), and the mixture was stirred at -78°C for 1 hr. To the reaction mixture was added saturated ammonium chloride aqueous solution, and the mixture was extracted twice with ethyl acetate. The organic layer was 20 washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=16:84 to ethyl acetate, thereafter ethyl acetate:methanol=50:50) to give the title 25 compound (443 mg).

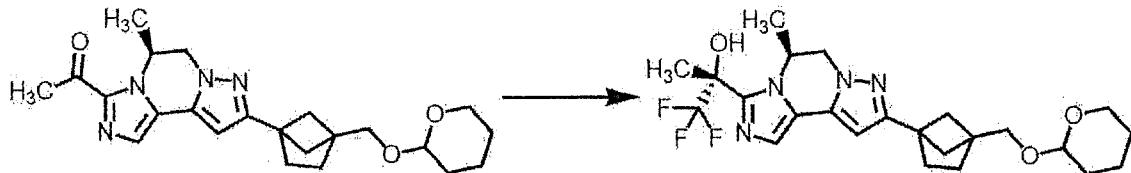
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.39 (d, J=6.94Hz, 3H), 1.46 - 1.92 (m, 12H), 1.99 - 2.07 (m, 2H), 2.68 (s, 3H), 3.46 - 3.54 (m, 2H), 3.82 - 3.91 (m, 2H), 4.31 - 4.40 (m, 2H), 4.58 - 4.63 (m, 1H), 5.75 - 5.86 (m, 1H), 6.41 (s, 1H), 7.34 (s, 1H)

5 [0561]

Step 13

(2R)-1,1,1-trifluoro-2-((5S)-5-methyl-9-(4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexan-1-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)propan-2-ol

10 [0562]



[0563]

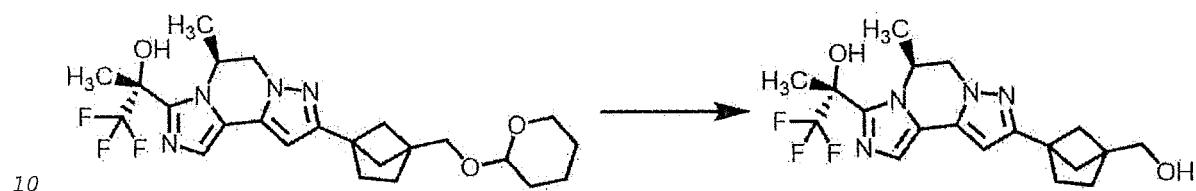
1-((5S)-5-Methyl-9-(4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexan-1-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)ethan-1-one (443 mg) obtained in the previous step and N,N-dimethylacetamide (1.994 ml) were mixed. Under ice-cooling, to the mixture were added lithium acetate (19.23 mg) and trifluoromethyltrimethylsilane (0.216 ml), and the mixture was stirred for 1 hr. Under ice-cooling, methanol (0.199 ml) and potassium carbonate (0.161 g) were added, and the mixture was stirred at room temperature for 1 hr. To the reaction mixture was added water, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=12:88 to ethyl acetate) to give the title compound (409.4 mg).

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.37 (d, J=5.98Hz, 3H), 1.45 - 1.94 (m,

12H), 1.96 - 2.08 (m, 5H), 3.11 (s, 1H), 3.45 - 3.57 (m, 2H),  
3.80 - 3.95 (m, 2H), 4.26 - 4.40 (m, 2H), 4.59 - 4.66 (m, 1H),  
5.28 - 5.39 (m, 1H), 6.31 (s, 1H), 7.23 (s, 1H)  
[0564]

5 Step 14

(R)-1,1,1-trifluoro-2-((S)-9-(4-  
(hydroxymethyl)bicyclo[2.1.1]hexan-1-yl)-5-methyl-5,6-  
dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)propan-2-ol  
[0565]



[0566]

(2R)-1,1,1-Trifluoro-2-((5S)-5-methyl-9-(4-((tetrahydro-  
2H-pyran-2-yl)oxy)methyl)bicyclo[2.1.1]hexan-1-yl)-5,6-  
dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)propan-2-ol

15 (409.4 mg) obtained in the previous step was mixed with  
methanol (4.094 ml). To the mixture was added 10-  
camphorsulfonic acid (39.6 mg), and the mixture was stirred at  
room temperature overnight. The reaction solution was stirred  
at 70°C for 3 hr. To the reaction mixture was added saturated  
20 aqueous sodium hydrogen carbonate solution, and the mixture  
was extracted twice with ethyl acetate. The organic layer was  
washed with saturated aqueous sodium chloride solution, and  
dried over sodium sulfate. Sodium sulfate was filtered off,  
and the filtrate was concentrated under reduced pressure. The  
25 obtained residue was purified by silica gel column  
chromatography (ethyl acetate:methanol=99:1 to 80:20) to give  
the title compound (349.3 mg).

<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.23 (d, J=6.47Hz, 3H), 1.28 - 1.33  
(m, 2H), 1.55 - 1.63 (m, 2H), 1.65 - 1.70 (m, 2H), 1.80 (s,  
30 3H), 1.87 - 1.94 (m, 2H), 3.51 (d, J=5.32Hz, 2H), 4.22 (dd,  
J=13.52, 4.28Hz, 1H), 4.34 (d, J=13.52Hz, 1H), 4.39 - 4.46 (m,

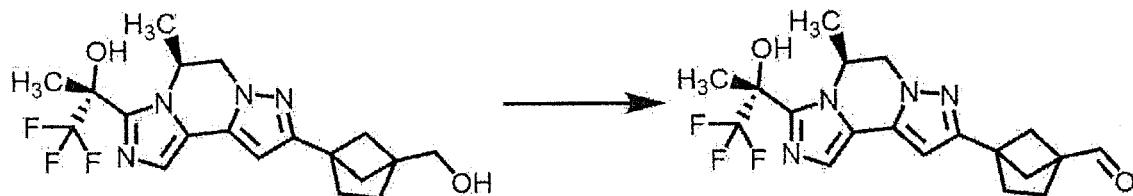
1H), 5.26 - 5.37 (m, 1H), 6.38 (s, 1H), 7.22 (s, 1H), 7.24 (s, 1H)

[0567]

Step 15

5 4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)bicyclo[2.1.1]hexane-1-carbaldehyde

[0568]



10 [0569]

(R)-1,1,1-Trifluoro-2-((S)-9-(4-(hydroxymethyl)bicyclo[2.1.1]hexan-1-yl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)propan-2-ol (175 mg) obtained in the previous step was mixed with 15 chloroform (4.946 ml)-acetonitrile (2.473 ml). Under ice-cooling, Dess-Martin periodinane (212 mg) was added, and the mixture was stirred at room temperature overnight. 5% Sodium thiosulfate aqueous solution and saturated aqueous sodium hydrogen carbonate solution were added, and the mixture was 20 stirred at room temperature for 1 hr and extracted twice with ethyl acetate. The organic layer was washed successively with 10% potassium carbonate aqueous solution, saturated aqueous sodium hydrogen carbonate solution, and saturated aqueous sodium chloride solution, and dried over sodium sulfate. 25 Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give a crude product (161 mg) of the title compound.

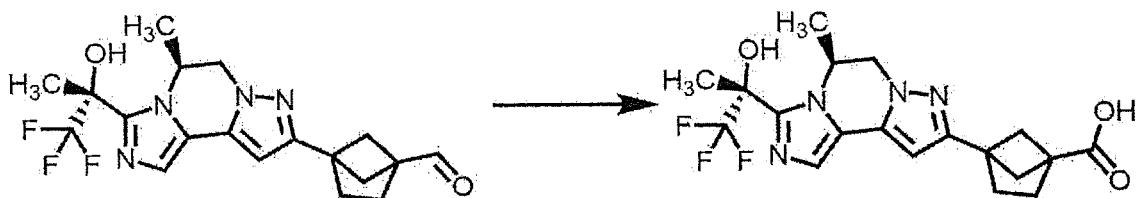
[0570]

Step 16

30 4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-

yl)bicyclo[2.1.1]hexane-1-carboxylic acid

[0571]



[0572]

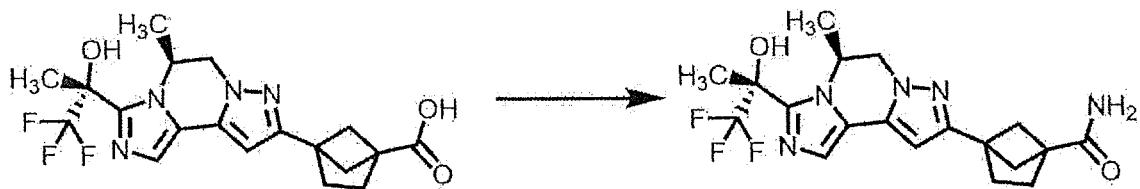
5 The crude product (161 mg) of 4-((S)-5-methyl-3-((R)-  
1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-  
a]pyrazolo[5,1-c]pyrazin-9-yl)bicyclo[2.1.1]hexane-1-  
carbaldehyde obtained in the previous step was mixed with  
tert-butanol (1.255 ml) and water (0.627 ml). 2-Methyl-2-  
10 butene (0.421 ml), sodium dihydrogen phosphate (239 mg), and  
sodium chlorite (135 mg) were added, and the mixture was  
stirred at room temperature for 2 hr. To the reaction mixture  
was added 5% sodium thiosulfate aqueous solution, and the  
mixture was stirred at room temperature for 30 min and  
15 extracted three times with ethyl acetate. The mixture was  
purified by reversed-phase silica gel chromatography  
(acetonitrile:water=5:95 to acetonitrile). To the obtained  
crude product was added water, and the mixture was adjusted to  
pH 6 to 7 with 1N aqueous hydrochloric acid solution, and  
20 extracted three times with ethyl acetate. The organic layer  
was washed with saturated aqueous sodium chloride solution,  
and dried over sodium sulfate. Sodium sulfate was filtered off,  
and the filtrate was concentrated under reduced pressure to  
give a crude product (163 mg) of the title compound.

25 [0573]

Step 17

4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-  
5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-  
yl)bicyclo[2.1.1]hexane-1-carboxamide

30 [0574]



[0575]

The crude product (161 mg) of 4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)bicyclo[2.1.1]hexane-1-carboxylic acid obtained in the previous step was mixed with DMF (1.633 ml). Under ice-cooling, 7 M ammonia/methanol solution (0.171 ml) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (227 mg) were added, and the mixture was stirred at room temperature overnight. Under ice-cooling, 7 M ammonia/methanol solution (0.085 ml) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (75.7 mg) were added, and the mixture was stirred at room temperature for 3 hr. The reaction mixture was purified by reversed-phase silica gel chromatography (acetonitrile:water=5:95 to acetonitrile) to give the title compound (95 mg).

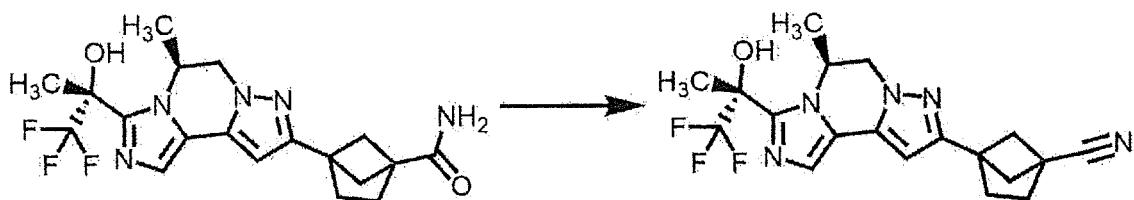
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.23 (d, J=6.47Hz, 3H), 1.57 - 1.61 (m, 2H), 1.80 (s, 3H), 1.84 - 1.90 (m, 2H), 1.90 - 1.97 (m, 4H), 4.23 (dd, J=13.64, 3.93Hz, 1H), 4.35 (d, J=13.64Hz, 1H), 5.27 - 5.37 (m, 1H), 6.42 (s, 1H), 6.86 (brs, 1H), 7.14 (brs, 1H), 7.23 (s, 1H), 7.25 (s, 1H)

[0576]

25 Step 18

4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)bicyclo[2.1.1]hexane-1-carbonitrile

[0577]



[0578]

4-((S)-5-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)bicyclo[2.1.1]hexane-1-carboxamide (95 mg) obtained in the previous step was mixed with tetrahydrofuran (0.886 ml). Under ice-cooling, triethylamine (0.151 ml) and trifluoroacetic anhydride (0.0459 ml) were added, and the mixture was stirred for 30 min. Under ice-cooling, to the reaction mixture was added trifluoroacetic anhydride (0.015 ml), and the mixture was stirred for 30 min. At room temperature, to the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted twice with ethyl acetate. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. To the obtained residue was added ethyl acetate/hexane=1/1, and the mixture was stirred at room temperature. The precipitated solid was collected by filtration to give the title compound (79.5 mg).

<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.22 (d, J=6.47Hz, 3H), 1.76 - 1.84 (m, 5H), 1.95 - 2.02 (m, 2H), 2.07 - 2.13 (m, 2H), 2.20 - 2.27 (m, 2H), 4.24 (dd, J=13.64, 3.93Hz, 1H), 4.36 (d, J=12.72Hz, 1H), 5.27 - 5.38 (m, 1H), 6.49 (s, 1H), 7.24 (s, 1H), 7.26 (s, 1H)

[0579]

Production Example 9-1

Synthesis of 1-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)-2-oxabicyclo[2.2.2]octane-4-carbonitrile

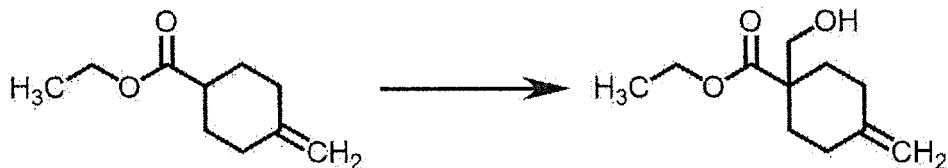
(Example 93)

[0580]

Step 1

ethyl 1-(hydroxymethyl)-4-methylenecyclohexane-1-carboxylate

5 [0581]



[0582]

Ethyl 4-methylenecyclohexane-1-carboxylate (23.98 g) was mixed with tetrahydrofuran (480 ml). The mixture was cooled to 10 -78°C, and 2 M lithium diisopropylamide/tetrahydrofuran-heptane-ethylbenzene solution (82 ml) was added dropwise. The mixture was stirred at -78°C for 30 min. To the mixture was added formaldehyde (6.42 g), and the mixture was stirred at -78°C for 30 min, and then stirred at room temperature for 4 hr. 15 To the reaction mixture was added saturated ammonium chloride aqueous solution, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was 20 concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=4:96 to 70:30) to give the title compound (21.1 g).

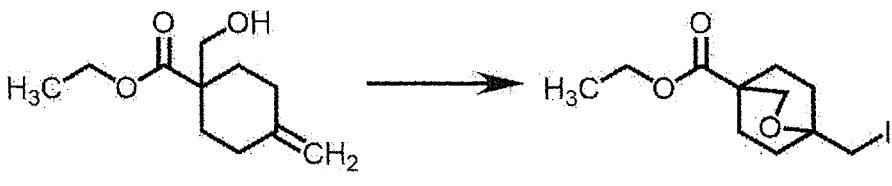
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.17 (t, J=7.09Hz, 3H), 1.21 - 1.33 (m, 2H), 1.94 - 2.06 (m, 4H), 2.10 - 2.20 (m, 1H), 3.39 (d, J=5.55Hz, 2H), 4.07 (q, J=7.09Hz, 2H), 4.59 (s, 2H), 4.81 (t, J=5.55Hz, 1H)

[0583]

Step 2

30 ethyl 1-(iodomethyl)-2-oxabicyclo[2.2.2]octane-4-carboxylate

[0584]



[0585]

Ethyl 1-(hydroxymethyl)-4-methylenecyclohexane-1-carboxylate (13.65 g) obtained in the previous step was mixed 5 with dichloromethane (341 ml). Under ice-cooling, to the mixture was added dropwise bis(2,4,6-trimethylpyridine)iodonium hexafluorophosphate (37.2 g)/dichloromethane (137 ml) solution, and the mixture was stirred for 1 hr. The reaction mixture was concentrated under 10 reduced pressure, 5% sodium thiosulfate aqueous solution was added, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated 15 under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=5:95 to 31:69) to give the title compound (10.176 g).

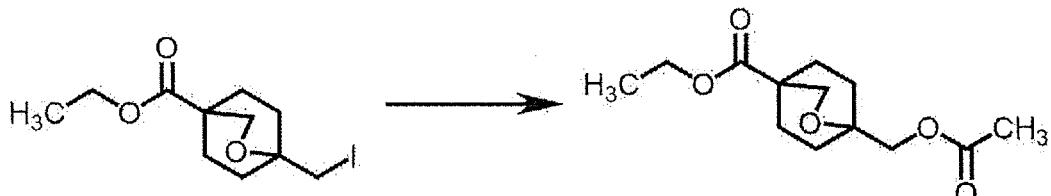
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.24 (t, J=7.11Hz, 3H), 1.68 - 1.83 (m, 2H), 1.90 - 2.06 (m, 6H), 3.16 (s, 2H), 4.00 (s, 2H), 4.12 (q, 20 J=7.11Hz, 2H)

[0586]

Step 3

ethyl 1-(acetoxymethyl)-2-oxabicyclo[2.2.2]octane-4-carboxylate

25 [0587]



[0588]

Ethyl 1-(iodomethyl)-2-oxabicyclo[2.2.2]octane-4-carboxylate (10.176 g) obtained in the previous step,

potassium acetate (9.24 g), and 18-crown-6 (1.659 g) were mixed with dimethyl sulfoxide (50.9 ml), and the mixture was stirred at 110°C for 2 days and at 120°C for 1 day. At room temperature, to the reaction mixture was added saturated 5 ammonium chloride aqueous solution, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The 10 obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=8:92 to 48:52) to give the title compound (7.3 g).

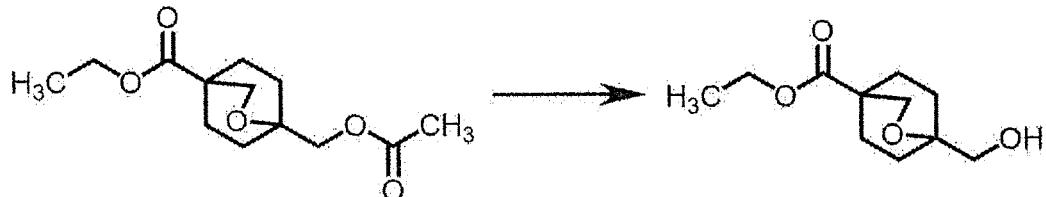
15  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 1.22 (t,  $J=7.09\text{Hz}$ , 3H), 1.53 – 1.64 (m, 2H), 1.86 – 2.03 (m, 6H), 2.08 (s, 3H), 3.93 (s, 2H), 3.98 (s, 2H), 4.10 (q,  $J=7.09\text{Hz}$ , 2H)

20 [0589]

Step 4

ethyl 1-(hydroxymethyl)-2-oxabicyclo[2.2.2]octane-4-carboxylate

25 [0590]



30 [0591]

Ethyl 1-(acetoxymethyl)-2-oxabicyclo[2.2.2]octane-4-carboxylate (7.3 g) obtained in the previous step was mixed 25 with ethanol (51.1 ml). Under ice-cooling, to the mixture was added dropwise 20% sodium ethoxide/ethanol solution (22.03 ml), and the mixture was stirred at room temperature for 5 hr. The reaction mixture was concentrated under reduced pressure, saturated ammonium chloride aqueous solution was added, and 30 the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride

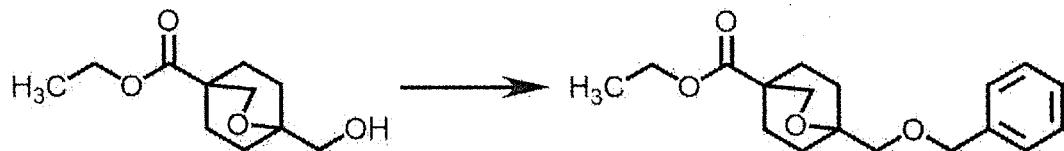
solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give the title compound (6.0 g).

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.24 (t, J=7.11Hz, 3H), 1.46 - 1.63 (m, 5 2H), 1.84 (t, J=6.73Hz, 1H), 1.88 - 2.04 (m, 6H), 3.40 (d, J=6.73Hz, 2H), 3.98 (s, 2H), 4.12 (q, J=7.11Hz, 2H)  
[0592]

Step 5

ethyl 1-((benzyloxy)methyl)-2-oxabicyclo[2.2.2]octane-4-  
10 carboxylate

[0593]



[0594]

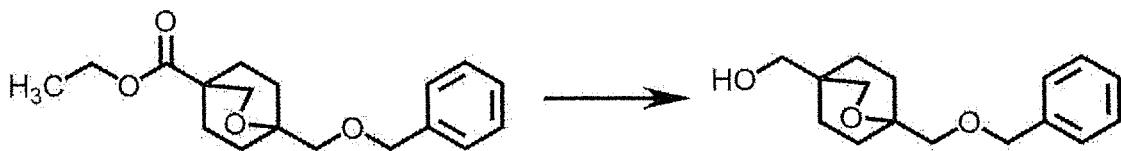
Ethyl 1-(hydroxymethyl)-2-oxabicyclo[2.2.2]octane-4-  
15 carboxylate (6.0 g) obtained in the previous step was mixed with tetrahydrofuran (60 ml). Under ice-cooling, to the mixture were added benzyl bromide (6.71 g) and potassium tert-butoxide (4.09 g), and the mixture was stirred for 1 hr. To the reaction mixture was added saturated ammonium chloride  
20 aqueous solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was  
25 purified by silica gel column chromatography (ethyl acetate:hexane=5:95 to 24:76) to give the title compound (7.21 g).

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.22 (t, J=7.17Hz, 3H), 1.55 - 1.68 (m, 2H), 1.84 - 2.02 (m, 6H), 3.27 (s, 2H), 3.98 (s, 2H), 4.09 (q, J=7.17Hz, 2H), 4.55 (s, 2H), 7.23 - 7.35 (m, 5H)  
30

[0595]

Step 6

(1-((benzyloxy)methyl)-2-oxabicyclo[2.2.2]octan-4-yl)methanol  
[0596]



[0597]

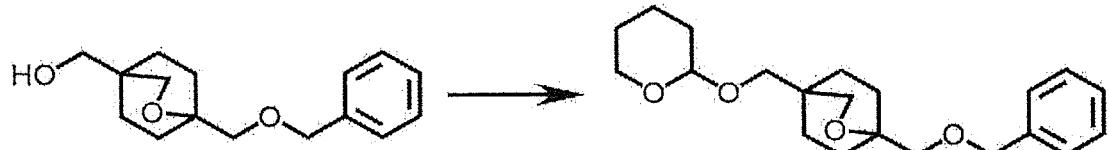
5       Ethyl 1-((benzyloxy)methyl)-2-oxabicyclo[2.2.2]octane-4-  
carboxylate (3.2 g) obtained in the previous step was mixed  
with tetrahydrofuran (32 ml). Under ice-cooling, to the  
mixture was added dropwise 2 M lithium aluminum  
hydride/tetrahydrofuran solution (6.31 ml), and the mixture  
10 was stirred for 30 min. Under ice-cooling, to the reaction  
mixture were successively added dropwise water (0.48 ml), 4N  
sodium hydroxide aqueous solution (0.48 ml), and water (1.44  
ml), and the mixture was stirred at room temperature for 1 hr.  
Solid was filtered off using celite as an aid, and the  
15 filtrate was concentrated under reduced pressure to give a  
crude product (2.82 g) of the title compound.

[0598]

Step 7

1-((benzyloxy)methyl)-4-(((tetrahydro-2H-pyran-2-  
20 yl)oxy)methyl)-2-oxabicyclo[2.2.2]octane

[0599]



[0600]

The crude product (2.76 g) of (1-((benzyloxy)methyl)-2-  
25 oxabicyclo[2.2.2]octan-4-yl)methanol obtained in the previous  
step was mixed with acetonitrile (27.6 ml). To the mixture  
were added pyridinium p-toluenesulfonate (0.528 g) and 3,4-  
dihydro-2H-pyran (1.061 g), and the mixture was stirred at  
room temperature overnight. The reaction mixture was  
30 concentrated under reduced pressure, and the obtained residue

was purified by silica gel column chromatography (ethyl acetate:hexane=2:98 to 20:80) to give the title compound (3.575 g).

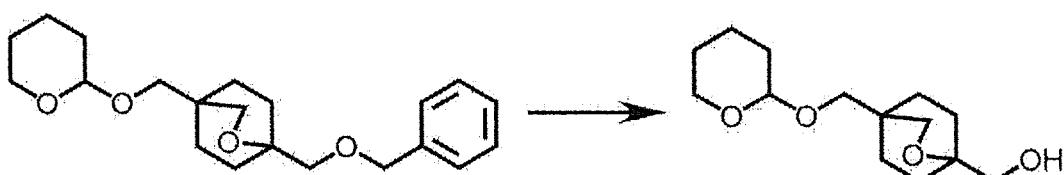
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.40 - 1.97 (m, 14H), 2.98 (d, J=9.71Hz, 1H), 3.26 (s, 2H), 3.40 - 3.52 (m, 2H), 3.72 - 3.83 (m, 3H), 4.49 (t, J=3.24Hz, 1H), 4.55 (s, 2H), 7.22 - 7.33 (m, 5H)

[0601]

Step 8

(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-  
10 oxabicyclo[2.2.2]octan-1-yl)methanol

[0602]



[0603]

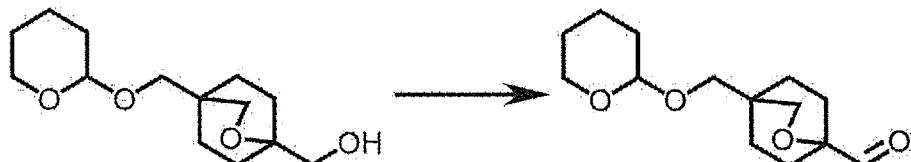
1-((Benzyl)oxy)methyl)-4-(((tetrahydro-2H-pyran-2-  
15 yl)oxy)methyl)-2-oxabicyclo[2.2.2]octane (3.275 g) obtained in  
the previous step was mixed with tetrahydrofuran (16.38 ml)  
and ethanol (16.38 ml). To the mixture was added palladium  
carbon (0.983 g) and the mixture was stirred overnight under a  
hydrogen atmosphere at room temperature. Palladium carbon was  
20 filtered off from the reaction mixture by using celite as an  
aid, and the filtrate was concentrated under reduced pressure  
to give a crude product (2.1 g) of the title compound.

[0604]

Step 9

25 4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-  
oxabicyclo[2.2.2]octane-1-carbaldehyde

[0605]



[0606]

The crude product (2.1 g) containing (4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-1-yl)methanol obtained in the previous step was mixed with chloroform (24.22 ml). Under ice-cooling, to the mixture was added Dess-Martin periodinane (4.81 g), and the mixture was stirred at room temperature overnight. Under ice-cooling, to the reaction mixture was added Dess-Martin periodinane (2.405 g), and the mixture was stirred at room temperature for 4 hr. To the reaction mixture were added 5% sodium thiosulfate aqueous solution and saturated aqueous sodium hydrogen carbonate solution, and the mixture was stirred at room temperature for 1 hr, and extracted twice with ethyl acetate. The organic layer was washed successively with 10% potassium carbonate aqueous solution, saturated aqueous sodium hydrogen carbonate solution, and saturated aqueous sodium chloride solution, and dried over magnesium sulfate. Magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give the title compound (1.277 g).

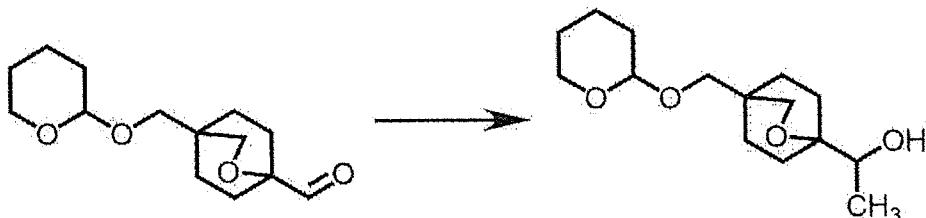
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.42 - 2.00 (m, 14H), 3.01 (d, J=9.71Hz, 1H), 3.43 - 3.52 (m, 2H), 3.72 - 3.82 (m, 1H), 3.86 (s, 2H), 4.46 - 4.53 (m, 1H), 9.57 (s, 1H)

[0607]

Step 10

25 1-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-1-yl)ethan-1-ol

[0608]



[0609]

30 4-(((Tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-

oxabicyclo[2.2.2]octane-1-carbaldehyde (1.277 g) obtained in the previous step was mixed with tetrahydrofuran (12.39 ml). Under ice-cooling, to the mixture was added dropwise 1 M methylmagnesium bromide/tetrahydrofuran solution (7.02 ml), 5 and the mixture was stirred for 30 min. Under ice-cooling, to the reaction mixture was added saturated ammonium chloride aqueous solution, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium 10 sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=12:88 to ethyl acetate) to give the title compound (863.9 mg).

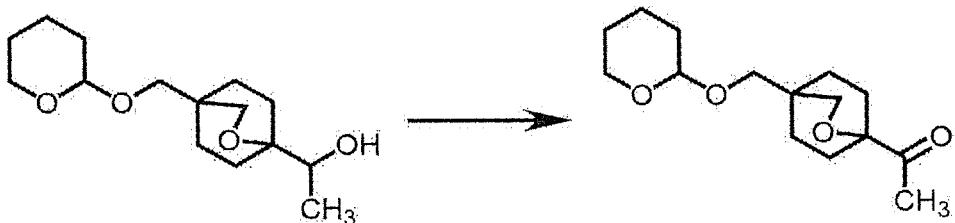
15  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 1.04 (d,  $J=6.70\text{Hz}$ , 3H), 1.42 – 2.00 (m, 14H), 2.40 (d,  $J=2.77\text{Hz}$ , 1H), 2.96 – 3.01 (m, 1H), 3.41 – 3.52 (m, 2H), 3.53 – 3.62 (m, 1H), 3.72 – 3.82 (m, 3H), 4.47 – 4.51 (m, 1H)

[0610]

20 Step 11

1-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-1-yl)ethan-1-one

[0611]



25 [0612]

1-(4-(((Tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-1-yl)ethan-1-ol (863.9 mg) obtained in the previous step was mixed with chloroform (8.207 ml). Under ice-cooling, to the mixture was added Dess-Martin periodinane 30 (1.931 g), and the mixture was stirred at room temperature

overnight. Under ice-cooling, to the reaction mixture were added sodium thiosulfate aqueous solution and saturated aqueous sodium hydrogen carbonate solution added, and the mixture was stirred at room temperature for 30 min, and 5 extracted twice with ethyl acetate. The organic layer was washed successively with 10% potassium carbonate aqueous solution, saturated aqueous sodium hydrogen carbonate solution, and saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the 10 filtrate was concentrated under reduced pressure and azeotroped with toluene to give the title compound (851 mg).

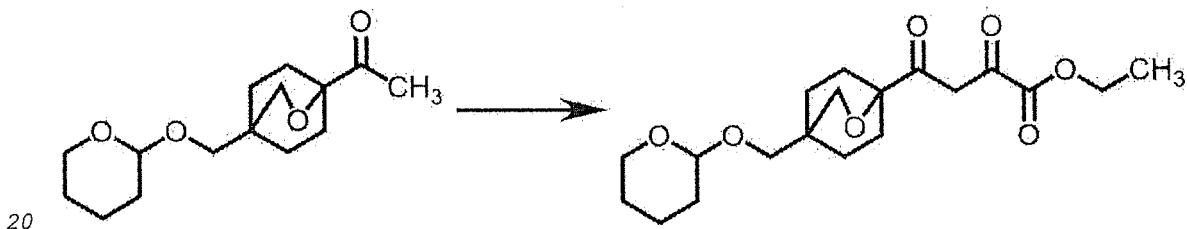
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.42 - 1.93 (m, 14H), 2.18 (s, 3H), 3.00 (d, J=9.71Hz, 1H), 3.42 - 3.53 (m, 2H), 3.71 - 3.88 (m, 3H), 4.47 - 4.52 (m, 1H)

15 [0613]

Step 12

ethyl 2,4-dioxo-4-((4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-1-yl)butanoate

20 [0614]



25 [0615]

1-(4-((4-((Tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-1-yl)ethan-1-one (851 mg) obtained in the previous step was mixed with tetrahydrofuran (8.17 ml).

Under ice-cooling, to the mixture was added diethyl oxalate (489 mg), 1 M potassium tert-butoxide/tetrahydrofuran solution (3.653 ml) was added dropwise, and the mixture was stirred for 30 min. Under ice-cooling, to the reaction mixture was added 1 M aqueous hydrochloric acid solution (21.3 ml), and the 30 mixture was extracted with ethyl acetate. The organic layer

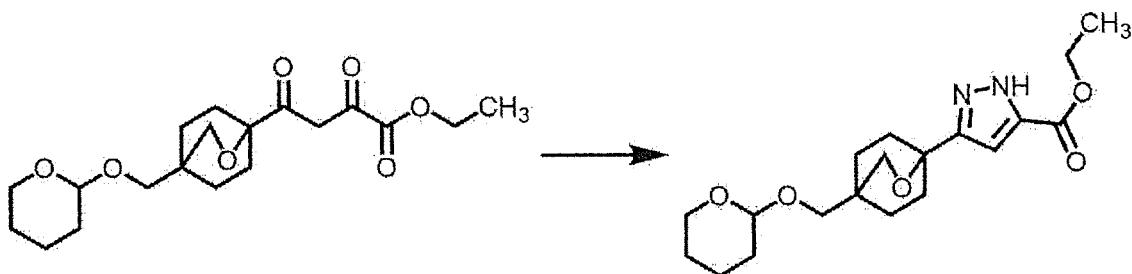
was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure and azeotroped with ethanol to give a crude product (1.168 g) of  
5 the title compound.

[0616]

Step 13

ethyl 3-((4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-1-yl)-1H-pyrazole-5-carboxylate

10 [0617]



[0618]

Ethyl 2,4-dioxo-4-((4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-1-yl)butanoate (1.168 g) obtained in the previous step was mixed with ethanol (11.2 ml). Under ice-cooling, hydrazine monohydrate (0.155 ml) was added dropwise, and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure. The obtained residue was purified by 15 silica gel column chromatography (ethyl acetate:hexane=12:88 to ethyl acetate) to give the title compound (978.4 mg).

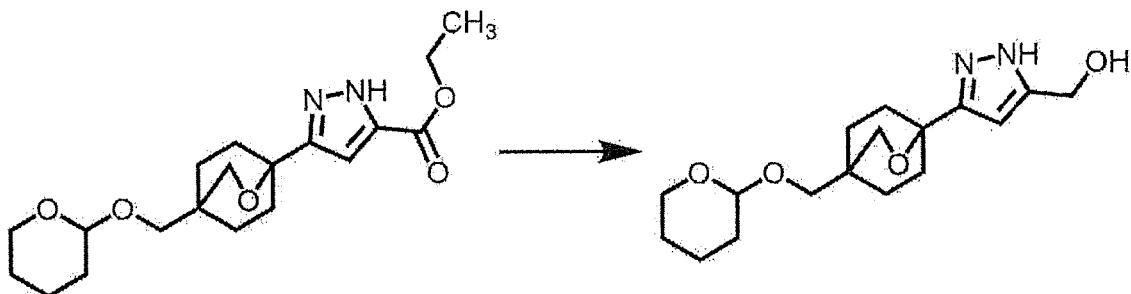
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.37 (t, J=7.09Hz, 3H), 1.44 - 1.90 (m, 10H), 1.93 - 2.04 (m, 2H), 2.04 - 2.17 (m, 2H), 3.04 (d, J=9.71Hz, 1H), 3.44 - 3.54 (m, 2H), 3.73 - 3.83 (m, 1H), 3.92 (s, 2H), 4.36 (q, J=7.09Hz, 2H), 4.48 - 4.55 (m, 1H), 6.60 (s, 1H)

[0619]

Step 14

(3-((4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-1-yl)-1H-pyrazol-5-yl)methanol

[0620]



[0621]

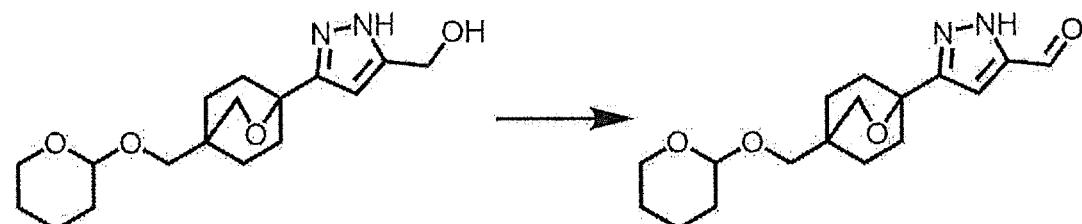
Ethyl 3-((4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-1-yl)-1H-pyrazole-5-carboxylate (978.4 mg) obtained in the previous step was mixed with tetrahydrofuran (14 ml). Under ice-cooling, to the mixture was added dropwise 2 M lithium aluminum hydride/tetrahydrofuran solution (2.255 ml), and the mixture was stirred for 50 min. Under ice-cooling, to the reaction mixture was added saturated Rochelle salt aqueous solution, and the mixture was stirred at room temperature for 1 hr, and extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give a crude product (769.6 mg) of the title compound.

[0622]

Step 15

3-((4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-1-yl)-1H-pyrazole-5-carbaldehyde

[0623]



[0624]

(3-((4-((Tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-

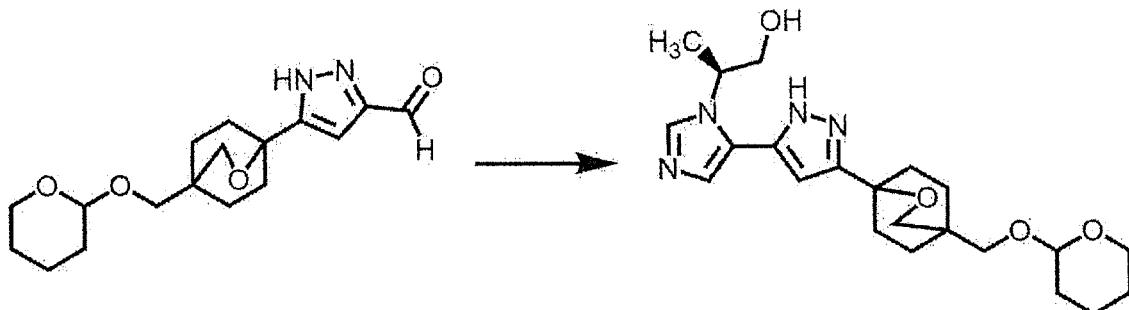
oxabicyclo[2.2.2]octan-1-yl)-1H-pyrazol-5-yl)methanol (769.6 mg) obtained in the previous step was mixed with 1,2-dimethoxyethane (23.088 ml). Manganese dioxide (2.309 g) was added, and the mixture was stirred at room temperature overnight. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (617.8 mg) of the title compound.

[0625]

Step 16

(2S)-2-(5-(3-((4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-1-yl)-1H-pyrazol-5-yl)-1H-imidazol-1-yl)propan-1-ol

[0626]



[0627]

The crude product (617.8 mg) of 3-(4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-1-yl)-1H-pyrazole-5-carbaldehyde obtained in the previous step and (S)-2-aminopropan-1-ol (152 mg) were mixed with 1,2-dimethoxyethane (24.712 ml) and methanol (12.36 ml). The mixture was stirred at 60°C for 2.5 hr. The reaction mixture was concentrated under reduced pressure. To the obtained residue were successively added DMF (6.18 ml), potassium carbonate (799 mg), and p-toluenesulfonylmethyl isocyanide (565 mg), and the mixture was stirred at room temperature for 3 days. At room temperature, water was added to the reaction mixture, and the mixture was extracted three times with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate.

