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Asymmetric Synthesis of the HMG-CoA Reductase Inhibitor Atorvastatin Calcium: An Organocatalytic Anhydride Desymmetrization and Cyanide-Free Side Chain Elongation Approach

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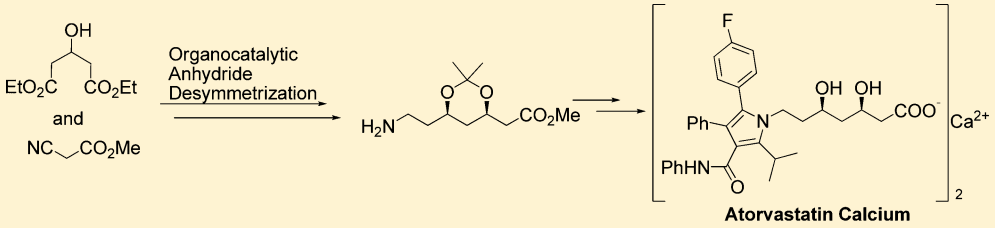
Supporting Information



ABSTRACT: An efficient asymmetric synthesis of atorvastatin calcium has been achieved from commercially available diethyl 3-hydroxyglutarate through a novel approach that involves an organocatalytic enantioselective cyclic anhydride desymmetrization to establish C(3) stereogenicity and cyanide-free assembly of C_7 amino type side chain via C_5+C_2 strategy as the key transformations.

Cardiovascular disease (CVD) poses a serious threat to world public health and continues to be the growing concern. The strong association between low-density lipoprotein cholesterol (LDL-c) as well as lipoprotein [LP(a)] levels and cardiovascular risk is well-defined and underlines their central role in the pathogenesis of arteriosclerotic plague.[1] Medications used for the treatment of hyperlipidemia are numerous, but no class of drugs is as widely prescribed as those that inhibit 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase (Statins).[2] The reason for extensive use of statins is their favorable efficiency, safe profiles, and long-term clinical benefits in reducing the risk for cardiovascular events and death in patients with or without established CVD. Atorvastatin calcium (Lipitor, **1**, Figure 1) was first introduced to the market in 1997 by Pfizer as an effective HMG-CoA reductase inhibitor for the treatment of hypercholesterolemia and arteriosclerosis and now ranks at the top of the drugs best sold in the world.[3] To date, joint synthetic development efforts led to a number of strategies that make use of chemoenzymatic resolution[4] or chiral auxiliary[5] at an appropriate stage, enantioselective catalysis,[6] or starting from the chiral pool.[7] However, to the best of our knowledge, none of the known synthetic routes appears to have a commercial advantage over the long used Paal–Knorr pyrrole approach via two advanced building blocks of diketone **2** and C_7 amino type side chain **3** with a *syn*-1,3-diol pattern developed by the Warner-Lambert company in 1989 (Scheme 1).[7a−c]

The major drawback of this large-scale synthesis lies in the manipulation of a large excess of high toxic cyanide in lengthening this C_7 statin skelton through a C_3 + C_1 + C_2 + C_1 route (the equivalent of C_1 synthon is NaCN or KCN). In addition, the dependence on a single synthetic process for the supply of such an important drug is unwise. As a result, development of alternative synthetic approaches toward **3**, which use cyanide-free material to complete asymmetric synthesis of **1**, is an urgent demand. Herein we report a new,

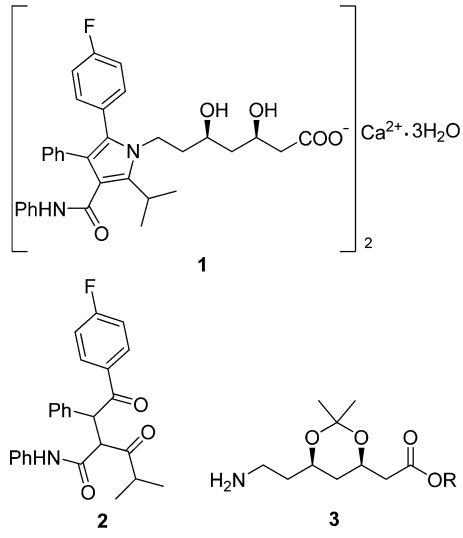


Figure 1. Structures of **1** and its important intermediate **2** and **3**.

