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Practical Synthesis of Low-Density Lipoprotein Receptor Upregulator, *N*-[1-(3-Phenylpropane-1-yl)piperidin-4-yl]-5-thia-1,8*b*-diazaacenaphthylene-4-carboxamide

Tatsuya Ito,* Tomomi Ikemoto, Yasushi Isogami, Hiroki Wada, Misayo Sera, Yukio Mizuno, and Mitsuhiro Wakimasu

Chemical Development Laboratories, Takeda Chemical Industries, Ltd., 2-17-85 Jusohonmachi, Yodogawa-ku, Osaka 532-8686, Japan

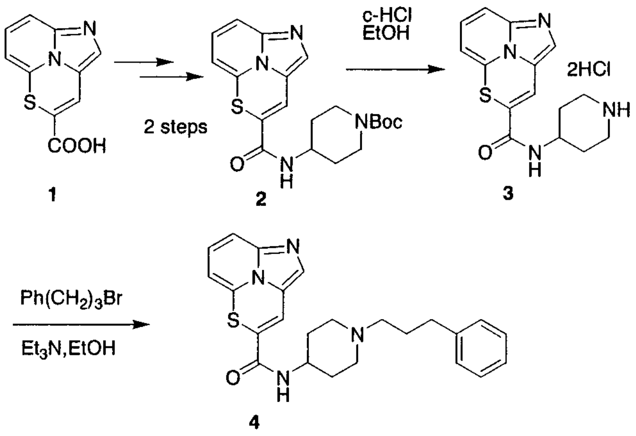
Abstract:

A shorter and more practical method for the preparation of *N*-[1-(3-phenylpropane-1-yl)piperidin-4-yl]-5-thia-1,8*b*-diazaacenaphthylene-4-carboxamide (4) as an upregulator of the LDL receptor has been developed. 1-(3-Phenylpropyl)piperidin-4-amine (7) was synthesized with 71% yield by the alkylation of 4-aminopyridine (5) with 3-phenylpropylbromide followed by reduction with $NaBH_4$ in the presence of base in a mixture of 2-propanol and methanol. The addition of base (1 equiv), for example, KOH and NaOMe, in the above reduction afforded a decrease of 1-(3-phenylpropyl)-*N*-[1-(3-phenylpropyl)piperidin-4-yl]piperidin-4-amine (8) to increase the yield of 7. The amidation of 5-thia-1,8*b*-diazaacenaphthylene-4-carboxylic acid (1) with the primary amine (7) using EDCI in the presence of HOBt (0.2 equiv) provided 4 in 94% yield.