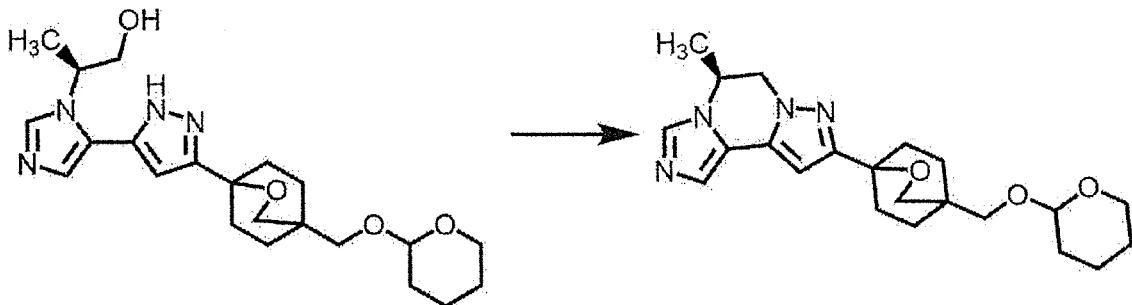
Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:methanol=2:98 to 50:50) to give a crude product (550 mg) of the title compound.

5 [0628]

Step 17

(5S)-5-methyl-9-((4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-1-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazine

10 [0629]



[0630]

(2S)-2-(5-(3-(4-((Tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-1-yl)-1H-pyrazol-5-yl)-1H-imidazol-1-yl)propan-1-ol (0.55 g) obtained in the previous step and triphenylphosphine (382 mg) were mixed with tetrahydrofuran (15.352 ml). Under ice-cooling, diisopropyl azodicarboxylate (295 mg) was added dropwise, and the mixture was stirred at room temperature for 1 hr. Under ice-cooling, triphenylphosphine (95.6 mg) and diisopropyl azodicarboxylate (73.7 mg) were added, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was purified by silica gel column chromatography (ethyl acetate:methanol=2:98 to 60:40) to give the title compound (520 mg).

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.45 - 1.73 (m, 10H), 1.75 - 1.91 (m, 3H), 1.97 - 2.08 (m, 2H), 2.20 - 2.32 (m, 2H), 3.04 (d, J=9.71Hz, 1H), 3.45 - 3.53 (m, 2H), 3.75 - 3.84 (m, 1H), 3.94 (s, 2H), 4.09 (dd, J=13.18, 7.86Hz, 1H), 4.44 (dd, J=13.18,

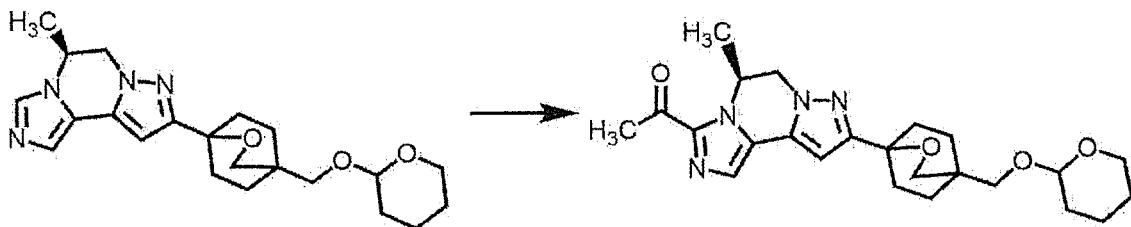
4.39Hz, 1H), 4.49 - 4.62 (m, 2H), 6.35 (s, 1H), 7.25 (s, 1H),  
7.58 (s, 1H)

[0631]

Step 18

5 1-((5S)-5-methyl-9-((4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-1-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)ethan-1-one

[0632]



10 [0633]

(5S)-5-Methyl-9-((4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-1-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazine (520 mg) obtained in the previous step was mixed with tetrahydrofuran (9.36 ml).

15 The mixture was cooled to -78°C, and 2 M lithium diisopropylamide/tetrahydrofuran-heptane-ethylbenzene solution (0.587 ml) was added dropwise. The mixture was stirred at -78°C for 30 min. To the mixture was added N-methoxy-N-methylacetamide (1.452 ml), and the mixture was stirred at -78°C for 30 min. To the mixture was added dropwise 2 M lithium diisopropylamide/tetrahydrofuran-heptane-ethylbenzene solution (0.587 ml), and the mixture was stirred at -78°C for 1 hr. To the reaction mixture was added saturated ammonium chloride aqueous solution, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=16:84 to ethyl acetate, thereafter ethyl

20

25

30

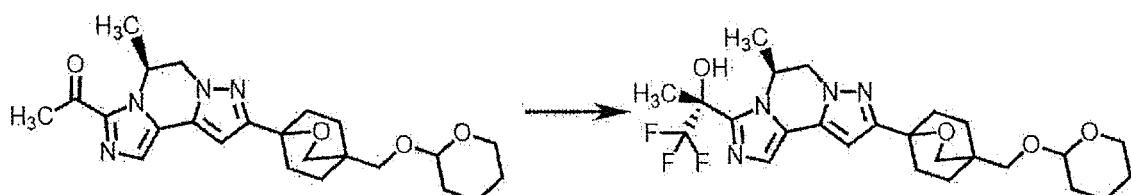
acetate:methanol=50:50) to give the title compound (356 mg).  
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.36 (d, J=6.70Hz, 3H), 1.44 - 1.94 (m, 10H), 1.98 - 2.10 (m, 2H), 2.20 - 2.32 (m, 2H), 2.67 (s, 3H), 3.05 (d, J=9.71Hz, 1H), 3.45 - 3.54 (m, 2H), 3.75 - 3.84 (m, 1H), 3.95 (s, 2H), 4.29 - 4.42 (m, 2H), 4.49 - 4.54 (m, 1H), 5.73 - 5.85 (m, 1H), 6.49 (s, 1H), 7.33 (s, 1H)

[0634]

Step 19

(2R)-1,1,1-trifluoro-2-((5S)-5-methyl-9-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-1-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)propan-2-ol

[0635]



[0636]

15 1-((5S)-5-Methyl-9-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-1-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)ethan-1-one (356 mg) obtained in the previous step was azeotroped with toluene and mixed with N,N-dimethylacetamide (1.78 ml). Under 20 ice-cooling, to the mixture were added lithium acetate (0.016 g) and trifluoromethyltrimethylsilane (0.966 ml), and the mixture was stirred for 1 hr. Under ice-cooling, methanol (0.642 ml) and potassium carbonate (0.721 g) were added, and the mixture was stirred at room temperature for 1 hr. To the 25 reaction mixture was added water, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The 30 obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=16:84 to ethyl acetate)

to give the title compound (317.5 mg).

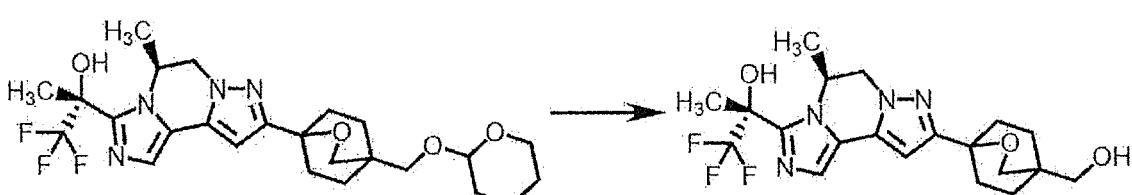
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.33 (d, J=6.47Hz, 3H), 1.45 - 1.73 (m, 7H), 1.74 - 1.90 (m, 3H), 1.93 - 2.11 (m, 5H), 2.18 - 2.34 (m, 2H), 3.01 - 3.07 (m, 2H), 3.44 - 3.53 (m, 2H), 3.73 - 3.85 (m, 5H), 3.95 (s, 2H), 4.29 - 4.34 (m, 2H), 4.49 - 4.54 (m, 1H), 5.25 - 5.36 (m, 1H), 6.37 (s, 1H), 7.20 (s, 1H)

[0637]

Step 20

(R)-1,1,1-trifluoro-2-((S)-9-(4-(hydroxymethyl)-2-oxabicyclo[2.2.2]octan-1-yl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)propan-2-ol

[0638]



[0639]

(2R)-1,1,1-Trifluoro-2-((5S)-5-methyl-9-(4-((tetrahydro-2H-pyran-2-yl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-1-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)propan-2-ol (317.5 mg) obtained in the previous step was mixed with methanol (3.175 ml). To the mixture was added 10-camphorsulfonic acid (28.9 mg), and the mixture was stirred at room temperature overnight. To the reaction mixture was added 10-camphorsulfonic acid (144 mg), and the mixture was stirred at room temperature for 1 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (methanol:ethyl acetate=1:99 to 20:80) to give the title compound (269.3 mg).

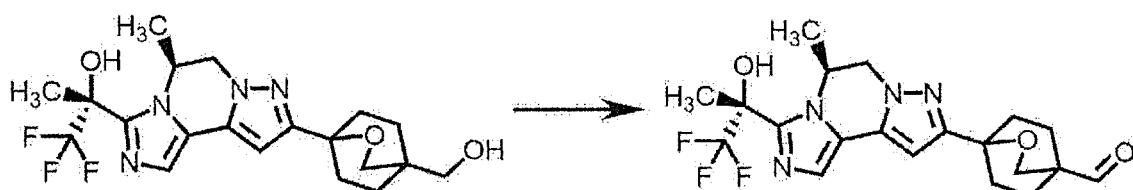
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.21 (d, J=6.47Hz, 3H), 1.43 - 1.55 (m, 2H), 1.58 - 1.69 (m, 2H), 1.80 (s, 3H), 1.84 - 1.99 (m, 2H), 2.00 - 2.14 (m, 2H), 3.12 (d, J=5.32Hz, 2H), 3.69 (s, 2H), 4.22 (dd, J=13.52, 4.05Hz, 1H), 4.33 (d, J=12.72Hz, 1H), 4.45 - 4.52 (m, 1H), 5.26 - 5.37 (m, 1H), 6.43 (s, 1H), 7.23 (s, 1H), 7.24 (s, 1H)

[0640]

Step 21

1-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)-2-oxabicyclo[2.2.2]octane-4-carbaldehyde

[0641]



[0642]

(R)-1,1,1-Trifluoro-2-((S)-9-(4-(hydroxymethyl)-2-oxabicyclo[2.2.2]octan-1-yl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)propan-2-ol (135 mg) obtained in the previous step was mixed with chloroform (3.698 ml) and acetonitrile (1.849 ml). Under ice-cooling, Dess-Martin periodinane (147 mg) was added, and the mixture was stirred at room temperature overnight. 5% Sodium thiosulfate aqueous solution and saturated aqueous sodium hydrogen carbonate solution were added, and the mixture was stirred at room temperature for 1 hr, and extracted twice with ethyl acetate. The organic layer was washed successively with 10% potassium carbonate aqueous solution, saturated aqueous sodium hydrogen carbonate solution, and saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give the title compound (124.6 mg).

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.33 (d, J=6.47Hz, 3H), 1.85 - 2.15 (m,

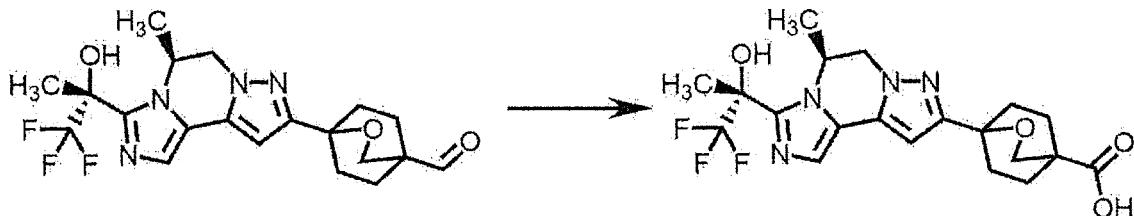
9H), 2.26 - 2.42 (m, 2H), 3.10 (s, 1H), 4.09 - 4.12 (m, 2H), 4.27 - 4.38 (m, 2H), 5.27 - 5.39 (m, 1H), 6.37 (s, 1H), 7.21 (s, 1H), 9.52 (s, 1H)

[0643]

5 Step 22

1-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)-2-oxabicyclo[2.2.2]octane-4-carboxylic acid

[0644]



10

[0645]

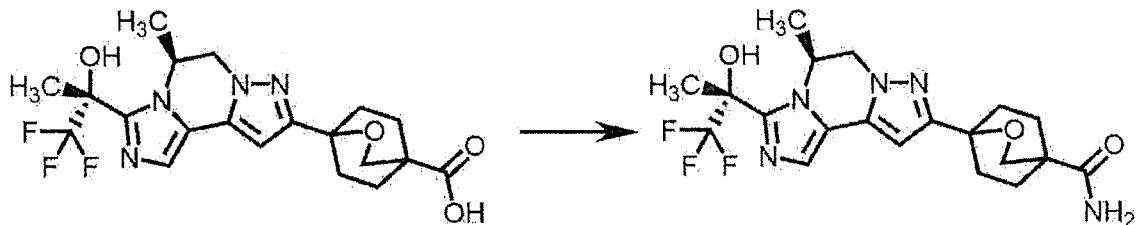
1-((S)-5-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)-2-oxabicyclo[2.2.2]octane-4-carbaldehyde (114.6 mg) obtained in the previous step was mixed with tert-butanol (0.871 ml) and water (0.435 ml). 2-Methyl-2-butene (0.272 ml), sodium dihydrogen phosphate (154 mg), and sodium chlorite (87 mg) were added, and the mixture was stirred at room temperature for 2 hr. Using the starting material (10 mg), a similar reaction was performed. The reaction mixtures were combined, 5% sodium thiosulfate aqueous solution was added, and the mixture was extracted three times with ethyl acetate. The organic layer was dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give a crude product (113 mg) of the title compound.

[0646]

Step 23

1-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)-2-oxabicyclo[2.2.2]octane-4-carboxamide

[0647]



[0648]

The crude product (113 mg) of 1-((S)-5-methyl-3-((R)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)-2-oxabicyclo[2.2.2]octane-4-carboxylic acid obtained in the previous step was mixed with DMF (1.273 ml). Under ice-cooling, 7 M ammonia/methanol solution (0.124 ml) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (165 mg) were added, and the mixture was stirred at room temperature overnight. Under ice-cooling, to the reaction mixture were added 7 M ammonia/methanol solution (0.124 ml) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (165 mg), and the mixture was stirred at room temperature for 3 hr. The reaction mixture was purified by reversed-phase chromatography (acetonitrile:water=5:95 to acetonitrile) to give the title compound (104.1 mg).

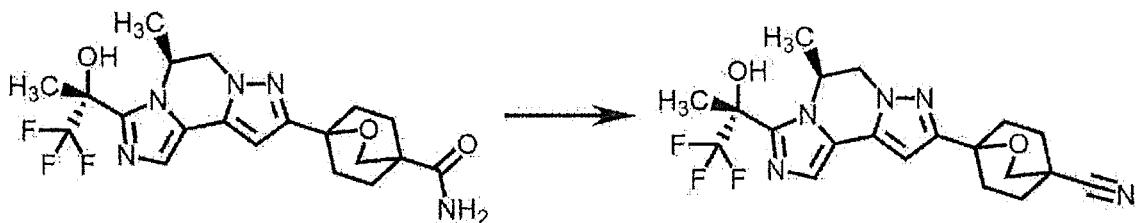
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.21 (d, J=6.47Hz, 3H), 1.80 (s, 3H), 1.85 - 1.99 (m, 6H), 2.03 - 2.20 (m, 2H), 3.88 (s, 2H), 4.23 (dd, J=13.18, 4.05Hz, 1H), 4.33 (d, J=13.18Hz, 1H), 5.26 - 5.39 (m, 1H), 6.45 (s, 1H), 6.92 (brs, 1H), 7.12 (brs, 1H), 7.23 (s, 1H), 7.25 (s, 1H)

[0649]

Step 24

1-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)-2-oxabicyclo[2.2.2]octane-4-carbonitrile

[0650]



[0651]

1-((S)-5-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)-2-oxabicyclo[2.2.2]octane-4-carboxamide (104.1 mg) obtained in the previous step was mixed with tetrahydrofuran (0.958 ml). Under ice-cooling, triethylamine (0.152 ml) and trifluoroacetic anhydride (0.0462 ml) were added, and the mixture was stirred for 30 min. Under ice-cooling, to the reaction mixture was added trifluoroacetic anhydride (0.0154 ml), and the mixture was stirred for 30 min. At room temperature, to the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted twice with ethyl acetate. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. To the obtained residue was added ethyl acetate/hexane=1/1, and the mixture was stirred at room temperature. The precipitated solid was collected by filtration to give the title compound (68.4 mg).

<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.20 (d, J=6.70Hz, 3H), 1.80 (s, 3H), 1.91 - 2.04 (m, 2H), 2.06 - 2.29 (m, 6H), 4.05 (s, 2H), 4.23 (dd, J=13.52, 4.05Hz, 1H), 4.34 (d, J=13.52Hz, 1H), 5.28 - 5.38 (m, 1H), 6.46 (s, 1H), 7.24 (s, 1H), 7.25 (s, 1H)

[0652]

Production Example 9-2

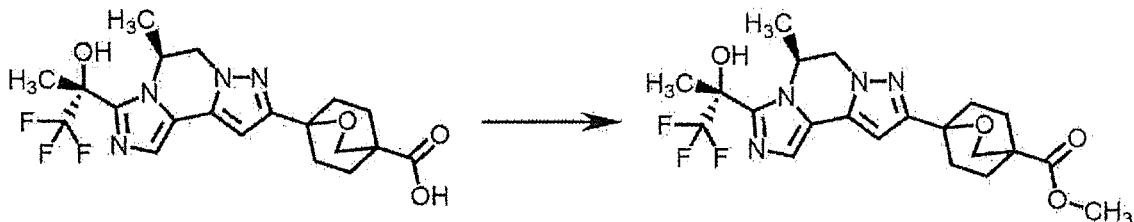
Synthesis of (R)-1,1,1-trifluoro-2-((S)-9-(4-(2-hydroxypropan-2-yl)-2-oxabicyclo[2.2.2]octan-1-yl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)propan-2-ol (Example 98)

[0653]

Step 1

methyl 1-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)-2-oxabicyclo[2.2.2]octane-4-carboxylate

[0654]



[0655]

The crude product (133 mg) of 1-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)-2-oxabicyclo[2.2.2]octane-4-carboxylic acid was mixed with methanol (3 ml). To the mixture was added dropwise 0.6 M trimethylsilyldiazomethane/hexane solution (0.675 ml) 3 times, and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=24:76 to ethyl acetate) to give the title compound (114.2 mg).

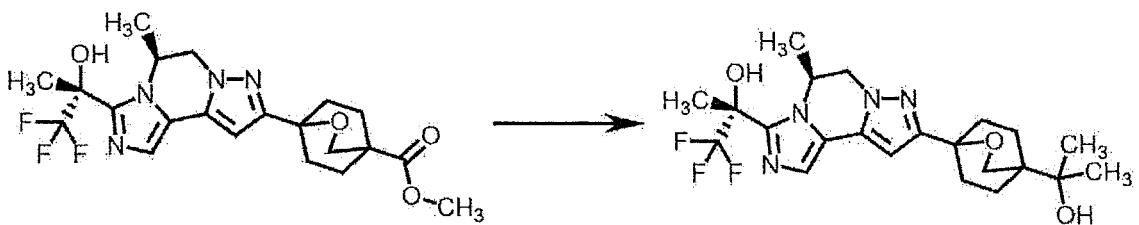
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.21 (d, J=6.47Hz, 3H), 1.80 (s, 3H), 1.90 - 2.23 (m, 8H), 3.61 (s, 3H), 3.94 (s, 2H), 4.23 (dd, J=13.64, 4.16Hz, 1H), 4.34 (d, J=13.64Hz, 1H), 5.26 - 5.38 (m, 1H), 6.46 (s, 1H), 7.24 (s, 1H), 7.25 (s, 1H)

[0656]

Step 2

(R)-1,1,1-trifluoro-2-((S)-9-(4-(2-hydroxypropan-2-yl)-2-oxabicyclo[2.2.2]octan-1-yl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)propan-2-ol

[0657]



[0658]

Methyl 1-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)-2-oxabicyclo[2.2.2]octane-4-carboxylate (30 mg) was mixed with tetrahydrofuran (1.8 ml). Under ice-cooling, 1.04 M methylmagnesium bromide/tetrahydrofuran solution (0.317 ml) was added dropwise, and the mixture was stirred for 1 hr, and then stirred at room temperature for 3 hr. At room temperature, saturated ammonium chloride aqueous solution was added, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was mixed with tetrahydrofuran (1.8 ml). At room temperature, 1.04 M methylmagnesium bromide/tetrahydrofuran solution (0.66 ml) was added dropwise, and the mixture was stirred for 2 hr. At room temperature, saturated ammonium chloride aqueous solution was added, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by preparative thin layer chromatography (ethyl acetate) to give the title compound (22.1 mg).

<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.01 (s, 6H), 1.21 (d, J=6.47Hz, 3H), 1.53 - 1.65 (m, 2H), 1.67 - 1.94 (m, 7H), 1.98 - 2.12 (m, 2H), 3.80 (d, J=6.24Hz, 2H), 4.08 (s, 1H), 4.22 (dd, J=13.76, 4.05Hz, 1H), 4.33 (d, J=13.76Hz, 1H), 5.27 - 5.37 (m, 1H), 6.43 (s, 1H), 7.23 (s, 1H), 7.24 (s, 1H)

[0659]

Production Example 10-1

Synthesis of 4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-5 c]pyrazin-9-yl)-2-oxabicyclo[2.2.2]octane-1-carbonitrile  
(Example 88)

[0660]

Step 1

1-((benzyloxy)methyl)-2-oxabicyclo[2.2.2]octane-4-carboxylic acid

[0661]



[0662]

Ethyl 1-(hydroxymethyl)-2-oxabicyclo[2.2.2]octane-4-carboxylate (4.19 g) obtained in the previous step was mixed with tetrahydrofuran (30.8 ml). Under ice-cooling, to the mixture were added potassium tert-butoxide (2.624 g) and benzyl bromide (4.308 g), and the mixture was stirred for 1 hr. To the reaction mixture were added ethanol (30.8 ml) and 2N sodium hydroxide aqueous solution (27 ml), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, diisopropyl ether was added and the layers were separated. The organic layer was washed with 1N sodium hydroxide aqueous solution. The aqueous layers were combined, adjusted to pH 2 with 6N hydrochloric acid, and extracted three times with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give the title compound (3.9 g).  
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.53 - 1.93 (m, 8H), 3.23 (s, 2H), 3.79 (s, 2H), 4.47 (s, 2H), 7.21 - 7.41 (m, 5H), 12.37 (brs,

1H)

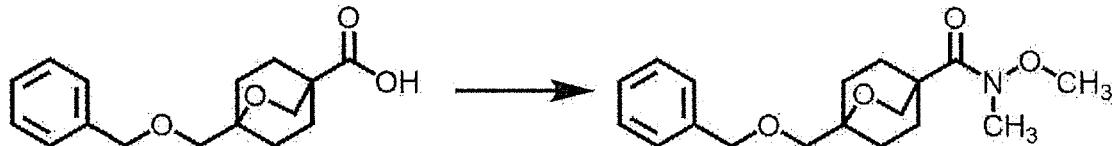
[0663]

Step 2

1-((benzyloxy)methyl)-N-methoxy-N-methyl-2-

5 oxabicyclo[2.2.2]octane-4-carboxamide

[0664]



[0665]

1-((Benzyl)oxy)methyl)-2-oxabicyclo[2.2.2]octane-4-  
10 carboxylic acid (2.5 g) was mixed with pyridine (12.5 ml). To  
the mixture were added 1-ethyl-3-(3-  
dimethylaminopropyl)carbodiimide hydrochloride (2.08 g) and  
N,O-dimethylhydroxylamine hydrochloride (1.059 g), and the  
mixture was stirred at room temperature for 16 hr. At room  
15 temperature, to the reaction mixture were added silica gel (30  
g) and ethyl acetate. Silica gel was filtered off and eluted  
with ethyl acetate. The filtrate was concentrated under  
reduced pressure. The obtained residue was purified by silica  
gel column chromatography (hexane:ethyl acetate=100:0 to  
20 0:100) to give the title compound (2.64 g).

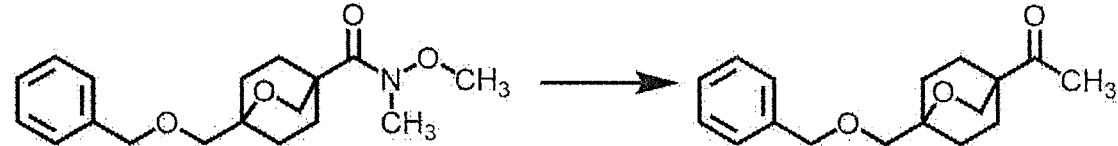
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.51 - 2.14 (m, 8H), 3.13 (s, 3H), 3.27  
(s, 2H), 3.65 (s, 3H), 4.10 (s, 2H), 4.55 (s, 2H), 7.25 - 7.34  
(m, 5H)

[0666]

25 Step 3

1-(1-((benzyloxy)methyl)-2-oxabicyclo[2.2.2]octan-4-yl)ethan-  
1-one

[0667]



30 [0668]

Under an argon atmosphere, 1-((benzyloxy)methyl)-N-methoxy-N-methyl-2-oxabicyclo[2.2.2]octane-4-carboxamide (2.64 g) obtained in the previous step was mixed with tetrahydrofuran (26.4 ml). The mixture was ice-cooled, 1.04 M 5 methylmagnesium bromide/tetrahydrofuran solution (9.54 ml) was added dropwise, and the mixture was stirred for 80 min. Saturated ammonium chloride aqueous solution was added. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride 10 solution, and sodium sulfate was added. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0 to 0:100) to give the title compound (1.62 g).

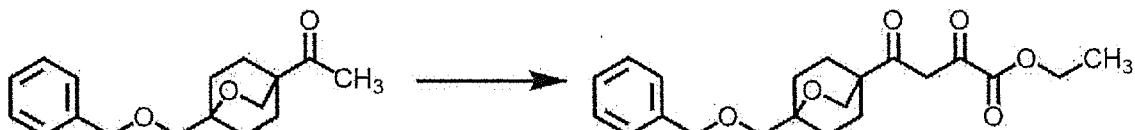
15  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 1.60 - 1.69 (m, 2H), 1.81 - 1.99 (m, 6H), 2.07 (s, 3H), 3.27 (s, 2H), 3.97 (s, 2H), 4.55 (s, 2H), 7.25 - 7.34 (m, 5H)

[0669]

Step 4

20 ethyl 4-((1-((benzyloxy)methyl)-2-oxabicyclo[2.2.2]octan-4-yl)-2,4-dioxobutanoate

[0670]



[0671]

25 1-((1-((benzyloxy)methyl)-2-oxabicyclo[2.2.2]octan-4-yl)ethan-1-one (2.13 g) was mixed with tetrahydrofuran (21.3 ml), and diethyl oxalate (1.156 ml) was added. The mixture was ice-cooled, 1 M potassium-tert-butoxide/tetrahydrofuran solution (9.32 ml) was added dropwise, and the mixture was 30 stirred for 30 min. 1N Hydrogen chloride solution (9.32 ml) was added. The mixture was extracted with ethyl acetate and washed with saturated aqueous sodium chloride solution. To the

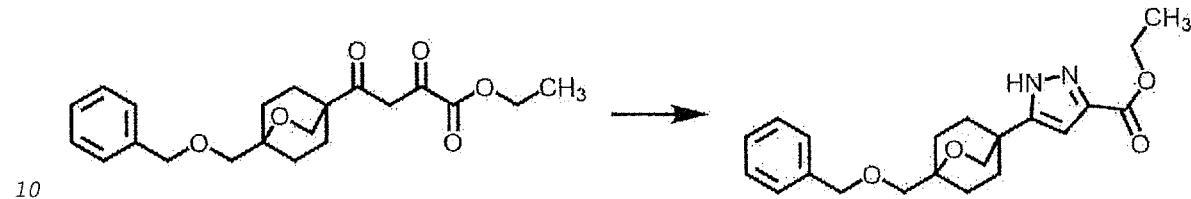
organic layer was added sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give a crude product (2.91 g) of the title compound.

5 [0672]

Step 5

ethyl 5-(1-((benzyloxy)methyl)-2-oxabicyclo[2.2.2]octan-4-yl)-1H-pyrazole-3-carboxylate

[0673]



[0674]

Ethyl 4-(1-((benzyloxy)methyl)-2-oxabicyclo[2.2.2]octan-4-yl)-2,4-dioxobutanoate (2.91 g) obtained in the previous step was mixed with ethanol (29.1 ml). Under ice-cooling, 15 hydrazine monohydrate (0.397 ml) was added. The mixture was stirred at room temperature for 16 hr. The reaction mixture was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0 to 0:100) to give the title compound (2.68 g).

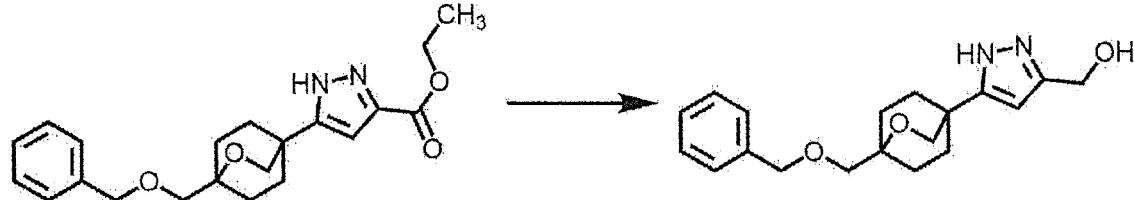
20  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 1.37 (t,  $J=7.85\text{Hz}$ , 3H), 1.56 – 2.16 (m, 8H), 3.32 (s, 2H), 4.01 (s, 2H), 4.36 (q,  $J=7.85\text{Hz}$ , 2H), 4.57 (s, 2H), 6.63 (s, 1H), 7.25 – 7.35 (m, 5H), 10.65 (brs, 1H)

[0675]

Step 6

25 (5-(1-((benzyloxy)methyl)-2-oxabicyclo[2.2.2]octan-4-yl)-1H-pyrazol-3-yl)methanol

[0676]



[0677]

Under an argon atmosphere, lithium aluminum hydride (0.549 g) was mixed with tetrahydrofuran (70 ml). The mixture was ice-cooled. A solution of ethyl 5-(1-((benzyloxy)methyl)-2-oxabicyclo[2.2.2]octan-4-yl)-1H-pyrazole-3-carboxylate (2.68 g) obtained in the previous step in tetrahydrofuran (10 ml) was added dropwise. The reaction mixture was stirred at room temperature for 30 min. Saturated potassium sodium tartrate aqueous solution was added dropwise, and the mixture was stirred at room temperature for 1 hr. The reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and sodium sulfate was added. Sodium sulfate was filtered off. The filtrate was concentrated under reduced pressure to give a crude product (2.14 g) of the title compound.

[0678]

Step 7

5-(1-((benzyloxy)methyl)-2-oxabicyclo[2.2.2]octan-4-yl)-1H-pyrazole-3-carbaldehyde

[0679]



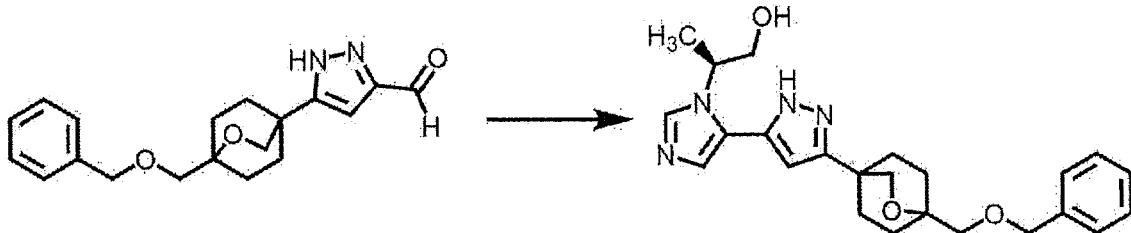
[0680]

(5-(1-((Benzyl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-4-yl)-1H-pyrazol-3-ylmethanol (1.14 g) obtained in the previous step was mixed with 1,2-dimethoxyethane (45.6 ml). Manganese dioxide (2.85 g) was added, and the mixture was stirred at room temperature for 22 hr. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (1.133 g) of the title compound.

[0681]

Step 8

(S)-2-(5-(3-(1-((benzyloxy)methyl)-2-oxabicyclo[2.2.2]octan-4-yl)-1H-pyrazol-5-yl)-1H-imidazol-1-yl)propan-1-ol  
[0682]



5 [0683]

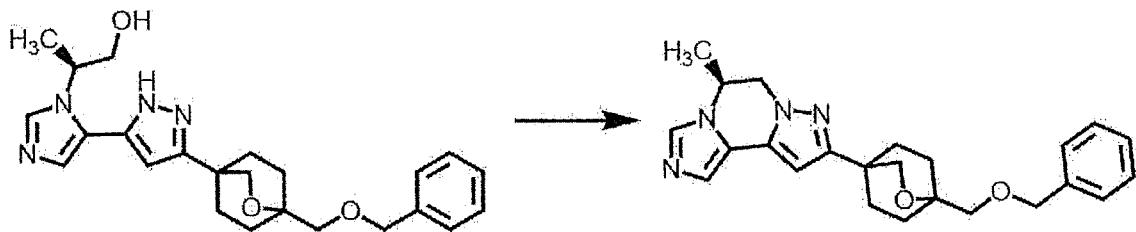
5-(1-((Benzyl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-4-yl)-1H-pyrazole-3-carbaldehyde (1.133 g) obtained in the previous step was mixed with DMF (12 ml). At room temperature, (S)-2-aminopropan-1-ol (0.274 g) was added, and the mixture was 10 stirred at room temperature for 16 hr. p-Toluenesulfonylmethyl isocyanide (0.813 g) and potassium carbonate (0.959 g) were added, and the mixture was stirred at room temperature for 71 hr. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure. To the 15 obtained residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained 20 residue was purified by silica gel column chromatography (ethyl acetate:hexane=25:75 to ethyl acetate, thereafter ethyl acetate:methanol=60:40) to give the title compound (1.2 g).

[0684]

Step 9

25 (S)-9-(1-((benzyloxy)methyl)-2-oxabicyclo[2.2.2]octan-4-yl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazine

[0685]



[0686]

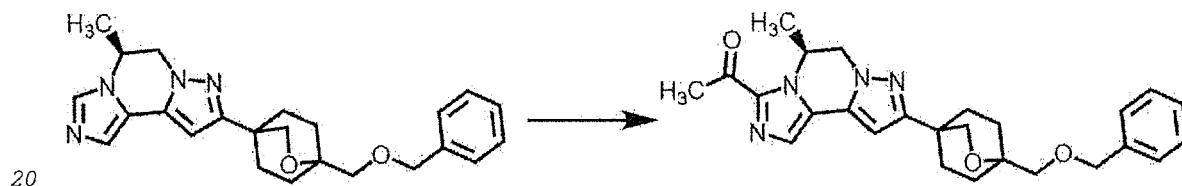
(S)-2-(5-(3-(1-(Benzyl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-4-yl)-1H-pyrazol-5-yl)-1H-imidazol-1-yl propan-1-ol (1.2 g) obtained in the previous step was mixed with tetrahydrofuran (24 ml). Under ice-cooling, triphenylphosphine (0.894 g) and diisopropyl azodicarboxylate (0.733 ml) were added, and the mixture was stirred at room temperature for 90 min. The reaction mixture was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=25:75 to ethyl acetate, thereafter ethyl acetate:methanol=60:40) to give the title compound (0.998 g).

[0687]

15 Step 10

(S)-1-(9-(1-(Benzyl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-4-yl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)ethan-1-one

[0688]



[0689]

(S)-9-(1-(Benzyl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-4-yl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazine (0.998 g) obtained in the previous step was mixed with tetrahydrofuran (19.96 ml). Under cooling in an acetone-dry ice bath, 2 M lithium diisopropylamide/tetrahydrofuran solution (1.172 ml) was added dropwise, and the mixture was

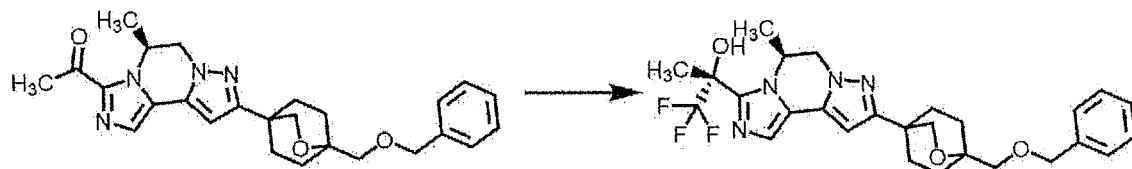
stirred for 30 min. To the mixture was added N-methoxy-N-methylacetamide (0.605 ml), and the mixture was stirred for 30 min. To the mixture was added dropwise 2 M lithium diisopropylamide/tetrahydrofuran solution (1.357 ml), and the 5 mixture was stirred for 90 min. Water was added, and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and sodium sulfate was added. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced 10 pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0 to 0:100) to give the title compound (0.899 g).

[0690]

Step 11

15 (R)-2-((S)-9-(1-((benzyloxy)methyl)-2-oxabicyclo[2.2.2]octan-4-yl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)-1,1,1-trifluoropropan-2-ol

[0691]



20 [0692]

(S)-1-(9-(1-((Benzyl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-4-yl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)ethan-1-one (0.899 g) obtained in the previous step was mixed with tetrahydrofuran (10 ml). Under ice-cooling, 25 to the mixture was added cesium fluoride (0.061 g), and (trifluoromethyl)trimethylsilane (0.596 ml) was added dropwise. The reaction mixture was stirred at room temperature for 1 hr. Under ice-cooling, methanol (5 ml) and potassium carbonate (0.362 g) were added, and the mixture was stirred at room 30 temperature for 150 min. Water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed

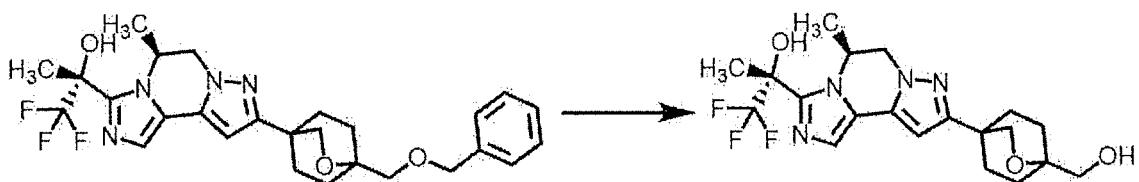
with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0 to 0:100) to give the title compound (0.68 g).

[0693]

Step 12

(S)-1,1,1-trifluoro-2-((S)-9-(1-(hydroxymethyl)-2-oxabicyclo[2.2.2]octan-4-yl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)propan-2-ol

[0694]



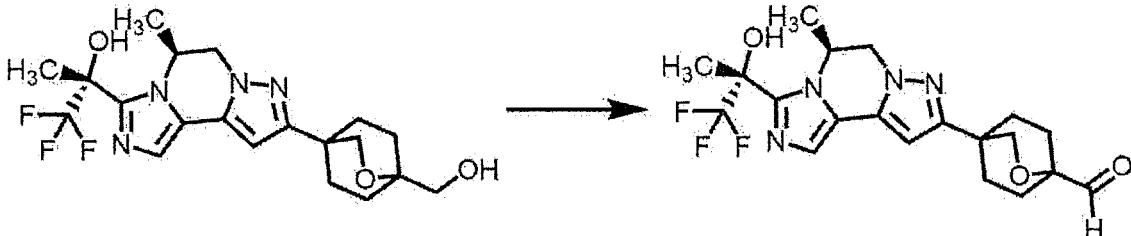
[0695]

(R)-2-((S)-9-(1-((Benzyl)oxy)methyl)-2-oxabicyclo[2.2.2]octan-4-yl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)-1,1,1-trifluoropropan-2-ol (0.68 g) obtained in the previous step was mixed with trifluoroacetic acid (8 ml), and the mixture was stirred at 90°C for 1 hr. The reaction mixture was concentrated under reduced pressure, and azeotroped with methanol. The residue was mixed with methanol (8 ml). Potassium carbonate (0.218 g) was added, and the mixture was stirred at room temperature for 1 hr. Water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure to give a crude product (0.55 g) of the title compound.

