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ARTICLE

# The Total Synthesis of Calcium Atorvastatin

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A practical and convergent asymmetric route to calcium atorvastatin (**1**) is reported. The synthesis of calcium atorvastatin (**1**) was performed using the remote 1,5-*anti* asymmetric induction in the boron-mediated aldol reaction of β-alkoxy methylketone (**4**) with pyrrolic aldehyde (**3**) as a key step. Calcium atorvastatin was obtained from aldehyde (**3**) after 6 steps, with a 41% overall yield.

## Introduction

Calcium atorvastatin (**1**), the active ingredient of Liptor®, a statin launched in 1997, competitively inhibits hydroxymethylglutaryl-CoA (HMG-CoA) reductase, the enzyme that catalyzes the rate-limiting step in cholesterol biosynthesis (Figure 1).[1] Due to its high efficacy for LDL cholesterol reduction and its established safety profile, an ongoing demand for calcium atorvastatin is expected, and the development of an efficient, robust and scalable synthetic route to (**1**) is of remarkable interest for academia and the pharmaceutical industry.[2,3]

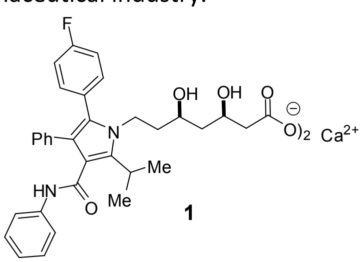
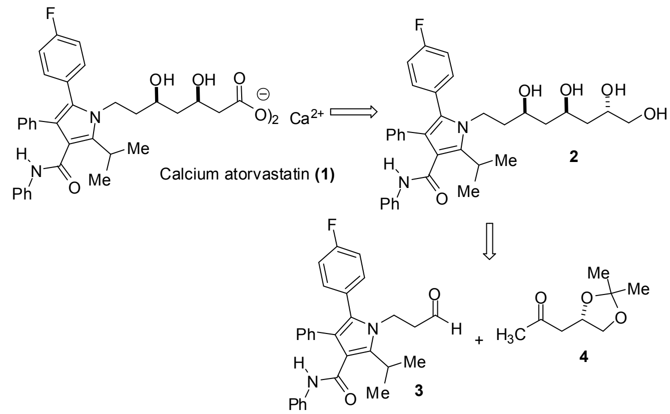


**Figure 1.** Calcium atorvastatin (**1**)

Many different routes to statin side chains have been reported using chemical and biocatalytic steps to introduce one of the two stereogenic centers.[4-9] Recently, Shibasaki and coworkers developed a direct catalytic asymmetric aldol reaction promoted by a soft Lewis acid catalyst using thioamides as the aldol donors, and they applied this methodology to the enantioselective synthesis of atorvastatin.[10]
In this study, we describe our approach to atorvastatin based on a 1,5-*anti* asymmetric aldol reaction of β–alkoxy methyl ketone **4** with aldehyde **3**.[11,12]

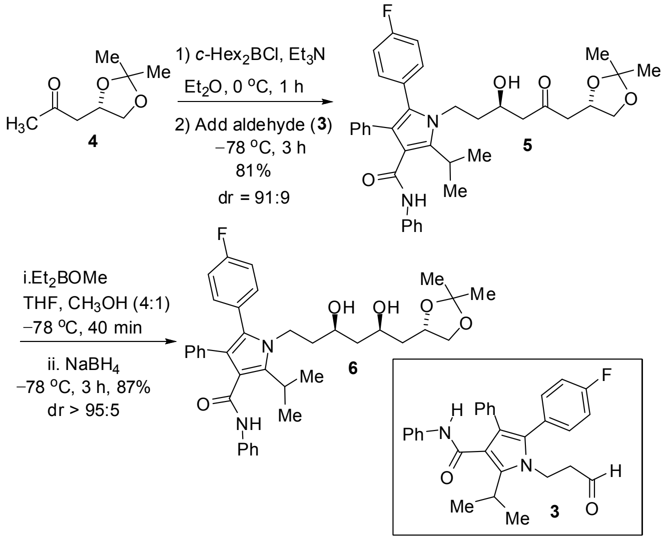
## Results and Discussion

A process chemistry development program was undertaken to improve the synthesis of calcium atorvastatin (**1**) using the remote 1,5-asymmetric induction in a boron-mediated aldol reaction of pyrrolic aldehyde (**3**)[13-16] with β-alkoxy methylketone (**4**)[17-19] as a key step (Scheme 1).



