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ARTICLE

New Chloramphenicol Schiff Base Ligands for the Titanium-Mediated Asymmetric Aldol Reaction of *α, β*-unsaturated Aldehydes with Diketene: A Short Synthesis of Atorvastatin Calcium

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Several novel chiral Schiff base ligands were prepared from a commercially available chloramphenicol base and applied to the titanium-mediated asymmetric aldol reaction of diketene with various *α, β*-unsaturated aldehydes. This reaction proceeded in good yield with high enantioselectivity. The synthetic utility of this methodology was demonstrated in the short synthesis of atorvastatin calcium.

Introduction

Although first reported more than 20 years ago,[1] the enormous potential of the titanium-mediated asymmetric aldol reaction in organic synthesis remained largely unexplored until fairly recently.[2] In particular, the stereoselective construction of δ-hydroxyl-β-ketoesters via an asymmetric aldol reaction represents an efficient strategy for the synthesis of stereodefined 1,3-diols, which can be found in numerous natural products and pharmaceutically important molecules[3]. Some of the most important developments in this area have focused on titanium-mediated asymmetric aldol reactions in the presence of chiral Schiff base ligands, including 2-amino alcohols-type ligands derived from α-amino acids, BINOL-type ligands, oxazoline-type ligands and ferrocene-type ligands (Figure 1).[4] However, most of the chiral Schiff base ligands reported to date were derived from expensive or commercially unavailable starting materials. The development of increasingly elegant and cost-effective chiral Schiff bases is therefore highly desirable.

(1*S*,2*S*)-2-Amino-1-(p-nitrophenyl)propane-1,3-diol (Chloramphenicol base, **5**) is produced as a by-product during the industrial manufacture of chloramphenicol. We previously reported a series of chloramphenicol base-driven processes to provide high levels of stereocontrol in several asymmetric transformations, including the enantioselective asymmetric alcoholysis of *meso*-cyclic anhydrides and asymmetric transfer hydrogenation/dynamic kinetic resolution processes.[5] As part of our ongoing work towards the utilization of chloramphenicol base in asymmetric synthesis, we herein describe a series of novel chiral Schiff bases ligands and their application to the enantioselective aldol reaction of diketene with a series of *α, β*-unsaturated aldehydes.

Results and discussion

The synthetic route used to prepare the new chloramphenicol Schiff base ligands **La–Lf** is outlined in Scheme 1. The known intermediate **6** was prepared from **5** according to a procedure from the literature.[6] Compound **6** was subsequently reacted with various substituted salicylaldehydes in boiling methanol in the presence of Na_2SO_4 to give the desired chiral chloramphenicol Schiff base ligands **La–Lf**.

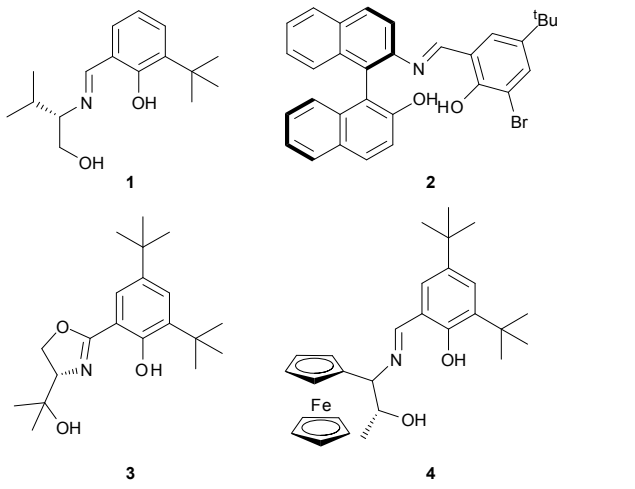

Fig 1. Structures of reported chiral Schiff base ligands

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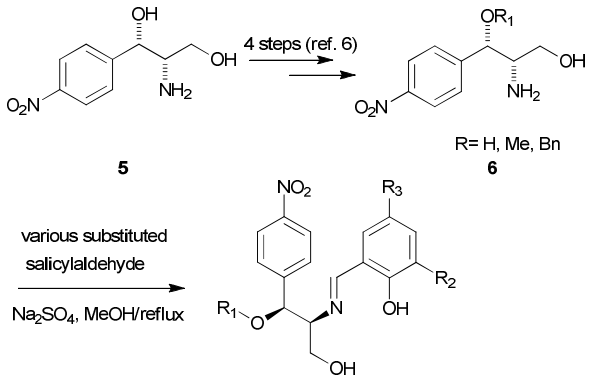
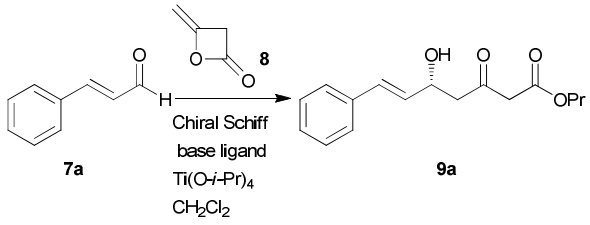
Cinnamaldehyde (**7a**) and diketene (**8**) were selected as model substrates to determine the best ligand for the titanium-catalyzed aldol reaction. The reaction of **7a** with **8** in the presence of Ti(O-i-Pr)$_4$ and ligand **La** in CH_2Cl_2 at −40 °C for 48 h gave the desired product **9a** in a low yield of 20% with no enantioselectivity (Table 1, entry 1). We then turned our attention to a series of chiral alkyl ether chloramphenicol Schiff base ligands. After screening several chiral chloramphenicol Schiff base ligands, we were pleased to find that ligand **Lf** was a good candidate for the model reaction, giving **9a** in 70% yield with 72% ee (Table 1, entry 6). Reducing the reaction temperature to −60 °C resulted in a decrease in the yield without any increase in the enantioselectivity, whereas increasing the reaction temperature to −20 °C led to a sharp decrease in the enantioselectivity (Table 1, entries 7, 9). Furthermore, the reaction failed to afford any of the desired product when it was conducted at −78 °C (Table 1, entry 8).



