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Diastereoselective synthesis of pitavastatin calcium *via* bismuth-catalyzed two-component hemiacetal/oxa-Michael addition reaction†

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An efficient and concise asymmetric synthesis of pitavastatin calcium (**1**) starting from commercially available (*S*)-epichlorohydrin is described. A convergent $C_1 + C_6$ route allowed for the assembly of the pitavastatin C_7 side chain *via* a Wittig reaction between phosphonium salt **2** and the enantiomerically pure C_6-formyl side chain **3**. The 1,3-*syn*-diol acetal motif in **3** was established with excellent stereo control by a diastereoselective bismuth-promoted two-component hemiacetal/oxa-Michael addition reaction of (*S*)-α,β-unsaturated ketone **4** with acetaldehyde.

Introduction

Over recent decades, the asymmetric synthesis of pitavastatin calcium (**1**, Fig. 1), an HMG-CoA reductase inhibitor, has aroused continuing interest.[1] As a result of its proven benefits in both primary and secondary prevention of cardiovascular events, many new synthetic strategies for the preparation of **1** continue to be developed.[2] However, to the best of our knowledge, none of the known synthetic approaches towards this statin appear to have a commercial advantage over the currently used process using a chiral C_6-formyl side chain with a *syn*-1,3-diol subunit developed by Sagami Chemical Research Center in 1993.[3] Although this synthesis continues to provide **1** on an industrial scale, there are still two principal limitations that involve the diethylmethoxyborane-mediated diastereoselective reduction for setting the (3*R*)-stereochemistry, and using a large excess of highly toxic cyanide.[4] As a consequence, enhanced efficiency in its synthesis remains a challenge. We took on the challenge and herein report our success in the development of a concise and efficient asymmetric synthesis of **1**.

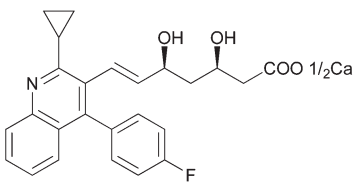

Fig. 1 Structure of pitavastatin calcium (**1**).

Results and discussion

The highly diastereoselective bismuth-mediated two-component hemiacetal/oxa-Michael addition of chiral δ-hydroxyl-α,β-unsaturated carbonyl compounds with alkyl aldehydes has recently been reported.[5] This reaction provides direct and convenient access to *syn*-1,3-diol acetals rich in synthetic potential, as exemplified by Evans' total synthesis of natural polyene macrolide RK-397. Applying this strategy to **1** leads to a retrosynthetic route as illustrated in Fig. 2.

The essential carbon–carbon double bond forming step would be achieved by Wittig olefination of phosphonium salt **2** with (3*R*,5*S*)-C_6-formyl derivative **3** for the assembly of the C_7-side chain skeleton of **1**. (3*R*,5*S*)-Aldehyde **3** should be attainable from (*S*)-α,β-unsaturated ketone **4** using a diastereoselective bismuth-mediated two-component hemi-acetal/oxa-Michael addition reaction. (*S*)-Epichlorohydrin (**5**) was chosen as a readily available starting material for the synthesis of **4**. The desired quinoline phosphonium salt **2** could be provided *via* Friedlander condensation of 2-amino-4′-fluorobenzophenone (**7**) with cyclopropyl α,β-unsaturated ketone **6**, derived from 1-cyclopropylethanone (**8**).

The synthesis of (3*R*,5*S*)-C_6-formyl side chain **3** began with commercially available (*S*)-(−)-epichlorohydrin (**5**) (Scheme 1). Following our previously reported procedures,[6] (*S*)-homoallylic alcohol **9** was prepared in 92% yield by treatment of **5** with

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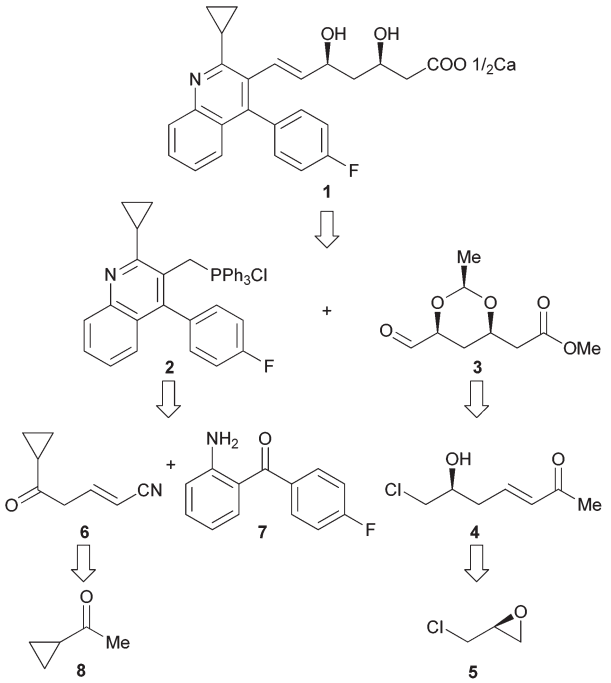
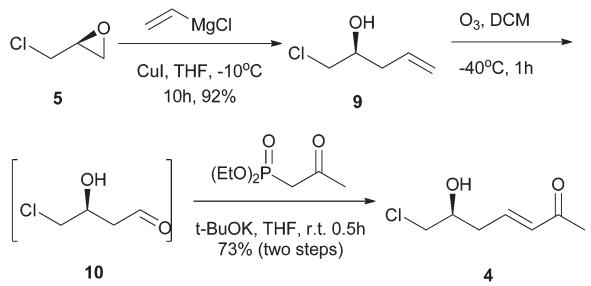


Fig. 2 Retrosynthesis of pitavastatin calcium (**1**).