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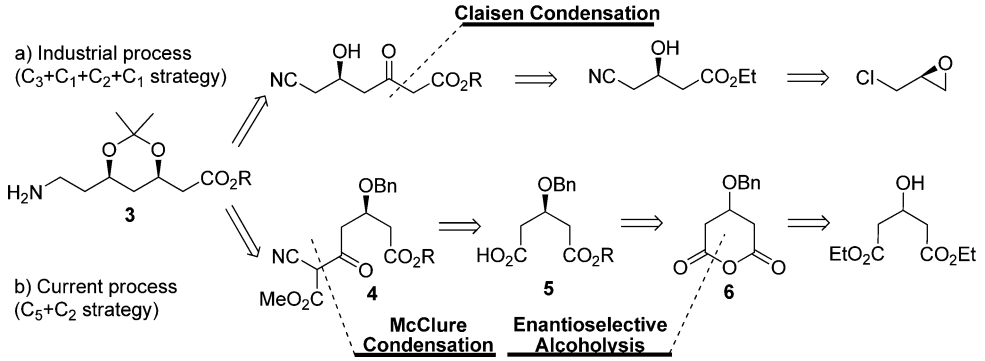
Scheme 1. Outline of the Industrial Process and the Current Process

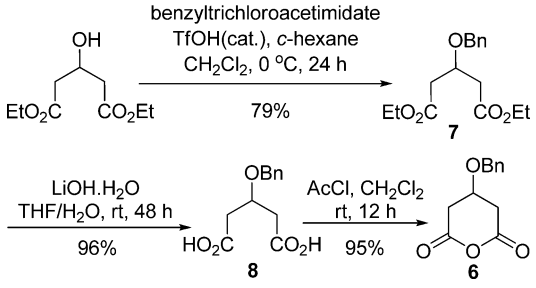


short, enantiocontrolled route to **1** starting from easily available diethyl 3-hydroxyglutarate.

Our approach toward this statin side chain **3** was designed with the view that its 3*R*-chirality and C_7 amino type side chain could be assembled through the use of an enantioselective desymmetrization and C_5 + C_2 strategy, respectively. As indicated in our synthetic plan (Scheme 1), the enantioselective alcoholysis using our developed bifunctional sulfonamide catalysts would be expected to set the requisite 3*R* stereochemistry from cyclic anhydride **6**, while the cyanide-free installation of C_7 cyano type side chain **4** could be reached through a DEPC-promoted condensation of chiral hemiester **5** (C_5 synthon) with methyl cyanoacetate (C_2 synthon), which would in turn be converted into **3** by a Krapcho decarboxylation, deprotection, Narasaka's reduction, protection, and reduction sequence.

Given the importance of enantiomerically pure hemiester **5** to the success of our planned asymmetric synthesis, we sought an efficient method to access the desired **5**. With this idea in mind, we paid our attention to organocatalytic enantioselective desymmetrization[8] of **6** by alcoholysis employing our developed bifunctional sulfonamide catalysts **9a–d**.[9] As delineated in Scheme 2, we initially prepared cyclic anhydride

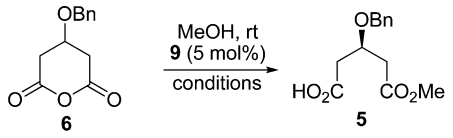
Scheme 2. Synthesis of Cyclic Anhydride 6

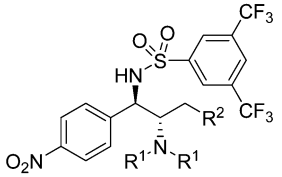


6 from commercially available diethyl 3-hydroxyglutarate. Treatment of diethyl 3-hydroxyglutarate with benzyl trichloroacetimidate in the presence of a catalytic amount of trifluoromethanesulfonic acid in cyclohexane and methylene chloride afforded the corresponding benzyl ether **7** in 79% yield,[10] which was subjected to LiOH-hydrolysis and dehydration with acetyl chloride in methylene chloride to yield **6** in 91% overall yield (over two steps).

With **6** in hand, we were poised to examine the desired catalytic enantioselective methanolysis under different reaction conditions. First, our developed bifunctional sulfonamide organocatalysts **9a–d** were screened for this transformation. As is seen from entries 1–4 in Table 1, the catalyst **9b** afforded the desired hemiester **5** of the highest enantioselectivity (80% ee) when the reaction of **6** with excess methanol was performed in methyl *tert*-butyl ether (MTBE) in the presence of 5 mol % organocatalysts **9a–d** at room temperature. The influence of solvent on enantioselectivity is very crucial. Very low enantioselectivities (42% and 36% ee) were detected in methylene chloride and acetonitrile using 5 mol % **9b**, and moderate enantioselectivities (70%, 76%, and 78% ee) were obtained in toluene, tetrahydrofuran, and diethyl ether, respectively (entries 5–9). MTBE is the best choice for this methanolysis. A slightly improvement in enantioselectivity

