HETEROCYCLES, Vol. 90, No. 2, 2015, pp. 967 - 977. © 2015 The Japan Institute of Heterocyclic Chemistry
Received, 30th June, 2014, Accepted, 30th July, 2014, Published online, 4th August, 2014
DOI: 10.3987/COM-14-S(K)64

CATALYTIC AND ENANTIOSELECTIVE SYNTHESIS OF A KEY INTERMEDIATE OF THE MCHr1 ANTAGONIST AMG 076

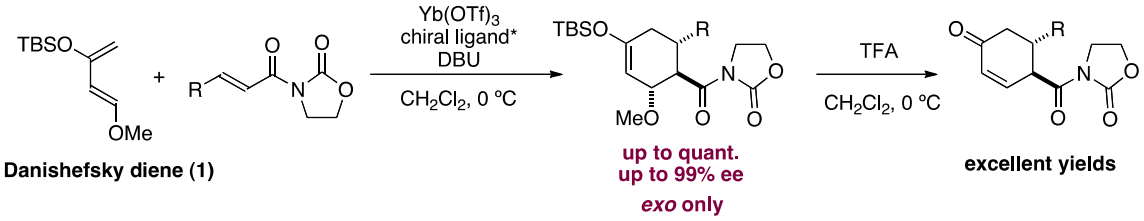
Shinji Harada, Haruka Ishii, Daisuke Shirasaki, and Atsushi Nishida*

Graduate School of Pharmaceutical Sciences, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8675, Japan. E-mail: nishida@p.chiba-u.ac.jp

Abstract – A chiral decahydroisoquinoline was constructed using our asymmetric Diels-Alder reaction catalyzed by a chiral Yb (ytterbium) complex as a key step. The decahydroisoquinoline is a synthetic intermediate of the anti-obesity drug candidate AMG 076 (Amgen).

INTRODUCTION

Biologically active compounds have various types of polycyclic skeletons. The construction of such skeletons in a chiral form with the least amount of waste is still a major challenge for synthetic organic chemists and medicinal chemists.

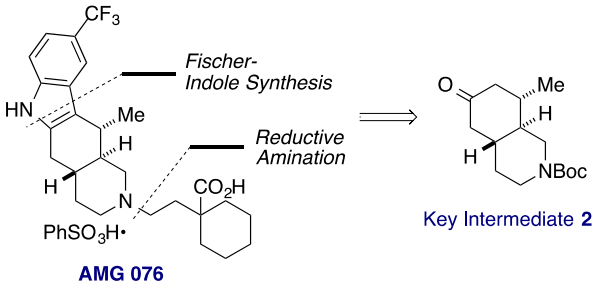


Scheme 1. Our Ytterbium-Catalyzed Asymmetric Diels-Alder Reaction of Danishefsky Diene

We have developed $Yb(OTf)_3$/chiral bis-amide (or bis-urea) ligand/DBU ternary catalyst.[1] This catalyst can activate various dienophiles which possess an oxazolidinone unit, and promote the asymmetric Diels-Alder reaction with Danishefsky diene[2] to give highly functionalized chiral cyclohexenes and cyclohexenones (Scheme 1). Only *exo* adducts are obtained in high yields and ees, and we have demonstrated conversions of these adducts, including the total synthesis of (–)-Platyphillide.[3] We demonstrate here a new synthetic application of our Diels-Alder adduct by constructing chiral decahydroisoquinoline, which is a key synthetic intermediate of AMG 076.

AMG 076 is an antagonist of MCHr1 (Melanin-Concentrating Hormone receptor 1), which was developed by Amgen Inc. as a potent anti-obesity drug.[4] MCH regulates food intake and the energy

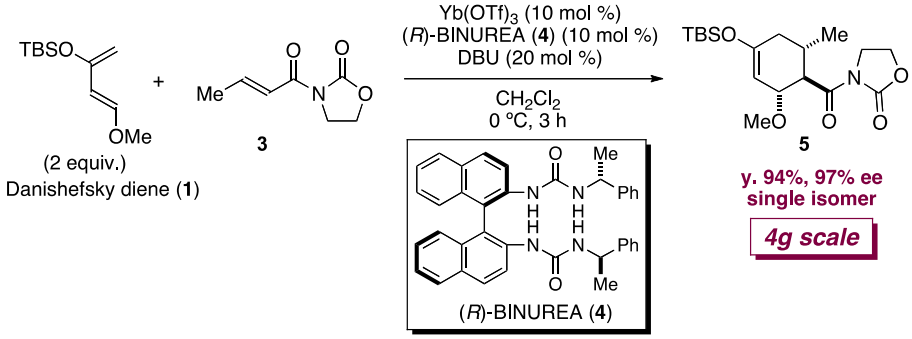
balance, and MCHr1 knockout mice have been shown to lose weight due to reduced food intake.[5] The structure of AMG 076 contains a tetracyclic skeleton including two heterocycles and three continuous chiral stereocenters (Scheme 2). Amgen reported the synthesis of this compound through Fischer-indole synthesis and reductive amination from key intermediate **2** having a decahydroisoquinoline core.[6] However, the synthetic route to **2** involved the generation of regio- and stereoisomers besides optical resolution, and resulted in low overall yield. Therefore, the regio- and stereoselective synthesis of optically active **2** in a catalytic manner should make possible the environmentally benign supply of AMG 076. We envisioned that the hydroisoquinoline skeleton of AMG 076 could be synthesized from our Diels-Alder adduct.



