Efficient Construction of the Nucleus of Rosuvastatin Calcium

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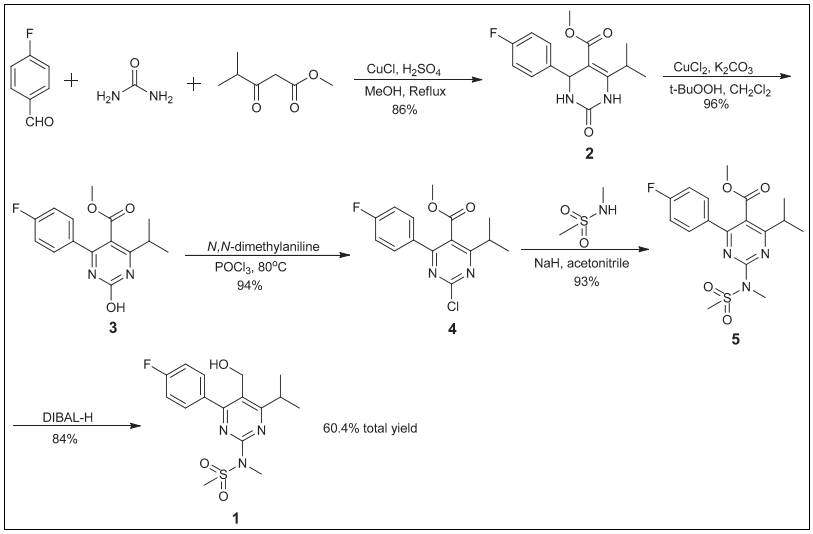


A novel and efficient five-step synthetic route, including a Biginelli reaction, dehydrogenation, chlorination, sulfonamidation, and reduction, for the core of Rosuvastatin was established. All steps were systematically studied. Tert-butylhydroperoxide aqueous solution was applied in the dehydrogenation instead of nitric acid. *N,N*-dimethylaniline was employed as a catalyst to accelerate the chlorination proceeding smoothly, and its catalytic mechanism is discussed. In the sulfonamidation, the conversion of compound **5** was obviously improved by use of NaH and acetonitrile. In addition, two sulfonamidation side products **6** and **7** were detected and isolated. Thus, under the optimized reaction conditions, the target product was obtained in 60.4% total yield, much higher than the reported yield (36.4%).

INTRODUCTION

As reported [1,2], Rosuvastatin calcium (Fig. 1) displays inhibiting activity for HMG-CoA reductase, a major rate-limiting enzyme in cholesterol biosynthesis. And it has been shown to induce the expression of the low-density lipoprotein receptor, which mediates the clearance of low-density lipoprotein cholesterol from plasma. Compared with other statins, Rosuvastatin is more efficient and exhibits fewer side effects.

As a quite popular first-line clinical drug, the synthetic technology of Rosuvastatin calcium [3] has been intensively studied [4–8]. 4-(4-fluorophenyl)-6-isopropyl-2-(methanesulfonyl-methyl-amino)-pyrimidin-5-yl methanol (**1**; Fig. 1), the nucleus of Rosuvastatin calcium, has received intensive attention. Over the years, several ways were reported [9–13] for the construction of the pyrimidine ring in compound **1**. Biginelli [14] presented a one-pot methodology for the synthesis of 3,4-dihydropyrimidin-2(1H)- one (DHPM; Fig. 1), but received little attention. Until 2003, owing to the pharmaceutical importance associated with the derivatives of this privileged heterocyclic core, DHPMs have surged rapidly [15–17].

