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Synthetic studies on statins. Part 1: a short and cyanide-free synthesis of atorvastatin calcium via an enantioselective aldol strategy

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ABSTRACT

A short and cyanide-free enantioselective synthesis of atorvastatin calcium has been achieved starting from a commercially available highly substituted 1,4-diketone in an overall yield of 40%. The key step in this approach is the asymmetric aldol reaction of an aldehyde with diketene in the presence of Ti(O-*i*-Pr)$_4$–Schiff base complex to create the (5*R*)-stereochemistry of atorvastatin calcium.

1. Introduction

Since its introduction in 1997 by Pfizer, atorvastatin calcium **1** (Lipitor), a 3-hydroxy-3-methyl-glutaryl coenzymeA (HMG-CoA) reductase inhibitor, has been one of the best-selling drugs for the treatment of hypercholesterolemia due to its efficiency, safety, and long-term benefits.[1] To date, considerable efforts have been spent on searching for an efficient and economic asymmetric approach toward **1**, leading to the development of a number of synthetic strategies including chiral pool synthesis,[2] chiral auxiliary method,[3] asymmetric catalysis,[4] and chemoenzymatic processes[5] and so on. The well-known Paal–Knorr pyrrole synthesis strategy, which proceeds via two important building blocks of substituted diketone **2** and C_7 amino type side chain **3** with a *syn*-1,3-diol unit, derived from (*S*)-epichlorohydrin as a chiral material, is a reliable process for the asymmetric synthesis of **1** on an industrial scale (Fig. 1). However, several drawbacks in this technique are associated with the statin side chain **3**, such as long multistep preparation sequences as well as the use of a large excess of highly toxic cyanide. The asymmetric aldol reaction is reported to be a simple and atom-economic method to construct optically active 5-hydroxy-3-oxoester,[6] an important building block for the enantioselective synthesis of statins.[7] This prompted us to disclose a short and cyanide-free enantioselective synthesis of **1** via a novel intermediate **9** by employing a Ti(O-*i*-Pr)$_4$-chiral Schiff base promoted asymmetric aldol reaction of aldehyde **8** with diketene.[8] Herein we report the results of our investigation on this subject.

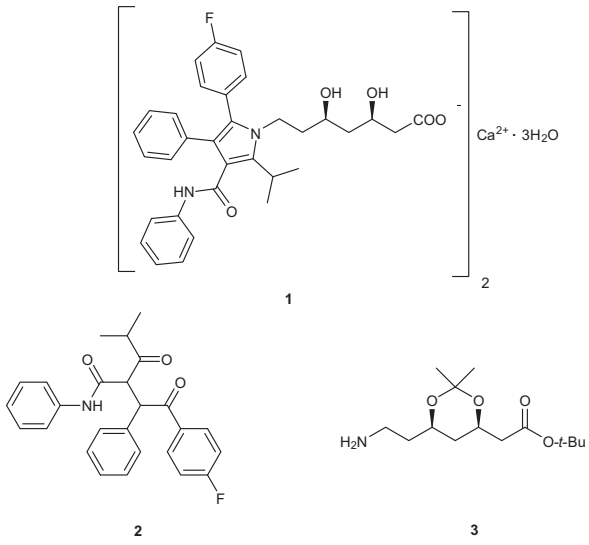

Figure 1. Structures of **1** and its advanced building blocks **2** and **3**.

2. Results and discussion

The retrosynthetic analysis of **1** is depicted in Scheme 1. The *syn*-selective reduction of key intermediate **9** was envisaged. The optically active 5-hydroxy-3-oxoester **9** could be obtained from **8** via a catalytic asymmetric aldol reaction. The substituted pyrrole aldehyde **8** could be assembled through the known Paal–Knorr pyrrole synthesis from diketone **2** and C_3 amino diethyl acetal **6**.

