HETEROCYCLES, Vol. 65, No. 11, 2005, pp. 2763 - 2770
Received, 14th July, 2005, Accepted, 18th August, 2005, Published online, 19th August, 2005

# A PRACTICAL SYNTHESIS OF 1-ALKYL-3-AMINO-4-ARYL-1,8-NAPHTHYRIDIN-2-(1*H*)-ONE, A PARTIAL STRUCTURE OF ACAT INHIBITOR SMP-797

**Hitoshi Ban,* Masami Muraoka, Kouji Morisita, and Naohito Ohashi**

Research Division, Sumitomo Pharmaceuticals Co., Ltd., 1-98, Kasugadenaka 3-Chome, Konohana-ku, Osaka 554-0022, Japan. e-mail : ban@sumitomopharm.co.jp

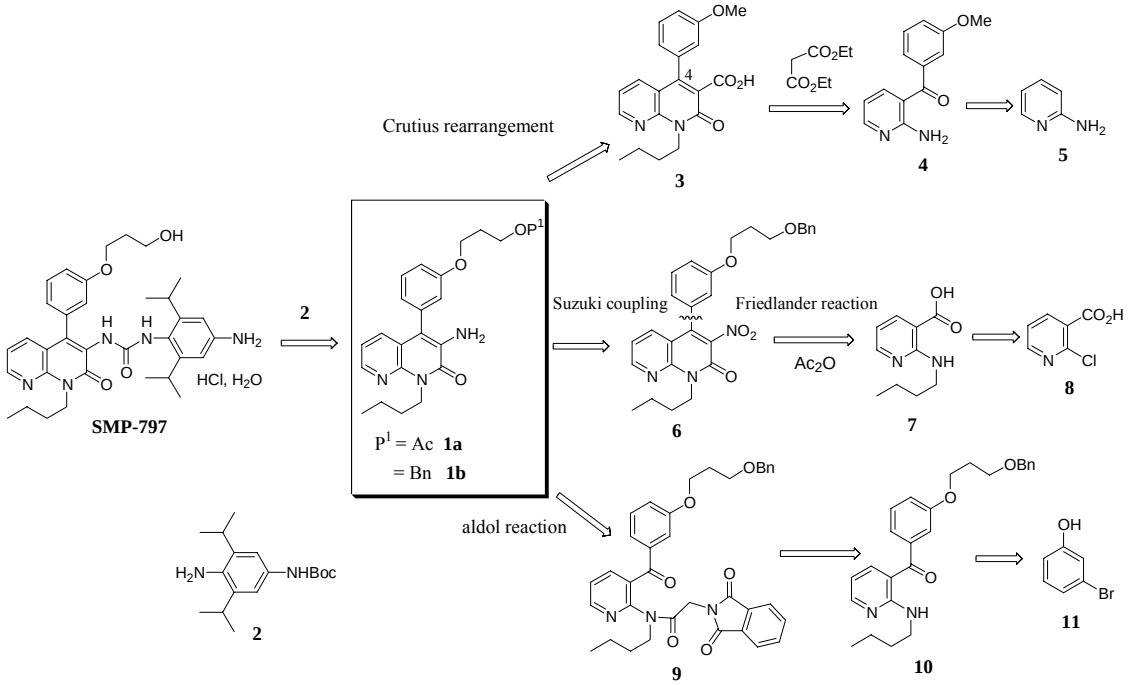
**Abstract** – 3-Amino-4-[3-(3-benzyloxypropoxy)phenyl]-1-butyl-1,8-naphthyridin-2(1*H*)-one, which is a naphthyridine part of a potent ACAT (acyl-CoA: cholesterol acyltransferase) inhibitor SMP-797, was effectively synthesized from *m*-bromophenol in 5 steps without isolating intermediates. The synthesis involved the intramolecular aldol reaction as a key step.