In 2003, Matsushita Akio *et al.* [18] firstly applied Biginelli reaction in the synthesis of Rosuvastatin and reported a four-step synthetic route, consisting of dehydrogenation, tautomerization, and nucleophilic substitution, for intermediate **5**, which is easily converted to compound **1**. However, excess 50–60% nitric acid was employed in the dehydrogenation of DHPM **2**, undoubtedly leading to serious environmental pollution and security problems. The following conventional tautomerization process normally included chlorination or sulfonylation, while, to get a high output, $POCl_3$ or RSO_2Cl was used at high temperatures in chlorination or

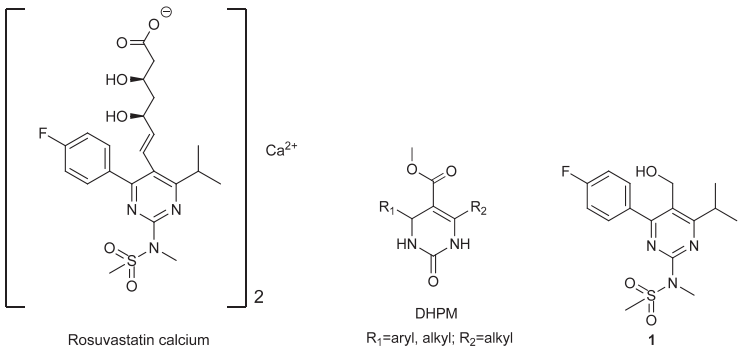


Figure 1. The structures of Rosuvastatin calcium, compound **1,** and DHPM.

sulfonylation. It could be problematic for substrates with sensitive functionalities and dangerous in industrial work. The coupling reaction of compound **4** with *N*-methyl methanesulfonamide in toluene proceeded slowly in the presence of K_2CO_3. The conversion of compound **4** was below 56.4%.

Herein, we describe an efficient and mild five-step process (Scheme 1), which allows the concise and practical synthesis of compound **1**. Under the optimized conditions, compound **1** was obtained with 99.1% purity and 60.4% total yield.

RESULTS AND DISCUSSION

As described in Scheme 1, the three-component Biginelli coupling reaction was carried out with CuCl as a catalyst in the presence of H_2SO_4. After refluxing for 24 h in methanol, compound **2** was directly crystallized from the reaction medium. Under simple optimization, 86% yield of DHPM was obtained (Table 1). As shown in Table 1, CuCl and methylisobutyryl acetate have obvious effect on this reaction rather than H_2SO_4 and urea [17].

As mentioned previously, excess of nitric acid was traditionally employed for the dehydrogenation of compound **2** in industry. The application of nitric acid certainly generated environmental contamination and security problems. So it is necessary to select some green and secure oxidant for this reaction. Initially, Pd/C, MnO_2, and $Mn(OAc)_3$ were respectively applied in the dehydrogenation of compound **2**. Unfortunately, the dehydrogenation of compound **2** was not observed. Subsequently, based on the work about the dehydrogenation of DHPMs, reported by Yamamoto *et.al.* [19] in 2005, TBHP aqueous solution (70 wt%, 2.5 equiv.) was employed as an oxidant for this reaction in