Table 1. Condition Optimization of the Enantioselective Methanolysis of Cyclic Anhydride 6[a]





9a: R^1= Me, R^2= OTr; **9b**: R^1= $(CH_2)_4$, R^2= OTr
9c: R^1= $(CH_2)_5$, R^2= OTr; **9d**: R^1= $(CH_2)_4$, R^2= F

entry	cat.	solvent	concn[c]	*T* (h)	yield[d] (%)	ee[e] (%)
1	**9a**	MTBE	0.1	96	93	79
2	**9b**	MTBE	0.1	96	92	80
3	**9c**	MTBE	0.1	120	91	52
4	**9d**	MTBE	0.1	120	87	54
5	**9b**	CH_2Cl_2	0.1	72	89	42
6	**9b**	toluene	0.1	120	89	70
7	**9b**	CH_3CN	0.1	120	90	36
8	**9b**	THF	0.1	96	90	76
9	**9b**	Et_2O	0.1	96	93	78
10	**9b**	MTBE	0.05	96	92	85
11	**9b**	MTBE	0.025	120	92	88
12	**9b**	MTBE	0.0125	168	92	88
13	**9b**[b]	MTBE	0.0125	168	93	90

[a]Unless otherwise noted, all reactions were carried out with **6** (0.5 mmol), **9** (0.025 mmol), and MeOH (5.0 mmol). [b]The catalyst loading was 10 mol %. [c]The concentration of **6** (mol/L). [d]Yield of isolated product. [e]Determined by HPLC.

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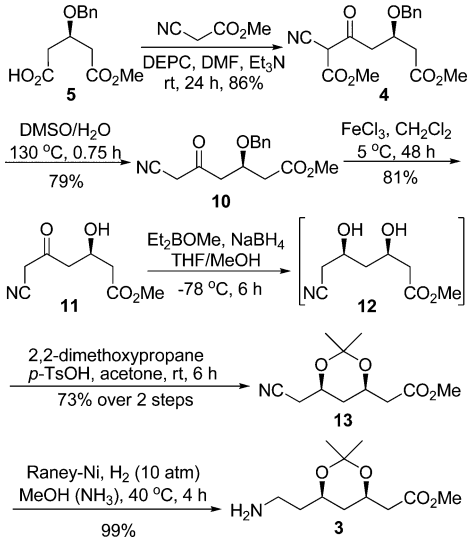
(from 80% to 88% ee) was observed by decreasing the concentration of substrate from 0.1 to 0.0125 mol/L in the presence of 5 mol % **9b** (entries 10−12). A tiny increase in enantioselectivity (90% ee) was achieved by enhancing catalyst loading from 5 to 10 mol % (entry 13). The absolute configuration of **5** was determined to be the required *R* by comparing the measured specific rotation with reported data.[11]

The remaining key step is the elongation of C_7 side chain **4** possessing a cyano functional group from C_5 side chain **5**. Treatment of **5** (90% ee) with methyl cyanoacetate in the presence of diethyl pyrocarbonate (DEPC) and excess triethylamine furnished the diester **4** in 86% yield under McClure's reaction condition.[12] Decarboxylation of **4** in wet DMSO at 130 °C was smoothly converted into the ketoester **10** in 79% yield. Cleavage of benzyl ether in **10** upon treating anhydrous ferric trichloride in anhydrous CH_2Cl_2 at 5 °C for 48 h gave rise to debenzyl product **11** in 81% yield (Scheme 3).

Scheme 3. Synthesis of Key Intermediate 3



Diastereoselective reduction of **11** using the procedure of the Narasaka group[13] gave the corresponding diol **12**, which was then protected with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid to furnish 1,3-dioxane **13** in an overall yield of 73% with excellent diastereoselectivity [(4*R*,6*R*)-1,3-dioxane **13a**/(4*R*,6*S*)-1,3-dioxane **13b** = 95/5, determined by GC−MS analysis). The stereochemistry of **13a** and **13b** confirmed by using NOESY experiments is consistent with the mechanism proposed by Narasaka et al. for the reduction of acyclic *β*-hydroxyketones via boron chelate with sodium borohydride in the stereoselective preparation of 1,3-diols (Figure 2).[13,16] Catalytic hydrogenation of **13** with a mixture of Raney-Ni and methanolic ammonia proceeded smoothly to afford the desired amine **3** in almost quantitative yield.[7c]

