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Facile and Highly Enantioselective Synthesis of (+)- and (−)-Fluvastatin and Their Analogues

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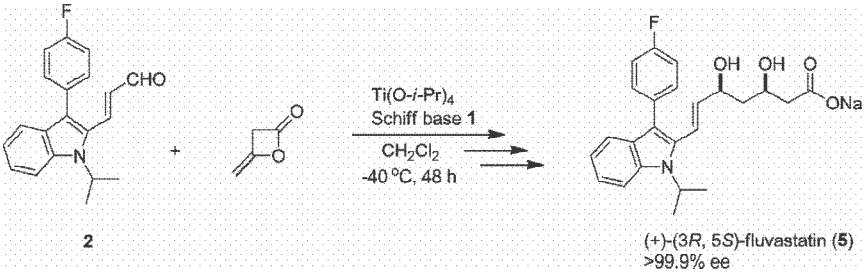

A highly enantioselective synthesis of (+)- and (−)-fluvastatin and their analogues has been facilitated by the reaction of an aldehyde with diketene in the presence of Ti(O-*i*-Pr)$_4$ and a chiral Schiff base ligand. Either enantiomer of the Schiff base could be employed to obtain (+)- or (−)-fluvastatin. Diastereoselective reductions of the resultant keto moiety of β-hydroxy ketoesters provided the *syn*-1,3-diol esters (91% ee), which were subsequently recrystallized and saponified to afford (+)- and (−)-fluvastatin in >99.9% ee.

1. Introduction

Statins represent a class of drugs that are capable of regulating the biosynthesis of cholesterol by inhibiting the enzyme that reduces 3-hydroxy-3-methylglutaric acid to mevalonic acid, namely, the HMG-CoA reductase inhibitors. Since the introduction of pravastatin by Sankyo and lovastatin by Merck to the pharmaceutical market, this class of drugs has been in eminent demand. Due to the importance of these drugs, various synthetic strategies aimed at the construction of statins have been reported. Many of these studies have focused on the introduction of the statin side chain.[1] During the course of our efforts to develop a facile synthesis of HMG-CoA reductase inhibitors, a three-step linear synthesis of fluvastatin **5** has been identified and successfully implemented. Most of the statins, such as atorvastatin calcium hydrate, simvastatin, and pravastatin sodium, are administered in the optically pure form. However, to our knowledge, fluvastatin has been approved as a racemic form. Actually, Novartis' group reported manufacturing process for fluvastatin in racemic form.[2] As for chiral version, Prasad and his Novartis' group reported the method using Wadworth−Horner−Emmons reaction.[3] Thus, we developed an interest in the respective biological activity of each of the four fluvastatin stereoisomers. There are two sets of enantiomers, which are diastereomeric relative to one another. For example, 4-*syn* and 4-*anti* are not enantiomers. Toward this end, a concise and efficient approach providing individual access to all four of the fluvastatin stereoisomers has been implemented. Gratifyingly, the reaction of the aldehyde **2** with diketene provided the β-hydroxy ketone in 91% ee. The diastereoselective reduction of the resultant β-hydroxy ketone provided a *syn*- 1,3-diol, of which the optical purity could be increased to >99.9% ee by a single recrystallization without resorting to the use of optical resolution reagents.

2. Results and Discussion

2.1. Synthesis of Chiral Schiff Base Ligands. The ligands (*S*)-**1** and (*R*)-**1** were prepared as depicted Scheme 1.[4]

(1) Christmann, M.; Bräse, M. *Asymmetric Synthesis—The Esentials*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2008; pp 342–347.

(2) Fuenfschiling, P. C.; Hoehn, P.; Mutz, J.-P. *Org. Process Res. Dev.* **2007**, *11*, 13–18.

(3) Tempkin, O.; Abel, S.; Chen, C.-P.; Underwood, R.; Prasad, K.; Cheng, K.-M.; Repic, O.; Blacklock, T. J. *Tetrahedron* **1997**, *53*, 10659–10670.

(4) (a) Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *J. Chem. Soc., Chem. Commun.* **1991**, 1752–1753. (b) Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *J. Org. Chem.* **1993**, *58*, 1515–1522.