Scheme 1. The synthetic route of compound **1.**

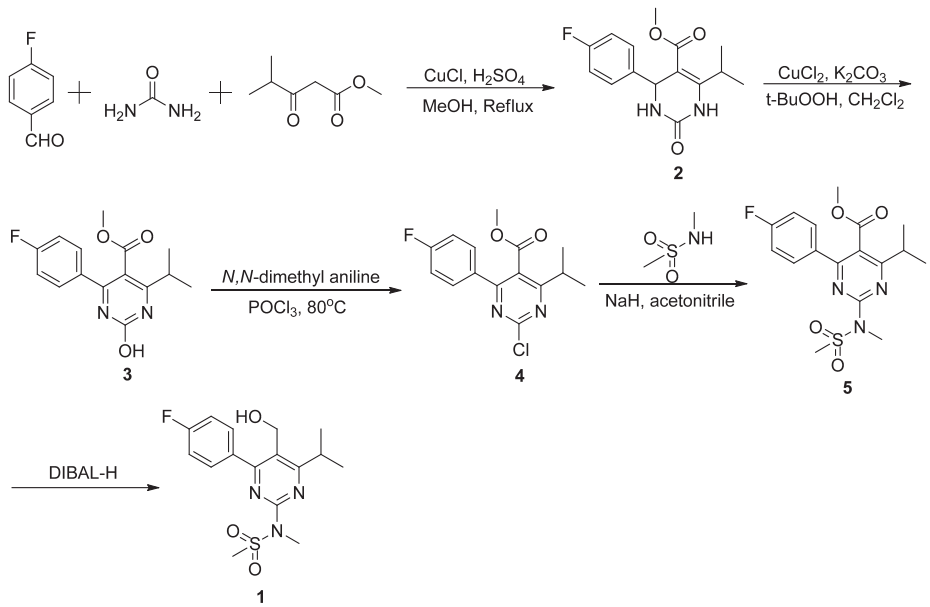


Table 1

Optimization of Biginelli reaction.

Molar ratio[a]	CuCl(equiv.)	98% H_2SO_4(equiv.)	Yield[b](%)
1.00:1.05:1.05	0.01	0.1	81
1.00:1.05:1.05	0.02	0.1	82
1.00:1.05:1.05	0.05	0.1	85
1.00:1.05:1.05	0.10	0.1	85
1.00:1.05:1.05	0.05	0.2	85
1.00:1.05:1.05	0.02	0.3	81
1.00:1.05:1.20	0.02	0.2	85
1.00:1.20:1.20	0.05	0.2	87
1.00:2.00:1.05	0.01	0.1	81

[a]4-Fluorobenzaldehyde : Urea : Methylisobutyryl acetate.
[b]Isolated yields.

the presence of $CuCl_2$ (1%) and K_2CO_3 (0.1 equiv.). Excitedly, compound **3** was obtained in 95.7% yield. Meanwhile, the excess TBHP can be easily removed by $Na_2S_2O_3$. The procedure was mild, practical, and economical compared with the traditional process.

The chlorination of pyrimidine to compound **4** was also carried out with $POCl_3$ at 105°C [20]. We speculated that an appropriate acid-binding agent was required to promote the reaction process. So catalytic amounts of *N, N*-dimethylaniline was added. Surprisingly, this reaction proceeded smoothly at 80°C for 2.5 h to afford compound **4** in 95.0% isolated yield with 100% conversion of compound **3**. However, with triethylamine as the acid-binding agent, the reaction proceeded very slowly. As the catalytic mechanism [21] described in Scheme 2, we supposed that *N,N*-dimethylaniline is a suitable hindered base with adaptive alkalinity, which can deprotonate compound **3** to induce the chlorination rather than couples with $POCl_3$.

Then, the nucleophilic substitution of compound **4** with *N*-methyl methanesulfonamide afforded compound **5**. Several bases and solvents were examined for the sulfonamidation. The results were summarized in Table 2. It was found when the reaction proceeded with

Table 2

The effect of base and solvent on sulfonamidation of chloropyrimidine **4.**

Base	Solvent	Yield[a] (%)
K_2CO_3	Toluene	59
K_2CO_3	Acetonitrile	35
K_2CO_3	1,4-dioxane	46
K_2CO_3	AcOt-Bu	81
NaH	AcOt-Bu	87
NaH	1,4-dioxane	90
NaH	Acetonitrile	97
NaH	Toluene	9

[a]Determined by HPLC: Chromatographic Column: ZORBAX SB-C 18, 5 μm, 4.6 × 150 mm;
Moving phase: CH_3OH: H_2O = 80:20 (v:v);
Velocity: 0.8 mL/min;
Wavelength: 254 nm.