Scheme 2. Structures of AMG 076 and Key Synthetic Intermediate **2** reported by Amgen

RESULTS AND DISCUSSION

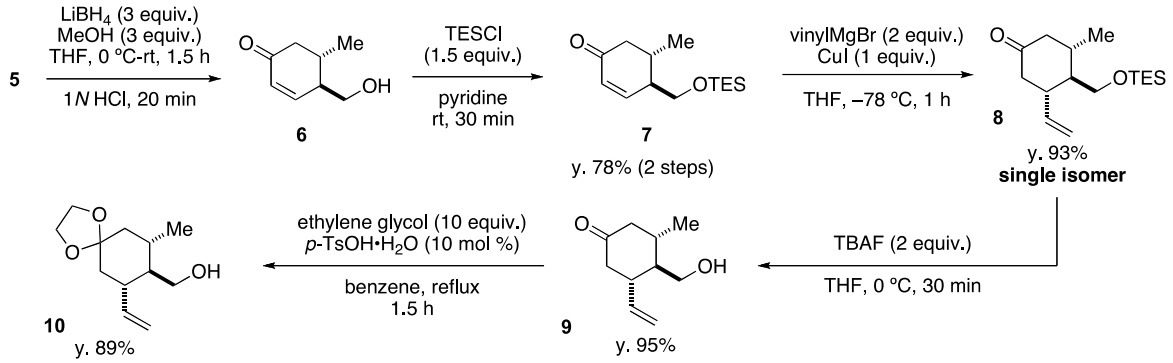
Our ytterbium-catalyzed asymmetric Diels-Alder reaction of Danishefsky diene (**1**) and electron-deficient olefin **3** afforded substituted cyclohexene **5** as a single isomer in 94% yield and 97% ee using chiral bis-urea ligand **4**. This reaction is tolerant to gram-scale synthesis (Scheme 3).



Scheme 3. Catalytic and Asymmetric Diels-Alder Reaction

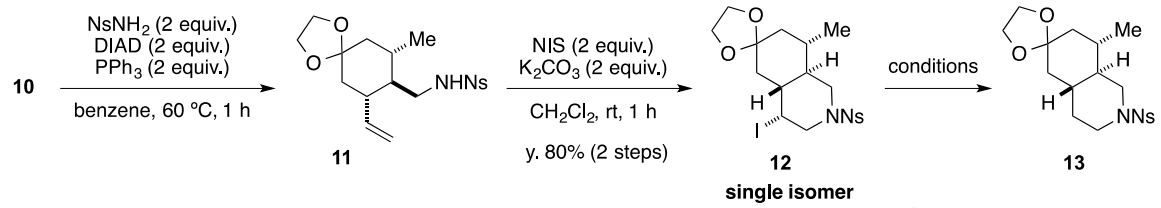
Reductive removal of the oxazolidone moiety of **5** gave primary alcohol **6** after acidic treatment to form cyclohexenone (Scheme 4). Subsequent protection of the alcohol with TES afforded **7** in 78% yield in 2 steps. 1,4-Addition of a vinyl group successfully proceeded to give **8** in 93% yield as a single isomer. At

this stage, all of the stereocenters required for the synthesis of AMG 076 were constructed, and it is noteworthy that no diastereoisomer was generated during this synthesis. Removal of a silyl protective group and ketal formation gave **10** in good yields.

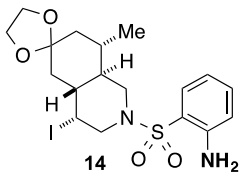


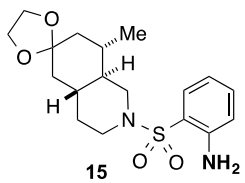
Scheme 4. Transformations of the Diels-Alder Adduct

Alcohol **10** under Mitsunobu conditions formed nosyl amine **11**. NIS-mediated cyclization proceeded smoothly to give decahydroisoquinoline **12** as a single isomer. We next tried the deiodination of **12** under reductive conditions. Tributyltin hydride did not work at all with AIBN or ultrasound (entries 1 and 2, Scheme 5).[7] Sodium borohydride in DMSO[8] decomposed the substrate (entry 3). Samarium iodide[9] did not remove the iodine, but rather reduced the nitro group on the nosyl unit to give compound **14** (entry 4). Deiodination occurred with palladium chloride and triethylsilane (entry 5),[10] where reduction of the nitro group was inevitable.



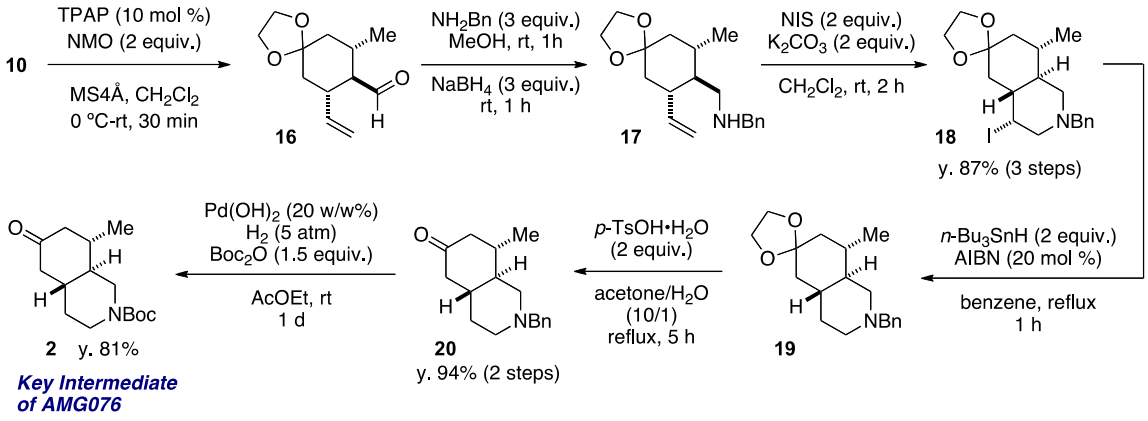
entry	conditions	result
1	nBu$_3$SnH, AIBN (20 mol %), benzene, reflux	no reaction
2	nBu$_3$SnH, toluene, ultrasound, 4-8 °C	no reaction
3	NaBH$_4$, DMSO, 85 °C, 1.5 h	decomp.
4	SmI$_2$ (3 equiv.), MeOH (5 equiv.), THF, rt, 5 min	**14** (y. 51%)
5	PdCl$_2$ (10 mol %), Et$_3$SiH, rt, 1 h	**15** (y. 61%)