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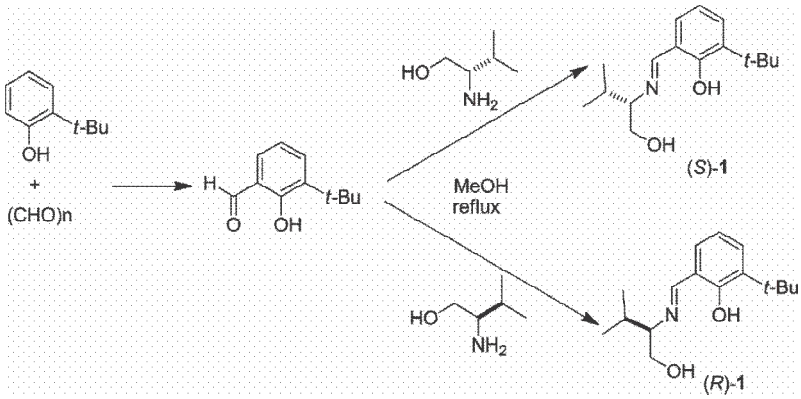
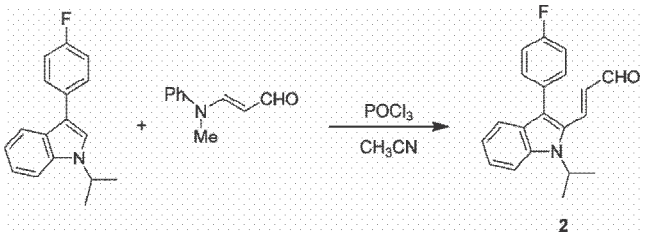
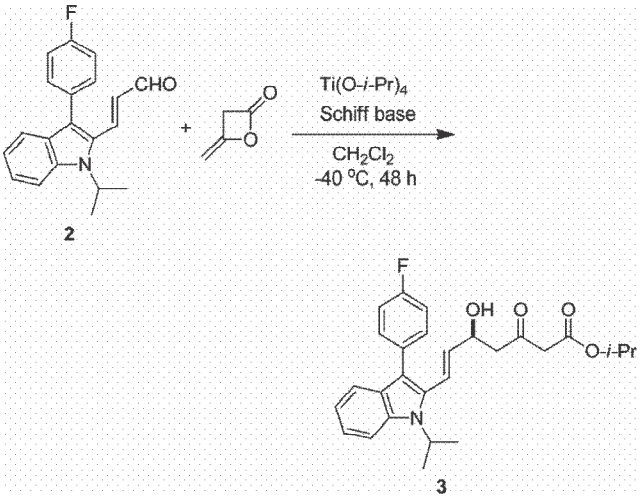
SCHEME 1. Preparation of Chiral Schiff Bases (*S*)-1 and (*R*)-1



SCHEME 2. Preparation of Aldehyde 2



SCHEME 3. Enantioselective Addition of Diketone to Aldehyde 2



Condensation of 3-*tert*-butylsalicylaldehyde with (*S*)-valinol or (*R*)-valinol afforded ligands (*S*)-**1** and (*R*)-**1**, respectively.[3]

2.2. Synthesis of 3-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1*H*-indol-2-yl]-(2*E*)-propenal (2).[5] The preparation of **2** (Scheme 2) was effected by the reaction of 3-(*N*-methyl-*N*-phenyl amino)-acrolein (MPAA)[3] with 3-(4-fluorophenyl)-1-(1-methylethyl)-1*H*-indole conducted in refluxing acetonitrile. Following the workup steps, the resultant aldehyde **2** was isolated as yellowish crystals in 89% yield.

2.3. Enantioselective Addition of Diketene to Aldehyde 2. The titanium-promoted asymmetric addition of diketene to **2** was carried out in the presence of the Ti(O-*i*-Pr)$_4$−Schiff base complex at −40 °C for 48 h (Scheme 3).[6] Each of the chiral Schiff base ligands [(*S*)-**1** or (*R*)-**1**] were used to synthesize each enantiomer of the β-hydroxy ketones in 91% ee, as depicted in Table 1. These results are in agreement with the fact that the ligands (*S*)-**1** and (*R*)-**1** are enantiomers and should produce the same magnitude of stereoinduction, differing only in the absolute configuration of the products (91% 5*S* and 91% 5*R*, respectively).