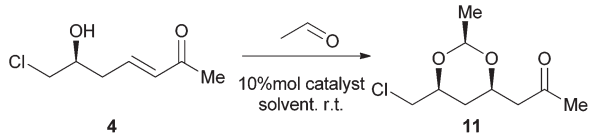


Scheme 1 Synthesis of (*S*)-α,β-unsaturated ketone **4**.

vinylmagnesium chloride under CuI catalysis in anhydrous THF. The carbon elongation was completed by Horner–Wadsworth–Emmons olefination of aldehyde **10**, obtained by ozonolysis of **9** under standard conditions (DCM, −40 °C, 1 h), with diethyl(2-oxopropyl)phosphonate. The (*S*)-α,β-unsaturated ketone **4** was obtained as a single *E* isomer with an overall yield of 73% from **9**.

The stereocenter at C_5 in this statin side chain was installed by the bismuth-mediated two-component hemiacetal/oxa-Michael addition[5] of **4** and acetaldehyde (Table 1). The diastereoselectivity of the reaction was determined by analysis of the crude product **11**. Purification by chromatography provided a 91% yield of pure **11** with a dr of >99 : 1 when using 10% mol $Bi(NO_3)_3$ as a catalyst in CH_2Cl_2 (entry 1). We then examined the effects of various solvents (EtOAc, MeCN and THF), and a dramatic decrease in the diastereoselectivity was observed in all cases (entries 2–4). Next, we investigated the

Table 1 Bismuth-catalyzed hemiacetal/oxa-Michael addition reaction of **4**[a]



Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	dr[c]
1	$Bi(NO_3)_3$	DCM	48	91	99 : 1
2	$Bi(NO_3)_3$	EtOAc	120	86	5 : 1
3	$Bi(NO_3)_3$	MeCN	48	90	50 : 1
4	$Bi(NO_3)_3$	THF	120	73	3 : 1
5	$BiCl_3$	DCM	120	83	4 : 1
6	BiI_3	DCM	120	61	6 : 1
7	$Bi_2(SO_4)_3$	DCM	120	55	3 : 1
8	$Bi(OTf)_3$	DCM	120	78	30 : 1

[a] All reactions were performed at r.t. on a 1 mmol scale. [b] Yield of isolated product. [c] Determined by GC analysis of the crude product.

same reaction using other bismuth salt catalysts including $BiCl_3$, BiI_3, Bi_2SO_4 and $Bi(OTf)_3$, and observed that all these catalysts gave a moderate yield of **11** and poor diastereoselectivity (entries 5–7), except for $Bi(OTf)_3$ (entry 8). These observations are now understood as the result of the thermodynamic control of this reaction as pointed out by Evans *et al.*[5] The minor diastereoisomer **11′** can be transformed into the stable *syn*-1,3-dioxane **11** under the reaction conditions (Fig. 3).

At the outset, we tried to convert the methylketone **11** to desired chloro-acid **12** using the bromoform reaction (NaOH/Br_2/H_2O/dioxane) at 0 °C. Unfortunately, only 10% of the desired product **12** was formed, along with 10% α-bromo by-product **13** and 70% decarboxylation by-product **14**. Significant effort was made to optimize the reaction conditions. It was found that the use of Br_2/NaOMe/MeOH instead of NaOH/Br_2/

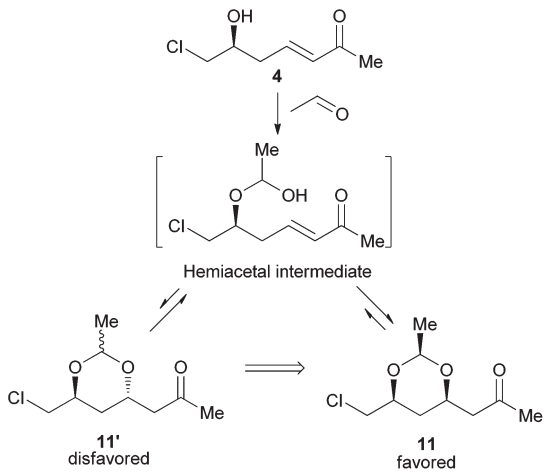


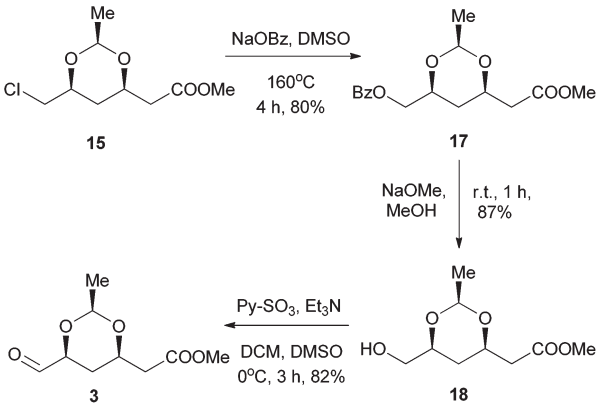
Fig. 3 Proposed mechanism for diastereoselective Michael addition between **4** and acetaldehyde.

H_2O/dioxane led to the formation of a 1 : 4 mixture of desired methyl ester **15** and its α-monobromo by-product **16**. No decarboxylation by-product **14** was detected. The mixture of **15** and **16** was directly subjected to reductive debromination with zinc powder in glacial acetic acid at 35 °C to furnish the pure chiral chloro-ester **15** as a single product in 90% yield over two steps (Scheme 2).