## INTRODUCTION

It was previously found in our group that SMP-797, which is a urea derivative of 3-amino-4-aryl-1,8-naphthyridin-2(1*H*)-one (**1**) and 4-amino2,6-diisopropylaniline (**2**), possessed potent ACAT inhibitory activity[1] (Scheme 1). For further pharmacological studies, a practical large-scale preparation of SMP-797 was needed. The key intermediate 4-amino-2,6-diisopropylaniline (**2**) was readily obtained from commercial 2,6-diisopropylaniline by nitration, reduction of the nitro group and protection of the 4-amino group.[1] As for synthesis of the other intermediate (**1**), we have previously reported two methods. The first method involved the Crutius rearrangement[2] of 4-aryl-3-carboxy-1,8-naphthyridin-2(1*H*)-one[3] (**3**), which was obtained by the Friedländer reaction[4] between 2-amino-3-benzolypyridine (**4**) and diethyl malonate. The methoxy group on the 4-phenyl moiety of **3** was then converted to 3-acetoxypropyloxy group. This synthesis of **1a** required 10 steps from 2-aminopyridine (**5**) which is relatively long. In addition, use of explosive acylazide in the Crutius rearrangement was not desirable. The second method involved reduction of 4-aryl-3-nitro-1,8-naphthyridin-2(1*H*)-one (**6**), which was constructed by the Suzuki coupling[5] of 4-halo-3-nitro-1,8-naphthyridin-2(1*H*)-ones. The compound (**6**) was readily obtained by the modified Friedländer reaction of 2-amino-3-benzoylpyridine (**7**) with acetic anhydride. This synthesis of **1b**

employed 6 steps from commercially 2-chloronicotinic acid (**8**). This method, however, still had problems: Several intermediates were purified by silica gel chromatography; expensive Pd-catayst was used in the Suzuki coupling. Less expensive synthesis of **1** was required (Scheme 1).

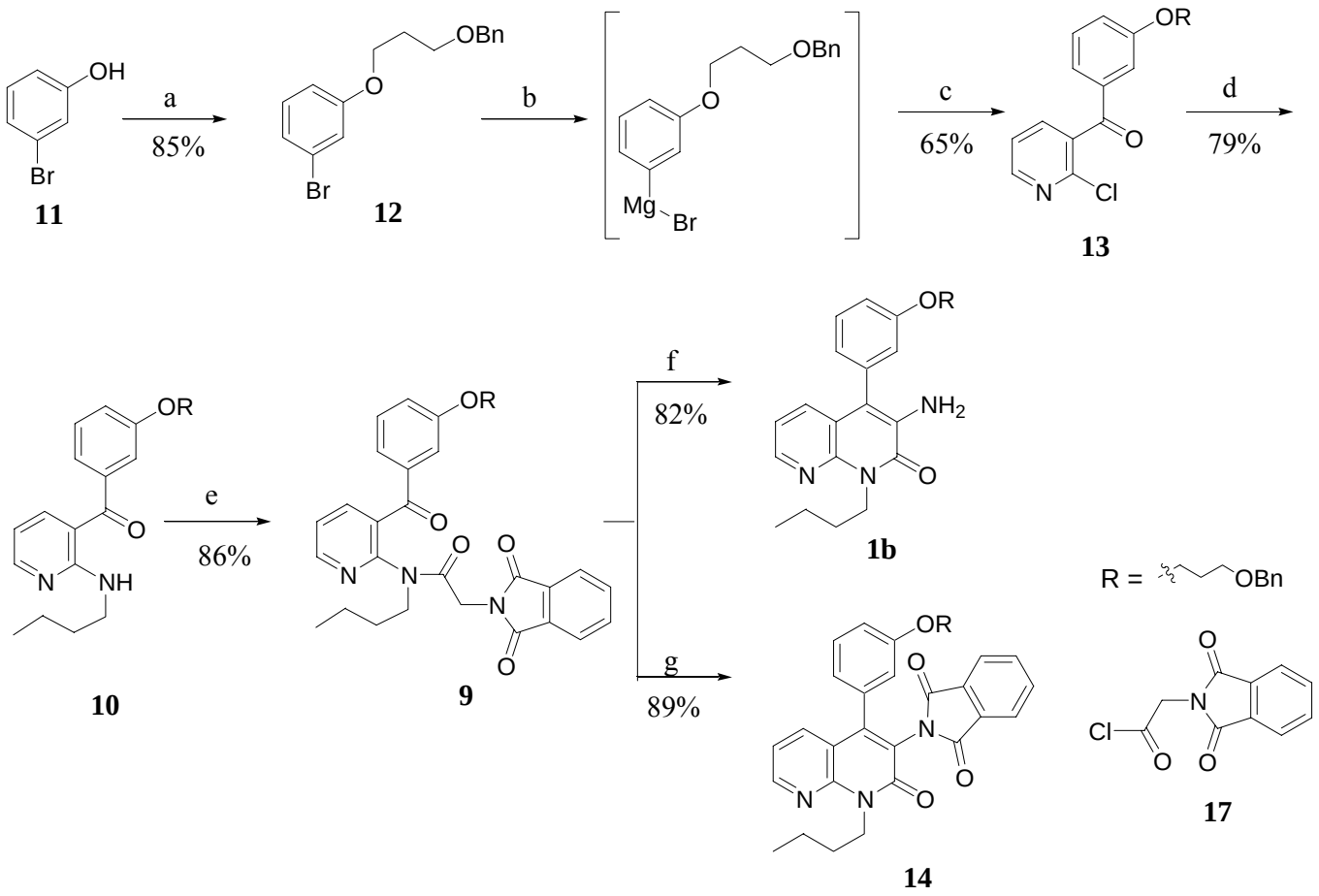
In this paper, we report the third synthesis of **1b** by using intramolecular aldol reaction of *N*-(3-benzoylpyridin-2-yl)-*N*-alkyl-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)acetamide (**9**). The synthesis has several advantages over the previous methods: 1) **1b** was obtained only in 5 steps from commercial *m*-bromophenol (**11**); 2) 3-amino group can be introduced from a glycine derivative without oxidation/reduction functional group transformation; 3) all the synthesis can be conducted without isolation of intermediates, which avoided purification by silica gel chromatography.