[0696]

Step 13

4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)-2-oxabicyclo[2.2.2]octane-1-carbaldehyde  
[0697]



[0698]

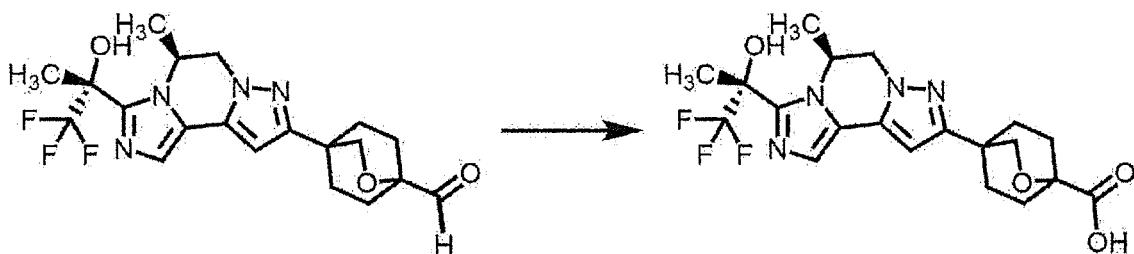
(S)-1,1,1-Trifluoro-2-((S)-9-(1-(hydroxymethyl)-2-oxabicyclo[2.2.2]octan-4-yl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)propan-2-ol (0.28 g) obtained in  
10 the previous step was mixed with chloroform (6 ml). Under ice-  
cooling, Dess-Martin periodinane (0.252 g) was added, and the  
mixture was stirred at room temperature for 16 hr. Under ice-  
cooling, Dess-Martin periodinane (0.334 g) was added, and the  
mixture was stirred at room temperature for 17 hr. To the  
15 reaction mixture were added saturated sodium thiosulfate  
aqueous solution and saturated aqueous sodium hydrogen  
carbonate solution, and the mixture was extracted with ethyl  
acetate. The organic layer was washed with saturated aqueous  
sodium chloride solution, and dried over sodium sulfate.  
20 Sodium sulfate was filtered off, and the filtrate was  
concentrated under reduced pressure to give a crude product  
(0.294 g) of the title compound.

[0699]

Step 14

25 4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)-2-oxabicyclo[2.2.2]octane-1-carboxylic acid

[0700]



[0701]

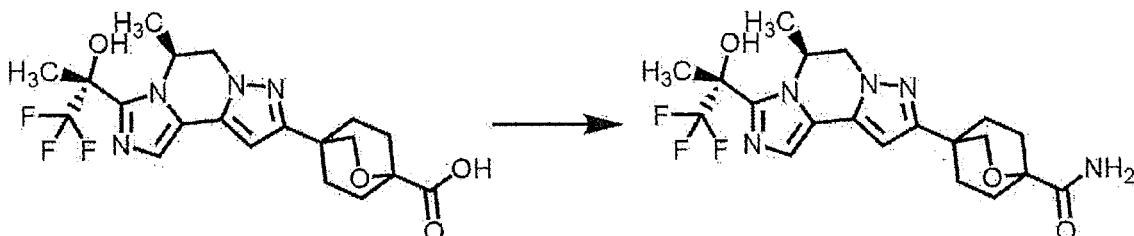
4-((S)-5-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)-2-oxabicyclo[2.2.2]octane-1-carbaldehyde (0.22 g) obtained in the previous step was mixed with acetone (6.6 ml). At room temperature, 2 M chromium trioxide sulfuric acid solution (0.259 ml) was added, and the mixture was stirred for 2 hr. The reaction mixture was purified by reversed-phase column chromatography (water:acetonitrile=90:10 to 0:100) to give a crude product (0.12 g).

[0702]

Step 15

4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)-2-oxabicyclo[2.2.2]octane-1-carboxamide

[0703]



[0704]

4-((S)-5-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)-2-oxabicyclo[2.2.2]octane-1-carboxylic acid (0.12 g) obtained in the previous step was mixed with DMF (2 ml). At room temperature, 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (0.155 g) and 7 M ammonia/methanol solution (0.117 ml) were added,

and the mixture was stirred for 16 hr. To the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed twice with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0 to 0:100) to give a crude product (0.065 g).

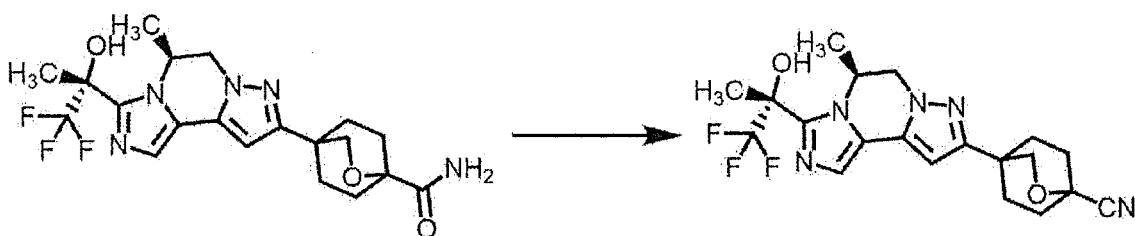
[0705]

10 Step 16

4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)-2-oxabicyclo[2.2.2]octane-1-carbonitrile

[0706]

15



[0707]

4-((S)-5-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)-2-oxabicyclo[2.2.2]octane-1-carboxamide (0.065 g) obtained in the previous step was mixed with tetrahydrofuran (2 ml). Under ice-cooling, triethylamine (0.103 ml) and trifluoroacetic anhydride (0.031 ml) were added, and the mixture was stirred for 1 hr. The reaction mixture was added to silica gel (10 g), and the mixture was eluted with ethyl acetate. The obtained solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0 to 0:100) to give the title compound (0.044 g).

<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.20 (d, J=6.47Hz, 3H), 1.80 (s, 3H), 1.92 - 2.18 (m, 6H), 2.25 - 2.35 (m, 2H), 3.94 (s, 2H), 4.20 -

4.25 (m, 1H), 4.32 - 4.37 (m, 1H), 5.36 - 5.28 (m, 1H), 6.44 (s, 1H), 7.23 (s, 1H), 7.26 (s, 1H)

[0708]

Production Example 10-2

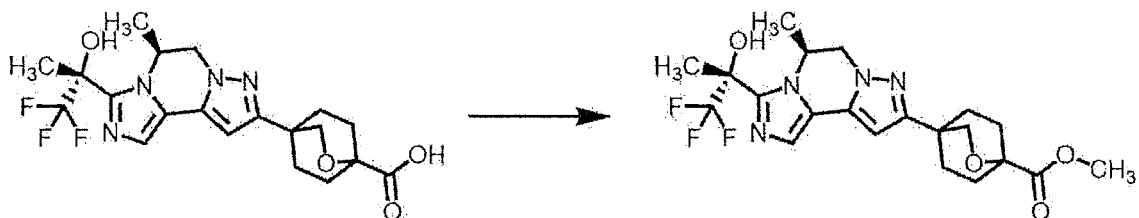
5 Synthesis of (R)-1,1,1-trifluoro-2-((S)-9-(1-(2-hydroxypropan-2-yl)-2-oxabicyclo[2.2.2]octan-4-yl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)propan-2-ol (Example 96)

[0709]

10 Step 1

methyl 4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)-2-oxabicyclo[2.2.2]octane-1-carboxylate

[0710]



15

[0711]

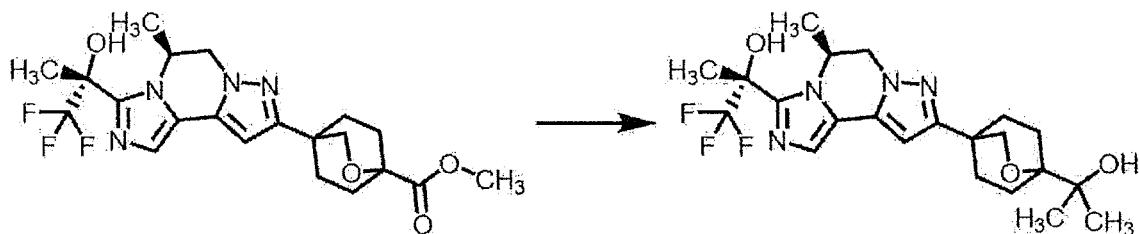
4-((S)-5-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)-2-oxabicyclo[2.2.2]octane-1-carboxylic acid (0.085 g) obtained in the previous step was mixed with methanol (3 ml). At room temperature, 0.6 M trimethylsilyldiazomethane/hexane solution (0.482 ml) was added, and the mixture was stirred for 15 min. The reaction mixture was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0 to 0:100) to give a crude product (0.053 g) of the title compound.

[0712]

Step 2

(R)-1,1,1-trifluoro-2-((S)-9-(1-(2-hydroxypropan-2-yl)-2-oxabicyclo[2.2.2]octan-4-yl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)propan-2-ol

[0713]



[0714]

Under an argon atmosphere, methyl 4-((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)-2-oxabicyclo[2.2.2]octane-1-carboxylate (0.053 g) obtained in the previous step was mixed with tetrahydrofuran (2 ml). The mixture was ice-cooled, and 1.04 M methylmagnesium bromide/tetrahydrofuran solution (0.561 ml) was added. The mixture was stirred at room temperature for 17 hr. To the reaction mixture was added saturated ammonium chloride aqueous solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and sodium sulfate was added. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0 to 0:100) to give the title compound (0.037 g).  
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.04 (s, 6H), 1.21 (d, J=6.47Hz, 3H), 1.64 ~ 1.72 (m, 2H), 1.78 ~ 1.96 (m, 9H), 3.84 (s, 2H), 3.93 (s, 1H), 4.19 ~ 4.25 (m, 1H), 4.32 ~ 4.37 (m, 1H), 5.36 ~ 5.27 (m, 1H), 6.40 (s, 1H), 7.22 (s, 1H), 7.26 (s, 1H)

[0715]

Production Example 11

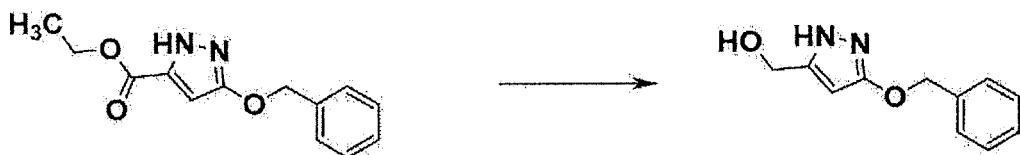
Synthesis of 3-(((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)oxy)methyl)bicyclo[1.1.1]pentane-1-carbonitrile (Example 97)

[0716]

Step 1

(3-(benzyloxy)-1H-pyrazol-5-yl)methanol

[0717]



[0718]

5 The crude product (19 g) of ethyl 3-(benzyloxy)-1H-pyrazole-5-carboxylate obtained in Auxiliary Step 1 was dissolved in cyclopentyl methyl ether (70 ml). Under ice-cooling, the solution was added dropwise to a solution of lithium borohydride (4.17 g) in cyclopentyl methyl ether (150 ml). The reaction mixture was stirred at 0°C for 5 min. Under ice-cooling, a solution of methanol (8 ml) in cyclopentyl methyl ether (50 ml), methanol (8 ml), and methanol (8 ml) were successively added dropwise. The reaction mixture was stirred at 0°C for 10 min. To the reaction mixture were added 10 saturated ammonium chloride aqueous solution and 1N aqueous hydrochloric acid solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was 15 concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=16:84 to ethyl acetate, thereafter ethyl acetate:methanol=82:18) to give the title compound (8.2 g).  
1H-NMR (400 MHz, CDCl<sub>3</sub>) 4.66 (s, 2H), 5.19 (s, 2H), 5.64 (s, 20 1H), 7.26 - 7.47 (m, 5H)

25 [0719]

Step 2

3-(benzyloxy)-1H-pyrazole-5-carbaldehyde

[0720]



30

[0721]

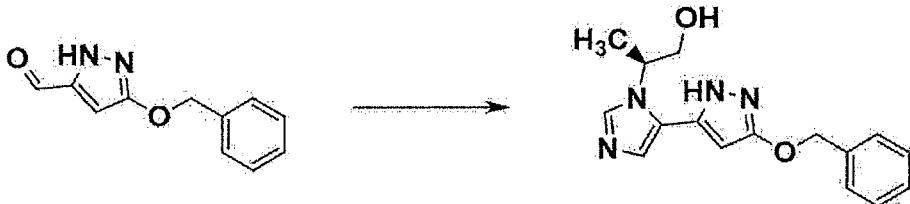
(3-(Benzylxy)-1H-pyrazol-5-yl)methanol (8.2 g) obtained in the previous step was dissolved in 1,2-dimethoxyethane (164 ml). At room temperature, manganese dioxide (41 g) was added, 5 and the mixture was stirred at 80°C for 1.5 hr. The mixture was allowed to cool to room temperature, and filtered through celite, and the filtrate was concentrated under reduced pressure to give a crude product (5.4 g) of the title compound.

[0722]

10 Step 3

(S)-2-(5-(3-(benzylxy)-1H-pyrazol-5-yl)-1H-imidazol-1-yl)propan-1-ol

[0723]



15 [0724]

The crude product (5.4 g) of 3-(benzylxy)-1H-pyrazole-5-carbaldehyde obtained in the previous step was mixed with methanol (54 ml). At room temperature, (S)-2-aminopropan-1-ol (2 g) was added, and the mixture was stirred at room 20 temperature overnight. Under ice-cooling, 1,2-dimethoxyethane (164 ml), p-toluenesulfonylmethyl isocyanide (7.82 g), and potassium carbonate (11.07 g) were added, and the mixture was stirred at room temperature overnight. The reaction mixture was filtered through celite, and the filtrate was concentrated 25 under reduced pressure. To the obtained residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated 30 under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=25:75

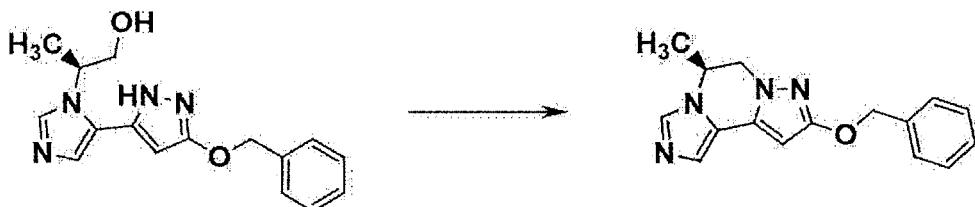
to ethyl acetate, thereafter ethyl acetate:methanol=60:40) to give a crude product (4.1 g) of the title compound.

[0725]

Step 4

5 (S)-9-(benzyloxy)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazine

[0726]



[0727]

10 The crude product (4.1 g) of (S)-2-(5-(3-(benzyloxy)-1H-pyrazol-5-yl)-1H-imidazol-1-yl)propan-1-ol obtained in the previous step and triphenylphosphine (4.69 g) were mixed with tetrahydrofuran (123 ml). Under ice-cooling, di-tert-butyl azodicarboxylate (4.11 g) was added, and the mixture was 15 stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure, and purified by silica gel column chromatography (ethyl acetate:hexane=25:75 to ethyl acetate, thereafter ethyl acetate:methanol=60:40) to give the title compound (2.98 g).

20  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ) 1.64 (d,  $J=6.70\text{Hz}$ , 3H), 3.97 (dd,  $J=12.95$ ,  $8.09\text{Hz}$ , 1H), 4.31 (dd,  $J=12.95$ ,  $4.39\text{Hz}$ , 1H), 4.54 - 4.65 (m, 1H), 5.21 (s, 2H), 5.86 (s, 1H), 7.26 (s, 1H), 7.29 - 7.49 (m, 5H), 7.59 (s, 1H)

[0728]

25 Step 5

(S)-1-(9-(benzyloxy)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)ethan-1-one

[0729]



[0730]

(S)-9-(Benzylxy)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazine (2.98 g) obtained in the previous step was mixed with tetrahydrofuran (29.8 ml). The mixture was 5 cooled to -78°C, and 2 M lithium diisopropylamide/tetrahydrofuran-heptane-ethylbenzene solution (13.29 ml) was added dropwise. The mixture was stirred at -78°C for 30 min. To the mixture was added N-methoxy-N-methylacetamide (5.25 ml), and the mixture was stirred at -78°C 10 for 1 hr. To the reaction mixture were added saturated ammonium chloride aqueous solution and ethyl acetate, and the precipitated solid was collected by filtration. The filtrate was partitioned, and the organic layer was washed with saturated aqueous sodium chloride solution and dried over 15 sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. To the obtained residue was added ethyl acetate/hexane=1/1 (10 ml), and the mixture was stirred at room temperature. The precipitated solid was collected by filtration. It was 20 combined with the solid collected earlier by filtration and mixed with ethyl acetate. The mixture was concentrated under reduced pressure to give the title compound (2 g).

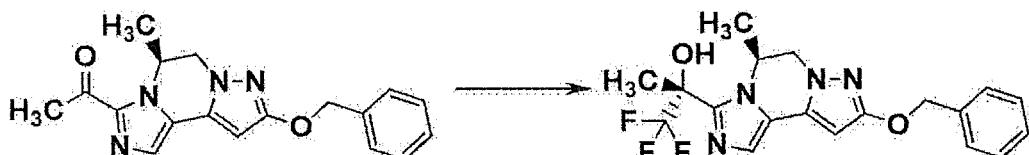
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.44 (d, J=6.58Hz, 3H), 2.69 (s, 3H), 4.19 (dd, J=13.45, 1.20Hz, 1H), 4.29 (dd, J=13.45, 4.63Hz, 1H), 25 5.24 (s, 2H), 5.75 - 5.84 (m, 1H), 5.98 (s, 1H), 7.32 - 7.50 (m, 6H)

[0731]

Step 6

(R)-2-((S)-9-(benzyloxy)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)-1,1,1-trifluoropropan-2-ol

[0732]



[0733]

(S)-1-(9-(Benzylxy)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)ethan-1-one (2 g) obtained in the previous step was mixed with tetrahydrofuran (29.8 ml).  
5 Under ice-cooling, to the mixture was added cesium fluoride (0.195 g), and then (trifluoromethyl)trimethylsilane (1.088 ml) was added dropwise. The reaction mixture was stirred at room temperature for 20 min. Under ice-cooling, methanol (24.84 ml) and potassium carbonate (1.065 g) were added, and 10 the mixture was stirred at room temperature for 45 min. The reaction mixture was concentrated under reduced pressure, water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate.  
15 Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=12:88 to 4:96) to give the title compound (2.2 g).

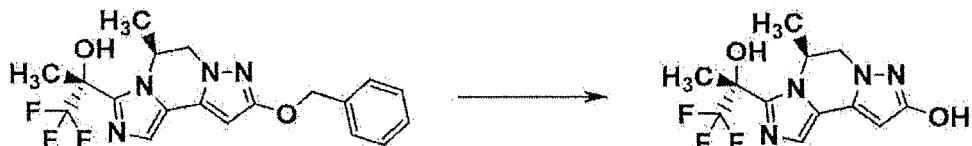
20  $^1\text{H-NMR}$  (400 MHz, DMSO- $\text{D}_6$ ) 1.28 (d,  $J=6.70\text{Hz}$ , 3H), 1.80 (s, 3H), 4.12 - 4.24 (m, 2H), 5.15 (s, 2H), 5.27 - 5.36 (m, 1H), 6.04 (s, 1H), 7.23 (s, 1H), 7.28 (s, 1H), 7.29 - 7.46 (m, 5H)

[0734]

Step 7

25 (S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-ol

[0735]



[0736]

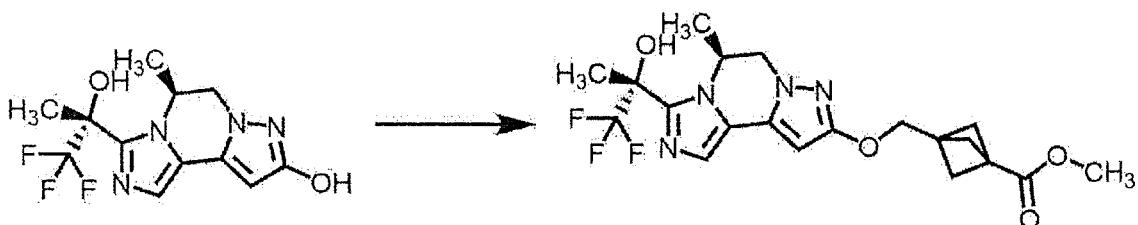
30 (R)-2-((S)-9-(Benzylxy)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-3-yl)-1,1,1-trifluoropropan-2-ol (2.2 g) obtained in the previous step and 10% palladium carbon

(0.44 g) were mixed with ethanol (44 g). Under hydrogen atmosphere, the mixture was stirred at room temperature for 1.5 hr. The reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure. The 5 obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=16:84 to ethyl acetate, thereafter purified by ethyl acetate:methanol=80:20). To the obtained crude product were successively added ethyl acetate (6 ml) and hexane (6 ml), and the mixture was stirred at room 10 temperature. The precipitated solid was collected by filtration to give the title compound (1.82 g). The steric configuration of the title compound was determined by X-ray crystal structure analysis.

<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.28 (d, J=6.58Hz, 3H), 1.81 (s, 3H), 15 4.07 - 4.11 (m, 2H), 5.23 - 5.36 (m, 1H), 5.75 (s, 1H), 7.20 (s, 1H), 7.26 (brs, 1H), 9.89 (brs, 1H)  
[0737]

#### Step 8

methyl 3-(((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-  
20 hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)oxy)methyl)bicyclo[1.1.1]pentane-1-carboxylate  
[0738]



[0739]

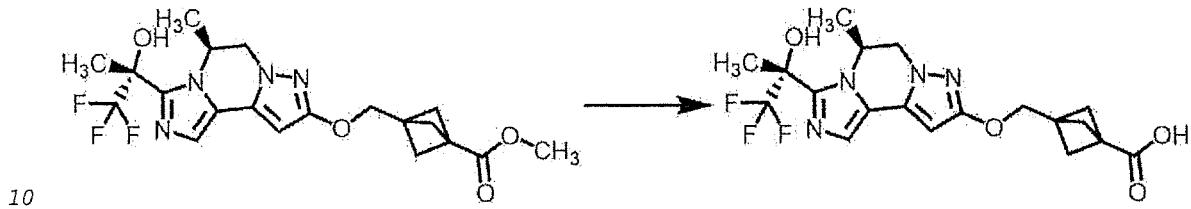
25 (S)-5-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-ol (0.1 g) and methyl 3-(hydroxymethyl)bicyclo[1.1.1]pentane-1-carboxylate (0.078 g) were mixed with tetrahydrofuran (3 ml). Under heating at 70°C, triphenylphosphine (0.13 g) and 30 diisopropyl azodicarboxylate (0.096 ml) were added, and the

mixture was stirred for 15 min. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0 to 0:100) to give a crude product (0.135 g).  
[0740]

5 Step 9

3-(((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)oxy)methyl)bicyclo[1.1.1]pentane-1-carboxylic acid

[0741]



[0742]

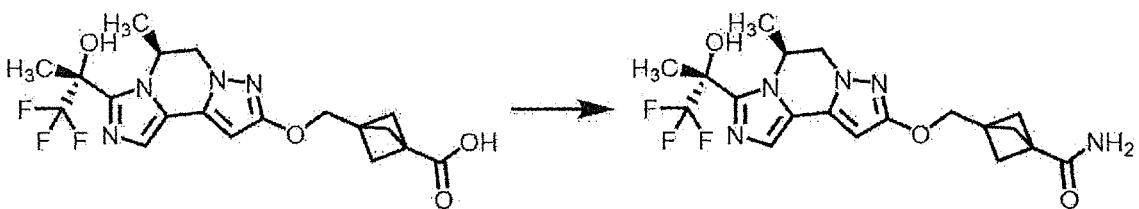
Methyl 3-(((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)oxy)methyl)bicyclo[1.1.1]pentane-1-carboxylate (0.135 g) obtained in the previous step was mixed with ethanol (2 ml). 2N Sodium hydroxide aqueous solution (1 ml) was added, and the mixture was stirred at 80°C for 8 hr. At room temperature, 2N hydrogen chloride solution (1 ml) was added, and the mixture was concentrated under reduced pressure. The obtained residue was extracted with ethyl acetate, and washed with saturated aqueous sodium chloride solution. Sodium sulfate was added. Sodium sulfate was filtered off. The filtrate was concentrated under reduced pressure to give a crude product (0.131 g) of the title compound.

25 [0743]

Step 10

3-(((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)oxy)methyl)bicyclo[1.1.1]pentane-1-carboxamide

30 [0744]



[0745]

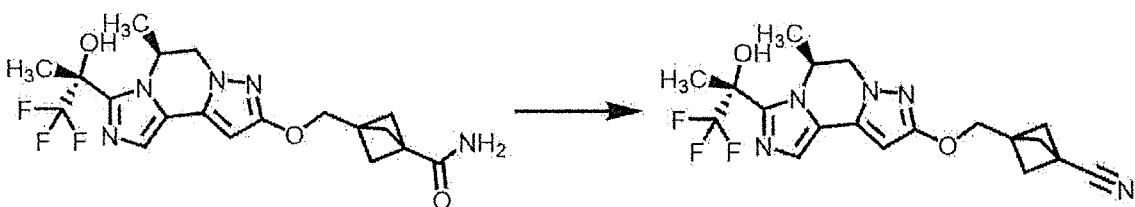
3-(((S)-5-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)oxy)methyl)bicyclo[1.1.1]pentane-1-carboxylic acid (0.131 g) obtained in the previous step was mixed with DMF (2 ml). At room temperature, 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (0.175 g) and 7 M ammonia/methanol solution (0.132 ml) were added, and the mixture was stirred for 16 hr. Water was added, and the mixture was extracted with ethyl acetate. The organic layer was washed twice with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0 to 0:100) to give a crude product (0.095 g).

[0746]

Step 11

20 3-(((S)-5-methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)oxy)methyl)bicyclo[1.1.1]pentane-1-carbonitrile

[0747]



25 [0748]

3-(((S)-5-Methyl-3-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-a]pyrazolo[5,1-c]pyrazin-9-yl)oxy)methyl)bicyclo[1.1.1]pentane-1-carboxamide (0.095 g)

obtained in the previous step was mixed with tetrahydrofuran (2 ml). Under ice-cooling, triethylamine (0.156 ml) and trifluoroacetic anhydride (0.047 ml) were added, and the mixture was stirred for 15 min. The reaction mixture was added 5 to silica gel (10 g), and the mixture was eluted with ethyl acetate. The obtained filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane:ethyl acetate=100:0 to 0:100) to give the title compound (0.077 g).

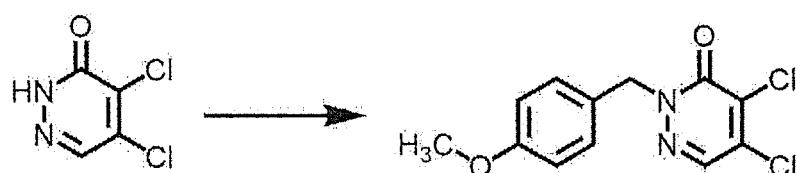
10  $^1\text{H-NMR}$  (400 MHz, DMSO- $\text{D}_6$ ) 1.25 (d,  $J=6.47\text{Hz}$ , 3H), 1.80 (s, 3H), 2.23 (s, 6H), 4.09 (s, 2H), 4.12 – 4.15 (m, 2H), 5.34 – 5.27 (m, 1H), 5.97 (s, 1H), 7.21 (s, 1H), 7.28 (s, 1H)  
[0749]

#### Production Example 12

15 Synthesis of mixture of (R)-1,1,1-trifluoro-2-((R)-5-methyl-9-(trifluoromethyl)-5,6-dihdropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-4-yl)propan-2-ol and (S)-1,1,1-trifluoro-2-((S)-5-methyl-9-(trifluoromethyl)-5,6-dihdropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-4-yl)propan-2-ol (Example 99) and (R)-1,1,1-trifluoro-2-((R)-5-methyl-9-(trifluoromethyl)-5,6-dihdropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-4-yl)propan-2-ol (Example 100)  
20 [0750]

#### Step 1

25 4,5-dichloro-2-(4-methoxybenzyl)pyridazin-3(2H)-one  
[0751]



[0752]

30 4,5-Dichloropyridazin-3(2H)-one (18.5 g) was dissolved in toluene (185 ml). At room temperature, to the reaction mixture were added 4-methoxybenzyl chloride (16.0 ml),

tetrabutylammonium bromide (6.35 g), and 2N potassium hydroxide aqueous solution (59.1 ml), and the mixture was heated under reflux at 120°C for 7 hr. Water was added to the reaction mixture, and a partitioning operation was performed.

5 The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=88:12

10 to ethyl acetate). The obtained solid was washed with hexane to give the title compound (8.8 g).

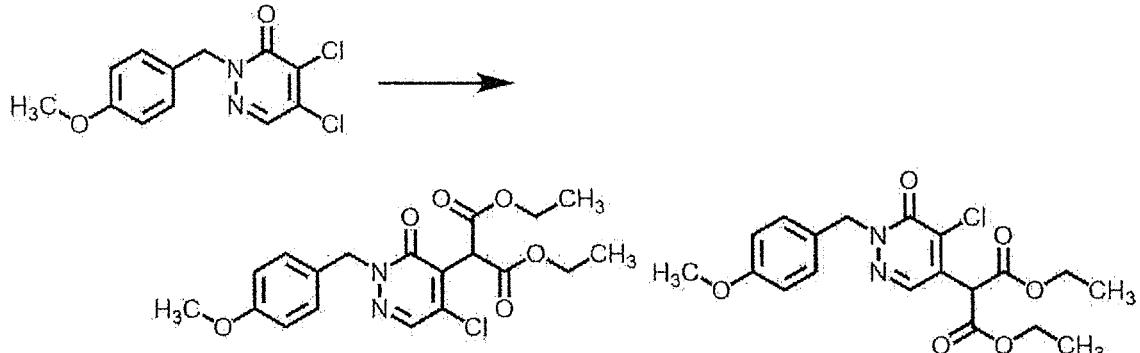
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 3.73 (s, 3H), 5.21 (s, 2H), 6.88 - 6.91 (m, 2H), 7.26 - 7.28 (m, 2H), 8.22 (s, 1H)

[0753]

15 Step 2

mixture of diethyl 2-(5-chloro-2-(4-methoxybenzyl)-3-oxo-2,3-dihydropyridazin-4-yl)malonate and diethyl 2-(5-chloro-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyridazin-4-yl)malonate

[0754]



20

[0755]

Diethyl malonate (21 ml) was dissolved in tetrahydrofuran (157 ml). At room temperature, to the reaction mixture was added sodium tert-pentoxide (15.2 g), and the mixture was stirred at room temperature for 15 min. To the reaction mixture was added 4,5-dichloro-2-(4-methoxybenzyl)pyridazin-3(2H)-one (15.7 g), and the mixture was stirred at 75°C for 3 hr. At room temperature, to the reaction mixture was added

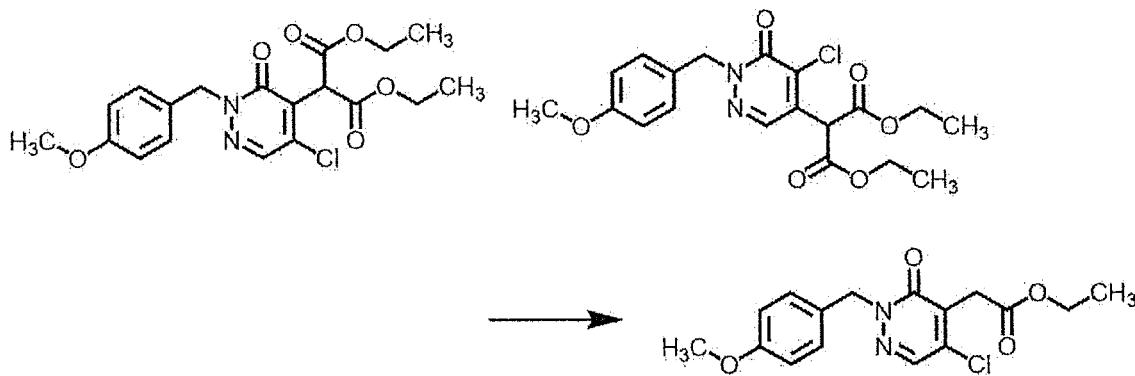
saturated ammonium chloride aqueous solution, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and filtered through a phase separator. The filtrate 5 was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane to ethyl acetate:hexane=50:50) to give a crude product (13.8 g) of the title compound.

[0756]

10 Step 3

ethyl 2-(5-chloro-2-(4-methoxybenzyl)-3-oxo-2,3-dihydropyridazin-4-yl)acetate

[0757]



15 [0758]

The mixture (13.75 g) of diethyl 2-(5-chloro-2-(4-methoxybenzyl)-3-oxo-2,3-dihydropyridazin-4-yl)malonate and diethyl 2-(5-chloro-1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyridazin-4-yl)malonate obtained in the previous step 20 was dissolved in dimethyl sulfoxide (53.6 ml). To the reaction mixture was added water (53.6 ml), and the mixture was stirred at 135°C overnight. At room temperature, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water 25 and saturated aqueous sodium chloride solution, and filtered through a phase separator. The filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane to ethyl

acetate:hexane=50:50) to give the title compound (10.6 g).

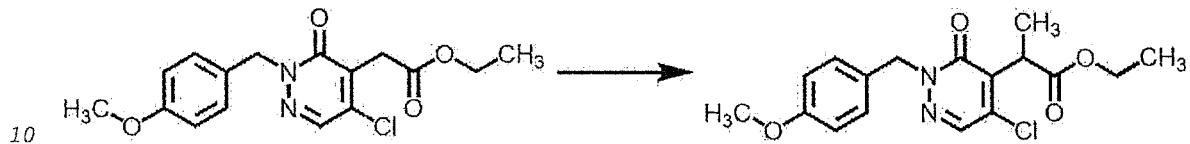
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.15 (t, J=7.07Hz, 3H), 3.70 (s, 2H), 3.72 (s, 3H), 4.08 (q, J=7.07Hz, 2H), 5.18 (s, 2H), 6.88 - 6.90 (m, 2H), 7.23 - 7.26 (m, 2H), 8.13 (s, 1H)

5 [0759]

Step 4

ethyl 2-(5-chloro-2-(4-methoxybenzyl)-3-oxo-2,3-dihydropyridazin-4-yl)propanoate

[0760]



[0761]

Ethyl 2-(5-chloro-2-(4-methoxybenzyl)-3-oxo-2,3-dihydropyridazin-4-yl)acetate (10.64 g) obtained in the previous step was dissolved in tetrahydrofuran (96 ml). At - 15 78°C, to the reaction mixture was added dropwise 1.08 M lithium bis(trimethylsilyl)amide/tetrahydrofuran solution (30.7 ml), and the mixture was stirred for 30 min. At -78°C, to the reaction mixture was added dropwise methyl iodide (2.1 ml), and the mixture was stirred for 3 hr while raising the 20 temperature to room temperature. To the reaction mixture was added saturated ammonium chloride aqueous solution at room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and filtered 25 through a phase separator. The filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane to ethyl acetate:hexane=50:50) to give the title compound (9.3 g).

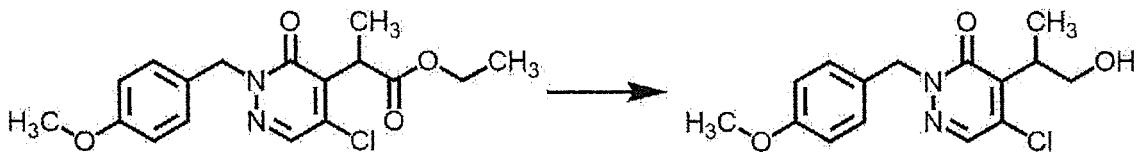
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.01 (t, J=7.06Hz, 3H), 1.30 (d, J=7.06Hz, 3H), 3.72 (s, 3H), 3.93 - 4.10 (m, 3H), 5.06 (d, J=13.99Hz, 1H), 5.26 (d, J=13.99Hz, 1H), 6.88 - 6.90 (m, 2H), 7.23 - 7.25 (m, 2H), 8.11 (s, 1H)

[0762]

Step 5

5-chloro-4-(1-hydroxypropan-2-yl)-2-(4-methoxybenzyl)pyridazin-3(2H)-one

5 [0763]



[0764]

Ethyl 2-(5-chloro-2-(4-methoxybenzyl)-3-oxo-2,3-dihydropyridazin-4-yl)propanoate (9.3 g) obtained in the 10 previous step was dissolved in diethyl ether (140 ml). Under ice-cooling, 2.0 M lithium borohydride/tetrahydrofuran solution (26.5 ml) was added dropwise, and the mixture was stirred at room temperature for 1 hr. Under ice-cooling, to the reaction mixture was added saturated ammonium chloride 15 aqueous solution, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and filtered through a phase separator. The filtrate was concentrated under reduced pressure. The obtained residue was purified by silica 20 gel column chromatography (ethyl acetate:hexane=25:75 to 67:33) to give the title compound (4.3 g).

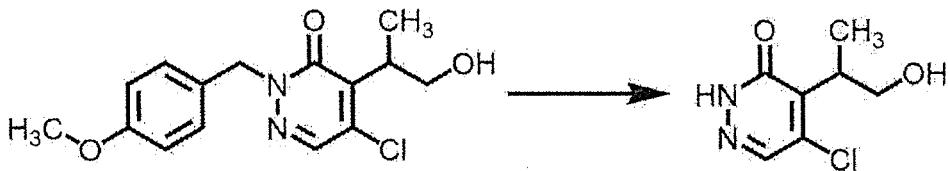
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.16 (d, J=7.17Hz, 4H), 3.28 - 3.36 (m, 1H), 3.54 - 3.60 (m, 1H), 3.71 (s, 3H), 3.80 - 3.86 (m, 1H), 4.68 (t, J=5.66Hz, 1H), 5.12 (dd, J=18.50, 14.10Hz, 2H), 25 6.87 - 6.89 (m, 2H), 7.23 - 7.25 (m, 2H), 7.98 (s, 1H)

[0765]

Step 6

5-chloro-4-(1-hydroxypropan-2-yl)pyridazin-3(2H)-one

[0766]



[0767]

5-Chloro-4-(1-hydroxypropan-2-yl)-2-(4-methoxybenzyl)pyridazin-3(2H)-one (4.3 g) obtained in the previous step was mixed with acetonitrile (43 ml). Under ice-cooling, to the reaction mixture was added dropwise a mixed solution of cerium(IV) ammonium nitrate (18.3 g) and water (21.5 ml), and the mixture was stirred at room temperature for 2 hr. At room temperature, to the reaction mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and filtered through a phase separator. The filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=50:50 to ethyl acetate) to give the title compound (1.92 g).