Scheme 5. Construction of an *N*-Nosyl Piperidine Ring Using NIS, and Trials for the Removal of Iodine

Since nosyl protection created problems for the deiodination process, we went back to alcohol **10** and planned to change the protective group. TPAP oxidation of the primary alcohol to an aldehyde, reductive amination, and sequential iodine-mediated amino-cyclization proceeded smoothly to give bicyclic compound **18** in 87% yield in 3 steps (Scheme 6). The reductive cleavage of iodine with tributyltin hydride and AIBN followed by deprotection afforded decahydroisoquinolone **20** in 94% yield. A Boc group was successfully introduced to nitrogen under pressurized hydrogen in the presence of $Pd(OH)_2$ and Boc_2O, and we achieved the synthesis of **2** in 38% overall yield from olefin **3** in 12 steps. Although this route is longer than that reported by Amgen (19% overall yield in 7 steps), the overall yield is better because we avoid the need for optical resolution.



Scheme 6. Synthetic Route to the Key Intermediate **2** of AMG 076

In conclusion, we have demonstrated the synthetic utility of our Diels-Alder reaction of Danishefsky diene by synthesizing a key intermediate of the MCHr1 antagonist AMG 076. While the overall number of steps is greater than that in the original synthetic route described by Amgen, the overall yield is better because our route generates no regio- and diastereoisomers, and we can avoid the need for optical resolution.

EXPERIMENTAL

General Methods: All reactions involving air- or moisture-sensitive reagents or intermediates were performed under an inert atmosphere of argon in glassware. Unless otherwise noted, solvents and reagents were reagent grade and used without further purification. DBU was distilled from CaH_2. Anhydrous THF, CH_2Cl_2 and toluene were used as received from Kanto, Chemical CO., INC. Analytical and preparative TLC were carried on E. Merck 0.25 mm silica gel 60 F_{254} plates. Silica gel column chromatography was performed using Fuji Silysia Chemical Ltd. Silica gel PSQ 60B. Celite® 545 was purchased from Aldrich. Optical rotations were measured on a JASCO P-1000 polarimeter at 589 nm.

Data are reported as follows: $[\alpha]_L^{temp.}$, concentration (*c* g/100 mL), and solvent. ^{1}H NMR and ^{13}C NMR spectra were taken on 400 MHz, 600 MHz for ^{1}H, and 100 MHz, 150 MHz for ^{13}C instruments (JEOL LNM-GSX 400, JEOL JNM-ECS 400, JEOL JNM-ECP 400, JEOL JNM-ECP 600) in the indicated solvent at rt. ^{1}H NMR spectra was recorded with $(CH_3)_4Si$ (TMS) as an internal reference δ 0.00 ppm, and ^{13}C NMR spectra was recorded with $CDCl_3$ as an internal reference δ 77.0 ppm. Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Infrared (IR) spectra was recorded on JASCO FT/IR-230 spectrometer. MS spectrometry was recorded using ESI mode. High performance liquid chromatography (HPLC) analyses were performed on Shimadzu LC-2010C (Shimadzu Ind., Ltd.), with detection at 254 nm, and on Chiralcel OJ-H, Daicel Chemical Ind., Ltd.

(4*R*,5*S*)-5-Methyl-4-(((triethylsilyl)oxy)methyl)cyclohex-2-enone (7).

To solution of **5** (150 mg, 0.41 mmol) in THF (4 mL) was added MeOH (60 mL, 1.23 mmol) and $LiBH_4$ (2.0 M in THF, 0.62 mL, 1.23 mmol) slowly at 0 °C. The mixture was stirred for 1.5 h at room temperature. The reaction was quenched by addition of 1*N* HCl at 0 °C and stirred for additional 20 min at same temperature. The mixture was extracted with $CHCl_3$, the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the crude alcohol **6** as yellow oil which was used to next reaction without further purification.

To a solution of **6** (~0.41 mmol) in pyridine (4 mL) was added TESCl (0.1 mL, 0.62 mmol) at room temperature. The mixture was stirred for 0.5 h at same temperature. The reaction was quenched by the addition of *sat*. NH_4Cl *aq.* and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. After concentration under reduced pressure, the resulting residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 20/1) to give **7** (80 mg, yield 78%, 2 steps) as colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.61 (6H, q, *J* = 7.6 Hz), 0.97 (9H, t, *J* = 7.6 Hz), 1.08 (3H, d, *J* = 6.0 Hz), 2.06-2.24 (3H, m), 2.49 (1H, dd, *J* = 2.8, 15.2 Hz), 3.60 (1H, dd, *J* = 6.8, 10.0 Hz), 3.86 (1H, dd, *J* = 4.8, 10.0 Hz). 6.04 (1H, dd, *J* = 2.4, 10.0 Hz), 6.99 (1H, dd, *J* = 2.4, 10.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 4.28, 6.73, 19.6, 31.1, 45.2, 46.1, 63.1, 129.5, 152.4, 200.0; IR (neat) 1679 cm^{-1}; HRMS(ESI) *m/z* calcd for $C_{14}H_{26}O_2SiNa$ $[M+Na]^+$ 277.1600, found 277.1592 ; $[\alpha]_D^{25}$ +123.2 (*c* 1.01, $CHCl_3$).