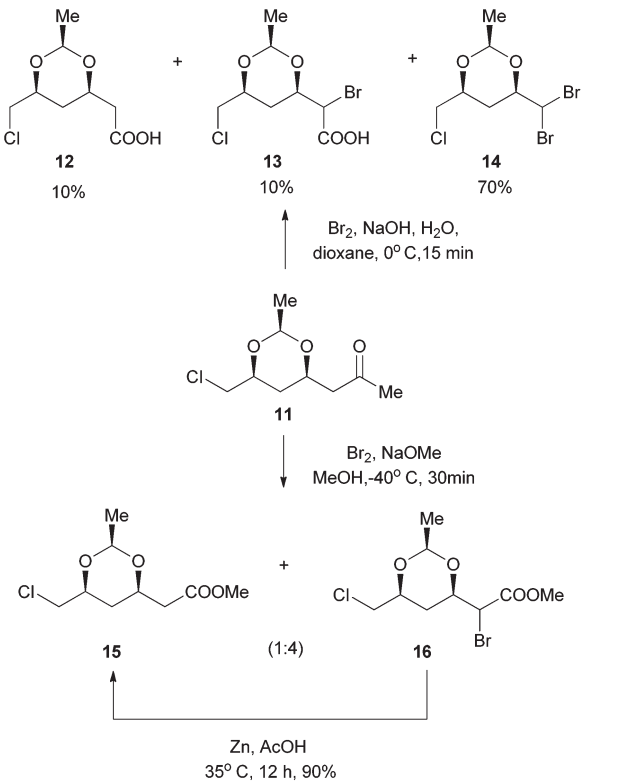
Heating **15** with sodium benzoate at 160 °C in DMSO led to displacement of the chloro moiety with a benzoyl group and diester **17** was isolated in 80% yield. Methanolysis of **17** with sodium methoxide in methanol at room temperature worked well to afford the corresponding alcohol **18** in 87% isolated yield. This then underwent a Parikh–Doering oxidation[7] (py-SO_3, NEt_3, DMSO, DCM, 0 °C, 3 h) to generate the (3*R*,5*S*)-C_6-formyl side chain **3** in 82% yield (Scheme 3).

Formylation of cyclopropylketone **8** in the presence of potassium *tert*-butoxide in anhydrous THF at room temperature proceeded smoothly to obtain the potassium enolate **19** in quantitative yield, which directly reacted with 2-(chlorotriphenylphosphoranyl) acetonitrile[8] in MeOH at room temperature to afford nitrile **6** (*E*/*Z* = 7 : 3, HPLC) in 64% isolated yield. Under the standard Friedlander condensation conditions[9] (MsOH, toluene, reflux, 13 h), the construction of the quinoline core was realized by the reaction of **6** with **7**, affording the quinoline nitrile **20** in 87% yield. HPLC analysis of the unpurified reaction mixture indicated an *E*/*Z* ratio of 3 : 1 for the Friedlander condensation. Cleavage of the double bond in **19** with ozone at −78 °C in MeOH/DCM, followed by reductive workup with $NaBH_4$, provided quinoline alcohol **21** in 74% yield. Chlorination[10] of **21** was carried out with mesyl chloride in the presence of trimethylamine in DCM to give quinoline chloride **22** quantitatively. Subsequent treatment with PPh_3 in acetonitrile formed the corresponding phosphonium salt **2** in 95% yield (Scheme 4).

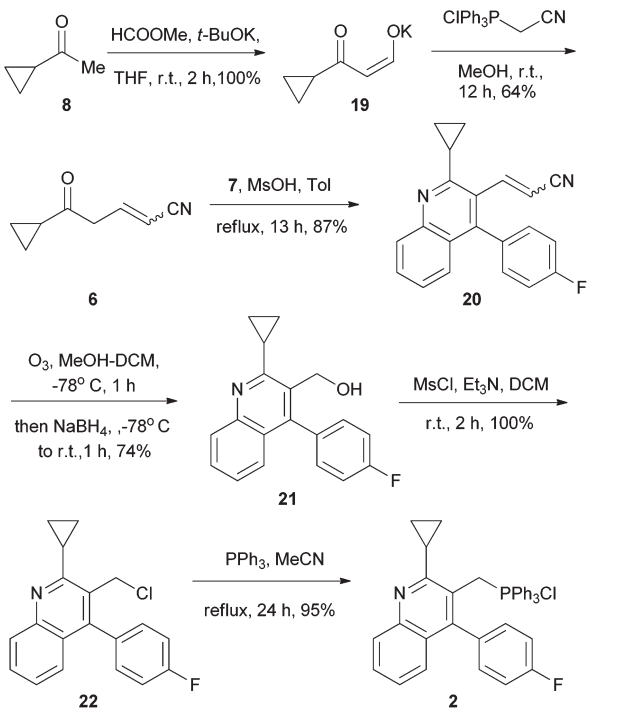
With efficient syntheses of both **2** and **3** secured, the Wittig coupling of the two building blocks was undertaken. The aldehyde **3** and phosphonium salt **2** were treated with anhydrous K_2CO_3 in DMSO at 70 °C,[11] and crude **23** was obtained as a mixture of *E*/*Z* > 17 : 1, determined by NMR spectroscopy. Chromatographic separation of the resulting *E*/*Z* olefin