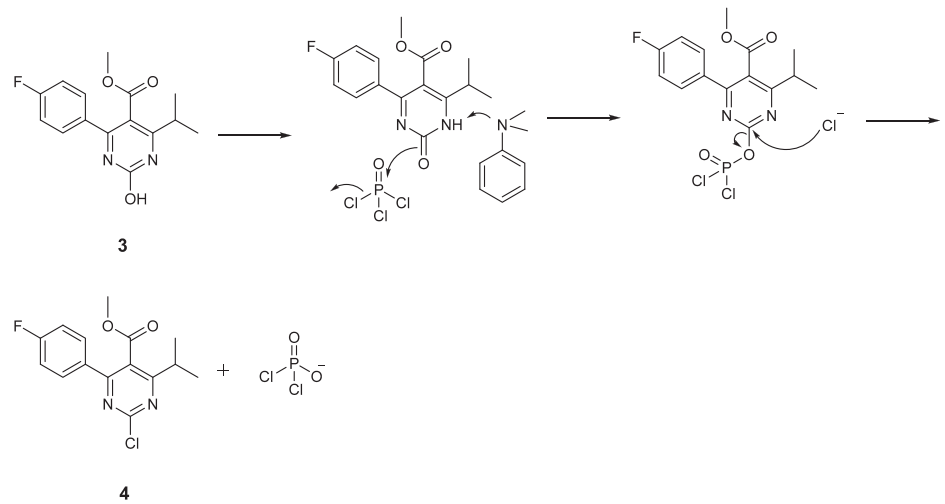
Table 3

The effect of molar ratio on the nucleophilic sulfonamidation.

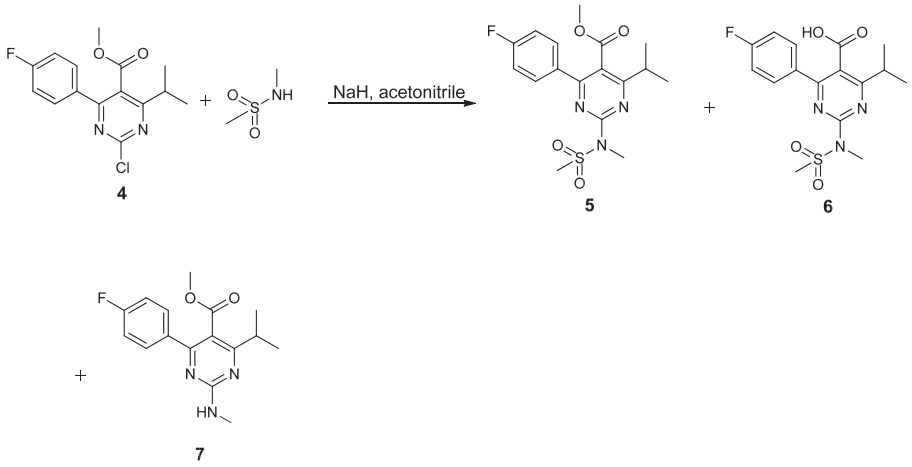
Molar ratio[a]	Solvent	Yield[b] (%)
1.0:1.2:1.2	Acetonitrile	78
1.0:1.2:2.0	Acetonitrile	97
1.0:2.0:2.0	Acetonitrile	81

[a]Compound **4** : NaH : Methanesulfonic acid methyl amide
[b]Determined by HPLC: Chromatographic Column: ZORBAX SB-C 18, 5 μm, 4.6 × 150 mm;
Moving phase: CH_3OH: H_2O = 80: 20 (v:v);
Velocity: 0.8 mL/min;
Wavelength: 254 nm.

Scheme 2. The catalytic mechanism of chlorination.



Scheme 3. The product mixture of coupling reaction of compound **4** with excess NaH.



NaH in acetonitrile, compound **5** was obtained in 97% yield. Compared with K_2CO_3, NaH was a stronger base, resulting in the deprotonation of *N*-methyl methanesulfonamide to the corresponding nitrogen anion, accelerating the nucleophilic substitution to present compound **5** in excellent yield. In addition, the results in Table 3 indicated that the ratio of NaH and compound **4** is quite important to this reaction; otherwise, two side products **6** and **7** were detected and isolated. Their structures were confirmed by ^{1}H NMR and ^{13}C NMR; their generation is possibly attributed to the highly active hydride ion present in the solution (Scheme 3).