**Scheme 1**

## RESULTS AND DISCUSSION

*m*-Bromophenol (**11**) was *O*-3-benzyloxypropylated, and was converted to the Grignard reagent. The reagent was reacted with 2-chloronicotinoyl chloride (**15**) to give ketone (**13**) in 65% isolated yield. Then, **13** was converted to 2-butylaminopyridine (**10**) by heating with butylamine at reflux for 2 h in 79% isolated yield, which was treated with phthalylglycyl chloride (**17**) in the presence of *i*-$Pr_2NEt$ in $CH_2Cl_2$ to give the key intermediate (**9**). The intramolecular aldol reaction of **9** was conducted by heating with $K_2CO_3$ in DMF at 120 ˚C for 3 h giving cyclized product (**14**) in 89% isolated yield. Strong bases such as NaH and NaOEt were not effective for this reaction. One-pot aldol reaction of **9** followed by treatment with $Me_2NH$ to remove *N*-phthaloyl group gave the desired **1b** in 82% isolated yield. Thus, **1b** could be obtained from **11** in 31 % in 5 total steps (Scheme 2).




**Scheme 2.** *Reagents and conditions*: (a) benzyl 3-bromopropyl ether (1.1 eq.), $K_2CO_3$ (3.0 eq.), DMF, 60ºC , 3 h; (b) Mg (1.1 eq.), cat. $I_2$, THF, rt, 1.5 h (c) **15** (1.0 eq. ), THF, rt, 2 h; (d) butylamine, reflux, 2 h; (e) **17** (2.5 eq.), *i*-$Pr_2NEt$ (2.8 eq.), $CH_2Cl_2$, reflux, 5 h; (f) $K_2CO_3$ (4.0 eq.), DMF, 120ºC, 3 h and then $MeNH_2$ (10 eq.), rt, 3 h; (g) $K_2CO_3$ (4.0 eq.), DMF, 120ºC, 3 h.