(3*S*,4*R*,5*S*)-3-Methyl-4-(((triethylsilyl)oxy)methyl)-5-vinylcyclohexanone (8).

To a solution of CuI (23 mg, 0.12 mmol) in THF (1.2 mL) was added vinylMgBr (1.0 M in THF, 0.24 mL, 0.24 mmol) at –78 °C. After being stirred for 30 min, a solution of **7** (30.5 mg, 0.12 mmol) in THF (1 mL) was gradually added to the reaction mixture at –78 °C and then stirred for 1 h at the same temperature. The reaction was quenched by addition of *sat*. NH_4Cl *aq.* and extracted with AcOEt. The combined organic layers were washed with brine and dried over Na_2SO_4. After concentration under

reduced pressure, the resulting residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 20/1) to give **8** (31.8 mg, yield 93%) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.56 (6H, q, *J* = 8.0 Hz), 0.94 (9H, t, *J* = 8.0 Hz), 1.05 (3H, d, *J* = 5.6 Hz), 1.07-1.22 (1H, m), 2.07-2.13 (2H, m), 2.26 (1H, dd, *J* = 13.2, 14.0 Hz), 2.34-2.39 (2H, m), 2.60-2.68 (1H, m), 3.71 (1H, dd, *J* = 2.4, 10.0 Hz), 3.77 (1H, dd, *J* = 2.4, 10.0 Hz), 5.04-5.08 (2H, m), 5.64 (1H, ddd, *J* = 8.8, 10.0, 18.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 4.29, 6.82, 20.2, 32.6, 43.4, 47.5, 49.0, 49.3, 59.6, 115.6, 140.6, 210.7; IR (neat) 1717 cm^{-1}; HRMS(ESI) *m/z* calcd for $C_{16}H_{30}O_2SiNa$ $[M+Na]^+$ 305.1913, found 305.1920 ; $[\alpha]_D^{21}$ +10.5 (*c* 1.00, $CHCl_3$).

(3*S*,4*R*,5*S*)-4-(Hydroxymethyl)-3-methyl-5-vinylcyclohexanone (9).

To a solution of **8** (37.0 mg, 0.13 mmol) in THF (1.23mL) was added TBAF (1.0 M in THF, 0.26 mL, 0.26 mmol) at 0 °C. The mixture was stirred for 0.5 h at same temperature. The reaction was quenched by addition of water and extracted with AcOEt. The combined organic layers were washed with brine and dried over Na_2SO_4. After concentration under reduced pressure, the resulting residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 2/1) to give **9** (20.7 mg, yield 95%) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.11 (3H, d, *J* = 6.8 Hz), 1.26-1.33 (1H, m), 1.97-2.06 (1H, m), 2.14 (1H, dd, *J* = 12.8, 13.6 Hz), 2.29 (1H, dd, *J* = 12.8, 13.6 Hz), 2.36-2.43 (2H, m), 2.53-2.62 (1H, m), 3.83 (2H, d, *J* = 2.8 Hz), 5.08-5.16 (2H, m), 5.7 (1H, ddd, *J* = 8.8, 10.0, 19.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.2, 32.7, 44.2, 47.2, 48.9, 49.3, 60.5, 116.0, 140.5, 209.8; IR (neat) 3412, 1700 cm^{-1}; HRMS(ESI) *m/z* calcd for $C_{10}H_{17}O_2$ $[M+H]^+$ 169.1223, found 169.1230; $[\alpha]_D^{23}$ –29.1 (*c* 1.00, $CHCl_3$).

((7*S*,8*R*,9*S*)-7-Methyl-9-vinyl-1,4-dioxaspiro[4.5]decan-8-yl)methanol (10).

To a solution of **9** (22.0 mg, 0.13 mmol) in benzene (5 mL) was added ethylene glycol (70 mL, 1.3 mmol) and *p*-TsOH·H_2O (2 mg, 0.013 mmol) and the mixture was stirred for 1.5 h under reflux conditions. The reaction was quenched by addition of *sat*. $NaHCO_3$ *aq.* and extracted with AcOEt. The combined organic layers were washed with brine and dried over Na_2SO_4. After concentration under reduced pressure, the resulting residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 3/1) to give **10** (24.5 mg, yield 89%) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85-0.92 (1H, m), 1.01 (3H, d, *J* = 6.4 Hz), 1.34 (1H, dd, *J* = 12.4, 13.2 Hz), 1.41 (1H, brs), 1.48 (1H, dd, *J* = 12.4, 13.2 Hz), 1.72-1.86 (3H, m), 2.36-2.45 (1H, m), 3.74 (2H, s), 3.95 (4H, s), 5.04 (1H, dd, *J* = 1.6, 10.0 Hz), 5.14 (1H, dd, *J* = 1.6, 16.8 Hz), 5.67 (1H, ddd, *J* = 9.6, 9.6, 19.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.8, 29.6, 41.3, 42.2, 43.4, 49.3, 61.4, 64.2, 64.4, 108.1, 115.1, 142.2; IR (neat) 3440, 1137 cm^{-1}; HRMS(ESI) *m/z* calcd for $C_{12}H_{20}O_3$ $[M+H]^+$ 213.1491, found 213.1489; $[\alpha]_D^{25}$ –19.3 (*c* 1.00, $CHCl_3$).

