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Synthetic studies on statins. Part 3: A facile synthesis of rosuvastatin calcium through catalytic enantioselective allylation strategy☆

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ABSTRACT

A concise and stereocontrolled synthesis of rosuvastatin calcium has been accomplished, with the key steps including a Keck enantioselective allylation of chloroacetaldehyde with allyltributylstannane to install 5*R*-stereocenter and a $VO(acac)_2$-catalyzed *syn*-diastereoselective epoxidation of (*S*)-1-chloropent-4-en-2-ol to set the requisite 3*R*-chirality.

1. Introduction

Rosuvastatin calcium (Crestor, **1**, Fig. 1) was marketed as a 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitor by AstraZeneca in 2003, and has been billed as a 'superstatin' because of its pronounced ability to reduce low-density lipoprotein cholesterol levels and increase high-density lipoprotein cholesterol compared with existing agents.[2] The development of a concise synthetic strategy for rosuvastatin calcium is therefore highly desired. One of the most commonly used strategies for construction of pyrimidine core attached to (3*R*,5*R*)-3,5-dihydroxy-heptenoic acid in **1** is adopted a Wittig-type olefination of the ylide **2** with the C_6 side chain aldehyde **3** (Fig. 1).[3] The efficient assembly of 3*R*-*syn*-3,5-diol subunit is the key issue for the synthesis of **3**. Considerable synthetic efforts have been directed towards the development of strategies for construction of **3**, and have culminated in several new methods based on chiral pool synthesis,[4] asymmetric catalysis,[5] or the use of chiral auxiliary[6] or chemoenzymatic process.[7] One of the major industrial processes for construction of C_6 side chain involves Blaise condensation of a C_2 synthon with a C_4 synthon (starting from (*S*)-epichlorohydrin).[4h–j] One of the major limitations of this route, however, is the use of Narasaka reduction to introduce the second stereogenic center, because this reaction

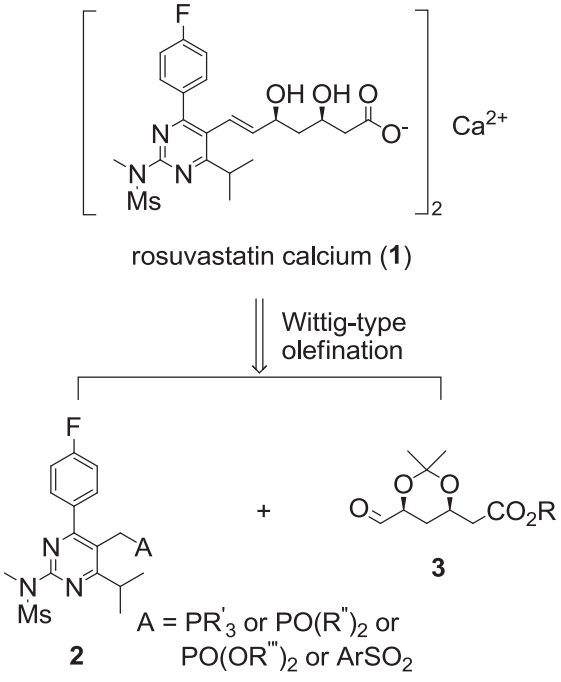

Fig. 1. The chemical structures of **1**, **2**, and **3**.

☆ See Ref. 1.

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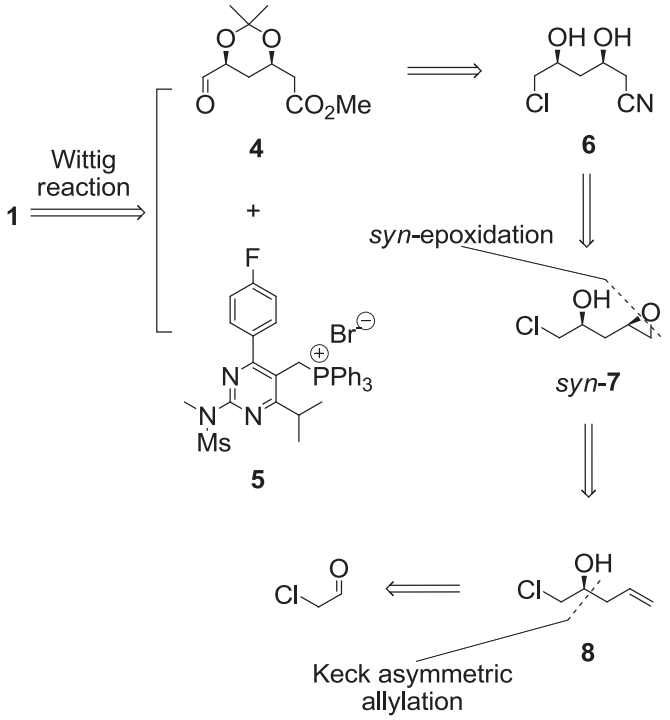
requires particularly harsh conditions (i.e., Et_3B or $Et_2BOMe/NaBH_4$/−78 °C). Herein, we describe the development of an efficient and alternative strategy for the synthesis of **1**, which avoids the use of Narasaka reduction.