2.3.1. Effect of Ligand Stoichiometry on the Enantioselective Addition of Diketene to Aldehyde 2. Various stoichiometries of the Schiff base were examined ranging from 1 equiv to catalytic amounts. Although a molar equivalent of Ti(O-*i*-Pr)$_4$ was necessary to obtain sufficient conversion, the amount of Schiff base could be reduced, which resulted in only a small decrease in enantioselectivity (Table 1). This phenomenon can be explained by invoking the concept of ligand-accelerated catalysis.[8] In other words, the Ti(O-*i*-Pr)$_4$−Schiff base complex accelerates the reaction relative to when Ti(O-*i*-Pr)$_4$ is used alone (Scheme 4). The identification of this phenomenon, in the specific case, allowed for the use of a catalytic amount of the Schiff base. In the absence of the Schiff base, the reaction proceeds comparatively slower than when even small quantities of the ligand were used. In this reaction, the ligand is serving a dual purpose of inducing stereocontrol, as well as accelerating the reaction rate.[7]

TABLE 1. Enantioselective Addition of Diketene to Aldehyde 2

entry	ligand (mol %)	yield[a] (%)	ee[b] (%)
1	no ligand	61	
2	(*S*)-**1** (100)	78	91 (*S*)
3	(*S*)-**1** (50)	73	83 (*S*)
4	(*S*)-**1** (10)	70	74 (*S*)
5	(*R*)-**1** (100)	84	91 (*R*)

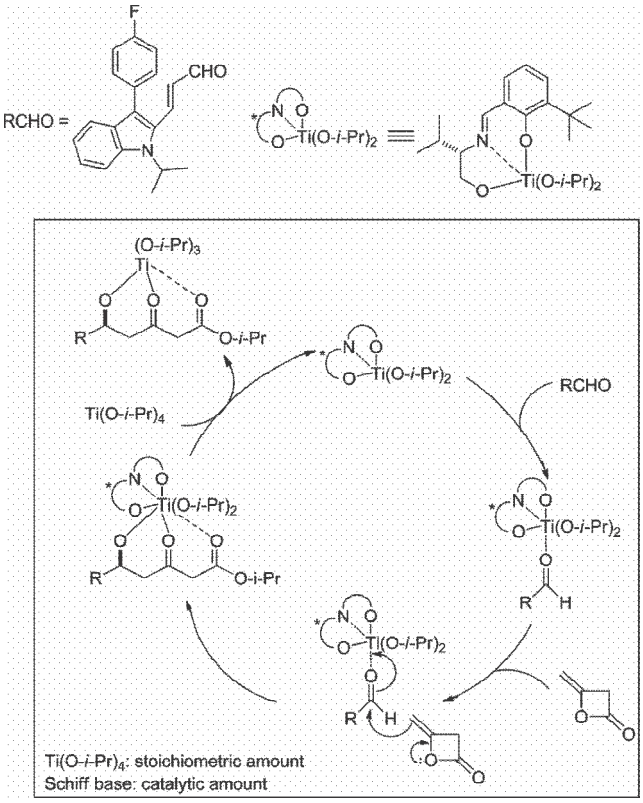
[a]Isolated yield after silca gel column chromatography. [b]Determined by HPLCanalysis (CHIRALPAK AD-H).

(5) Lee, G. T.; Amedio, J. C.; Underwood Jr., Prasad, K.; Repic, O. *J. Org. Chem.* **1992**, *57*, 3250–3252.

(6) The first report of enantioselective addition of diketene to aldehydes: (a) Hayashi, M.; Inoue, T.; Oguni, N. *J. Chem. Soc., Chem. Commun.* **1994**, 341–342. (b) Hayashi, M.; Kaneda, H.; Oguni, N. *Tetrahedron: Asymmetry* **1995**, *6*, 2511–2516.

