Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/c5ob02245b

Stereocontrolled synthesis of rosuvastatin calcium *via* iodine chloride-induced intramolecular cyclization†

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Received 31st October 2015,
Accepted 5th December 2015

DOI: 10.1039/c5ob02245b

www.rsc.org/obc

A novel, stereoselective approach towards rosuvastatin calcium from the known (*S*)-homoallylic alcohol has been developed. The synthesis is highlighted by a regio- and stereocontrolled ICl-induced intramolecular cyclization of chiral homoallylic carbonate to deliver the C_6-formyl statin side chain with a *syn*-1,3-diol moiety. An improved synthesis of the rosuvastatin pyrimidine core moiety is also included. Moreover, this methodology is useful in the asymmetric synthesis of structural variants of statins such as pitavastatin calcium and atorvastatin calcium and their related analogs.

Introduction

Rosuvastatin calcium (Crestor, **1**, Fig. 1) is one of the most important HMG-CoA reductase inhibitors.[1] The significant and sustained interest in the development of an efficient and scalable synthetic route to this important statin stems from its favorable efficiency, safe profiles, and long-term clinical benefits in reducing the risk for cardiovascular events as an antilipidemic agent.

A key structural subunit embedded in this statin molecule is a *syn*-1,3-diol, which itself presents a significant challenge to synthesis.[2] A number of procedures involving different strategies for the control of the two stereocenters of the rosuvastatin skeleton have been reported.[3] The industrial preparation method has mostly centered on the manipulation of the chiral diol C_6-side chain **3** by well-established diastereoselective Narasaka–Prasad reduction of chiral β-hydroxy-3-ketoester **2** starting from readily available (*S*)-epichlorohydrin[4] (Scheme 1). However, this process is limited by the use of hazardous triethylborane or diethylmethoxyborane/sodium borohydride as reduction systems under cryogenic conditions. Furthermore, the usage of expensive DIBAL-H for the synthesis of the pyrimidine core moiety **6** is also problematic in industry.[5] As a result, an alternative approach to build a new *syn*-diol C_6-side chain with the (4*S*,6*S*)-stereocenter and an improved synthetic

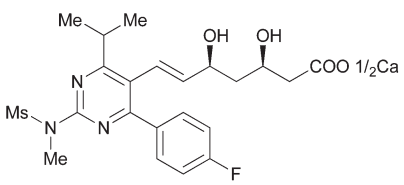
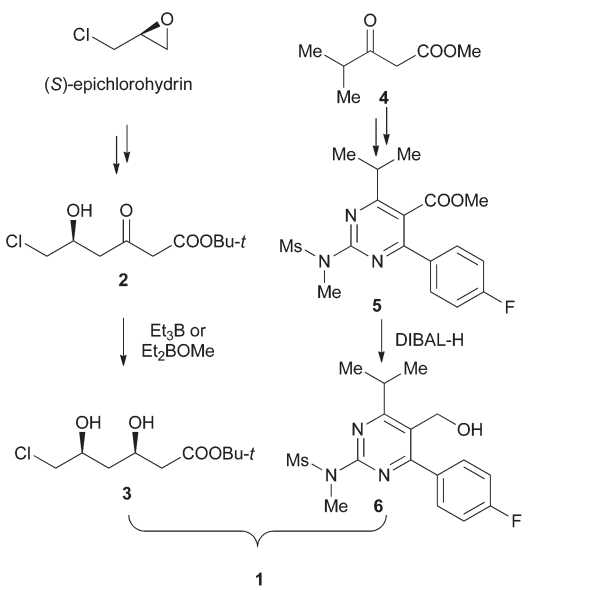


Fig. 1 Structure of rosuvastatin calcium (**1**).



Scheme 1 Industrial synthetic route of rosuvastatin calcium (**1**) starting from (*S*)-epichlorohydrin.

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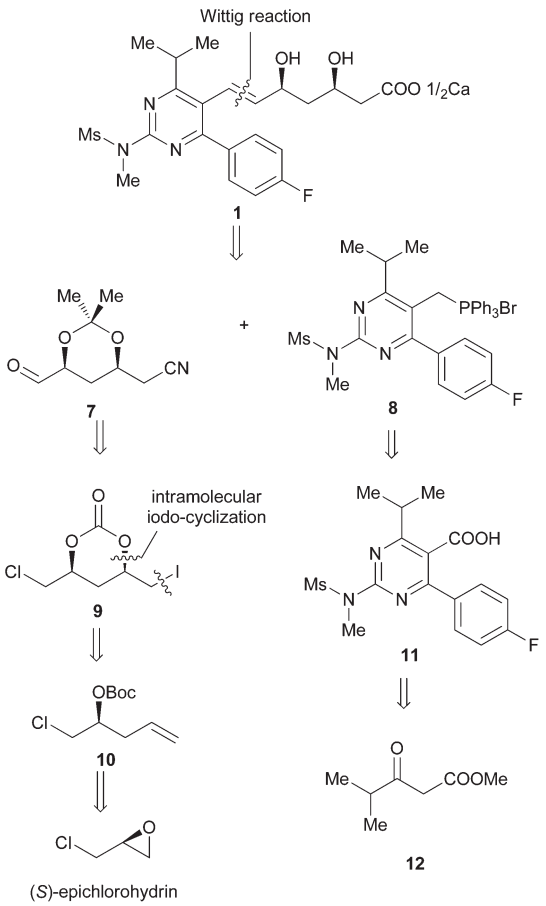
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c5ob02245b

procedure for the rosuvastatin pyrimidine core are urgently needed to improve upon the synthesis of rosuvastatin calcium (**1**). Herein, we report an efficient and stereoselective synthesis of **1** by utilizing the regio- and diastereoselective ICl-induced intramolecular iodo-cyclization reaction, thus continuing our work on the asymmetric synthesis of statins.[6]