Our asymmetric synthesis of **1** is shown in Scheme 2. The C_3-side chain **6** was prepared in 62% overall yield from commercially available acrolein according to a slightly improved literature procedure.[9] The Michael addition of acrolein and sodium nitrite in HOAc/THF/H_2O at 0 °C proceeded smoothly to afford nitroaldehyde **4** in 89% yield, which was protected as a diethyl acetal upon treatment of triethyl orthoformate in the presence of *p*-TsOH in EtOH at room temperature in 71% yield. The hydrogenation of **5** under 10

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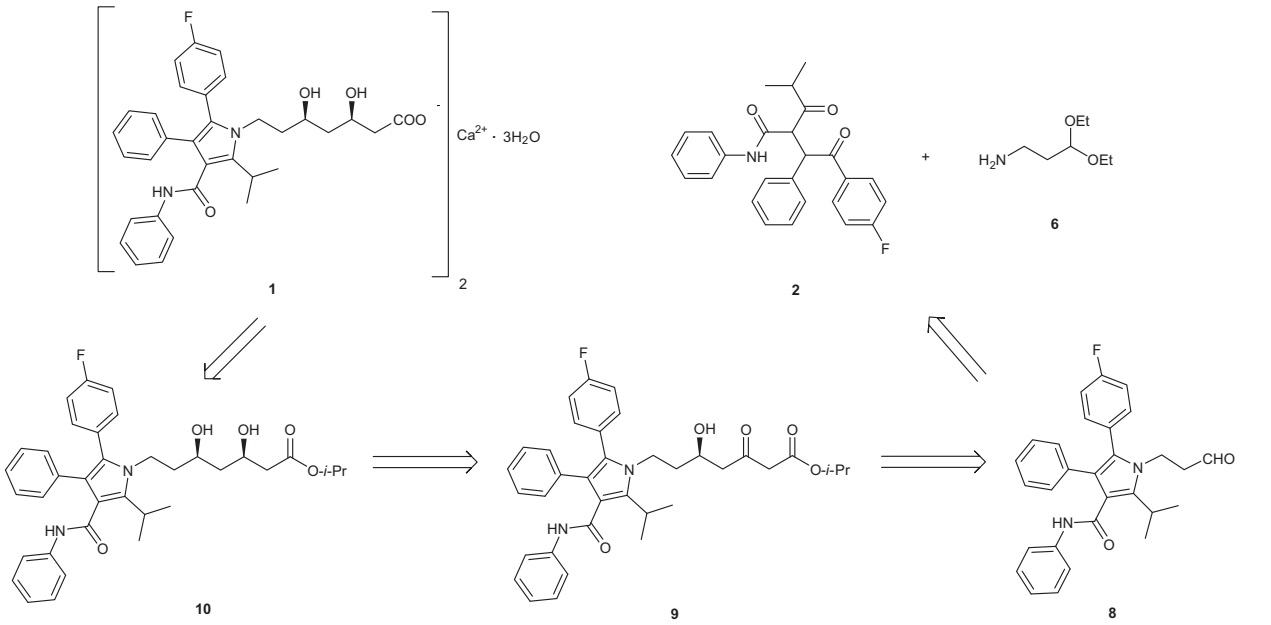
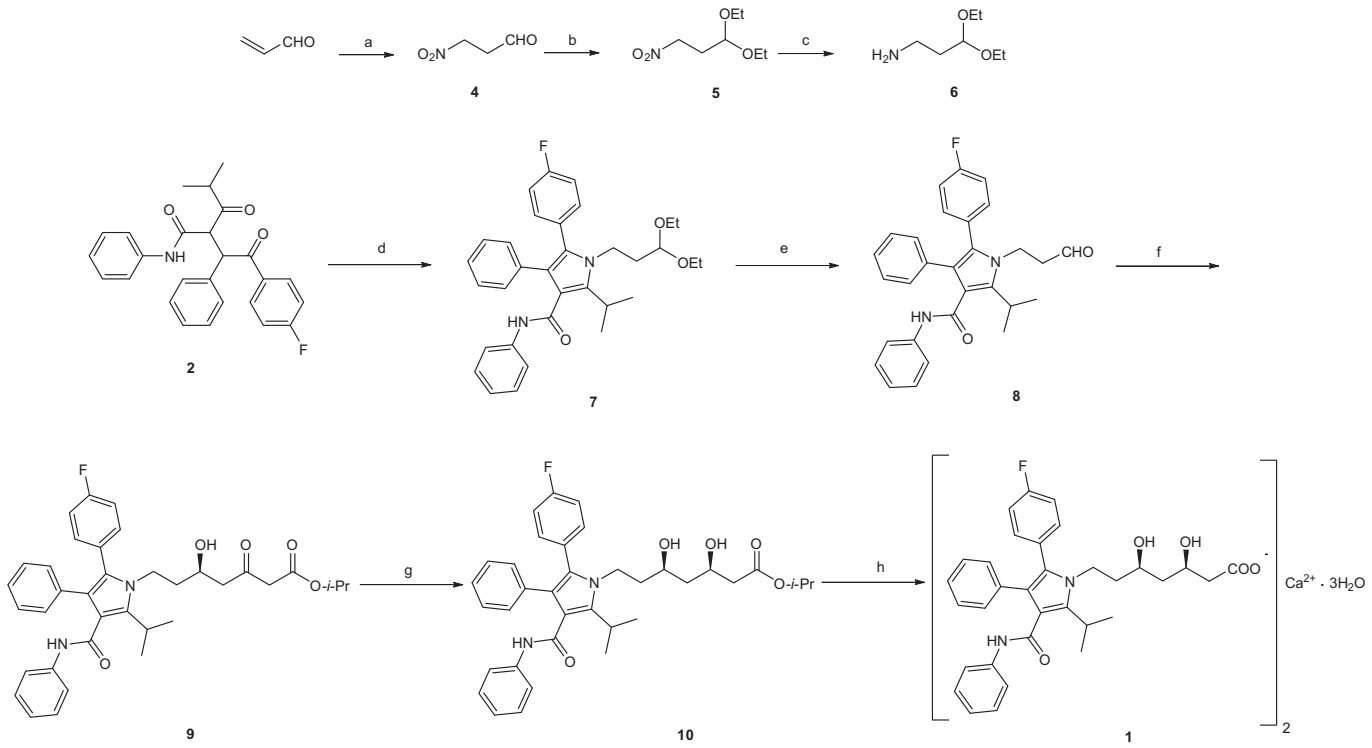