Finally, the reduction of compound **5** to compound **1** was respectively investigated with $NaBH_4$, $LiAlH_4$, and diisobutylaluminium hydride (DIBAL-H). It was found that $NaBH_4$ blended with lewis acid did not have enough reduction ability to convert ester **5** into the corresponding alcohol **1**; decomposed side products were detected with $LiAlH_4$ as a reducing agent. Finally, this reaction was realized with DIBAL-H in 84% yield and 99.1% purity.

CONCLUSION

In conclusion, an efficient five-step synthetic method for the nucleus of Rosuvastatin **1** was established on the basis of one-pot three-component Biginelli reaction and dehydrogenation, chlorination, sulfonamidation, and reduction. In which, dehydrogenation, chlorination, and sulfonamidation were systematically studied. Tert-butylhydroperoxide (TBHP) aqueous solution was applied in the dehydrogenation instead of nitric acid, which was more mild and practical. *N,N*-dimethylaniline was employed as a catalyst to accelerate the chlorination. Meanwhile, several bases and solvents were examined for the nucleophilic substitution of compound **4**. NaH in acetonitrile was preferable for this sulfonamidation, leading to a rapid conversion. In addition, two side products **6** and **7** were detected and isolated in this sulfonamidation. The target product was obtained in 60.4% total yield and 99.1% purity.

EXPERIMENTAL

Reagents and solvents were obtained from commercial suppliers. All reactions were monitored by thin layer chromatography using commercial silica gel plates. The purity of products was detected by HPLC on Agilent 1100 series. Melting points were observed on YRT-3 Melting Point Tester and uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III 400 MHz spectrometer.

Methyl 4-(4-Fluorophenyl)-6-Isopropyl-2-oxo-1,2,3,4-Tetrahydropyrimidine-5-Carboxylate (2). A mixture of 4-fluorobenzaldehyde (5.00 g, 0.040 mol), methylisobutyryl acetate (6.97 g, 0.048 mol), urea (2.90 g, 0.048 mol), copper (I) chloride (0.20 g, 0.002 mol), concentrated H_2SO_4 (0.435 mL), and methanol (45 mL) were stirred for 24 h at 80°C under an N_2 atmosphere. Afterwards, the reaction mixture was cooled to room temperature, and a white solid appeared. The precipitate was collected by filtration, washed with methanol (210 mL) and dried at 50°C under vacuum to give product **2** as a white solid (10 g, 86% yield based on 4-fluorobenzaldehyde). mp 222.0–225.0°C. (lit.[18] 223–225°C). ^{1}H NMR (400 MHz, DMSO-*d6*) δ: 1.14–1.18 (m, 6H), 3.55 (s, 3H), 4.14–4.17 (m, 1H), 5.17 (d, J = 3.2 Hz, 1H), 7.19 (t, J = 8.8 Hz, 2H), 7.26–7.30 (m, 2H), 7.78 (s, 1H), 8.94 (s,

1H). ^{13}C NMR (100 MHz, DMSO-*d6*) δ: 19.43, 19.65, 27.56, 51.42, 53.56, 98.41, 115.74 (d, J_{CF} = 21.1 Hz), 128.62 (d, J_{CF} = 8.2 Hz), 141.29 (d, J_{CF} = 2.9 Hz), 153.13, 157.35, 161.87 (d, J_{CF} = 241.8 Hz), 166.23. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{15}H_{17}FN_2O_3$ 315.1121; found: 315.1121.