Scheme 1. Synthesis of the chiral Schiff base ligands **La–Lf**

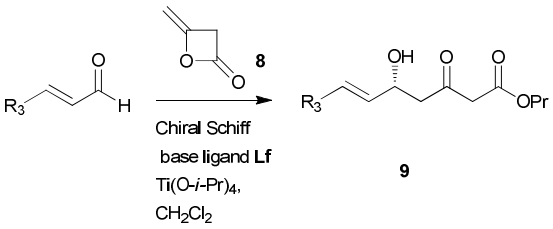
Table 1. Asymmetric aldol reaction of diketene with cinnamaldehyde promoted by the chiral Schiff Base ligands **La–Lf**

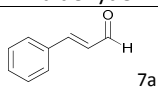
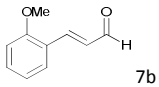
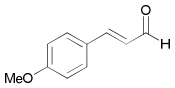
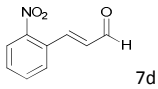
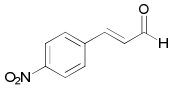
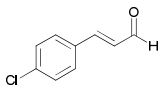
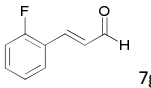
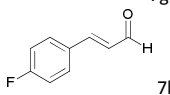
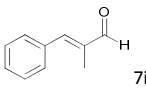
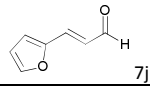


Entry	Catalyst[a]	Temp[(o)C]	Time (h)	Yield (%)[b]	ee (%) [c]
1	**La**	-40	48	20	n.d.
2	**Lb**	-40	48	69	62
3	**Lc**	-40	48	63	66
4	**Ld**	-40	48	72	69
5	**Le**	-40	48	67	71
6	**Lf**	-40	48	70	72
7	**Lf**	-60	70	46	68
8	**Lf**	-78	70	trace	n.d.
9	**Lf**	-20	20	70	47

[a] All of these reactions were carried out in CH_2Cl_2 using 2.0 equiv. of Ti(O-i-Pr)$_4$ and 2.2 equiv. of chiral Schiff base ligands at –40 °C. [b] Isolated yield after silica-gel column chromatography. [c] HPLC analysis (CHIRALPAKAD).

Table 2. Asymmetric aldol reactions of various aldehydes with diketene promoted by the chiral Schiff Base **Lf** and Ti(O-i-Pr)$_4$



Entry	aldehyde[a]	*T* (h)	Yield(%)[b]	*ee* (%)[c]
1	 7a	48	70	72
2	 7b	48	61	75
3	 7c	48	68	70
4	 7d	48	65	69
5	 7e	48	60	71
6	 7f	48	71	68
7	 7g	48	67	60
8	 7h	48	72	64
9	 7i	48	70	70
10	 7j	48	60	80

[a] All of these reactions were carried out in CH_2Cl_2 using 2.0 equiv. of Ti(O-i-Pr)$_4$ and 2.2 equivalents of chiral Schiff base **Lf** at –40 °C. [b] Isolated yield after silica-gel column chromatography. [c] HPLC analysis (CHIRALPAKAD).

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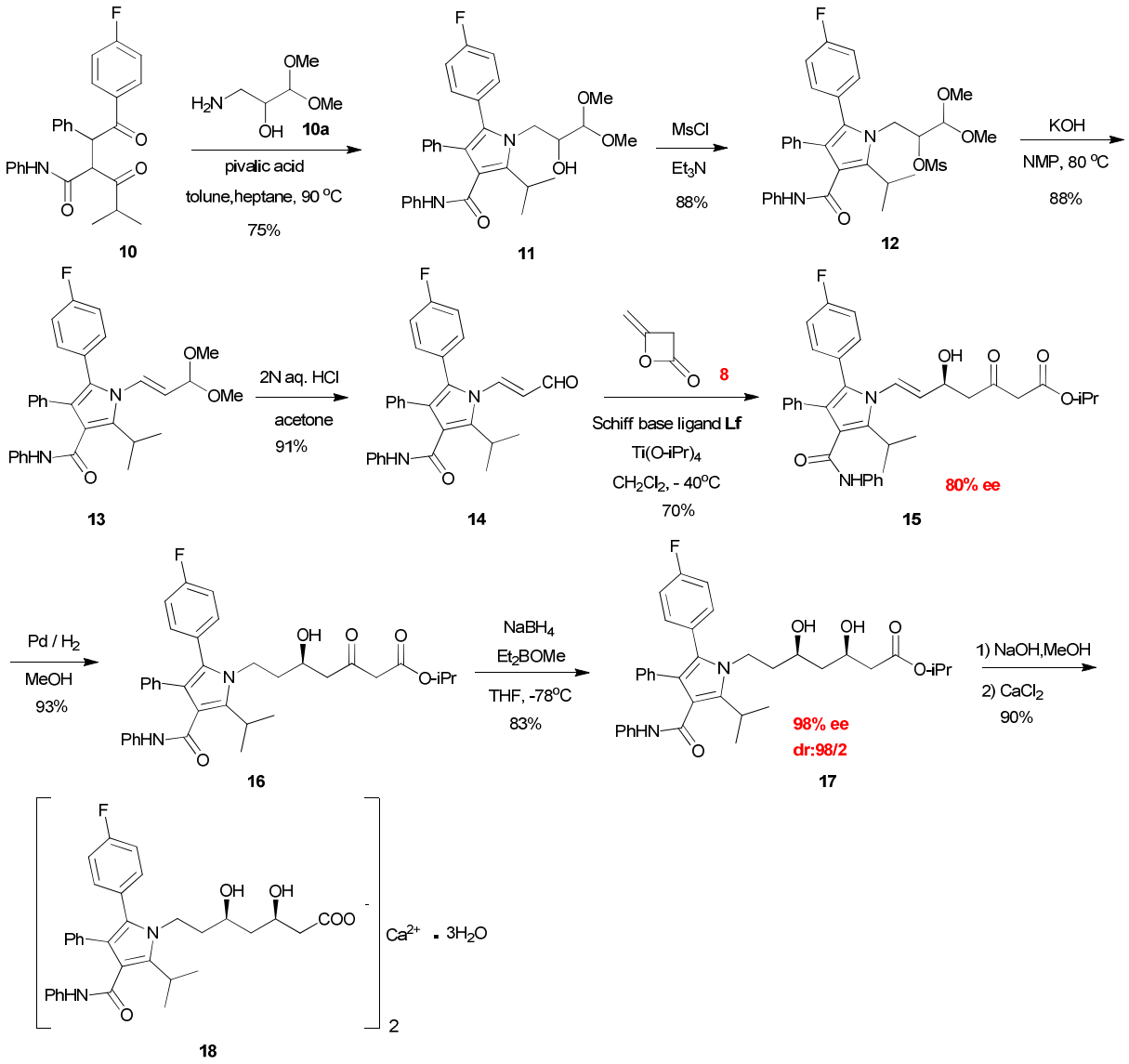

Scheme 2. Synthesis of atorvastatin calcium.