Scheme 1. Retrosynthetic analysis of atorvastatin calcium.

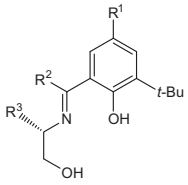


Scheme 2. Reagents and conditions: (a) $NaNO_2$, HOAc, THF/H_2O (1:2), 0 °C, 4 h, 89%; (b) triethyl orthoformate, *p*-T_SOH (cat.), EtOH, rt, 6 h, 71%; (c) Pd/C, H_2, MeOH, rt, 12 h, 98%; (d) **6**, pivalic acid, toluene/heptane (9:1), reflux, 14 h, 83%; (e) 2 M HCl, acetone/water (2:1), reflux, 1 h, 95%; (f) diketene, Ti(O-*i*-Pr)$_4$, Schiff base **11a**, CH_2Cl_2, −40 °C, 48 h, 62%; (g) $Et_2B(OMe)$, $NaBH_4$, THF/MeOH (4:1), −78 °C, 2 h, 85%; (h) (1) 1 M NaOH, MeOH, 50 °C, 1 h; (2) $CaCl_2$, rt, 1 h, 94%.

atmospheres of H_2 over 10% Pd/C at room temperature for 12 h furnished amino diethyl acetal **6** in almost quantitative yield.

The Paal–Knorr condensation of diketone **2**[10] and **6** was carried out in refluxing toluene/heptane (9:1, v/v) with azeotropic removal of water in the presence of pivalic acid to give pyrrole **7** in 83% yield. The deprotection of **7** by dilute HCl in acetone/water (1:1, v/v) gave the desired aldehyde **8**[11] in 95% yield.

With aldehyde **8** in hand, we were in a position to construct the (5*R*)-stereochemistry of **1** by asymmetric addition of diketene to **8** with the Ti(O-*i*-Pr)$_4$–Schiff base complex. To evaluate the ligands, initial examinations were performed using 1.0 equiv of promoter prepared in situ from several chiral Schiff base ligands **11a–g**[12] (Fig. 2) and Ti(O-*i*-Pr)$_4$ in CH_2Cl_2 at −40 °C for 48 h (Table 1, entries 1–7). As can be seen from Table 1, **11a** was identified as the most



11a: R^1=R^2=H, R^3=*i*-Pr
11b: R^1=*t*-Bu, R^2=H, R^3=*i*-Pr
11c: R^1=*t*-Bu, R^2=H, R^3=Bn
11d: R^1=*t*-Bu, R^2=Ph, R^3=*i*-Pr
11e: R^1=*t*-Bu, R^2=Ph, R^3=Bn
11f: R^1=*t*-Bu, R^2=Me, R^3=*i*-Pr
11g: R^1=*t*-Bu, R^2=Me, R^3=Bn

Figure 2. Structures of chiral Schiff base ligands **11a**–**g**.

