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Asymmetric Synthesis of 3,5-Dihydroxy-6(*E*)-heptenoate-containing HMG-CoA Reductase Inhibitors

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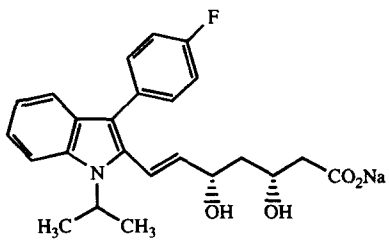
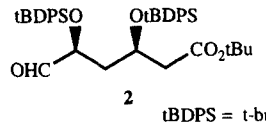
Abstract: A 'one-pot' conversion of aldehyde **6** to hydroxyketoester **10** with high enantioselection, culminating in a practical asymmetric synthesis of (3*R*,5*S*) isomer of the antihyperlipoproteinemic agent fluvastatin, **1**, is described. All four 3,5-dihydroxy-6(*E*)-heptenoate stereoisomers were prepared in enantiopure form starting from **10**, utilizing selective reduction and oxidation methods. © 1997 Elsevier Science Ltd.

In the course of our continuing investigation into the practical synthesis of HMG-CoA reductase inhibitors[1], we have focused our efforts on the stereoselective construction of the 3,5-dihydroxy-6(*E*)-heptenoate units inherent to many of these compounds (e.g., the antihyperlipoproteinemic agent fluvastatin, **1**). Our earlier endeavors involved the synthesis of enantiomerically pure six-carbon chiral synthons[2] **2-5** and their



1



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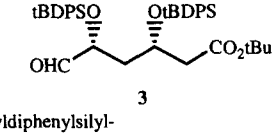

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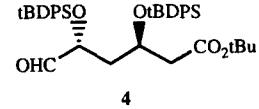
tBDPS = t-butyldiphenylsilyl-



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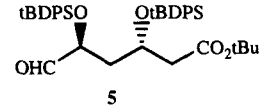
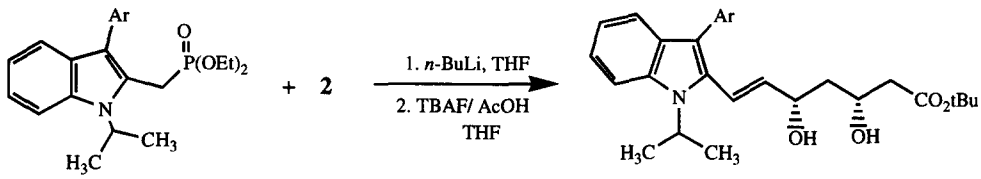


5

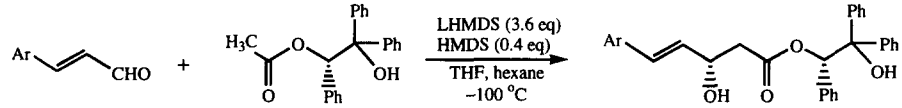
conversion to (*E*)-3,5-dihydroxy-6-heptenoates using Wadsworth-Horner-Emmons methodology[3] (for example, Scheme I). The approach to the aldehydes **2-5** hinged on the highly selective reduction of optically pure δ-hydroxy-β-ketoesters to either the 1,3-*syn* diols using our *syn*-selective reduction methodology,[4] or to the 1,3-*anti* diols using the reduction method of Evans[5]. This flexible strategy allowed for the highly diastereo- and enantioselective construction of 3,5-dihydroxy-6(*E*)-heptenoates but did not appear practical for large scale production from the perspectives of synthetic efficiency, cost, and throughput.



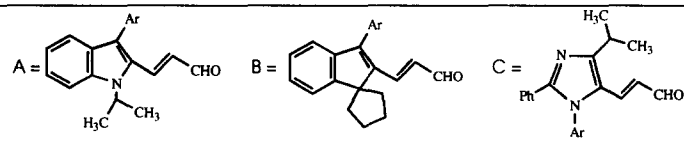
Scheme I

These limitations motivated us to investigate stereoselective aldol reactions of enantiomerically pure acetates as a route to the requisite stereogenic diols. We turned to the asymmetric aldol method originally reported by Braun[6] and found, for example, that the aldol reaction of (*S*)-monoacetyltriphenylglycol with unsaturated aldehydes gave the corresponding β-hydroxyesters with high ee (Table I).[7] The selectivity obtained depended on the nature of the aldehyde/ base combination and in some cases was as high as 98:2. The use of excess amine compared to n-BuLi was found to be advantageous with regard to stereoselectivity.