Extensive examination of the formation of **9**, **10**, **12** and **13** revealed that by-products are readily removable by extraction or evapolation. For example, *m*-bromophenol (**11**) in the formation of **12**, carboxylic acid (**8**) formed in the Grignard reaction of **15**, and *N*-phthaloylglycyine (**16**) formed in the acylation of **10** could readily be removed by extraction under basic condition. In the amination of **13**, excess butylamine was readily removed by evaporation and washing under acidic condition. It was therefore considered that the synthesis of **1b** could be conducted without isolating the intermediates. Starting from **11**, crude *O*-alkylated phenol (**12**) was converted to the Grignard reagent, and reaction with **15** proceeded to give crude **13**. Then, crude **13** was converted to crude **10** by the amination with exess butylamine. In the acylation of crude **10** with **17**, inexpensive pyridine was used in place of *i*-$Pr_2NEt$, and the key aldol reaction smoothly proceeded to give crude **1b**. Finally, **1b** could be purified by fractional crystallization from diisopropyl ether after absorption of polar by-products to silica. Fortunately, this synthesis without isolating of intermediates gave a better yield 37% than the stepwise methods.

In summary, we developed a 5-steps synthetic method for 3-amino-4-[3-(3-benzyloxypropoxy)phenyl]-1-butyl-1,8-naphthyridin-2(1*H*)-one, which is a naphthyridine part of SMP-797, without isolating the intermediates.

## EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus without correction. $^1$H NMR spectra were recorded on a JEOL JNM-LA300 spectrometer in the stated solvents using tetramethylsilane as an internal standard. IR spectra were obtained on a JEOL JIR-SPX60 or a Perkin-Elmer 1600 FT-IR spectrometer. High resolution MS spectra were measured at Sumitomo Analytical Center Inc. Thin layer chromatography and flash column chromatography were performed on silica gel glass-backed plates (5719, Merck & Co.) and silica gel 60 (230-400 or 70-230 mesh, Merck & Co.), respectively. Unless otherwise noted, all the materials were obtained from commercial suppliers, and were used without further purification. All solvents were commercially available grade. All reactions were carried out under a nitrogen atmosphere unless otherwise mentioned.

### 1-(3-Benzyloxypropoxy)-3-bromobenzene (**12**)

To a suspension of 3-bromophenol (**11**) (3.00 g, 17.3 mmol) and $K_2CO_3$ (7.19 g, 52.0 mmol) in DMF (20 mL) was added benzyl 3-bromopropyl ether (3.92 g, 19.1 mmol) at rt. The mixture was stirred at 60 ˚C for 3 h. After cooled to rt, water was added. The extract was extracted with AcOEt, washed with water, dried over $MgSO_4$, and concentrated *in vacu*. The residue was purified by silica gel chromatography using hexane-AcOEt (20:1 to 10:1 gradient) as eluent to give **12** (4.71 g, 85%) as a colorless oil.

IR (film): ν 1589, 1466 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$, 300 MHz), δ (ppm) 1.98 (2H, tt, $J$ = 6.2, 6.2 Hz), 3.57 (2H, t, $J$ = 6.2 Hz), 4.06 (2H, t, $J$ = 6.2 Hz), 4.48 (2H, s), 6.92-6.96 (1H, m), 7.10-7.13 (2H, m), 7.21-7.36 (6H, m); HRMS (ESI) $(M+H)^+$ calcd for $C_{16}H_{18}O_2Br$ 321.0490, found 321.0512.

### [3-(3-Benzloxypropoxy)phenyl](2-chloropyridin-3-yl)methanone (**13**)

To a suspension of Mg (71.8 mg, 2.96 mmol) and a catalytic amount of $I_2$ in THF (5 mL) was added a solution of **12** (863 mg, 2.69 mmol) in THF (1 mL) dropwise at rt. The mixture was stirred for 1.5 h at reflux. The resulted Grignard reagent was added to a solution of **15** (466 mg, 2.96 mmol) in THF (15 mL) at -10 ˚C. The mixture was warmed to rt, and stirred for 2 h. Then, 1 M $H_2SO_4$ was added, and the organic materials were extracted with toluene. The extracts were washed twice with saturated aqueous $NH_4Cl$, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography using hexane-AcOEt (8:1 to 4:1 gradient) as eluent to give **13** (669 mg, 65%) as a pale yellow oil.