**Scheme 1.** Retrosynthetic analysis of calcium atorvastatin (**1**)

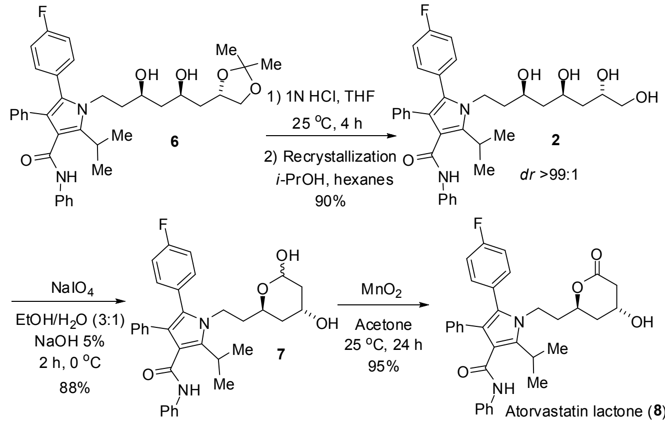
The key building blocks aldehyde **3** and methylketone **4** are know compounds and synthesized by described procedures, with slight modifications (see supporting information file).[13-19] We began our approach with the boron-mediated aldol reaction. For this purpose, methylketone (**4**) was treated with dicyclohexyl chloroborane ($c$-Hex$_2$BCl) in Et$_2$O, at 0 °C, followed by the addition of excess triethylamine to generate the corresponding kinetic boron enolate over 1 h (Scheme 2). The reaction was cooled to –78 °C, the solution of the pyrrole aldehyde (**3**) in Et$_2$O was added slowly, and the reaction was maintained for 3 h at this temperature.[11,12]




**Scheme 2.** Aldol reaction and diastereoselective reduction of β-hydroxyketone **5**

The respective aldol product **5** was obtained in 81% yield with a selectivity of 91:9 in favor of the desired 1,5-*anti* diastereoisomer, according to the NMR analysis of the crude mixture (Scheme 2). The aldol reaction was performed on a scale of 50 g of the pyrrole aldehyde (**3**) without affecting the yield and stereoselectivity of the reaction. The product in the form of the diastereoisomeric mixture was used in the next step without purification. An analytical sample was chromatographed on silica gel to achieve the physical characterization of the β-hydroxyketone product **5**.

The diastereoselective *syn*-reduction reaction of β-hydroxyketone **5** was achieved using $NaBH_4$ as the reducing agent in the presence of diethyl methoxy borane as a chelating agent (Scheme 2).[20] The *syn*-1,3-diol acetonide product **6** was obtained in 87% yield with a high diastereomeric ratio > 95:5 in favor of the desired 1,3-*syn*-isomer. The crude product was used in the next step without purification. An analytical sample was chromatographed on silica gel to achieve the physical characterization of **6**. In the next step, the diol acetonide was subjected to simple acid hydrolysis (HCl 1N, $H_2O$/THF), providing tetra-ol (**2**), as depicted in Scheme 3. At this stage, we were able to purify the tetra-ol (**2**) to obtain the single isomer. Crude tetra-ol (**2**) (17.2 g) was dissolved in isopropyl alcohol (20 mL) under stirring at 25 °C. Then, hexanes (100 mL) were slowly added over 1 h, and the mixture was allowed to stand in a refrigerator at 4 °C overnight to afford the tetra-ol as a white crystalline solid and as a single isomer in 90% yield, as observed by NMR analysis (*dr* > 99:1).