2. Results and discussion

Our retrosynthetic approach towards **1** is depicted in Scheme 1. It was envisaged that **1** could be derived from aldehyde **4** and phosphonium salt **5**. **4** could be accessed through a series of transformations from *syn*-diol **6**, which could be synthesized via epoxy addition of **7** with sodium cyanide. Compound **7** could be prepared by a $VO(acac)_2$-catalyzed *syn*-diastereoselective epoxidation of homoallylic alcohol **8**. Keck enantioselective allylation of chloroacetaldehyde with allyltributylstannane would allow for introduction of the requisite 2*R* stereochemistry in **8**.

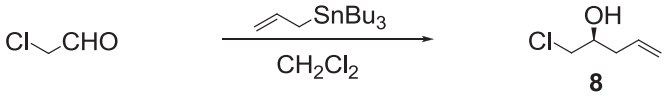


Scheme 1. Retrosynthetic strategy for **1**.

Our asymmetric synthesis of rosuvastatin calcium (**1**) commenced with anhydrous chloroacetaldehyde,[8] which was subjected to Keck asymmetric allylation[9] with allyltributylstannane in the presence of (*S*)-BINOL/$Ti(O^iPr)_4$ at −20 °C for 96 h furnished homoallylic alcohol **8** in 67% yield with the desired (*S*)-configuration, which was verified by optical rotation analysis.[10] The optical purity of **8** (94% ee) was determined by HPLC analysis of its benzoyl-protected derivative **9** (Table 1, entry 1). (*S*)-VANOL/$Ti(O^iPr)_4$ and (*R*)-VAPOL/$Ti(O^iPr)_4$ were screened against this reaction, but gave very low yields (41 and 37%) and poor enantioselectivities (54 and 46% ee) (Table 1, entries 2 and 3), and the use of (*S*)-BINOL/$FeCl_3$ and (*S*)-BINOL/$InCl_3$ gave even worse results (8 and 30% ee) (Table 1, entries 4 and 5).

Many researchers have explored the *syn*-epoxidation of acyclic homoallylic alcohols using a wide variety of oxidants and/or catalysts,[11] Of these, the $VO(acac)_2$/*tert*-butyl hydroperoxide (TBHP) oxidation system has become one of the most commonly used systems for this transformation.[11a] As shown in Table 2, treatment of **8** with TBHP in the presence of 5 mol % $VO(acac)_2$ afforded **7** in 69% yield as an inseparable 5:2 mixture of epimers (Table 2, entry 1).

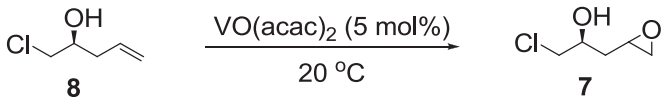
Table 1
Optimization of Keck asymmetric allylation of chloroacetaldehyde[a]



Entry	Catalyst	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	(*S*)-BINOL, $Ti(O^iPr)_4$	−20	96	67	94
2	(*S*)-VANOL, $Ti(O^iPr)_4$	0	96	41	54
3	(*R*)-VAPOL, $Ti(O^iPr)_4$	0	96	37	46
4	(*S*)-BINOL, $FeCl_3$	0	72	54	8
5	(*S*)-BINOL, $InCl_3$	0	60	46	30

[a] All reactions were carried out in the presence of chloroacetaldehyde (1.0 mmol), allyltributylstannane (2.0 mmol), chiral ligands (0.22 mmol), Lewis acids (0.2 mmol), and 4 Å MS in CH_2Cl_2 (10 mL).
[b] Isolated yields.
[c] The ee values of **8** were determined by its benzoate derivant **9**.

Table 2
Optimization of *syn*-epoxidation of homoallylic alcohol **8**[a]



Entry	Oxidant	Solvent[b]	Time (h)	Yield[c] (%)	dr[d]
1	TBHP	CH_2Cl_2 (1.0 M)	36	69	5:2
2	CHP	CH_2Cl_2 (1.0 M)	48	67	2:1
3	UHP	THF (1.0 M)	48	—	—
4	$NaBO_3$	THF (1.0 M)	48	—	—
5	TBHP	CH_2Cl_2 (0.5 M)	60	67	13:5
6	TBHP	CH_2Cl_2 (0.1 M)	60	76	3:1

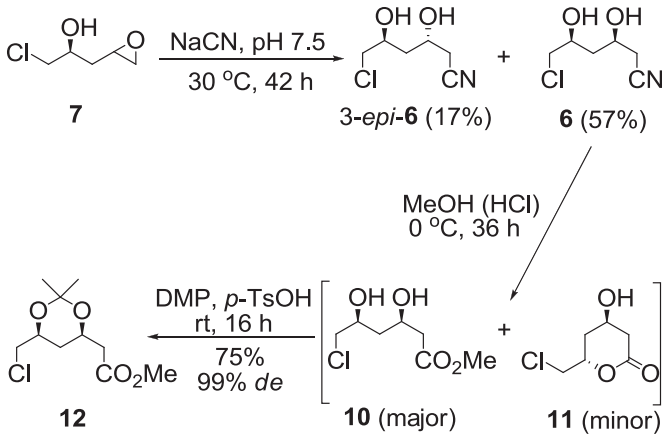
[a] All reactions were carried out in the presence of **8** (2.0 mmol), $VO(acac)_2$ (0.1 mmol), oxidants (3.0 mmol), and 3 Å MS at 20 °C.
[b] In parentheses are concentration of **8**.
[c] Isolated yields.
[d] The dr values were determined by ^1H NMR analysis.