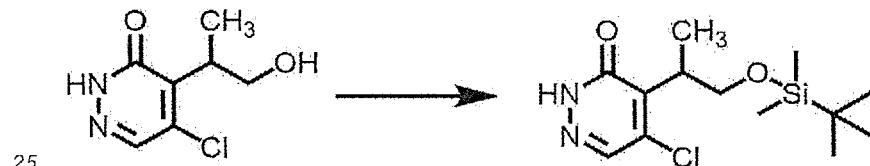
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.18 (d, J=6.94Hz, 3H), 3.28 - 3.34 (m, 1H), 3.58 (dd, J=10.29, 6.47Hz, 1H), 3.85 (dd, J=10.29, 8.32Hz, 1H), 7.90 (s, 1H), 13.10 (s, 1H)

[0768]

Step 7

4-(1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-5-chloropyridazin-3(2H)-one

[0769]



[0770]

5-Chloro-4-(1-hydroxypropan-2-yl)pyridazin-3(2H)-one (1.92 g) obtained in the previous step was mixed with dimethylformamide (19.2 ml). At room temperature, imidazole

(1.0 g), tert-butyldimethylchlorosilane (1.69 g), and 4-dimethylaminopyridine (0.12 g) were added, and the mixture was stirred for 30 min. The reaction mixture was purified by silica gel column chromatography (hexane to ethyl acetate:hexane=50:50) to give the title compound (2.74 g).

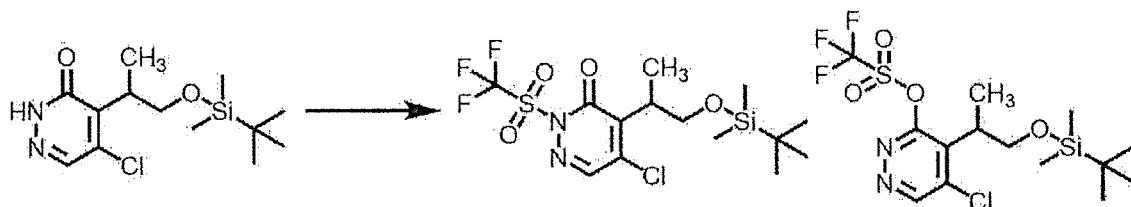
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 0.06 (s, 3H), 0.08 (s, 3H), 0.85 (s, 9H), 1.27 (d, J=7.17Hz, 3H), 3.40 – 3.49 (m, 1H), 3.82 (dd, J=9.42, 6.24Hz, 1H), 4.14 (t, J=9.42Hz, 1H), 8.00 (s, 1H), 13.22 (s, 1H)

10 [0771]

Step 8

mixture of 4-(1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-5-chloro-2-((trifluoromethyl)sulfonyl)pyridazin-3(2H)-one and 4-(1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-5-chloropyridazin-3-yl trifluoromethylsulfonate

15 [0772]



20 [0773]

4-(1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-5-chloropyridazin-3(2H)-one (2.74 g) obtained in the previous step was mixed with dichloromethane (27.4 ml). Under ice-cooling, to the mixture were added pyridine (2.2 ml) and trifluoromethanesulfonic anhydride (2.3 ml). The reaction mixture was stirred overnight while raising the temperature to room temperature. The reaction mixture was purified by silica gel column chromatography (hexane to ethyl acetate:hexane=33:67) to give a crude product (3.37 g) of the title compound.

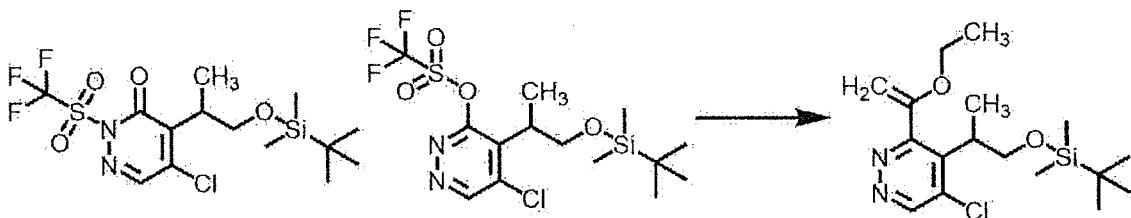
25 [0774]

30 Step 9

4-(1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-5-chloro-3-(1-

ethoxyvinyl)pyridazine

[0775]



[0776]

5 The mixture (3.37 g) of 4-(1-((tert-  
butyldimethylsilyl)oxy)propan-2-yl)-5-chloro-2-  
((trifluoromethyl)sulfonyl)pyridazin-3(2H)-one and 4-(1-  
((tert-butyldimethylsilyl)oxy)propan-2-yl)-5-chloropyridazin-  
3-yl trifluoromethylsulfonate obtained in the previous step  
10 was mixed with 1,4-dioxane (33.7 ml). At room temperature, to  
the reaction mixture were added tributyl(1-  
ethoxyvinyl)stannane (2.88 ml), lithium chloride (0.66 g), and  
copper iodide (0.15 g). The reaction mixture was stirred at  
95°C for 2.5 hr, and then stirred at 110°C for 2 hr. The  
15 reaction mixture was filtered through celite, and the filtrate  
was concentrated under reduced pressure. The crude product was  
filtered through aminosilica, and the filtrate was  
concentrated under reduced pressure. The obtained residue was  
purified by aminosilica gel chromatography (hexane to ethyl  
20 acetate:hexane=50:50) to give the title compound (1.08 g).

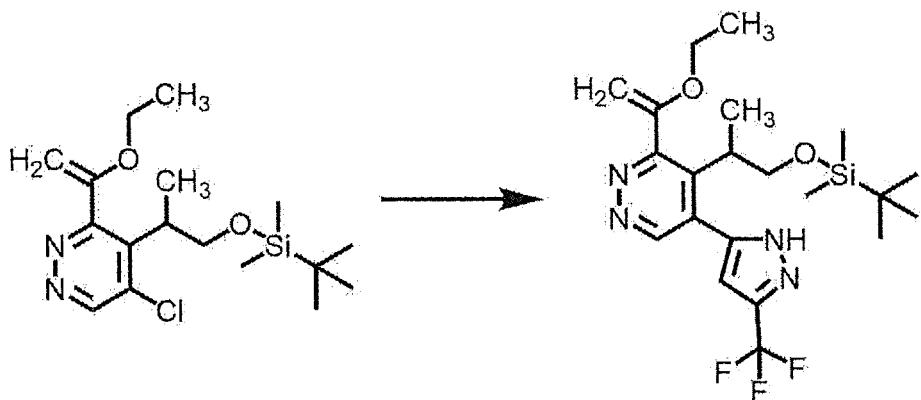
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) - 0.08 (s, 3H), - 0.04 (s, 3H), 0.70  
(s, 9H), 1.28 - 1.32 (m, 6H), 3.38 - 3.40 (m, 1H), 3.83 (dd,  
J=9.54, 7.19Hz, 1H), 3.94 (q, J=7.19Hz, 2H), 4.03 (t, J=9.54Hz,  
1H), 4.42 (d, J=2.66Hz, 1H), 4.64 (d, J=2.66Hz, 1H), 9.24 (s,  
25 1H)

[0777]

Step 10

4-(1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-3-(1-  
ethoxyvinyl)-5-(3-(trifluoromethyl)-1H-pyrazol-5-yl)pyridazine

30 [0778]



[0779]

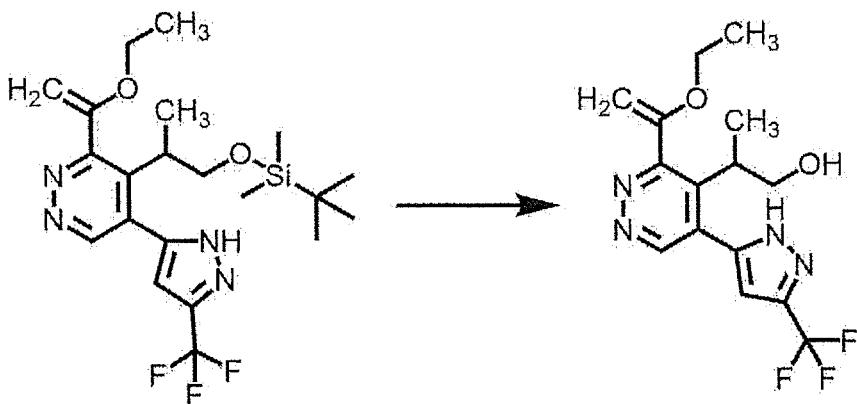
4-((tert-butyldimethylsilyl)oxy)propan-2-yl 5-chloro-3-(1-ethoxyvinyl)pyridazine (0.1 g) obtained in the previous 5 step was mixed with 1,4-dioxane (2.0 ml) and water (1.0 ml). To the reaction mixture were added tripotassium phosphate (18.3 g), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)-1H-pyrazole (18.3 g), and Xphos Pd G4 (0.024 g), and the mixture was stirred at 110°C for 1 hr. At room 10 temperature, to the reaction mixture was added saturated ammonium chloride aqueous solution, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and filtered through a phase separator. The filtrate 15 was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=25:75 to ethyl acetate) to give a crude product (0.067 g) of the title compound.

[0780]

20 Step 11

2-(3-(1-ethoxyvinyl)-5-(3-(trifluoromethyl)-1H-pyrazol-5-yl)pyridazin-4-yl)propan-1-ol

[0781]



[0782]

The crude product (0.067 g) of 4-(1-((tert-butyldimethylsilyl)oxy)propan-2-yl)-3-(1-ethoxyvinyl)-5-(3-(trifluoromethyl)-1H-pyrazol-5-yl)pyridazine obtained in the previous step was mixed with tetrahydrofuran (1.0 ml). Under ice-cooling, to the reaction mixture was added 1.0 M tetrabutylammonium fluoride/tetrahydrofuran solution (0.22 ml), and the mixture was stirred at room temperature for 1 hr. To the reaction mixture was added saturated ammonium chloride aqueous solution, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and filtered through a phase separator. The filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=50:50 to ethyl acetate, thereafter ethyl acetate:methanol=90:10) to give the title compound (0.026 g).

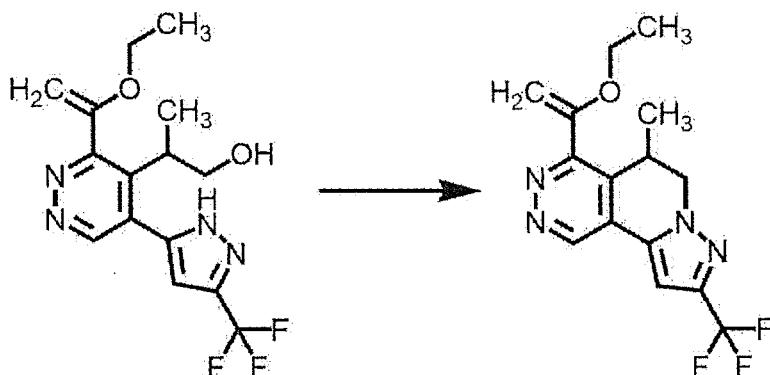
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.12 (d, J=6.94Hz, 3H), 1.32 (t, J=6.82Hz, 3H), 3.19 - 3.21 (m, 1H), 3.40 - 3.42 (m, 1H), 3.51 (dd, J=10.29, 7.03Hz, 1H), 3.96 (q, J=7.03Hz, 2H), 4.43 (d, J=2.66Hz, 1H), 4.64 (d, J=2.66Hz, 1H), 7.09 (s, 1H), 9.10 (s, 1H)

[0783]

Step 12

4-(1-ethoxyvinyl)-5-methyl-9-(trifluoromethyl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazine

[0784]



[0785]

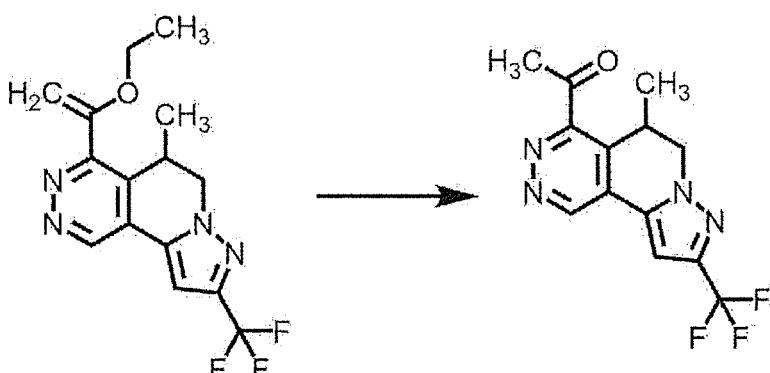
2-(3-(1-Ethoxyvinyl)-5-(3-(trifluoromethyl)-1H-pyrazol-5-yl)pyridazin-4-yl)propan-1-ol (0.026 g) obtained in the previous step was mixed with tetrahydrofuran (0.52 ml). To the reaction mixture were added triphenylphosphine (0.023 g) and diisopropyl azodicarboxylate (0.018 ml), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=30:70 to ethyl acetate, thereafter ethyl acetate:methanol=80:20) to give a crude product (0.031 g) of the title compound containing impurity.

[0786]

Step 13

1-(5-methyl-9-(trifluoromethyl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-4-yl)ethan-1-one

[0787]



[0788]

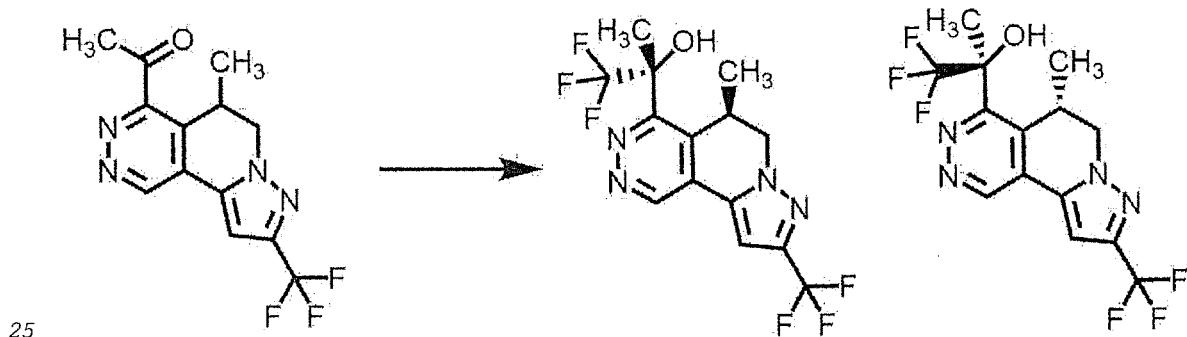
The crude product (0.031 g) of 4-(1-ethoxyvinyl)-5-methyl-9-(trifluoromethyl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazine obtained in the previous step was mixed with tetrahydrofuran (0.31 ml) and 5 methanol (0.31 ml). To the reaction mixture was added 6 M hydrochloric acid (0.096 ml), and the mixture was stirred at 50°C for 1 hr. At room temperature, to the reaction mixture was added 2 M sodium hydroxide aqueous solution (0.3 ml), and the mixture was extracted with ethyl acetate. The organic 10 layer was washed successively with water and saturated aqueous sodium chloride solution, and filtered through a phase separator. The filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=30:70 to 90:10) to 15 give a crude product (0.025 g) of the title compound.

[0789]

Step 14

mixture of (R)-1,1,1-trifluoro-2-((R)-5-methyl-9-(trifluoromethyl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-4-yl)propan-2-ol and (S)-1,1,1-trifluoro-2-((S)-5-methyl-9-(trifluoromethyl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-4-yl)propan-2-ol

[0790]



[0791]

The crude product (0.025 g) of 1-(5-methyl-9-(trifluoromethyl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-

d]pyridazin-4-yl)ethan-1-one obtained in the previous step was mixed with tetrahydrofuran (0.5 ml). Under ice-cooling, to the mixture was added cesium fluoride (0.006 g), and then added dropwise (trifluoromethyl)trimethylsilane (0.025 ml). The 5 reaction mixture was stirred for 1 hr while raising the temperature to room temperature. At room temperature, methanol (0.5 ml) and potassium carbonate (0.035 g) were added, and the mixture was stirred at room temperature for 1 hr. To the reaction mixture was added saturated ammonium chloride aqueous 10 solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated aqueous sodium chloride solution, and filtered through a phase separator, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by reversed-phase 15 silica gel chromatography (acetonitrile:water=0:100 to 100:0) to give the title compound (0.009 g) as a racemate.

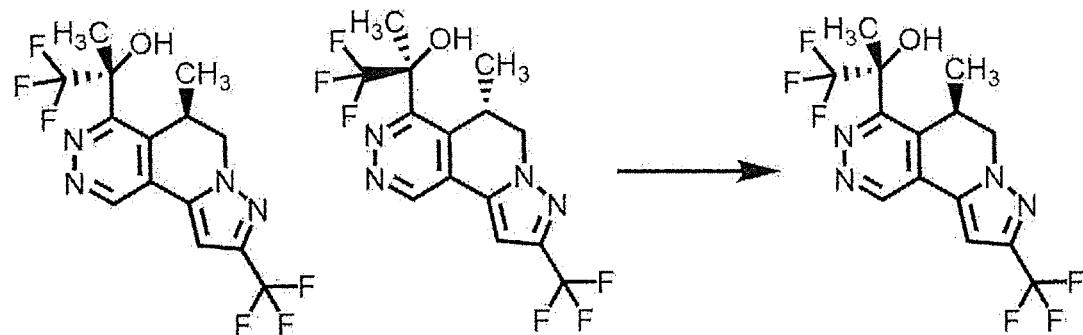
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.13 (d, J=6.70Hz, 3H), 2.01 (s, 3H), 4.32 – 4.35 (m, 2H), 4.49 – 4.52 (m, 1H), 7.38 (s, 1H), 7.66 (s, 1H), 9.66 (s, 1H)

20 [0792]

### Step 15

(R)-1,1,1-trifluoro-2-((R)-5-methyl-9-(trifluoromethyl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-4-yl)propan-2-ol

25 [0793]



[0794]

The mixture (0.0067 g) of (R)-1,1,1-trifluoro-2-((R)-5-methyl-9-(trifluoromethyl)-5,6-

dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-4-yl)propan-2-ol and (S)-1,1,1-trifluoro-2-((S)-5-methyl-9-(trifluoromethyl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-4-yl)propan-2-ol obtained in the previous step was 5 subjected to optical resolution using supercritical fluid chromatography (apparatus name: Waters SFC Prep15 System, column: Daicel CHIRALPAK IC/SFC, 10 mm(I.D.) x 250 mm(L), 5  $\mu$ m, column temperature: 40°C, column back pressure: 120 bar, mobile phase flow rate: 15 ml/min, mobile phase mixing ratio: 10 isocratic, carbon dioxide:methanol=93:7, fraction trigger: UV 214 nm) to give the title compound (0.002 g) as the first peak fraction.

<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 1.23 (d, J=6.94Hz, 3H), 2.16 (s, 3H), 3.49 (s, 1H), 4.29 - 4.33 (m, 2H), 4.45 (d, J=12.02Hz, 1H), 15 7.05 (s, 1H), 9.31 (s, 1H)  
[0795]

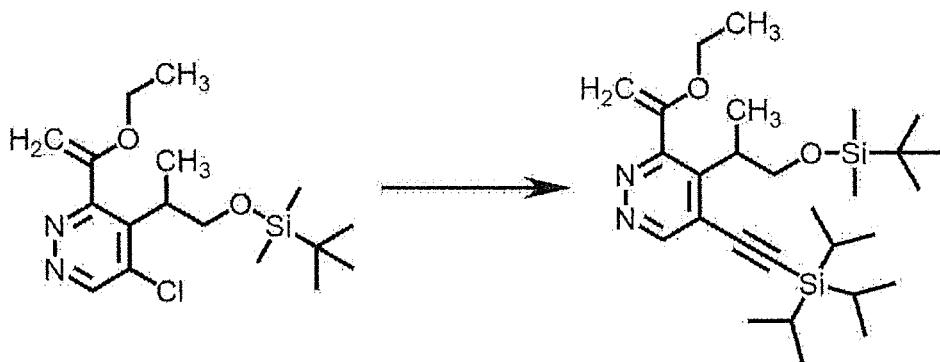
#### Production Example 13

Synthesis of (R)-1,1,1-trifluoro-2-[(R)-9-(1-fluorocyclopropyl)-5-methyl-5,6- 20 dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-4-yl]propan-2-ol and (S)-1,1,1-trifluoro-2-[(S)-9-(1-fluorocyclopropyl)-5-methyl-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-4-yl]propan-2-ol (Example 101)

[0796]

#### 25 Step 1

4-{1-[(tert-butyldimethylsilyl)oxy]propan-2-yl}-3-(1-ethoxyvinyl)-5-[(triisopropylsilyl)ethynyl]pyridazine  
[0797]



[0798]

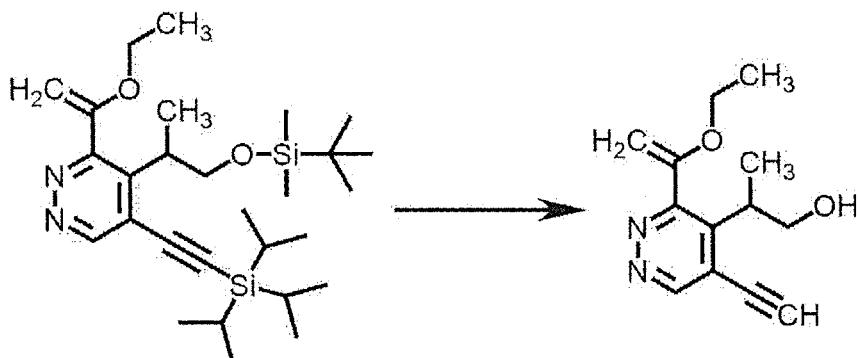
To a suspension of 4-{1-[(tert-butyldimethylsilyl)oxy]propan-2-yl}-5-chloro-3-(1-ethoxyvinyl)pyridazine (300 mg) obtained in the previous step,  
<sup>5</sup> bis(acetonitrile)palladium(II) dichloride (22 mg), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (120 mg), and cesium carbonate (821 mg) in acetonitrile (5 ml) was added ethynyltriisopropylsilane (0.28 ml) under an argon atmosphere,  
<sup>10</sup> and the mixture was stirred at 85°C for 15 hr. To the reaction mixture was added ethyl acetate, and insoluble material was filtered off through celite. The filtrate was concentrated under reduced pressure and the obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane) to  
<sup>15</sup> give a mixture (260 mg) containing a crude product of the title compound.

[0799]

Step 2

2-[(3-(1-ethoxyvinyl)-5-ethynylpyridazin-4-yl)propan-1-ol

<sup>20</sup> [0800]



[0801]

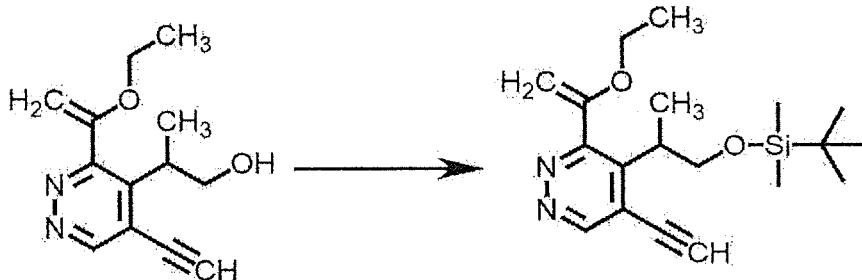
To a solution of 4-{1-[(tert-butyldimethylsilyl)oxy]propan-2-yl}-3-(1-ethoxyvinyl)-5-[(triisopropylsilyl)ethynyl]pyridazine (260 mg) obtained in the previous step in tetrahydrofuran (5 ml) was added under 5 ice-cooling 1 M tetrabutylammonium fluoride/tetrahydrofuran solution (1.2 ml), and the mixture was stirred for 10 min. The mixture was returned to room temperature and stirred for 2 hr. Saturated ammonium chloride aqueous solution was added, and the mixture was extracted with ethyl acetate. The organic 10 layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane) to give a crude product (92 mg) of the title compound.

15 [0802]

Step 3

4-{1-[(tert-butyldimethylsilyl)oxy]propan-2-yl}-3-(1-ethoxyvinyl)-5-ethynylpyridazine

[0803]



[0804]

To a solution of 2-[3-(1-ethoxyvinyl)-5-ethynylpyridazin-4-yl]propan-1-ol (35 mg) obtained in the previous step in N,N-dimethylformamide (0.35 ml) were added imidazole (15 mg) and 25 tert-butyldimethylsilyl chloride (27 mg), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure and the obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane) to give a crude product (48 mg) of the title

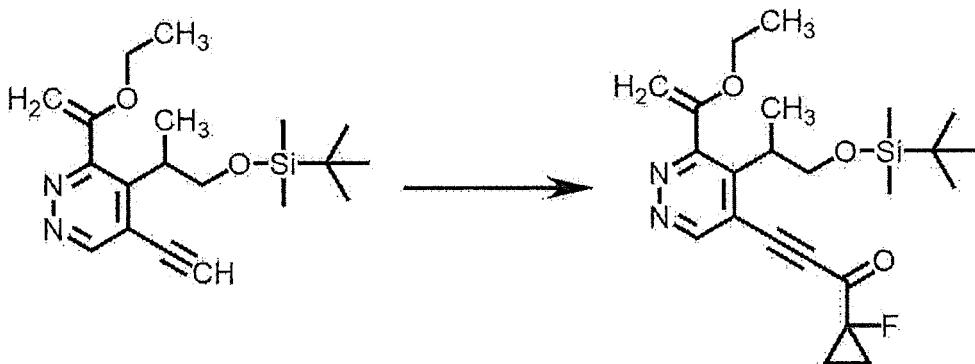
compound.

[0805]

Step 4

3-(5-{1-[ (tert-butyldimethylsilyl)oxy]propan-2-yl}-6-(1-ethoxyvinyl)pyridazin-4-yl)-1-(1-fluorocyclopropyl)prop-2-yn-1-one

[0806]



[0807]

Under an argon atmosphere, to a solution of 4-{1-[ (tert-butyldimethylsilyl)oxy]propan-2-yl}-3-(1-ethoxyvinyl)-5-ethynylpyridazine (18 mg) obtained in the previous step in tetrahydrofuran (0.27 ml) was added dropwise at -75°C 2 M lithium diisopropylamide/tetrahydrofuran-heptane-ethylbenzene solution (0.052 ml), and the mixture was stirred for 30 min.

At -75°C, a solution of 1-fluoro-N-methoxy-N-methylcyclopropane-1-carboxamide (15 mg) obtained in Auxiliary Step 6 in tetrahydrofuran (0.27 ml) was added dropwise through a cannula. After the dropwise addition, the mixture was stirred at room temperature for 1 hr. Under ice-cooling, 2 M lithium diisopropylamide/tetrahydrofuran-heptane-ethylbenzene solution (0.052 ml) and a solution of 1-fluoro-N-methoxy-N-methylcyclopropane-1-carboxamide (15 mg) in tetrahydrofuran (0.27 ml) were added again, and the mixture was stirred at room temperature for 1 hr. To the reaction mixture was added under ice-cooling saturated ammonium chloride aqueous solution, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent

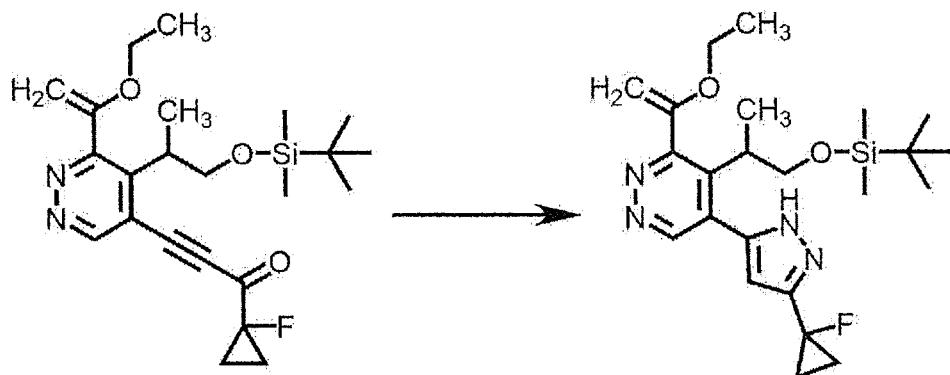
was evaporated under reduced pressure. The obtained residue was purified by thin layer silica gel column chromatography (ethyl acetate:hexane=1:2) to give a crude product (11 mg) of the title compound.

5 [0808]

Step 5

4-{1-[*tert*-butyldimethylsilyl]oxy}propan-2-yl}-3-(1-ethoxyvinyl)-5-[3-(1-fluorocyclopropyl)-1*H*-pyrazol-5-yl]pyridazine

10 [0809]



[0810]

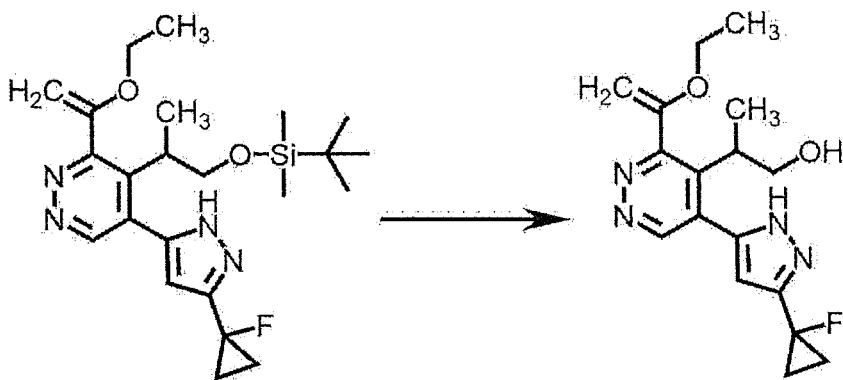
To a solution of 3-(5-{1-[*tert*-butyldimethylsilyl]oxy}propan-2-yl)-6-(1-ethoxyvinyl)pyridazin-4-yl)-1-(1-fluorocyclopropyl)prop-2-yn-1-one (11 mg) obtained in the previous step in ethanol (0.33 ml) was added hydrazine monohydrate (0.0015 ml), and the mixture was stirred at 80°C for 1 hr. The reaction mixture was concentrated under reduced pressure, and the obtained residue was purified by thin layer silica gel column chromatography (ethyl acetate:chloroform=3:1) to give a crude product (6 mg) of the title compound.

[0811]

Step 6

25 2-{3-(1-ethoxyvinyl)-5-[3-(1-fluorocyclopropyl)-1*H*-pyrazol-5-yl]pyridazin-4-yl}propan-1-ol

[0812]



[0813]

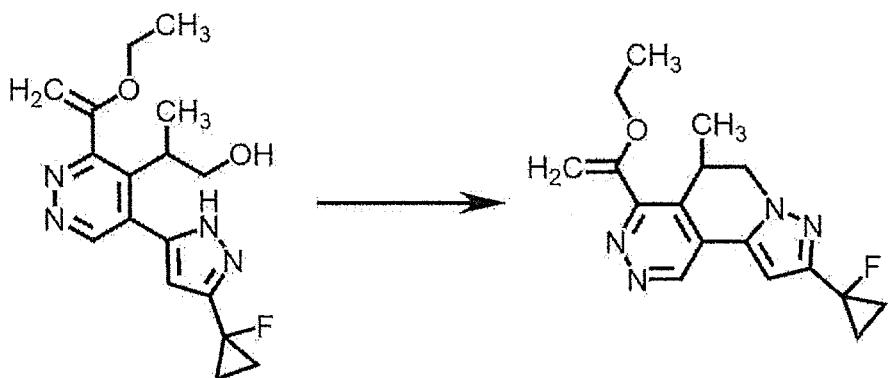
Under an argon atmosphere, to a solution of 4-[(tert-butyldimethylsilyl)oxy]propan-2-yl-3-(1-ethoxyvinyl)-5-[3-(1-fluorocyclopropyl)-1H-pyrazol-5-yl]pyridazine (6 mg) obtained in the previous step in tetrahydrofuran (0.2 ml) was added under ice-cooling 1 M tetrabutylammonium fluoride/tetrahydrofuran solution (0.02 ml), and the mixture was stirred for 10 min. After stirring at room temperature for 1 hr, saturated ammonium chloride aqueous solution was added, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by thin layer silica gel column chromatography (ethyl acetate) to give a crude product (4 mg) of the title compound.

[0814]

Step 7

4-(1-ethoxyvinyl)-9-(1-fluorocyclopropyl)-5-methyl-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazine

[0815]



[0816]

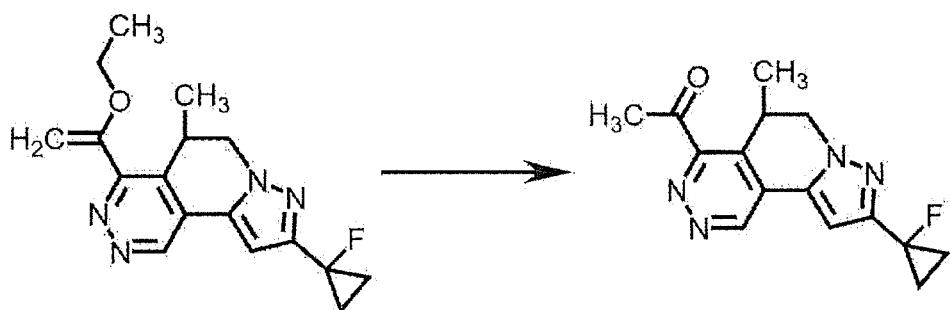
To a solution of 2-{3-(1-ethoxyvinyl)-5-[3-(1-fluorocyclopropyl)-1H-pyrazol-5-yl]pyridazin-4-yl}propan-1-ol (4 mg) obtained in the previous step in tetrahydrofuran (0.15 ml) were added triphenylphosphine (5 mg) and 1,1'-azobis(N,N-dimethylformamide) (3 mg), and the mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated under reduced pressure and the obtained residue was purified by thin layer silica gel column chromatography (ethyl acetate:hexane=9:1) to give a crude product (3.4 mg) of the title compound.

[0817]

Step 8

1-[9-(1-fluorocyclopropyl)-5-methyl-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-4-yl]ethan-1-one

[0818]



[0819]

To a mixed solution of 4-(1-ethoxyvinyl)-9-(1-fluorocyclopropyl)-5-methyl-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazine (3.4 mg) obtained in the previous step in tetrahydrofuran (0.05 ml) and methanol (0.05 ml) was added 6N hydrochloric acid (0.011 ml), and the mixture was stirred at room temperature for 3 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced

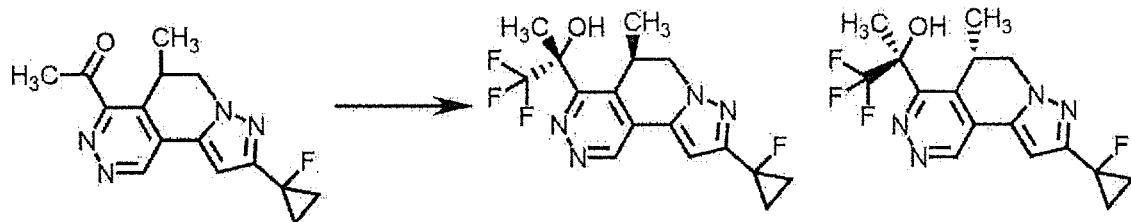
pressure. The obtained residue was purified by thin layer silica gel column chromatography (ethyl acetate:hexane=3:1) to give a crude product (3 mg) of the title compound.

[0820]

5 Step 9

(R)-1,1,1-trifluoro-2-[ (R)-9-(1-fluorocyclopropyl)-5-methyl-5,6-dihdropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-4-yl]propan-2-ol and (S)-1,1,1-trifluoro-2-[ (S)-9-(1-fluorocyclopropyl)-5-methyl-5,6-dihdropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-4-yl]propan-2-ol

[0821]



[0822]

15 Under an argon atmosphere, a solution of 1-[9-(1-fluorocyclopropyl)-5-methyl-5,6-dihdropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-4-yl]ethan-1-one (3 mg) obtained in the previous step in tetrahydrofuran (0.1 ml) were added under ice-cooling

20 trimethyl(trifluoromethyl)silane (0.003 ml) and cesium fluoride (0.3 mg), and the mixture was stirred for 1 hr. Trimethyl(trifluoromethyl)silane (0.003 ml) and cesium fluoride (0.3 mg) were added again and the mixture was stirred under ice-cooling for 1 hr. To the reaction mixture were added

25 methanol (0.1 ml) and potassium carbonate (4 mg), and the mixture was stirred at room temperature for 3 hr. To the reaction mixture was added saturated brine, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated

30 under reduced pressure. The obtained residue was purified by

thin layer silica gel column chromatography (ethyl acetate:hexane=3:2) to give the title compound (2 mg).

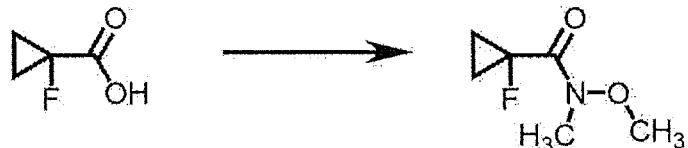
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.09-1.18 (m, 5H), 1.41-1.50 (m, 2H), 2.00 (s, 3H), 4.12-4.38 (m, 3H), 7.24 (s, 1H), 7.31 (s, 1H), 5 9.58 (s, 1H).

[0823]

Auxiliary Step 6

1-fluoro-N-methoxy-N-methylcyclopropane-1-carboxamide

[0824]



[0825]

To a solution of 1-fluorocyclopropanecarboxylic acid (500 mg) in acetonitrile (5 ml) were added N,O-dimethylhydroxylamine hydrochloride (515 mg) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (2.19 g). Further, N,N-diisopropylethylamine (1.68 ml) was added dropwise, and the mixture was stirred at room temperature overnight. To the reaction mixture were added sodium hydrogen carbonate aqueous solution and ethyl acetate, and the precipitated insoluble material was filtered off. Two layers of the filtrate were separated, and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with 5% potassium hydrogen sulfate aqueous solution, and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by thin layer silica gel column chromatography (ethyl acetate:hexane) to give the title compound (453 mg).

[0826]

30 Production Example 14

Synthesis of 4-[(R)-5-methyl-4-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-

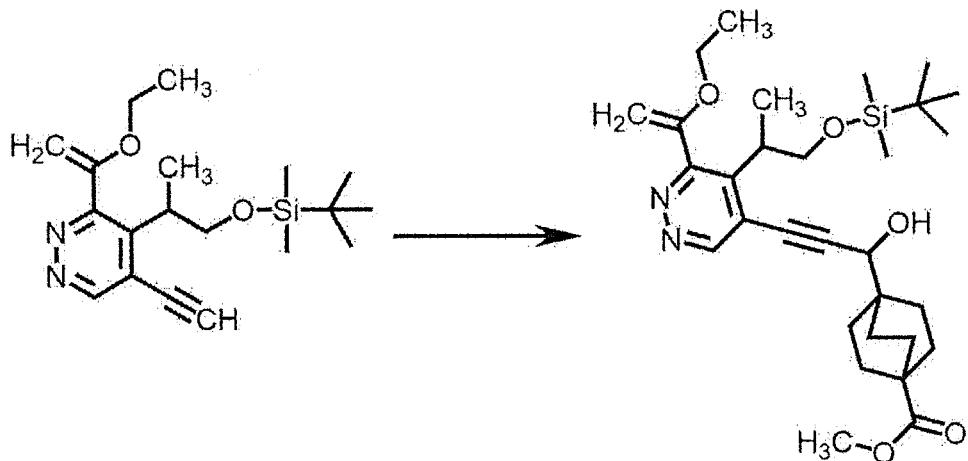
d]pyridazin-9-yl]bicyclo[2.2.2]octane-1-carbonitrile and 4-[(S)-5-methyl-4-((S)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[2.2.2]octane-1-carbonitrile (Example 103)

5 [0827]

Step 1

methyl 4-{3-[5-{1-[(tert-butyldimethylsilyl)oxy]propan-2-yl}-6-(1-ethoxyvinyl)pyridazin-4-yl]-1-hydroxyprop-2-yn-1-yl}bicyclo[2.2.2]octane-1-carboxylate

10 [0828]



[0829]

Under an argon atmosphere, to a solution of 4-{1-[(tert-butyldimethylsilyl)oxy]propan-2-yl}-3-(1-ethoxyvinyl)-5-ethynylpyridazine (20 mg) obtained in Production Example 13, Step 3, in tetrahydrofuran (0.2 ml) was added dropwise at -75°C 2 M lithium diisopropylamide/tetrahydrofuran-heptane-ethylbenzene solution (0.04 ml), and the mixture was stirred for 30 min. A solution of methyl 4-formylbicyclo[2.2.2]octane-1-carboxylate (15 mg) in tetrahydrofuran (0.2 ml) was added dropwise through a cannula, and the mixture was stirred under ice-cooling for 1 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was

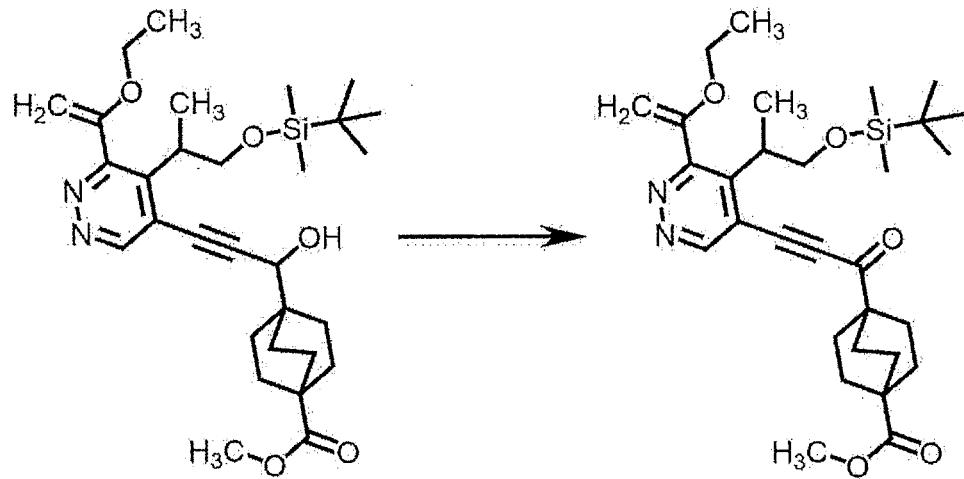
purified by thin layer silica gel column chromatography (ethyl acetate:hexane=1:1) to give a crude product (18 mg) of the title compound.