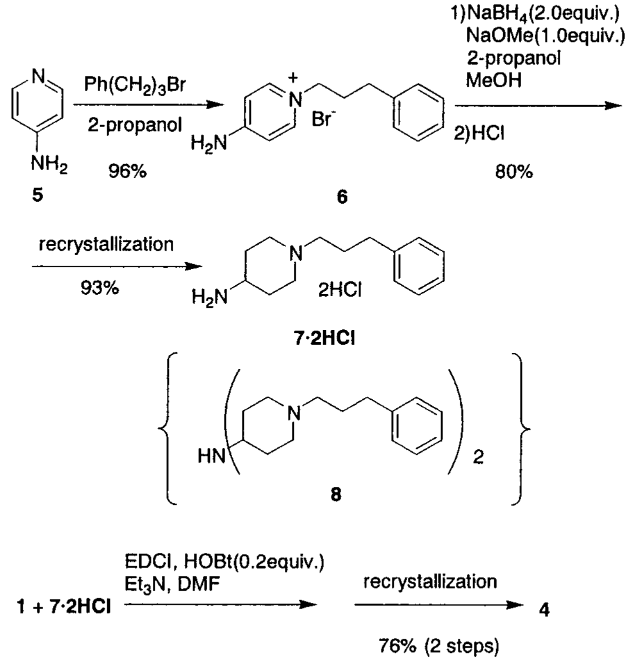
Introduction

In the search for new therapeutic drugs for hyperlipidemia, 5-thia-1,8*b*-diazaacenaphthylene derivatives were found to reduce plasma total- and low-density lipoprotein (LDL) cholesterol.[1] In particular, *N*-[1-(3-phenylpropane-1-yl)piperidin-4-yl]-5-thia-1,8*b*-diazaacenaphthylene-4-carboxamide (**4**)[1] was found to be especially effective. Hence, the preparation of **4** on a large scale was required to support toxicological evaluation. The route for synthesizing **4** from a carboxylic acid derivative (**1**),[1a,b] reported by Takatani et al., is shown in Scheme 1. However, this procedure had several limitations for large-scale preparation, for example, the requirement of a protective and deprotective process, multisteps, and tedious chromatographic methods. Notably, the alkylation reaction of the piperidine derivative (**3**) with 3-phenylpropylbromide gave **4** accompanied with by-products requiring chromatographic purification. We therefore developed an alternative convergent synthesis of **4** by the amidation of **1** with the 4-aminopiperidine derivative (**7**) as shown in Scheme 2. This scalable process did not require protective processes or chromatographic methods.

Scheme 1. **Previous synthetic route of 4**



Scheme 2. **New synthetic route of 4**



Results and Discussion

Synthesis of 7. Because 4-amino-1-alkylpiperidine skeletons have useful biological activities,[2] many procedures for their synthesis have been reported.[2,3] To prepare **4**, we chose the 4-amino-1-alkylpiperidine derivative (**7**) as a key intermediate. The synthesis of **7** was carried out by the following simple method (Scheme 2). Pyridinium bromide (**6**) was

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(2) Leurquin, J.-P. GB1466991.

(3) (a) Sato, M.; Arimoto, M. *Chem. Pharm. Bull.* **1982**, *30 (2)*, 719. (b) Archibald, J. L.; Alps, B. J.; Cavalla, J. F.; Jackson, J. L. *J. Med. Chem.* **1971**, *14*, 1054.

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Table 1. **Reduction of 6 with $NaBH_4$**

run	solvent	addition of MeOH[a]	conditions	$NaBH_4$ (equiv)	7(%)[b]
1	$MeOH-H_2O$	−	65 °C, 2 h	74	24.4
2	diglyme	+	95−98 °C, 2 h	15.5	80.4
3	dimethoxyethane	+	70−82 °C, 2 h	15.5	78.6
4	2-propanol	+	74−80 °C, 2 h	7.5	77.9 (70.8)[c]

[a] MeOH was added to a mixture of **6**, $NaBH_4$, and solvent under refluxing conditions. [b] area % by HPLC at 210 nm. [c] The value in parentheses shows the yield determined by HPLC.

Table 2. **Reduction of 6 with $NaBH_4$ in 2-Propanol and MeOH[a]**

run	$NaBH_4$ (equiv)	base[b]	7(%)[c]	8(%)[c]	yield(%) of 7[d]	isolated yield (%) of 7·2HCl
1	7.75	-	77.9	7.4	70.8	g
2	7.75	KOH	91.3	1.3	79.5	g
3	7.75	NaOMe	96.9	1.2	85.9	85.0 (95.0%)[h]
4[e]	7.75	NaOMe	97.6	0.7	86.6	80.0 (98.4%)[h]
5	2.0	NaOMe	96.2	1.4	82.0	81.6 (94.4%)[h]
6[f]	2.0	NaOMe	94.1	1.6	83.1	80.0 (98.6%)[h]

[a] MeOH was added to a mixture of **6**, $NaBH_4$, and 2-propanol under refluxing conditions. [b] 1 equiv was used. [c] Area % by HPLC at 210 nm. [d] Determined by HPLC. [e] **6** (32 kg) was used. [f] **6** (2.0 kg) was used. [g] **7·2HCl** was not isolated. [h] The value in parentheses shows purity.