Table I: Variation of Aldehyde



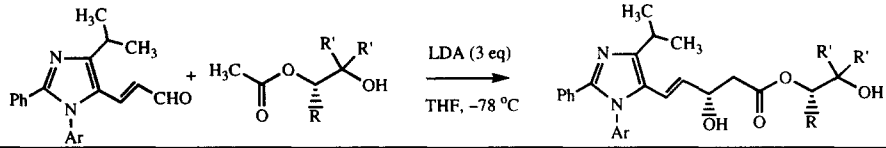
Entry	Aldehyde	Ratio (*S,S* : *R,S*)
1	A	95:5
2	B	98:2
3	C	98:2



Ar = 4-fluorophenyl

We also investigated the ramifications of varying the substituents on the chiral acetate (Table II). These results showed that the substituents on both the 1- and 2-carbons of the auxiliary must be phenyls or substituted phenyls for the reaction to proceed with maximum stereoselection. Replacement of phenyl with other groups, such as methyl or isopropyl, resulted in a dramatic decline in diastereoselectivity. A similar effect was noted using *ortho*- or *meta*-substituted aromatics.

Table II: Variation of Chiral Auxiliary

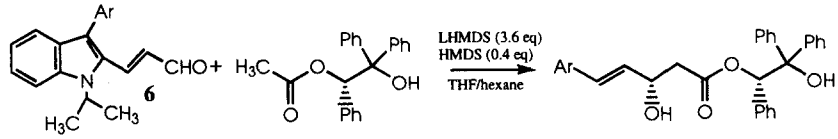


Entry	R	R'	ee (%)[a]
1	CH_3	Ph	60
2	iPr	Ph	58
3	Ph	Ph	92
4	Ph	CH_3	42
5	Ph	*o*-tolyl	74
6	Ph	*m*-tolyl	60
7	Ph	*p*-tolyl	88

[a]After removal of chiral auxiliary and conversion to methyl ester.

The effect of reaction temperature on the outcome of these aldol reactions is shown in Table III. The optimal selectivity was obtained at −100 °C. In the case of aldehyde **6**, required for fluvastatin synthesis, the −100 °C temperature posed a practical yet not insurmountable difficulty during scale-up on the plant scale. This aldol reaction, when carried out at the easily achieved −78 °C, resulted in only a small decrease in the enantiomeric excess.