**Scheme 3.** Acid hydrolysis reaction of acetonide **6** and preparation of lactone **8.**

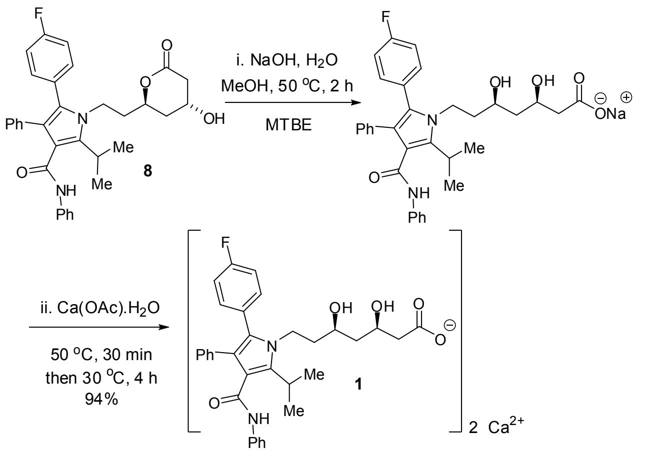
Following the reaction sequence, tetra-ol (**2**) was subjected to an oxidative cleavage reaction with sodium periodate in alkaline medium,[21] providing atorvastatin lactol (**7**) in 88% yield as a white crystalline solid (Scheme 3). Atorvastatin lactol (**7**) has been described in the literature, although it was obtained through a different process.[22] A small analytical sample of (**7**) was purified by flash column chromatography on silica gel to achieve its physical characterization, which was performed using NMR spectroscopy and HRMS analysis. The physical data were appropriately compared with the literature data.[22]

Atorvastatin lactol (**7**) was subjected to selective oxidation in the presence of excess activated $MnO_2$ to provide atorvastatin lactone (**8**), which was obtained in 95% isolated yield after recrystallization (Scheme 3).[22] Atorvastatin lactone (**8**) is a key intermediate in the original synthesis of calcium atorvastatin (**1**). The physical data for atorvastatin lactone (**8**) ($[\alpha]_D^{20}$ = +25°, c = 1, $CHCl_3$, Lit: $[\alpha]_D^{20}$ +26°, c = 1, $CHCl_3$) are in full agreement with the literature.[1c,4b,22]

In the last step, the treatment of lactone (**8**) with 10% sodium hydroxide in MeOH and MBTE followed by treatment of the resulting salt with calcium acetate monohydrate in acetone, at rt, provided calcium atorvastatin (**1**) in 94% isolated yield (Scheme 4). To confirm that the active amorphous calcium atorvastatin (**1**) was obtained, we performed powder X-ray and solid-state NMR analysis. The physical data (nuclear magnetic resonance, powder X-ray diffraction[23] and optical rotation[4b]) are in full agreement with the values reported in the literature.





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

**Conclusions**

In summary, we developed a scalable, practical asymmetric synthesis of calcium atorvastatin (**1**). The scalable process employs a highly efficient 1,5-asymmetric induction in a boron-mediated aldol reaction as a key step. In the process development, 3 new atorvastatin intermediates (compounds **2**, **5** and **6**) were produced. Calcium atorvastatin (**1**) was obtained after 6 steps with 41% overall yield.