Methyl 4-(4-Fluorophenyl)-2-Hydroxy-6-Isopropylpyrimidine-5-Carboxylate (3). Dihydropyrimidinone **2** (5.00 g, 17.00 mmol) was dissolved in methylene chloride (40 mL). Copper (II) chloride (0.03 g, 0.17 mmol) and potassium carbonate (0.23 g, 1.70 mmol) were added, and the mixture was cooled to 25°C. Then, aqueous TBHP solution (70 wt%, 5.47 g, 42.5 mmol) was added dropwise. The mixture was warmed to 40°C and stirred for 7 h. At that time, the solution was cooled to room temperature, and the potassium iodide-starch test paper was used to detect residual peroxide. If the paper turned to blue, 15% $Na_2S_2O_4$ aqueous solution was added to quench the peroxide. If not, the solution was diluted with water (50 mL) and extracted with CH_2Cl_2 (50 mL × 2). The organic phases were combined and concentrated under reduced pressure to give a slightly yellow solid. The solid was vacuum dried to give 4.75 g of **3** (95.66% yield). mp 186.0–190.0°C. (lit.[18] 193°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.47 (d, J = 6.4 Hz, 6H), 3.24–3.27 (m, 1H), 3.64 (s, 3H), 7.16 (t, J = 7.4 Hz, 2H), 7.66 (s, 2H). (The hydroxy proton at 5.0 ppm was not observed). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.58, 31.85, 52.60, 115.67, 115.89, 130.07, 130.16, 163.08, 165.59, 167.13, 167.21, 167.34. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{15}H_{15}FN_2O_3$ 313.0965; found: 315.0966.

Methyl 2-Chloro-4-(4-Fluorophenyl)-6-Isopropylpyrimidine-5-Carboxylate (4). Compound **3** (4.75 g, 0.016 mol) was suspended in $POCl_3$ (20.08 g, 0.131 mol) at room temperature. *N,N*-dimethylaniline (0.97 g, 0.008 mol) was added, and the mixture was stirred for 2.5 h at 80°C under nitrogen. At that time, the mixture was cooled to 0°C and slowly quenched with a dropwise addition of water (100 mL). When the addition was complete, the mixture was warmed to room temperature and stirred for 5 min. The aqueous solution was extracted with CH_2Cl_2 (100 mL × 2). The organic phases were combined and concentrated under reduced pressure. The crude material was purified by recrystallization in ethanol/water. The solid was vacuum dried to give 4.68 g of **4** (93.60% yield). mp 102.0°C (lit.[18] 99–101°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26 (d, J = 4.4 Hz, 6H), 3.04–3.07 (m, 1H), 3.68 (s, 3H), 7.08 (t, J = 5.8 Hz, 2H), 7.59–7.62 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.58, 33.67, 52.98, 115.96 (d, J_{CF} = 21.9 Hz), 123.29, 130.58 (d, J_{CF} = 8.7 Hz), 132.52 (d, J_{CF} = 3.2 Hz), 161.27, 163.08, 165.23 (d, J_{CF} = 72.1 Hz), 167.81, 176.65. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{15}H_{14}ClFN_2O_2$ 331.0626; found: 331.0625.

Methyl 4-(4-Fluorophenyl)-6-Isopropyl-2-(Methanesulfonyl-Methyl-Amino)-Pyrimidine-5-Carboxylate (5). Sodium hydride (0.73 g, 0.018 mol, 60% suspension in mineral oil) was suspended in acetonitrile (30 mL). *N*-methyl Methanesulfonamide (3.15 g, 0.030 mol) was added dropwise. The resulting suspension was stirred for 5 min, and compound **4** (4.68 g, 0.015 mol) was added, washed in with acetonitrile (20 mL). The mixture was heated to reflux and stirred for 7 h. After cooled to room temperature, the mixture was extracted with ethyl acetate (80 mL) and water (120 mL). The organic phase was separated and concentrated under reduced pressure to give crude product. Then it was purified by recrystallization in methanol. The solid was dried in vacuum to yield **5** (5.33 g, 93.2% yield). mp 132.1–132.7°C. (lit.[5] 130.0–132.5°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (d, J = 6.8 Hz, 6H), 3.20–3.27 (m, 1H), 3.55 (s, 3H), 3.63 (s, 3H), 3.74 (s, 3H), 7.18 (t, J = 8.6 Hz, 2H), 7.70–7.73 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.79, 33.09, 33.37, 42.43, 52.69, 115.77 (d, J_{CF} = 21.8 Hz), 118.82, 130.46 (d, J_{CF} = 8.6 Hz), 133.80 (d, J_{CF} = 3.3 Hz), 158.56, 163.00 (d, J_{CF} = 32.0 Hz), 165.34, 168.71, 174.79. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{17}H_{20}FN_3O_4S$ 404.1057; found: 404.1057.