Scheme 3. **Propsoed reaction mechanism**

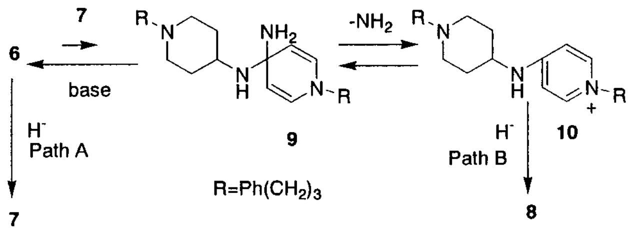

Table 3. **Hydrogenation of 6 catalyzed with 5%Rh−C[a]**

run	conditions	additive	yield(%) of 7[b]
1	64 °C, 6 h	-	73
2	64 °C, 2 h	KOH (2 equiv)	77
3	64 °C, 2 h	KOH (1 equiv)	86
4	40 °C, 4 h	KOH (1 equiv)	94
5	64 °C, 3.5 h	25%NH_3 (2 equiv)	91
6	40 °C, 5 h	NaOMe (1 equiv)	96

[a] Reaction was carried out under 8 kgf/cm^2 hydrogen pressure in methanol. [b] Determined by HPLC.

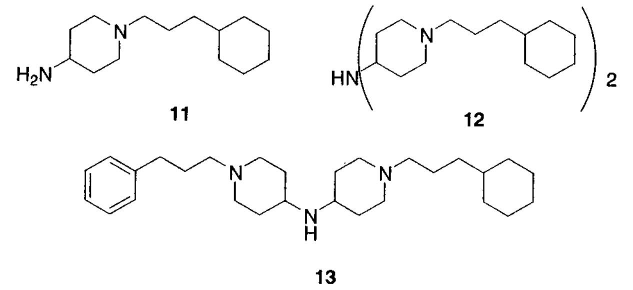

Figure 1. **Undesired products by reduction with 5% Rh−C.**

prepared from **5** and 3-phenylpropylbromide in 96% yield (purity 99.0%). The reduction of **6** with $NaBH_4$ (74 equiv) in aqueous methanol gave **7** in lower yield, as reported[4] (Table 1, run 1). Analysis of the reaction mixture by HPLC and LC-MS revealed a large residual quantity of **6** and the formation of a secondary amine (**8**) as undesired product. To improve the yield, we examined the reduction of **6** with $NaBH_4$ in a mixed solvent (Table 1, runs 2, 3, and 4).[5] The reaction of **6** in diglyme/methanol or dimethoxyethane/methanol as a solvent gave good results to decrease the amount of $NaBH_4$ (15.5 equiv). However, it was difficult to stir the reaction mixtures for large-scale preparation, since this mixture gelled. The utilization of 2-propanol/methanol as a solvent in the same reaction reduced the amount of $NaBH_4$ (7.75 equiv) and improved the stirring solution to provide **7** in 70.8% yield. We further optimized the reduction of **6** with $NaBH_4$ in 2-propanol/methanol (Table 2). In general, it is known that the addition of base in the reduction of a nitrile group to a primary amine reduces the formation of secondary amine.[6] Since the reduction of pyridium salt to piperidine was thought to involve a reaction that proceeded through a similar intermediate, the effect of base was examined. The reduction of **6** in the presence of base, for example, KOH and NaOMe, increased the yield of **7** to decrease the formation of **8** as compared with the reaction in the absence of base (Table 2, runs1, 2, 3, and 4). Moreover, the amount of $NaBH_4$ was diminished in the presence of base (Table 2, runs 5 and 6). As a result, the reduction of **6** (2 kg) with 2.0 equiv of $NaBH_4$ and 1.0 equiv of NaOMe in a mixture of 2-propanol and methanol followed by the treatment of hydrochloride gave **7** dihydrochloride (**7·2HCl)** (purity 98.6%) in 80% isolated yield without chromatographic purification (Table 2, run 6). Subsequently, the recrystallization from methanol and acetonitrile successfully produced the high-quality **7·2HCl** (purity 99.7%) in 93% yield. The proposed reaction mechanism is shown in Scheme 3. In the absence of base, the pyridinium salt (**10**) was formed by the deamination of **9** generated from **6** and **7**, and reduced to **8** (Path B). Addition of the base may have favored the reverse reaction to **6** from **9**, hence the primary amine (**7**).