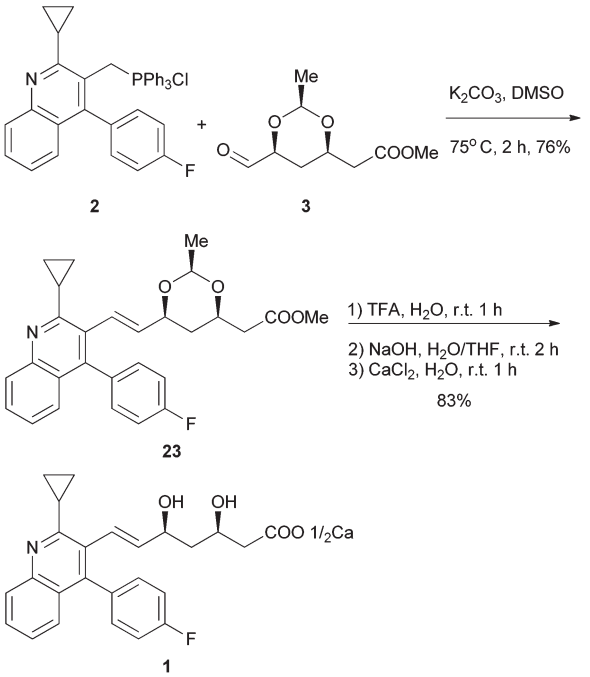
Scheme 3 Synthesis of (3*R*,5*S*)-C_6-formyl side chain **3**.



Scheme 2 Synthesis of (3*R*,5*S*)-chloro-ester **15**.



Scheme 4 Synthesis of phosphonium salt **2**.



Scheme 5 Synthesis of pitavastatin calcium (**1**).

isomers provided (*E*)-**23** in 76% yield with >99% isomeric purity. Finally, pitavastatin calcium (**1**) was prepared by deprotection of **23** in the presence of TFA, basic hydrolysis with NaOH, and calcium salt formation with $CaCl_2$, in a one-pot protocol, in an 83% yield over three steps (Scheme 5).

Experimental

All reagents and solvents were obtained from commercial sources and used without further purification. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR were recorded on a Bruker Avance 400 spectrometer using TMS or $CDCl_3$ as internal standards, IR spectra were recorded on a Nicolet iS5 FT-IR spectrometer, 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.

(*S*,*E*)-7-Chloro-6-hydroxyhept-3-en-2-one (4)

To a solution of (*S*)-1-chloropent-4-en-2-ol (1.20 g, 10 mmol) in DCM (25 mL) was bubbled with O_3 (1 ml min^{-1}) at −40 °C for 10 min, and purged with O_2 for 1 min, then dimethylsulfide (2 mL) was added under stirring and the reaction mixture was warmed to r.t., the solvent was removed *in vacuo* and THF (10 mL) was added. This THF solution of **10** was directly used in the next step.

To a stirring solution of *t*-BuOK (1.12 g, 10 mmol) in dry THF (20 mL) was added diethyl(2-oxopropyl)phosphonate (1.94 g, 10 mmol) at 0 °C and stirred for 30 min, then the solution of **10** in THF was added dropwise within 10 min at 0 °C, stirring was continued for 1 h at r.t. The solvent was evaporated *in vacuo* and water (20 mL) was added, extracted with DCM (20 mL × 3), washed with 10% aq. $NaHCO_3$ and sat. aq. NH_4Cl, dried over Na_2SO_4 and evaporated *in vacuo* to afford **4** (1.18 g, 73%) as a yellow oil, which could be used in the next step without further purification. Analytical sample was achieved by flash chromatography (petroleum ether/EtOAc = 5 : 1). $[\alpha]_D^{29}$ = −11.3 (*c* 1, MeOH). FT-IR (ATR): ν 3283, 1713, 1435, 1118, 720, 693 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.81 (dt, *J* = 16, 7.2 Hz, 1H), 6.18 (d, *J* = 16.0 Hz, 1H), 3.99 (s, 1H), 3.63 (dd, *J* = 11.2, 4 Hz, 1H), 3.52 (dd, *J* = 11.2, 6.4 Hz, 1H), 2.65–2.34 (m, 3H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.4, 142.5, 133.8, 70.2, 49.4, 37.2, 27.1 MS (ESI): *m*/*z* = 185 $[M + Na]^+$. HRMS (ESI) calcd for $C_7H_{12}ClO_2$ $[M + H]^+$ 163.0520, found 163.0520.

1-((2*S*,4*R*,6*S*)-6-(Chloromethyl)-2-methyl-1,3-dioxan-4-yl)-propan-2-one (11)

To a suspension of **4** (1.62 g, 10 mmol), bismuth nitrate pentahydrate (0.48 g, 1 mmol) in DCM (25 mL) was added freshly prepared acetaldehyde (2.20 g, 50 mmol) and stirred at r.t. for 48 h. The reaction mixture was filtered through a short column of silica gel and evaporated *in vacuo* to afford **11** (1.87 g, 91%) as a clear yellow oil. $[\alpha]_D^{26}$ = +6.4 (*c* 1, MeOH). FT-IR (ATR): ν 2871, 1713, 1123, 937 693 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.74 (q, *J* = 5.2 Hz, 1H), 4.05–4.16 (m, 1H), 3.82–3.90 (m, 1H), 3.55 (dd, *J* = 11.2, 6.0 Hz, 1H), 3.45 (dd, *J* = 11.2, 5.6 Hz, 1H), 2.79 (dd, *J* = 16.4, 7.2 Hz, 1H), 2.50 (dd, *J* = 16.4, 5.6 Hz, 1H), 2.18 (s, 3H), 1.79–1.70 (m, 1H), 1.36–1.24 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.2, 98.8, 75.5, 71.9, 49.3, 46.3, 33.9, 31.1, 20.9. MS (EI): *m*/*z* = 205 $[M - H]^+$. HRMS (ESI) calcd for $C_9H_{16}ClO_3$ $[M + H]^+$ 207.0782, found 207.0772.