After screening other oxidants, we found that the diastereoisomeric ratio could be reduced to 2:1 using cumene hydroperoxide (CHP), whereas the use of urea hydrogen peroxide (UHP) or sodium perborate proved to be ineffective (Table 2, entries 2–4). The concentration of **8** was found to have a significant impact on the diastereoselectivity of the epoxidation, and a reduction in the concentration of substrate from 1.0 to 0.1 M led to a gradual increase in the dr value (from 5:2 to 3:1) (Table 2, entries 1, 5, and 6).

With requisite epoxide **7** in hand, we proceeded to investigate nucleophilic addition of sodium cyanide to allow for the introduction of cyano group to C_5 side chain. The reaction of **7** with sodium cyanide under weakly basic conditions (pH=7.5–8.0) proceeded smoothly to afford the desired nitrile **6** in an isolated yield of 57%. The byproduct (3-*epi*-**6**) was also isolated in 17% yield (Scheme 2). Subsequent Pinner reaction of **6** with a saturated solution of hydrogen chloride in methanol at 0 °C for 36 h afforded a mixture of ester **10** and lactone **11** (resulting from an intramolecular Pinner reaction), which was used directly in next reaction without further purification. Protection of the mixture with 2,2-dimethoxypropane (DMP) in the presence of 10 mol % *p*-toluenesulfonic acid gave 1,3-dioxane **12** in an overall yield of 75% over two steps with 99% de, which was confirmed by GC–MS analysis relative to 4-*epi*-**12** derived from 3-*epi*-**6** (Scheme 2).

The stereochemical assignment of **12** was confirmed by a NOESY study, which revealed strong NOE correlations between H-3/H-5, H-3/H-9, and H-5/H-9. These correlations indicated that H-3, H-5, and H-9 were on the same side of the molecule (Fig. 2).

Reaction of **12** with potassium acetate or sodium benzoate in the presence of tetrabutyl ammonium bromide furnished **13a** or **13b**, respectively, in moderate yields as white solids. The optical purity of **13** was only 95%, fortunately, it could be upgraded to 99% by



Scheme 2. Synthesis of intermediate **12**.

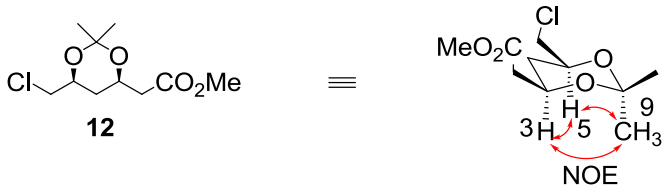
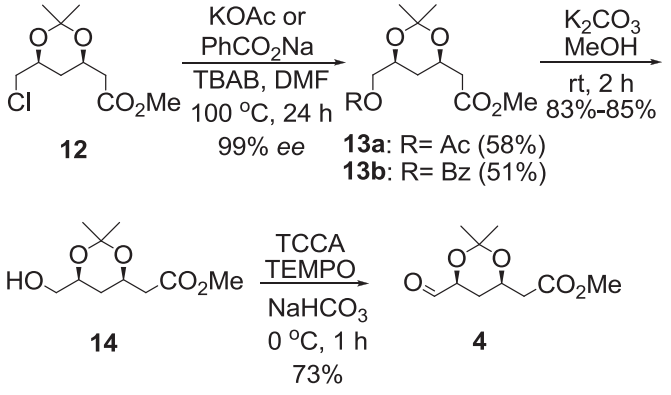


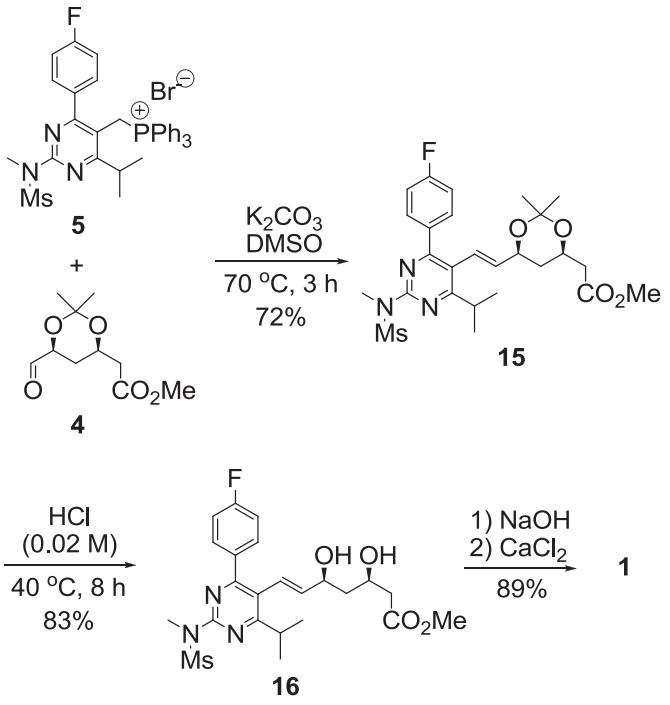
Fig. 2. The NOESY correlations of intermediate **12**.

recrystallization from *n*-heptane with recovered yields in the range of 85–88%. Compounds **13** were then hydrolyzed with aqueous potassium carbonate at room temperature for 2 h to afford alcohol **14** in excellent yields. The key building block **4** was readily synthesized in 73% yield by treatment of **14** with trichloroisocyanuric acid (TCCA) in the presence of a catalytic amount of 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) (Scheme 3).[12]



Scheme 3. Synthesis of the key intermediate **4**.