Next, we tried to synthesize **7** by the hydrogenation of **6** catalyzed by 5% Rh−C (Table 3).[7] The reaction of **6** at 64 °C under 0.8 MPa hydrogen pressure gave **7** in 73% yield with **8** and undesired products, cyclohexyl forms (Figure 1, **11**,**12**, and **13**), as revealed by LC-MS (Table 3, run1). When the hydrogenation of **6** was also carried out in the presence of base (KOH, NH_3, NaOMe), the reaction afforded an increase in the yield of **7** (Table 3, runs 2−6). However, cyclohexyl forms (**11**, **12**, and **13)** could not be removed by recrystallization.

Synthesis of 4. Our attention was focused on developing a facile process for the coupling of **1** and **7·2HCl** (Table 4). The treatment of **1** with oxalyl chloride or thionyl chloride in the presence of a catalytic amount of DMF in THF followed by concentration and a reaction with **7·2HCl** in

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(7) For a patent, see: (a) reduction with Raney Ni; Archbald, J. L. GB1425706. (b) reduction with PtO_2; Hershenson, F. M. U.S. Patent 4267318.

Table 4. **Coupling of 1 and 7·2HCl**[a]

run	reagent and solvent	conditions	yield(%) of **4**
1	$(COCl)_2$,[b] DBU	50 °C, 1 h	77.7
2	$SOCl_2$,[c] DBU	50 °C, 1 h	71.1
3	EDCI,[d] HOBt (1.05equiv), Et_3N)	50 °C, 1 h	94.6
4	EDCI,[d] N-hydroxyphthalimide (1.05eq), Et_3N	50 °C, 2 h	21.4
5	EDCI,[d] HONB (1.05equiv), Et_3N	50 °C, 6 h	93.9
6	EDCI,[d] HOSu (1.05equiv), Et_3N	50 °C, 2 h	52.1
7	EDCI,[d] HOBt (0.2equiv), Et_3N	50 °C, 4 h	93.9
8	EDCI,[d] HOBt (0.2equiv), Et_3N	70 °C, 2 h	94.4

[a] DMF was used as solvent. [b] $(COCl)_2$ (2.0 equiv) was used. [c] $SOCl_2$ (2.0 equiv) was used. [d] EDCI (1.05 equiv) was used.

DMF gave the desired **4** in 78 or 71% yield, respectively (Table 4, runs 1 and 2). The hygroscopicity of **1** and **7·2HCl** affected these reactions. The amidation of **1** with **7·2HCl** using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) in the presence of 1-hydroxybenzotriazole (HOBt) or *N*-hydroxy-5-norbornene-endo-2,3-dicarboxylic acid imide (HONB) at 50 °C gave **4** in excellent yield, although the same reaction with *N*-hydroxyphthalimide or *N*-hydroxysuccinimide (HOSu) produced unsatisfactory results (Table 4, runs 3−6). As a result, the preparation of **4** was accomplished by the reaction of **1** with **7·2HCl** using EDCI in the presence of HOBt (0.2 equiv) at 70 °C in 94% yield (Table 4, run 8). Amide (**4**) was crystallized by addition of aqueous $NaHCO_3$ solution to the reaction mixture and refined by filtration without chromatographic purification. Subsequently, recrystallization of wet **4** from aqueous ethanol denatured with methanol afforded the high-quality **4** in 76% (purity 99.6%) yield from **1** in a large-scale preparation.

In conclusion, we have been able to achieve the practical preparation of **1** in short steps for large-scale production without chromatographic purification. This new efficient process was based on a novel and convenient reduction of pyridinium bromide (**6**) with $NaBH_4$ in the presence of base in a mixture of 2-propanol and methanol. The addition of base in the above reduction caused a decrease of secondary amine (**8**) to increase the yield of **7**. This alternative pathway has been used to prepare multikilogram quantities of bulk substances for toxicological trials.