With the optimal conditions in hand, we proceeded to investigate the scope of this reaction using a variety of *α*, *β*-unsaturated aldehydes and **8** in the presence of Ti(O-i-Pr)$_4$ with the chiral chloramphenicol Schiff base ligand **Lf** (Table 2). As shown in Table 2, the yields and enantioselectivities were generally moderate to high for *α*, *β*-unsaturated aldehydes bearing an electron-donating or electron-withdrawing group on their phenyl ring (Tale 2, entries 2–8). Pleasingly, substrate **7i** bearing a 4-methyl group on its phenyl ring also reacted smoothly under the optimized conditions to give the corresponding product in 70% yield and 70% ee (Table 2, entry 9). When benzene ring was replaced with a furan ring, we observed a remarkable increase in the enantioselectivity of the reaction (Table 2, entry 10).

To illustrate the value of this new methodology, we performed a novel formal total synthesis of atorvastatin calcium (**18**), which is currently used in clinical practice as a HMG-CoA reductase inhibitor.[7] The route used for the synthesis to **18** is shown in scheme 2. The Paal–Knorr condensation[8] of diketone **10** with amine **10a** was carried out in refluxing toluene/heptane (9:1, v/v) in the presence of pivalic acid for 48 h to give the fully substituted pyrrole **11** in 75% yield. The subsequent reaction of **11** with methanesulfonyl chloride at room temperature gave sulfonate **12** in 88% yield, which was reacted with powdered KOH in NMP at 80 °C to give the vinyl acetal **13** in 88% yield. The selective hydrolysis of **13** with 2 N aq. HCl in acetone at room temperature afforded (*E*)-α,β-unsaturated aldehyde **14** as a single stereoisomer, as determined by NMR analysis. The stereogenic center at the C5-

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position of the side chain in atorvastatin calcium (**18**) was installed by the enantioselective aldol reaction of **14** with diketene **8**. This reaction was conducted in the presence of the chiral chloramphenicol Schiff base ligand **Lf** and $Ti(O\text{-}i\text{-}Pr)_4$ in CH_2Cl_2 at −40 °C, affording the δ-hydroxyl-β-ketoester **15** in 70% yield with 80% ee. The hydrogenation of **15** using palladium on carbon under an atmosphere of hydrogen (1 atm.) provided saturated ester **16**. The subsequent diastereoselective reduction of **16** gave the syn-1,3-diol ester **17** in 83% yield, with the syn-isomer being formed as the major product (98:2, syn/anti) without any discernible loss of enantiomeric purity.[9] Pleasingly, the optical purity of **17** was further improved to 98% ee by its recrystallization from CH_3CN/H_2O (5:1, v/v). The hydrolysis of the syn-1,3-diol ester **17**, followed by the treatment of the carboxylate with $CaCl_2$ gave atorvastatin calcium (**18**) in 90% yield over two steps. All spectral data collected for **18** were in complete agreement with those reported in the literature.[10]

Conclusions

In conclusion, we have evaluated a series of novel chiral chloramphenicol Schiff base ligands for the titanium-mediated asymmetric aldol reaction of various *α*, *β*-unsaturated aldehydes with diketene. The results revealed that ligand **Lf** afforded the highest levels of enantioselectivity of all of the ligands evaluated in the current study. We subsequently used this method to achieve a novel asymmetric synthesis of Atorvastatin Calcium, thereby highlighting its synthetic utility. Further studies towards expanding the scope of this method are currently underway in our laboratory.

Experimental section

Unless otherwise specified, all reagents and solvent were purchased from commercial suppliers and used without further purification. CH_2Cl_2 was distilled from calcium hydride; THF was distilled from sodium–benzophenone. ^1H (400 MHz), ^1H (500 MHz) and ^{13}C (100 MHz) NMR were recorded on a Bruker Avance 400 or 500 spectrometer using TMS as internal standards. Melting points were measured on WRS-1B digital metlting-point apparatus. Optical rotations were measured by a JASCO P1020 digital polarimeter. HRMS were recorded on a Bruker micrOTOF spectrometer. HPLC analysis were performed with Daicel Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm). Racemic products were prepared at room temperature without chiral Schiff base ligand. The enantiomericratios, expressed as % ee, were determined by HPLC analysis as specified in the individual experimental descriptions and verified using the appropriate racemic mixtures. The absolute configurations of 9a,[4a, 4f] 16,[10] 17[10] and 18[10] were established by comparisons of their optical rotations with literature values. All other absolute configurations were assigned by analogy, unless otherwise stated.

General procedure for the preparation of the chiral Schiff base ligands La-Lf

To a solution of **6** (3.54 mmol) in MeOH (10 mL) was added substituted salicylaldehyde (3.54 mmol) and Na_2SO_4 (2.5 g, 17.7mmol, 5eq.). Then the reaction mixture was stirred to reflux for 16 hours. The misxture was filtered,concentrated, and purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 1:1, v/v) to afford the chiral Schiff base ligands **La-Lf** as yellow solid.

(1S,2S)-2-((E)-(3,5-di-tert-butyl-2-hydroxybenzylidene)amino) -1-(4-nitrophenyl)propane-1,3-diol. (La)

The compound **La** was prepared in 92% yield as a yellow solid. mp: 56-58 °C, $[\alpha]^{20}_D$ = + 216.6 (c 1, $CHCl_3$). 1H NMR(400 MHz, $CDCl_3$): δ = 8.33 (s, 1H), 8.16 (d, 8.4 Hz, 2H), 7.53 (d, 8.8 Hz, 2H),7.43 (s, 1H), 7.07 (d, 2.4 Hz, 1H), 5.10 (d, 5.6 Hz, 1H), 3.75-3.72 (m, 2H), 3.48 (q, 5.2, 1H), 1.43 (s, 9H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, CDCl3): δ = 168.4, 160.3, 147.8, 146.1, 137.5, 130.2, 130.0, 128.3, 123.7, 118.3, 118.1, 83.2, 75.4, 63.2, 57.6, 34.8, 29.3. HRMS (ESI) calcd for $C_{24}H_{33}N_2O_5$ $[M+H]+$ 429.2384, found 429.2378.