Finally, Wittig olefination of **4** with phosphonium salt **5**[3d] was performed under basic conditions (i.e., K_2CO_3, DMSO, 70 °C) to yield olefin **15** in 72% yield. Subsequent treatment of **15** with hydrochloric acid (0.02 mol/L, 5 mol %) in acetonitrile at 40 °C for 8 h allowed for the deprotection of ketal to give diol **16** in 83% yield, which was subjected to sequential hydrolysis and salification steps to furnish **1** in yield of 89% over two steps (Scheme 4).[3d]



Scheme 4. Synthesis of rosuvastatin calcium (**1**).

3. Conclusions

In summary, we have developed an efficient 11-step sequence for the synthesis of rosuvastatin calcium (**1**) starting from readily available material chloroacetaldehyde. Keck asymmetric allylation of chloroacetaldehyde with allyltributylstannane followed by a $VO(acac)_2$-catalyzed stereoselective epoxidation of the resulting homoallylic alcohol **8** allowed for rapid construction of the 3*R*-*syn*-1,3-diol subunit of the target. Our newly developed approach is superior to existing methodologies for preparation of **4** because it avoids the use of Narasaka reduction. Although a large number of synthetic strategies for **1** have already been reported in the literature, our newly developed strategy represents a unique approach and should provide a platform for the synthesis of **1** and its derivatives.

4. Experimental section

4.1. General

Melting points were determined on a WRS-1 digital melting point apparatus. Optical rotations were obtained on a JASCO P1020 digital polarimeter. ^1H and ^{13}C NMR spectra were obtained on a Bruker Avance 400 spectrometer (400, 100 MHz, respectively) in $CDCl_3$ or DMSO-d_6 using $CDCl_3$ (^1H, δ 7.26) or DMSO-d_6 (^1H, δ 2.50) and $CDCl_3$ (^{13}C, δ 77.0) or DMSO-d_6 (^{13}C δ 39.5) as internal standards. IR spectra were recorded on a Nicolet FTIR 4200 spectrometer as KBr pellets. Mass spectra were measured on a Waters Quattro Micromass instrument using electrospray ionization (ESI) techniques. Enantiomeric excesses (ee) were determined by HPLC analysis using Chiralpak columns. Unless otherwise noted all reactions were conducted in oven-dried glassware under inert atmosphere of dried Ar or N_2. (*S*)-BINOL, (*S*)-VANOL, and (*R*)-VAPOL were purchased from Aldrich.

4.2. (*S*)-1-Chloropent-4-en-2-ol (8)

A mixture of (*S*)-BINOL (62 mg, 0.22 mmol) and 4 Å MS (100 mg) in 5 mL anhydrous CH_2Cl_2 was added $Ti(O^iPr)_4$ (60 μL, 0.2 mmol). The reaction was heated at 40 °C under argon atmosphere for 1 h before cooled to room temperature and a solution of chloroacetaldehyde (1.0 mmol) in 5 mL CH_2Cl_2 was added. The contents were cooled to −20 °C and allyltributylstannane (0.62 mL,

2.0 mmol) was added. The reaction was stirred at −20 °C for 96 h before being added saturated $NaHCO_3$ (2 mL) and stirred at room temperature for 2 h. The molecular sieves were removed and the aqueous layer was extracted with CH_2Cl_2 (2×25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure (20 mmHg), then purified by column chromatography (silica gel, EtOAc/PE, 1:15) to afford **8** (80 mg, 67%) as a pale yellow oil and recovered (*S*)-BINOL (51 mg, 83%); $[\alpha]_D^{21.1}$ +4.6 (*c* 2.0, $CHCl_3$, 94% ee), lit.[10] $[\alpha]_D^{25}$ +5.2 (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.34 (m, 3H), 3.48–3.52 (m, 1H), 3.60–3.63 (m, 1H), 3.87 (m, 1H), 5.13–5.19 (m, 2H), 5.76–5.86 (m, 1H); MS (EI): *m*/*z* (%)=120 (1), 79 (100); IR (thin film): 3379, 2951, 1645, 991 cm^{-1}.