(4'*R*,4a'*R*,8'*S*,8a'*R*)-4'-Iodo-8'-methyl-2'-((2-nitrophenyl)sulfonyl)octahydro-1'H-spiro[[1,3]dioxolane-2,6'-isoquinoline] (12).

To a solution of **10** (73.4 mg, 0.35 mmol) in benzene (4 mL) was added PPh_3 (184 mg, 0.70 mmol), $NsNH_2$ (142 mg, 0.70 mmol) and DIAD (1.9 M solution in toluene, 0.37 mL, 0.70 mmol) at room temperature. After being stirred for 1 h at 60 °C, concentration under reduced pressure, the resulting residue was roughly purified by flash column chromatography (SiO_2, hexane/ EtOAc = 3/1) to give crude **11** as yellow oil. To a solution of crude **11** (~0.35 mmol) in CH_2Cl_2 (4 mL) was added NIS (157.5 mg, 0.70 mmol) and K_2CO_3 (96.7 mg, 0.70 mmol) at room temperature. After being stirred for 1 h at the same temperature, the reaction was diluted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. After concentration under reduced pressure, the resulting residue was purified by flash column chromatography (SiO_2, hexane/ EtOAc = 6/1) to give **12** (145.4 mg, yield 80%, 2 steps) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (3H, d, *J* = 6.6 Hz), 1.19-1.26 (2H, m), 1.35 (1H, dd, *J* = 13.2, 13.2 Hz), 1.59-1.65 (1H, m), 1.73-1.76 (1H, m), 1.96-1.99 (1H, m), 3.08 (1H, dd, *J* = 11.4, 11.4 Hz), 2.05-2.14 (2H, m), 3.33 (1H, ddd, *J* = 1.2, 5.4, 10.8 Hz), 3.41 (1H, dd, *J* = 1.8, 10.8 Hz), 3.63 (1H, dd, *J* = 4.8, 10.8 Hz), 3.94-3.95 (5H, m), 7.68-7.73 (3H, m), 8.08-8.10 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.9, 19.8, 31.6, 37.5, 43.0, 48.0, 49.3, 53.3, 63.5, 64.5, 64.5, 108.9, 124.3, 130.7, 131.8, 133.3, 133.7, 148.2; IR (neat) 1542, 1162 cm^{-1}; HRMS(ESI) *m/z* calcd for $C_{18}H_{24}IN_2O_6SNa$ $[M+Na]^+$ 523.0400, found 522.0406; $[\alpha]_D^{23}$ +92.6 (*c* 1.02, $CHCl_3$).

2-(((4'*R*,4a'*R*,8'*S*,8a'*R*)-4'-Iodo-8'-methylhexahydro-1'H-spiro[[1,3]dioxolane-2,6'-isoquinolin]-2'(7'H)-yl)sulfonyl)aniline (14).

To a solution of **12** (33 mg, 0.06 mmol) in THF (0.6 mL) was added MeOH (12 mL, 0.3 mmol), SmI_2 (0.1 M solution in THF, 1.8 mL, 0.18 mmol) at room temperature. The mixture was stirred for 5 min at same temperature. The reaction was quenched by addition of *sat*. NH_4Cl *aq.* and extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. After concentration under reduced pressure, the resulting residue was purified by flash column chromatography (SiO_2, hexane/ EtOAc = 20/1) to give **14** (15 mg, yield 51%) as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.81 (3H, d, *J* = 6.4 Hz), 0.87-0.95 (1H, m), 1.11 (1H, dd, *J* = 12.8, 13.2 Hz), 1.19-1.27 (1H, m), 1.47-1.57 (1H, m), 1.68 (1H, ddd, *J* = 2.4, 3.6, 13.2 Hz), 1.83-1.93 (1H, m), 2.03 (1H, ddd, *J* = 2.0, 3.2, 12.4 Hz), 2.87 (1H, dd, *J* = 11.2, 11.6 Hz), 3.26 (1H, ddd, *J* = 2.0, 6.0, 10.4 Hz), 3.48 (1H, dd, *J* = 2.0, 10.4 Hz), 3.67 (1H, dd, *J* = 6.0, 10.4 Hz), 3.76 (1H, dd, *J* = 6.4, 11.2 Hz), 3.91-3.95 (4H, m), 5.09 (2H, s), 6.73-6.79 (2H, m), 7.30-7.34 (1H, m), 7.67 (1H, dd, *J* = 1.6, 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.7, 19.8, 31.5, 38.0, 42.9, 48.0, 49.5, 52.2, 63.0, 64.4, 64.5, 109.0, 117.4, 117.8 , 120.0, 130.1, 134.4, 146.2; IR (neat) 3471, 3370, 1542, 1162 cm^{-1}; HRMS(ESI) *m/z* calcd for $C_{18}H_{26}IN_2O_4S$ $[M+H]^+$ 493.0658, found 493.0657; $[\alpha]_D^{20}$ +63.8 (*c* 0.75, $CHCl_3$).

2-(((4a'R,8'S,8a'R)-8'-Methylhexahydro-1'H-spiro[[1,3]dioxolane-2,6'-isoquinolin]-2'(7'H)-yl)-sulfonyl)aniline (15).