**Experimental**

**Materials and methods**

Unless noted, all reactions were performed under an atmosphere of argon with dry solvents and magnetic stirring. Triethylamine ($Et_3N$) was distilled from $CaH_2$. Tetrahydrofuran (THF) and diethyl ether ($Et_2O$) were distilled from sodium/benzophenone. Methanol (MeOH) was distilled from $Mg(OMe)_2$ and stored over molecular sieves. Yields refer to homogeneous materials obtained after purification of reaction products by flash column chromatography using silica gel (200-400 mesh). Analytical thin-layer chromatography was performed on silica-gel 60 and GF (5-40 μm thickness) plates, and visualization was accomplished using UV light and phosphomolybdic acid staining followed by heating. Optical rotations were measured with a sodium lamp and are reported as follows: $[\alpha]_D^{T\,(°C)}$ (*c* (g/100 mL), solvent). Melting points are uncorrected. For infrared spectra (IR), wavelengths of maximum absorbance ($\nu_{max}$) are quoted in wavenumbers ($cm^{-1}$). $^1H$ and proton-decoupled $^{13}C$ NMR spectra were acquired in $C_6D_6$, $CDCl_3$, DMSO-d6 or $CD_3OD$ at 250 MHz ($^1H$) and 62.5 MHz ($^{13}C$), at 400 MHz ($^1H$) and 100 MHz ($^{13}C$), at 500 MHz ($^1H$) and 125 MHz ($^{13}C$), or at 600 MHz ($^1H$) and 150 MHz ($^{13}C$). Chemical shifts ($\delta$) are reported in ppm using residual undeuterated solvent as an internal standard ($C_6D_6$ at 7.16 ppm, $CDCl_3$ at 7.25 ppm, $CD_3OD$ at 3.30 ppm, and TMS at 0.00 ppm for $^1H$ NMR spectra and $C_6D_6$ at 128.0 ppm, $CDCl_3$ at 77.0 ppm, $CD_3OD$ at 49.0 ppm for $^{13}C$ NMR spectra). Multiplicity data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, br s = broad singlet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, dtd = doublet of triplet of doublets, dqd = doublet of quartet of doublets, m = multiplet, and br m = broad multiplet. The multiplicity is followed by the coupling constant(s) in Hz and integration. High-resolution mass spectra (HRMS) were measured using electrospray ionization (ESI). Samples were analyzed using a hybrid 7T Fourier transform ion cyclotron nanoelectrospray ionization source. The nanoelectrospray conditions were a flow rate of 200 nL $min^{-1}$, back pressure of approximately 0.4 psi, and electrospray voltages of 1.5-2.0 kV over 60 s and were controlled by ChipSoft software. Mass resolution was fixed at 100,000 at *m/z* 400. Data were obtained as transient files (scans recorded in the time domain). All samples were evaluated in positive ESI(+) ion mode, and spectra were acquired in the *m/z* 150–1500 range. Samples were analyzed directly in a 10 μg $mL^{-1}$ methanol solution without any sample treatment or dilution.

**Synthesis**

**1-(*R*)-6-(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-5-oxohexyl)-5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1H-pyrrole-3-carboxamide (5).** To a solution of methylketone (**4**) (35.0 g, 220 mmol) in anhydrous $Et_2O$ (700 mL) under argon atmosphere at 0 °C was added *c*-$Hex_2BCl$ (95.0 mL, 440 mmol) over 50 min. Next, triethylamine (108.0 mL, 770 mmol) was slowly added over 40 min. The reaction mixture was stirred for 1 h at 0 °C to generate the kinetic boron enolate. Then, the reaction was cooled to –78 °C, and pyrrole aldehyde (**3**) (50.0 g, 110 mmol) dissolved in $Et_2O$ (300 mL) was slowly added to the solution of the generated boron enolate over 1 h. The reaction was stirred for 3 h at –78 °C, quenched by the addition of methanol (100 mL) and warmed to 25 °C. The solvent was removed under reduced pressure (30 °C/150 mmHg), and the residue was purified by passing through a plug of silica (hexanes/acetate 7:3). The unreacted ketone (**4**) (15.7 g) was recovered. The product **5** (dr 91:9 according $^1H$ NMR analysis) was obtained as a white solid (81% yield; 54.6 g). Mp 62-64 °C. $[\alpha]_D^{20}$= + 2.3° (c = 1.0, $CHCl_3$). $^1H$ NMR (250 MHz, $C_6D_6$) $\delta$ 1.33 (s, 3H), 1.43 (s, 3H), 1.50-1.78 (m, 3H), 1.86 (d, *J* = 7.0 Hz, 6H), 1.92-2.01 (m, 2H), 2.32 (dd, *J* = 15.0 Hz, 6.7 Hz, 1H), 2.94 (s, 1H), 3.34 (t, *J* = 7.5 Hz, 1H), 3.73-3.79 (m, 2H), 3.94-4.00 (m, 2H), 4.13-4.31 (m, 2H), 6.77-7.01 (m, 7H), 7.10-7.16 (m, 4H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H). $^{13}C$ NMR (125 MHz, $C_6D_6$) $\delta$ 21.9, 22.1, 25.5, 26.7, 27.0, 38.2, 41.4, 47.2, 49.4, 64.8, 69.3, 71.7, 109.0, 115.6 (d, $J_{C-F}$ = 21.3 Hz), 116.9, 119.4, 122.4, 123.5, 126.7, 127.8, 127.9, 128.5, 128.8 (d, $J_{C-F}$ = 5.0 Hz), 129.0, 133.5 (d, $J_{C-F}$ = 8.8 Hz), 135.2, 139.5, 141.8, 162.5 (d, $J_{C-F}$ = 247.6 Hz), 164.7, 208.2. IR (thin film, $cm^{-1}$): 3405, 2975, 1729, 1671. HRMS (ESI-TOF) *m/z* calcd for $C_{37}H_{42}FN_2O_5$ $(M + H)^+$ 613.3077, found 613.3078.