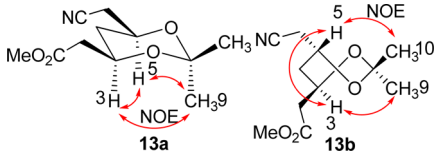
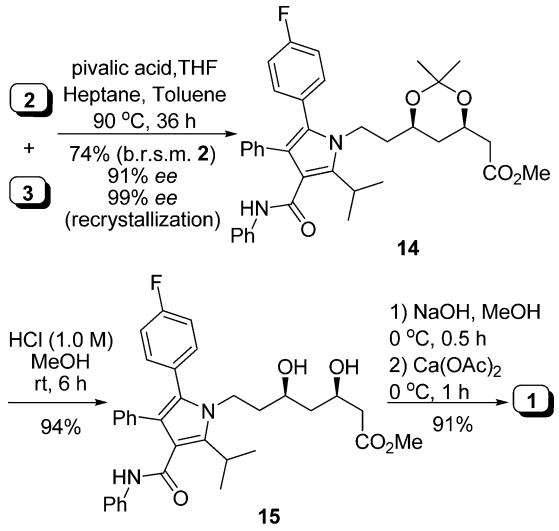


Figure 2. NOESY correlations of **13a** and **13b**.

Finally, the Paal−Knorr condensation[7c] of diketone **2** and amine **3** was carried out in the presence of pivalic acid at 90 °C for 36 h to provide pyrrolic compound **14** in 74% yield (brsm **2**) with 91% ee, which was upgraded to 99% ee after recrystallization using EtOAc/PE (1:8) in 81% recovered yield. The deprotection of **14** by treatment with hydrochloric acid (1.0 M) in methanol at room temperature afforded diol **15** in 94% yield. Hydrolysis of **15** with sodium hydroxide (1.0 M) in methanol at 0 °C and salification with 5% aqueous calcium acetate at 0 °C in sequence furnished **1** in an overall yield of 91% over two steps (Scheme 4). In addition, we have

Scheme 4. Synthesis of Atorvastatin Calcium (1)



determined the crystalline form of **1** by X-ray powder diffraction. The crystalline form observed is consistent with Form I reported by the Warner-Lambert company.[17]

In conclusion, the organocatalytic anhydride desymmetrization and cyanide-free side chain elongation strategy detailed in this paper represents an efficient and practical process for the asymmetric synthesis of atorvastatin calcium (**1**) starting from readily available and cheap diethyl 3-hydroxyglutarate. We believe that our approach would be of great benefit to industrial application after further optimization of reaction conditions in each step.

EXPERIMENTAL SECTION

Diethyl 3-(Benzyloxy)-glutarate (7).[10] To a stirred solution of diethyl 3-hydroxyglutarate (20.4 g, 0.10 mol) and benzyltrichloroacetimidate (20.3 mL, 0.11 mol) in 500 mL of 4:1 *c*-hexane/CH_2Cl_2 at 0 °C was added TfOH (0.44 mL, 5 mmol). The reaction mixture was stirred at 0 °C for 24 h before being quenched by Et_3N and filtered. The filtrate was concentrated and purified by column chromatography (silica gel, PE/EtOAc 20:1) to afford **7** (23.3 g, 79%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 6H), 2.60 (dd, J = 5.6, 15.6 Hz, 2H), 2.67 (dd, J = 6.8, 15.6 Hz, 2H), 4.14 (q, J = 7.2 Hz, 4H), 4.31−4.37 (m, 1H), 4.59 (s, 2H), 7.24−7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 39.7, 60.5, 72.1, 72.8, 127.6, 127.7, 128.3, 138.0, 170.9; IR (thin film) 2980, 1732, 1453, 822, 742 cm^{-1}; MS (EI) m/z (%) = 249.0 [M − EtO] (1), 91.1 [Bn] (100).

3-(Benzyloxy)-glutaric Acid (8).[10] To a stirred solution of **7** (14.7 g, 0.05 mol) in 100 mL of 4:1 THF/H_2O was added LiOH·H_2O (5.25 g, 0.125 mol) at 20 °C. The reaction mixture was stirred at 20 °C for 48 h before the THF was evaporated. The aqueous layer was washed with EtOAc (50 mL), acidified with 2.0 M HCl, and then

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extracted with EtOAc (3 × 200 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford **8** (11.4 g, 96%) as a white solid that was pure enough to be used in next step directly: mp 147.8−151.2 °C (EtOAc); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.54 (d, J = 6.4 Hz, 4H), 4.13−4.20 (m, 1H), 4.52 (s, 2H), 7.24−7.34 (m, 5H), 12.30 (brs, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 39.1, 70.8, 73.0, 127.4, 127.5, 128.2, 138.6, 172.4; IR (KBr) 3063, 1709, 1427, 923, 754, 701 cm^{-1}; MS (ESI) m/z = 261 (M + Na$^+$).