[0830]

5 Step 2

methyl 4-{3-[5-{1-[(tert-butyldimethylsilyl)oxy]propan-2-yl}-6-(1-ethoxyvinyl)pyridazin-4-yl]propioloyl}bicyclo[2.2.2]octane-1-carboxylate

[0831]



10

[0832]

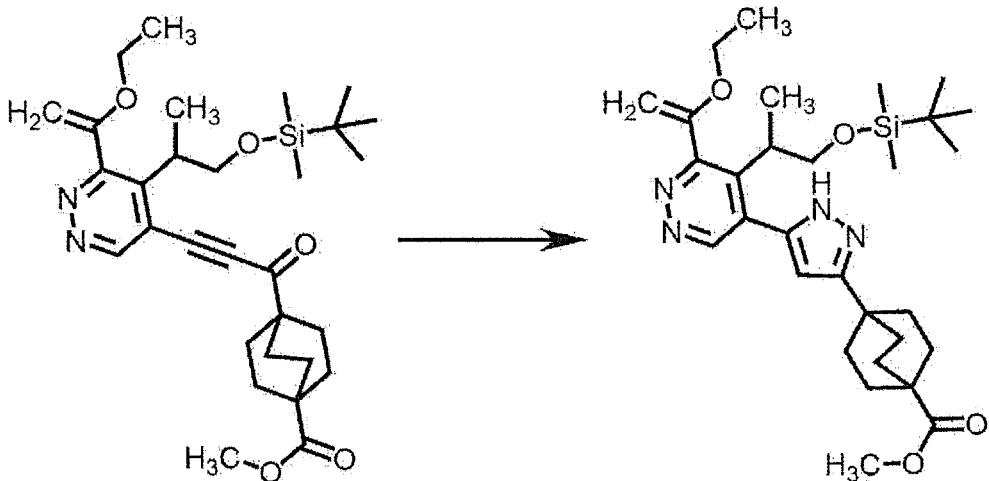
To a solution of methyl 4-{3-[5-{1-[(tert-butyldimethylsilyl)oxy]propan-2-yl}-6-(1-ethoxyvinyl)pyridazin-4-yl]-1-hydroxyprop-2-yn-1-yl}bicyclo[2.2.2]octane-1-carboxylate (9 mg) obtained in the previous step in methylene chloride (0.27 ml) was added manganese dioxide (90 mg), and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate, and insoluble material was filtered through celite. The filtrate was concentrated under reduced pressure and the obtained residue was purified by thin layer silica gel column chromatography (ethyl acetate:hexane=2:3) to give a crude product (7 mg) of the title compound.

[0833]

25 Step 3

methyl 4-{5-[5-{1-[(tert-butyldimethylsilyl)oxy]propan-2-yl}-

6-(1-ethoxyvinyl)pyridazin-4-yl]-1H-pyrazol-3-yl}bicyclo[2.2.2]octane-1-carboxylate  
[0834]



5 [0835]

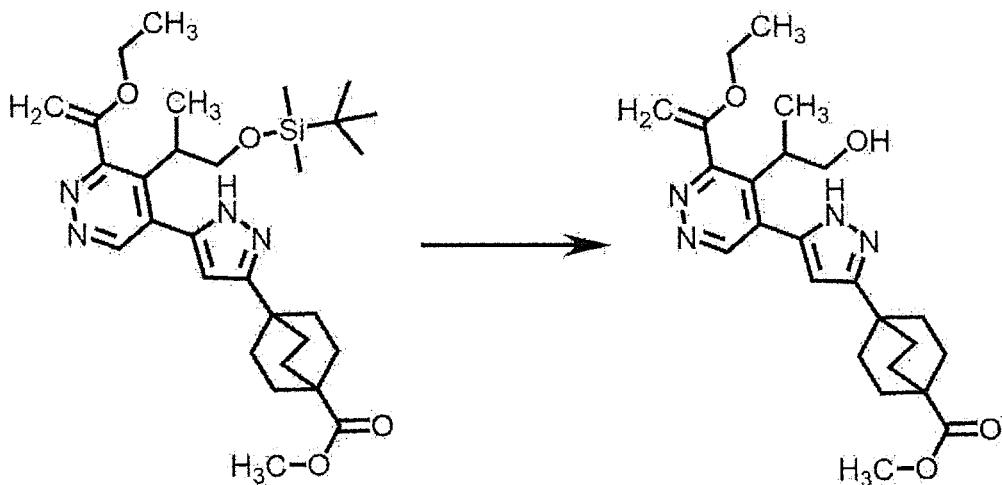
To a solution of methyl 4-{3-[5-{1-[ (tert-butyldimethylsilyl)oxy]propan-2-yl}-6-(1-ethoxyvinyl)pyridazin-4-yl]propioloyl}bicyclo[2.2.2]octane-1-carboxylate (15 mg) obtained in the previous step in ethanol (0.45 ml) was added hydrazine monohydrate (0.002 ml), and the mixture was stirred at 85°C for 1 hr. The reaction mixture was concentrated under reduced pressure and the obtained residue was purified by thin layer silica gel column chromatography (ethyl acetate:hexane=4:1) to give a crude product (13 mg) of the title compound.

[0836]

Step 4

methyl 4-{5-[6-(1-ethoxyvinyl)-5-(1-hydroxypropan-2-yl)pyridazin-4-yl]-1H-pyrazol-3-yl}bicyclo[2.2.2]octane-1-carboxylate

[0837]



[0838]

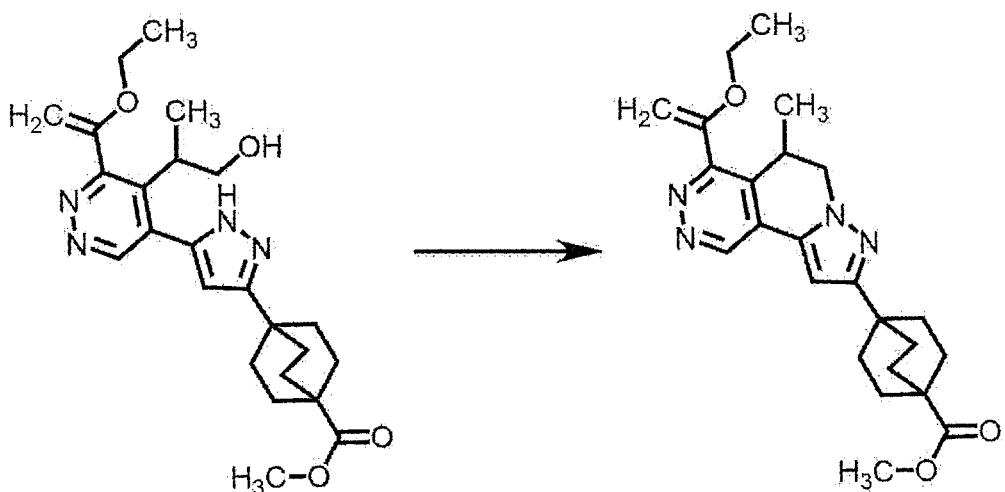
To a solution of methyl 4-{5-[5-{1-[*tert*-butyldimethylsilyl]oxy}propan-2-yl}-6-(1-ethoxyvinyl)pyridazin-4-yl]-1*H*-pyrazol-3-yl)bicyclo[2.2.2]octane-1-carboxylate (13 mg) obtained in the previous step in tetrahydrofuran (0.45 ml) was added under ice-cooling 1 M tetrabutylammonium fluoride/tetrahydrofuran solution (0.035 ml), and the mixture was stirred for 10 min. After stirring at room temperature for 1 hr, saturated ammonium chloride aqueous solution was added, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by thin layer silica gel column chromatography (ethyl acetate) to give a crude product (10 mg) of the title compound.

[0839]

Step 5

methyl 4-[4-(1-ethoxyvinyl)-5-methyl-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[2.2.2]octane-1-carboxylate

[0840]



[0841]

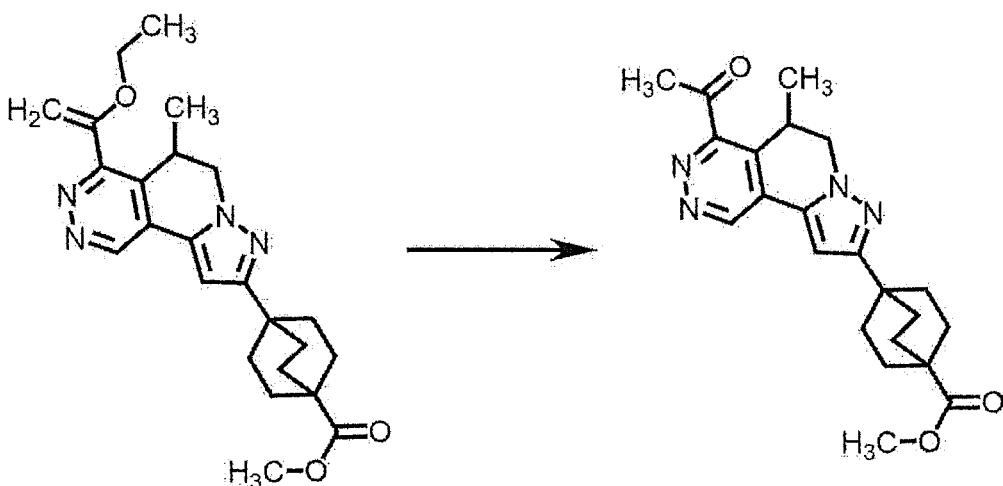
To a solution of methyl 4-{5-[6-(1-ethoxyvinyl)-5-(1-hydroxypropan-2-yl)pyridazin-4-yl]-1H-pyrazol-3-yl}bicyclo[2.2.2]octane-1-carboxylate (10 mg) obtained in the previous step in tetrahydrofuran (0.3 ml) were added triphenylphosphine (9 mg) and 1,1'-azobis(N,N-dimethylformamide) (6 mg), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and the obtained residue was purified by thin layer silica gel column chromatography (ethyl acetate; hexane=4:1) to give a crude product (9 mg) of the title compound.

[0842]

15 Step 6

methyl 4-(4-acetyl-5-methyl-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl)bicyclo[2.2.2]octane-1-carboxylate

[0843]



[0844]

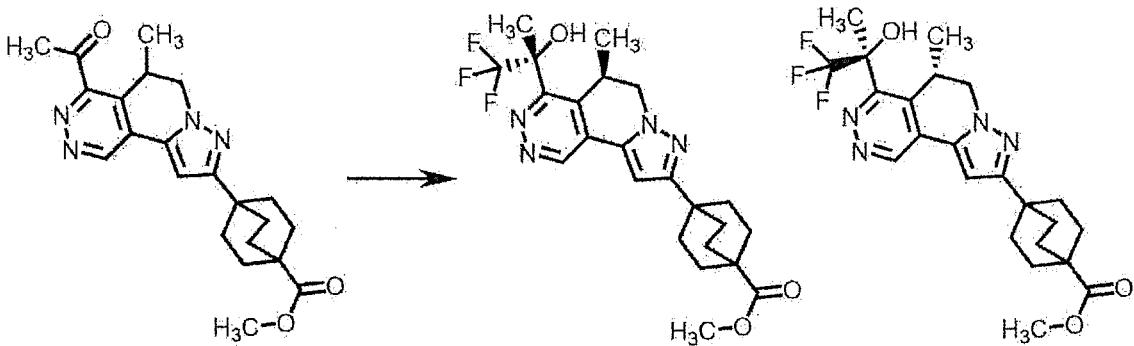
To a mixed solution of methyl 4-[4-(1-ethoxyvinyl)-5-methyl-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[2.2.2]octane-1-carboxylate (9 mg) obtained in the previous step in tetrahydrofuran (0.13 ml) and methanol (0.13 ml) was added 6N hydrochloric acid (0.021 ml), and the mixture was stirred at room temperature for 2 hr. 6N Hydrochloric acid (0.010 ml) was added, and the mixture was stirred at room temperature for 1 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by thin layer silica gel column chromatography (ethyl acetate:chloroform=3:2) to give a crude product (7.5 mg) of the title compound.

[0845]

Step 7

Synthesis of methyl 4-[ (R)-5-methyl-4-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[2.2.2]octane-1-carboxylate and methyl 4-[ (S)-5-methyl-4-((S)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[2.2.2]octane-1-carboxylate (Example 102)

[0846]



[0847]

Under an argon atmosphere, to a solution of methyl 4-(4-acetyl-5-methyl-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl)bicyclo[2.2.2]octane-1-carboxylate (7.5 mg) obtained in the previous step in tetrahydrofuran (0.23 ml) were added under ice-cooling trimethyl(trifluoromethyl)silane (0.006 ml) and cesium fluoride (0.65 mg), and the mixture was stirred for 1 hr. Trimethyl(trifluoromethyl)silane (0.006 ml) and cesium fluoride (0.65 mg) were added again, and the mixture was stirred under ice-cooling for 1 hr. To the reaction mixture were added methanol (0.23 ml) and potassium carbonate (10 mg), and the mixture was stirred at room temperature for 1 hr. To the reaction mixture was added saturated brine, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by thin layer silica gel column chromatography (ethyl acetate:chloroform=1:1) to give the title compound (7 mg).

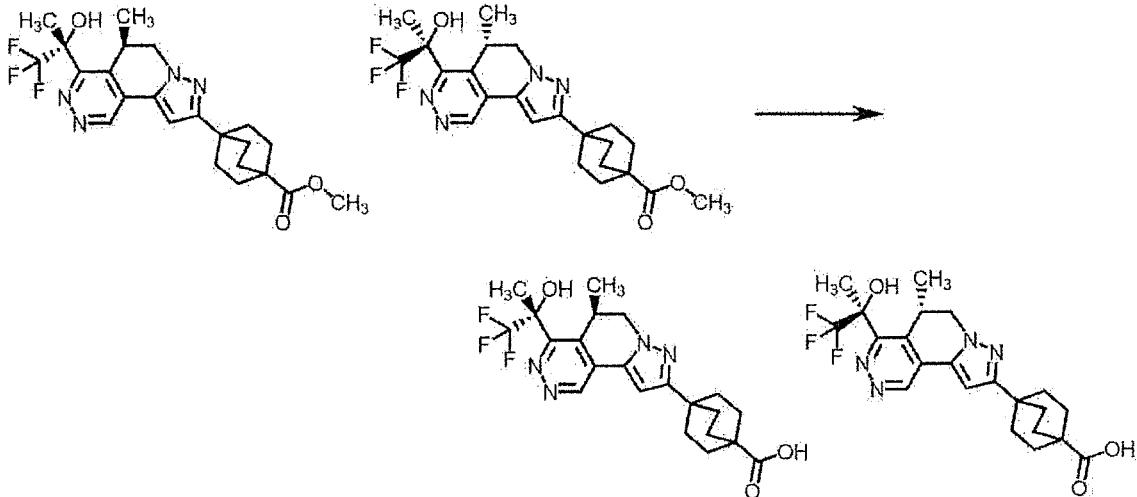
<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.09 (d, J= 6.73 Hz, 3H), 1.83 (s, 12H), 1.99 (s, 3H), 3.60 (s, 3H), 4.04-4.35 (m, 3H), 6.94 (s, 1H), 7.28 (s, 1H), 9.48 (s, 1H).

[0848]

25 Step 8

4-[(R)-5-methyl-4-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[2.2.2]octane-1-carboxylic acid and 4-[(S)-5-methyl-

4-((S)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[2.2.2]octane-1-carboxylic acid  
[0849]



[0850]

To a mixed solution of the mixture (5.4 mg) of methyl 4-[(R)-5-methyl-4-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[2.2.2]octane-1-carboxylate and methyl 4-[(S)-5-methyl-4-((S)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[2.2.2]octane-1-carboxylate obtained in the previous step in tetrahydrofuran (0.05 ml) and ethanol (0.2 ml) was added 4N sodium hydroxide aqueous solution (0.029 ml), and the mixture was stirred at 60°C overnight. To the reaction mixture was added 2N hydrochloric acid (0.06 ml), and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue (5.4 mg) was used as it was in the next step.

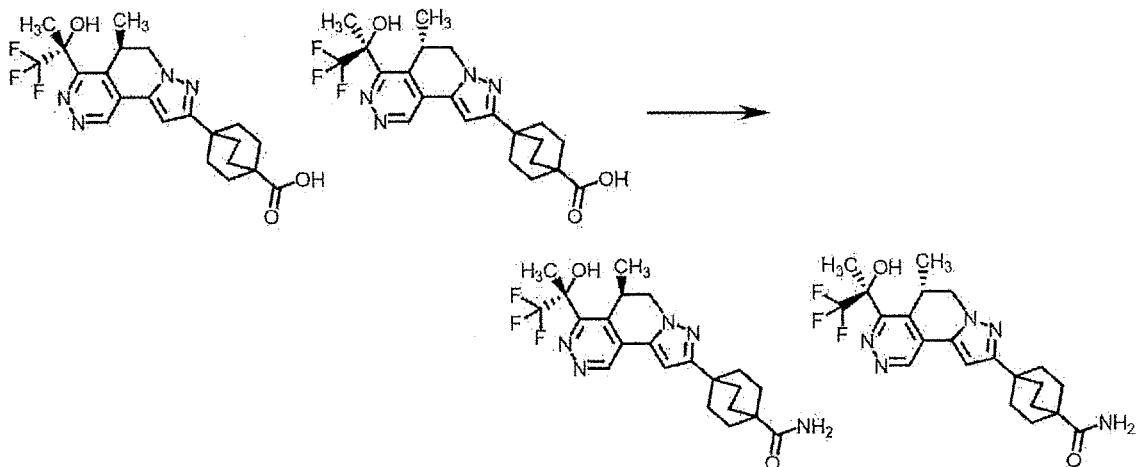
[0851]

Step 9

4-[(R)-5-methyl-4-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-

yl]bicyclo[2.2.2]octane-1-carboxamide and 4-[ (S)-5-methyl-4-((S)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[2.2.2]octane-1-carboxamide

5 [0852]



[0853]

To a solution of the mixture (5.4 mg) of 4-[ (R)-5-methyl-4-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[2.2.2]octane-1-carboxylic acid and 4-[ (S)-5-methyl-4-((S)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[2.2.2]octane-1-carboxylic acid obtained in the previous step in N,N-dimethylformamide (0.3 ml) were added 7 M ammonia/methanol solution (0.009 ml) and 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (6.8 mg), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and the obtained residue was purified by thin layer silica gel column chromatography (ethyl acetate:methanol=10:1) to give a crude product (5.4 mg) of the title compound.

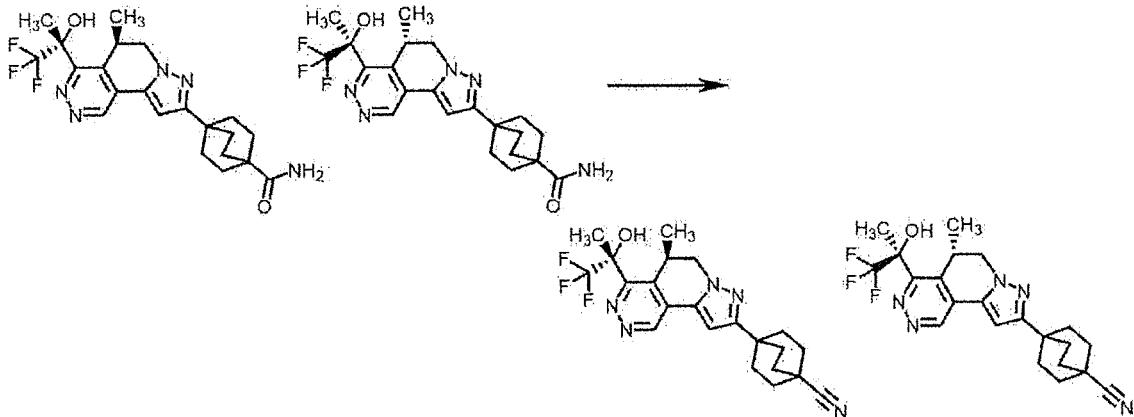
[0854]

25 Step 10

4-[ (R)-5-methyl-4-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-

5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[2.2.2]octane-1-carbonitrile and 4-[(S)-5-methyl-4-((S)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[2.2.2]octane-1-carbonitrile

5 [0855]



6 [0856]

To a solution of the mixture (5.4 mg) of 4-[(R)-5-methyl-4-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[2.2.2]octane-1-carboxamide and 4-[(S)-5-methyl-4-((S)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[2.2.2]octane-1-carboxamide obtained in the previous step in tetrahydrofuran (0.27 ml) were added under ice-cooling triethylamine (0.008 ml) and trifluoroacetic anhydride (0.003 ml), and the mixture was stirred for 30 min. Triethylamine (0.008 ml) and trifluoroacetic anhydride (0.003 ml) were added, and the mixture was stirred for 30 min. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by thin layer silica gel column chromatography (ethyl acetate:hexane=3:2) to give the title compound (4 mg).

<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.09 (d, J= 6.70 Hz, 3H), 1.80-1.90 (m, 6H), 1.94-2.04 (m, 9H), 4.04-4.35 (m, 3H), 6.94 (s, 1H), 7.27 (s, 1H), 9.48 (s, 1H).

[0857]

## 5 Production Example 15

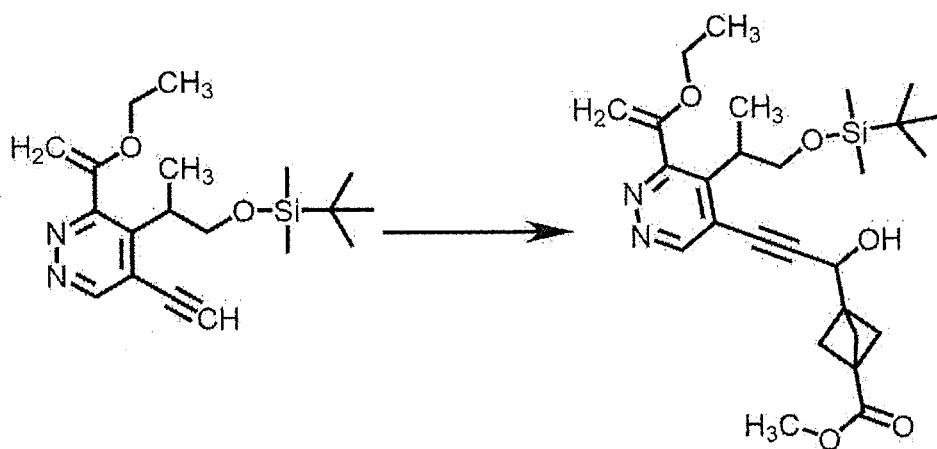
Synthesis of 3-[*(R)*-5-methyl-4-[(*R*)-1,1,1-trifluoro-2-hydroxypropan-2-yl]-5,6-dihdropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[1.1.1]pentane-1-carbonitrile and 3-[*(S)*-5-methyl-4-[(*S*)-1,1,1-trifluoro-2-hydroxypropan-2-yl]-5,6-dihdropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[1.1.1]pentane-1-carbonitrile (Example 104)

[0858]

### Step 1

15 methyl 3-{3-[5-{1-[tert-butyldimethylsilyl]oxy}propan-2-yl]-6-(1-ethoxyvinyl)pyridazin-4-yl}-1-hydroxyprop-2-yn-1-yl)bicyclo[1.1.1]pentane-1-carboxylate

[0859]



[0860]

Under an argon atmosphere, to a solution of 4-{1-[(tert-butyldimethylsilyl)oxy]propan-2-yl}-3-(1-ethoxyvinyl)-5-ethynylpyridazine (65 mg) obtained in Production Example 13, Step 3, in tetrahydrofuran (0.65 ml) was added dropwise at -75°C 2 M lithium diisopropylamide/tetrahydrofuran-heptane-ethylbenzene solution (0.13 ml), and the mixture was stirred for 30 min. A solution of methyl 3-

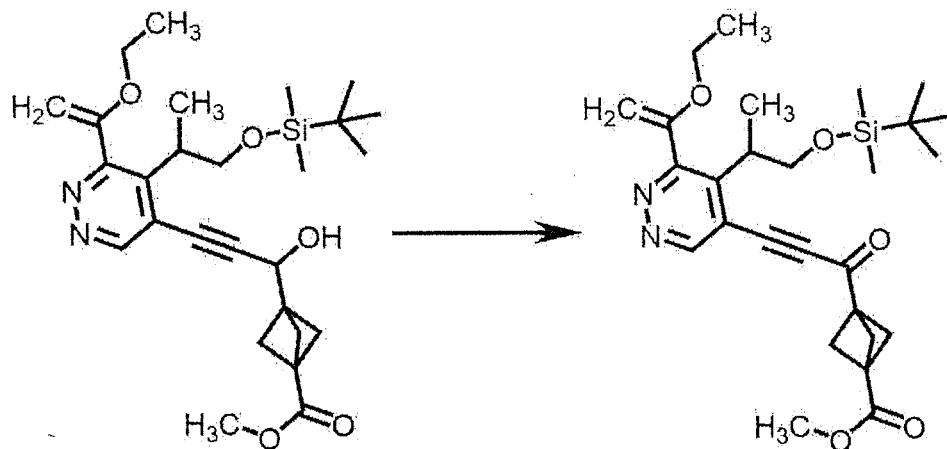
formylbicyclo[1.1.1]pentane-1-carboxylate (38 mg) in tetrahydrofuran (0.65 ml) was added dropwise through a cannula, and the mixture was stirred at -40°C for 1 hr. 2 M lithium diisopropylamide/tetrahydrofuran-heptane-ethylbenzene solution (0.13 ml) and a solution of methyl 3-formylbicyclo[1.1.1]pentane-1-carboxylate (38 mg) in tetrahydrofuran (0.65 ml) were added again, and the mixture was stirred at -30°C for 1 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane) to give a crude product (40 mg) of the title compound.

[0861]

Step 2

methyl 3-{3-[5-{1-[(tert-butyldimethylsilyl)oxy]propan-2-yl}-6-(1-ethoxyvinyl)pyridazin-4-yl]propioloyl}bicyclo[1.1.1]pentane-1-carboxylate

[0862]



[0863]

To a solution of methyl 3-{3-[5-{1-[(tert-butylidemethylsilyl)oxy]propan-2-yl}-6-(1-ethoxyvinyl)pyridazin-4-yl]-1-hydroxyprop-2-yn-1-

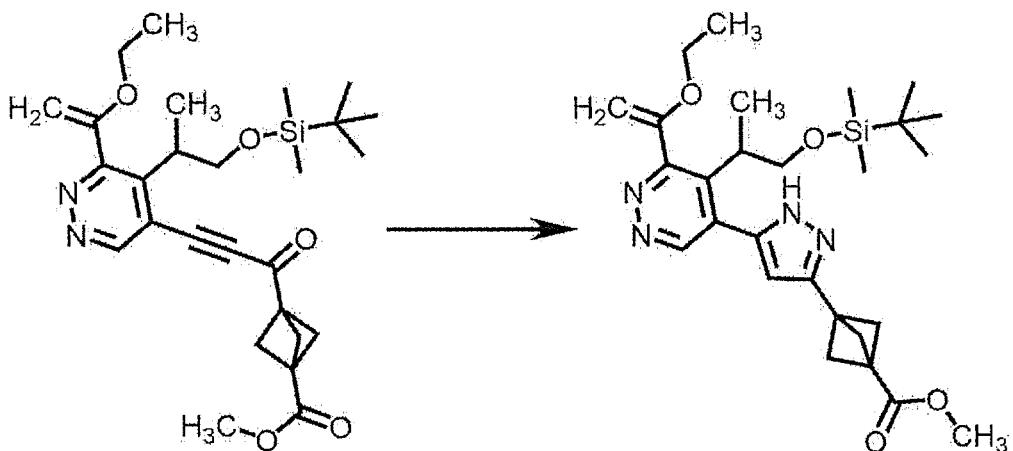
yl}bicyclo[1.1.1]pentane-1-carboxylate (40 mg) obtained in the previous step in methylene chloride (1.2 ml) was added manganese dioxide (400 mg), and the mixture was stirred at room temperature overnight. The reaction mixture was diluted 5 with ethyl acetate, and insoluble material was filtered through celite. The filtrate was concentrated under reduced pressure and the obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane) to give a crude product (25 mg) of the title compound.

10 [0864]

Step 3

methyl 3-{5-[5-{1-[ (tert-butyldimethylsilyl)oxy]propan-2-yl}-6-(1-ethoxyvinyl)pyridazin-4-yl]-1H-pyrazol-3-yl}bicyclo[1.1.1]pentane-1-carboxylate

15 [0865]



[0866]

To a solution of methyl 3-{3-[5-{1-[ (tert-butyldimethylsilyl)oxy]propan-2-yl}-6-(1-ethoxyvinyl)pyridazin-4-yl]propioloyl}bicyclo[1.1.1]pentane-1-carboxylate (25 mg) obtained in the previous step in ethanol 20 (1.0 ml) was added hydrazine monohydrate (0.003 ml), and the mixture was stirred at 85°C for 1 hr. The reaction mixture was concentrated under reduced pressure and the obtained residue 25 was purified by thin layer silica gel column chromatography (ethyl acetate:chloroform=1:1) to give a crude product (15 mg)

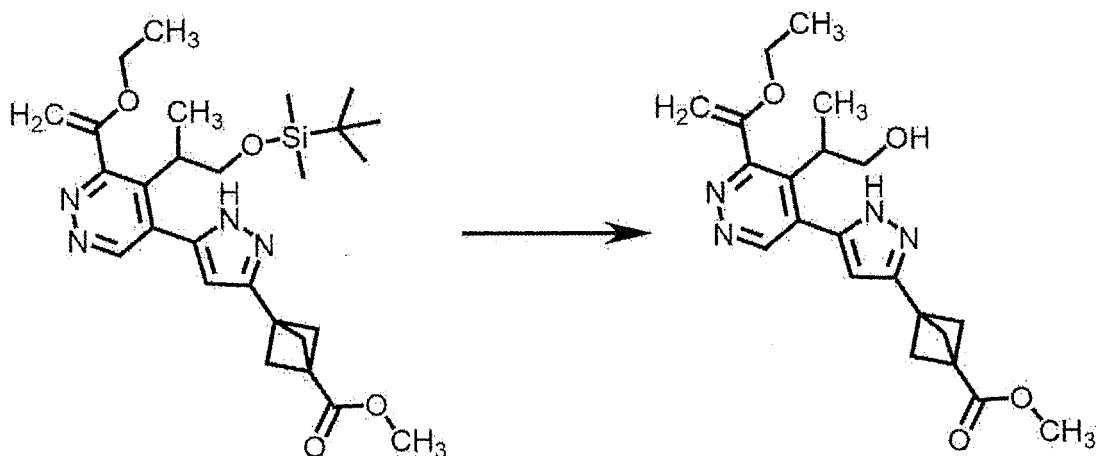
of the title compound.

[0867]

Step 4

5 methyl 3-{5-[6-(1-ethoxyvinyl)-5-(1-hydroxypropan-2-yl)pyridazin-4-yl]-1H-pyrazol-3-yl}bicyclo[1.1.1]pentane-1-carboxylate

[0868]



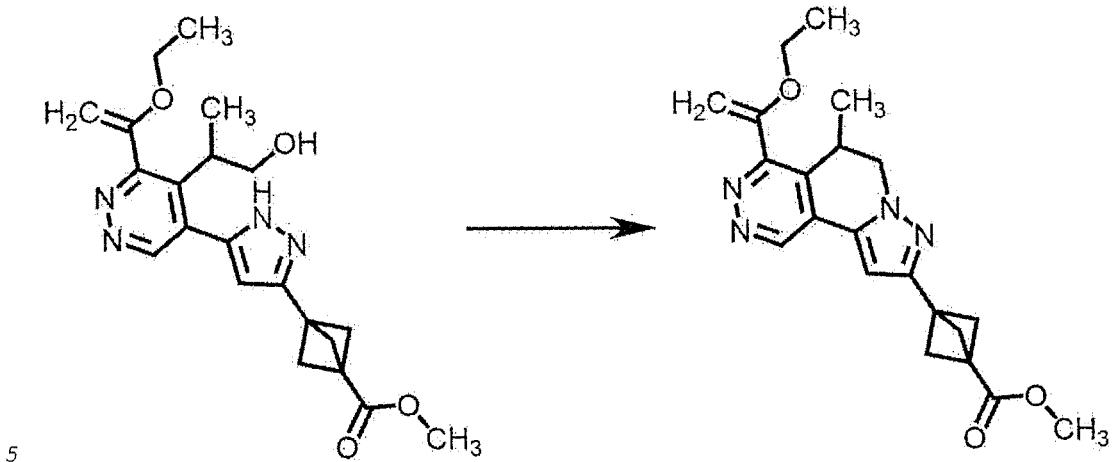
[0869]

10 To a solution of methyl 3-{5-[5-{1-[ (tert-  
butyldimethylsilyl)oxy]propan-2-yl}-6-(1-  
ethoxyvinyl)pyridazin-4-yl]-1H-pyrazol-3-  
yl}bicyclo[1.1.1]pentane-1-carboxylate (15 mg) obtained in the  
previous step in tetrahydrofuran (0.5 ml) was added under ice-  
15 cooling 1 M tetrabutylammonium fluoride/tetrahydrofuran  
solution (0.044 ml), and the mixture was stirred for 10 min.  
The mixture was returned to room temperature and stirred for 1  
hr, saturated ammonium chloride aqueous solution was added,  
and the mixture was extracted with ethyl acetate. The organic  
20 layer was dried over anhydrous sodium sulfate, and the solvent  
was evaporated under reduced pressure. The obtained residue  
was purified by thin layer silica gel column chromatography  
(ethyl acetate) to give a crude product (11.5 mg) of the title  
compound.

25 [0870]

Step 5

methyl 3-[4-(1-ethoxyvinyl)-5-methyl-5,6-dihdropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[1.1.1]pentane-1-carboxylate  
[0871]



[0872]

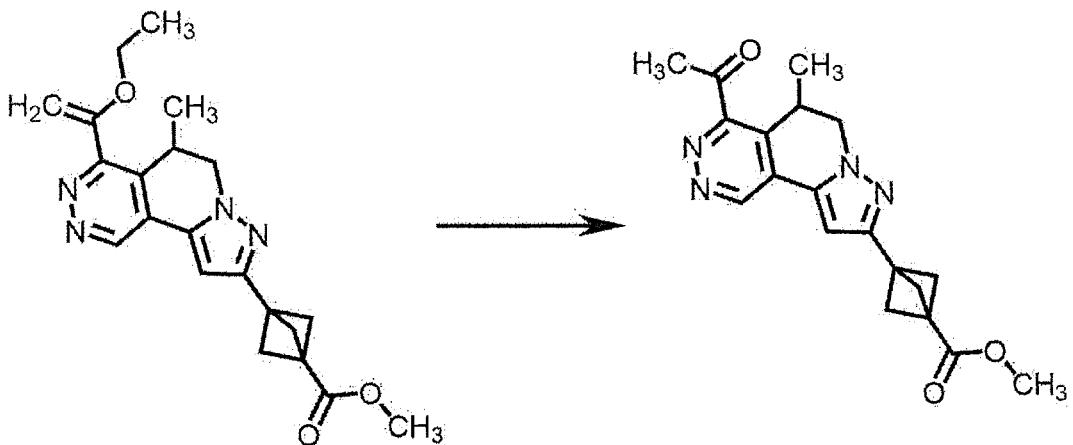
To a solution of methyl 3-[5-[6-(1-ethoxyvinyl)-5-(1-hydroxypropan-2-yl)pyridazin-4-yl]-1H-pyrazol-3-yl]bicyclo[1.1.1]pentane-1-carboxylate (11.5 mg) obtained in the previous step in tetrahydrofuran (0.3 ml) were added triphenylphosphine (11.5 mg) and 1,1'-azobis(N,N-dimethylformamide) (7.5 mg), and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and the obtained residue was purified by thin layer silica gel column chromatography (ethyl acetate; hexane=9:1) to give a crude product (9.5 mg) of the title compound.

[0873]

Step 6

methyl 3-(4-acetyl-5-methyl-5,6-dihdropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl)bicyclo[1.1.1]pentane-1-carboxylate

[0874]



[0875]

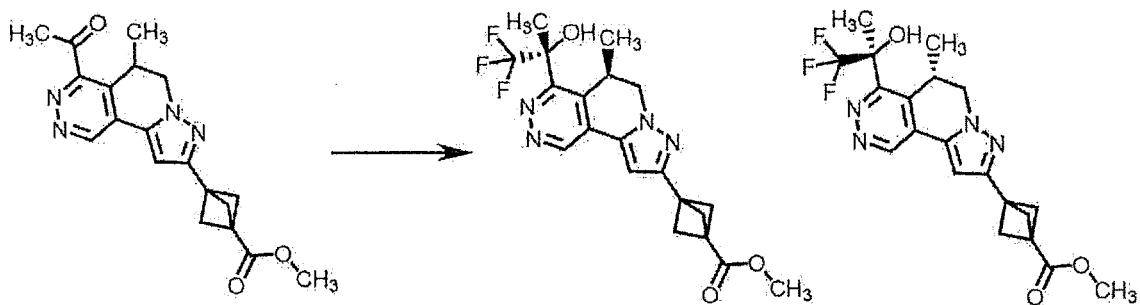
To a mixed solution of methyl 3-[4-(1-ethoxyvinyl)-5-methyl-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[1.1.1]pentane-1-carboxylate (9 mg) obtained in the previous step in tetrahydrofuran (0.13 ml) and methanol (0.13 ml) was added 6N hydrochloric acid (0.025 ml), and the mixture was stirred at room temperature for 2 hr. 6N Hydrochloric acid (0.025 ml) was added, and the mixture was stirred at room temperature for 2 hr. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by thin layer silica gel column chromatography (ethyl acetate:chloroform=2:1) to give a crude product (7.5 mg) of the title compound.