**1-(3*R*,5*R*)-6-[(*S*)-2,2-(dimethyl-1,3-dioxolan-4-yl)]-3,5-dihydroxyhexyl-5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (6).** To a solution of (**5**) (50.0 g, 81.7 mmol) in THF/MeOH (4:1) (600 mL) under argon atmosphere at –78 °C was slowly added $Et_2B(OMe)$ (15.0 mL, 89.8 mmol) over 30 min. After 40 min, $NaBH_4$ (3.4 g, 89.8 mmol) was added in portions, and the reaction mixture was maintained at –78 °C for 3 h. The reaction was quenched by the addition of glacial acetic acid (70 mL), methanol (70 mL) and 30% $H_2O_2$ (20 mL). The mixture was vigorously stirred for 30 min and was extracted with ethyl acetate (3 x 400 mL). Next, the organic phase was washed with brine (2 x 200 mL), and the solvent was removed under reduced pressure. The product (**6**) can be used in the next step without purification. An analytical sample was purified by silica gel flash column chromatography (hexane/acetate 8:2) to achieve the physical characterization of 1,3-diol (**6**). The product (**6**) was obtained as a white solid in 87% yield (43.6 g, 71.0 mmol). Mp 71-73 $^{o}$C. $[\alpha]_D^{20}$= +2.5 (c = 1.0, $CHCl_3$). $^1$H NMR (500 MHz, $C_6D_6$) $\delta$ 1.26-1.33 (m, 10H), 1.60-1.73 (m, 2H), 1.77 (d, *J* = 7.2 Hz, 6H), 3.29-3.32 (m, 1H), 3.40 (s, 1H), 3.61 (s, 1H), 3.74-3.77 (m, 3H), 3.90-4.08 (m, 3H), 4.15-4.23 (m, 1H), 6.71 (t, *J* = 8.5 Hz, 2H), 6.80 (s, 1H), 6.82-6.95 (m, 4H), 7.03-7.16 (m, 4H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H). $^{13}$C NMR (125 MHz, $C_6D_6$) $\delta$ 22.0, 22.2, 25.6, 26.7, 26.9, 39.9, 40.6, 41.5, 43.0, 69.3, 69.9, 70.2, 73.3, 109.0, 115.4 (d, $J_{C\text{-}F}$ = 21.3 Hz), 116.7, 119.5, 122.4, 123.6, 126.7, 127.9, 128.2, 128.4 (d, $J_{C\text{-}F}$ = 5.0 Hz), 129.0, 130.7, 133.5 (d, $J_{C\text{-}F}$ = 7.5 Hz), 135.8, 139.4, 141.7, 162.5 (d, $J_{C\text{-}F}$ = 247.6 Hz), 165.0. HRMS (ESI-TOF) *m/z* calcd for $C_{37}H_{44}FN_2O_5$ $(M + H)^+$ 615.3234, found 615.3235. IR (thin film, $cm^{-1}$): 3415, 2973, 1669.