Creating new stereocenters through substrate control remains an important strategy in asymmetric synthesis. We are interested in the development of an efficient method for the construction of *syn*-1,3-diol moieties in statins from stereodefined homoallylic carbonate using the Bartlett–Smith intramolecular iodo-cyclization reaction.[7] Our retrosynthetic route for **1** is depicted in Scheme 2. The side chain double bond was formed by the Wittig olefination of the C_6-formyl side chain **7** and triphenylphosphonium salt **8** with a pyrimidine core. The chiral side chain **7** was accessible to iodocarbonate **9** through routine transformations. The (4*S*,6*S*)-stereocenters in **7** were established by intramolecular iodocyclization of homoallylic *tert*-butyl carbonate **10** derived from commercially available (*S*)-epichlorohydrin. The phosphonium salt **8** was prepared *via* pyrimidine acid **11** by a modification of the ketone ester **12** using a known procedure[5b] reported by Matsushita.

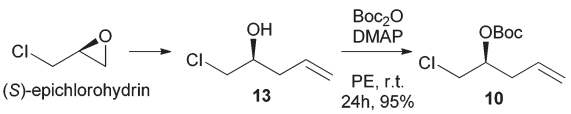


Scheme 2 Retrosynthetic analysis of rosuvastatin calcium (**1**).

Results and discussion

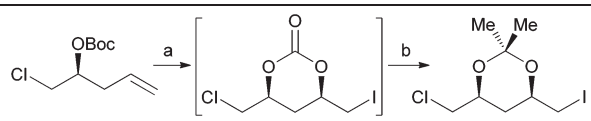
We began our synthesis towards **10** upon the treatment of homoallylic alcohol **13**, obtained by our previously reported process[6e] from (*S*)-epichlorohydrin, with di-*tert*-butyl dicarbonate (Boc_2O) in petroleum ether (60–90 °C) under 4-dimethylamino-pyridine (DMAP) catalysis (Scheme 3). The homoallylic *tert*-butyl carbonate **5** was obtained in 95% yield with >99% purity.

The next step in the sequence utilized the intramolecular iodocyclization methodology to construct the chiral 1,3-*syn* diol motif in rosuvastatin calcium. Initially, the reaction using 3 equiv. of IBr was conducted under the standard reaction conditions (MeCN, −40 °C) reported by Smith[7b] with slight modifications (Table 1). Analysis of the crude product of this reaction showed that the desired product **9** (by NMR) was an unstable component, which underwent acetonidation with acetone in the presence of *p*-TsOH.[8] Without purification, the acetonide **14** was obtained in 45% yield with excellent diastereoselectivity (dr > 300 : 1) (Table 1, entry 1). Our experimental results revealed that the diastereoselectivity of this reaction depended upon the reaction temperature. Increasing the reaction temperature from −40 °C to −20 °C and 0 °C resulted in dr > 200 : 1 and dr 98 : 2, respectively (Table 1, entries 2 and 3). It is worth noting that 1.5 equiv. of IBr was sufficient to obtain the desired product in excellent diastereoselectivity at the optimal



Scheme 3 Synthesis of homoallylic *tert*-butylcarbonate **10**.

Table 1 Intramolecular iodo-cyclization of homoallylic *tert*-butyl carbonate **10**



Entry	Reagent	Solvent	Temp. (°C)	Yield[c](%)	dr[d]
1	IBr (3 equiv.)	MeCN	−40	45	>300 : 1
2	IBr (3 equiv.)	MeCN	−20	37	>200 : 1
3	IBr (3 equiv.)	MeCN	0	41	98 : 2
4	IBr (1.5 equiv.)	MeCN	−40	47	>300 : 1
5	IBr (1.2 equiv.)	MeCN	−40	32	>300 : 1
6	IBr (1.5 equiv.)	CH_2Cl_2	−40	60	>300 : 1
7	IBr (1.5 equiv.)	*t*-BuOMe	−40	58	>300 : 1
8	I_2 (1.5 equiv.)	CH_2Cl_2	−40	47	>300 : 1
9	ICl (1.5 equiv.)	CH_2Cl_2	−40	63	>300 : 1
10	NIS (1.5 equiv.)	CH_2Cl_2	−40	22	>300 : 1

[a] Reaction conditions: **10** (1.1 g, 5 mmol), reagent (see table), solvent (20 mL), 1 h. [b] Reaction conditions: **9**, *p*-TsOH·H_2O (0.5 g, 2.5 mmol), acetone (10 mL), r.t. 48 h. [c] Isolated yield of **9** (two steps). [d] dr of **14** determined by GC-MS.

reaction temperature (−40 °C) in MeCN (Table 1, entry 4). However, when 1.2 equiv. of IBr was used, the yield was decreased to as low as 32% (Table 1, entry 5). Changing the solvent from MeCN to CH_2Cl_2 or t-BuOMe further improved the yield of this iodocyclization (Table 1, entries 6 and 7). In addition, screening of the other iodocyclization reagents (I_2, ICl, and NIS) found that ICl was the best reagent for this conversion, giving 63% yield of **14** (Table 1, entry 9).