2-((E)-(((1S,2S)-1-(benzyloxy)-3-hydroxy-1-(4-nitrophenyl)propan-2-yl)imino)methyl)-4,6-di-tert-butylphenol. (Lb)

The compound **Lb** was prepared in 56% yield as a yellow solid. mp: 75-77 °C, $[\alpha]^{20}_D$ = +150.0 (c 1, $CHCl_3$). 1H NMR(400 MHz, $CDCl_3$): δ = 8.40 (s, 1H), 8.25 (d, 8.8 Hz, 2H), 7.58 (d, 8.4 Hz, 2H),7.45 (d, 2.0 Hz, 1H), 7.30-7.28 (m, 1H), 5.10 7.23-7.20(m, 1H), 7.11 (s,1H), 4.71(d, 6 Hz, 1H), 4.54 (d, 12 Hz, 1H), 4.25 (d, 12 Hz, 1H), 3.64-3.53 (m, 3H), 1.49 (s, 9H), 1.32 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0, 158.0, 147.8, 146.3, 140.3, 137.1, 136.7, 128.5, 128.4, 127.9, 127.8, 127.6, 126.4, 123.8, 117.6, 79.9, 75.6, 71.1, 63.0, 35.0, 34.1, 31.4, 29.4. HRMS (ESI) calcd for $C_{31}H_{38}N_2O_5$ $[M+H]^+$ 519.2853, found 519.2849.

2-(tert-butyl)-6-((E)-(((1S,2S)-3-hydroxy-1-methoxy-1-(4-nitrophenyl)propan-2-yl)imino)methyl)-4-((4-vinylbenzyl)oxy)phen -ol (Lc)

The compound **Lc** was prepared in 91% yield as a yellow solid. mp: 64-66 °C, $[\alpha]^{20}_D$ = + 132.1 (c 1, $CHCl_3$). 1H NMR(400 MHz, $CDCl_3$): δ = 8.24 (t, 8.0 Hz, 3H), 7.54 (d, 8.4 Hz, 2H), 7.40 (dd, J_1 = 8.4 Hz, J_2 = 19.2 Hz, 4H), 7.08 (d, 2.8 Hz, 1 H), 6.73 (dd, J_1 =10.8 Hz, J_2 = 17.6 Hz, 1H), 6.65 (d, 2.8 Hz, 1H), 5.76 (d, 17.6 Hz, 1H),7.43 (s, 1H), 5.26 (d, 10.8 Hz, 1H), 4.99 (s, 2 H), 4.53 (d, 6.4 Hz, 1H), 3.71-3.58 (m, 2H), 3.51-3.47 (m, 1H), 3.25 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2, 155.1, 150.5, 147.9, 146.1, 139.2, 136.7, 136.4, 128.3, 127.7, 126.4, 123.7, 119.8, 117.7, 114.1, 113.2, 83.2, 75.5, 70.6, 63.2, 57.6, 35.0, 29.3. HRMS (ESI) calcd for $C_{30}H_{35}N_2O_6$ $[M+H]^+$ 519.2490, found 519.2496.

2,4-di-tert-butyl-6-((E)-(((1S,2S)-3-hydroxy-1-methoxy-1-(4-nitrophenyl)propan-2-yl)imino)methyl)phenol (Ld).

The compound **Ld** was prepared in 90% yield as a yellow solid. mp : 69-70 °C. $[\alpha]^{20}_D$ = + 145.7 (c 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 13.3 (s, 1H), 8.36 (s, 1H), 8.24 (d, 8.4 Hz, 2H), 7.55 (d, 8.8 Hz, 2H), 7.43 (d, 8.8 Hz, 1H), 7.10 (d, 2.0 Hz, 1H), 4.53 (d, 6.0 Hz, 1H), 3.69-3.58 (m, 2H), 3.52-3.48 (m, 1H),3.25

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(s, 3H), 1.46 (s, 9H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 158.0, 147.9, 146.2, 140.5, 136.8, 128.4, 127.7, 126.5, 123.8, 117.6, 83.3, 75.6, 63.3, 57.7, 35.1, 34.2, 31.5, 29.5. HRMS (ESI) calcd for $C_{25}H_{35}N_2O_5$ $[M+H]^+$ 443.2540, found 443.2540.

2-(adamantan-1-yl)-6-((E)-(((1S,2S)-3-hydroxy-1-methoxy-1-(4-nitrophenyl)propan-2-yl)imino)methyl)-4-methylphenol. (Le)

The compound **Le** was prepared in 93% yield as a yellow solid. mp: 214-216°C. [α] $^{20}_D$ = + 159.5 (c 1, $CHCl_3$). ^{1}H NMR(400 MHz, $CDCl_3$): δ = 13.3 (s, 1H), 8.31-8.26 (m, 3H), 7.53 (d, 8.4 Hz, 2H), 7.11 (s, 1H), 6.89 (s, 1H), 4.53 (d, 6.0 Hz, 1H), 3.68-3.57 (m, 2H), 3.48-3.46 (m, 1H), 3.24 (s, 3H), 2.28 (s, 3H), 2.17 (s, 5H), 2.09 (s, 3H), 1.80 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 158.3, 147.8, 146.2, 137.5, 131.1, 130.0, 128.3, 127.0, 123.7, 118.0, 83.2, 75.6, 63.2, 57.6, 40.3, 37.1, 36.9, 29.0, 20.6. HRMS (ESI) calcd for $C_{28}H_{35}N_2O_5$ $[M+H]^+$ 479.2540, found 479.2548.

2-(tert-butyl)-6-((E)-(((1S,2S)-3-hydroxy-1-methoxy-1-(4-nitrophen yl)propan-2-yl)imino)methyl)phenol. (Lf)

The compound **Lf** was prepared in 88% yield as a yellow solid. mp :113-115°C. [α] $^{20}_D$ = + 196.8 (c 1, $CHCl_3$). ^{1}H NMR(400 MHz, $CDCl_3$): δ = 13.6 (s, 1H), 8.33 (s, 1H), 8.23 (d, 8.8 Hz, 2H), 7.54 (d, 8.8 Hz, 2H), 7.36 (d, 7.6 Hz, 1H), 6.83 (t, J_1 =7.6 Hz, J_2 =, 1H), 4.54 (d, 6.4 Hz, 1H), 3.72-3.59 (m, 2H), 3.52-3.48 (m, 1H), 3.25 (s, 3H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 160.3, 147.8, 146.1, 137.4, 130.2, 130.0, 128.3, 123.7, 118.4, 118.1, 83.2, 75.4, 63.2, 57.6, 34.8, 29.3. HRMS (ESI) calcd for $C_{21}H_{27}N_2O_5$ $[M+H]^+$ 387.1914, found 387.1908.

General procedure of asymmetric aldol reaction of various aldehydes 7a-j promoted by chiral Schiff Base Lf.