4.3. (*S*)-1-Chloropent-4-en-2-yl benzoate (9)

To a stirred solution of **8** (60 mg, 0.5 mmol) and pyridine (81 μL, 1.0 mmol) in 2 mL anhydrous CH_2Cl_2 under argon atmosphere at 0 °C was added benzoyl chloride (70 μL, 0.6 mmol). The reaction mixture was stirred at room temperature for 3 h before being quenched by the addition of 10 mL brine. The mixture was extracted with 30 mL EtOAc, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure, then purified by column chromatography (silica gel, PE) to afford **9** (106 mg, 95%) as a colorless oil; ee: 94%, determined by HPLC analysis, Daicel, Chiralpak AD-H column (25 cm×4.6 mm×5 μm), *n*-hexane/*i*-propanol=98/2, 0.3 mL/min, 254 nm, 30 °C, *t* (major)=16.9 min, *t* (minor)=17.6 min; $[\alpha]_D^{21.3}$ −2.0 (*c* 2.0, $CHCl_3$, 94% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 2.61 (t, *J*=6.6 Hz, 2H), 3.73 (dd, *J*=5.2, 12.0 Hz, 1H), 3.77 (dd, *J*=4.8, 12.0 Hz, 1H), 5.16 (dd, *J*=1.2, 10.0 Hz, 1H), 5.22 (dd, *J*=1.2, 16.8 Hz, 1H), 5.30–5.36 (m, 1H), 5.77–5.87 (m, 1H), 7.45 (t, *J*=7.6 Hz, 2H), 7.58 (t, *J*=7.6 Hz, 1H), 8.06 (d, *J*=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.9, 45.0, 72.5, 119.1, 128.4, 129.7, 129.9, 132.1, 133.2, 165.7; MS (EI): *m*/*z* (%)=224 (1), 105 (100); HRMS (ESI-TOF) *m*/*z* calcd for $C_{12}H_{14}ClO_2$ ($M+H^+$) 225.0677, found 225.0679; IR (thin film): 2926, 1723, 1271, 992, 706 cm^{-1}.

4.4. (2*S*)-1-Chloro-3-(oxiran-2-yl)propan-2-ol (7)

A mixture of **8** (240 mg, 2.0 mmol), $VO(acac)_2$ (26 mg, 0.1 mmol), and 3 Å MS (100 mg) in 20 mL anhydrous CH_2Cl_2 was added TBHP (0.9 mL, 3.3 M in toluene)[13] under argon atmosphere at 0 °C. The reaction was stirred at 20 °C for 60 h before being quenched by the addition of 10 mL saturated sodium sulfite. The molecular sieves were removed and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure, then purified by column chromatography (silica gel, EtOAc/PE, 1:4) to afford **7**[14] (colorless oil, 207 mg, 76%) as an inseparable 3:1 mixture of epimers. *syn*-isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 1.60 (ddd, *J*=6.8, 14.0, 21.6 Hz, 1H), 1.87 (dt, *J*=4.4, 14.0 Hz, 1H), 2.46 (dd, *J*=2.8, 4.4 Hz, 1H), 2.71 (t, *J*=4.4 Hz, 1H), 3.02 (m, 1H), 3.34 (br s, 1H), 3.49–3.57 (m, 2H), 3.96 (m, 1H); *anti*-isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (ddd, *J*=4.0, 7.6, 14.4 Hz, 1H), 1.95 (dt, *J*=4.4, 14.0 Hz, 1H), 2.49 (dd, *J*=2.8, 4.4 Hz, 1H), 2.75 (t, *J*=4.4 Hz, 1H), 3.06 (m, 1H), 3.34 (br s, 1H), 3.40–3.57 (m, 2H), 3.93–3.95 (m, 1H); MS (EI): *m*/*z* (%)=135 (1), 57 (100); IR (thin film): 3396, 2955, 1719, 1641 cm^{-1}.

4.5. (5*S*)-6-Chloro-3,5-dihydroxyhexanenitrile (6 and 3-*epi*-6)

To a stirred solution of **7** (6.8 g, 50 mmol) in 10 mL water at 0 °C was added dropwise a solution of sodium cyanide (2.94 g, 60 mmol) in 15 mL water maintained pH=7.5–8.0 by saturated citric acid. The reaction was stirred at 30 °C for 42 h and the aqueous layer was extracted with EtOAc (5×100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure, then purified by column chromatography (silica gel, EtOAc/PE, 1:1) to afford **6** (4.64 g, 57%) as a pale yellow oil and 3-*epi*-**6** (1.38 g, 17%) as a white solid. **6**: $[\alpha]_D^{28.1}$ +3.4 (*c* 5.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.73–1.83 (m, 2H), 2.55 (dd, *J*=6.0, 16.8 Hz, 1H), 2.62 (dd, *J*=4.8, 16.8 Hz, 1H), 3.50 (dd, *J*=6.0, 11.2 Hz, 1H), 3.56 (dd, *J*=4.4, 11.2 Hz, 1H), 3.98 (br s, 1H), 4.06 (m, 1H), 4.17 (m, 1H), 4.40 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 38.9, 49.1, 66.6, 70.6, 117.7; MS (EI): *m*/*z* (%)=163 (1), 68 (100); HRMS (ESI-TOF) *m*/*z* calcd for $C_6H_9^{35}ClNO_2$ ($M-H^-$) 162.0316, found 162.0312; IR (thin film): 3400, 2256, 1723, 1641, 974 cm^{-1}. 3-*epi*-**6**: mp 46–48 °C; $[\alpha]_D^{28.4}$ −30.6 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, DMSO-d_6) δ 1.43–1.50 (m, 1H), 1.57–1.66 (m, 1H), 2.56 (dd, *J*=6.0, 16.8 Hz, 1H), 2.65 (dd, *J*=4.8, 16.8 Hz, 1H), 3.51 (dd, *J*=5.2, 11.2 Hz, 1H), 3.56 (dd, *J*=4.8, 11.2 Hz, 1H), 3.80–3.87 (m, 1H), 3.89–3.96 (m, 1H), 5.09 (d, *J*=5.6 Hz, 1H), 5.27 (d, *J*=5.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 26.1, 40.8, 50.3, 63.2, 66.8, 119.1; MS (EI): *m*/*z* (%)=163 (1), 68 (100); HRMS (ESI-TOF) *m*/*z* calcd for $C_6H_9^{35}ClNO_2$ ($M-H^-$) 162.0316, found 162.0310; IR (thin film): 3392, 2955, 2252, 1413, 930 cm^{-1}.