This stereoselective iodocyclization could be attributed to the thermo-favoured *syn*-intermediate with all substitutes on the equatorial-bond rather than the axial bond.[7a,c] (Fig. 2).

The treatment of **14** with NaCN in DMSO under mild conditions afforded the corresponding nitrile **15** in 91% yield. Nitrile **15** was subjected to S_{N2} nucleophilic displacement by treatment with sodium benzoate in DMSO at 160 °C to furnish benzoate **16** in 83% yield. The selective alkaline-hydrolysis of **16** under mild conditions (K_2CO_3, MeOH, r.t. 1 h) provided alcohol **17** in 93% yield. Oxidation of **17** with TCCA at 0 °C under TEMPO[9] catalysis afforded the C_6-formyl side chain **7** in 87% yield (Scheme 4).

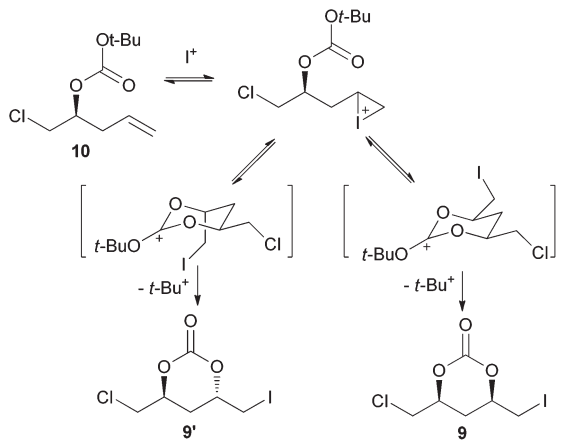
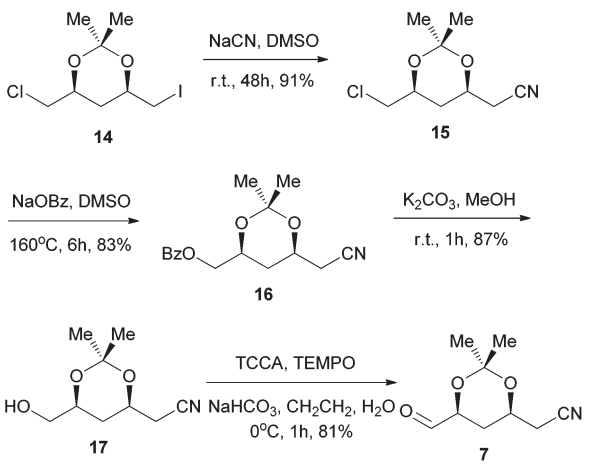


Fig. 2 Proposed mechanism for iodo-cyclization reaction of **10**.

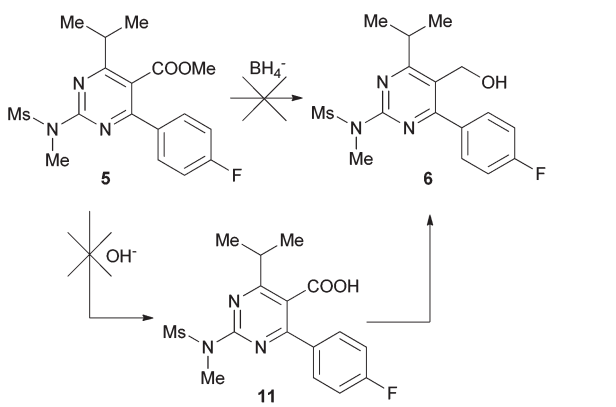


Scheme 4 Synthesis of C_6-formyl side chain **7**.

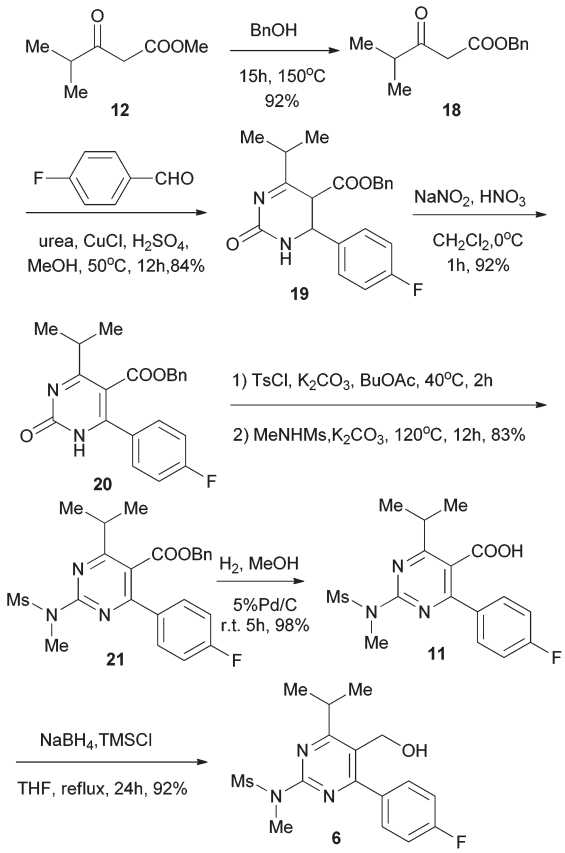
The original industrial synthetic approach developed by Koike[5b] for this pyrimidine core **6** involved the use of expensive DIBAL-H to perform the reduction of pyrimidine ester **5** to **6**. Hence, it is strongly desirable to eliminate it from the productive process. All attempts to convert **5** into **6** using various borohydrides did not produce the desired product **6** upon workup. The attempted two-step synthesis (alkaline hydrolysis of the ester group in **5** followed by reduction with borohydride/Lewis acid) for **6** according to the procedure of Lin and coworkers[10] (Scheme 5) was also unsuccessful. A difficulty of this method was the inability to remove the ester group of **5**.