(7) Early attempts toward the enantioselective addition of diketene to **2** using other types of Schiff bases were unsuccessful. Before arriving at the results shown in Table 1, several attempts were made using the oxazoline Schiff bases such as **1** and **2** (Scheme 4). The use of Schiff bases as in **1** resulted in the production of the *R* enantiomer of the β-hydroxy ketone, while the Schiff bases as in **2** resulted in the production of the *S* enantiomer. As summarized in the Supporting Information, the best ee was 78% *S* when R_1 = Et and 38% *R* when R_1 = Me. These results prompted us to try other types of Schiff bases. (b) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263–4265.

SCHEME 4. Proposed Reaction Mechanism of the Ti(O-*i*-Pr)$_4$–Schiff Base Catalyzed Addition of Diketene to Aldehyde 2 (Ligand Acceleration Effect[8])



2.3.2. Effect of Temperature on the Enantioselective Addition of Diketene to Aldehyde 2. Table 2 illustrates a general trend in which a decrease in the temperature resulted in an increased enantioselectivity with a concomitant decreased chemical yield. An optimum temperature for this reaction was found to be −40 °C, which provided the product in 91% ee and 78% yield.

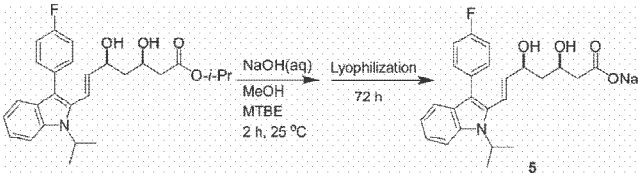
2.4. Diastereoselective Reductions of *β*-Hydroxy Ketones to Provide *syn*-1,3-Diols. A diastereoselective *syn*-reduction of either the (*S*)-**3** or (*R*)-**3** *β*-hydroxy ketone was achieved by using $NaBH_4$ as the reducing agent in the presence of diethyl methoxy borane as a chelating agent (Narasaka's method)[8] The reaction provided high *syn*-selectivity (99:1, *syn*/*anti*) and afforded the *syn*-1,3-diol **4** [(3*R*,5*S*) or (3*S*,5*R*)] in 78−79% yield. The preferential formation of the *syn*-product can be rationalized by the preorganization of the substrate with the chelating agent (Et_2BOMe) prior to the intermolecular axial hydride attack ($NaBH_4$) occurring at the ketone.

Alternatively, we performed an *anti*-reduction on either the (*S*)-**3** or (*R*)-**3** *β*-hydroxy ketone using the Evans method [$Me_4NHB(OAc)_3$].[9] This protocol provided the *anti*-1,3-diol **4** with 91:9 *anti*/*syn* selectivity [(3*R*,5*R*) or (3*S*,5*S*)]. In this case, the reducing agent [$Me_4NBH(OAc)_3$] effects an intramolecular hydride transfer, which results in the preferential formation of the *anti*-isomer.[10,11]

(8) (a) Narasaka, K.; Pai, F. C. *Tetrahedron* **1984**, *40*, 2233–2238. (b) Chen, K.-M.; Hardmann, G. E.; Prasada, K.; REpic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155–158.

(9) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.

TABLE 2. Effect of Temperature on the Enantioselectivity in Addition of Diketene to Aldehyde



entry	temp (°C)	yield[a] (%)	ee[b] (%)
1	25	84	12 (*S*)
2	−20	81	70 (*S*)
3	−40	78	91 (*S*)
4	−60	38	93 (*S*)

[a]Isolated yield after silica gel column chromatography. [b]Determined by HPLC analysis (CHIRALPAK AD-H).

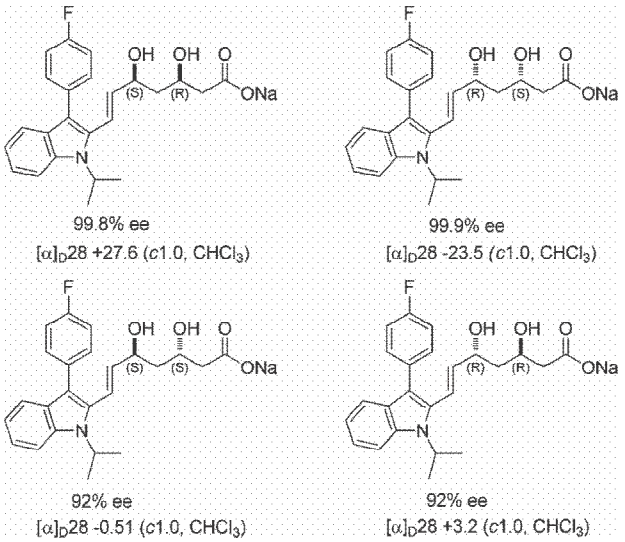
TABLE 3. Diastereoselective Reductions of *β*-Hydroxy Ketones To Provide 1,3-Diols