Experimental Section

Melting points were recorded on a Büchi B-540 micro melting apparatus and were uncorrected. IR spectra were recorded on a Horiba FT-210 spectrophotometer. ^1H NMR spectra were recorded on a Bruker DPX-300 spectrometer using tetramethylsilane as an internal standard. HPLC was performed on a YMC-Pack ODS-A302 column (4.6 i.d. × 150 mm) with 0.05M KH_2PO_4 aqueous solution−MeCN (55:45, and 7:3) or Develosil ODS-UG-3 column (4.6 i.d. × 75 mm) with 0.1 M KH_2PO_4 aqueous solution−MeCN (85:15) at 25 °C. Detection was effected with a Shimadzu SPD-10A spectrophotometric detector at 254 or 210 nm. Elemental analysis was carried out by Takeda Analytical Research Laboratories, Ltd.

1-(3-Phenylpropyl)pyridin-4-(1*H*)-iminium bromide (6). A solution of 4-aminopyridine (5.91 kg) and 3-phenylpropylbromide (13.13 kg) in 2-propanol (58 L) was stirred for 7 h under refluxing conditions. After the reaction was completed, the reaction mixture was cooled at 64 °C and stirred for 2 h at the same temperature, and then at 0−10 °C for 1 h. The resulting crystals were collected by filtration, washed with 2-propanol (10 L), and dried under reduced pressure at 40 °C to give **6** (17.7 kg, yield 96%) as a white crystalline powder. Mp 147−148 °C. Anal. Calcd for $C_{14}H_{17}N_2Br$: C, 57.35; H, 5.84; N, 9.55. Found: C, 57.34; H, 5.64; N, 9.59. ^1H NMR (DMSO-d_6, δ, 300 MHz) 2.05−2.13 (2H, m), 2.58 (2H, t, $J = 7.1$ Hz), 4.16 (2H, t, $J = 7.1$ Hz), 6.83 (2H, d, $J = 7.2$ Hz), 7.19−7.32 (5H, m), 8.09 (2H,br), 8.20 (2H,d, $J = 7.2$ Hz). IR (KBr, cm^{-1}) 3274, 3085, 1643, 1535, 1189.

4-Ammonio-1-(3-phenylpropyl)piperidium dichloride (7·2HCl). Methanol (5.2 L) was added dropwise to a solution of **6** (2 kg), $NaBH_4$ (520 g), and NaOMe (368 g) in 2-propanol (32 kg) under refluxing conditions. The resulting mixture was stirred for 2 h in the same conditions and cooled to 20−30 °C. Water (26 L) and 6 N HCl (8 L) were added, and the reaction mixture was stirred for 1.5 h. To the resulting mixture was added 30% NaOH (6.8 L). The whole was concentrated. The residue was extracted with AcOEt (20 L × 3). The organic layers were combined and washed successively with water (10 L × 2). To the resulting organic layer, was added Na_2SO_4 (2.5 kg), and the suspension was stirred for about 0.5 h. The Na_2SO_4 was filtered off and washed with AcOEt (5 L). The filtrate and washings were combined and concentrated. To the residue dissolved with ethanol denatured with methanol (4 L) was added 3.96 N HCl/ethanol denatured with methanol (3 L) dropwise at 0−10 °C, and then the mixture was stirred for 0.5 h at the same temperature and warmed to 20−30 °C. After isopropyl ether (10.6 L) was added, the mixture was stirred for 2 h at 20−30 °C, cooled to 0−10 °C, and stirred for 1 h at the same temperature. The resulting crystals were collected by filtration, washed with isopropyl ether (500 mL × 2), and dried under reduced pressure at 40 °C to give crude **7·2HCl** (1.58 kg, yield 80%) as a white crystalline powder. To a solution of crude **7·2HCl** (1.58 kg) in methanol (2.3 L) was added CH_3CN (23.7 L) at 60 °C. The resulting mixture was stirred for 0.5h at 60 °C, and gradually cooled to 20−30 °C. The whole mixture was stirred for 2 h at the same temperature and gradually cooled to 0−10 °C for 1 h. The resulting crystals were collected by filtration and washed with CH_3CN (1 L × 3), and dried under reduced pressure at 40 °C to give **7·2HCl** (1.46 kg, yield 93%) as a white crystalline powder. Mp 275−276 °C. Anal. Calcd for $C_{14}H_{24}N_2Cl_2 \cdot 0.3H_2O$: C, 56.63; H, 8.29; N, 9.44; Cl, 23.60. Found: C, 56.43; H, 8.51; N, 9.45; Cl, 23.53. ^1H NMR (D_2O, δ, 300 MHz) 2.01−2.34 (4H, m), 2.60 (2H, d, $J = 13.8$ Hz), 2.90 (2H, t, $J = 7.2$ Hz), 3.19−3.53 (4H, m), 3.69−4.01 (3H, m), 7.50−7.74 (5H, m). IR (Nujol, cm^{-1}) 3353, 2919, 2051, 1459.