To a solution of Schiff base **Lf** (1.1 mmol) in dichloromethane (5 mL) was added Ti(O-i-Pr)$_4$ (1 mmol) at r.t. under N_2 atmosphere. After stirring for 1 h, the mixture was cooled to - 40 °C and various aldehydes 7a-j (0.5 mmol) was added followed by diketene 8 (420 mg, 5 mmol). The resulting mixture was stirred at- 40 °C for 48 h, then mixture was quenched with 1 N HCl solution (5 mL) and was added MTBE (10 mL). The mixture was stirred vigorously at r.t. for 1 h. The mixture was extracted with MTBE (30 mL × 3), washed with saturated aq. $NaHCO_3$ solution (10 mL ×3). The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated and purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 4:1, v/v) to afford 9a-9j as a yellow oil.

(***R, E*)-isopropyl 5-hydroxy-3-oxo-7-phenylhept-6-enoate 9a.** 97 mg (70%). [α] $^{20}_D$ = + 7.4 (c 0.9, $CHCl_3$), lit.[4a, 4f] [α] $^{28}_D$ = + 18.2 (c 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 72% ee by HPLC analysis. Absolute configuration of the major isomer was determined as (*R*) by the comparison of the specific rotation value with those previously published.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 5H), 6.66 (d, J = 16.0 Hz, 1H), 6.22 (dd, J = 15.9, 6.1 Hz, 1H), 5.07 (dt, J = 12.5, 6.3 Hz, 1H), 4.80 (d, J = 6.0 Hz, 1H), 3.49 (s, 2H), 3.11 (s, 1H), 2.94 – 2.81 (m, 2H), 1.27 (d, J = 6.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.87, 166.55, 136.48, 130.63, 130.08, 128.63, 127.85, 126.58, 77.48, 77.16, 76.84, 69.31, 68.42, 50.34, 49.69, 21.74. HRMS (ESI) calcd for $C_{16}H_{20}NaO_4$ $[M+Na]^+$ 299.1254, found 299.1266.

(*R, E*)-isopropyl 5-hydroxy-7-(2-methoxyphenyl)-3-oxohept-6-enoate 9b. 84 mg (61%). [α] $^{20}_D$ = + 5.5 (c 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 75% ee by HPLC analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, J = 7.6, 1.5 Hz, 1H), 7.24 – 7.18 (m, 1H), 6.96 – 6.83 (m, 3H), 6.22 (dd, J = 16.1, 6.3 Hz, 1H), 5.04 (dd, J = 12.6, 6.3 Hz, 1H), 4.78 (dd, J = 11.9, 5.9 Hz, 1H), 3.82 (s, 3H), 3.47 (s, 2H), 2.93 – 2.81 (m, 2H), 1.25 (d, J = 6.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.93, 166.57, 156.90, 130.71, 128.96, 127.09, 125.74, 125.43, 120.70, 110.94, 77.48, 77.16, 76.84, 69.27, 69.01, 55.47, 50.40, 49.81, 21.76. HRMS (ESI) calcd for $C_{17}H_{22}NaO_5$ $[M+Na]^+$ 329.1359, found 329.1363.

(*R, E*)-isopropyl 5-hydroxy-7-(4-methoxyphenyl)-3-oxohept-6-enoate 9c. 94 mg (68%). [α] $^{20}_D$ = - 3.4 (c 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 70% ee by HPLC analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.57 (d, J = 15.9 Hz, 1H), 6.06 (dd, J = 15.9, 6.4 Hz, 1H), 5.10 – 5.01 (m, 1H), 4.75 (d, J = 5.4 Hz, 1H), 3.79 (s, 3H), 3.46 (s, 2H), 2.89 (s, 1H), 2.84 (d, J = 6.5 Hz, 2H), 1.25 (d, J = 6.3 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.01, 166.56, 159.53, 130.41, 129.26, 127.88, 127.85, 127.81, 114.13, 77.41, 77.16, 76.91, 69.37, 68.73, 55.40, 50.44, 49.83, 21.81. HRMS (ESI) calcd for $C_{17}H_{22}NaO_5$ $[M+Na]^+$ 329.1359, found 329.1364.

(*R, E*)-isopropyl 5-hydroxy-7-(2-nitrophenyl)-3-oxohept-6-enoate 9d. 90 mg (65%). [α] $^{20}_D$ = + 24.5 (c 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 69% ee by HPLC analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.85 (m, 1H), 7.55 – 7.50 (m, 2H), 7.36 (ddd, J = 8.5, 6.4, 2.5 Hz, 1H), 7.07 (dd, J = 15.8, 1.3 Hz, 1H), 6.18 (dd, J = 15.8, 5.7 Hz, 1H), 5.05 – 5.00 (m, 1H), 4.85 – 4.76 (m, 1H), 3.47 (s, 2H), 2.88 (d, J = 6.1 Hz, 2H), 1.23 (d, J = 6.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.73, 166.56, 147.91, 135.65, 133.18, 132.40, 128.88, 128.32, 125.87, 124.55, 77.48, 77.16, 76.84, 69.38, 68.01, 50.28, 49.34, 21.91, 21.72. HRMS (ESI) calcd for $C_{16}H_{19}NNaO_6$ $[M+Na]^+$ 344.1105, found 344.1119.

(*R, E*)-isopropyl 5-hydroxy-7-(4-nitrophenyl)-3-oxohept-6-enoate 9e. 83 mg (60%). [α] $^{20}_D$ = + 19.6 (c 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 71% ee by HPLC analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 8.8 Hz, 2H), 6.75 (d, J = 16.0 Hz, 1H), 6.38 (dd, J = 15.9, 5.4 Hz, 1H), 5.06 (dt, J = 12.5, 6.3 Hz, 1H), 4.85 (s, 1H), 3.48 (s, 2H), 3.07 (d, J = 3.7 Hz, 1H), 2.90 (dd, J = 9.2, 6.0 Hz, 2H), 1.26 (d, J = 6.3 Hz, 6H). ^{13}C NMR (100 MHz, CDCl3) δ 202.85, 166.52, 147.13, 143.14, 134.94, 128.37, 127.15, 124.10, 77.48, 77.16, 76.84, 69.54, 67.89, 50.27, 49.32, 21.79. HRMS (ESI) calcd for $C_{16}H_{19}NNaO_6$ $[M+Na]^+$ 344.1105, found 344.1128.