**5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1-((3*R*,5*R*,7*S*)-3,5,7,8-tetrahydroxyoctyl)-1*H*-pyrrole-3-carboxamide (2).** To a solution of 1-((3*R*,5*R*)-6-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,5-dihydroxyhexyl)-5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (**6**) (40.0 g, 65.1 mmol) in THF (600 mL) at 25 °C was slowly added aqueous 1 M HCl (64.0 mL) over 15 min. The reaction mixture was kept under stirring for 4 h, and over this time, a saturated aqueous $NaHCO_3$ solution (200 mL) was added (until pH = 8). The mixture was extracted with ethyl acetate (3 x 400 mL), the solvent was removed under *vacuum*, and the residue was recrystallized from isopropyl alcohol/hexanes. Tetra-ol (**2**) was obtained as a white solid in 90% yield (33.6 g, 58.6 mmol) as a single isomer according to $^1$H NMR analysis. Mp 85-88 $^{o}$C. $[\alpha]_D^{20}$= +3.2 (c = 1.0, MeOH). $^1$H NMR (500 MHz, $CD_3OD$) $\delta$ 1.37-1.41 (m, 2H), 1.48-1.54 (m, 7H), 1.59-1.80 (m, 3H), 3.30-3.40 (m, 3H), 3.65 (s, 1H), 3.78-3.92 (m, 4H), 7.01-7.31 (m, 14H). $^{13}$C NMR (125 MHz, MeOD) $\delta$ 22.8, 27.6, 40.4, 41.8, 42.3, 45.3, 67.8, 68.0, 69.0, 70.0, 116.3 (d, $J_{C\text{-}F}$ = 22.6 Hz), 118.0, 121.5, 123.3, 125.2, 126.9, 128.9, 129.6, 130.2 (d, $J_{C\text{-}F}$ = 3.8 Hz), 130.3, 130.9, 134.7 (d, $J_{C\text{-}F}$ = 8.8 Hz), 136.3, 139.1, 139.8, 163.8 (d, $J_{C\text{-}F}$ = 246.3 Hz), 169.5. HRMS (ESI-TOF) *m/z* calcd for $C_{34}H_{40}FN_2O_5$ $(M + H)^+$ 575.2922, found 575.2921. IR (thin film, $cm^{-1}$): 3413, 2972, 1668.

**1-[2-((2*R*,4*R*)-4,6-dihydroxytetrahydro-2*H*-pyran-2-yl)ethyl]-5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (7).** To a solution of tetra-ol (**2**) (32.0 g, 54.8 mmol) in anhydrous ethanol (500 mL) at 0 °C was slowly added a solution of $NaIO_4$ (35.2 g, 164.4 mmol) and NaOH (0.216 g, 5.4 mmol) in 90 mL of $H_2O$. The reaction mixture was stirred for 2 h at 25 °C, and a saturated aqueous solution of $NH_4Cl$ (300 mL) was added. The mixture was extracted with ethyl acetate (3 x 400 mL) and washed with brine (200 mL). Lactol (**7**) was obtained as a white solid in 88% yield (25.6 g, 47.4 mmol). Mp 103-107 $^{o}$C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.37-1.50 (m, 1H), 1.53 (d, *J* = 7.0 Hz, 6H), 1.65-1.83 (m, 3H), 1.86-1.89 (m, 2H), 3.51-3.54 (m, 1H), 3.82-3.94 (m, 1H), 4.08-4.13 (m, 4H), 4.27 (d, *J* = 7.5 Hz, 1H), 5.18 (s, 1H), 6.90 (s, 1H), 6.96-7.20 (m, 14H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 21.7, 21.8, 26.1, 35.0, 37.4, 39.5, 41.4, 60.4, 65.0, 92.5, 115.3 (d, $J_{C\text{-}F}$ = 21.3 Hz), 119.6, 120.1, 121.8, 123.6, 126.5, 128.1 (d, $J_{C\text{-}F}$ = 2.5 Hz), 128.5, 128.8, 129.7, 130.4, 133.1 (d, $J_{C\text{-}F}$ = 8.8 Hz), 134.5, 138.1, 141.2, 162.2 (d, $J_{C\text{-}F}$ = 247.6 Hz), 165.0. HRMS (ESI-TOF) *m/z* calcd for $C_{33}H_{36}FN_2O_4$ $(M + H)^+$ 543.2659, found 543.2659. IR (thin film, $cm^{-1}$): 3414, 2973, 1670.