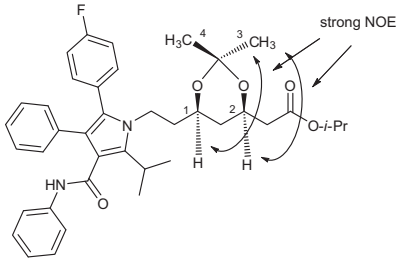


Figure 3. The NOE correlation for **12**.

suitable ligand for the enantioselective aldol reaction (Table 1, entry 1, 62% yield, 82% ee).

Table 1
Effect of the Ti(O-*i*-Pr)$_4$-Schiff base **11a**–**g** complex on the enantioselectivity with the addition of diketene to aldehyde **8**[a]

Entry	Schiff base	Yield[b] (%)	ee[c] (%)
1	**11a**	62	82
2	**11b**	55	71
3	**11c**	57	31
4	**11d**	60	71
5	**11e**	61	20
6	**11f**	55	79
7	**11g**	58	61

[a] All reactions were conducted with aldehyde **8** (0.5 mmol, 1 equiv), diketene (2.5 mmol, 5 equiv), Ti(O-*i*-Pr)$_4$ (0.5 mmol, 1 equiv), and Schiff base **11a**–**g** (0.5 mmol, 1 equiv) in CH_2Cl_2 (5 mL) at −40 °C for 48 h.
[b] Isolated yield after silica gel column chromatography.
[c] Determined by HPLC analysis (CHIRALPAK AD-H).

With this successful result for the catalytic efficiency in the initial screening in hand, we conducted the reaction with different amounts of **11a** at a wide range of temperatures. As illustrated in Table 2, a decrease in the temperature resulted in an increase in enantioselectivity along with a decrease in chemical yield even after a prolonged reaction time. We found −40 °C to be the optimum temperature for this reaction, which provided the aldol product **9** in 82% ee and 62% yield. A decrease in the amount of Schiff base caused a decrease in both the enantioselectivity and chemical yield. Therefore, an equimolar amount of the Schiff base was necessary in order to obtain satisfactory results.

The *syn*-selective reduction of **9** using Narasaka's method[13] [$Et_2B(OMe)/NaBH_4$, THF/MeOH(4:1), −78 °C] gave diol **10** in 85% yield in favor of the *syn*-isomer (99:1, *syn*/*anti*). The enantiomeric excess was improved to over 99% by recrystallization. The *syn*-configuration was confirmed via NOESY NMR spectroscopy of ketal **12** obtained from **10** by treatment of 2,2-dimethoxypropane in the presence of a catalytic amount of PPTS. This clearly shows a strong NOE interaction between C3-H (δ = 1.39 ppm) and C1-H (δ = 3.70–3.74 ppm) as well as C2-H (δ = 4.19–4.25 ppm), and no NOE interaction between C4-H (δ = 1.32 ppm) and C1-H (δ = 3.70–3.74 ppm) or C2-H (δ = 4.19–4.25 ppm), thus implying a *syn*-configuration for C1-H and C2-H (Fig. 3).

Table 2
Effect of the reaction conditions on the enantioselectivity with the addition of diketene to aldehyde **8**[a]

Entry	Ligand (mol %)	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	100	0	30	70	63
2	100	−20	40	67	68
3	100	−40	48	62	82
4	100	−60	55	51	86
5	50	−40	48	51	77
6	10	−40	48	46	57

[a] All reactions were conducted with aldehyde **8** (0.5 mmol, 1 equiv), diketene (2.5 mmol, 5 equiv), Ti(O-*i*-Pr)$_4$ (0.5 mmol, 1 equiv), and Schiff base **11a** in CH_2Cl_2 (5 mL).
[b] Isolated yield after silica gel column chromatography.
[c] Determined by HPLC analysis (CHIRALPAK AD-H).

The saponification of isopropyl ester **10** with 1 M aq NaOH and subsequent calcium salt formation upon treatment with $CaCl_2{\cdot}2H_2O$ provided atorvastatin calcium **1**. The enantiomeric purity of **1** was determined to be >99% ee by chiral HPLC according to the European Pharmacopoeia 7.1.