3-(Benzyloxy)-glutaric Anhydride (6).[14] To a stirred suspension of **8** (11.4 g, 48 mmol) in 50 mL of CH_2Cl_2 at 0 °C was added AcCl (16.9 mL, 240 mmol). The reaction mixture was stirred at rt for 12 h before being concentrated. The crude anhydride was dissolved in 300 mL of CH_2Cl_2, washed with 5% aq $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to afford **6** (10.0 g, 95%) as a white solid that was pure enough to be used in next step directly: mp 82.6−84.8 °C (EtOAc), lit.[14] mp 79−80 °C ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (dd, J = 2.0, 16.8 Hz, 2H), 3.08 (dd, J = 2.8, 16.8 Hz, 2H), 4.07 (m, 1H), 4.55 (s, 2H), 7.27−7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.6, 66.9, 70.8, 127.6, 128.1, 128.5, 136.5, 165.0; IR (KBr) 2939, 1819, 1773, 1427, 934, 739 cm^{-1}; MS (ESI) m/z = 243 (M + Na$^+$).

(*R*)-3-(Benzyloxy)-5-methoxy-5-oxopentanoic Acid (5).[11] To a stirred solution of **6** (110 mg, 0.5 mmol) and catalysts **9a−d** (0.025 mmol) in anhydrous solvent (see Table 1) under argon atmosphere at rt was added MeOH (0.2 mL, 5.0 mmol). The reaction was stirred until the starting material was consumed before being concentrated and then purified by column chromatography (silica gel, PE/EtOAc/AcOH 5:1:0.05 to EtOAc/MeOH 20:1) to afford **5** (pale yellow oil, yields 87−93%) and recover **9a−d** (white solid, recovered yields 88−92%), ee of **5**: 36−90%, determined by HPLC analysis, Daicel, Chiralpak AS-H column (25 cm × 4.6 mm × 5 μm), n-hexane/isopropanol = 95/5, 0.5 mL/min, 258 nm, 30 °C, t_R (major) = 45.8 min, t_R (minor) = 71.5 min; $[\alpha]^{12.3}_D$ +2.3 (c 1.0, $CHCl_3$, 90% ee), lit.[11] (*S*)-**5**: $[\alpha]^{25}_D$ −0.3 (c 10.0, $CHCl_3$, 40% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62−2.76 (m, 4H), 3.69 (s, 3H), 4.30−4.36 (m, 1H), 4.61 (s, 2H), 7.26−7.35 (m, 5H), 10.80 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.2, 39.3, 51.8, 72.1, 72.3, 127.8, 127.8, 128.3, 137.7, 171.3, 176.9; IR (thin film) 3530, 1732, 1712, 1495, 746, 693 cm^{-1}; MS (ESI) m/z = 251 (M − H$^+$).

(5*R*)-Dimethyl 5-(Benzyloxy)-2-cyano-3-oxoheptanedioate (4). To a stirred solution of **5** (12.6 g, 50 mmol, 90% ee) and methyl cyanoacetate (4.4 mL, 50 mmol) in 75 mL of anhydrous DMF under argon atmosphere at 0 °C was added triethylamine (20.8 mL, 150 mmol). The reaction mixture was stirred at 0 °C for 15 min before diethyl pyrocarbonate (8.7 mL, 60 mmol) was added. The mixture was then stirred at 20 °C for 24 h before being quenched by brine and addition of dilute HCl to adjust to pH = 5 at 0 °C. The mixture was extracted with 1000 mL of EtOAc and washed with brine, dried over Na_2SO_4, concentrated, and then purified by column chromatography (silica gel, PE/EtOAc/AcOH 4:1:0.05) to afford **4** (14.3 g, 86%) as a pale brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (dd, J = 6.0, 16.0 Hz, 1H), 2.74 (dd, J = 7.2, 16.0 Hz, 1H), 2.90 (dd, J = 6.0, 14.0 Hz, 1H), 2.97 (dd, J = 6.8, 14.0 Hz, 1H), 3.68 (s, 3H), 3.88 (s, 3H), 4.30−4.36 (m, 1H), 4.59 (s, 2H), 7.27−7.34 (m, 5H), 13.56 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.4, 39.5, 51.8, 53.0, 72.1, 72.9, 82.6, 114.4, 127.8, 127.9, 128.3, 137.4, 170.2, 170.9, 187.2; IR (thin film) 2956, 2228, 1737, 1660, 879, 750, 696 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{17}H_{20}NO_6$ (M + H)$^+$ 334.1285, found 334.1290.