Subsequently, an improved synthesis of **6** was undertaken (Scheme 6). Conversion of the β-keto methyl ester **12** into β-keto benzyl ester **18** [11] was achieved with 92% yield by simply performing the reaction with benzyl alcohol at 150 °C and removing MeOH under distillation. The dihydropyrimidone **19** was obtained in 84% yield *via* the Biginelli reaction of **18**, 4-fluorobenzaldehyde, and urea in the presence of CuCl and conc. H_2SO_4 in MeOH. The exposure of **19** to 62% HNO_3 in CH_2Cl_2 at 0 °C afforded pyrimidine ester **20** in 92% yield. The treatment of **20** with tosyl chloride in BuOAc in the presence of anhydrous K_2CO_3 under mild conditions followed by reaction with *N*-methylmethanesulfonamide at 120 °C resulted in the formation of the desired sulfonamide ester **21** in 83% yield. Palladium-promoted debenzylation of **21** in MeOH at room temperature afforded the desired pyrimidine acid **11** in an almost quantitative yield.

Our initial reduction of **11** was carried out using $NaBH_4$ in THF at reflux temperature for 24 h. Unfortunately, we were unable to reduce this carboxyl group in **11** (Table 2, entry 1). However, this reaction was conducted using a $NaBH_4/AlCl_3$ reducing system that resulted in 76% conversion of **11** (Table 2, entry 2). Increasing the reaction time from 24 h to 72 h did not improve the outcome of the reaction. Other additives such as $ZnCl_2$, LiCl, LiBr, I_2, and H_2SO_4 did not generate any product (Table 2, entries 3–7). Surprisingly, the use of TMSCl[12] as an additive was found to be very efficient for reduction of **6** (100% conversion). The desired pyrimidine alcohol **17** was obtained with 92% isolated yield in the presence of glass beads[13] (Table 2, entry 8).

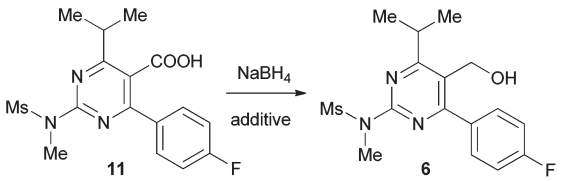


Scheme 5 Efforts for synthesis of **6** from **5** without DIBAL-H.



Scheme 6 Synthesis of pyrimidine alcohol **6**.

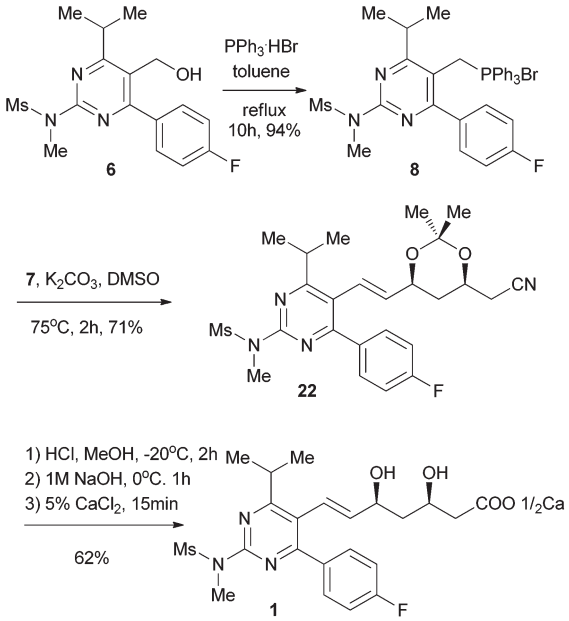
Table 2 Reduction of acid **11** with $NaBH_4$ [a]



Entry	Reagent	Conversion[b]	Yield[c](%)
1	—	—	—
2	$AlCl_3$	76%	61%
3	LiCl	Trace	—
4	LiBr	Trace	—
5	$ZnCl_2$	Trace	—
6	I_2	Complex	—
7	H_2SO_4	—	—
8	TMSCl	100%	92%

[a] Reaction conditions: **11** (367 mg, 1 mmol), $NaBH_4$ (80 mg, 2 mmol), additive (2 mmol), THF (10 mL), N_2 atmosphere, reflux, 24 h. [b] Determined by HPLC. [c] Isolated yield.

Triphenylphosphonium salt **8** was easily prepared by a one-step sequence with 94% yield by refluxing **6** with triphenylphosphine hydrobromide in toluene. With both **7** and **8** synthesized, the Wittig reaction was carried out by treating **7** and **8** with K_2CO_3 at 75 °C in DMSO for 2 h to form crude **22** with $E/Z > 30:1$ (by NMR), which was purified by chromatography to afford pure (*E*)-**22** in 71% yield. Hydrolysis of the nitrile and acetonide groups of **22** by HCl and NaOH and treatment with $CaCl_2$ in a one-pot procedure gave the final product rosuvastatin calcium **1** in 62% yield (Scheme 7).



Scheme 7 Synthesis of rosuvastatin calcium **1**.