Methyl 1-((4*R*,6*S*)-6-(chloromethyl)-2-methyl-1,3-dioxan-4-yl)-acetate (15)

To a stirred solution of **11** (2.00 g, 10 mmol), MeONa (5.40 g, 0.1 mol) in MeOH (50 mL) was added Br_2 (5.60 g, 35 mmol) dropwise at −40 °C within 10 min, stirring was continued for 30 min and then poured into sat. aq. $NaHSO_3$ (50 mL), the reaction mixture was adjusted to pH 6–8 with Na_2SO_3. MeOH was removed *in vacuo*, extracted with EtOAc (25 mL × 3) and evaporated *in vacuo*. To the residue was added zinc dust (1.3 g, 20 mmol) and glacial acetic acid (20 mL), the stirring was continued for 12 h at 35 °C, then water (20 mL) was added and extracted with DCM (20 mL × 3), washed with sat. aq. $NaHCO_3$, dried with Na_2SO_4 and evaporated *in vacuo* to afford **15** (1.95 g, 90%) as a yellow oil. $[\alpha]_D^{25}$ = +5.6 (*c* 1, $CHCl_3$). FT-IR (ATR): ν 3248, 2953, 1737, 1123, 1028 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.86–4.70 (m, 1H), 4.25–4.02 (m, 1H), 4.02–3.84 (m, 1H), 3.72 (s, 3H), 3.59 (dd, *J* = 11.2, 6.0 Hz, 1H), 3.49 (dd, *J* = 11.2, 5.6 Hz, 1H), 2.68 (dd, *J* = 15.6, 7.2 Hz, 1H), 2.49 (dd, *J* = 15.6, 6.0 Hz, 1H), 1.81 (d, *J* = 12.8 Hz, 1H), 1.46–1.26 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 98.9, 75.5, 72.3, 51.8, 46.3,

40.6, 33.8, 20.9. MS (EI): m/z = 221 $[M - H]^+$. HRMS (ESI) calcd for $C_9H_{16}ClO_4$ $[M + H]^+$ 223.0732, found 223.0733.

((4*S*,6*R*)-6-(2-Methoxy-2-oxoethyl)-2-methyl-1,3-dioxan-4-yl)-methyl benzoate (17)

A mixture of **15** (1.11 g, 5 mmol) and NaOBz (1.44 g, 10 mmol) in DMSO (10 mL) was stirred at 160 °C for 4 h under a N_2 atmosphere. The reaction mixture was cooled to r.t. and water (50 mL) was added, extracted with EtOAc/petroleum ether (1 : 1, 40 mL × 3), the combined organic phase was washed with water, dried with Na_2SO_4 and purified by using a filter through a short column of silica gel to afford **17** (1.23 g, 80%) as a light brown syrup. $[\alpha]_D^{20}$ = +4.7 (*c* 1, MeOH). FT-IR (ATR): ν 2950, 1716, 1270, 1111, 710 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, J = 7.6 Hz, 2H), 7.56 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 4.79 (q, J = 5.2 Hz, 1H), 4.44–4.27 (m, 2H), 4.19–4.10 (m, 1H), 4.00–4.10 (m, 1H), 3.70 (s, 3H), 2.66 (dd, J = 15.6, 7.2 Hz, 1H), 2.48 (dd, J = 15.6, 6.0 Hz, 1H), 1.69 (d, J = 12.8 Hz, 1H), 1.47 (q, J = 12 Hz, 1H), 1.35 (d, J = 5.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 166.4, 133.1, 129.9, 129.8, 128.4, 98.8, 73.8, 72.3, 66.8, 51.8, 40.7, 32.6, 21.0. MS (EI): m/z = 293 $[M - CH_3]^+$. HRMS (ESI) calcd for $C_{16}H_{21}O_6$ $[M + H]^+$ 309.1333, found 309.1344.

Methyl 2-((4*R*,6*S*)-6-(hydroxymethyl)-2-methyl-1,3-dioxan-4-yl)-acetate (18)

A mixture of **17** (310 mg, 1 mmol) and NaOMe (10 mg, 0.2 mmol) in MeOH (5 mL) was stirred at r.t. for 1 h, and then sat. aq. NH_4Cl (1 mL) was added, the solution was washed with PE (10 mL × 3) and the methanolic phase was evaporated *in vacuo*, then water (10 mL) was added and extracted with DCM (20 mL × 3), dried (Na_2SO_4) and evaporated *in vacuo* to afford **18** (178 mg, 87%) as a colorless oil. $[\alpha]_D^{20}$ = +11.5 (*c* 1, $CHCl_3$). FT-IR (ATR): ν 3464, 2953, 2871, 1731, 1129 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.77 (q, J = 5.2 Hz, 1H), 4.15–4.07 (m, 1H), 3.84–3.77 (m, 1H), 3.69 (s, 3H), 3.65 (dd, J = 11.6, 2.8 Hz, 1H), 3.56 (dd, J = 11.6, 6.4 Hz, 1H), 2.64 (dd, J = 15.6, 7.2 Hz, 1H), 2.45 (dd, J = 15.6, 6.0 Hz, 1H), 1.72 (br, 1H), 1.56–1.50 (m, 1H), 1.41 (dd, J = 24, 11.2 Hz, 1H), 1.33 (d, J = 5.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 105.8, 98.7, 76.3, 72.3, 65.5, 51.8, 40.7, 31.8, 21.0. MS (EI): m/z = 203 $[M - H]^+$. HRMS (ESI) calcd for $C_9H_{17}O_5$ $[M + H]^+$ 205.1071, found 205.1076.