***N*-[1-(3-phenylpropane-1-yl)piperidin-4-yl]-5-thia-1,8*b*-diazaacenathenaphthylen-4-carboxamide (4).** To a solution of **7·2HCl** (2.24 kg) in DMF (13 L) was added NEt_3 (2.15 L) dropwise at 20−30 °C. The mixture was stirred for 30 min at the same temperature. To the resulting mixture was added **1** (1.595 kg), HOBt (225 g) and EDCI (1.47 kg), and the whole was stirred for 2 h at 70−80 °C. A solution of $NaHCO_3$ (61 g) in water (65 L) was added dropwise to the reaction mixture at 20−30 °C, and the whole mixture was stirred for 3 h at the same temperature. The resulting crystals were collected by filtration and washed with water (10 L × 3). The solution of crude wet **4** and water (12.4 L) in ethanol denatured with methanol (32.9 L) was refluxed for 0.5 h. The resulting solution was filtered through filter paper, and then the filter paper was washed with a mixture of water (1.5 L) and ethanol denatured with methanol (3.5 L). The filtrate and washings were combined and gradually cooled to 0−5 °C for 3 h. The resulting crystals were collected by filtration and washed with a mixture of water (1.2 L) and ethanol denatured with methanol (2.8 L), and dried under reduced pressure at 50 °C to give **4** (2.33 kg, yield 76%) as a red crystalline powder. Mp. 191−192 °C. Anal. Calcd for $C_{24}H_{26}N_4OS$: C, 68.87; H, 6.26; N, 13.39; S, 7.66. Found: C, 68.93; H, 6.36; N, 13.51; S, 7.80. ^1H NMR ($CDCl_3$, δ, 300 MHz) 1.45−1.51 (2H, m), 1.77−1.85 (2H, m), 1.91−1.95 (2H, m), 2.03−2.12 (2H, m), 2.35 (2H, t, $J = 7.9$ Hz), 2.62 (2H, t, $J = 7.8$ Hz), 2.80−2.85 (2H, m), 3.78−3.81 (1H, m), 5.68 (1H, d, $J = 7.7$ Hz), 5.75−5.78 (1H, m), 6.58−6.67 (3H, m), 7.02 (1H, s), 7.15−7.30 (5H, m) (lit.[1b] ($CDCl_3$, δ, 200 MHz) 1.41−1.64 (2H, m), 1.75−2.21 (6H, m), 2.31−2.47 (2H, m), 2.63 (2H, t, $J = 7.7$ Hz), 2.79−2.96 (2H, m), 3.72−3.92 (1H, m), 5.75−5.80 (2H, m), 6.57−6.69 (3H, m), 7.03 (1H, s), 7.16−7.32 (5H, m)). IR (Nujol, cm^{-1}) 3216, 1718, 1631, 1548, 1452.

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