IR (film): ν 1670, 1578 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz), δ (ppm) 1.99 (1.4H, tt, *J* = 6.2, 6.2 Hz), 1.99 (0.6H, tt, *J* = 6.2, 6.2 Hz), 3.57 (1.4H, t, *J* = 6.2 Hz), 3.58 (0.6H, t, *J* = 6.2 Hz), 4.07 (0.6H, t, *J* = 6.2 Hz), 4.10 (1.4H, t, *J* = 6.2 Hz), 4.46 (1.4H, s), 4.47 (0.6H, s), 6.87-6.95 (1H, m), 7.23-7.32 (7H, m), 7.37 (0.3H, t, *J* = 8.2 Hz), 7.47 (0.7H, t, *J* = 8.2 Hz), 7.60 (0.7H, dd, *J* = 4.8, 7.5 Hz), 7.65 (0.3H, dd, *J* = 4.8, 7.5 Hz), 8.04 (0.7H, dd, *J* = 1.8, 7.5 Hz), 8.52 (0.3H, dd, *J* = 1.8, 7.5), 8.60 (0.7H, dd, *J* = 1.8, 4.5 Hz), 8.67 (0.3H, dd, *J* = 1.8, 4.8 Hz); HRMS (ESI) $(M+H)^+$ calcd for $C_{22}H_{21}NO_3Cl$ 382.1204, found 382.1210.

**[3-(3-Benzloxypropoxy)phenyl](2-butylaminopyridin-3-yl)methanone** (**10**)

A mixture of **13** (200 mg, 0.524 mmol) and butylamine (5 mL, 50.6 mmol) was stirred at reflux for 2 h. Then, 1 M HCl and AcOEt were added. The organic layer was separated, washed twice with 1 M HCl and once with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography using hexane-AcOEt (10:1) as eluent to give **10** (173 mg, 79%) as a yellow oil.

IR (film): ν 3332, 1620, 1572 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz), δ (ppm) 0.91 (3H, t, *J* = 7.1 Hz), 1.37 (2H, tq, *J* = 7.1, 7.1 Hz), 1.58 (2H, tt, *J* = 7.1, 7.1 Hz), 1.99 (2H, ddt, *J* = 6.2, 6.2, 6.2 Hz), 3.50 (2H, dt, *J* = 6.2, 6.2 Hz), 3.57 (2H, t, *J* = 6.2 Hz), 4.09 (2H, t, *J* = 7.1 Hz), 4.46 (2H, s), 6.57 (1H, dd, *J* = 4.8, 7.9 Hz), 7.05-7.16 (3H, m), 7.22-7.30 (5H, m), 7.41 (1H, t, *J* = 7.9 Hz), 7.69 (1H, dd, *J* = 1.3, 7.9 Hz), 8.31 (1H, dd, *J* = 1.3, 4.8 Hz), 8.71 (1H, t, *J* = 5.9 Hz); HRMS (ESI) $(M+H)^+$ calcd for $C_{26}H_{31}N_2O_3$ 419.2329, found 419.2329.

***N*-{3-[3-(3-Benzloxypropoxy)benzoyl]pyridin-2-yl}-*N*-butyl-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)acetamide** (**9**)

To a solution of **10** (173 mg, 0.413 mmol) and *i*-$Pr_2NEt$ (0.200 mL, 1.16 mmol) in $CH_2Cl_2$ (5 mL) was added **17** (240 mg, 1.07 mmol) at rt. The mixture was stirred at reflux for 5 h. After cooled to rt, water was added. The organic materials were extracted with AcOEt, and the extract was washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography using hexane-AcOEt (3:1 to 1:1 gradient) as eluent to give **9** (225 mg, 86%) as a pale yellow amorphous solid.

IR (film): ν 1716, 1672 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 60 °C, 300 MHz), δ (ppm) 0.72 (3H, br), 1.18 (2H, br), 1.36 (2H, br), 2.00 (2H, tt, *J* = 6.2, 6.2 Hz), 3.15 (2H, s), 3.59 (2H, t, *J* = 6.2 Hz), 4.12 (2H, t, *J* = 6.2 Hz), 4.27 (2H, br), 4.46 (2H, s), 7.22-7.33 (8H, m), 7.46 (1H, br), 7.62 (1H, br), 7.84 (8H, br), 8.06 (1H, br), 8.77 (1H, br); HRMS (ESI) $(M+H)^+$ calcd for $C_{36}H_{36}N_3O_6$ 606.2598, found 606.2603.