To a solution of **12** (14 mg, 0.027 mmol) in Et_3SiH (0.3 mL) was added $PdCl_2$ (0.5 mg, 0.003 mmol) at room temperature. The resulting mixture was stirred for 1 h at same temperature. Filtration of the reaction mixture through a Celite pad afforded a residue, which was purified by flash column chromatography (SiO_2, hexane/ EtOAc = 3/1) to give **15** (6 mg, yield 61%) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.82 (3H, d, *J* = 6.8 Hz), 1.10-1.32 (4H, m), 1.35 (2H, d, *J* = 6.0 Hz), 1.43-1.52 (1H, m), 1.69 (1H, ddd, *J* = 2.0, 3.2, 12.0 Hz), 1.81 (1H, ddd, *J* = 2.0, 3.6, 13.2 Hz), 2.88 (1H, dd, *J* = 11.2, 11.2 Hz), 3.34-3.41 (1H, m), 3.81 (1H, dd, *J* = 6.8, 11.2 Hz), 3.90-3.92 (5H, m), 5.04 (2H, s), 6.71-6.77 (2H, m), 7.26-7.31 (1H, m), 7.65 (1H, dd, *J* = 1.6, 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.8, 20.1, 31.9, 37.1, 43.0, 49.1, 49.7, 52.1, 61.1, 64.4, 109.3, 117.2, 117.6, 120.6, 130.0, 134.0, 146.1; IR (neat) 3350, 1152 cm^{-1}; HRMS(ESI) *m/z* calcd for $C_{18}H_{26}N_2O_4SNa$ $[M+Na]^+$ 389.1511, found 389.1510; $[\alpha]_D^{20}$ +27.8 (*c* 0.30, $CHCl_3$).

(7*S*,8*R*,9*S*)-7-Methyl-9-vinyl-1,4-dioxaspiro[4.5]decane-8-carbaldehyde (16).

To a solution of **10** (114 mg, 0.54 mmol), NMO (127 mg, 1.08 mmol) and MS4Å (250 mg) in CH_2Cl_2 (5.4 mL) was added TPAP (19 mg, 0.054 mmol) at 0 °C. The resulting mixture was stirred for 0.5 h at room temperature. Filtration of the reaction mixture through a pad of Celite afforded a residue, which was purified by flash column chromatography (SiO_2, hexane/AcOEt = 3/1) to give **16** as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92 (3H, d, *J* = 6.4 Hz), 1.30 (1H, dd, *J* = 12.8, 13.2 Hz), 1.44 (1H, dd, *J* = 12.8, 13.2 Hz), 1.74-1.86 (3H, m), 2.03-2.11 (1H, m), 2.63-2.72 (1H, m), 3.98 (4H, m), 4.99-5.06 (2H, m), 5.59 (1H, ddd, *J* = 8.4, 10.4, 18.8 Hz), 9.43 (1H, d, *J* = 5.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.8, 29.4, 39.5, 40.1, 60.8, 64.3, 64.5, 107.7, 115.8, 139.3, 204.7; IR (neat) 1722, 1078 cm^{-1}; HRMS(ESI) *m/z* calcd for $C_{12}H_{18}O_3Na$ $[M+Na]^+$ 233.1154, found 233.1156; $[\alpha]_D^{24}$ –12.0 (*c* 1.00, $CHCl_3$).

***N*-Benzyl-1-((7*S*,8*R*,9*S*)-7-methyl-9-vinyl-1,4-dioxaspiro[4.5]decan-8-yl)methanamine (17).**

To a solution of crude **16** (~0.54 mmol) in MeOH (5 mL) was added benzylamine (0.18 mL, 1.62 mmol) at room temperature. After being stirred for 1 h at the same temperature, $NaBH_4$ (61 mg, 1.62 mmol) was added and then stirred for 1 h. The reaction was quenched by addition of *sat*. NH_4Cl *aq.* and extracted with AcOEt. The combined organic layers were washed with brine and dried over Na_2SO_4. After concentration under reduced pressure, the resulting residue was purified by flash column chromatography (SiO_2, hexane/AcOEt = 1/1) to give **17** as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85-0.90 (1H, m), 0.92 (3H, d, *J* = 6.4 Hz), 1.30 (1H, dd, *J* = 12.8, 12.8 Hz), 1.44 (1H, dd, *J* = 12.8, 12.8 Hz), 1.70-1.87 (3H, m), 2.32-2.41 (1H, m), 2.67 (2H, d, *J* = 3.2 Hz), 3.73 (2H, d, *J* = 4.8 Hz), 3.94 (4H, s), 4.95 (1H, dd, *J* = 2.0, 10.0 Hz), 5.05 (1H, dd, *J* = 2.0, 17.6 Hz), 5.62 (1H, ddd, *J* = 10.0, 10.0, 19.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.9, 30.9, 41.4, 42.9, 43.6, 47.7, 47.9, 54.4, 64.1, 64.3, 108.3, 114.5, 126.7, 128.1, 128.1, 128.1, 128.3, 140.8, 142.1; IR (neat) 3026, 1141 cm^{-1}; HRMS(ESI) *m/z* calcd for $C_{19}H_{27}NO_2$ $[M+H]^+$ 302.2120, found 302.2121; $[\alpha]_D^{22}$ –3.46 (*c* 1.02, $CHCl_3$).

(4'*R*,4a'*R*,8'*S*,8a'*R*)-2'-Benzyl-4'-iodo-8'-methyloctahydro-1'H-spiro[[1,3]dioxolane-2,6'-isoquinoline] (18).