Experimental

All reagents and solvents were purchased from commercial sources and used without further purification. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker Avance 400 spectrometer using TMS or $CDCl_3$ as an internal standard, IR spectra were recorded on a Nicolet iS5 FT-IR spectrometer, and optical rotations were measured by using a JASCO P1020 digital polarimeter. EI-MS were recorded on an Agilent 6890N/5975 spectrometer and ESI-MS were recorded on a Waters Micromass Quattro Micro spectrometer. HRMS were recorded on a Bruker micrOTOF spectrometer (ESI) or Waters Micromass GCT Premier (EI).

(*S*)-*tert*-Butyl (1-chloropent-4-en-2-yl) carbonate(10)

To a stirred solution of Boc_2O (21.8 g, 0.1 mol) and DMAP (0.56 g, 5 mmol) in petroleum ether (200 mL, bp 60–90 °C) was added (*S*)-1-chloropent-4-en-2-ol[6e] (12 g, 0.1 mol) dropwise at r. t. within 30 min, stirring was continued for 24 h. The reaction mixture was filtered and washed with water, the organic phase was dried (Na_2SO_4) and concentrated to dryness to afford **10** (21.0 g, 98%) as brown oil, which was used without further purification. ^1H NMR (400 MHz, CDCl3) δ = 5.77 (ddt, J = 17.2, 10.1, 7.1 Hz, 1H), 5.23–5.10 (m, 2H), 4.93–4.79 (m, 1H),

3.65 (dd, J = 11.7, 4.7 Hz, 1H), 3.60 (dd, J = 11.7, 5.6 Hz, 1H), 2.57–2.32 (m, 2H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.0, 132.2, 119.2, 82.8, 75.1, 44.94, 36.1, 27.9. MS (EI): m/z = 164 [M-*t*-Bu + H]$^+$. HRMS (EI): m/z [M-*t*-Bu + H]$^+$ calcd for $C_6H_9ClO_3$: 164.0240; found: 164.0243.

(4*S*,6*R*)-4-(Chloromethyl)-6-(iodomethyl)-2,2-dimethyl-1,3-dioxane (14)

To a stirred solution of **10** (2.2 g, 10 mmol) in CH_2Cl_2 (40 mL) at −40 °C was added ICl (2.4 g, 15 mmol). The reaction mixture was stirred at −40 °C for 1 h and quenched with sat. aq. $NaHCO_3$ (20 mL) and 10% aq. Na_2SO_3 (20 mL), the organic phase was dried (Na_2SO_4) and evaporated to dryness *in vacuo* below 20 °C. The crude **5** should be used in the next step immediately due to its instability. Acetone (20 mL) and *p*-TsOH (0.95 g, 5 mmol) were added to crude **5** and stirred at room temperature for 48 h to protect from light. The reaction mixture was concentrated under vacuum and the residue was dissolved in petroleum ether (100 mL, bp 60–90 °C), washed with sat. aq. $NaHCO_3$ (20 mL) and 10% aq. Na_2SO_3 (20 mL), dried (Na_2SO_4) and evaporated to dryness *in vacuo* to afford **14** (1.63 g, 63%) as orange oil. An analytical sample was achieved by silica gel column chromatography eluting with petroleum ether. $[\alpha]_D^{18}$ = +0.3 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.05 (m, 1H), 3.90 (m, 1H), 3.53 (dd, J = 11.2, 5.6 Hz, 1H), 3.42 (dd, J = 11.2, 5.6 Hz, 1H), 3.18 (dd, J = 10, 5.6 Hz, 1H), 3.12 (dd, J = 10, 6 Hz, 1H), 1.99 (dt, J = 12.8, 2.4 Hz, 1H), 1.57 (s, 1H), 1.44 (d, J = 4.4 Hz, 6H), 1.18 (dd, J = 24, 11.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 99.9, 69.2, 68.9, 46.9, 34.3, 29.7, 19.9, 8.9. MS (EI): m/z = 289 [M − Me]$^+$. HRMS (EI): m/z [M]$^+$ calcd for $C_8H_{14}ClIO_2$ 303.9727; found: 303.9733.

2-((4*S*,6*S*)-6-(Chloromethyl)-2,2-dimethyl-1,3-dioxan-4-yl) acetonitrile (15)

14 (1.52 g, 5 mmol), NaCN (228 mg, 6 mmol) and DMSO (10 mL) were stirred at room temperature for 48 h. The reaction mixture was quenched with water (20 mL) and extracted with CH_2Cl_2 (20 mL × 4). The combination organic phase was washed with brine and dried with Na_2SO_4, the solvent was removed under vacuum to afford **15** (0.92 g, 91%) as yellow oil. $[\alpha]_D^{15}$ = +7.2 (c 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.15 (m, 1H), 4.07 (m, 1H), 3.54 (dd, J = 11.2, 5.4 Hz, 1H), 3.41 (dd, J = 11.2, 6.4 Hz, 1H), 2.61–2.48 (m, 2H), 1.88 (dt, J = 12.8, 2.4 Hz, 1H), 1.44 (d, J = 16 Hz, 6H), 1.34 (dd, J = 24, 11.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.7, 99.8, 68.8, 64.9, 33.4, 29.6, 24.9, 19.7. MS (EI): m/z = 188 [M − Me]$^+$. HRMS (EI): m/z [M − H]$^+$ calcd for $C_9H_{13}ClNO_2$ 202.0635; found: 202.0631.