(***R, E*)-isopropyl 7-(4-chlorophenyl)-5-hydroxy-3-oxohept-6-enoate 9f**. 98 mg (71%). [α] $^{20}_D$ = + 7.23 (c 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 68% ee by HPLC analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (dd, J = 5.1, 2.8 Hz, 4H), 6.54 (dd, J = 15.9, 1.1 Hz, 1H), 6.17 – 6.11 (m, 1H),

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5.04 – 4.98 (m, 1H), 4.73 (dt, J = 7.2, 5.9 Hz, 1H), 3.44 (s, 2H), 2.86 – 2.77 (m, 2H), 1.23 – 1.20 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.69, 166.53, 134.97, 133.27, 130.82, 129.16, 128.69, 127.72, 77.41, 77.16, 76.91, 69.25, 68.11, 50.22, 49.54, 21.65. HRMS (ESI) calcd for $C_{16}H_{19}ClNaO_4$ $[M+Na]^+$ 333.0864, found 333.0869.

(*R*, *E*)-isopropyl 7-(2-fluorophenyl)-5-hydroxy-3-oxohept-6-enoate 9g. 92 mg (67%). $[\alpha]_D^{20}$ = + 7.5 (c 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 60% ee by HPLC analysis. ^{1}H NMR (400 MHz, CDCl3) δ 7.42 (t, J = 7.0 Hz, 1H), 7.24 – 7.16 (m, 1H), 7.05 (dt, J = 19.0, 8.0 Hz, 2H), 6.79 (d, J = 16.1 Hz, 1H), 6.30 (dd, J = 16.1, 6.0 Hz, 1H), 5.06 (dt, J = 12.3, 6.2 Hz, 1H), 4.81 (s, 1H), 3.48 (s, 2H), 2.95 (s, 1H), 2.88 (d, J = 5.5 Hz, 2H), 1.26 (d, J = 6.2 Hz, 6H). 13C NMR (101 MHz, CDCl3) δ 202.99, 166.53, 161.72, 159.24, 132.71, 132.66, 129.25, 129.16, 127.81, 127.78, 124.39, 124.26, 124.23, 123.37, 123.34, 116.00, 115.78, 77.48, 77.16, 76.84, 69.46, 68.60, 50.42, 49.59, 21.82. HRMS (ESI) calcd for $C_{16}H_{19}FNaO_4$ $[M+Na]^+$ 317.1160, found 317.1166.

(*R*, *E*)-isopropyl 7-(4-fluorophenyl)-5-hydroxy-3-oxohept-6-enoate 9h. 99 mg (72%). $[\alpha]_D^{20}$ = + 5.9 (c 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 64% ee by HPLC analysis. ^{1}H NMR (400 MHz, CDCl3) δ 7.36 – 7.28 (m, 2H), 7.05 – 6.91 (m, 2H), 6.59 (d, J = 15.3 Hz, 1H), 6.10 (dd, J = 15.9, 6.1 Hz, 1H), 5.04 (dt, J = 12.5, 6.3 Hz, 1H), 4.76 (q, J = 5.8 Hz, 1H), 3.46 (s, 2H), 3.08 (s, 1H), 2.84 (d, J = 6.1 Hz, 2H), 1.24 (d, J = 6.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.92 (s), 166.56 (s), 163.71 (s), 161.26 (s), 132.69 (d, J = 3.3 Hz), 129.82 (d, J = 2.1 Hz), 129.52 (s), 128.13 (d, J = 8.1 Hz), 115.67 (s), 115.46 (s), 77.48 (s), 77.16 (s), 76.84 (s), 69.38 (s), 68.35 (s), 50.35 (s), 49.67 (s), 21.76 (s). HRMS (ESI) calcd for $C_{16}H_{19}FNaO_4$ $[M+Na]^+$ 317.1160, found 317.1177.

(*R*, *E*)-isopropyl 5-hydroxy-6-methyl-3-oxo-7-phenylhept-6-enoate 9i. 97 mg (70%). $[\alpha]_D^{20}$ = + 13.6 (c 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 70% ee by HPLC analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (t, J = 7.5 Hz, 2H), 7.31 – 7.21 (m, 3H), 6.61 (s, 1H), 5.10 (dt, J = 9.3, 6.2 Hz, 1H), 4.69 (d, J = 5.2 Hz, 1H), 3.52 (s, 2H), 2.88 (dd, J = 10.2, 6.7 Hz, 2H), 1.91 (t, J = 2.8 Hz, 3H), 1.29 (d, J = 6.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.39, 166.63, 138.25, 137.37, 129.10, 128.26, 126.74, 126.09, 77.48, 77.16, 76.84, 73.14, 69.41, 50.48, 48.45, 21.84, 14.06. HRMS (ESI) calcd for $C_{17}H_{22}NaO_4$ $[M+Na]^+$ 313.1410, found 313.1422.

(*R*, *E*)-isopropyl 7-(furan-2-yl)-5-hydroxy-3-oxohept-6-enoate 9j. 83 mg (60%). $[\alpha]_D^{20}$ = + 10.2 (c 1.0, $CHCl_3$). The enantiomeric excess of the product was determined as 80% ee by HPLC analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 1.5 Hz, 1H), 6.48 (dd, J = 15.8, 1.3 Hz, 1H), 6.36 (dd, J = 3.3, 1.8 Hz, 1H), 6.24 (d, J = 3.3 Hz, 1H), 6.13 (dd, J = 15.8, 5.8 Hz, 1H), 5.06 (dt, J = 12.6, 6.3 Hz, 1H), 4.75 (s, 1H), 3.46 (s, 2H), 2.88 (s, 1H), 2.83 (dd, J = 6.0, 2.7 Hz, 2H), 1.26 (d, J = 6.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.98, 166.52, 152.27, 142.23, 128.52, 119.03, 111.46, 108.61, 77.48, 77.16, 76.84, 69.46, 68.02, 50.43, 49.66, 21.82. HRMS (ESI) calcd for $C_{14}H_{18}NaO_5$ $[M+Na]^+$ 289.1046, found 289.1064.

5-(4-fluorophenyl)-1-(2-hydroxy-3,3-dimethoxypropyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide. 11

Diketone 10 (9.3 g, 22.2 mmol), compound 10a (9 g, 66.7 mmol), and pivalic acid (1.58 g, 15.5 mmol) were dissolved in heptane (90 mL) and toluene (10 mL). The mixture was heated at reflux with azeotropic removal of water for 12 h and then cooled to rt, filtered, washed with heptane (3 × 30 mL), and purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 1:1, v/v) to afford 11 (8.6 g, 75%) as a white powder. mp: 160-162 °C ^{1}H NMR(400 MHz, $CDCl_3$): δ = 7.28 -7.20 (m, 9H), 7.11-7.09 (m, 2H), 7.03-6.95 (m, 4H), 4.18-4.10 (m, 2H), 4.04-3.98 (m, 1H), 3.75-3.72 (m, 1H), 3.55-3.44 (m, 1H), 3.34 (s, 3H), 3.28 (s, 3H), 2.39 (br, 1H), 1.57 (t, 7.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 163.4, 161.0, 142.1, 138.3, 134.6, 133.7, 133.6, 130.3, 129.0, 128.6, 128.2, 126.4, 123.5, 122.0, 119.6, 115.7, 115.3, 115.1, 105.1, 71.2, 55.4, 55.1, 45.5, 26.4, 21.7, 21.6. HRMS (ESI) calcd for $C_{31}H_{34}N_2O_4$ $[M+H]^+$ 517.2497, found 517.2498.