		diolester	
entry	*β*-ketoester/ee (%)	yield[a] (%)	*syn*/*anti*[b] (ee[c] (%))
1	91 (5*S*)	78	99/1 (99.8(3*R*,5*S*))
2	91 (5*R*)	79	99/1 (99.9(3*S*,5*R*))
3	91 (5*S*)	44	9/91 (92(3*S*,5*S*))
4	91 (5*R*)	46	9/91 (92(3*R*,5*R*))

[a]Isolated yield after silica gel column chromatography followed by recrystallization. [b]Determined by HPLC analysis (CHIRALCEL OD-H). [c]Enantiomeric excess of major isomer determined by HPLC analysis (CHIRALCEL OD-H) after recrystallization.

The increased diastereoselectivity of the *syn*-reduction relative to that of the *anti*-reduction is a remarkable breakthrough, which provides the means of obtaining the biologically potent *syn*-isomers in excellent enantiopurity and yield: 99.8% ee (3*R*,5S) and 99.9% ee (3*S*,5*R*) after recrystallization (Table 3).

2.5. Saponification To Provide Fluvastatin 5. The isopropyl ester was saponified (aq NaOH) and lyophilized to provide fluvastatin sodium in good yield (78%).



(10) Tempkin, O.; Abel, S.; Chen, C. P.; Underwood, R.; Prasad, K.; Cheng, K. M.; Repic, O.; Blacklock, T. J. *Tetrahedron* **1997**, *53*, 10659–10670.

3. Conclusion

In summary, a concise and efficient synthesis of each of the four stereoisomers of fluvastatin has been established. This was realized by employing a stereodivergent approach from β-hydroxy ketone precursor: *syn*-reduction (Et_2BOMe, $NaBH_4$) or *anti*-reduction [$Me_4NHB(OAc)_3$]. Recrystallization of the resultant 1,3-diol upgraded the enantiopurity to >99.9% ee for the *syn*-isomers and >92% ee of the *anti*-isomers. The increased diastereoselectivity observed in the *syn*-reduction enabled the formation of the biologically potent *syn*-isomers (3*R*,5*S*) and (3*S*,5*R*) in excellent enantiopurity.

4. Experimental Section

General Procedures. All starting materials were obtained from commercial sources and used without further purification, except for diketene, which was distilled under reduced pressure prior to its use. Reactions that required anhydrous conditions were carried out using dehydrated solvents under an argon atmosphere. ^1H and ^{13}C NMR spectra (400 and 100.6 MHz, respectively) were recorded using Me_4Si as an internal standard (0 ppm). HPLC analyses were carried out equipped with diode array detector using chiral columns CHIRALPAC AD-H or CHIRALCEL OD-H (250 mm × 4.6 mm × 5 μm).

Synthesis of 3-*tert*-Butylsalicylaldehyde. To a solution of 2-*tert*-butylphenol (3 g, 20 mmol) in toluene (50 mL) were added paraformaldehyde (1.8 g, 60 mmol), anhydrous tin(II) chloride (0.38 g, 2 mmol), and 4-picoline (0.75 g, 8 mmol). The mixture was allowed to stir at 95 °C for 6 h. The mixture was subsequently cooled to room temperature, and the resultant suspension was filtered and concentrated to provide a residue. The residue was extracted with diethyl ether (30 mL × 2), and the combined organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4, and evaporated to provide the crude material. The crude material was purified by distillation at reduced pressure to afford the desired product as thick yellow oil: yield 1.87 g (52%); bp 120−122 °C/17 mmHg; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H), 4.86 (s, 1H), 6.6−7.8 (m, 3H), 9.86 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 29.2, 34.7, 65.5, 77.0, 116.5, 138.2, 161.2, 197.2.