((4*S*,6*S*)-6-(Cyanomethyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl benzoate (16)

15 (1.02 g, 5 mmol), NaOBz (1.44 g, 10 mmol) and DMSO (10 mL) were stirred at 160 °C under a N_2 atmosphere for 6 h. The reaction mixture was then cooled to room temperature and quenched with water (20 mL), extracted with EtOAc (20 mL × 3). The combination organic phase was washed with brine and dried with Na_2SO_4, the solvent was removed under vacuum. The residue was purified by silica gel column chromatography (petroleum ether : EtOAc = 2 : 1) to afford **16** (1.34 g, 83%) as yellow oil. $[\alpha]_D^{17}$ = +5.2 (c 1.4, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, J = 7.6 Hz, 2H), 7.57 (t, J = 7.2 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 4.38–4.14 (m, 4H), 2.63–2.46 (m, 2H), 1.77 (d, J = 12.4 Hz, 1H), 1.48 (s, 3H), 1.44 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4, 133.2, 129.9, 129.7, 128.5, 116.7, 99.6, 67.0, 66.9, 64.9, 32.5, 29.7, 25.0, 19.6. MS (EI): m/z = 274 [M − Me]$^+$. HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{16}H_{19}NO_4Na$ 312.1206; found: 312.1209.

2-((4*S*,6*S*)-6-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxan-4-yl) acetonitrile (17)

To a stirred solution of **16** (3.20 g, 11 mmol) in MeOH (25 mL) was added K_2CO_3 (1.50 g, 11 mmol), the stirring was continued for 1 h and then sat. aq. NH_4Cl (5 mL) was added, the reaction mixture was washed with petroleum ether (50 mL × 3) to remove MeOBz. The methanolic phase was concentrated to remove MeOH *in vacuo*. The residue was dissolved in EtOAc and washed with brine, dried (Na_2SO_4) and evaporated to dryness *in vacuo* to afford **17** (1.82 g, 87%) as yellow oil. $[\alpha]_D^{17}$ = −0.5 (c 0.7, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.12–4.22 (m, 1H), 4.06–3.97 (m, 1H), 3.64 (dd, J = 11.6, 3.2 Hz, 1H), 3.53 (dd, J = 11.6, 6.0 Hz, 1H), 2.60–2.44 (m, 2H), 1.65–1.55 (m, 1H), 1.47 (s, 3H), 1.46–1.38 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.8, 99.5, 69.1, 65.7, 64.8, 31.4, 29.7, 25.0, 19.8. MS (EI): m/z = 170 [M − Me]$^+$. HRMS (ESI): m/z [M − Me]$^+$ calcd for $C_8H_{12}NO_3$ 170.0817; found: 170.0816.

2-((4*S*,6*S*)-6-Formyl-2,2-dimethyl-1,3-dioxan-4-yl)acetonitrile (7)

To a stirred solution of **17** (1.60 g, 8.6 mmol), $NaHCO_3$ (5 g, 60 mmol) and TEMPO (30 mg) in CH_2Cl_2 (20 mL) and water (20 mL) was added TCCA (2.10 g, 9 mmol) in portions at 0 °C, stirring was continued for 1 h. After completion of the reaction, the mixture was extracted with CH_2Cl_2 (50 mL × 3), washed with 10% aq. Na_2SO_3 and $NaHCO_3$ successively, dried (Na_2SO_4) and evaporated to dryness *in vacuo* to afford crude **7** (1.29 g, 81%) as colorless oil. This unstable material should be used immediately in the next step. MS (EI): m/z = 183 [M]$^+$.

Benzyl 4-methyl-3-oxopentanoate (18)

Methyl 4-methyl-3-oxopentanoate (14.4 g, 0.1 mol) and BnOH (21.6 g, 0.2 mol) were heated at 150 °C with continuous removal of MeOH until no MeOH was distilled out (*ca*. 5 h). The reaction mixture was distilled under vacuum and bp 143–144 °C per 1 kPa fraction was collected to afford **18** (15.0 g, 68%) as colorless oil. The reaction was repeated with a front cut fraction containing methyl 4-methyl-3-oxopentanoate and BnOH resulted in a second crop of **18** (5.2 g, 24%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (m, 5H), 5.17 (s, 2H), 3.55 (s, 2H), 2.70 (hept, J = 7.2 Hz, 1H), 1.12 (d, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.4, 167.3, 135.4, 128.6, 128.4, 128.3, 67.1, 47.1, 41.3, 17.9.MS (EI): m/z = 220 [M]$^+$.

Benzyl 6-(4-fluorophenyl)-4-isopropyl-2-oxo-1,2,5,6-tetrahydropyrimidine-5-carboxylate (19)

18 (11.0 g, 50 mmol), 4-fluorobenzaldehyde (6.2 g, 50 mmol), urea (5.0 g, 83 mmol), CuCl (50 mg), conc. H_2SO_4 (0.5 mL) and MeOH (50 mL) were stirred at 50 °C for 12 h. The solvent was removed under vacuum and the residue was allowed to stand at 0 °C for crystallization. The crystal was filtered and washed with water, dried *in vacuo* to afford **19** (15.5 g, 84%) as a colorless crystalline solid. mp 135–137 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.28 (m, 3H), 7.21–7.07 (m, 4H), 6.93 (t, J = 8.6 Hz, 3H), 5.65 (m, 1H), 5.37 (d, J = 2.7 Hz, 1H), 5.03 (dd, J = 27, 12 Hz, 2H), 4.21 (hept, J = 6.8 Hz, 1H), 1.18 (dd, J = 10.8, 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 163.6, 155.0, 154.9, 152.5, 147.7, 139.5, 135.8, 128.5, 128.4, 128.3, 128.2, 128.1, 115.8, 115.5, 99.6, 66.1, 55.2, 27.5, 19.9, 19.7. MS (EI): m/z = 368 $[M]^+$. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{21}H_{22}FN_2O_3$ 369.1609; found: 369.1601.