3-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl)-1,1-dimethoxypropan-2-yl methanesulfona-te. 12

To a solution of compound 11 (64 g, 124 mmol) in dichloromethane (400 mL) was added Et_3N (19.3 g, 186 mmol) and MsCl (15.6 g, 136 mmol) at 0°C. Then the reaction mixture was stirred for 3 hours. The mixture was concentrated, dissolved in dichloromethane (200 mL) and washed with 0.5 N HCl solution (50 mL ×3). The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated and purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 3:1, v/v) to afford 12 (65 g, 88%) as a white solid. mp: 151-153 °C. ^{1}H NMR(400 MHz, $CDCl_3$): δ = 7.28 -7.19 (m, 7H), 7.14-7.00 (m, 7H), 6.96 (br, 1H), 4.45 (br, 1H), 4.39-4.30 (m, 3H), 3.52-3.49 (m, 1H), 3.36 (s, 3H), 3.23 (s, 3H), 2.77 (s, 3H), 1.57 (t, 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.5, 163.5, 161.1, 138.1, 134.0, 133.1, 130.1, 128.7, 128.5, 127.4, 126.9, 123.7, 122.6, 119.6, 116.7, 115.7, 115.5, 104.1, 56.3, 55.8, 42.1, 37.8, 26.4, 22.1, 21.5. HRMS (ESI) calcd for $C_{32}H_{36}N_2O_6S$ $[M+H]^+$ 595.2273, found 595.2271.

(E)-1-(3,3-dimethoxyprop-1-en-1-yl)-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide. 13

The mixture of 12 (65 g, 110 mmol) and powdered KOH (31 g, 550 mmol) in NMP (400 mL) was stirred at 80 °C for 2 hours under N_2 atmosphere. The mixture was cooled to room temperature and was poured into ice water (500 mL). The mixture was filtered and the filter cake was washed with water (100 mL ×4). The filter cake was dried to give desired product 13 (48 g, 88%) as a white solid. mp: 116-118 °C. ^{1}H NMR(400 MHz, $CDCl_3$): δ = 7.28 -7.19 (m, 7H), 7.15-7.09 (m, 4H), 7.04-6.94 (m, 5H), 5.26 (dd, J_1 = 4.0, J_2 =14.0, 1H), 4.86 (d, J = 4.0 Hz, 1H), 3.18 (s, 6H), 1.51 (d, 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.1, 163.1, 160.7, 142.4, 138.1, 134.1, 133.1, 133.0 130.6, 128.7, 128.6, 128.5, 128.4, 127.8, 127.7, 127.0, 123.6, 122.5, 119.5, 116.2, 115.2, 115.0, 99.9, 52.2, 26.1, 21.3. HRMS (ESI) calcd for $C_{31}H_{32}N_2O_3$ $[M+H]^+$ 499.2391, found 499.2399.

(E)-5-(4-fluorophenyl)-2-isopropyl-1-(3-oxoprop-1-en-1-yl)-N,4-diphenyl-1H-pyrrole-3-carboxamide.14

The mixture of compound 13 (45 g, 90 mmol) in acetone (300 mL) was added 2 N HCl solution (200 mL) and then stirred for

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30 minutes. The mixture was concentrated to remove atone, filtered and washed with water (100 mL ×4). The residue was purified by slurrying in dither ether (50 ml ×3) and dried under vacuum to give product 14 (37 g, 91%) as a white solid. mp: 214-215 °C.^{1}HNMR (400 MHz, $CDCl_3$): δ = 9.42 (d, *J* = 7.2 Hz, 1H), 7.78 (d, *J* = 14.8 Hz, 1H), 7.28-7.16 (m, 9H), 7.11-7.01 (m, 5H), 6.94 (br, 1H), 5.50 (q, *J* = 7.2 Hz, 1H), 3.99-3.91 (m, 1H), 1.57 (d, *J* = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.2, 163.4, 161.4, 145.2, 142.7, 137.6, 132.8, 132.7, 132.6, 130.1, 129.2, 160.7, 142.4, 138.1, 134.1, 133.1, 133.0 130.6, 128.7, 128.6, 127.6, 126.8, 126.7, 125.7, 124.2, 121.0, 119.8, 119.7, 116.1, 115.9, 25.8, 21.7. HRMS (ESI) calcd for C29H26N2O2 $[M+H]^+$ 453.1973, found 453.1986.

(E)-isopropyl 7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl)-5-hydroxy-3-oxohept-6-enoate. 15

To a solution of Schiff base Lf (425 mg, 1.1 mmol) in dichloromethane (5 mL) was added $Ti(O\text{-}i\text{-}Pr)_4$ (284 mg, 1 mmol) at r.t. under N_2 atmosphere. After stirring for 1 h, the mixture was cooled to – 40 °C and compound 14 (226 mg, 0.5 mmol) was added followed by diketene (420 mg, 5 mmol). The resulting mixture was stirred at- 40°C for 48 h, then mixture was quenched with 1 N HCl solution (5 mL) and was added MTBE (10 mL). The mixture was stirred vigorously at r.t. for 1 h. The mixture was extracted with MTBE (30 mL ×3), washed with saturated aq. $NaHCO_3$ solution (10 mL ×3). The organic layer was dried over anhydrous Na_2SO_4, filtered, concentrated and purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 4:1, v/v) to afford 15 (210 mg, 70%) as a white power. The enantiomeric excess of the product was determined as 80% ee by HPLC analysis. mp: 65-67°C, $[\alpha]_D^{20}$ = + 10.4 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (ddd, J = 19.9, 13.3, 6.1 Hz, 7H), 7.09 (t, J = 6.8 Hz, 4H), 6.96 (ddd, J = 24.8, 15.6, 10.8 Hz, 5H), 5.24 (dd, J = 13.9, 5.5 Hz, 1H), 5.07 (dt, J = 12.5, 6.3 Hz, 1H), 4.69 – 4.59 (m, 1H), 3.82 (dq, J = 13.6, 6.9 Hz, 1H), 3.38 (s, 2H), 3.12 (s, 1H), 2.52 (dd, J = 7.8, 6.3 Hz, 1H), 1.48 (d, J = 7.1 Hz, 6H), 1.27 (d, J = 6.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.53, 166.39, 164.39, 163.14, 160.68, 142.62, 138.23, 134.37, 133.38, 133.30, 132.62, 130.75, 128.93, 128.79, 128.62, 128.08, 128.04, 127.14, 125.50, 123.78, 122.23, 119.67, 116.02, 115.20, 114.98, 77.48, 77.16, 76.84, 69.47, 65.97, 50.05, 48.90, 26.26, 21.75, 21.44, 21.42. HRMS (ESI) calcd for $C_{36}H_{38}FN_2O_5$ $[M+H]^+$ 597.2759, found 597.2765.