[0876]

Step 7

methyl 3-[ (R)-5-methyl-4-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[1.1.1]pentane-1-carboxylate and methyl 3-[ (S)-5-methyl-4-((S)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[1.1.1]pentane-1-carboxylate

[0877]



[0878]

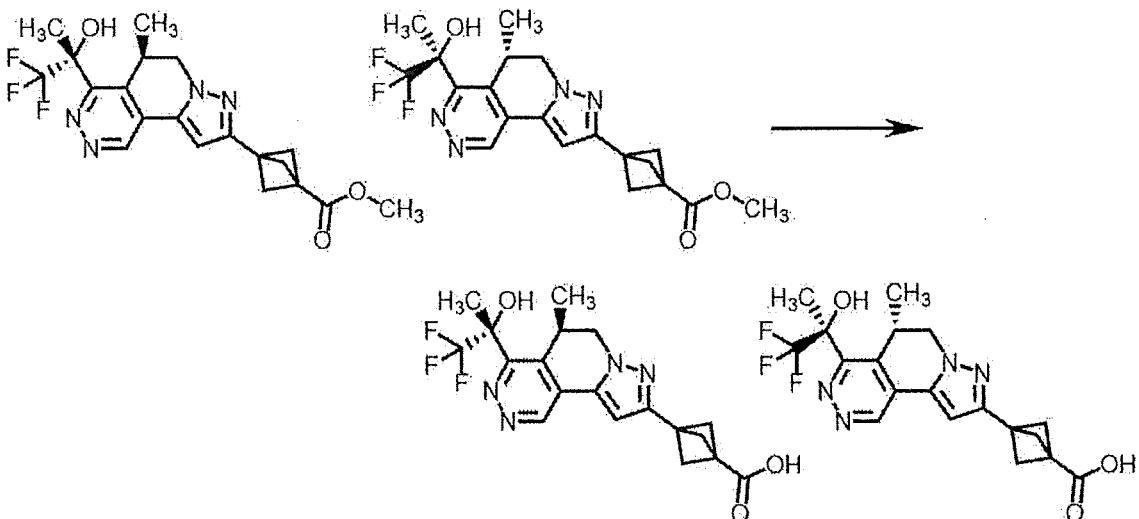
Under an argon atmosphere, to a solution of methyl 3-(4-acetyl-5-methyl-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl)bicyclo[1.1.1]pentane-1-carboxylate (7.5 mg) obtained in the previous step in tetrahydrofuran (0.25 ml) were added under ice-cooling trimethyl(trifluoromethyl)silane (0.0065 ml) and cesium fluoride (1.0 mg), and the mixture was stirred for 1 hr. Trimethyl(trifluoromethyl)silane (0.0065 ml) and cesium fluoride (1.0 mg) were added again, and the mixture was stirred under ice-cooling for 1 hr. To the reaction mixture were added methanol (0.25 ml) and potassium carbonate (12 mg), and the mixture was stirred at room temperature for 2 hr. To the reaction mixture was added saturated brine, and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by thin layer silica gel column chromatography (ethyl acetate:chloroform=3:2) to give a crude product (6.5 mg) of the title compound.

[0879]

Step 8

3-[(R)-5-methyl-4-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[1.1.1]pentane-1-carboxylic acid and 3-[(S)-5-methyl-4-((S)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[1.1.1]pentane-1-carboxylic acid

[0880]



[0881]

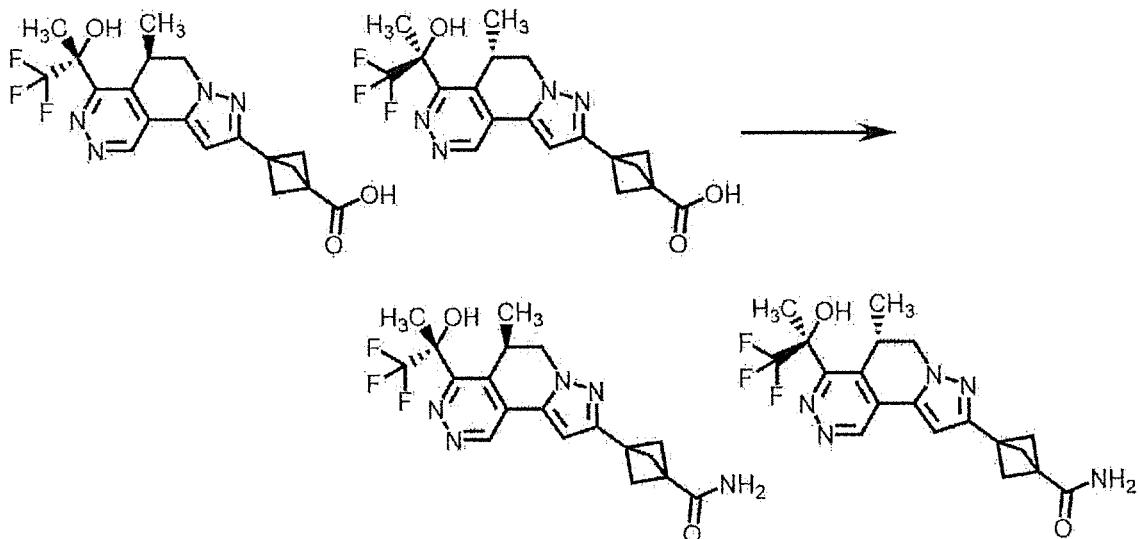
To a mixed solution of the mixture (6.5 mg) of methyl 3-[(R)-5-methyl-4-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihdropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[1.1.1]pentane-1-carboxylate and methyl 3-[(S)-5-methyl-4-((S)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihdropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[1.1.1]pentane-1-carboxylate obtained in the previous step in tetrahydrofuran (0.065 ml) and ethanol (0.26 ml) was added 4N sodium hydroxide aqueous solution (0.039 ml), and the mixture was stirred at 60°C for 2 hr. To the reaction mixture was added 2N hydrochloric acid (0.077 ml), and the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue (6 mg) was used as it was in the next step.

[0882]

Step 9

3-[(R)-5-methyl-4-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihdropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[1.1.1]pentane-1-carboxamide and 3-[(S)-5-methyl-4-((S)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihdropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[1.1.1]pentane-1-carboxamide

[0883]



[0884]

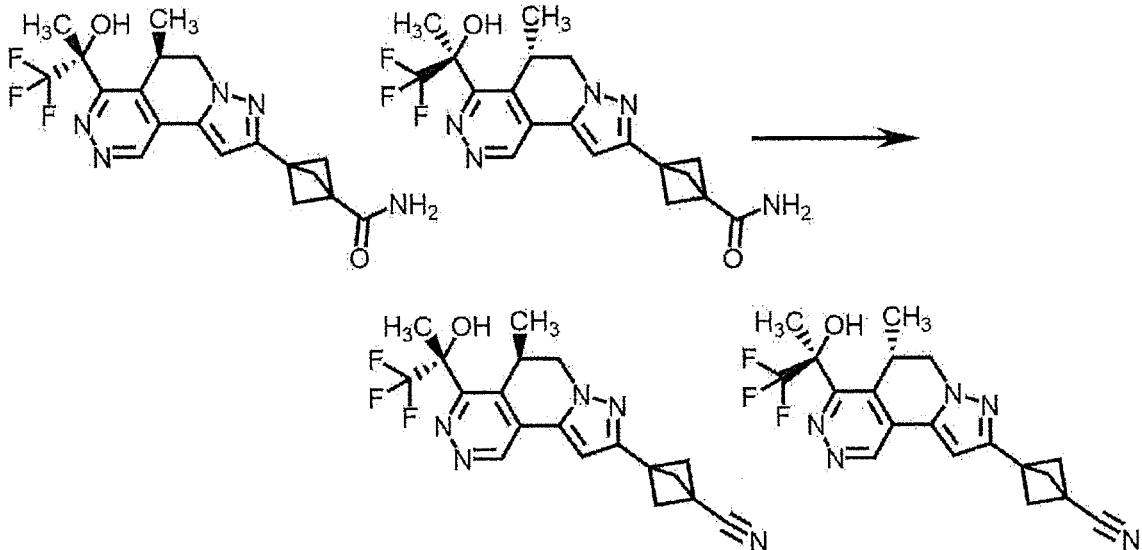
To a solution of 3-[(R)-5-methyl-4-((R)-1,1,1-trifluoro-  
5 2-hydroxypropan-2-yl)-5,6-  
dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-  
yl]bicyclo[1.1.1]pentane-1-carboxylic acid and 3-[(S)-5-  
methyl-4-((S)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-  
dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-  
10 yl]bicyclo[1.1.1]pentane-1-carboxylic acid mixture (6 mg)  
obtained in the previous step in N,N-dimethylformamide (0.32  
ml) were added 7 M ammonia/methanol solution (0.011 ml) and 1-  
[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-  
b]pyridinium 3-oxide hexafluorophosphate (9.0 mg), and the  
15 mixture was stirred at room temperature overnight. The  
reaction mixture was concentrated under reduced pressure and  
the obtained residue was purified by thin layer silica gel  
column chromatography (ethyl acetate:methanol=10:1) to give a  
crude product (6.0 mg) of the title compound.

20 [0885]

Step 10

3-[(R)-5-methyl-4-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-  
5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-  
yl]bicyclo[1.1.1]pentane-1-carbonitrile and 3-[(S)-5-methyl-4-  
25 ((S)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-

dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[1.1.1]pentane-1-carbonitrile  
[0886]



5 [0887]

To a solution of the mixture (6 mg) of 3-[(R)-5-methyl-4-((R)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[1.1.1]pentane-1-carboxamide and 3-[(S)-5-methyl-4-((S)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-5,6-dihydropyrazolo[1',5':1,2]pyrido[3,4-d]pyridazin-9-yl]bicyclo[1.1.1]pentane-1-carboxamide obtained in the previous step in tetrahydrofuran (0.3 ml) were added under ice-cooling triethylamine (0.010 ml) and trifluoroacetic anhydride (0.004 ml), and the mixture was stirred for 30 min. To the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and insoluble material was filtered off. The filtrate was concentrated under reduced pressure and the obtained residue was purified by thin layer 20 silica gel column chromatography (ethyl acetate:hexane=3:2) to give the title compound (3.5 mg).

<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.09 (d, J= 6.94 Hz, 3H), 1.98 (s, 3H), 2.57 (s, 6H), 4.08-4.37 (m, 3H), 6.99 (s, 1H), 7.29 (s, 1H), 9.49 (s, 1H).

[0888]

Production Example 16

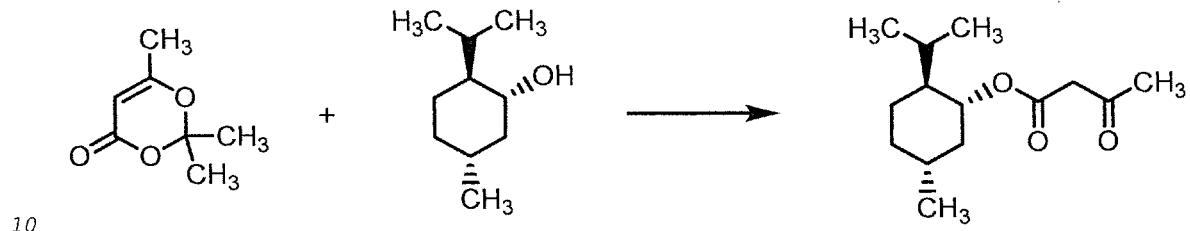
Synthesis of (1*S*,4*r*)-1-methyl-4-((*S*)-4-methyl-3-((*R*)-1,1,1-trifluoro-2-hydroxypropan-2-yl)-4,5-dihydro-7*H*-isoxazolo[5,4-  
5]indazol-7-yl)cyclohexan-1-ol (Example 105)

[0889]

Step 1

(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 3-oxobutanoate

[0890]



[0891]

(-)-Menthol (19.9 g) was mixed with toluene (100 ml). At room temperature, 2,2,6-trimethyl-1,3-dioxin-4-one (20 g) was added, and the mixture was stirred using a Dean-Stark apparatus at 140°C for 1.5 hr. The reaction mixture was concentrated under reduced pressure. The obtained residue was distilled under reduced pressure to give the title compound (28.18 g).

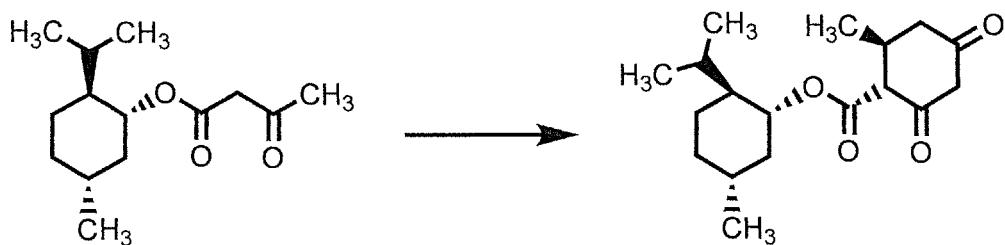
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 0.77 (d, J=6.73Hz, 3H), 0.79 - 2.09 (m, 15H), 2.26 (s, 3H), 3.43 (s, 2H), 4.74 (td, J=11.03, 4.24Hz, 1H)

[0892]

Step 2

(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (1*R*,2*S*)-2-methyl-4,6-dioxocyclohexane-1-carboxylate

[0893]



[0894]

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 3-oxobutanoate (28.18 g) obtained in the previous step was mixed with *tert*-butanol (127 ml). Potassium *tert*-butoxide (12.91 g) was added, and the mixture was stirred at 125°C for 45 min. To the reaction mixture was added dropwise ethyl crotonate (13.72 ml), and the mixture was heated under reflux for 1.5 hr. After cooling the reaction mixture to room temperature, 5 v/v% sulfuric acid aqueous solution (100 ml) and dichloromethane (120 ml) were added and the layers were separated. The aqueous layer was extracted twice with dichloromethane (120 ml). The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure. The obtained residue was mixed with toluene (120 ml), and the mixture was stirred at 120°C for 30 min. The mixture was stirred overnight while allowing to cool to room temperature. The obtained solid was collected by filtration to give the title compound (7.76 g).

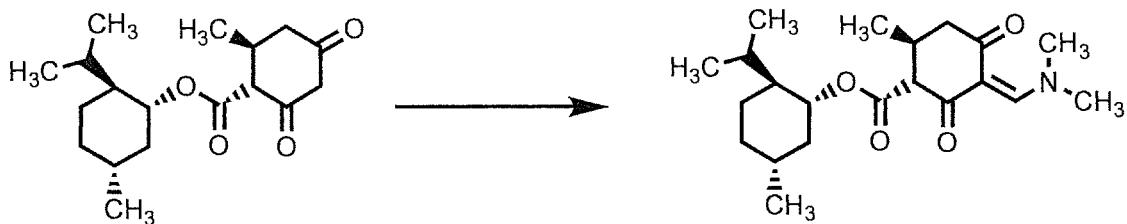
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 0.78 (d, J=6.73Hz, 3H), 0.91 (t, J=7.11Hz, 6H), 0.98 - 1.07 (m, 1H), 1.10 (d, J=6.73Hz, 3H), 1.36 - 1.46 (m, 1H), 1.46 - 1.78 (m, 5H), 1.82 - 1.96 (m, 1H), 1.97 - 2.09 (m, 1H), 2.39 (dd, J=15.71, 8.98Hz, 1H), 2.56 - 2.68 (m, 1H), 2.81 (dd, J=15.71, 4.49Hz, 1H), 3.30 (d, J=8.98Hz, 1H), 3.40 (d, J=17.20Hz, 1H), 3.63 (d, J=17.20Hz, 1H), 4.79 (td, J=10.85, 4.49Hz, 1H)

[0895]

Step 3

(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (1*R*,2*S*,*E*)-3-((dimethylamino)methylene)-6-methyl-2,4-dioxocyclohexane-1-  
30 carboxylate

[0896]



[0897]

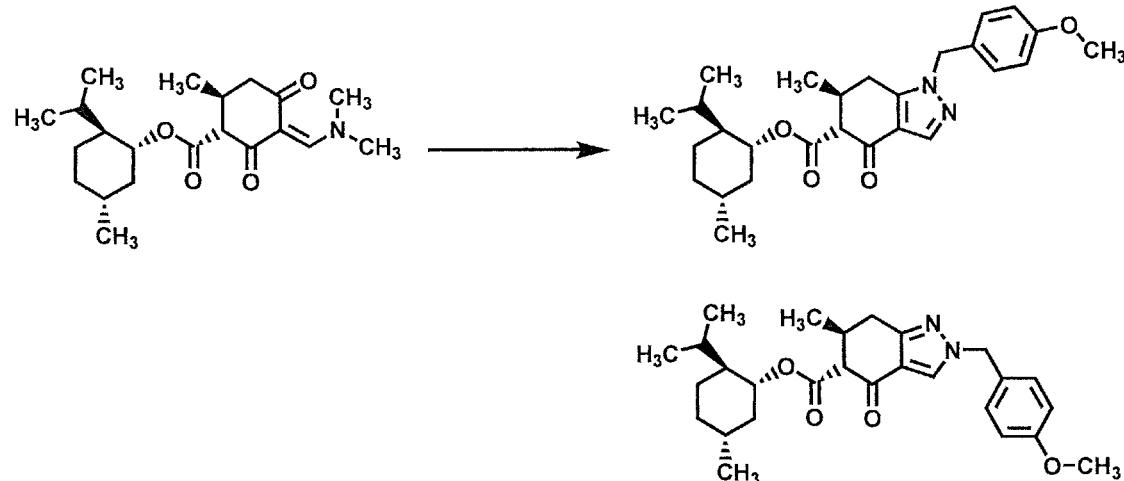
(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (1*R*,2*S*)-2-methyl-4,6-dioxocyclohexane-1-carboxylate (7.76 g) obtained in the previous step was mixed with *N,N*-dimethylformamide dimethyl acetal (6.74 ml). The reaction mixture was stirred at 120°C for 1 hr. The reaction mixture was concentrated under reduced pressure and azeotroped twice with toluene. The obtained residue was dried under reduced pressure to give a crude product (8.7 g) of the title compound.

[0898]

Step 4

mixture of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (5*R*,6*S*)-1-(4-methoxybenzyl)-6-methyl-4-oxo-4,5,6,7-tetrahydro-1*H*-indazole-5-carboxylate and (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (5*R*,6*S*)-2-(4-methoxybenzyl)-6-methyl-4-oxo-4,5,6,7-tetrahydro-2*H*-indazole-5-carboxylate

[0899]



20

[0900]

To the crude product (8 g) of (1*R*,2*S*,5*R*)-2-isopropyl-5-

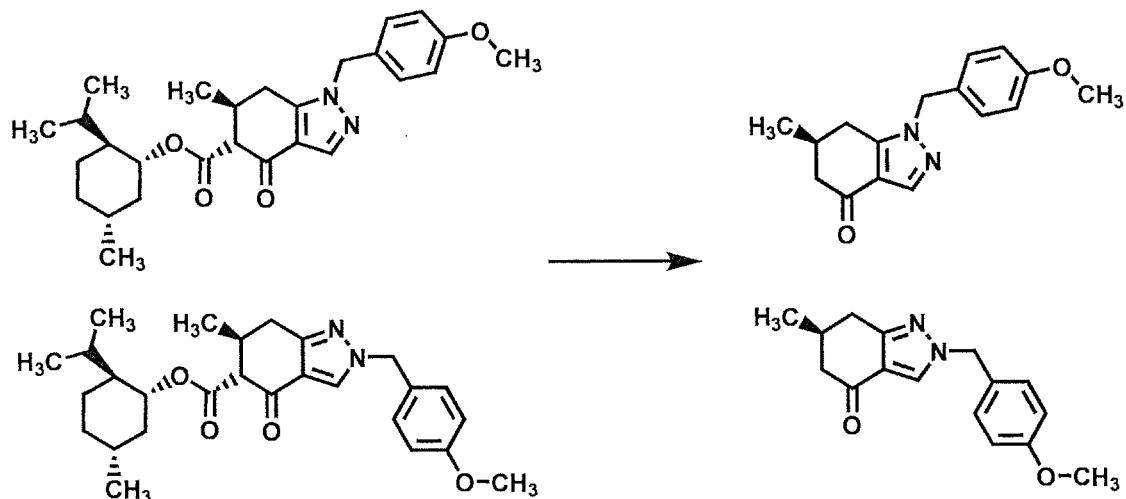
methylcyclohexyl (1R,2S,E)-3-((dimethylamino)methylene)-6-methyl-2,4-dioxocyclohexane-1-carboxylate obtained in the previous step and (4-methoxybenzyl)hydrazine hydrochloride (4.34 g) was added isopropanol (120 ml), and the mixture was 5 stirred at 50°C for 30 min. To the reaction mixture was added acetic acid (6.27 ml), and the mixture was stirred at 140°C for 6 hr. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. To the obtained residue were added ethyl acetate and 1N sodium 10 hydroxide aqueous solution, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated aqueous sodium chloride solution. After filtration through a phase separator, the filtrate was concentrated under reduced pressure to give a crude product 15 (9.85 g) of the title compound.

[0901]

Step 5

mixture of (S)-1-(4-methoxybenzyl)-6-methyl-1,5,6,7-tetrahydro-4H-indazol-4-one and (S)-2-(4-methoxybenzyl)-6-methyl-2,5,6,7-tetrahydro-4H-indazol-4-one 20

[0902]



[0903]

The crude product (9.85 g) of the mixture of (1R,2S,5R)-25 2-isopropyl-5-methylcyclohexyl (5R,6S)-1-(4-methoxybenzyl)-6-

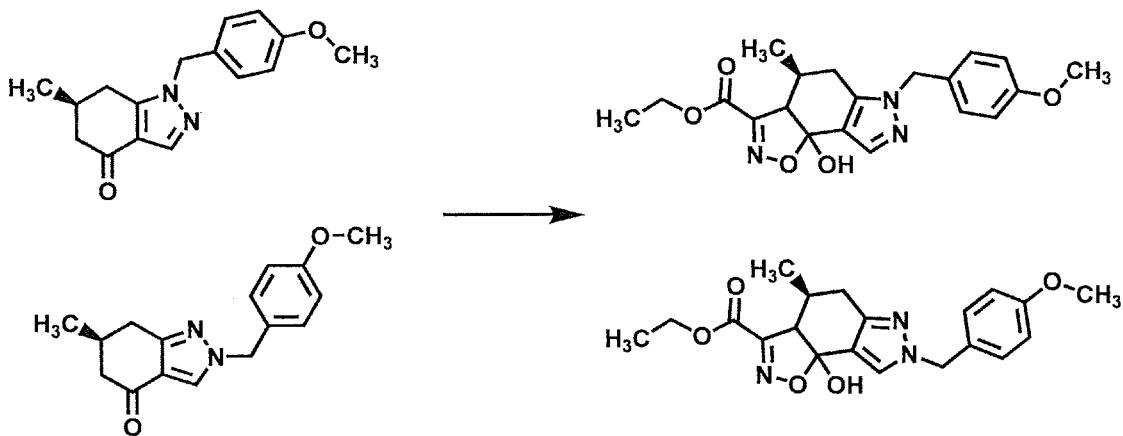
methyl-4-oxo-4,5,6,7-tetrahydro-1H-indazole-5-carboxylate and (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (5*R*,6*S*)-2-(4-methoxybenzyl)-6-methyl-4-oxo-4,5,6,7-tetrahydro-2*H*-indazole-5-carboxylate obtained in the previous step was mixed with 5 DMSO (148 ml)-water (4.93 ml). To the mixture was added 4-dimethylaminopyridine (4.25 g), and the mixture was stirred at 160°C for 4 hr. At room temperature, water was added to the reaction mixture, and the mixture was extracted with toluene. The organic layer was washed successively with water and 10 saturated aqueous sodium chloride solution, and filtered through a phase separator, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane:ethyl acetate=80:20 to 24:76) to give a mixture (3.7 g) of the title compound.

15 [0904]

Step 6

mixture of ethyl (4*S*)-8*b*-hydroxy-6-(4-methoxybenzyl)-4-methyl-3*a*,5,6,8*b*-tetrahydro-4*H*-isoxazolo[5,4-*e*]indazole-3-carboxylate and ethyl (4*S*)-8*b*-hydroxy-7-(4-methoxybenzyl)-4-methyl-20 3*a*,5,7,8*b*-tetrahydro-4*H*-isoxazolo[5,4-*e*]indazole-3-carboxylate

[0905]



[0906]

ethyl 2-chloro-2-(hydroxyimino)acetate (2.489 g) was 25 mixed with tetrahydrofuran (37 ml). To this solution was added dropwise at -78°C 1.3 M lithium bis(trimethylsilyl)amide/tetrahydrofuran solution (13.69 ml)

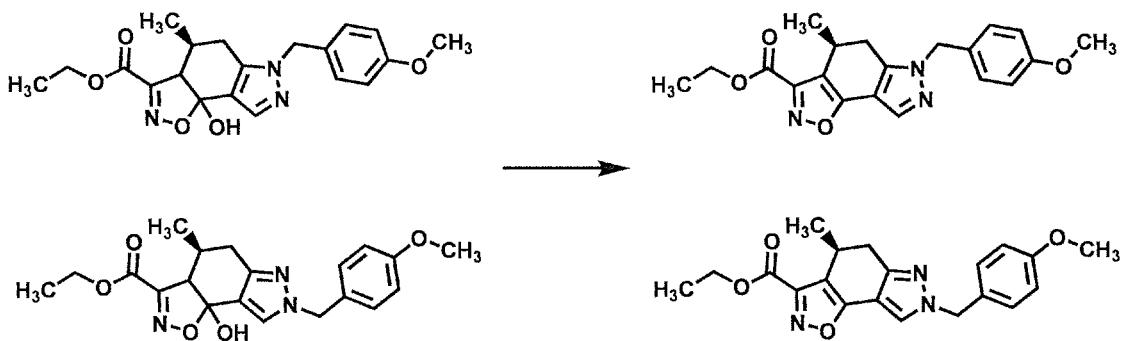
to prepare a nitrile oxide solution. In a separate reaction vessel, the mixture (3.7 g) of (S)-1-(4-methoxybenzyl)-6-methyl-1,5,6,7-tetrahydro-4H-indazol-4-one and (S)-2-(4-methoxybenzyl)-6-methyl-2,5,6,7-tetrahydro-4H-indazol-4-one obtained in the previous step was mixed with tetrahydrofuran (37 ml). To this solution was added dropwise at -78°C 1.3 M lithium bis(trimethylsilyl)amide/tetrahydrofuran solution (12.63 ml). The reaction mixture was added dropwise through a cannula to the aforementioned nitrile oxide solution cooled to -78°C, and the mixture was stirred for 1 hr. The reaction mixture was stirred for 1 hr while raising the temperature to room temperature. To the reaction mixture was added dropwise at room temperature 2N hydrochloric acid (41.1 ml), saturated aqueous sodium hydrogen carbonate solution was added, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=40:60 to 85:15) to give a crude product (3.4 g) of the title compound.

[0907]

Step 7

mixture of ethyl (S)-6-(4-methoxybenzyl)-4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazole-3-carboxylate and ethyl (S)-7-(4-methoxybenzyl)-4-methyl-5,7-dihydro-4H-isoxazolo[5,4-e]indazole-3-carboxylate

[0908]



[0909]

The mixture (3.4 g) of ethyl (4S)-8b-hydroxy-6-(4-methoxybenzyl)-4-methyl-3a,5,6,8b-tetrahydro-4H-isoxazolo[5,4-e]indazole-3-carboxylate and ethyl (4S)-8b-hydroxy-7-(4-methoxybenzyl)-4-methyl-3a,5,7,8b-tetrahydro-4H-isoxazolo[5,4-e]indazole-3-carboxylate obtained in the previous step was dissolved in tetrahydrofuran (77.16 ml). Under ice-cooling, to the reaction mixture were successively added triethylamine (3.69 ml) and methanesulfonic anhydride (1.998 g). The reaction mixture was stirred at 0°C for 30 min. At room temperature, to the reaction mixture was added triethylamine (3.69 ml), and the mixture was heated under reflux at 70°C overnight. The reaction mixture was concentrated under reduced pressure. To the obtained residue was added at room temperature saturated ammonium chloride aqueous solution, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution and dried over magnesium sulfate. Magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=25:75 to 80:20) to give a mixture (2.4 g) of the title compound.

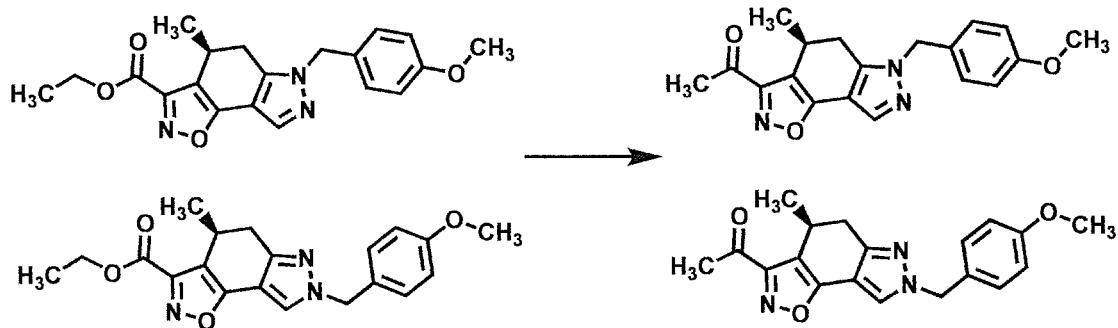
[0910]

25 Step 8

mixture of (S)-1-(6-(4-methoxybenzyl)-4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)ethan-1-one and (S)-1-(7-(4-methoxybenzyl)-4-methyl-5,7-dihydro-4H-isoxazolo[5,4-

e]indazol-3-yl)ethan-1-one

[0911]



[0912]

5 The mixture (2.4 g) of ethyl (S)-6-(4-methoxybenzyl)-4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazole-3-carboxylate and ethyl (S)-7-(4-methoxybenzyl)-4-methyl-5,7-dihydro-4H-isoxazolo[5,4-e]indazole-3-carboxylate obtained in the previous step was dissolved in toluene (24 ml). Under cooling  
10 at -20°C, a mixture of triethylamine (4.1 ml) and 1.04 M methylmagnesium bromide/tetrahydrofuran solution (7.85 ml) was added dropwise, and the mixture was stirred at 0°C for 1 hr. Under ice-cooling, a mixture of triethylamine (1.27 ml) and 1.08 M methylmagnesium bromide/tetrahydrofuran solution (2.4  
15 ml) was further added dropwise, and the mixture was stirred at 0°C for 1 hr. To the reaction mixture was added 2N hydrochloric acid, and the mixture was extracted twice with ethyl acetate. The organic layer was washed successively with saturated aqueous sodium hydrogen carbonate solution and  
20 saturated aqueous sodium chloride solution, and dried over magnesium sulfate. Magnesium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=30:70 to 53:47) to give a mixture (1.54  
25 g) of the title compound.

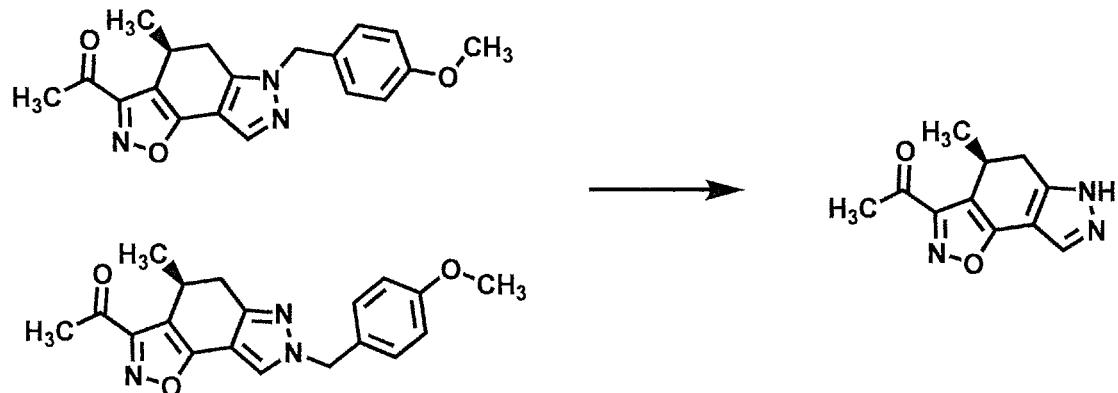
[0913]

Step 9

(S)-1-(4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazol-3-

yl) ethan-1-one

[0914]



[0915]

5 The mixture (1.2 g) of (S)-1-(6-(4-methoxybenzyl)-4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)ethan-1-one and (S)-1-(7-(4-methoxybenzyl)-4-methyl-5,7-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)ethan-1-one obtained in the previous step was mixed with trifluoroacetic acid (11.6 ml).

10 To the reaction mixture was added anisole (0.75 ml), and the mixture was stirred at 130°C for 1 hr under microwave (Biotage (registered trademark) Initiator+) radiation. To the reaction mixture was added toluene, and the mixture was concentrated under reduced pressure. The obtained residue was purified by 15 silica gel column chromatography (ethyl acetate:hexane=20:80 to 85:15) to give the title compound (0.71 g).

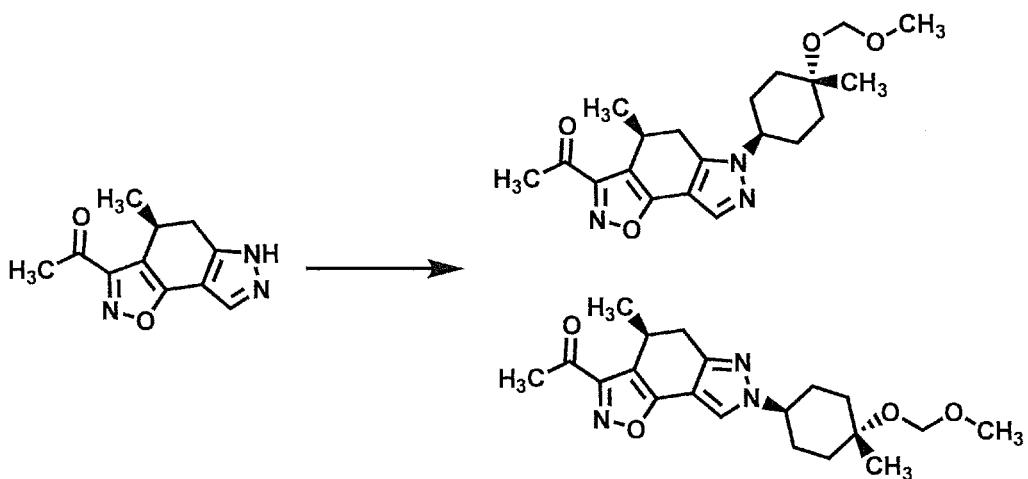
<sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) 0.99 (d, J=6.94Hz, 3H), 2.58 (s, 3H), 2.70 - 2.81 (m, 1H), 2.88 - 3.00 (m, 1H), 3.41 - 3.52 (m, 1H), 8.20 (s, 1H), 13.07 (s, 1H)

20 [0916]

Step 10

mixture of 1-((S)-7-((1r,4r)-4-(methoxymethoxy)-4-methylcyclohexyl)-4-methyl-5,7-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)ethan-1-one and 1-((S)-6-((1r,4r)-4-(methoxymethoxy)-4-methylcyclohexyl)-4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)ethan-1-one

25 [0917]



[0918]

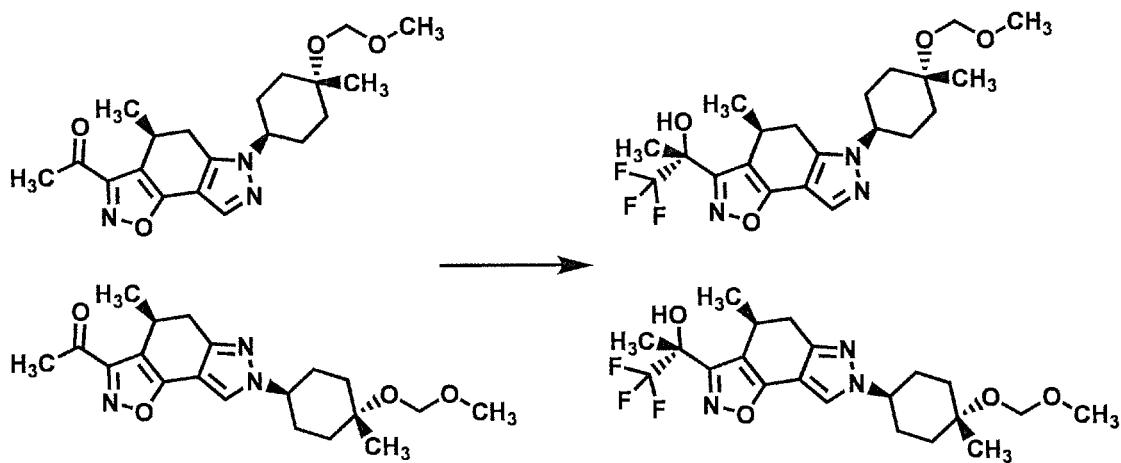
(S)-1-(4-Methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)ethan-1-one (0.8 g) obtained in the previous step was mixed with dimethylformamide (0.728 ml). To the reaction mixture were added cesium carbonate (2.184 g) and cis-4-(methoxymethoxy)-4-methylcyclohexyl methanesulfonate (0.1314 g), and the mixture was stirred at 80°C for 3 hr. At room temperature, to the reaction mixture was added saturated ammonium chloride aqueous solution, and the mixture was extracted with ethyl acetate. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (ethyl acetate:hexane=12:88 to 100:0) to give a mixture (897.9 mg) of the title compound.

[0919]

Step 11

mixture of (R)-1,1,1-trifluoro-2-((S)-7-((1r,4S)-4-(methoxymethoxy)-4-methylcyclohexyl)-4-methyl-5,7-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)propan-2-ol and (R)-1,1,1-trifluoro-2-((S)-6-((1r,4S)-4-(methoxymethoxy)-4-methylcyclohexyl)-4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)propan-2-ol

[0920]



[0921]

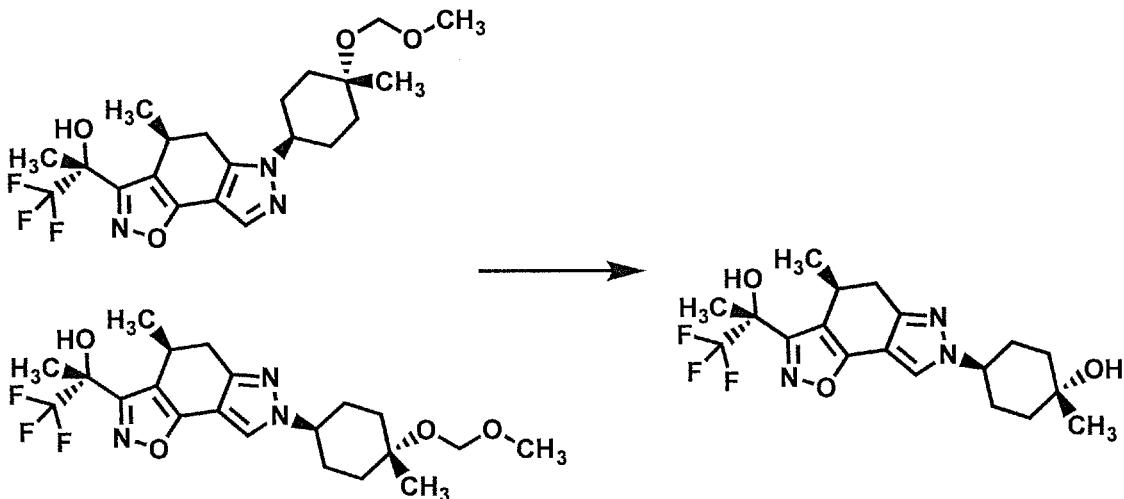
The mixture (897.9 mg) of 1-((S)-7-((1r,4r)-4-(methoxymethoxy)-4-methylcyclohexyl)-4-methyl-5,7-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)ethan-1-one and 1-((S)-6-((1r,4r)-4-(methoxymethoxy)-4-methylcyclohexyl)-4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)ethan-1-one obtained in the previous step was mixed with N,N-dimethylacetamide (4.041 ml). Under ice-cooling, to the mixture was added lithium acetate (42.8 mg), and then (trifluoromethyl)trimethylsilane (0.481 ml) was added dropwise. The reaction mixture was stirred under ice-cooling for 1 hr. Under ice-cooling, methanol (0.404 ml) and potassium carbonate (0.359 g) were added, and the mixture was stirred at room temperature overnight. To the reaction mixture was added water, and the mixture was extracted twice with ethyl acetate. The organic layer was washed successively with water and saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (ethyl acetate:hexane=8:92 to 66:34) to give a mixture (774 mg) of the title compound.