Benzyl 4-(4-fluorophenyl)-2-hydroxy-6-isopropylpyrimidine-5-carboxylate (20)

To a stirred solution of $NaNO_2$ (70 mg) in 62% HNO_3 (20 ml) was added a solution of **19** (3.68 g, 10 mmol) in CH_2Cl_2 (10 mL) dropwise at 0 °C. After the completion of addition, the stirring was continued for 1 h and then quenched with water (50 mL) and CH_2Cl_2 (50 mL), the mixture was adjusted to pH 6–8 with 50% aq. NaOH. The organic phase was separated, dried (Na_2SO_4) and evaporated to dryness to afford **20** (3.37 g, 92%) as an almost white solid. mp 146–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.82 (br, 1H) 7.53 (dd, J = 8.4, 5.2 Hz, 2H) 7.26–7.35(m, 3H) 7.03 (d, J = 6.8 Hz, 2H) 6.97 (t, J = 8.4 Hz, 2H) 5.06 (s, 2H) 3.22 (hept, J = 7.2 Hz, 1H) 1.39 (d, J = 6.8, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.4, 165.6, 163.2, 158.3, 134.3, 130.3, 130.2, 128.83, 128.8, 128.7, 115.9, 115.7, 110.6, 67.9, 20.7. MS (ESI): m/z = 367 $[M + H]^+$. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{21}H_{20}FN_2O_3$ 367.1452; found: 367.1467.

Benzyl 4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methylmethylsulfonamido)pyrimidine-5-carboxylate (21)

To a stirred mixture of **20** (3.66 g, 10 mmol) and K_2CO_3 (1.8 g, 13 mmol) in BuOAc (40 mL) was added TsCl (1.9 g, 10 mmol) at 40 °C, stirring was continued for 2 h and cooled to room temperature. K_2CO_3 (2.07 g, 15 mmol) and *N*-methyl-methanesulfonamide (1.64 g, 15 mmol) were added and stirred at 120 °C for 12 h. Then the reaction mixture was cooled to room temperature, washed with water, dried with Na_2SO_4, the solvent was removed under vacuum and the residue was recrystallized from MeOH to afford **21** (3.79 g, 83%) as a colorless crystalline solid. mp 113–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (dd J = 8.8, 5.6 Hz, 2H), 7.27–7.35 (m, 3H), 7.10 (d J = 6.4 Hz, 2H), 6.98 (t J = 8.4 Hz, 2H), 5.16 (s, 2H), 3.58 (s, 3H), 3.50 (s, 3H), 3.20 (hept J = 6.8 Hz, 1H), 1.28 (d J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.8, 167.9, 163.3, 158.5, 134.4, 133.6, 130.5, 130.4, 128.8, 128.7, 128.6, 118.8, 115.8, 115.6, 67.8, 42.5, 33.3, 33.1, 21.8. MS (ESI): m/z = 458 $[M + H]^+$. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{25}FN_3O_4S$ 458.1544; found: 458.1540.

4-(4-Fluorophenyl)-6-isopropyl-2-(*N*-methylmethylsulfonamido)pyrimidine-5-carboxylic acide (11)

21 (2.28 g, 5 mmol) and 5%Pd/C (20 mg) were suspended in MeOH (50 mL) and stirred under a H_2 atmosphere at r.t. for 5 h. The reaction mixture was filtered and evaporated to dryness to afford **11** (1.80 g, 98%) as a white crystalline solid. mp 208 °C (*dec.*). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.80 (br, 1H) 7.79 (dd, J = 8.8, 5.6 Hz, 2H) 7.38 (t, J = 8.8 Hz, 2H) 3.55 (s, 3H) 3.47 (s, 3H) 3.23 (m, 1H) 1.25 (d, J = 6.8, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.5, 169.5, 165.2, 162.7, 1.61.9, 158.4, 134.1, 131.2, 131.1, 120.9, 116.4, 116.2, 42.1, 33.7, 33.2, 22.0. MS (ESI): m/z = 366 $[M - H]^-$. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{16}H_{19}FN_3O_4S$ 368.1075; found: 368.1076.

***N*-(4-(4-Fluorophenyl)-5-(hydroxymethyl)-6-isopropylpyrimidin-2-yl)-*N*-methylmethanesulfonamide (6)**

To a stirred suspension of $NaBH_4$ (0.38 g, 10 mmol) in anhydrous THF (40 mL) and glass beads (2–3 mm, 10 mL) was added TMSCl (2.1 g, 20 mmol) at r.t. and heated to reflux for 3 h, then **11** (1.83 g, 5 mmol) was added and refluxed for an additional 24 h. The reaction mixture was cooled to 0 °C and quenched with sat. aq. NH_4Cl, extracted with CH_2Cl_2(20 mL × 3), washed with 10% aq. Na_2CO_3, dried (Na_2SO_4) and evaporated to dryness under vacuum to afford **6** (1.62 g, 92%) as a white crystalline solid. mp 137–139 °C (Lit.[14] mp 131.5–133.6 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.82 (m, 2H), 7.15 (t, J = 8.4 Hz, 2H), 4.63 (s, 2H), 3.56 (s, 3H), 3.47–3.54 (m, 4H), 1.84 (br, 1H), 1.33(d, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.8, 166.3, 165.0, 162.5, 158.0, 134.0, 131.6, 131.5, 120.6, 115.5, 115.3, 57.7, 42.5, 33.1, 31.6, 22.3. MS (ESI): m/z = 354 $[M + H]^+$.