4.6. Methyl 2-((6*S*)-6-(chloromethyl)-2,2-dimethyl-1,3-dioxan-4-yl) acetate (12 and 4-*epi*-12)

To a stirred solution of **6** (3.3 g, 20 mmol) in 40 mL dry methanol saturated with hydrogen chloride under argon atmosphere was reacted at 0 °C for 36 h before being quenched by saturated $NaHCO_3$ solution. The methanol was evaporated under reduced pressure and the aqueous layer was extracted with ethyl acetate (3×100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford a mixture of **10** and **11** that was pure enough to be used in next step. To a stirred solution of a mixture of **10** and **11** and 2,2-dimethoxypropane (12 mL, 100 mmol) in 50 mL acetone under argon atmosphere at room temperature was added 4-methylbenzenesulfonic acid monohydrate (380 mg, 2.0 mmol). The mixture was stirred at room temperature for 16 h before being quenched by the addition of 0.3 mL triethylamine and removed solvent under reduced pressure. the residue was purified by column chromatography (silica gel, EtOAc/PE, 1:8) to afford **12** (pale yellow oil, 75% from **6**); diastereomeric excess: 99%, t_R=14.2 min, the de value was measured by GC–MS: Agilent, HP-5MS column (30 m×0.25 mm×0.25 μm), injector temperature: 280 °C, oven temperature program from 50 °C (2 min) to 280 °C at 10 °C/min, carrier gas: He, flow rate: 0.9 mL/min, ionization energy 70 eV in the electronic ionization (EI) mode; $[\alpha]_D^{28.3}$ +3.3 (*c* 2.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (dt, *J*=11.6, 12.8 Hz, 1H), 1.35 (s, 3H), 1.43 (s, 3H), 1.75 (dt, *J*=2.4, 12.8 Hz, 1H), 2.38 (dd, *J*=6.0, 15.6 Hz, 1H), 2.54 (dd, *J*=6.8, 15.6 Hz, 1H), 3.36 (dd, *J*=6.0, 11.2 Hz, 1H), 3.48 (dd, *J*=5.6, 11.2 Hz, 1H), 3.65 (s, 3H), 4.01–4.07 (m, 1H), 4.27–4.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 29.7, 33.8, 40.9, 46.9, 51.6, 65.5, 69.0, 99.2, 171.0; MS (EI): *m*/*z* (%)=221 (100), 59 (90); IR (thin film): 2994, 1737, 988, 950 cm^{-1}.

4-*epi*-**12** was prepared by the similar procedure of **12**: (pale yellow oil, 73% from 3-*epi*-**6**); 99% de, t_R=13.6 min; $[\alpha]_D^{22.4}$ −23.5 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.37 (s, 3H), 1.71 (ddd, *J*=6.4, 9.6, 12.8 Hz, 1H), 1.80 (ddd, *J*=6.0, 9.2, 12.8 Hz, 1H), 2.45 (dd, *J*=5.2, 15.6 Hz, 1H), 2.55 (dd, *J*=8.4, 15.6 Hz, 1H), 3.46–3.54 (m, 2H), 3.67 (s, 3H), 3.98–4.05 (m, 1H), 4.24–4.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 24.6, 35.3, 40.3, 46.7, 51.6, 63.3, 66.8, 101.1, 171.1; MS (EI): *m*/*z* (%)=221 (100), 59 (80); HRMS (ESI-TOF) *m*/*z* calcd for $C_{10}H_{17}ClNaO_4$ ($M+Na^+$) 259.0707, found 259.0701; IR (thin film): 2990, 2955, 1740, 1440, 999 cm^{-1}.

4.7. General procedure for synthesis of 13

To a stirred solution of **12** (710 mg, 3 mmol), potassium acetate or sodium benzoate (15 mmol), and TBAB (966 mg, 3 mmol) in