Synthesis of (*S*)-2-(*N*-3-*tert*-Butylsalicylidene)amino-3-methyl-1-butanol (Ligand (*S*)-1). A mixture of 3-*tert*-butylsalicylaldehyde (892 mg, 5 mmol), (*S*)-valinol (515.8 mg, 5 mmol, 1 equiv), and methanol (30 mL) was refluxed for 9 h in the presence of anhydrous Na_2SO_4 (5 g). The mixture was filtered through a pad of Celite, and the filtrate was concentrated to provide the crude residue. The crude material was purified by recrystallization from petroleum ether to afford **2a** as yellow needles: yield 1.28 g (97%); mp 56.9−57.5 °C (lit.[4b] 57−58 °C); $[\alpha]^{24}_D$ −39.8; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, *J* = 8.8 Hz, 6H), 1.41 (s, 9H), 1.9−2.0 (m, 1H), 2.17 (s, 1H), 3.0−3.1 (m, 1H), 3.7−3.9 (m, 2H), 4.87 (s, 1H), 6.8−7.4 (m, 3H), 8.37 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.8, 29.3, 34.8, 64.6, 77.3, 117.9, 129.5, 160.4, 166.7.

Synthesis of 3-(*N*-Methyl-*N*-phenylamino)acrolein (MPAA). To a precooled (−10 °C) solution of oxalyl chloride $(COCl)_2$ (7.0 g, 55.1 mmol, 1.1 equiv) and acetonitrile (10 mL) was slowly added a mixture of *N*-methylformanilide (6.8 g, 50.1 mmol) and butyl vinyl ether (5.4 g, 53.6 mmol) in acetonitrile over 30 min while maintaining the internal temperature at −5 to −10 °C. The reaction mixture was to 20 °C over 30 min, and stirring was continued for 1 h. The reaction contents were cooled to 0 °C, and a solution of Na_2CO_3 (6.4 g, 60.12 mmol) in water (30 mL) was added over 45 min while maintaining the internal temperature at 8−10 °C. Then toluene (25 mL) was added, and the solution was stirred at 20−22 °C for 15 min. The solution was allowed to settle for 15 min. The layers were separated, and the toluene layer was washed with water (25 mL × 2). The combined toluene layer was concentrated to give thick stirrable oil (7.6 g, 94%). Purification of crude MPAA was done by dissolving the crude MPAA in 2-propanol (IPA) (5 mL) at 45−50 °C, and then hexane (8.5 mL) was added with continuous stirring. The mixture was cooled to 0 °C over 30 min under vigorous agitation. A few seed crystals of MPAA were added, and the slurry was further chilled to −15 °C for 1 h. The solid was collected by rapid suction filtration at −10 °C. The product was washed with a cold (−10 °C) solution of IPA/hexane (35/65, 25 mL × 2) and then dried to a constant weight: yield 9.6 g (94%); mp 44−45 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.37 (s, 3H), 3.51, (s, 1H), 5.4−5.5 (m, 1H), 7.1−7.6 (m, 5H), 9.27 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.7, 62.9, 77.0, 104.8, 119.8, 124.7, 129.0, 189.5.