3. Conclusion

In conclusion, a novel and 5-step asymmetric synthesis of atorvastatin calcium **1** was accomplished in 40% overall yield starting from diketone **2** by employing a Ti(O-*i*-Pr)$_4$–Schiff base complex promoted asymmetric aldol reaction as the key step. This approach toward **1** is the shortest in comparison to other reported methods.

4. Experimental

4.1. General

Anhydrous CH_2Cl_2 was distilled from CaH_2 prior to use. Other reagents were obtained from commercial sources and used as received. All melting points were measured on a WRS-1B digital melting point apparatus. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$, DMSO using TMS and $CDCl_3$ (^{13}C, δ = 77.0 ppm) as internal standards. Mass spectra were recorded on a Waters Quattro Micromass instrument using ESI techniques. IR spectra were recorded on a Jasco FT/IR-4200 spectrophotometer. Optical rotations were obtained on a Jasco P1020 digital polarimeter. The Schiff base ligands **11a**–**g** were prepared from chiral β-amino alcohols and substituted salicylaldehyde or hydroxyl arylketone according to Oguni's procedure.[12] The enantiomeric excess of **9** was determined by HPLC using CHIRALPAK AD-H column (250 mm × 4.6 mm × 5 μm), run time 30 min, flow rate 1.0 mL/min, injection volume 10 μL, mobile phase hexane/isopropyl alcohol 90:10 (v/v) containing 0.01% of trichloroacetic acid. The enantiomeric excess of **1** was determined by HPLC using CHIRALPAK AD-H column (250 mm × 4.6 mm × 5 μm), run time 30 min, flow rate 1.0 mL/min, injection volume 10 μL, mobile phase hexane/anhydrous ethanol 94:6 (v/v) containing 0.1% of trichloroacetic acid.

4.2. 3-Nitropropanal 4

To a well-stirred solution of $NaNO_2$ (41.5 g, 0.6 mol) and acrolein (28 g, 0.5 mol) in a mixture of H_2O (100 mL) and THF (200 mL) was added glacial acetic acid (33 g, 0.55 mol) dropwise at 0 °C under N_2. The resulting mixture was stirred at 0 °C for 4 h, quenched with satd aq $NaHCO_3$ (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (3 × 20 mL), dried ($MgSO_4$), filtered and concentrated

under reduced pressure to give **4** (45.8 g, 89%) as a clear oil. The crude was used for the next step without further purification.

4.3. 3-Nitropropanal diethyl acetal 5

To a stirred solution of **4** (30.9 g, 0.3 mol) and triethyl orthoformate (59.3 g, 0.40 mol) in EtOH (100 mL) was added *p*-TsOH·H_2O (1.2 g, 6.3 mmol) at 0 °C. After stirring at rt for 6 h, the mixture was concentrated under reduced pressure. The residue was neutralized with satd aq $NaHCO_3$ (20 mL) and diluted with EtOAc (30 mL). The aqueous layer was separated and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (2 × 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to afford **5** (37.7 g, 71%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (t, 6H, J = 6.8 Hz), 2.28 (q, 2H, J = 6.0 Hz), 3.49 (q, 2H, J = 7.2 Hz), 3.67 (q, 2H, J = 7.2 Hz), 4.46 (t, 2 H, J = 6.8 Hz), 4.58 (t, 1 H, J = 5.2 Hz); IR (neat): 2941, 2836, 1553, 1449 cm^{-1}; MS (EI): m/z: 177 [M$^+$].

4.4. 1-Amino-3,3-diethoxypropane 6

To a solution of **5** (17.7 g, 0.1 mol) in MeOH (20 mL) was added Pd/C (10%, 15 mg) and stirred at rt for 12 h under 10 atmospheres of H_2. The filtrate through Celite was concentrated under reduced pressure to give **6** (14.4 g, 98%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (t, 6H, J = 6.8 Hz), 1.29 (br s, 2H), 1.71 (q, 2H, J = 6.4 Hz), 2.73 (t, 2H, J = 6.4 Hz), 3.45 (q, 2H, J = 7.2 Hz), 3.60 (q, 2H, J = 7.2 Hz), 4.53 (t, 1H, J = 5.2 Hz). IR (neat): 3385, 2953, 2831, 1621, 1389 cm^{-1}; MS (EI): m/z: 147 [M$^+$].