To a solution of crude **17** (~0.54 mmol) in CH_2Cl_2 (5 mL) was added NIS (243 mg, 1.08 mmol) and K_2CO_3 (149 mg, 1.08 mmol) at room temperature. After being stirred for 2 h at the same temperature, the reaction was diluted with CH_2Cl_2. The resulting solution was washed with brine and dried over Na_2SO_4. After concentration under reduced pressure, the resulting residue was purified by flash column chromatography (SiO_2, hexane/ AcOEt = 6/1) to give **18** (200 mg, yield 87%, 3 steps) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (3H, d, *J* = 6.4 Hz), 1.12-1.25 (2H, m), 1.34 (1H, dd, *J* = 12.4, 12.8 Hz), 1.47-1.63 (2H, m), 1.70 (1H, dt, *J* = 2.8, 13.2 Hz), 1.83 (1H, dd, *J* = 10.8, 11.2 Hz), 2.24 (1H, dt, *J* = 2.8, 12.8 Hz), 2.53 (1H, dd, *J* = 11.2, 11.2 Hz), 3.14 (1H, dd, *J* = 2.8, 10.8 Hz), 3.31 (1H, dd, *J* = 4.0, 11.2 Hz), 3.48 (1H, d, *J* = 12.8 Hz), 3.59 (1H, d, *J* = 12.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.6, 32.9, 36.8, 42.4, 44.2, 47.5, 48.1, 56.9, 62.0, 64.2, 64.3, 64.3, 108.3, 127.2, 128.3, 128.9, 137.7; IR (neat) 1345, 1119 cm^{-1}; HRMS(ESI) *m/z* calcd for $C_{19}H_{26}O_2NI$ $[M+H]^+$ 428.1087, found 428.1085; $[\alpha]_D^{23}$ –23.2 (*c* 1.01, $CHCl_3$).

(4a'*R*,8'*S*,8a'*R*)-2'-Benzyl-8'-methyloctahydro-1'H-spiro[[1,3]dioxolane-2,6'-isoquinoline] (19).

To a solution of **18** (89 mg, 0.21 mmol) in benzene (2 mL) was added AIBN (7 mg, 0.042 mmol) and *n*Bu_3SnH (1.0 M in cyclohexane, 0.42 mL, 0.42 mmol), then the mixture was stirred for 1 h under reflux conditions. After concentration under reduced pressure, the resulting residue was purified by flash column chromatography (KF/silica gel, AcOEt) to give **19** as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (3H, d, *J* = 6.4 Hz), 0.92-1.00 (1H, m), 1.25-1.33 (5H, m), 1.50-1.54 (1H, m), 1.67-1.74 (2H, m), 1.90 (1H, dd, *J* = 11.2, 14.0 Hz), 2.85 (1H, d, *J* = 11.6 Hz), 3.08 (1H, dd, *J* = 2.4, 11.2 Hz), 3.43 (1H, d, *J* = 13.2 Hz), 3.59 (1H, d, *J* = 13.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.9, 32.6, 32.9, 38.3, 41.4, 43.7, 46.6, 53.5, 57.6, 63.5, 64.1, 64.3, 108.8, 126.8, 128.1, 129.1, 138.4; IR (neat) 1359, 1101 cm^{-1}; HRMS(ESI) *m/z* calcd for $C_{19}H_{28}NO_2$ $[M+H]^+$ 302.2120, found 302.2120; $[\alpha]_D^{22}$ +7.13 (*c* 1.05, $CHCl_3$).

(4a'*R*,8'*S*,8a'*R*)-2'-Benzyl-8'-methyloctahydro-1'H-spiro[[1,3]dioxolane-2,6'-isoquinoline] (20).

To a solution of crude **19** (~0.21 mmol) in acetone/H_2O (10/1, 10 mL) was added *p*-TsOH·H_2O (72 mg, 0.42 mmol) and the mixture was stirred for 5 h under reflux conditions. The reaction was quenched by addition of *sat*. $NaHCO_3$ *aq.* and extracted with AcOEt. The combined organic layers were washed with brine and dried over Na_2SO_4. After concentration under reduced pressure, the resulting residue was purified by flash column chromatography (SiO_2, AcOEt) to give **20** (50 mg, yield 94%, 2 steps) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (3H, d, *J* = 6.4 Hz), 1.25-1.47 (3H, m), 1.53-1.69 (3H, m), 1.93 (1H, dd, *J* = 2.8, 23.2 Hz), 2.05-2.14 (2H, m), 2.32-2.37 (2H, m), 2.89-2.92 (1H, m), 3.17-3.20 (1H, m), 3.48 (1H, d, *J* = 13.2 Hz), 3.63 (1H, d, *J* = 13.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2, 33.0, 36.4, 41.2, 46.2, 47.9, 49.9, 53.2, 57.3, 63.3, 127.0, 128.2, 129.1, 138.0, 210.4; IR (neat) 1717, 1241 cm^{-1}; HRMS(ESI) *m/z* calcd for $C_{17}H_{23}NO$ $[M+H]^+$ 258.1852, found 258.1853; $[\alpha]_D^{21}$ –13.5 (*c* 1.01, $CHCl_3$).

(4*aR*,8*S*,8*aR*)-*tert*-Butyl 8-methyl-6-oxooctahydroisoquinoline-2(1H)-carboxylate (2).