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

A solution of Py·SO_3 (0.5 g, 3 mmol) in DMSO (2 mL) was stirred at 0 °C for 30 min, and then the solution of **18** (200 mg, 1 mmol) and Et_3N (600 mg, 6 mmol) in DCM (2 mL) was added, the reaction mixture was stirred for an additional 3 h and water (20 mL) was added, extracted with DCM (20 mL × 3), washed with brine (10 mL), dried with Na_2SO_4 and evaporated *in vacuo* to give **3** (159 mg, 82%) as a yellow syrup. This instable material should be used immediately in the next step without further purification. (EI): m/z = 201 $[M - H]^+$.

Potassium 3-cyclopropyl-3-oxoprop-1-en-1-olate (19)

To a solution of 1-cyclopropylethanone (4.2 g, 50 mmol), *t*-BuOK (5.6 g, 50 mmol) in dry THF (50 mL) was added ethyl formate (7.4 g, 0.1 mol) dropwise within 5 min, the stirring was continued for 3 h and evaporated *in vacuo* to afford **19** (7.5 g, 100%) as a yellow solid.

5-Cyclopropyl-5-oxopent-2-enenitrile (6)

A mixture of **18** (1.5 g, 10 mmol) and (cyanomethyl)triphenylphosphonium chloride (3.37 g, 10 mmol) in MeOH (20 mL) was stirred at r.t. for 24 h. The solvent was evaporated *in vacuo* and purified by silica column chromatography (petroleum ether/EtOAc = 5 : 1) to afford **6** (0.86 g, 64%) as an orange oil (E/Z = 7 : 3, HPLC). FT-IR (ATR): ν 3341, 3008, 2225, 1693, 1385, 1062 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.93–6.46 (m, 1H), 5.57–5.35 (m, 1H), 3.79–3.26 (m, 2H), 2.22–1.77 (m, 1H), 1.15–0.80 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.4, 205.4, 198.8, 147.4, 146.9, 133.1, 131.7, 116.9, 115.9, 115.7, 103.2, 102.2, 46.6, 45.1, 20.9, 20.8, 20.4, 20.3, 11.9, 11.8, 11.7. MS (EI): m/z = 135 $[M]^+$. HRMS (ESI) calcd for $C_8H_{10}N_1O_1$ $[M + H]^+$ 136.0757, found 136.0756.

3-(2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl)acrylonitrile (20)

A mixture of **6** (1.60 g, 12 mmol), 2-amino-4′-fluorobenzophenone (2.14 g, 10 mmol) and methanesulfonic acid (100 μl) in toluene (50 mL) was stirred under reflux for 13 h, the solvent was removed *in vacuo* and the residue was purified by silica column chromatography (petroleum ether/EtOAc = 5 : 1) to afford **20** (2.73 g, 87%) as a yellow crystalline solid. (E/Z = 3 : 1, HPLC). The analytic samples of *E* and *Z* isomers were achieved by preparative HPLC by using Venusil XBP-C18 column with the eluent MeOH/H_2O = 80 : 20.

E-Isomer. Almost white powder. mp 169–172 °C (lit.[12] mp 145–146 °C). FT-IR (ATR): ν 3072, 3002, 2221, 1512, 1488, 1218, 1162, 761, 738 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.4 Hz, 1H), 7.70–7.65 (m, 1H), 7.52 (d, J = 17.0 Hz, 1H), 7.40–7.35 (m, 2H), 7.29–7.18 (m, 5H), 5.58 (d, J = 17.0 Hz, 1H), 2.40–2.17 (m, 1H), 1.49–1.38 (m, 2H), 1.14–1.08 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 161.7, 159.3, 148.1, 147.7, 146.5, 131.8, 131.7, 131.6, 131.5, 130.5, 129.2, 126.5, 126.4, 126.0, 125.7, 117.6, 116.3, 116.1, 104.1, 16.6, 10.6. MS (EI): m/z = 313 $[M - H]^+$.

Z-Isomer. Almost white powder. mp 127–129 °C. FT-IR (ATR): ν 3059, 3013, 2871, 2244, 2214, 1489, 1218, 829, 765 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 1H), 7.67 (t, J = 6.9 Hz, 1H), 7.45–7.27 (m, 5H), 7.20 (t, J = 8.6 Hz, 2H), 5.63 (d, J = 11.5 Hz, 1H), 2.23–2.11 (m, 1H), 1.48–1.33 (m, 2H), 1.13–1.06 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 161.6, 159.2, 149.1, 148.1, 145.7, 132.0, 131.8, 131.7, 130.1, 129.2, 126.6, 126.1, 126.1, 125.5, 116.0, 115.8, 115.6, 104.8, 16.1, 10.9. MS (EI): m/z = 313 $[M - H]^+$.

(2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl)methanol (21)

To a stirred solution of **20** (314 mg, 1 mmol) in MeOH (10 mL) and DCM (10 mL) was bubbled with ozone (0.5 ml min^{-1}) at

−78 °C. The reaction was carefully monitored by TLC (*ca.* 45 min), then $NaBH_4$ (80 mg, 2 mmol) was added and the reaction was allowed to reach r.t. The stirring was continued for 30 min, the solvent was evaporated *in vacuo*, and the residue was purified by silica column chromatography (petroleum ether/EtOAc = 4 : 1) to afford **21** (214 mg, 73%) as a colorless crystal. mp 131–133 °C (lit.[12] mp 132–133 °C). FT-IR (ATR): ν 3419, 3065, 3008, 2899, 2738, 1577, 1510, 1494, 1223, 981, 840, 771 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, J = 8.4 Hz, 1H), 7.64–7.60 (m, 1H), 7.38–7.21 (m, 6H), 4.75 (s, 2H), 2.64–2.54 (m, 1H), 1.63 (br, 1H), 1.42–1.34 (m, 2H), 1.15–1.06 (m, 2H). MS (EI): m/z = 293 $[M]^+$.