Synthesis of 3-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1*H*-indol-2-yl]-(2*E*)-propenal 2[5]**.** A solution of $POCl_3$ (908 mg, 5.92 mmol, 3.0 equiv) in 2 mL of acetonitrile was cooled to −5 °C, then a solution of MPAA (947 mg, 5 mmol, 2.5 equiv) in 1 mL of acetonitrile was added slowly over 45 min under argon atmosphere and stirred at 5−7 °C for 10 min. A solution of 3-(4-fluorophenyl)-1-(1-methylethyl)-1*H*-indole (508 mg, 2 mmol) in 5 mL of acetonitrile was injected rapidly into the mixture, and the reaction content was heated to reflux for 3 h. The mixture was allowed to cool to room temperature and quenched with 5 mL of water. The solution was then warmed to 55 °C for 2 h and then cooled to 15 °C and diluted with 20 mL of toluene. The organic layer was separated and washed with 50 mL × 2 of water, dried over anhydrous Na_2SO_4, and concentrated to a residue. The oily residue was purified by silica gel column chromatography (5:1, hexane/ethyl acetate). The fractions of interest were combined, and evaporated and the residue was recrystallized from isopropyl alcohol to give 551 mg (89%) of pale yellow crystals: R_f 0.27 (5:1, hexane/ethyl acetate); mp 129−130 °C (lit.[5] 129−130 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 1.72 (d, *J* = 6.8 Hz, 6H), 2.84 (s, 1H).4.9−5.0 (m, 1H), 6.2−6.3 (m, 1H), 7.1−7.6 (m, 8H), 9.56 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.8, 25.4, 48.3, 76.7, 77.3, 112.5, 115.8, 120.6, 124.6, 131.9, 137.5, 141.1, 193.3.

Synthesis of 3-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1*H*-indol-2-yl]-5-hydroxy-3-oxo-(6*E*)-heptenoic acid-1-isopropyl ester 3. In an ampular tube were placed Schiff base (*S*)-**1** ligand (144.9 mg, 0.55 mmol) and CH_2Cl_2 (5 mL). To this solution was added $Ti(O\text{-}i\text{-}Pr)_4$ (142.1 mg, 0.5 mmol) at room temperature and stirred for 1 h, then the mixture was cooled to −40 °C. Aldehyde (153.7 mg, 0.5 mmol) was added followed by diketene (210.2 mg, 2.5 mmol). The mixture was stirred at −40 °C for 48 h. Then after, isopropyl alcohol (2 mL) was added to the mixture, and the mixture was further stirred for 3 h. The reaction mixture was poured into a mixture of 1 M HCl (10 mL) and diethyl ether (10 mL) and stirred vigorously for 1 h at room temperature. The mixture was extracted with ethyl acetate (30 mL × 3), and the combined extract was washed with saturated $NaHCO_3$ (30 mL × 3) and brine (30 mL x 3) and dried over anhydrous Na_2SO_4 and then evaporated to a residue. The residue was purified by column chromatography on silica gel using hexane/ethyl acetate (5:1) to give the *S* enantiomer of the β-hydroxy ketoester **3**. The *R* enantiomers of the β-hydroxy ketoester were obtained following the same procedure by only substituting the (*S*)-**1** ligand with (*R*)-**1** ligand: R_f 0.15, hexane/ethyl acetate (5:1). Enantiomeric excess of the β-hydroxy-ketoester (91% ee) 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, retention time 17.38 min (5*R*) and 25.31 min (5*S*): ^1H NMR (400 MHz, $CDCl_3$) δ 1.2−1.3 (m, 6H), 1.42 (s, 1H), 1.5−1.7 (m, 6H), 2.17 (s, 1H), 2.6−2.7 (m, 1H), 3.42 (s, 2H), 4.1−4.2 (d, *J* = 7.2 Hz, 2H), 4.84 (s, 1H), 5.0−5.1 (m, 1H), 5.68 (d, *J* = 5.2 Hz, 1H), 6.75 (d, *J* = 14.4 Hz, 1H), 7.1−7.6 (m, 8H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ14.2, 21.7, 47.8, 48.9, 50.2, 60.4, 68.1, 69.4, 77.1, 96.1, 111.7, 136.9, 166.4.