4.4.1. 1-(3,3-Diethoxypropyl)-5-(4-fluoropheny)-2-(1-methyl ethy)-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide 7

Diketone **2** (12.51 g, 30 mmol), compound **6** (5.88 g, 40 mmol), and pivalic acid (2.14 g, 21 mmol) were dissolved in heptane (54 mL) and toluene (6 mL). The mixture was heated at reflux with azeotropic removal of water for 14 h and then cooled to rt, filtered, washed with heptane (3 × 30 mL), and dried to give **7** (13.15 g, 83%) as a white powder. Mp 125.0–126.3 °C (Lit.[11] 125.1–127.7 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, 6H, J = 6.8), 1.54 (d, 6H, J = 7.2), 1.80–1.84 (m, 2H), 3.26–3.32 (m, 2H), 3.42–3.47 (m, 2H), 3.58–3.63 (m, 1H), 3.95–3.99 (m, 2H), 4.33 (t, J = 4.8 Hz, 1H), 6.86 (s, 1H), 6.98–7.20 (m, 14H); IR (KBr): 3412, 2975, 1665, 1596, 1433 cm^{-1}. MS (ESI) m/z: 529 [M+H$^+$].

4.4.2. 5-(4-Fluorophenyl)-2-(1-methylethyl)-1-(3-oxopropyl)-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide 8

A solution of **7** (10.56 g, 20 mmol) in acetone (100 mL) and 2 N aq HCl (50 mL) was heated at reflux for 1 h and then cooled to rt, filtered, washed with hexane (3 × 30 mL) and dried to give **8** (8.63 g, 95%) as a white powder. Mp 163.7–164.9 °C (Lit.[3a] 164–165 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51 (d, 6H, J = 7.2 Hz), 2.67 (t, 2H, J = 7.2 Hz), 3.58–3.66 (m, 1H), 4.25 (t, 2H, J = 8.0 Hz), 6.85 (s, 1H), 6.99–7.19 (m, 14H), 9.59 (s, 1H); IR (KBr): 3397, 2955, 1711, 1683, 1591, 1517 cm^{-1}. MS (ESI) m/z: 455 [M+H$^+$].

4.4.3. (*R*)-Isopropyl 7-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-pheny1-4-[(phenylamino)carbonyl]-1*H*-pyrrol-1-yl]-5-hydroxy-3-oxoheptanoate 9

To a solution of Schiff base **11a** (144.9 mg, 0.55 mmol) in CH_2Cl_2 (5 mL) was added Ti(O-*i*-Pr)$_4$ (142.1 mg, 0.5 mmol) at rt under N_2. After stirring for 1 h, the mixture was cooled to −40 °C. Compound **8** (227.5 mg, 0.5 mmol) was added followed by diketene (210.2 mg, 2.5 mmol). The resulting mixture was stirred at −40 °C for 48 h, then poured into a mixture of 1 M aq HCl (10 mL) and Et_2O (10 mL) and stirred vigorously at rt for 1 h. The mixture was extracted with EtOAc (3 × 30 mL), washed with satd aq $NaHCO_3$ (3×30 mL) and brine (3×30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, EtOAc/PE, 1:3) to give **9** (185.7 mg, 62%) as a white powder. Ee = 82%; $[\alpha]_D^{20}$ = +9.1 (*c* 1.0, $CHCl_3$); Mp 75.3–76.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (d, 6H, J = 6.4 Hz), 1.54 (dd, 6H, J = 6.8 Hz), 1.62–1.68 (m, 2H), 2.52–2.54 (m, 2H), 2.75 (d, J = 2.4 Hz, 1H), 3.36 (s, 2H), 3.53–3.60 (m, 1H), 3.89–3.98 (m, 2H), 4.11–4.17 (m, 1H), 5.01–5.07 (m, 1H), 6.86 (s, 1H), 6.98–7.20 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.66, 21.69, 21.84, 26.17, 37.73, 41.31, 49.21, 49.97, 65.02, 69.42, 115.39, 115.60, 119. 62, 121.95, 123.55, 126.62, 128.26, 128.30, 128.37, 128.69, 128.79, 130.45, 130.50, 133.15, 133.24, 134.60, 138.39, 141.49, 166.29; IR (KBr): 3405, 3027, 2933, 1771, 1559, 1508 cm^{-1}. MS (ESI) m/z: 599 [M+H$^+$].