[0922]

25 Step 12

(1S,4r)-1-methyl-4-((S)-4-methyl-3-((R)-1,1,1-trifluoro-2-

hydroxypropan-2-yl)-4,5-dihydro-7H-isoxazolo[5,4-e]indazol-7-yl)cyclohexan-1-ol  
[0923]



5 [0924]

The mixture (774 mg) of (R)-1,1,1-trifluoro-2-((S)-7-((1r,4S)-4-(methoxymethoxy)-4-methylcyclohexyl)-4-methyl-5,7-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)propan-2-ol and (R)-1,1,1-trifluoro-2-((S)-6-((1r,4S)-4-(methoxymethoxy)-4-methylcyclohexyl)-4-methyl-5,6-dihydro-4H-isoxazolo[5,4-e]indazol-3-yl)propan-2-ol obtained in the previous step was mixed with tetrahydrofuran (6.656 ml). At room temperature, to the reaction mixture was added 6N hydrochloric acid (1.251 ml), and the mixture was stirred at 60°C for 30 min. Under ice-cooling, to the reaction mixture was added saturated aqueous sodium hydrogen carbonate solution, and the mixture was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, and dried over sodium sulfate. Sodium sulfate was filtered off, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel chromatography (ethyl acetate:hexane=80:20 to 100:0). A fraction containing a more-polar isomer was concentrated under reduced pressure, ethyl acetate (1 ml) was added, and the mixture was stirred at room temperature. The precipitated solid was collected by

filtration to give the title compound (192.8 mg). The steric configuration of the title compound was determined by X-ray crystal structure analysis.

<sup>1</sup>H-NMR (400 MHz, DMSO-D<sub>6</sub>) 1.03 (d,  $J=6.73$ Hz, 3H), 1.16 (s, 3H),  
5 1.50 - 1.62 (m, 4H), 1.74 (s, 3H), 1.87 - 1.99 (m, 4H), 2.71  
(d,  $J=16.09$ Hz, 1H), 2.84 (dd,  $J=16.09$ , 6.73Hz, 1H), 3.35 -  
3.37 (m, 1H), 4.14 - 4.19 (m, 1H), 4.40 (s, 1H), 7.03 (s, 1H),  
8.22 (s, 1H)

[0925]

10 The compounds of Examples 1 to 105 were obtained by methods similar to those of the above-mentioned Production Method 1 to Production Method 10, and Production Examples 1 to 16, and by using other known methods as necessary. The structural formulas and property data of the Example compounds 15 are shown in the following Tables. Remarks in the Tables show the following contents.

[0926]

Remarks

1 (Examples 14 to 24, 26, 27, 29, 30, 32, 34 to 39, 42 to 58,  
20 99 and 101 to 104)

racemate

2 (Example 26)

cis-trans of cyclobutane moiety undetermined, cis-trans isomer of Example 29

25 3 (Example 27)

cis-trans of cyclobutane moiety undetermined, cis-trans isomer of Example 30

4 (Example 29)

cis-trans of cyclobutane moiety undetermined, cis-trans isomer 30 of Example 26

5 (Example 30)

cis-trans of cyclobutane moiety undetermined, cis-trans isomer of Example 27

Example	Structure	$^1\text{H-NMR}$	Mass M+1	Mass M-1	Remarks
1		(400 MHz, DMSO-D6) 1.21 (d, $J$ =6.94Hz, 3H), 1.82 (s, 3H), 3.56 - 3.60 (m, 1H), 4.40 (d, $J$ =3.24Hz, 2H), 7.49 (s, 1H)	357	401 (M-1+46)	
2		(400 MHz, DMSO-D6) 1.15 (d, $J$ =6.94Hz, 3H), 1.32 - 1.34 (m, 1H), 1.47 - 1.49 (m, 1H), 1.53 - 1.62 (m, 2H), 1.81 (s, 3H), 3.55 (t, $J$ =5.90Hz, 1H), 4.22 (dd, $J$ =12.77, 4.74Hz, 1H), 4.37 (d, $J$ =12.77Hz, 1H), 7.42 (s, 1H)	397	441 (M-1+46)	
3		(400 MHz, DMSO-D6) 1.15 (d, $J$ =7.17Hz, 3H), 1.80 (s, 3H), 2.22 (t, $J$ =19.54Hz, 3H), 3.51 - 3.57 (m, 1H), 4.33 (d, $J$ =13.41, 5.09Hz, 1H), 4.44 (d, $J$ =13.41Hz, 1H), 7.43 (s, 1H)	353	397 (M-1+46)	
4		(400 MHz, DMSO-D6) 1.16 (d, $J$ =6.47Hz, 3H), 1.81 (t, $J$ =7.86Hz, 6H), 1.87 (d, $J$ =15.95Hz, 3H), 3.50 - 3.53 (m, 1H), 4.29 (dd, $J$ =13.00, 4.97Hz, 1H), 4.51 (d, $J$ =13.00Hz, 1H), 7.41 (s, 1H)	349	393 (M-1+46)	
5		(400 MHz, DMSO-D6) 0.95 - 1.05 (m, 4H), 1.16 (d, $J$ =6.94Hz, 3H), 1.79 (s, 3H), 2.06 - 2.08 (m, 1H), 3.51 - 3.52 (m, 1H), 4.13 (dd, $J$ =13.53, 5.55Hz, 1H), 4.38 (d, $J$ =13.53Hz, 1H), 7.36 (s, 1H)	329	373 (M-1+46)	

[Table 1-2]

Example	Structure	<sup>1</sup> H-NMR	Mass M+1	Mass M+1	Remarks
6		(400 MHz, DMSO-D6) 1.15 (d, <i>J</i> =6.70Hz, 3H), 1.80 (s, 3H), 2.44 (s, 3H), 3.50 - 3.52 (m, 1H), 4.06 (dd, <i>J</i> =12.89, 4.74Hz, 1H), 4.23 (d, <i>J</i> =12.89Hz, 1H), 7.37 (s, 1H)	303	347 (M-1+46)	
7		(400 MHz, DMSO-D6) 1.14 (d, <i>J</i> =6.94Hz, 3H), 1.82 (s, 3H), 3.51 - 3.57 (m, 1H), 4.27 (d, <i>J</i> =12.72Hz, 1H), 4.41 (dd, <i>J</i> =13.29, 4.97Hz, 1H), 7.42 (s, 1H), 7.47 (t, <i>J</i> =8.79Hz, 2H), 7.81 - 7.83 (m, 2H)	383	427 (M-1+46)	
8		(400 MHz, DMSO-D6) 1.17 (d, <i>J</i> =6.94Hz, 3H), 1.27 - 1.37 (m, 2H), 1.52 - 1.65 (m, 2H), 1.80 (s, 3H), 3.53 - 3.59 (m, 1H), 4.45 - 4.27 (m, 2H), 7.41 (s, 1H)	347	391 (M-1+46)	
9		(400 MHz, DMSO-D6) 1.16 (t, <i>J</i> =4.05Hz, 3H), 1.81 (s, 3H), 2.49 - 2.60 (m, 6H), 3.43 - 3.49 (m, 1H), 4.17 (dd, <i>J</i> =12.77, 5.20Hz, 1H), 4.43 (d, <i>J</i> =12.77Hz, 1H), 7.40 (s, 1H)	423	467 (M-1+46)	
10		(400 MHz, DMSO-D6) 1.15 (d, <i>J</i> =7.17Hz, 3H), 1.80 (s, 3H), 2.49 - 2.58 (m, 6H), 3.43 - 3.48 (m, 1H), 3.66 (s, 3H), 4.16 (dd, <i>J</i> =13.12, 5.20Hz, 1H), 4.40 (d, <i>J</i> =13.12Hz, 1H), 7.39 (s, 1H)	413	457 (M-1+46)	

[09291]

[Table 1-3]

Example	Structure	<sup>1</sup> H-NMR	Mass M+1	Mass M-1	Remarks
11		(400 MHz, DMSO-D <sub>6</sub> ) 1.13 (d, J=7.17Hz, 3H), 1.77 - 1.86 (m, 9H), 1.90 - 2.04 (m, 6H), 3.39 - 3.45 (m, 1H), 3.59 (s, 3H), 4.11 - 4.18 (m, 1H), 4.66 (d, J=12.48Hz, 1H), 7.35 (s, 1H)	455	499 (M-1+46)	
12		(400 MHz, DMSO-D <sub>6</sub> ) 1.01 (s, 6H), 1.12 (d, J=6.70Hz, 3H), 1.53 - 1.59 (m, 6H), 1.78 (s, 3H), 1.86 - 1.97 (m, 6H), 3.38 - 3.45 (m, 1H), 3.92 (s, 1H), 4.08 - 4.15 (m, 1H), 4.66 - 4.60 (m, 1H), 7.36 (s, 1H)	455	499 (M-1+46)	
13		(400 MHz, DMSO-D <sub>6</sub> ) 1.09 (s, 6H), 1.14 (d, J=6.94Hz, 3H), 1.80 (s, 3H), 2.04 - 2.13 (m, 6H), 3.46 - 3.48 (m, 1H), 4.14 (dd, J=13.46, 4.97Hz, 1H), 4.30 (s, 1H), 4.36 (d, J=13.46Hz, 1H), 7.38 (s, 1H)	413	457 (M-1+46)	
14		(400 MHz, DMSO-D <sub>6</sub> ) 1.18 - 1.21 (m, 9H), 1.78 (s, 3H), 3.39 - 3.41 (m, 1H), 3.87 (s, 2H), 4.08 - 4.10 (m, 2H), 4.62 (s, 1H), 6.25 (s, 1H), 7.29 (s, 1H)	376	420 (M-1+46)	1

[Table 1-4]

Example	Structure	<sup>1</sup> H-NMR	Mass M+1	Mass M+1	Remarks
15		(400 MHz, DMSO-D6) 1.20 (d, J=6.94Hz, 3H), 1.78 (s, 3H), 3.41 - 3.42 (m, 1H), 4.12 (d, J=3.24Hz, 2H), 5.20 (s, 2H), 6.32 (s, 1H), 7.30 - 7.48 (m, 6H)	394	438 (M-1+46)	1
16		(400 MHz, DMSO-D6) 1.04 (d, J=6.94Hz, 3H), 1.58 (s, 9H), 1.73 (s, 3H), 3.01 - 3.11 (m, 1H), 3.23 - 3.42 (m, 2H), 7.02 (s, 1H), 7.71 (s, 1H)	344	no peak	1
17		(400 MHz, DMSO-D6) 1.16 (d, J=6.94Hz, 3H), 1.78 (s, 3H), 3.44 - 3.46 (m, 1H), 4.25 (dd, J=13.00, 5.20Hz, 1H), 4.34 (d, J=13.00Hz, 1H), 6.79 (d, J=1.85Hz, 1H), 7.29 (s, 1H), 7.64 (d, J=2.08Hz, 1H)	288	332 (M-1+46)	1
18		(400 MHz, DMSO-D6) 0.93 - 1.14 (m, 7H), 1.73 (s, 3H), 2.98 - 3.06 (m, 2H), 3.35 - 3.46 (m, 1H), 3.58 - 3.68 (m, 1H), 7.04 (s, 1H), 7.71 (s, 1H)	328	372 (M-1+46)	1
19		(400 MHz, DMSO-D6) 0.92 - 0.99 (m, 2H), 1.01 (d, J=6.94Hz, 3H), 1.04 - 1.10 (m, 2H), 1.73 (s, 3H), 2.67 (d, J=15.95Hz, 1H), 2.81 (dd, J=15.95, 6.70Hz, 1H), 3.27 - 3.39 (m, 1H), 3.67 - 3.77 (m, 1H), 7.03 (s, 1H), 8.19 (s, 1H)	328	no peak	1

[0931]

[Table 1-5]

Example	Structure	<sup>1</sup> H-NMR	Mass M+1	Mass M-1	Remarks
20		(400 MHz, DMSO-D6) 1.01 (d, J=6.94Hz, 3H), 1.73 (s, 3H), 2.62 - 2.92 (m, 2H), 3.32 - 3.41 (m, 1H), 7.02 (s, 1H), 8.13 (s, 1H), 12.98 (s, 1H)	288	286	1
21		(400 MHz, DMSO-D6) 1.06 (d, J=6.94Hz, 3H), 1.74 (s, 3H), 3.11 - 3.17 (m, 2H), 3.38 - 3.51 (m, 1H), 7.13 (s, 1H), 7.94 (t, J=57.68Hz, 1H), 8.15 (s, 1H)	338	382 (M-1+46)	1
22		(400 MHz, DMSO-D6) 1.05 (t, J=7.51Hz, 3H), 1.75 (s, 3H), 2.81 (d, J=15.95Hz, 1H), 2.93 (dd, J=16.41, 6.70Hz, 1H), 3.37 - 3.48 (m, 1H), 7.15 (s, 1H), 7.80 (t, J=58.84Hz, 1H), 8.67 (s, 1H)	338	382 (M-1+46)	1
23		(400 MHz, DMSO-D6) 1.01 (d, J=6.94Hz, 3H), 1.73 (s, 3H), 2.68 (d, J=15.84Hz, 1H), 2.83 (dd, J=15.84, 6.94Hz, 1H), 3.28 - 3.39 (m, 1H), 3.83 (s, 3H), 7.03 (s, 1H), 8.09 (s, 1H)	302	no peak	1
24		(400 MHz, DMSO-D6) 1.05 (d, J=6.94Hz, 3H), 1.73 (s, 3H), 2.90 - 2.96 (m, 2H), 3.29 - 3.44 (m, 1H), 3.80 (s, 3H), 7.03 (s, 1H), 7.74 (s, 1H)	302	no peak	1

Example	Structure	<sup>1</sup> H-NMR	Mass M+1	Mass M-1	Remarks
25		(400 MHz, DMSO-D6) 1.16 (t, J=3.47Hz, 3H), 1.80 (s, 3H), 3.55 (t, J=6.01Hz, 1H), 4.30 (dd, J=13.35, 4.97Hz, 1H), 4.42 (d, J=13.35Hz, 1H), 7.44 (s, 1H), 7.51 (t, J=51.44Hz, 1H)	339	383 (M-1+46)	
26		(400 MHz, DMSO-D6) 1.04 (d, J=6.94Hz, 3H), 1.74 (s, 3H), 2.70 - 3.05 (m, 6H), 3.38 - 3.40 (m, 1H), 3.50 - 3.53 (m, 1H), 5.24 - 5.26 (m, 1H), 7.05 (s, 1H), 7.89 (s, 1H)	367	411 (M-1+46)	1, 2
27		(400 MHz, DMSO-D6) 1.04 (d, J=6.94Hz, 3H), 1.74 (s, 3H), 2.73 - 2.93 (m, 6H), 3.35 - 3.38 (m, 1H), 3.45 - 3.51 (m, 1H), 5.18 - 5.20 (m, 1H), 7.06 (s, 1H), 8.25 (s, 1H)	367	411 (M-1+46)	1, 3
28		(400 MHz, DMSO-D6) 1.01 (d, J=6.94Hz, 3H), 1.73 (s, 3H), 2.62 - 2.92 (m, 2H), 3.32 - 3.41 (m, 1H), 7.02 (s, 1H), 8.13 (s, 1H), 12.98 (s, 1H)	288	286	
29		(400 MHz, DMSO-D6) 1.04 (d, J=6.70Hz, 3H), 1.74 (s, 3H), 2.76 - 2.94 (m, 6H), 3.24 - 3.27 (m, 1H), 3.37 - 3.41 (m, 1H), 4.95 - 4.97 (m, 1H), 7.05 (s, 1H), 7.92 (s, 1H)	367	411 (M-1+46)	1, 4

[Table 1-7]

Example	Structure	<sup>1</sup> H-NMR	Mass M+1	Mass M-1	Remarks
30		(400 MHz, DMSO-D6) 1.02 (d, J=6.94Hz, 3H), 1.73 (s, 3H), 2.72 - 2.91 (m, 6H), 3.19 - 3.24 (m, 1H), 3.34 - 3.38 (m, 1H), 4.83 - 4.90 (m, 1H), 7.04 (s, 1H), 8.29 (s, 1H)	367	411 (M-1+46)	1, 5
31		(400 MHz, DMSO-D6) 1.16 - 1.20 (m, 9H), 1.77 (s, 3H), 3.38 - 3.41 (m, 1H), 3.87 (s, 2H), 4.08 - 4.09 (m, 2H), 4.61 (s, 1H), 6.24 (s, 1H), 7.28 (s, 1H)	376	420 (M-1+46)	
32		(400 MHz, DMSO-D6) 1.04 (d, J=6.94Hz, 3H), 1.75 (s, 3H), 2.74 (d, J=14.85Hz, 1H), 2.87 (dd, J=14.85, 5.66Hz, 1H), 3.10 (t, J=6.47Hz, 2H), 3.37 - 3.40 (m, 1H), 4.41 (t, J=6.47Hz, 2H), 7.06 (s, 1H), 8.24 (s, 1H)	341	385 (M-1+46)	1
33		(400 MHz, DMSO-D6) 1.14 - 1.19 (m, 7H), 1.76 (s, 3H), 3.37 - 3.42 (m, 1H), 4.08 - 4.09 (m, 2H), 4.15 (s, 2H), 6.31 (s, 1H), 7.27 (s, 1H)	383	427 (M-1+46)	
34		(400 MHz, DMSO-D6) 1.15 (s, 6H), 1.19 (d, J=7.17Hz, 3H), 1.77 (s, 3H), 1.83 (t, J=7.23Hz, 2H), 3.38 - 3.40 (m, 1H), 4.09 (d, J=3.01Hz, 2H), 4.21 (t, J=7.23Hz, 2H), 4.35 (s, 1H), 6.23 (s, 1H), 7.29 (s, 1H)	390	434 (M-1+46)	1

[0934]

[Table 1-8]

Example	Structure	<sup>1</sup> H-NMR		Mass M+1	Mass M-1	Remarks
		Chemical Shift (ppm)	Integration			
35		(400 MHz, DMSO-D6) 1.19 (d, J=6.94Hz, 3H), 1.60 - 1.63 (m, 2H), 1.77 (s, 3H), 2.00 - 2.02 (m, 2H), 3.41 - 3.47 (m, 3H), 3.84 - 3.86 (m, 2H), 4.09 (d, J=3.24Hz, 2H), 4.66 - 4.67 (m, 1H), 6.28 (s, 1H), 7.27 (s, 1H)	388	432 (M-1+46)	1	
36		(400 MHz, DMSO-D6) 1.20 (d, J=6.94Hz, 3H), 1.77 (s, 3H), 2.02 - 2.04 (m, 1H), 2.17 - 2.21 (m, 1H), 3.39 - 3.41 (m, 1H), 3.72 - 3.80 (m, 1H), 3.83 - 3.86 (m, 3H), 4.10 (d, J=3.24Hz, 2H), 5.14 (s, 1H), 6.27 (s, 1H), 7.28 (s, 1H)	374	418 (M-1+46)	1	
37		(400 MHz, DMSO-D6) 1.16 (d, J=17.11Hz, 3H), 1.19 (q, J=6.94Hz, 3H), 1.38 - 1.41 (m, 2H), 1.57 - 1.66 (m, 4H), 1.77 (s, 3H), 1.89 - 1.93 (m, 2H), 3.37 - 3.41 (m, 1H), 4.08 (d, J=3.24Hz, 2H), 4.16 (s, 1H), 4.56 - 4.61 (m, 1H), 6.24 (s, 1H), 7.27 (s, 1H)	416	460 (M-1+46)	1	
38		(400 MHz, DMSO-D6) 1.02 (d, J=6.94Hz, 3H), 1.06 (s, 3H), 1.07 (s, 3H), 1.73 (s, 3H), 2.68 - 2.74 (m, 1H), 2.80 - 2.87 (m, 1H), 3.33 - 3.40 (m, 1H), 4.01 (s, 2H), 4.71 (s, 1H), 7.03 (s, 1H), 8.00 (s, 1H)	360	404 (M-1+46)	1	
39		(400 MHz, DMSO-D6) 1.02 (d, J=6.94Hz, 3H), 1.07 (s, 3H), 1.12 (s, 3H), 1.73 (s, 3H), 2.88 - 2.95 (m, 1H), 3.00 - 3.07 (m, 1H), 3.33 - 3.40 (m, 1H), 4.02 (s, 2H), 4.62 (s, 1H), 7.01 (s, 1H), 7.77 (s, 1H)	360	404 (M-1+46)	1	

Example	Structure	<sup>1</sup> H-NMR	Mass M+1	Mass M-1	Remarks
40		(400 MHz, DMSO-D6) 1.06 (d, <i>J</i> =6.73Hz, 3H), 1.12 (s, 6H), 1.74 (s, 3H), 1.81 - 1.83 (m, 2H), 2.92 - 2.99 (m, 2H), 3.40 - 3.41 (m, 1H), 4.18 - 4.20 (m, 2H), 4.45 (s, 1H), 7.04 (s, 1H), 7.76 (s, 1H)	374	418 (M-1+46)	
41		(400 MHz, DMSO-D6) 1.03 (d, <i>J</i> =7.48Hz, 3H), 1.12 (s, 6H), 1.74 (s, 3H), 1.91 - 1.92 (m, 2H), 2.70 (d, <i>J</i> =16.39Hz, 1H), 2.84 (d, <i>J</i> =6.39, 7.11Hz, 1H), 3.28 - 3.38 (m, 1H), 4.19 (t, <i>J</i> =7.85Hz, 2H), 4.43 (s, 1H), 7.03 (s, 1H), 8.15 (s, 1H)	374	418 (M-1+46)	
42		(400 MHz, DMSO-D6) 1.20 (d, <i>J</i> =6.94Hz, 3H), 1.78 (s, 3H), 3.43 - 3.44 (m, 1H), 4.16 - 4.17 (m, 2H), 5.17 (s, 2H), 6.42 (s, 1H), 7.31 (s, 1H)	343	387 (M-1+46)	1
43		(400 MHz, DMSO-D6) 1.19 (d, <i>J</i> =6.94Hz, 3H), 1.78 (s, 3H), 3.30 (s, 3H), 3.39 - 3.42 (m, 1H), 3.63 (t, <i>J</i> =4.51Hz, 2H), 4.09 (d, <i>J</i> =3.24Hz, 2H), 4.22 - 4.24 (m, 2H), 6.26 (s, 1H), 7.29 (s, 1H)	362	406 (M-1+46)	1
44		(400 MHz, DMSO-D6) 1.20 (d, <i>J</i> =6.94Hz, 3H), 1.78 (s, 3H), 3.42 - 3.44 (m, 1H), 4.16 (s, 2H), 5.81 (q, <i>J</i> =2.39Hz, 1H), 5.95 (q, <i>J</i> =2.39Hz, 1H), 6.47 (s, 1H), 7.30 (s, 1H)	336	380 (M-1+46)	1

[0936] Table I-101

Example	Structure	<sup>1</sup> H-NMR	Mass M+1	Mass M-1	Remarks
50		(400 MHz, DMSO-D <sub>6</sub> ) 1.06 (d, J=6.73 Hz, 3H), 1.75 (s, 3H), 2.98 (dd, J=16.27, 7.11 Hz, 1H), 3.09 (d, J=16.27 Hz, 1H), 3.41 - 3.48 (m, 1H), 5.58 (s, 2H), 7.09 (s, 1H), 7.95 (s, 1H)	327	371 (M-1+46)	1
51		(400 MHz, DMSO-D <sub>6</sub> ) 1.07 (d, J=6.73 Hz, 3H), 1.74 (s, 3H), 2.84 - 2.90 (m, 6H), 3.04 (d, J=4.49 Hz, 2H), 3.37 - 3.41 (m, 1H), 7.07 (s, 1H), 7.86 (s, 1H)	379	423 (M-1+46)	1
52		(400 MHz, DMSO-D <sub>6</sub> ) 1.15 (d, J=6.94 Hz, 3H), 1.58 - 1.71 (m, 2H), 1.76 (s, 3H), 1.79 - 1.88 (m, 2H), 2.80 - 2.93 (m, 1H), 3.36 - 3.49 (m, 3H), 3.83 - 3.93 (m, 2H), 4.17 (dd, J=13.41, 5.09 Hz, 1H), 4.24 (d, J=12.02 Hz, 1H), 6.65 (s, 1H), 7.25 (s, 1H)	372	416 (M-1+46)	1
53		(400 MHz, DMSO-D <sub>6</sub> ) 1.03 (d, J=6.94 Hz, 3H), 1.56 (s, 3H), 1.73 (s, 3H), 2.59 (dd, J=11.97, 9.02 Hz, 1H), 2.73 (dd, J=11.97, 8.67 Hz, 1H), 2.91 - 3.03 (m, 4H), 3.37 - 3.39 (m, 1H), 5.13 - 5.15 (m, 1H), 7.03 (s, 1H), 7.88 (s, 1H)	381	425 (M-1+46)	1

[Table 1-12]

Example	Structure	$^1\text{H-NMR}$	Mass M+1	Mass M-1	Remarks
54		(400 MHz, DMSO-D6) 1.03 (d, J=6.94Hz, 3H), 1.57 (s, 3H), 1.74 (s, 3H), 2.64 - 2.67 (m, 2H), 2.75 (d, J=15.95Hz, 1H), 2.87 (dd, J=15.95, 6.47Hz, 1H), 2.96 - 2.98 (m, 2H), 3.37 - 3.38 (m, 1H), 5.06 - 5.11 (m, 1H), 7.06 (s, 1H), 8.27 (s, 1H)	381	425 (M-1+46)	1
55		(400 MHz, DMSO-D6) 1.03 (d, J=6.73Hz, 3H), 1.17 (s, 3H), 1.50 - 1.62 (m, 4H), 1.74 (s, 3H), 1.87 - 1.99 (m, 4H), 2.71 (d, J=16.09Hz, 1H), 2.84 (dd, J=16.09, 6.73Hz, 1H), 3.35 - 3.37 (m, 1H), 4.14 - 4.19 (m, 1H), 4.40 (s, 1H), 7.03 (s, 1H), 8.22 (s, 1H)	400	444 (M-1+46)	1
56		(400 MHz, DMSO-D6) 1.05 (d, J=6.73Hz, 3H), 1.20 (s, 3H), 1.56 - 1.64 (m, 4H), 1.74 (s, 3H), 1.83 - 1.96 (m, 4H), 2.94 - 3.01 (m, 2H), 3.39 - 3.40 (m, 1H), 4.25 - 4.26 (m, 1H), 4.43 (s, 1H), 7.03 (s, 1H), 7.77 (s, 1H)	400	444 (M-1+46)	1
57		(400 MHz, DMSO-D6) 1.04 (d, J=6.73Hz, 3H), 1.62 (s, 3H), 1.74 (s, 3H), 2.58 - 2.64 (m, 2H), 2.88 - 3.14 (m, 4H), 3.39 - 3.41 (m, 1H), 5.20 - 5.22 (m, 1H), 7.05 (s, 1H), 7.92 (s, 1H)	381	425 (M-1+46)	1

Example	Structure	<sup>1</sup> H-NMR	Mass M+1	Mass M-1	Remarks
58		(400 MHz, DMSO-D6) 1.04 (d, J=6.73Hz, 3H), 1.59 (s, 3H), 1.74 (s, 3H), 2.61 - 2.63 (m, 2H), 2.77 (d, J=15.71Hz, 1H), 2.88 (d, J=15.71, 6.73Hz, 1H), 2.96 - 3.02 (m, 2H), 3.36 - 3.39 (m, 1H), 5.11 - 5.13 (m, 1H), 7.05 (d, J=3.74Hz, 1H), 8.24 (s, 1H)	381 (M-1+46)	425 (M-1+46)	1
59		(400 MHz, DMSO-D6) 1.19 (d, J=6.94Hz, 3H), 1.60 - 1.63 (m, 2H), 1.77 (s, 3H), 2.00 - 2.02 (m, 2H), 3.41 - 3.47 (m, 3H), 3.84 - 3.86 (m, 2H), 4.09 (d, J=3.24Hz, 2H), 4.66 - 4.67 (m, 1H), 6.28 (s, 1H), 7.27 (s, 1H)	388 (M-1+46)	432 (M-1+46)	
60		(400 MHz, DMSO-D6) 1.16 (d, J=6.94Hz, 3H), 1.78 (s, 3H), 3.44 - 3.46 (m, 1H), 4.25 (dd, J=13.00, 5.20Hz, 1H), 4.34 (d, J=13.00Hz, 1H), 6.79 (d, J=1.85Hz, 1H), 7.29 (s, 1H), 7.64 (d, J=2.08Hz, 1H)	288 (M-1+46)	332 (M-1+46)	
61		(400 MHz, DMSO-D6) 1.15 (d, J=6.94Hz, 3H), 1.58 - 1.71 (m, 2H), 1.76 (s, 3H), 1.79 - 1.88 (m, 2H), 2.80 - 2.93 (m, 1H), 3.36 - 3.49 (m, 3H), 3.83 - 3.93 (m, 2H), 4.17 (dd, J=13.41, 5.09Hz, 1H), 4.24 (d, J=12.02Hz, 1H), 6.65 (s, 1H), 7.25 (s, 1H)	372 (M-1+46)	416 (M-1+46)	
62		(400 MHz, DMSO-D6) 1.15 (s, 6H), 1.19 (d, J=7.17Hz, 3H), 1.77 (s, 3H), 1.83 (t, J=7.23Hz, 2H), 3.38 - 3.40 (m, 1H), 4.09 (d, J=3.01Hz, 2H), 4.21 (t, J=7.23Hz, 2H), 4.35 (s, 1H), 6.23 (s, 1H), 7.29 (s, 1H)	390 (M-1+46)	434 (M-1+46)	

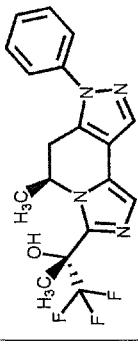
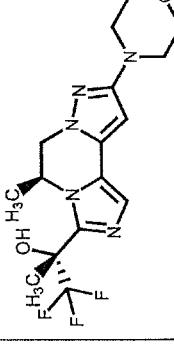
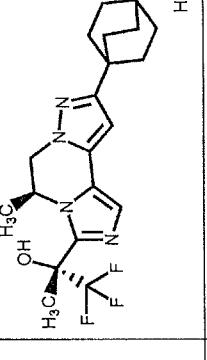
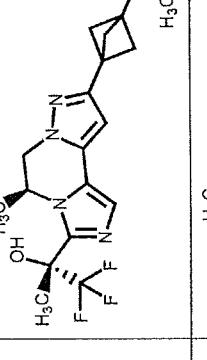
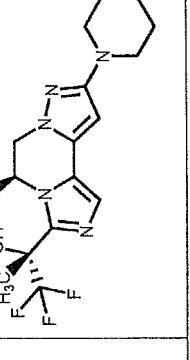
[Table 1-14]

Example	Structure	<sup>1</sup> H-NMR	Mass M+1	Mass M-1	Remarks
63		(400 MHz, DMSO-D6) 1.19 (d, J=7.17Hz, 3H), 1.54 (s, 3H), 1.77 (s, 3H), 2.26 - 2.27 (m, 2H), 2.95 - 3.01 (m, 2H), 3.38 - 3.41 (m, 1H), 4.10 - 4.10 (m, 2H), 4.97 (t, J=7.28Hz, 1H), 6.28 (s, 1H), 7.28 (s, 1H)	397	441 (M-1+46)	
64		(400 MHz, DMSO-D6) 1.20 (d, J=6.94Hz, 3H), 1.78 (s, 3H), 3.42 - 3.44 (m, 1H), 4.16 (s, 2H), 5.81 (q, J=2.39Hz, 1H), 5.95 (q, J=2.39Hz, 1H), 6.47 (s, 1H), 7.30 (s, 1H)	336	380 (M-1+46)	
65		(400 MHz, DMSO-D6) 1.16 (d, J=17.11Hz, 3H), 1.19 (q, J=6.94Hz, 3H), 1.38 - 1.41 (m, 2H), 1.57 - 1.66 (m, 4H), 1.77 (s, 3H), 1.89 - 1.93 (m, 2H), 3.37 - 3.41 (m, 1H), 4.08 (d, J=3.24Hz, 2H), 4.16 (s, 1H), 4.56 - 4.61 (m, 1H), 6.24 (s, 1H), 7.27 (s, 1H)		416 (M-1+46)	460
66		(400 MHz, DMSO-D6) 1.27 (d, J=6.70Hz, 3H), 1.80 (s, 3H), 4.10 - 4.22 (m, 2H), 4.28 (t, J=3.81Hz, 1H), 4.36 (t, J=3.81Hz, 1H), 4.64 (t, J=3.81Hz, 1H), 4.76 (t, J=3.81Hz, 1H), 5.26 - 5.36 (m, 1H), 6.02 (s, 1H), 7.24 (s, 1H), 7.28 (s, 1H)		349	347
67		(400 MHz, DMSO-D6) 1.27 (d, J=6.47Hz, 3H), 1.80 (s, 3H), 3.79 (s, 3H), 4.10 - 4.21 (m, 2H), 5.26 - 5.35 (m, 1H), 5.98 (s, 1H), 7.23 (s, 1H), 7.27 (s, 1H)		317	315

[0941]

[Table 1-15]

Example	Structure	<sup>1</sup> H-NMR	Mass M+1	Mass M-1	Remarks
68		(400 MHz, DMSO-D6) 1.27 (d, J=6.24Hz, 3H), 1.80 (s, 3H), 3.28 (s, 3H), 3.58 - 3.65 (m, 2H), 4.09 - 4.22 (m, 4H), 5.26 - 5.35 (m, 1H), 5.98 (d, J=1.16Hz, 1H), 7.23 (s, 1H), 7.27 (s, 1H)	361	359	
69		(400 MHz, DMSO-D6) 1.21 (d, J=6.47Hz, 3H), 1.37 - 1.44 (m, 6H), 1.71 - 1.77 (m, 6H), 1.80 (s, 3H), 3.05 (d, J=5.55Hz, 2H), 4.17 - 4.23 (m, 1H), 4.28 - 4.33 (m, 2H), 5.34 - 5.27 (m, 1H), 6.33 (s, 1H), 7.20 (s, 1H), 7.24 (s, 1H)	425	469 (M-1+46)	
70		(400 MHz, DMSO-D6) 1.22 (d, J=6.70Hz, 3H), 1.80 (s, 3H), 1.87 (s, 6H), 3.42 (d, J=5.55Hz, 2H), 4.18 - 4.25 (m, 1H), 4.30 - 4.36 (m, 1H), 4.49 - 4.53 (m, 1H), 5.36 - 5.28 (m, 1H), 6.34 (s, 1H), 7.22 (s, 1H), 7.25 (s, 1H)	383	427 (M-1+46)	
71		(400 MHz, DMSO-D6) 1.22 (d, J=6.73Hz, 3H), 1.80 - 1.86 (m, 9H), 1.94 - 1.99 (m, 6H), 4.19 - 4.25 (m, 1H), 4.30 - 4.36 (m, 1H), 5.36 - 5.28 (m, 1H), 6.37 (s, 1H), 7.23 (s, 1H), 7.27 (s, 1H)	420	464 (M-1+46)	
72		(400 MHz, DMSO-D6) 1.22 (d, J=6.73Hz, 3H), 1.81 (s, 3H), 2.50 (s, 6H), 4.22 - 4.28 (m, 1H), 4.33 - 4.39 (m, 1H), 5.38 - 5.30 (m, 1H), 6.44 (s, 1H), 7.26 (s, 1H), 7.29 (s, 1H)	378	422 (M-1+46)	

Example	Structure	<sup>1</sup> H-NMR	Mass M+1	Mass M+1	Remarks
73		(400 MHz, DMSO-D6) 1.09 (d, J=6.24Hz, 3H), 1.81 (s, 3H), 2.99 (d, J=16.93Hz, 1H), 3.46 (dd, J=16.93, 7.28Hz, 1H), 5.33 - 5.35 (m, 1H), 7.05 (s, 1H), 7.08 (s, 1H), 7.42 - 7.43 (m, 1H), 7.53 - 7.59 (m, 4H), 7.97 (s, 1H)	363	407 (M-1+46)	
74		(400 MHz, DMSO-D6) 1.26 (d, J=6.47Hz, 3H), 1.80 (s, 3H), 3.06 - 3.10 (m, 4H), 3.66 - 3.70 (m, 4H), 4.08 - 4.21 (m, 2H), 5.25 - 5.33 (m, 1H), 6.03 (s, 1H), 7.19 (s, 1H), 7.25 (s, 1H)	372	370	
75		(400 MHz, DMSO-D6) 0.99 (s, 6H), 1.21 (d, J=6.70Hz, 3H), 1.38 - 1.43 (m, 1H), 1.56 - 1.47 (m, 5H), 1.69 - 1.76 (m, 6H), 1.80 (s, 3H), 3.82 (s, 1H), 4.16 - 4.23 (m, 1H), 4.28 - 4.34 (m, 1H), 5.26 - 5.34 (m, 1H), 6.32 (s, 1H), 7.20 (s, 1H), 7.24 (s, 1H)	453	497 (M-1+46)	
76		(400 MHz, DMSO-D6) 1.11 (s, 6H), 1.28 (d, J=6.47Hz, 3H), 1.86 (s, 3H), 1.89 (s, 6H), 4.20 (s, 1H), 4.25 - 4.31 (m, 1H), 4.37 - 4.42 (m, 1H), 5.42 - 5.34 (m, 1H), 6.40 (s, 1H), 7.29 (s, 1H), 7.32 (s, 1H)	411	455 (M-1+46)	
77		(400 MHz, DMSO-D6) 1.26 (d, J=6.70Hz, 3H), 1.81 (s, 3H), 1.82 - 1.85 (m, 4H), 3.05 - 3.09 (m, 4H), 4.07 - 4.18 (m, 2H), 4.32 (s, 4H), 5.26 - 5.32 (m, 1H), 6.03 (s, 1H), 7.18 (s, 1H), 7.25 (s, 1H)	412	410	

Example	Structure	$^1\text{H-NMR}$	Mass M+1	Mass M-1	Remarks
78		(400 MHz, DMSO-D6) 1.27 (d, $J=6.47\text{Hz}$ , 3H), 1.81 (s, 3H), 2.57 - 2.61 (m, 2H), 3.49 - 3.53 (m, 2H), 3.57 - 3.60 (m, 2H), 4.07 - 4.20 (m, 2H), 5.25 - 5.32 (m, 1H), 5.81 (s, 1H), 7.20 (s, 1H), 7.26 (s, 1H)	404	402	
79		(400 MHz, DMSO-D6) 1.29 (d, $J=6.47\text{Hz}$ , 3H), 1.69 (dd, $J=17.22$ , 9.83Hz, 1H), 1.82 (s, 3H), 1.94 - 1.99 (m, 1H), 2.94 - 2.99 (m, 2H), 3.45 (dd, $J=10.17$ , 2.54Hz, 2H), 3.72 - 3.75 (m, 2H), 4.11 (dd, $J=13.29$ , 3.81Hz, 1H), 4.17 - 4.21 (m, 1H), 5.25 - 5.33 (m, 1H), 5.87 (s, 1H), 7.22 (s, 1H), 7.26 (s, 1H)	418	416	
80		(400 MHz, DMSO-D6) 1.27 (d, $J=6.47\text{Hz}$ , 3H), 1.81 (s, 3H), 2.88 - 2.92 (m, 2H), 3.07 - 3.10 (m, 2H), 3.21 - 3.25 (m, 2H), 3.46 (dd, $J=8.90$ , 4.05Hz, 2H), 3.83 - 3.87 (m, 2H), 4.10 (dd, $J=13.52$ , 4.05Hz, 1H), 4.17 - 4.20 (m, 1H), 5.27 - 5.31 (m, 1H), 5.88 (s, 1H), 7.20 (s, 1H), 7.25 (s, 1H)	398	396	
81		(400 MHz, DMSO-D6) 1.28 (d, $J=6.47\text{Hz}$ , 3H), 1.75 - 1.78 (m, 1H), 1.81 (s, 3H), 1.86 (dd, $J=9.94$ , 1.85Hz, 1H), 3.08 (d, $J=9.48\text{Hz}$ , 1H), 3.34 - 3.37 (m, 1H), 3.66 - 3.68 (m, 1H), 3.71 (d, $J=7.40\text{Hz}$ , 1H), 4.11 (dd, $J=13.41$ , 3.70Hz, 1H), 4.17 - 4.20 (m, 1H), 4.28 (s, 1H), 4.54 (s, 1H), 5.29 - 5.31 (m, 1H), 5.90 (s, 1H), 7.19 (s, 1H), 7.26 (s, 1H)	384	382	