3-(Chloromethyl)-2-cyclopropyl-4-(4-fluorophenyl)quinoline (22)

To a stirred solution of **21** (300 mg, 1 mmol), Et_3N (200 mg, 2 mmol) in DCM (5 mL) was added mesyl chloride (228 mg, 2 mmol) at r.t., the stirring was continued for 2 h. Then DCM (20 mL) was added, washed with water, dried with Na_2SO_4, evaporated *in vacuo* to afford **22** (320 mg, 100%) as a yellow crystalline solid, mp 126–130 °C. FT-IR (ATR): ν 3014, 1507, 1494, 1221, 839, 762, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, J = 8.4 Hz, 1H), 7.69–7.58 (m, 1H), 7.41–7.23 (m, 6H), 4.69 (s, 2H), 2.66–2.32 (m, 1H), 1.43–1.35 (m, 2H), 1.17–1.10 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 161.7, 161.5, 147.5, 146.9, 131.8, 131.7, 131.3, 131.2, 129.6, 129.0, 127.2, 126.5, 126.1, 125.8, 115.8, 115.6, 41.5, 14.6, 9.8. MS (EI): m/z = 310 $[M - H]^+$. HRMS (ESI) calcd for $C_{19}H_{16}ClF_1N_1$ $[M + H]^+$ 312.0950, found 312.0946.

((2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl)methyl)triphenylphosphonium chloride (2)

A mixture of **22** (311 mg, 1 mmol) and triphenylphosphine (262 mg, 1 mmol) in MeCN (10 mL) was stirred under reflux for 24 h and evaporated to dryness to afford **2** (544 mg, 95%), the crude product was used in the next step without further purification. FT-IR (ATR): ν 3014, 1507, 1494, 1221, 839, 762, 742 cm^{-1}. MS (ESI): m/z = 538 $[M - Cl]^+$. HRMS (ESI) calcd for $C_{37}H_{31}F_1N_1P$ $[M - Cl]^+$ 538.2094, found 538.2094.

Methyl 2-((4*R*,6*S*)-6-((*E*)-2-(2-cyclopropyl-4-(4-fluorophenyl)-quinolin-3-yl)vinyl)-2-methyl-1,3-dioxan-4-yl)acetate (23)

A mixture of **3** (159 mg, 0.8 mmol), **2** (460 mg, 0.8 mmol), anhydrous K_2CO_3 (220 mg, 1.6 mmol) in DMSO (5 mL) was stirred at 70 °C for 2 h under a N_2 atmosphere, and cooled to r.t., water (20 mL) was added. The reaction mixture was extracted with DCM (20 × 3), dried with Na_2SO_4 and evaporated *in vacuo* to dryness. The residue was purified by silica column chromatography (petroleum ether/EtOAc = 10 : 1) to afford **23** (350 mg, 76%) as a colorless syrup. $[\alpha]_D^{20}$ = +8.6 (*c* 0.84, $CHCl_3$). FT-IR (ATR): ν 3361, 3059, 2974, 1510, 1489, 1432, 1220, 1108, 744, 687 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, J = 8.4 Hz, 1H), 7.58 (t, J = 7.4 Hz, 1H), 7.38–7.27 (m, 2H), 7.24–7.11 (m, 4H), 6.59 (d, J = 16.4 Hz, 1H), 5.60 (dd, J = 16.4, 6.0 Hz, 1H), 4.75 (q, J = 5.2 Hz, 1H), 4.19–4.10 (m, 1H), 4.10–4.00 (m, 1H), 3.71 (s, 3H), 2.62 (dd, J = 15.6, 6.8 Hz, 1H), 2.40 (dd, J = 15.4, 6.0 Hz, 2H), 1.44–1.23 (m, 7H), 1.11 (dd, J = 24, 11.2 Hz, 1H), 1.04 (dd, J = 8.0, 3.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 163.6, 161.2, 160.8, 147.0, 144.5, 137.1, 133.5, 132.2, 132.1, 131.9, 131.8, 129.3, 129.0, 128.9, 126.6, 126.2, 125.5, 115.5, 115.4, 115.3, 115.3, 98.7, 76.4, 72.4, 51.9, 40.7, 36.2, 21.1, 16.1, 10.6, 10.3. MS (ESI): m/z = 462 $[M + H]^+$. HRMS (ESI) calcd for $C_{28}H_{29}F_1N_1O_4$ $[M + H]^+$ 462.2075, found 462.2074.