20 mL DMF under argon atmosphere was heated to 100 °C for 24 h before added 150 mL petroleum ether. The organic phase was washed with water (3×20 mL) and brine (3×20 mL), then dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/PE, 1:15) to afford **13**. **13a**:[6c] (white solid, 453 mg, 58%), mp 48–49 °C (*n*-heptane), lit.[6c] mp 49–50 °C; The ee value of **13a** was upgraded to over 99% by recrystallization using *n*-heptane (recovered yield: 85%) and determined by HPLC analysis of its derivant **13b**, Daicel, Chiralpak OD-H column (25 cm×4.6 mm×5 μm), *n*-hexane/*i*-propanol=90/10, 0.3 mL/min, 254 nm, 30 °C, *t* (major)=21.0 min, *t* (minor)=26.5 min; $[\alpha]_D^{12.2}$ +16.2 (*c* 1.0, $CHCl_3$, 99% ee), lit.[6c] $[\alpha]_D$ +12 (*c* 0.92, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.19–1.28 (m, 1H), 1.36 (s, 3H), 1.44 (s, 3H), 1.57 (dt, *J*=2.0, 12.4 Hz, lH), 2.05 (s, 3H), 2.38 (dd, *J*=6.0, 15.6 Hz, 1H), 2.54 (dd, *J*=6.8, 15.6 Hz, 1H), 3.66 (s, 3H), 3.96–4.05 (m, 2H), 4.06–4.11 (m, 1H), 4.28–4.34 (m, 1H); MS (EI): *m*/*z* (%)=245 (70), 59 (100); IR (KBr): 3002, 2959, 1736, 1719, 1460, 941 cm^{-1}. **13b**:[7e] (white solid, 492 mg, 51%), mp 80–81 °C (*n*-heptane); The ee value of **13b** was upgraded from 95% to over 99% by recrystallization using *n*-heptane (recovered yield: 88%) and determined by HPLC analysis, Daicel, Chiralpak OD-H column (25 cm×4.6 mm×5 μm), *n*-hexane/*i*-propanol=90/10, 0.3 mL/min, 254 nm, 30 °C, *t* (major)=21.0 min, *t* (minor)=26.5 min; $[\alpha]_D^{12.8}$ +5.7 (*c* 1.0, $CHCl_3$, 99% ee), lit.[7e] $[\alpha]_D^{20}$ +2.4 (*c* 0.9, $CHCl_3$, 98% ee); ^1H NMR (400 MHz, $CDCl_3$) δ 1.32–1.40 (m, 1H), 1.40 (s, 3H), 1.48 (s, 3H), 1.68 (dt, *J*=2.0, 12.4 Hz, lH), 2.42 (dd, *J*=6.0, 15.6 Hz, 1H), 2.58 (dd, *J*=6.8, 15.6 Hz, 1H), 3.68 (s, 3H), 4.25–4.31 (m, 1H), 4.28 (s, 2H), 4.33–4.40 (m, 1H), 7.43 (t, *J*=7.6 Hz, 2H), 7.55 (t, *J*=7.6 Hz, 1H), 8.04 (d, *J*=7.6 Hz, 2H); MS (EI): *m*/*z* (%)=307 (30), 105 (100); IR (KBr): 2980, 1730, 1712, 991, 945 cm^{-1}.

4.8. Methyl 2-((4*R*,6*S*)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (14)

To a stirred solution of **13** (2 mmol) in 5 mL methanol and 2 mL water at 0 °C was added potassium carbonate (690 mg, 5 mmol). The reaction mixture was stirred at room temperature for 2 h before being quenched by the addition of NH_4Cl. The methanol was evaporated under reduced pressure and the aqueous layer was extracted with EtOAc (3×50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, then purified by column chromatography (silica gel, EtOAc/PE, 1:2) to afford **14** as colorless oil (yields: 85% from **13a**, 83% from **13b**); $[\alpha]_D^{15.2}$ +9.9 (*c* 2.0, $CHCl_3$), lit.[6c] $[\alpha]_D$ +9.7 (*c* 1.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.21–1.34 (m, 1H), 1.37 (s, 3H), 1.46 (s, 3H), 1.50 (dt, *J*=2.4, 12.4 Hz, lH), 2.19 (br s, 1H), 2.38 (dd, *J*=6.0, 15.6 Hz, 1H), 2.55 (dd, *J*=7.2, 15.6 Hz, 1H), 3.45–3.50 (m, 1H), 3.55–3.62 (m, 1H), 3.67 (s, 3H), 3.98–4.02 (m, 1H), 4.30–4.36 (m, 1H); MS (EI): *m*/*z* (%)=217 (1), 59 (100); IR (thin film): 3460, 2994, 1737, 1084, 992 cm^{-1}.

4.9. Methyl 2-((4*R*,6*S*)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl) acetate (4)

To a stirred solution of **14** (654 mg, 3 mmol), TEMPO (5 mg, 0.03 mmol), and $NaHCO_3$ (2.0 g, 24 mmol) in 15 mL CH_2Cl_2 and 15 mL water at 0 °C was added TCCA (852 mg, 90% purity, 3.3 mmol) in batches. The reaction mixture was stirred at 0 °C for 1 h before being extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford **4** as a pale yellow oil (473 mg, 73%) that was pure enough to be used in next step; $[\alpha]_D^{13.3}$ −15.9 (*c* 1.0, $CHCl_3$), lit.[7b] $[\alpha]_D$ −14.9 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.29–1.39 (m, 1H), 1.44 (s, 3H), 1.48 (s, 3H), 1.84 (dt, *J*=2.4, 12.8 Hz, lH), 2.42 (dd, *J*=6.0, 15.6 Hz, 1H), 2.57 (dd, *J*=6.8, 15.6 Hz, 1H), 3.68 (s, 3H), 4.28–4.38 (m, 2H), 9.57 (s, 1H); MS (EI): *m*/*z* (%)=201 (30), 59 (100); IR (thin film): 2994, 2952, 1736, 1440, 999 cm^{-1}.