To a solution of **20** (50 mg, 0.19 mmol) in AcOEt (8 mL) was added Boc_2O (62 mg, 0.29 mmol) and 20 w/w% $Pd(OH)_2$ (10 mg). The reaction mixture was under the pressure of hydrogen (5 atm) for 1 day at room temperature. The excess amount of Boc anhydride was destroyed by adding imidazole (excess) and stirring for 3 h at same temperature, and the palladium catalyst was removed through a pad of Celite. The resulting residue was extracted with AcOEt and the combined organic layers were washed with 1% HCl and dried over Na_2SO_4. Concentration under reduced pressure gave **2** (41 mg, yield 81%) as white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (3H, d, J = 6.4 Hz), 1.21-1.27 (1H, m), 1.33 (1H, ddd, J = 4.4, 13.0, 13.0 Hz), 1.48 (9H, s), 1.51-1.65 (1H, m), 2.11 (2H, ddd, J = 2.4, 13.0, 13.0 Hz), 2.20-2.33 (1H, m), 2.38 (2H, dddd, J = 2.4, 4.4, 16.0, 16.0 Hz), 2.69 (1H, br, t, J = 12.4 Hz), 4.16 (1H, br, s), 4.44 (1H, br, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.1, 28.4, 33.0, 36.1, 41.3, 44.2, 46.1, 46.8, 47.8, 49.7, 79.6, 154.7, 209.6; IR (neat) 1687, 1137 cm^{-1}; HRMS(ESI) *m/z* calcd for $C_{15}H_{25}NO_3Na$ $[M+Na]^+$ 290.1732, found 290.1728; $[\alpha]_D^{24}$ –31.6 (*c* 1.05, $CHCl_3$).

ACKNOWLEDGEMENTS

This work was supported by JSPS KAKENHI Grant Numbers 22790007, 25460006 (SH), and 21390002, 25293001 (AN).

REFERENCES

1. (a) Y. Sudo, D. Shirasaki, S. Harada, and A. Nishida, *J. Am. Chem. Soc.*, 2008, **130**, 12588; (b) S. Harada, N. Toudou, S. Hiraoka, and A. Nishida, *Tetrahedron Lett.*, 2009, **50**, 5652; (c) S. Harada, T. Morikawa, S. Hiraoka, and A. Nishida, *J. Synth. Org. Chem., Jpn.*, 2013, **71**, 818.
2. S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, 1974, **96**, 7807.
3. S. Hiraoka, S. Harada, and A. Nishida, *J. Org. Chem.*, 2010, **75**, 3871.
4. A. S. Motani, J. Luo, L. Liang, J. T. Mihalic, X. Chen, L. Tang, L. Li, J. Jaen, J. -L. Chen, and K. Dai, *Pharmacol. Res. Perspect.*, 2013, **1**, e00003. And see also references therein.
5. The selected examples of recent medicinal research on MCHr1 antagonist as an anti-obesity drug, see: (a) B. M. Fox, R. Natero, K. Richard, R. Connors, P. M. Roveto, H. Beckmann, K. Haller, J. Golde, S. -H. Xiao, and F. Kayser, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 2460; (b) J. T. Mihalic, X. Chen, P. Fan, X. Chen, Y. Fu, L. Liang, M. Reed, L. Tang, J. -L. Chen, J. Jaen, L. Li, and K. Dai, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 7001; (c) J. T. Mihalic, P. Fan, X. Chen, X. Chen, Y. Fu, A. Motani, L. Liang, M. Lindstrom, L. Tang, J. -L. Chen, J. Jaen, K. Dai, and L. Li, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 3781; (d) S. Kasai, M. Kamaura, M. Kamata, K. Aso, H. Ogino, Y. Nakano, K. Watanabe, T. Kaisho, M. Tawada, Y. Nagisa, S. Takekawa, K. Kato, N. Suzuki, and Y. Ishihara,

Bioorg. Med. Chem., 2011, **19**, 6261; (e) M. Kamata, T. Yamashita, T. Imaeda, T. Tanaka, S. Masada, M. Kamaura, S. Kasai, R. Hara, S. Sasaki, S. Takekawa, A. Asami, T. Kaisho, N. Suzuki, S. Ashina, H. Ogino, Y. Nakano, Y. Nagisa, K. Kato, K. Kato, and Y. Ishihara, *J. Med. Chem.*, 2012, **55**, 2353; (f) S. Sasmal, G. Balaji, H. R. Kanna Reddy, D. Balasubrahmanyam, G. Srinivas, S. Kyasa, P. K. Sasmal, I. Khanna, R. Talwar, J. Suresh, V. P. Jadhav, S. Muzeeb, D. Shashikumar, K. Harinder Reddy, V. J. Sebastian, T. M. Frimurer, Ø. Rist, L. Elster, and T. Högberg, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 3157; (g) S. Sasmal, D. Balasubrahmanyam, H. R. Kanna Reddy, G. Balaji, G. Srinivas, S. Cheera, C. Abbineni, P. K. Sasmal, I. Khanna, V. J. Sebastian, V. P. Jadhav, M. P. Singh, R. Talwar, J. Suresh, D. Shashikumar, K. Harinder Reddy, V. Sihorkar, T. M. Frimurer, Ø. Rist, L. Elster, and T. Högberg, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 3163; (h) T. Högberg, T. M. Frimurer, and P. K. Sasmal, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 6039.

6. D. Andersen, T. Storz, P. Liu, X. Wang, L. Li, P. Fan, X. Chen, A. Allgeier, A. Burgos, J. Tedrow, J. Baum, Y. Chen, R. Crockett, L. Huang, R. Syed, R. D. Larsen, and M. Martinelli, *J. Org. Chem.*, 2007, **72**, 9648.
7. E. Nakamura, D. Machii, and T. Inubushi, *J. Am. Chem. Soc.*, 1989, **111**, 6849.
8. R. O. Hutchins, D. Kandasamy, F. Dux III, C. A. Maryanoff, D. Rotstein, B. Goldsmith, W. Burgoyne, F. Cistone, J. Dalessandro, and J. Puglis, *J. Org. Chem.*, 1978, **43**, 2259.
9. G. A. Molander and G. Hahn, *J. Org. Chem.*, 1986, **51**, 1135.
10. R. Boukherroub, C. Chatgilialoglu, and G. Manuel, *Organometallics,* 1996, **15**, 1508.