Example	Structure	<sup>1</sup> H-NMR	Mass M+1	Mass M-1	Remarks
82		(400 MHz, DMSO-D <sub>6</sub> ) 1.27 (d, J=6.47 Hz, 3H), 1.75 - 1.79 (m, 1H), 1.81 (s, 3H), 1.85 - 1.88 (m, 1H), 3.10 (d, J=9.71 Hz, 1H), 3.34 - 3.35 (m, 1H), 3.66 - 3.68 (m, 1H), 3.70 (d, J=7.63 Hz, 1H), 4.11 (dd, J=13.64, 3.47 Hz, 1H), 4.17 - 4.20 (m, 1H), 4.28 (s, 1H), 4.54 (s, 1H), 5.28 - 5.31 (m, 1H), 5.91 (s, 1H), 7.20 (s, 1H), 7.26 (s, 1H)	384	382	
83		(400 MHz, DMSO-D <sub>6</sub> ) 1.24 - 1.31 (m, 5H), 1.79 - 1.84 (m, 5H), 2.82 - 2.86 (m, 1H), 3.21 (dd, J=11.44, 7.74 Hz, 2H), 4.08 - 4.19 (m, 3H), 5.27 - 5.32 (m, 1H), 5.95 (s, 1H), 7.19 (s, 1H), 7.25 (s, 1H)	368	366	
84		(400 MHz, DMSO-D <sub>6</sub> ) 1.26 (d, J=6.47 Hz, 3H), 1.81 (s, 3H), 2.83 (t, J=12.60 Hz, 4H), 3.87 (s, 4H), 4.10 - 4.16 (m, 2H), 5.28 - 5.30 (m, 1H), 5.80 (s, 1H), 7.20 (s, 1H), 7.26 (s, 1H)	418	418 (M-1+46)	
85		(400 MHz, DMSO-D <sub>6</sub> ) 1.20 (d, J=6.47 Hz, 3H), 1.60 - 1.97 (m, 11H), 3.19 (d, J=6.01 Hz, 2H), 3.84 (s, 2H), 4.18 - 4.25 (m, 1H), 4.32 - 4.37 (m, 1H), 4.49 - 4.53 (m, 1H), 5.35 - 5.28 (m, 1H), 6.41 (s, 1H), 7.22 (s, 1H), 7.25 (s, 1H)	427	427 (M-1+46)	

[Table 1-19]

Example	Structure	<sup>1</sup> H-NMR	Mass M+1	Mass M-1	Remarks
86		(400 MHz, DMSO-D6) 1.22 (d, J=6.47Hz, 3H), 1.64 - 1.74 (m, 2H), 1.80 (s, 3H), 1.83 - 1.92 (m, 2H), 1.92 - 2.10 (m, 6H), 4.23 (dd, J=13.41, 3.93Hz, 1H), 4.35 (d, J=13.41Hz, 1H), 5.27 - 5.39 (m, 1H), 6.45 (s, 1H), 7.23 (s, 1H), 7.25 (s, 1H)	406	404	
87		(400 MHz, DMSO-D6) 1.23 (d, J=6.47Hz, 3H), 1.25 - 1.35 (m, 2H), 1.46 (s, 2H), 1.58 - 1.71 (m, 4H), 1.80 (s, 3H), 1.84 - 1.95 (m, 2H), 3.47 (d, J=5.32Hz, 2H), 4.21 (dd, J=13.52, 4.05Hz, 1H), 4.33 (d, J=13.52Hz, 1H), 4.42 (t, J=5.32Hz, 1H), 5.26 - 5.36 (m, 1H), 6.37 (s, 1H), 7.21 (s, 1H), 7.23 (s, 1H)	411	409	
88		(400 MHz, DMSO-D6) 1.20 (d, J=6.47Hz, 3H), 1.80 (s, 3H), 1.92 - 2.18 (m, 6H), 2.25 - 2.35 (m, 2H), 3.94 (s, 2H), 4.20 - 4.25 (m, 1H), 4.32 - 4.37 (m, 1H), 5.36 - 5.28 (m, 1H), 6.44 (s, 1H), 7.23 (s, 1H), 7.26 (s, 1H)	422	466 (M-1+46)	
89		(400 MHz, DMSO-D6) 1.26 (d, J=6.70Hz, 3H), 1.48 - 1.54 (m, 6H), 1.80 (s, 3H), 1.84 - 1.90 (m, 6H), 3.71 (s, 2H), 4.10 - 4.14 (m, 2H), 5.34 - 5.26 (m, 1H), 5.95 (s, 1H), 7.20 (s, 1H), 7.26 (s, 1H)	450	494 (M-1+46)	
90		(400 MHz, DMSO-D6) 1.27 (d, J=6.47Hz, 3H), 1.38 - 1.44 (m, 2H), 1.68 - 1.75 (m, 4H), 1.78 - 1.86 (m, 5H), 1.91 - 2.00 (m, 2H), 4.13 - 4.18 (m, 4H), 5.35 - 5.28 (m, 1H), 5.99 (s, 1H), 7.22 (s, 1H), 7.27 (s, 1H)	436	480 (M-1+46)	

[0946]

[Table 1-201]

Example	Structure	<sup>1</sup> H-NMR	Mass M+1	Mass M-1	Remarks
91		(400 MHz, DMSO-D6) 1.22 (d, J=6.47Hz, 3H), 1.76 - 1.84 (m, 5H), 1.95 - 2.02 (m, 2H), 2.07 - 2.13 (m, 2H), 2.20 - 2.27 (m, 2H), 4.24 (dd, J=13.64, 3.93Hz, 1H), 4.36 (d, J=12.72Hz, 1H), 5.27 - 5.38 (m, 1H), 6.49 (s, 1H), 7.24 (s, 1H), 7.26 (s, 1H)	392	390	
92		(400 MHz, DMSO-D6) 1.23 (d, J=6.47Hz, 3H), 1.29 - 1.33 (m, 2H), 1.55 - 1.62 (m, 2H), 1.65 - 1.70 (m, 2H), 1.80 (s, 3H), 1.87 - 1.94 (m, 2H), 3.51 (d, J=5.32Hz, 2H), 4.22 (dd, J=13.52, 4.28Hz, 1H), 4.34 (d, J=12.48Hz, 1H), 4.43 (t, J=5.32Hz, 1H), 5.27 - 5.37 (m, 1H), 6.38 (s, 1H), 7.22 (s, 1H), 7.24 (s, 1H)	397	395	
93		(400 MHz, DMSO-D6) 1.20 (d, J=6.70Hz, 3H), 1.80 (s, 3H), 1.91 - 2.04 (m, 2H), 2.06 - 2.29 (m, 6H), 4.05 (s, 2H), 4.23 (dd, J=13.52, 4.05Hz, 1H), 4.34 (d, J=13.52Hz, 1H), 5.28 - 5.38 (m, 1H), 6.46 (s, 1H), 7.24 (s, 1H), 7.25 (s, 1H)	422	420	
94		(400 MHz, DMSO-D6) 1.21 (d, J=6.47Hz, 3H), 1.43 - 1.55 (m, 2H), 1.58 - 1.68 (m, 2H), 1.80 (s, 3H), 1.84 - 1.98 (m, 2H), 2.00 - 2.14 (m, 2H), 3.12 (d, J=5.32Hz, 2H), 3.69 (s, 2H), 4.22 (dd, J=13.52, 4.05Hz, 1H), 4.33 (d, J=12.72Hz, 1H), 4.48 (t, J=5.32Hz, 1H), 5.26 - 5.37 (m, 1H), 6.43 (s, 1H), 7.23 (s, 1H), 7.24 (s, 1H)	427	425	
95		(400 MHz, DMSO-D6) 1.24 (s, 1H), 1.26 (s, 6H), 1.35 (d, J=6.70Hz, 3H), 1.39 - 1.48 (m, 3H), 1.69 (s, 2H), 1.76 - 1.85 (m, 2H), 1.87 - 2.00 (m, 7H), 3.07 (s, 1H), 4.25 - 4.37 (m, 2H), 5.25 - 5.36 (m, 1H), 6.28 (s, 1H), 7.21 (s, 1H)	439	437	

[0947]  
[Table 1-21]

Example	Structure	<sup>1</sup> H-NMR	Mass M+1	Mass M-1	Remarks
96		(400 MHz, DMSO-D6) 1.04 (s, 6H), 1.21 (d, J=6.47Hz, 3H), 1.64 - 1.72 (m, 2H), 1.78 - 1.96 (m, 9H), 3.84 (s, 2H), 3.93 (s, 1H), 4.19 - 4.25 (m, 1H), 4.32 - 4.37 (m, 1H), 5.36 - 5.27 (m, 1H), 6.40 (s, 1H), 7.22 (s, 1H), 7.26 (s, 1H)	455	499 (M-1+46)	
97		(400 MHz, DMSO-D6) 1.25 (d, J=6.47Hz, 3H), 1.80 (s, 3H), 2.23 (s, 6H), 4.09 (s, 2H), 4.12 - 4.15 (m, 2H), 5.34 - 5.27 (m, 1H), 5.97 (s, 1H), 7.21 (s, 1H), 7.28 (s, 1H)	408	452 (M-1+46)	
98		(400 MHz, DMSO-D6) 1.01 (s, 6H), 1.21 (d, J=6.47Hz, 3H), 1.53 - 1.65 (m, 2H), 1.67 - 1.94 (m, 7H), 1.98 - 2.12 (m, 2H), 3.80 (d, J=6.24Hz, 2H), 4.08 (s, 1H), 4.22 (dd, J=13.76, 4.05Hz, 1H), 4.33 (d, J=13.76Hz, 1H), 5.27 - 5.37 (m, 1H), 6.43 (s, 1H), 7.23 (s, 1H), 7.24 (s, 1H)	455	499 (M-1+46)	
99		(400 MHz, DMSO-D6) 1.13 (d, J=6.70Hz, 3H), 2.01 (s, 3H), 4.32 - 4.35 (m, 2H), 4.49 - 4.52 (m, 1H), 7.38 (s, 1H), 7.66 (s, 1H), 9.66 (s, 1H)	367	411 (M-1+46)	1

Example	Structure	<sup>1</sup> H-NMR	Mass M+1	Mass M-1	Remarks
100		(400 MHz, CDCl <sub>3</sub> ) 1.23 (d, J=6.94Hz, 3H), 2.16 (s, 3H), 3.49 (s, 1H), 4.29 - 4.33 (m, 2H), 4.45 (d, J=12.02Hz, 1H), 7.05 (s, 1H), 9.31 (s, 1H)	367	411 (M-1+46)	
101		(400 MHz, DMSO-D <sub>6</sub> ) 1.09-1.18 (m, 5H), 1.41-1.50 (m, 2H), 2.00 (s, 3H), 4.12-4.38 (m, 3H), 7.24 (s, 1H), 7.31 (s, 1H), 9.58 (s, 1H)	357	355	1
102		(400 MHz, DMSO-D <sub>6</sub> ) 1.03 (d, J=6.94Hz, 3H), 1.57 (s, 3H), 1.74 (s, 3H), 2.64 - 2.67 (m, 2H), 2.75 (d, J=15.95Hz, 1H), 2.87 (dd, J=15.95, 6.47Hz, 1H), 2.96 - 2.98 (m, 2H), 3.37 - 3.38 (m, 1H), 5.06 - 5.11 (m, 1H), 7.06 (s, 1H), 8.27 (s, 1H)	381	425 (M-1+46)	1

Example	Structure	$^1\text{H-NMR}$	Mass M+1	Mass M-1	Remarks
103		(400 MHz, DMSO-D6) 1.09 (d, $J$ = 6.70 Hz, 3H), 1.80-1.90 (m, 6H), 1.94-2.04 (m, 9H), 4.04-4.35 (m, 3H), 6.94 (s, 1H), 7.27 (s, 1H), 9.48 (s, 1H)	432	430	1
104		(400 MHz, DMSO-D6) 1.09 (d, $J$ = 6.94 Hz, 3H), 1.98 (s, 3H), 2.57 (s, 6H), 4.08-4.37 (m, 3H), 6.99 (s, 1H), 7.29 (s, 1H), 9.49 (s, 1H)	390	388	1
105		(400 MHz, DMSO-D6) 1.03 (d, $J$ = 6.73 Hz, 3H), 1.16 (s, 3H), 1.50 - 1.62 (m, 4H), 1.74 (s, 3H), 1.87 - 1.99 (m, 4H), 2.71 (d, $J$ = 16.09 Hz, 1H), 2.84 (dd, $J$ = 16.09, 6.73 Hz, 1H), 3.35 - 3.37 (m, 1H), 4.14 - 4.19 (m, 1H), 4.40 (s, 1H), 7.03 (s, 1H), 8.22 (s, 1H)	400	444 (M-1+46)	

[0950]

Experimental Example 1

(Inhibitory action of PDHK2 activity)

In the case of human PDHK2 (hPDHK2, NCBI Reference

5 Database Accession number NM\_002611.4), modified hPDHK2 cDNA  
wherein FLAG-Tag sequence was added to the N terminal of  
hPDHK2 cDNA clone (pReceiver-M01/PDK2-GeneCopoeia) as the base  
was prepared by polymerase chain reaction (PCR) and ligated to  
the NdeI/EcoRI site of pET-17b vector (Merck KGaA, Catalog  
10 Number 69663-3). The recombinant construct was transformed  
into Escherichia coli DH5 $\alpha$ . The recombinant clones were  
identified, and plasmid DNA was isolated and subjected to the  
DNA sequence analysis. One clone which had the expected  
nucleic acid sequence was selected for expression work.

15 [0951]

For expression of hPDHK2 activity, Escherichia coli  
strain BL21(DE3) cells (Merck KGaA, Catalog Number 69450-4)  
were transformed with the pET17b vector containing modified  
hPDHK2 cDNA. The Escherichia coli were grown to an optical  
20 density 0.6 (600 nmol/L) at 30°C. Protein expression was  
induced by the addition of 500  $\mu$ mol/L isopropyl- $\beta$ -  
thiogalactopyranoside. The Escherichia coli were cultured at  
20°C for 17 to for 18 hr and harvested by centrifugation. The  
harvested Escherichia coli was resuspended in a suspension  
25 buffer (20 mmol/L HEPES-NaOH, 500 mmol/L sodium chloride, 1%  
ethylene glycol, 0.1% Pluronic (registered trademark) F-68 (pH  
8.0), cOmplete, EDTA-free (Roche) (pH 8.0)), and disrupted by  
a microfluidizer M-110H (MIZUHO INDUSTRIAL CO., LTD.). The  
precipitate was removed by centrifugation and the supernatant  
30 was added to DDDDK-tagged Protein PURIFICATION GEL (MEDICAL &  
BIOLOGICAL LABORATORIES CO., LTD., Code No. 3329). DDDDK-  
tagged Protein PURIFICATION GEL was washed with a washing  
buffer (20 mmol/L HEPES-NaOH, 500 mmol/L sodium chloride, 1%  
ethylene glycol, 0.1% Pluronic F-68 (pH 8.0)) and the bound

protein was eluted with elution buffer 1 (20 mmol/L HEPES-NaOH, 100 µg/mL peptide (amino acid sequence DYKDDDDK) (SEQ ID NO: 1), 500 mmol/L sodium chloride, 1% ethylene glycol, 0.1% Pluronic F-68 (pH 8.0)). The eluted fractions containing FLAG-Tagged 5 protein were pooled, concentrated by an ultrafiltration method, added to a gel filtration column (HiLoad 26/60 Superdex 200 (GE Healthcare Life Sciences, Code No. 17-1070-01)), and eluted with elution buffer 2 (20 mmol/L HEPES-NaOH, 150 mmol/L sodium chloride, 0.5 mmol/L ethylenediaminetetraacetic acid 10 (EDTA), 1% ethylene glycol, 0.1% Pluronic F-68 (pH 8.0)). The eluted fractions were pooled and preserved at -80°C.

[0952]

PDH (porcine heart PDH complex, Sigma P7032) and 0.5 µg/mL hPDHK2 were mixed in an assay buffer (50 mmol/L 3- 15 morpholinopropanesulfonic acid (pH 7.0), 20 mmol/L dipotassium hydrogen phosphate, 60 mmol/L potassium chloride, 2 mmol/L magnesium chloride, 0.4 mmol/L EDTA, 0.2% poloxamer, 2 mmol/L dithiothreitol) so that the final concentration of PDH was 0.025 U/mL, and the mixture was incubated at 4°C overnight to 20 obtain a PDH/hPDHK2 complex solution.

PDH was mixed with the assay buffer so that the final concentration was 0.025 U/mL, and the mixture was incubated at 4°C overnight to prepare a PDH solution.

The test compounds were diluted with DMSO. To measure an 25 inhibitory action of the test compound on the PDHK activity in the PDH/hPDHK2 complex solution, PDH/hPDHK2 complex solution (20 µL), test compound (1.5 µL) and 1.06 µmol/L ATP (diluted with assay buffer) (8.5 µL) were added to a 384 well microplate (Greiner Bio-One 781801) and PDHK reaction was performed at 30 room temperature for 45 min (test compound well). DMSO (1.5 µL) was added to control wells instead of test compound. In addition, DMSO (1.5 µL) was added to blank wells instead of the test compound, and PDH solution was added instead of the PDH/hPDHK2 complex solution. To measure an inhibitory action

of the test compound on the PDHK activity inherent in the PDH solution, a test compound was added and the PDH solution instead of the PDH/hPDHK2 complex solution was added to a blank + test compound well.

5 [0953]

Then, 10  $\mu$ L of substrates (5 mmol/L sodium pyruvate, 5 mmol/L Coenzyme A, 12 mmol/L NAD, 5 mmol/L thiamine pyrophosphate, diluted with assay buffer) were added. The mixture was incubated at room temperature for 90 min, and the 10 residual PDH activity was measured.

[0954]

The absorbance of each well at 340 nm was measured using a microplate reader to detect NADH produced by the PDH reaction. The PDH activity of each well was calculated from 15 the changes in the absorbance before and after the PDH reaction. The PDH activity of the test compound-treated sample was calculated from the formula {PDH activity of test compound well - (PDH activity of blank + test compound well - PDH activity of blank well)}. The hPDHK2 inhibition rate (%) of 20 the test compound was calculated from the formula [{(PDH activity of the test compound-treated sample - PDH activity of control well)/PDH activity of blank well - PDH activity of control well}  $\times$  100]. IC<sub>50</sub> value was calculated according to a logistic regression method based on a test compound 25 concentration and hPDHK2 inhibitory rate (%).

[0955]

The results are shown in the following Tables. When IC<sub>50</sub> value could not be calculated, the inhibitory rate at the lowest or highest concentration of the test compound in the 30 assay is shown. For example, the compound of Example 102 showed 3% hPDHK2 inhibitory rate at 100.0 nM.

[0956]

[Table 2-1]

Example No.	hPDHK2 IC <sub>50</sub> (nM)
1	24.3
2	19.2
3	20.4
4	10.9
5	10.6
6	11.7
7	9.2
8	11.7
9	9.5
10	9.4
11	6.6
12	6.0
13	7.5
14	14.4
15	10.9
16	12.2
17	21.3
18	12.5
19	13.8
20	22.6
21	19.8
22	22.4
23	18.8
24	25.4
25	15.7
26	18.2
27	31.5
28	8.5
29	23.6
30	21.2

[0957]

[Table 2-2]

Example No.	hPDHK2 IC <sub>50</sub> (nM)
31	13.7
32	20.1
33	8.7
34	14.7
35	17.8
36	14.0
37	17.2
38	25.2
39	14.4
40	5.8
41	9.1
42	19.2
43	28.2
44	18.3
45	26.4
46	15.9
47	25.8
48	18.1
49	19.5
50	14.5
51	13.7
52	15.0
53	8.8
54	7.2
55	14.3
56	10.7
57	28.5
58	20.4
59	7.1
60	6.7

[0958]

[Table 2-3]

Example No.	hPDHK2 IC <sub>50</sub> (nM)
61	9.8
62	8
63	9.1
64	7.5
65	6.6
66	13.7
67	11.5
68	15.2
69	18.0
70	21.2
71	6.6
72	12.3
73	15.7
74	18.4
75	10.0
76	14.5
77	14.4
78	15.1
79	35.2
80	43.4
81	29.8
82	34.0
83	18.6
84	36.5
85	16.6
86	14.1
87	11.0
88	23.8
89	37.7
90	30.5

[0959]

[Table 2-4]

Example No.	hPDHK2 IC <sub>50</sub> (nM)
91	23.3
92	31.9
93	33.4
94	49.5
95	35.0
96	32.5
97	8.8
98	9.1
99	23.4
100	11.1
101	29.2
102	>100.0 (3%)
103	24.3
104	36.9
105	10.0

[0960]

5 As Formulation Examples of the present invention, the following preparations can be mentioned. However, the present invention is not limited by these Formulation Examples.

[0961]

Formulation Example 1: Production of capsule

10 1) compound of Example 1 30 mg  
2) crystalline cellulose 10 mg  
3) lactose 19 mg  
4) magnesium stearate 1 mg  
1), 2), 3) and 4) are mixed and filled in a gelatin  
15 capsule.

[0962]

Formulation Example 2: Production of tablet

1) compound of Example 1 10 g

2) lactose	50 g
3) cornstarch	15 g
4) carmellose calcium	44 g
5) magnesium stearate	1 g

5        The total amount of 1), 2), 3) and 30 g of 4) are kneaded with water, vacuum dried, and sieved. The sieved powder is mixed with 14 g of 4) and 1 g of 5), and the mixture is punched by a tabletting machine. In this way, 1000 tablets each containing 10 mg of the compound of Example 1 per tablet are  
10 obtained.

[0963]

Formulation Example 3: Production of injection

1) compound of Example 1	5 mg
2) D-mannitol	5 g
15 3) distilled water	100 mL

1) and 2) are dissolved in 3) and the solution is filled in a container for injection, sealed and sterilized.

[Industrial Applicability]

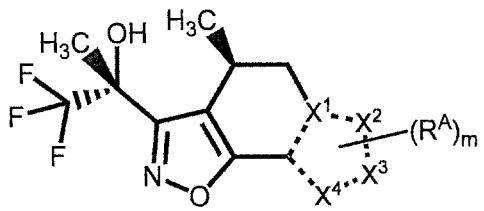
[0964]

20        Since the compound of the formula [I], the formula [II] or the formula [III] or a pharmaceutically acceptable salt thereof of the present invention has a PDHK inhibitory activity, it is useful as an active ingredient of a medicament for the treatment or prophylaxis of diabetes (type 1 diabetes, type 2 diabetes etc.), insulin resistance syndrome, metabolic syndrome, hyperglycemia, hyperlactacidemia, diabetic complications (diabetic neuropathy, diabetic retinopathy, diabetic nephropathy, cataract etc.), cardiac failure (acute cardiac failure, chronic cardiac failure), cardiomyopathy, myocardial ischemia, myocardial infarction, angina pectoris, dyslipidemia, atherosclerosis, peripheral arterial disease, intermittent claudication, chronic obstructive pulmonary disease, brain ischemia, cerebral apoplexy, mitochondrial disease, mitochondrial encephalomyopathy, cancer, pulmonary

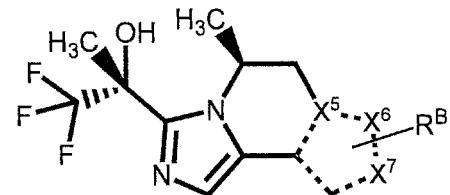
hypertension, Alzheimer disease, vascular dementia (large-vessel type or small-vessel type vascular dementia), glaucoma, diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion, ischemic optic neuropathy, or chronic kidney disease.

[CLAIMS]

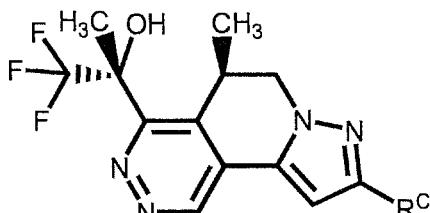
1. A compound of the formula [I], the formula [II], or the formula [III], or a pharmaceutically acceptable salt thereof:



[ I ]



[ II ]



[ III ]

5

wherein

-- is a single bond or a double bond,

X<sup>1</sup>, X<sup>2</sup>, X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup>, X<sup>6</sup> and X<sup>7</sup> are each independently C or N,

R<sup>A</sup> is

10 (1) C<sub>1-6</sub> alkyl wherein the C<sub>1-6</sub> alkyl is optionally substituted by one substituent selected from the group consisting of hydroxy and cyano,

(2) halo C<sub>1-4</sub> alkyl,

(3) -OR<sup>a</sup> wherein R<sup>a</sup> is

15 (i) C<sub>1-6</sub> alkyl wherein the C<sub>1-6</sub> alkyl is optionally substituted by one substituent selected from the group consisting of

20 (c) C<sub>1-4</sub> alkoxy,

(d) C<sub>3-6</sub> cycloalkyl optionally substituted by one cyano,

(e) phenyl, and

(f) 4- to 6-membered saturated heterocyclyl having one oxygen atom,

- (ii) halo  $C_{1-4}$  alkyl,
- (iii) 4- to 6-membered saturated heterocyclyl having one oxygen atom, or
- (iv)  $C_{3-6}$  cycloalkyl wherein the  $C_{3-6}$  cycloalkyl is 5 optionally substituted by 1 or 2 substituents independently selected from the group consisting of  $C_{1-6}$  alkyl, hydroxy, and cyano,
- (4) phenyl optionally substituted by one halogen,
- (5)  $C_{3-6}$  cycloalkyl wherein the  $C_{3-6}$  cycloalkyl is optionally 10 substituted by 1 or 2 substituents independently selected from the group consisting of
  - (i) halogen,
  - (ii)  $C_{1-4}$  alkyl,
  - (iii) halo  $C_{1-4}$  alkyl,
  - 15 (iv) hydroxy, and
  - (v) cyano,
- (6) 4- to 6-membered saturated heterocyclyl having one oxygen atom, or
- (7) bridged  $C_{5-10}$  cycloalkyl wherein the bridged  $C_{5-10}$  cycloalkyl 20 is optionally substituted by one substituent selected from the group consisting of
  - (i)  $C_{1-4}$  alkoxy carbonyl,
  - (ii) hydroxy  $C_{1-4}$  alkyl,
  - (iii) halo  $C_{1-4}$  alkyl, and
  - 25 (iv) cyano,

$m$  is 0 or 1,

$R^B$  is

- (1) phenyl,
- (2) 4- to 6-membered saturated heterocyclyl having 1 or 2 30 hetero atoms independently selected from a nitrogen atom and an oxygen atom,
- (3) 6- to 10-membered saturated fused heterocyclyl having 1 or 2 hetero atoms independently selected from a nitrogen atom and an oxygen atom wherein the saturated fused heterocyclyl is

optionally substituted by 1 or 2 halogens,

(4) 6- to 10-membered spiro heterocyclyl having 1 or 2 hetero atoms independently selected from a nitrogen atom and an oxygen atom wherein the spiro heterocyclyl is optionally

5 substituted by 1 or 2 halogens,

(5) 5- to 10-membered bridged heterocyclyl having 1 or 2 hetero atoms independently selected from a nitrogen atom and an oxygen atom wherein the bridged heterocyclyl is optionally substituted by 1 or 2 substituents independently selected from

10 the group consisting of halogen, cyano, and hydroxy C<sub>1-4</sub> alkyl,

(6) bridged C<sub>5-10</sub> cycloalkyl wherein the bridged C<sub>5-10</sub> cycloalkyl is optionally substituted by one substituent selected from the group consisting of hydroxy C<sub>1-4</sub> alkyl and cyano, or

(7) -OCH<sub>2</sub>Cy<sup>1</sup> wherein Cy<sup>1</sup> is bridged C<sub>5-10</sub> cycloalkyl optionally substituted by one cyano, and

R<sup>c</sup> is

(1) halo C<sub>1-4</sub> alkyl,

(2) C<sub>3-6</sub> cycloalkyl optionally substituted by one halogen, or

(3) bridged C<sub>5-10</sub> cycloalkyl wherein the bridged C<sub>5-10</sub> cycloalkyl

20 is optionally substituted by one substituent selected from the group consisting of cyano and C<sub>1-4</sub> alkoxy carbonyl.

2. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, which is a compound of the formula [I] or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1 or 2, wherein R<sup>A</sup> is

(1) halo C<sub>1-4</sub> alkyl,

(2) -OR<sup>a</sup> wherein R<sup>a</sup> is

30 (i) C<sub>1-6</sub> alkyl wherein the C<sub>1-6</sub> alkyl is optionally substituted by one substituent selected from the group consisting of

(a) hydroxy,

(b) C<sub>3-6</sub> cycloalkyl optionally substituted by one cyano,

and

(c) 4- to 6-membered saturated heterocyclyl having one oxygen atom,

(ii) halo C<sub>1-4</sub> alkyl,

5 (iii) 4- to 6-membered saturated heterocyclyl having one oxygen atom, or

(iv) C<sub>3-6</sub> cycloalkyl wherein the C<sub>3-6</sub> cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of C<sub>1-6</sub> alkyl, hydroxy, and 10 cyano,

(3) C<sub>3-6</sub> cycloalkyl wherein the C<sub>3-6</sub> cycloalkyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of

(i) C<sub>1-4</sub> alkyl,

15 (ii) hydroxy, and

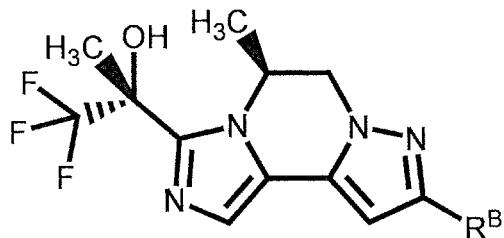
(iii) cyano, or

(4) 4- to 6-membered saturated heterocyclyl having one oxygen atom, or a pharmaceutically acceptable salt thereof.

20 4. The compound according to claim 1 or 2, wherein m is 0, or a pharmaceutically acceptable salt thereof.

5. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, which is a compound of the formula

25 [II-a]:



[II-a]

wherein R<sup>B</sup> is

(1) 6- to 10-membered spiro heterocyclyl having 1 or 2 hetero atoms independently selected from a nitrogen atom and an

oxygen atom wherein the spiro heterocyclyl is optionally substituted by 1 or 2 halogens,

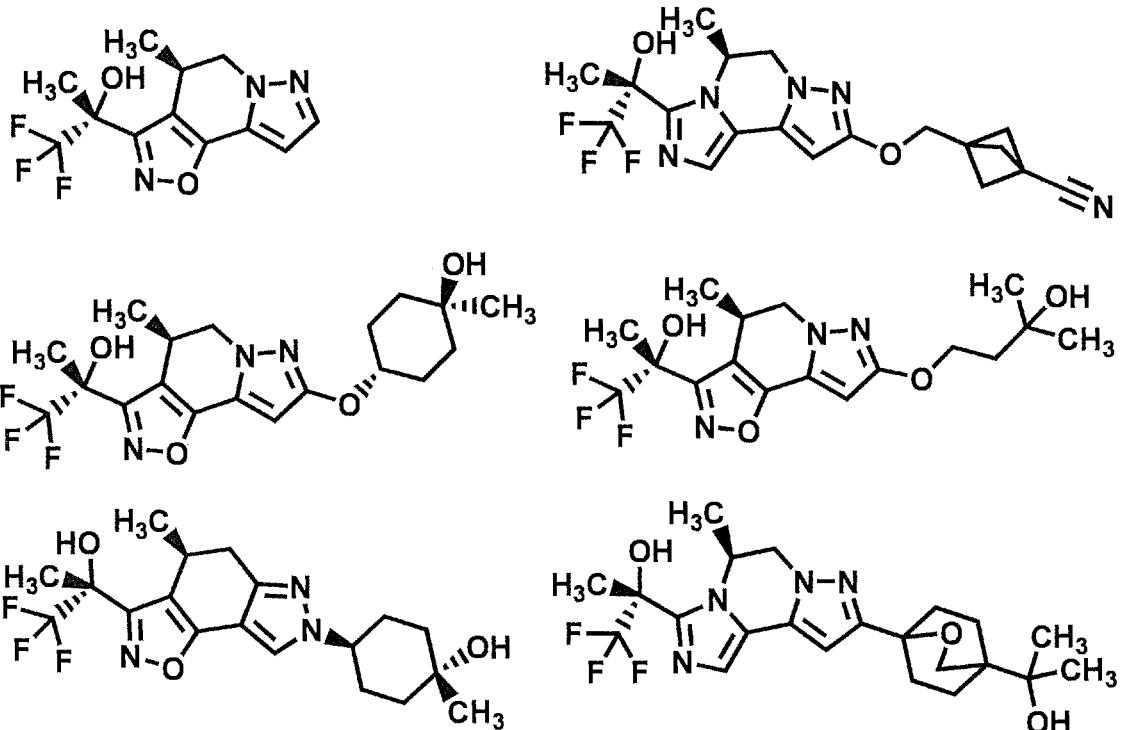
(2) 5- to 10-membered bridged heterocyclyl having 1 or 2 hetero atoms independently selected from a nitrogen atom and an oxygen atom wherein the bridged heterocyclyl is optionally substituted by 1 or 2 substituents independently selected from the group consisting of halogen, cyano, and hydroxy C<sub>1-4</sub> alkyl,

5 (3) bridged C<sub>5-10</sub> cycloalkyl wherein the bridged C<sub>5-10</sub> cycloalkyl is optionally substituted by one substituent selected from the group consisting of hydroxy C<sub>1-4</sub> alkyl and cyano, or

(4) -OCH<sub>2</sub>Cy<sup>1</sup> wherein Cy<sup>1</sup> is bridged C<sub>5-10</sub> cycloalkyl optionally substituted by one cyano,

10 or a pharmaceutically acceptable salt thereof.

15 6. A compound selected from the following formulas:



or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition comprising the compound  
20 according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable

carrier.

8. A PDHK inhibitor comprising the compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt 5 thereof.

9. A PDHK2 inhibitor comprising the compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof.

10

10. An agent for the treatment or prophylaxis of diabetes, insulin resistance syndrome, metabolic syndrome, hyperglycemia, hyperlactacidemia, diabetic complication, cardiac failure, cardiomyopathy, myocardial ischemia, myocardial infarction, 15 angina pectoris, dyslipidemia, atherosclerosis, peripheral arterial disease, intermittent claudication, chronic obstructive pulmonary disease, brain ischemia, cerebral apoplexy, mitochondrial disease, mitochondrial encephalomyopathy, cancer, pulmonary hypertension, Alzheimer 20 disease, vascular dementia, glaucoma, diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion, ischemic optic neuropathy or chronic kidney disease, the agent comprising the compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof.

25

11. The agent according to claim 10, wherein the diabetes is type 1 diabetes or type 2 diabetes.

12. The agent according to claim 10, wherein the vascular 30 dementia is a large-vessel type of vascular dementia or a small-vessel type of vascular dementia.

13. The agent according to claim 10, wherein the cardiac failure is acute cardiac failure or chronic cardiac failure.

14. The agent according to claim 10, wherein the pulmonary hypertension is pulmonary arterial hypertension.

5 15. A method for inhibiting PDHK, comprising administering a therapeutically effective amount of the compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof to a mammal.

10 16. A method for treating or preventing a disease selected from the group consisting of diabetes, insulin resistance syndrome, metabolic syndrome, hyperglycemia, hyperlactacidemia, diabetic complication, cardiac failure, cardiomyopathy, myocardial ischemia, myocardial infarction, angina pectoris, 15 dyslipidemia, atherosclerosis, peripheral arterial disease, intermittent claudication, chronic obstructive pulmonary disease, brain ischemia, cerebral apoplexy, mitochondrial disease, mitochondrial encephalomyopathy, cancer, pulmonary hypertension, Alzheimer disease, vascular dementia, glaucoma, 20 diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion, ischemic optic neuropathy and chronic kidney disease, the method comprising administering a therapeutically effective amount of the compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof to 25 a mammal.

17. The method according to claim 16, wherein the diabetes is type 1 diabetes or type 2 diabetes.

30 18. The method according to claim 16, wherein the vascular dementia is a large-vessel type of vascular dementia or a small-vessel type of vascular dementia.

19. The method according to claim 16, wherein the cardiac

failure is acute cardiac failure or chronic cardiac failure.

20. The method according to claim 16, wherein the pulmonary hypertension is pulmonary arterial hypertension.

5

21. Use of the compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof in the manufacture of a PDHK inhibitor.

10 22. Use of the compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof in the manufacture of an agent for the treatment or prophylaxis of a disease selected from the group consisting of diabetes, insulin resistance syndrome, metabolic syndrome, hyperglycemia, 15 hyperlactacidemia, diabetic complication, cardiac failure, cardiomyopathy, myocardial ischemia, myocardial infarction, angina pectoris, dyslipidemia, atherosclerosis, peripheral arterial disease, intermittent claudication, chronic obstructive pulmonary disease, brain ischemia, cerebral 20 apoplexy, mitochondrial disease, mitochondrial encephalomyopathy, cancer, pulmonary hypertension, Alzheimer disease, vascular dementia, glaucoma, diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion, ischemic optic neuropathy and chronic kidney disease.

25

23. The use according to claim 22, wherein the diabetes is type 1 diabetes or type 2 diabetes.

24. The use according to claim 22, wherein the vascular 30 dementia is a large-vessel type of vascular dementia or a small-vessel type of vascular dementia.

25. The use according to claim 22 wherein the cardiac failure is acute cardiac failure or chronic cardiac failure.

26. The use according to claim 22 wherein the pulmonary hypertension is pulmonary arterial hypertension.

5 27. The compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof for use in the treatment or prophylaxis of a disease selected from the group consisting of diabetes, insulin resistance syndrome, metabolic syndrome, hyperglycemia, hyperlactacidemia, diabetic 10 complication, cardiac failure, cardiomyopathy, myocardial ischemia, myocardial infarction, angina pectoris, dyslipidemia, atherosclerosis, peripheral arterial disease, intermittent claudication, chronic obstructive pulmonary disease, brain ischemia, cerebral apoplexy, mitochondrial disease, 15 mitochondrial encephalomyopathy, cancer, pulmonary hypertension, Alzheimer disease, vascular dementia, glaucoma, diabetic retinopathy, retinopathy of prematurity, retinal vein occlusion, ischemic optic neuropathy and chronic kidney disease.

20

28. The compound according to claim 27 or a pharmaceutically acceptable salt thereof, wherein the diabetes is type 1 diabetes or type 2 diabetes.

25 29. The compound according to claim 27 or a pharmaceutically acceptable salt thereof, wherein the vascular dementia is a large-vessel type of vascular dementia or a small-vessel type of vascular dementia.

30 30. The compound according to claim 27 or a pharmaceutically acceptable salt thereof, wherein the cardiac failure is acute cardiac failure or chronic cardiac failure.

31. The compound according to claim 27 or a pharmaceutically

acceptable salt thereof, wherein the pulmonary hypertension is pulmonary arterial hypertension.