(*R*)-Methyl 3-(Benzyloxy)-6-cyano-5-oxohexanoate (10). A stirred solution of **4** (1.3 g, 4 mmol) in 12 mL of DMSO and 3 mL of H_2O under argon atmosphere was heated to 130 °C for 45 min. The mixture was added to 200 mL of EtOAc and washed with brine, dried over Na_2SO_4, concentrated, and then purified by column chromatography (silica gel, PE/EtOAc 3:1) to afford **10** (0.86 g, 79%) as a pale yellow oil; $[\alpha]^{14.7}_D$ +27.7 (c 1.0, $CHCl_3$, 90% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.59 (dd, J = 6.4, 15.6 Hz, 1H), 2.67 (dd, J = 5.6, 15.6 Hz, 1H), 2.82 (dd, J = 4.8, 16.4 Hz, 1H), 2.90 (dd, J = 7.2, 16.4 Hz, 1H), 3.45 (s, 2H), 3.68 (s, 3H), 4.29−4.35 (m, 1H), 4.49 (d, J = 11.2 Hz, 1H), 4.60 (d, J = 11.2 Hz, 1H), 7.27−7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.0, 38.4, 46.7, 51.8, 71.8, 72.1, 113.5, 127.9, 128.0, 128.5, 137.3, 170.9, 195.9; IR (thin film) 3033, 2262, 1732, 1627, 1498, 885, 770 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{15}H_{18}NO_4$ (M + H)$^+$ 276.1230, found 276.1246.

(*R*)-Methyl 3-Hydroxy-6-isocyano-5-oxohexanoate (11). To a stirred suspension of anhydrous $FeCl_3$ (1.36 g, 8 mmol) in 30 mL of anhydrous CH_2Cl_2 under argon atmosphere at 0 °C was added a solution of **10** (560 mg, 2 mmol) in 20 mL of anhydrous CH_2Cl_2. The reaction mixture was stirred at 5 °C for 48 h before being quenched by water, concentrated, and then purified by column chromatography (silica gel, PE/EtOAc 3:2) to afford **11** (300 mg, 81%) as a pale yellow oil; $[\alpha]^{25.8}_D$ +8.6 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55 (d, J = 6.0 Hz, 2H), 2.75 (dd, J = 4.0, 16.0 Hz, 1H), 2.79 (brs, 1H), 2.82 (dd, J = 8.0, 16.0 Hz, 1H), 3.60 (s, 2H), 3.72 (s, 3H), 4.46−4.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.1, 40.2, 47.8, 52.0, 64.2, 113.5, 172.2, 196.9; IR (thin film) 3442, 2962, 2263, 1730, 1442, 1065 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_8H_{12}NO_4$ (M + H)$^+$ 186.0761, found 186.0763.