Synthesis of 3-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1*H*-indol-2-yl]-3,5-dihydroxy-(6*E*)-heptenoic acid-1-isopropyl ester 4. Sodium borohydride (50 mg, 1.32 mmol) was added to a mixture of THF (8 mL) and MeOH (2 mL) at −78 °C in a three-necked flask under argon atmosphere. Diethylmethoxyborane (1 M solution in THF) (0.52 mL, 0.52 mmol) was added dropwise and stirred for 15 min. β-Hydroxy ketoester **3** (200 mg, 0.44 mmol) was added dropwise over 1 h as a solution in 4:1 THF/MeOH (15 mL). Stirring was continued at −78 °C for 2 h after addition. The reaction mixture was diluted with saturated $NaHCO_3$ (20 mL), heptane (40 mL), and ethyl acetate (20 mL). The upper organic layer was washed with brine and saturated $NaHCO_3$ solution, then dried with anhydrous Na_2SO_4 and evaporated to a residue. The residue was coevaporated with MeOH three times to hydrolyze the excess borane. Column chromatography on silica gel using hexane/ethyl acetate (5:1) as eluting solvent gave the pure *syn*-product of the 3,5-dihydroxyester **4** with *syn*/*anti* diastereoselectivity of >99:1. Alternatively the *anti*-product of the 3,5-dihydroxyester was achieved following the Evans method [$(Me_4NBH(OAc)_3$] with *anti*/*syn* diastereoselectivity of 91:9. The diastereoselectivity ratios were measured by HPLC using CHIRALCEL OD-H (250 mm × 4.6 mm × 5 μm) column, run time 30 min, flow rate 1.0 mL/min, injection volume 10 μL, mobile phase hexane/isopropyl alcohol 95:5 (v/v) containing 0.01% of trichloroacetic acid, retention times 8.47 min (3*S*,5*S*), 9.43 min (3*R*,5*R*), 13.79 min (3*R*,5*S*), and 14.85 min (3*S*,5*R*). The enantiomeric excess of the *syn*- and *anti*-stereoisomers was improved by a single recrystallization from 91% to over 99.9% for the *syn*-isomers and 94% for the *anti*-isomers using acetonitrile/water (9:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.2−1.3 (m, 6H), 1.42 (s, 1H), 1.5−1.7 (m, 6H), 2.17 (s, 1H), 2.6−2.7 (m, 1H), 3.42 (s, 2H), 4.1−4.2 (d, J = 7.2 Hz, 2H), 4.84 (s, 1H), 5.0−5.1 (m, 1H), 5.68 (d, J = 5.2 Hz, 1H), 6.75 (d, J = 14.4 Hz, 1H), 7.1−7.6 (m, 8H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.7, 41.6, 42.2, 47.7, 68.5, 72.2, 76.7, 77.0, 77.3, 111.6, 115.1, 118.3, 119.4, 121.7, 128.4.131.9, 134.9, 138.8, 172.3.

Synthesis of 3-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1*H*-indol-2-yl]-3,5-dihydroxy-(6*E*)-heptenoic acid Sodium Salt 5. The 3,5-dihydroxyester **4** (150 mg, 0.33 mmol) was added to a 50 mL three-necked round-bottomed flask equipped with a magnetic stirrer and a dropping funnel. To the flask was added methanol (20 mL). A solution of NaOH (1.0 N NaOH) in water (0.32 mL) was placed in the dropping funnel and was added slowly to the flask over 5 min while maintaining the temperature at 25 °C. The suspension was stirred for 2 h, and then the reaction mixture was filtered and diluted with water (15 mL) and methyl-*tert*-butyl ether (MTBE) (15 mL). The lower aqueous layer was washed with MTBE, and the combined organic layer was concentrated to a volume of about 20 mL. The heterogeneous mixture was then lyophilized for 72 h to obtain **5** as a pale yellow powder: R_f 0.45; mp 141−143 °C; ^{1}H NMR (400 MHz, DMSO) δ 1.2−1.3 (m, 6H), 1.3−1.7 (m, 6H), 2.05 (s, 2H), 2.3−2.4 (m, 1H), 3.31 (s, 1H), 4.0−4.1 (m, 2H), 4.85 (s, 1H), 5.0−5.1 (m, 1H), 5.77 (d, J = 16 Hz, 1H), 6.76 (d, J = 16 Hz, 1H), 7.0−7.5 (m, 8H); ^{13}C NMR (100.6 MHz, DMSO) δ 21.7, 25.2, 25.3, 38.9, 39.1, 39.3, 39.5, 39.7, 39.9, 40.1, 95.7, 176.2.

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Supporting Information Available: Details of experimental procedures and characterization data (^{1}H, ^{13}C, HPLC chromatograms) for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Publication. Table 4 was removed from this paper because it appears in the Supporting Information. It was reposted without Table 4 on October 21, 2010.