**2-{4-[3-(3-Benzyloxypropoxy)phenyl]-1-butyl-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl}-1*H*-iso-**

**indole-1,3(2*H*)-dione** (**14**)

A suspension of **9** (238 mg, 0.393 mmol) and $K_2CO_3$ (217 mg, 1.57 mmol) in DMF (5 mL) was stirred at 120 ˚C for 3 h. Then, AcOEt and $H_2O$ were added. The organic layer was separated, washed with $H_2O$, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography using hexane-AcOEt (2:1 to 1:1 gradient) as eluent to give **14** (205 mg, 89%) as colorless crystals.

mp 155-156 ºC (AcOEt). IR (film): ν 1718, 1656 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz), δ (ppm) 0.92 (3H, t, *J* = 7.3 Hz), 1.37 (2H, tq, *J* = 7.3, 7.3 Hz), 1.67 (2H, tt, *J* = 7.3, 7.3 Hz), 1.90 (2H, tt, *J* = 6.2, 6.2 Hz), 3.49 (2H, t, *J* = 6.2 Hz), 3.89-4.05 (2H, m), 4.40 (2H, s), 4.48 (2H, t, *J* = 7.3 Hz), 6.83-6.85 (2H, m), 6.94-6.97 (1H, m), 7.21-7.39 (7H, m), 7.69 (1H, dd, *J* = 1.5, 8.1 Hz), 7.82-7.90 (4H, m), 8.80 (1H, dd, *J* = 1.5, 4.6 Hz); Anal. Calcd for $C_{36}H_{33}N_3O_5$: C, 73.58; H, 5.66; N, 7.15. Found: C, 73.24; H, 5.65; N, 7.06.

**3-Amino-4-[3-(3-benzyloxypropoxy)phenyl]-1-butyl -1,8-naphthyridin-2(1*H*)-one**[1] (**1b**)

A suspension of **9** (225 mg, 0.371 mmol) and $K_2CO_3$ (205 mg, 1.49 mmol) in DMF (10 mL) was stirred at 120 ˚C for 3 h. After cooled to rt, 30% $MeNH_2$/EtOH (288 mg, 3.71 mmol) was added. The mixture was stirred at rt for 3 h, when saturated aqueous $NH_4Cl$ was added. The organic materials were extracted twice with AcOEt, and the extract was washed twice with saturated aqueous $NH_4Cl$, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel chromatography using hexane-AcOEt (3:2) as eluent to give **1** (139 mg, 82%) as colorless crystals.

mp 100-101 ºC (AcOEt/hexane). IR (film): ν 3446, 3344, 1585, 1571 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz), δ (ppm) 0.95 (3H, t, *J* = 7.3 Hz), 1.39 (2H, tq, *J* = 7.3, 7.3 Hz), 1.69 (2H, tt, *J* = 7.3, 7.3 Hz), 2.00 (2H, tt, *J* = 6.2, 6.2 Hz), 3.59 (2H, t, *J* = 6.2 Hz), 4.09 (2H, t, *J* = 6.2 Hz), 4.47 (2H, s), 4.53 (2H, t, *J* = 7.3 Hz), 5.12 (2H, s), 6.86-6.89 (2H, m), 7.04 (1H, dd, *J* = 2.6, 9.7 Hz), 7.13 (1H, dd, *J* = 4.6, 7.9 Hz), 7.24-7.33 (6H, m), 7.48 (1H, t, *J* = 7.9 Hz), 8.34 (1H, dd, *J* = 1.8, 4.6 Hz); Anal. Calcd for $C_{28}H_{31}N_3O_3$: C, 73.50; H, 6.83; N, 9.18. Found: C, 73.72; H, 6.76; N, 8.98.