(R)-isopropyl 7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl)-5-hydroxy-3-oxoheptanoa Te 16.

To a solution of compound 15 (0.27 g, 0.45 mmol) in MeOH (5 mL) was added Pd/C (0.1 g, 5%) under N_2 atmosphere. The mixture was stirred at room temperature under under H_2 atmosphere (1 atm) for 12 hours. The mixture was filtered concentrated and purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 3:1, v/v) to afford 16 (250 mg, 93%) as a white solid. mp: 75-77°C, $[\alpha]_D^{20}$ = + 8.8 (c 1.0, $CHCl_3$), {Lit.[10] $[\alpha]_D^{20}$ = + 9.1 (c 1.0, $CHCl_3$), mp: 75.3-76.8 °C} ; ^{1}HNMR (400 MHz, $CDCl_3$): δ =7.20-7.12 (m, 9H), 7.08-7.00 (m, 5H), 6.87 (br, 1H), 5.07-5.01 (m, 1H), 4.19-4.11 (m, 1H), 3.98-3.91 (m, 2H), 3.60-3.52 (m, 1H), 3.36 (m, 2H), 2.77 (br, 1H), 2.54-2.50 (m, 1H), 1.75-1.58 (m,2H), 1.54 (d, J = 7.2 Hz, 6H), 1.24 (d, J = 6.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.4, 116.2, 164.7, 161.0, 141.4, 138.3, 134.5, 133.2, 133.1, 130.4, 128.7, 128.6, 128.3, 128.2, 126.6, 123.5, 121.9, 119.5, 115.6, 115.3, 69.4, 64.9, 49.9, 49.1, 41.2, 37.7, 26.1, 21.6. HRMS (ESI) calcd for $C_{29}H_{26}N_2O_2$ $[M+H]^+$ 599.2916, found 599.2937.

(3R,5R)-isopropyl 7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl)-3,5-dihydroxyheptanoat e.17

To a solution of 16 (240 mg, 0.4 mmol) in THF (6 mL) and MeOH (1 mL) was added diethylmethoxyborane (0.8 mL, 0.8 mmol, 1 M solution in THF) at -78 °C under N_2 atmosphere. The mixture was stirred for 1 hour and then $NaBH_4$ (30 mg, 0.8 mmol) was added in portions. After stirring for an additional 2 hours at -78 °C, the reaction was quenched with glacial acetic acid (2 mL), diluted with ethyl acetate (20 mL) and then allowed to warm to room temperature. Then saturated aq. $NaHCO_3$ (20 mL) was added and the aqueous layer was extracted with ethyl acetate (20 mL ×3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was coevaporated with MeOH three times to hydrolyze the excess borane, and then purified by column chromatography (silica gel, petroleum ether/ethyl acetate = 3:1, v/v) to a give the syn-product 17 (200 mg, 83%) with syn/anti diastereoselectivity of 98:2 as a white powder. The ee (80%) was improved to over 98% by its recrystallization from CH_3CN/H_2O (5:1, v/v). mp: 133-135 °C, $[\alpha]_D^{20}$ = + 8.933 (c 1.2, $CHCl_3$), lit.[10] { $[\alpha]_D^{20}$ = + 14.3 (c 1.0, $CHCl_3$) mp: 134.1-135.5 °C} ; ^{1}HNMR (400 MHz, $CDCl_3$): δ =7.20-7.14 (m, 9H), 7.07-6.97 (m, 5H), 6.87 (br, 1H), 5.09-4.99 (m, 1H), 4.17-4.08 (m, 2H), 3.98-3.90 (m, 1H), 3.75 (br, 1H), 3.67 (br, 1H), 3.63-3.54 (m, 1H), 2.36 (d, J = 6.0 Hz, 1H), 1.80-1.59 (m, 2H), 1.54 (d, J = 7.2 Hz, 1H), 1.48-1.42 (m, 1H), 1.24 (d, J = 6.4 Hz, 1H). ^{13}C NMR (100 MHz, CDCl3): δ = 172.2, 164.8, 163.4, 161.0, 141.5, 138.3, 134.6, 133.2, 133.1, 130.4, 128.7, 128.6, 128.3, 126.5, 123.5, 121.8, 119.6, 115.5,115.3, 115.2, 69.6, 69.0, 68.6, 41.7, 41.5, 41.3, 39.0, 26.1, 21.7, 21.6. HRMS (ESI) calcd for $C_{29}H_{26}N_2O_2$ $[M+H]^+$ 601.3072, found 601.3066.

Atorvastatin calcium 18

To a stirring solution of 17 (120.0 mg, 0.2 mmol) in MeOH (20 mL) was added 1 M aq. NaOH (0.3 mL). The mixture was stirred at room temperature for 1 hour and then $CaCl_2$ (22.2 mg, 0.2 mmol) was added to the solution. The resulting mixture was stirred at room temperature for 1 hour, filtered, washed and dried in vacuo to give 18 (mg, 90%) as a white powder. mp 173–175.5 °C, $[\alpha]_D^{20}$ = -6.9 (c 1.0 DMSO) {Lit.[10] $[\alpha]_D^{20}$ = -7.4 (c 1.0, DMSO), mp 173.7–175.9}; ^{1}HNMR (400 MHz, $CDCl_3$): δ =9.82 (s, 1H), 7.50 (d, J =8.4, 2H), 7.25-7.15 (m, 6H), 7.08-7.05 (m, 4H), 7.01-6.95 (m, 2H), 3.99-3.88 (m, 1H), 3.79-3.68 (m, 2H), 3.56-3.49 (m, 1H), 3.27-3.18 (m, 2H), 2.07-2.02 (m, 1H), 1.93-1.87 (m, 1H), 1.63-1.46 (m, 1H), 1.36 (d, J = 6.8 Hz), 1.24-1.18 (m, 1H). MS (ESI) m/z = 559 (acid, M + H^+).

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