**5-(4-fluorophenyl)-1-[2-((2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl)ethyl]-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (8) (atorvastatin lactone).** To a solution of atorvastatin lactol (**7**) (24.0 g, 44.2 mmol) in acetone (350 mL) was added activated $MnO_2$ (37.4 g, 442.0 mmol) at 25 °C. The suspension was kept under stirring for 24 h at 25 °C. The reaction mixture was filtered, and the solvent evaporated. Atorvastatin lactone (**8**) was obtained in 95% (22.7 g, 42.0 mmol) yield as a white crystalline solid. Mp 159-161 $^{o}$C. $[\alpha]_D^{20}$ = +26.9$^{o}$ (c = 1.0, $CHCl_3$) (obtained). Lit:[4b] $[\alpha]_D^{20}$ = +26.0$^{o}$ (c = 1.0, $CHCl_3$). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.52 (d, *J* = 7.0 Hz, 6H), 1.58-1.90 (m, 4H), 2.54-2.58 (m, 2H), 2.89 (s, 1H), 3.49-3.55 (m, 1H), 4.01-4.24 (m, 3H), 4.48-4.52 (m, 1H); 6.91 (s, 1H), 6.99-7.21 (m, 14H). $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ 21.6, 21.9, 26.1, 35.5, 37.0, 38.4, 40.6, 62.1, 73.0, 115.5 (d, $J_{C\text{-}F}$ = 21.3 Hz), 115.7, 119.7, 122.0, 123.7, 126.6, 127.9, 128.3, 128.6 (d, $J_{C\text{-}F}$ = 5.6 Hz), 128.8, 130.3, 133.0 (d, $J_{C\text{-}F}$ = 8.2 Hz), 134.3, 138.0, 141.2, 162.3 (d, $J_{C\text{-}F}$ = 247.8 Hz), 165.0, 169.7. IR (thin film, $cm^{-1}$): 3410, 2952, 1750, 1673.

**Calcium atorvastatin (1).** To a solution of atorvastatin lactone (**8**) (20.0 g, 37.0 mmol) in methanol (50 mL) and methyl-*tert*-butyl ether (MTBE) (130 mL) was added NaOH (1.53 g, 38.1 mmol) dissolved in water (250 mL). The resulting mixture was stirred for 2 h at 50 °C. After cooling (20 °C), the phases were separated, and the aqueous phase (which contains the product) was washed with MTBE (80 mL). The aqueous phase was separated and the pH was adjusted to 8.0 by the addition of aqueous 1 M HCl; the solution was then heated at 50 °C. The resulting mixture was treated with a solution of calcium acetate monohydrate (3.27 g, 20.3 mmol) in water (70 mL), and the mixture was heated to 50 °C. The reaction was stirred for 30 min, and it was slowly cooled to 30 °C for 4 h. The precipitated product (**1**) was filtered and washed with methanol/$H_2O$ (1:1) (150 mL). Calcium atorvastatin (**1**) was obtained as a white amorphous solid in 94% yield (20.1 g, 17.4 mmol) after recrystallization in THF/MeOH/$H_2O$ and drying under high *vacuum* for 12 h. Purity by HPLC: 99.98%, (>99.5 ee). Mp 174-178 °C. Lit.[22a] mp 177-182 °C. $[\alpha]_D^{20} = -7.1^o$ (c = 1.0, DMSO). Lit[4b] $[\alpha]_D^{20} = -7.4^o$ (c = 1.0, DMSO). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 1.22-1.25 (m, 1H), 1.37 (d, *J* = 7.0 Hz, 6H), 1.40-1.42 (m, 1H), 1.51-1.62 (m, 2H), 1.94-1.98 (m, 1H), 2.08-2.11 (m, 1H), 3.21-3.24 (m, 1H) 3.36 (s, 2H), 3.54 (s, 1H), 3.70-3.78 (m, 2H), 3.93-3.97 (m, 1H), 6.86-7.01 (m, 2H), 7.06-7.08 (m, 4H), 7.16-7.26 (m, 6H), 7.51 (d, *J* = 8.0 Hz, 2H), 9.80 (s, 1H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 22.2, 22.3, 25.6, 39.9, 40.8, 43.6, 43.9, 66.2 (2C), 115.3 (d, $J_{C-F}$ = 20.1 Hz), 117.4, 119.4, 120.5, 122.9, 125.3, 127.2, 127.6, 128.5, 128.7 (d, $J_{C-F}$ = 2.5 Hz), 129.1, 133.3 (d, $J_{C-F}$ = 8.7 Hz), 134.9, 135.9, 139.4, 161.5 (d, $J_{C-F}$ = 245.1 Hz), 166.1, 178.1. IR (KBr, $cm^{-1}$) 3418, 3062, 2961, 2873, 1793, 1660, 1528, 1480.

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**Notes and references**

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† Electronic Supplementary Information (ESI) available: $^1$H NMR, $^{13}$C NMR, IR, and HRMS spectra of the prepared compounds. See DOI: 10.1039/b000000x/

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