4.10. Methyl 2-((4*R*,6*S*)-6-((*E*)-2-(4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methylmethylsulfonamido)pyrimidin-5-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (15)

To a stirred solution of **4** (298 mg, 1.38 mmol), **5** (849 mg, 1.25 mmol), and potassium carbonate (173 mg, 1.25 mmol) in 10 mL anhydrous DMSO under argon atmosphere was heated to 70 °C for 3 h before added 100 mL EtOAc. The organic phase was washed with water (3×20 mL) and brine (20 mL), then dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/PE, 1:12) to afford **15** (482 mg, 72%) as a white solid; mp 122–124 °C, lit.[15] mp 130–132 °C; $[\alpha]_D^{12.3}$ +5.6 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.09–1.21 (m, 1H), 1.26 (d, *J*=6.8 Hz, 3H), 1.27 (d, *J*=6.8 Hz, 3H), 1.40 (s, 3H), 1.49 (s, 3H), 1.53–1.58 (m, 1H), 2.38 (dd, *J*=6.4, 16.0 Hz, 1H), 2.57 (dd, *J*=6.4, 16.0 Hz, 1H), 3.37 (hept, *J*=6.8 Hz, 1H), 3.51 (s, 3H), 3.57 (s, 3H), 3.70 (s, 3H), 4.29–4.36 (m, 1H), 4.41–4.45 (m, 1H), 5.46 (dd, *J*=5.6, 16.0 Hz, 1H), 6.52 (d, *J*=16.0 Hz, 1H), 7.08 (t, *J*=8.4 Hz, 2H), 7.64 (dd, *J*=5.2, 8.0 Hz, 2H); MS (ESI): *m*/*z*=536 ($M+H^+$), 558 ($M+Na^+$); IR (KBr): 2996, 2951, 1739, 1600, 1442, 1152, 968, 848 cm^{-1}.

4.11. (3*R*,5*S*,*E*)-Methyl 7-(4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methylmethylsulfonamido)pyrimidin-5-yl)-3,5-dihydroxyhept-6-enoate (16)

To a stirred solution of **15** (268 mg, 0.5 mmol) in 5 mL acetonitrile at 40 °C was added hydrochloric acid (1.25 mL, 0.02 M, 0.025 mmol) dropwise. The reaction mixture was stirred at 40 °C for 8 h before being quenched by Et_3N and removed solvent under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/PE, 1:1) to afford **16**[16] (205 mg, 83%) as a colorless spumy solid; $[\alpha]_D^{13.5}$ −4.7 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, *J*=6.8 Hz, 6H), 1.35–1.60 (m, 2H), 2.43–2.51 (m, 2H), 3.36 (hept, *J*=6.8 Hz, 1H), 3.51 (s, 3H), 3.56 (s, 3H), 3.72 (s, 3H), 4.21 (m, 1H), 4.45 (m, 1H), 5.46 (dd, *J*=5.2, 16.0 Hz, 1H), 6.63 (d, *J*=16.0 Hz, 1H), 7.08 (t, *J*=8.4 Hz, 2H), 7.63 (dd, *J*=6.0, 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 21.6, 32.1, 33.1, 41.1, 41.8, 42.4, 51.9, 68.4, 71.9, 115.0 (d, J_{C-F}=21.5 Hz), 121.4, 122.7, 132.1 (d, J_{C-F}=8.3 Hz), 134.5 (d, J_{C-F}=3.2 Hz), 139.3, 157.2, 163.2 (d, J_{C-F}=248.2 Hz), 163.5, 172.9, 174.9; MS (ESI): *m*/*z*=496 ($M+H^+$), 518 ($M+Na^+$); IR (KBr): 3462, 2966, 2931, 2871, 1732, 1548, 1438, 1386, 1152, 964, 840, 795 cm^{-1}.

4.12. Rosuvastatin calcium (1)

To a stirred solution of **16** (149 mg, 0.3 mmol) in MeOH (2 mL) at 0 °C was added NaOH (0.36 mL, 1.0 M, 0.36 mmol), then reacted at 0 °C for 1 h before being added the solution of $CaCl_2$ (1.5 mL, 0.2 M, 0.3 mmol). The mixture was stirred at 20 °C for 0.5 h before filtrated the resulting white slurry, washed, and dried in vacuum to afford **1** (133 mg, 89%) as a white powder; mp 145–149 °C, lit.[17] mp 145–150 °C; $[\alpha]_D^{14.5}$ −7.3 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, *J*=6.0 Hz, 6H), 1.28–1.36 (m, 1H), 1.47–1.54 (m, 1H), 1.97–2.03 (m, 1H), 2.12–2.16 (m, 1H), 3.36–3.43 (m, 1H), 3.43 (s, 3H), 3.54 (s, 3H), 3.76 (m, 1H), 4.20 (m, 1H), 5.52 (dd, *J*=5.6, 16.0 Hz, 1H), 6.50 (d, *J*=16.0 Hz, 1H), 7.27 (t, *J*=8.4 Hz, 2H), 7.70 (dd, *J*=6.0, 8.0 Hz, 2H); MS (ESI): *m*/*z*=482 (acid, $M+H^+$), 504 (acid, $M+Na^+$); IR (KBr): 3376, 2973, 2931, 2875, 1604, 1548, 1442, 1073, 968, 844, 776 cm^{-1}.

Supplementary data

Copies of ^1H, ^{13}C NMR, HPLC, and GC–MS spectra for the compounds. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.06.077.

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