Pitavastatin calcium (1)

A mixture of **22** (230 mg, 0.5 mmol), TFA (2 mL) and water (0.2 mL) was stirred at r.t. for 1 h, the TFA was removed *in vacuo*, then THF (2 mL) and 1 M aq. NaOH (0.5 mL) were added and stirred at r.t. for 2 h, the organic solvent was removed *in vacuo* and water (2 mL) was added, 5% aq. $CaCl_2$ (2 mL) was added dropwise and stirring was continued for 1 h, the precipitant was collected by filtration and dried *in vacuo* to afford **1** (183 mg, 83%) as a white solid. mp 214 °C (dec.), $[\alpha]_D^{17}$ = +22.3 (*c* 1, MeCN/H_2O 1 : 1) (lit.[2e] $[\alpha]_D^{20}$ = +23.1 (*c* 1, MeCN/H_2O 1 : 1)). ^1H NMR (400 MHz, DMSO-d_6): δ = 7.84 (d, J = 8.0 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.40–7.22 (m, 6H), 6.48 (d, J = 16.0 Hz, 1H), 5.58 (dd, J = 16.0, 5.2 Hz, 1H), 4.91 (br, 1H), 4.12 (q, J = 5.6 Hz, 1H), 3.75–3.49 (m, 1H), 2.07 (dd, J = 15.2, 3.6 Hz, 1H), 1.91 (dd, J = 15.2, 8.0 Hz, 1H), 1.54–1.30 (m, 1H), 1.25–1.15 (m, 1H), 1.12–1.06 (m, 1H), 1.05–0.97 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.7, 162.8, 160.6, 160.4, 146.0, 143.7, 142.2, 133.1, 132.2, 132.1, 131.9, 131.8, 129.7, 128.8, 128.4, 125.7, 125.7, 125.6, 123.2, 115.4, 115.3, 115.2, 115.1, 68.9, 65.7, 44.2, 43.9, 15.4, 10.8, 10.7.

Conclusions

In summary, we have successfully implemented a stereocontrolled preparation of the key chiral C_6-formyl building block with a 1,3-diol pattern starting from commercially available (*S*)-epichlorohydrin using a bismuth-catalyzed two-component hemiacetal/oxa-Michael addition reaction as the key step. This process constitutes a practical and concise synthesis of pitavastatin calcium (**1**), and offers a general and economic synthetic route to the statin-family HMG-CoA reductase inhibitors.

Notes and references

1 (*a*) Z. Časar, *Curr. Org. Chem.*, 2010, **14**, 816–845; (*b*) J. Wang, M. Sanchez-Rosello, J. L. Acena, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506.

2 (*a*) S. Takano, T. Kamikubo, T. Sugihara, M. Suzuki and K. Ogasawara, *Tetrahedron: Asymmetry*, 1993, **4**, 201–204; (*b*) K. Takahashi, T. Minami, Y. Ohara and T. Hiyama, *Tetrahedron Lett.*, 1993, **34**, 8263–8266; (*c*) N. Miyachi, Y. Yanagawa, H. Iwasaki, Y. Ohara and T. Hiyama, *Tetrahedron Lett.*, 1993, **34**, 8267–8270; (*d*) T. Hiyama, T. Minami, Y. Yanagawa and Y. Ohara, *WO Pat*. 9511898, 1995; *Chem. Abst.*, 1995, **123**, 313782; (*e*) M. Suzuki, Y. Yanagawa, H. Iwasaki, H. Kanda, K. Yanagihara,

H. Matsumoto, Y. Ohara, Y. Yazaki and R. Sakoda, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2977–2982; (*f*) M. Acemoglu, A. Brodbeck, A. Garcia, D. Grimier, M. Hassel, B. Riss and R. Schreiber, *Helv. Chim. Acta*, 2007, **90**, 1069–1081; (*g*) J. Fabris, Z. Časar and I. G. Smilović, *Synthesis*, 2012, 1700–1710; (*h*) J. Fabris, Z. Časar, I. G. Smilović and M. Črnugeljb, *Synthesis*, 2014, 2333–2346.

3 T. Hyama, T. Minami, S. Yanagawa and Y. Obara, *JP Pat*. 05310700, 1993; *Chem. Abstr.*, 1994, **120**, 244704.

4 (*a*) H. I. Shin, B. S. Choi, K. K. Lee, H. Choi, J. H. Chang, K. W. Lee, D. H. Nam and N. S. Kim, *Synthesis*, 2004, 2629–2632; (*b*) H. Choi and H. Shin, *Synlett*, 2008, 1523–1525; (*c*) R. Sun, F. Q. Zhang,T. J. Du, L. P. Fang and F. M. Meng, *CN Pat*. 102180862, 2011; *Chem. Abstr.*, 2011, **155**, 457681.

5 P. A. Evans, A. Grisin and M. J. Lawler, *J. Am. Chem. Soc.*, 2012, **134**, 2856–2859.

6 F. J. Xiong, J. Li, X. F. Chen, W. X. Chen and F. E. Chen, *Tetrahedron: Asymmetry*, 2014, **25**, 1205–1208.

7 (*a*) N. S. Joshi, A. S. Khile, Y. B. Kajale and H. H. Kamble, *WO Pat*. 2008059519, 2008; *Chem. Abstr.*, 2008, **148**, 585906; (*b*) J. R. Parikh and W. v. E. Doering, *J. Am. Chem. Soc.*, 1967, **89**, 5505–5507.

8 R. A. Abramovitch and B. W. Cue, *J. Org. Chem.*, 1980, **45**, 5316–5319.

9 K. Nagashima, T. Fukumoto, T. Hayashibara and M. Torihara, *WO Pat*. 2004041787, 2004; *Chem. Abstr.*, 2004, **140**, 423596.

10 Y. M. Zhang, X. D. Fan, S. M. Yang, R. H. Scannevin, S. L. Burke, K. J. Rhodes and P. F. Jackson, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 405–408.

11 S. R. Manne, K. R. Bairy, K. R. Chepyala, K. K. Muppa, R. T. Srinivasan, E. Sajja and S. R. Maramreddy, *Orient. J. Chem.*, 2007, **23**, 559–564.

12 M. Suzuki, H. Iwasaki, Y. Fujikawa, M. Kitahara, M. Sakashita and R. Sakoda, *Bioorg. Med. Chem.*, 2001, **9**, 2727–2743.