4.4.4. (3*R*,5*R*)-Isopropyl 7-[2-(4-fluorophenyl)-5-(1-methyl ethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoate 10

To a solution of **9** (300.0 mg, 0.5 mmol) in THF (8 mL) and MeOH (2 mL) was added diethylmethoxyborane (0.6 mL, 0.6 mmol, 1 M solution in THF) at −78 °C under N_2. The mixture was stirred for 1 h and then $NaBH_4$ (37.9 mg, 1 mmol) was added in portions. After stirring for an additional 2 h at −78 °C, the reaction was quenched with glacial acetic acid (2 mL), diluted with EtOAc (10 mL) and then allowed to warm to rt Next, satd aq $NaHCO_3$ (20 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was coevaporated with MeOH three times to hydrolyze the excess borane, and then purified by chromatography (silica gel, EtOAc/PE, 1:2) to give the *syn*-product **10** (255.1 mg, 85%) with *syn/anti* diastereoselectivity of 99:1 as a white powder. The ee was improved to over 99% by recrystallization from acetonitrile/water. $[\alpha]_D^{20}$ = +14.3 (*c* 1.0, $CHCl_3$); Mp 134.1–135.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (d, 6H, J = 6.4 Hz), 1.54 (d, 6H, J = 7.2 Hz), 1.63–1.68 (m, 2H), 2.37 (d, 2H, J = 6.0 Hz), 3.56–3.60 (m, 2H), 3.70–3.74 (m, 2H), 3.94–3.96 (m, 1H), 4.08–4.16 (m, 2H), 5.03–5.06 (m,1H), 6.86 (s, 1H), 6.97–7.20 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.69, 21.80, 26.16, 39.11, 41.34, 41.57, 41.85, 68.65, 69.07, 69.68, 115.29, 115.34, 115.51, 115.58, 119.62, 121.87, 123.53, 126.57, 128.36, 128.69, 128.76, 128.80, 130.51, 133.18, 133.26, 134.69, 138.42, 172.25; IR (KBr): 3407, 3028, 2932, 2874, 1725, 1558. MS (ESI) m/z: 600 [M+H$^+$].

4.4.5. Isopropyl 2-((4*R*,6*R*)-6-(2-(2-(4-fluorophenyl)-5-isopropyl -3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate 12

Compound **10** (120.0 mg, 0.2 mmol) was added to 2,2-dimethoxypropane (10 mL) followed by a catalytic amount of PPTS (5.02 mg, 0.02 mmol). The resulting mixture was stirred at rt overnight, and then satd aq $NaHCO_3$ (1 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), washed with brine (3 × 30 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give **12** (117.9 mg, 92%) as a white powder. $[\alpha]_D^{20}$ = +5.8 (*c* 1.0, $CHCl_3$); Mp 210.1–212.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (d, 6H, J = 6.4 Hz), 1.32 (s, 3H), 1.39 (s, 3H), 1.55 (d, 6H, J = 7.2 Hz), 1.68–1.70 (m, 2H), 2.31 (dd, 1H, J_1 = 15.2 Hz, J_2 = 6.0 Hz), 2.65, (dd, 1H, J_1 = 15.2 Hz, J_2 = 6.8 Hz), 3.56–3.63 (m, 1H), 3.70–3.74 (m, 1H), 3.81–3.88 (m, 1H), 4.06–4.14 (m, 1H), 4.19–4.25 (m, 1H), 5.00–5.07 (m, 1H), 6.88 (s, 1H), 6.99–7.20 (m, 14H). IR (KBr): 3386, 2992, 2921, 1725, 1609, 1434 cm^{-1}; MS (ESI) m/z: 641 [M+H$^+$].

4.4.6. Atorvastatin calcium 1

To a stirring solution of **10** (120.0 mg, 0.2 mmol) in MeOH (20 mL) was added 1 M aq NaOH (0.3 mL). The mixture was stirred

at 50 °C for 1 h and then cooled to rt. Next, $CaCl_2 \cdot H_2O$ (29.4 mg, 0.2 mmol) was added to the solution and the resulting slurry was maintained at rt for 1 h, filtered, washed and dried in vacuo to give **1** (113.6 mg, 94%) as a white powder. $[\alpha]_D^{20} = -7.5$ (*c* 1.0, DMSO) {Lit.[2i] $[\alpha]_D = -7.4$ (*c* 1.0, DMSO)}; Mp 173.7–175.9 °C; IR (KBr): 3400, 3016, 2922, 2881, 1725.

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