**Synthesis of 1b from 11 without isolating intermediates**

To a suspension of 3-bromophenol (**11**) (15.9 g, 91.7 mmol) and $K_2CO_3$ (36.2 g, 262 mmol) in DMF (500 mL) was added benzyl 3-bromopropyl ether (20.0 g, 87.3 mmol) at rt. The mixture was stirred at 60 ˚C for 3 h. After cooled to rt, water (500 mL) was added. The organic materials were extracted twice with heptane (500 mL), and the extract was washed twice with 1 M NaOH (500 mL) and once with brine (500 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give crude **12** (27.2 g). To a suspension of Mg (1.91 g, 78.8 mmol) and a catalytic amount of $I_2$ in THF (100 mL) a solution of crude **12** (23.0 g) in THF (20 mL) was added dropwise at rt. The mixture was stirred for 1.0 h at reflux. The resulted Grignard reagent was added to a solution of **15** (13.8 g, 78.8 mmol) in THF (300 ml) at 0 ˚C. The mixture was

warmed to rt, and stirred for 1.5 h. Then, 1 M HCl (400 mL) was added, and the organic materials were extracted twice with toluene (400 mL). The extracts were washed twice with 1 M NaOH (400 mL) and once with brine (400 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give crude **13** (27.2 g). A mixture of crude **13** (27.2 g) and butylamine (200 mL, 202 mmol) was stirred at 60 ˚C for 4 h. After cooled, volatile materials were evaporated *in vacuo*, and 1 M HCl (500 mL) was added to the residue. The organic materials were extracted twice with toluene (500 mL). The combined organic layers were washed once with 1 M HCl (500 mL) and twice with saturated aqueous $NaHCO_3$ (500 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give crude **10** (27.9 g). To a solution of crude **10** (27.9 g) in pyridine (270 mL) was added **17** (14.9 g, 66.7 mmol) at rt. The mixture was stirred at 60 ˚C for 1 h, to which another portion of **17** (14.9 g, 66.7 mmol) was more added to the mixture at rt. The mixture was stirred at 70 ˚C for 3 h. After cooled, volatile materials were evaporated *in vacuo*, and the residue was diluted with toluene (500 mL) and 1 M HCl (500 mL). Insoluble materials were removed by passing through Celite, and the organic materials were extracted twice with toluene (500 mL). The combined organic layer was washed twice with 1 M HCl (500 mL) and twice with 1 M NaOH (500 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give crude **9** (41.2 g). A suspension of crude **9** (41.2 g) and $K_2CO_3$ (37.6 g, 272 mmol) in DMF (500 mL) was stirred at 120 ˚C for 3 h. After cooled to rt, 30% $MeNH_2$/EtOH (288 mg, 3.71 mmol) was added. The mixture was stirred at rt overnight. The volatile materials were evaporated *in vacuo*, and the residue was diluted with toluene (500 mL) and water (500 mL). The organic materials were extracted twice with toluene (500 mL). The combined organic layers were washed twice with 1 M HCl (500 mL) and twice with 1 M NaOH (500 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give crude **1b**. The product was dissolved in AcOEt (150 mL)-heptane (150 mL), to which $SiO_2$ (30 g) was added. The mixture was stirred at rt for 1 h. $SiO_2$ was filtrated, and washed three times with AcOEt (150 mL)-heptane (150 ml). The combined solution was concentrated *in vacuo.* Diisopropyl ether (300 mL) was added to the residue, and the mixture was stirred at 0 ˚C for 1 h. The separated white crystals were filtered, and dried to give **1b** (10.1 g, overall yield 37% from **11**). The purity of **1b** was determined to be 96.3% by HPLC analysis.[6]

## REFERENCES

1. H. Ban, M. Muraoka, and N. Ohashi, *Tetrahedron*, *in press*
2. T. Curtius, *Ber*., 1902, **35**, 3226.
3. S. Ohnuma, K. Ioriya, M. Muraoka, and N. Ohashi, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1309.
4. Reviews for the synthesis of 1,8-naphtyridin-2(1*H*)-ones: (a) W. W. Paudler and T. J. Kress, *Adv. Heterocycl. Chem.*, 1970, **11**, 123; (b) C. Cheng and S.-J. Yan, *Org. React*., 1982, **28**, 37; (c) W. W. Paudler and R. M. Sheets, *Adv. Heterocycl. Chem.*, 1983, **33**, 147.

5. N. Miyaura and A. Suzuki, *Chem. Rev*., 1995, **95**, 2457.
6. HPLC condition are follows: Column; Puresil C18 120Å 5μm, 4.6mm x 15cm (Waters), mobile phase; 0.1% trifluoroacetic acid in acetonitrile/water (70:30 to 100:0 gradient over 45 min), flow rate; 0.5 mL/min, detection; UV 220 nm.