***N*-(5-((Bromotriphenylphosphoranyl)methyl)-4-(4-fluoro-phenyl)-6-isopropylpyrimidin-2-yl)-*N*-methylmethanesulfon-amide (8)**

6 (1.77 g, 5 mmol) and triphenylphosphine hydrobromide (1.72 g, 5 mmol) in toluene (40 mL) were stirred under reflux for 10 h. The reaction was cooled to r.t. with a white solid precipitated. It was filtered and dried to afford **8** (3.18 g, 94%) as a white solid. mp 232–236 °C (Lit.[14] mp 238–242 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.87(m, 3H), 7.63 (m, 6H), 7.27(m, 8H), 7.13(t, J = 8.4 Hz, 2H), 5.08 (d, J = 13.6 Hz, 2H), 3.49 (s, 3H), 3.40 (s, 4H), 2.86(m, 1H), 0.79(d, J = 4.4 Hz, 6H). MS (ESI): m/z = 598 $[M - Br]^+$.

***N*-(5-((*E*)-2-((4*S*,6*S*)-6-(Cyanomethyl)-2,2-dimethyl-1,3-dioxan-4-yl)vinyl)-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-*N*-methylmethanesulfonamide (22)**

7 (0.92 g, 5 mmol), **8** (3.39 g, 5 mmol), K_2CO_3 (1.38 g, 10 mmol) and DMSO (25 mL) were stirred at 75 °C under a N_2 atmosphere for 3 h. The reaction mixture was quenched with water (100 mL) and extracted with CH_2Cl_2 (50 mL × 3). The combined organic phase was washed with brine and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue

was purified by silica gel column chromatography (petroleum ether : EtOAc = 5 : 1) to afford **22** (1.78 g, 71%) as foam like solid. mp 46–53 °C. $[\alpha]_D^{16}$ = +5.8 (*c* 0.5, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.67 (dd, *J* = 8.4, 5.2 Hz, 2H), 7.12 (t, *J* = 8.4 Hz, 2H), 6.57 (d, *J* = 16.4 Hz, 1H), 5.49 (dd, *J* = 16.0, 5.2 Hz, 1H), 4.50–4.40 (m, 1H), 4.23–4.10 (m, 1H), 3.59 (s, 3H), 3.54 (s, 3H), 3.38 (hept, *J* = 6.8 Hz, 1H), 2.63–2.47 (m, 2H), 1.68–1.60 (m, 1H), 1.48 (d, *J* = 19.2 Hz, 6H), 1.35–1.20 (m, 7H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.9, 164.6, 163.6, 162.1, 157.4, 136.6, 134.4, 134.4, 132.3, 132.2, 123.9, 121.0, 116.7, 115.2, 114.9, 99.5, 68.7, 64.9, 42.4, 35.4, 33.1, 32.0, 29.8, 24.9, 21.8, 21.7, 19.7. MS (ESI): *m*/*z* = 503 $[M + H]^+$. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{32}FN_4O_4S$ 503.2123; found: 503.2121.

Rosuvastatin calcium (1)

To a stirred saturated methanolic solution of HCl (10 mL) was added **22** (1.01 mg, 2 mmol) at −20 °C, the stirring was continued for 2 h. The reaction mixture was adjusted to pH 6–8 by using sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2 (50 mL × 3). The combined organic phase was concentrated under vacuum, to the residue was added MeOH (10 mL) and 1 M aq. NaOH (2.5 mL) and stirred at 0 °C for 1 h, then MeOH was removed *in vacuo*, 5% aq. $CaCl_2$ (10 mL) was added dropwise and stirred for 15 min, the precipitate was filtered and dried under vacuum to afford **1** (0.62 g, 62%) as white powder. mp 140–144 °C. $[\alpha]_D^{20}$ = +15.1 (*c* 0.3, 50%MeOH) (Lit.[15] $[\alpha]_D^{20}$ = +14.8 (*c* 1, 50% MeOH)). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.82–7.59 (m, 2H), 7.26 (t, *J* = 8.8 Hz, 2H), 6.49 (d, *J* = 16.0 Hz, 1H), 5.51 (dd, *J* = 16.0, 5.2 Hz, 1H), 4.26–4.10 (m, 1H), 3.74 (s, 1H), 3.53 (s, 3H), 3.41 (m, 4H), 2.20–2.10 (m, 1H), 2.05–1.96 (m, 1H), 1.55–1.45 (m, 1H), 1.26–1.35 (m, 1H), 1.19 (d, *J* = 6.4 Hz, 6H).

Conclusions

In summary, we have developed an efficient synthesis for rosuvastatin calcium by a stereocontrolled intramolecular iodocyclization strategy starting from commercially available (*S*)-epichlorohydrin in addition to an improved synthesis of the pyrimidine core intermediate. This synthesis not only provides a practical approach to rosuvastatin calcium but is also useful for the synthesis of other statins and analogs.

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