Methyl 2-((4*R*)-6-(Cyanomethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (13). To a stirred solution of **11** (1.84 g, 10 mmol) in 100 mL of anhydrous THF and 20 mL of methanol under argon atmosphere at −10 °C was added Et_2BOMe (12 mL, 1.0 M in THF). The reaction mixture was stirred for 30 min at −10 °C before being cooled to −78 °C, and then $NaBH_4$ (456 mg, 12 mmol) was added in batches. The mixture was stirred at −78 °C for 6 h before being quenched by HOAc. The solvent was removed, then extracted with EtOAc (3 × 100 mL), dried over Na_2SO_4, and concentrated. The residue was coevaporated with MeOH to afford the diol **12** (1.6 g, 86%) as a colorless oil. To a stirred solution of **12** (1.6 g, 8.6 mmol) and 2,2-dimethoxypropane (5.3 mL, 43.0 mmol) in 20 mL of acetone under argon atmosphere at rt was added p-TsOH·H_2O (0.16 g, 0.86 mmol). The reaction mixture was stirred at 20 °C for 6 h before being quenched by Et_3N, and solvents were removed to obtain **13** (1.6 g, 73% from **11**) as a colorless oil that was pure enough to be used in next step directly. The dr of the residue was measured by GC−MS: Agilent, HP-5MS column (30 m × 0.25 mm × 0.25 μm), injector temperature 280 °C, oven temperature program from 80 °C (2 min) to 280 °C at 10 °C/min, carrier gas He, flow rate 0.9 mL/min, ionization energy 70 eV in the electronic ionization (EI) mode, t_R (minor) = 13.0 min, t_R (major) = 13.4 min. The analytic sample was purified by column chromatography (silica gel, PE/EtOAc 8:1) to afford the **13a**[4e] and **13b**; **13a**: $[\alpha]^{22.9}_D$ +1.2 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26−1.35 (m, 1H), 1.36 (s, 3H), 1.45 (s, 3H), 1.74 (dt, J = 2.4, 12.8 Hz, 1H), 2.40 (dd, J = 6.0, 15.6 Hz, 1H), 2.50 (dd, J = 4.0, 6.0 Hz, 2H), 2.56 (dd, J = 6.8, 15.6 Hz, 1H), 3.67 (s, 3H), 4.13 (ddt, J = 2.4, 6.0, 11.6 Hz, 1H), 4.32 (ddt, J = 2.0, 6.4, 11.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 24.9, 29.6, 35.3, 40.8, 51.7, 64.9, 65.3, 99.5, 116.7, 171.0; IR (thin film) 2998, 2255, 1740, 1442, 987, 937, 884 cm^{-1}; MS (ESI) m/z = 228 (M + H$^+$); **13b**: $[\alpha]^{19.0}_D$ +27.5 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.38 (s, 3H), 1.75−1.86 (m, 2H), 2.46 (dd, J = 5.6, 15.6 Hz, 1H), 2.53 (d, J = 6.0 Hz, 2H), 2.57 (dd, J = 8.0, 15.6 Hz, 1H), 3.69 (s, 3H), 4.05−4.12 (m, 1H), 4.28−4.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 24.3, 24.6, 36.7, 40.2, 51.7, 62.6, 63.1, 101.4, 116.9, 170.9; IR (thin film) 2991, 2252, 1737, 1442, 994 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{11}H_{17}NNaO_4$ (M + Na)$^+$ 250.1050, found 250.1056.

Methyl 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 (14). A high pressure steel autoclave was filled with **13** (240 mg, 1.0 mmol) and 0.2 g of Raney-Ni suspended in MeOH (10 mL) saturated with ammonia gas. The autoclave was pressurized to 10 atm with H_2 and stirred at 40 °C for 4 h. The mixture was filtered and concentrated to afford crude amine **3** (240 mg, 99%) as a pale yellow oil. To a stirred solution of diketone **2** (340 mg, 0.8 mmol) and amine **3** (240 mg, 1.0 mmol) in heptane (8 mL)/toluene (1 mL)/THF (1 mL) at rt was added pivalic acid (92 mg, 0.9 mmol). The reaction mixture was heated to 90 °C for 36 h before solvents were removed. The residue was purified by column chromatography (silica gel, PE/EtOAc 6:1) to afford **14** [320 mg, 63%, (74%, brsm **2**)] as a white solid: mp 78.3−80.6 °C (EtOAc).

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The ee of **14** was upgraded from 91% to over 99% by a single recrystallization using EtOAc/PE (1:8), determined by HPLC analysis, Daicel, Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm), *n*-hexane/isopropanol = 98/2, 1.0 mL/min, 254 nm, 30 °C, t_R (minor) = 32.4 min, t_R (major) = 36.0 min; recovered yield 81%; $[\alpha]^{27.1}_D$ +7.5 (*c* 1.0, $CHCl_3$, 99% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24−1.30 (m, 1H), 1.30 (s, 3H), 1.36 (s, 3H), 1.53 (d, *J* = 7.2 Hz, 6H), 1.67 (m, 3H), 2.32 (dd, *J* = 6.4, 15.6 Hz, 1H), 2.51 (dd, *J* = 6.8, 15.6 Hz, 1H), 3.53−3.60 (m, 1H), 3.67 (s, 3H), 3.71 (m, 1H), 3.79−3.86 (m, 1H), 4.04−4.11 (m, 1H), 4.17−4.23 (m, 1H), 6.87 (s, 1H), 6.96−7.01 (m, 3H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.16−7.19 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 21.5, 21.7, 26.1, 29.9, 35.9, 38.0, 40.8, 41.0, 51.6, 65.5, 66.3, 98.8, 115.2, 115.3 (d, J_{C-F} = 3.3 Hz), 115.4, 119.5, 121.8, 123.5, 126.5, 128.3, 128.5 (d, J_{C-F} = 43.2 Hz), 128.6, 130.5, 133.2 (d, J_{C-F} = 8.3 Hz), 134.6, 138.4, 141.5, 162.2 (d, J_{C-F} = 247.3 Hz), 164.8, 171.2; IR (KBr) 3407, 2955, 1740, 1666, 753, 688 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{37}H_{42}FN_2O_5$ $(M + H)^+$ 613.3072, found 613.3090.