With extra NaH in this reaction, two side products were detected.

Methyl 4-(4-Fluorophenyl)-6-Isopropyl-2-(Methanesulfonyl-Methyl-Amino)-Pyrimidine-5-Carboxylic Acid (6). mp 208.8–209.6°C. ^{1}H NMR (400 MHz, CD_3OD) δ: 1.35 (d, J = 6.4 Hz, 6H), 3.33–3.34 (m, 1H), 3.54 (s, 3H), 3.58 (s, 3H), 7.23 (t, J = 8.6 Hz, 2H), 7.83–7.87 (m, 2H). (The hydroxy proton at 11.0 ppm was not observed). ^{13}C NMR (100 MHz, CD_3OD) δ: 20.76, 32.30, 33.21, 40.89, 115.11 (d, J_{CF} = 22.0 Hz), 120.02, 130.58 (d, J_{CF} = 8.7 Hz), 133.85 (d, J_{CF} = 3.3 Hz), 158.50, 162.70 (d, J_{CF} = 44.7 Hz), 165.40, 169.93, 173.91. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{16}H_{18}FN_3O_4S$ 390.0900; found: 390.0906.

Methyl 4-(4-Fluorophenyl)-6-Isopropyl-2-(Methylamino)-Pyrimidine-5-Carboxylate (7). mp 100-100.6°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28 (d, J = 6.8 Hz, 6H), 3.05 (d, J = 5.2 Hz, 3H), 3.15–3.21 (m, 1H), 3.63 (s, 3H), 5.37 (s, 1H) 7.12 (t, J = 8.6 Hz, 2H), 7.60 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.60, 28.01, 32.83, 52.04, 114.10, 115.34 (d, J_{CF} = 21.6 Hz), 129.93 (d, J_{CF} = 8.3 Hz), 135.32 (d, J_{CF} = 3.0 Hz), 162.25, 163.27 (d, J_{CF} = 192.0 Hz), 164.78, 169.74, 174.94. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{16}H_{18}FN_3O_2$ 304.1461; found: 304.1460.

4-(4-Fluorophenyl)-6-Isopropyl-2-(Methanesulfonyl-Methyl-Amino)-Pyrimidin-5-yl Methanol (1). Compound **5** (5.00 g, 0.013 mol) was dissolved in toluene (30 mL). The mixture was cooled to −15°C, and DIBAL (1 M in toluene, 33 mL, 0.033 mol) was added dropwise over 30 min. The internal temperature was kept below −15°C during the

addition. When the addition was complete, the solution was warmed to 0°C and stirred for 1 h. At that time, the reaction was slowly quenched with methanol (5 mL) and 2 N NaOH (50 mL). The mixture was warmed to room temperature and stirred for 30 min. The solution was diluted with water (200 mL) and extracted with CH_2Cl_2 (450 mL). The organic phase was concentrated and vacuum dried to give alcohol **1** (3.89 g, 84%) as a white yellow solid. The product was analyzed by: HPLC, method A, RT 17.4 min, UV detector 254 nm 99.1% pure. mp 140.0–140.4°C. (lit.[9] 131.5°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 (d, J = 6.4 Hz, 6H), 2.28 (s, 1H), 3.48–3.53 (m, 4H), 3.57 (s, 3H), 4.63 (d, J = 3.6 Hz, 2H), 7.15 (t, J = 8.6 Hz, 2H), 7.80–7.83 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.23, 31.58, 33.12, 42.38, 57.53, 115.38 (d, J_{CF} = 21.5 Hz), 120.78, 131.53 (d, J_{CF} = 8.4 Hz), 134.00 (d, J_{CF} = 3.1 Hz), 157.92, 162.48, 165.60 (d, J_{CF} = 126.8 Hz), 177.83. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{16}H_{20}FN_3O_3S$ 376.1107; found: 376.1112.

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