(3*R*,5*R*)-Methyl 7-(2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl)-3,5-dihydroxyheptanoate (15). To a stirred solution of **14** (240 mg, 0.4 mmol) in MeOH (6 mL) at rt was added HCl (1 mL, 1.0 M, 1.0 mmol), which was then reacted for 6 h before being quenched by 5% $NaHCO_3$. The reaction mixture was added to 30 mL of brine, extracted with EtOAc (3 × 50 mL), dried over Na_2SO_4, concentrated, and then purified by column chromatography (silica gel, PE/EtOAc 3:2) to afford **15**[15] (220 mg, 94%) as a white powder: mp 92.7−96.3 °C (EtOAc), lit.[15] mp 110−112 °C; $[\alpha]^{27.7}_D$ −1.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43−1.49 (m, 1H), 1.54 (d, *J* = 7.2 Hz, 6H), 1.58−1.74 (m, 2H), 2.41 (d, *J* = 6.0 Hz, 2H), 3.54−3.61 (m, 1H), 3.70 (s, 3H), 3.74 (m, 2H), 3.90−3.98 (m, 1H), 4.07−4.18 (m, 2H), 6.88 (s, 1H), 6.96−7.01 (m, 3H), 7.06 (d, *J* = 8.0 Hz, 2H), 7.15−7.19 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 21.7, 26.1, 39.0, 41.2, 41.2, 41.7, 51.8, 68.8, 69.5, 115.2, 115.3 (d, J_{C-F} = 3.4 Hz), 115.4, 119.6, 121.8, 123.5, 126.5, 128.3, 128.5 (d, J_{C-F} = 37.6 Hz), 128.6, 130.4, 133.2 (d, J_{C-F} = 8.1 Hz), 134.6, 138.3, 141.4, 162.2 (d, J_{C-F} = 246.3 Hz), 164.8, 172.9; IR (KBr) 3413, 2952, 1730, 1651, 1601, 838, 753 cm^{-1}; MS (ESI) *m*/*z* = 595 $(M + Na^+)$.

Atorvastatin Calcium (1). To a stirred solution of **15** (120 mg, 0.2 mmol) in MeOH (1 mL) at 0 °C was added NaOH (0.5 mL, 1.0 M, 0.5 mmol), which was then reacted at 0 °C for 30 min before a solution of 5% $Ca(OAc)_2$ was added. The mixture was stirred at 0 °C for 1 h before the resulting white slurry was filtrated, washed, and dried in a vacuum to afford **1**[7c] (105 mg, 91%) as a white powder: mp 172.9−175.5 °C (water), lit.[18] mp 177−182 °C; 99% ee, determined by HPLC analysis, Daicel, Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm), *n*-hexane/EtOH/HOAc = 92/8/0.3, 1.0 mL/min, 244 nm, 30 °C, t_R (major) = 26.7 min, t_R (minor) = 18.4 min; $[\alpha]^{26.9}_D$ −7.9 (*c* 0.7, DMSO), lit.[7c] $[\alpha]_D$ −7.4 (*c* 1.0, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.19−1.25 (m, 1H), 1.37 (d, *J* = 6.8 Hz, 6H), 1.49−1.54 (m, 1H), 1.55−1.65 (m, 1H), 1.91 (dd, *J* = 7.6, 15.2 Hz, 1H), 2.05 (dd, *J* = 4.0, 15.2 Hz, 1H), 3.19−3.28 (m, 1H), 3.53 (m, 2H), 3.68−3.80 (m, 2H), 3.91−3.98 (m, 1H), 6.96−7.03 (m, 2H), 7.06−7.08 (m, 4H), 7.16−7.26 (m, 6H), 7.50 (d, *J* = 8.0 Hz, 2H), 9.80 (s, 1H); IR (KBr) 3360, 2962, 1656, 842, 810, 745 cm^{-1}; MS (ESI) *m*/*z* = 559 (acid, $M + H^+$).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR, GC−MS, HPLC, and XRPD spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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