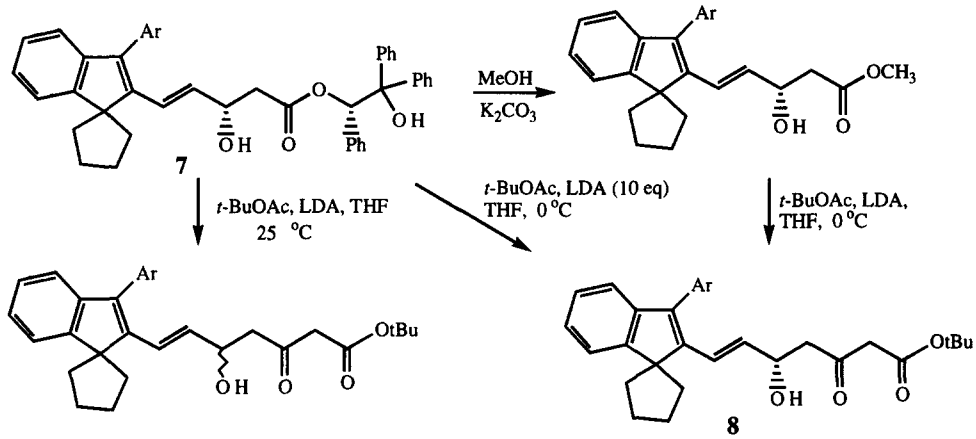
Table III: Variation of Temperature



Entry	Temperature, °C	ee %[a]
1	−20	78
2	−50	85
3	−60	87
4	−75	89
5	−100	90

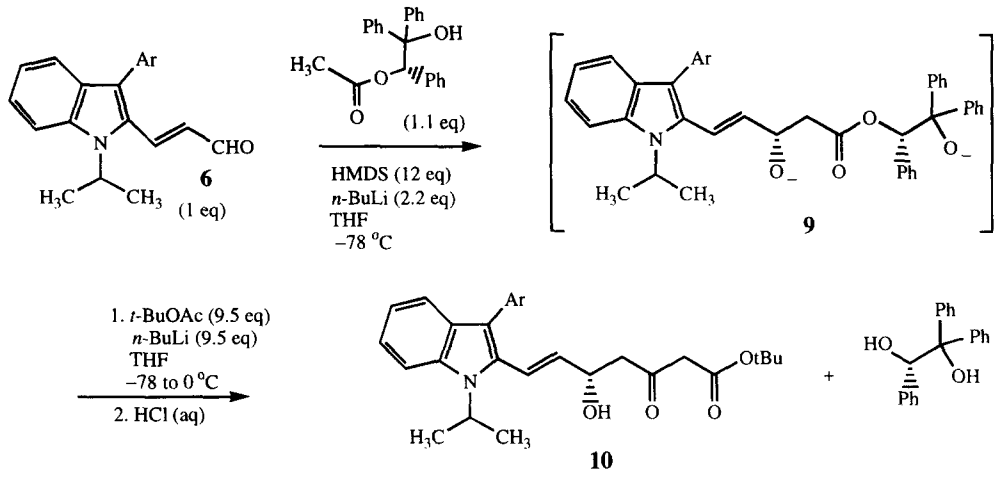
[a]After removal of chiral auxiliary and conversion to methyl ester.

Our next goal was the conversion of the chiral hydroxy ester to the hydroxyketoester (Scheme II). To avoid epimerization of the newly formed stereogenic center, we initially carried out this homologation via conversion to the methyl ester analogous to literature precedents from laboratories at Merck[8] and Hoechst.[9] However, we were pleased to find that the direct conversion of **7** to **8** could in fact be achieved without racemization by using a large excess (10.5 equivalents) of LDA/*t*-butyl acetate at 0 °C. This improvement allowed us to reach the hydroxyketoester without the separate step to the methyl ester. The hydroxyketoester was ultimately isolated in high yield together with the glycol by quenching the reaction mixture with dilute hydrochloric acid.



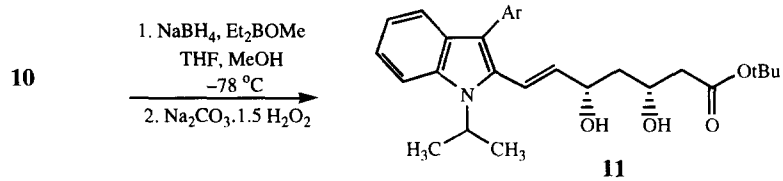
Scheme II

In the case of the aldehyde **6**, we further streamlined the sequence outlined in Scheme II by combining both enolate additions into a single one-pot reaction (Scheme III). After initial addition of the chiral enolate to aldehyde **6**, forming intermediate alkoxide dianion **9**, the lithium enolate of *t*-butyl acetate was generated in the same vessel, giving hydroxyketoester **10**. The formation of lithium hexamethyldisilazide (LiHMDS) must be controlled carefully. Though all of the hexamethyldisilazane (HMDS) needed for completion of both reactions was added at the outset of the first addition, *n*-BuLi was added in two portions (2.2 equivalents for the generation of the chiral enolate, then 9.5 equivalents for the generation of the *t*-butyl acetate enolate). This method was necessary for the successful completion of the one-pot modification without decomposition or formation of side-products. When more than two equivalents of LiHMDS were present from the outset, the first aldol reaction failed to proceed to completion. The economy of the one-pot operation is obvious. In addition to reducing time and solvent volume, substantial amounts of the bases needed (HMDS/ *n*-BuLi) were conserved.



Scheme III

The crude final reaction mixture, containing hydroxyketoester and chiral glycol, was recrystallized from heptane and isopropanol, enriching the desired enantiomer **10** to 97% ee. Reduction of the hydroxyketoester to the *syn*-diol ester **11** proceeded with excellent diastereoselection (>98:2) using conditions reported earlier (Et_2BOMe, $NaBH_4$, THF, MeOH, −78 °C; Scheme IV).[4] Addition of the $NaBH_4$ at the outset

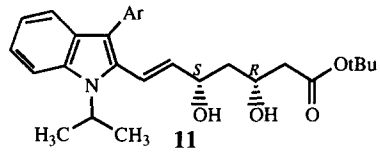


Scheme IV

of the reaction avoided enolization of the ketone and made the reduction essentially instantaneous. One recrystallization of the *syn*-diol ester **11** from 9:1 acetonitrile/water effectively removed the chiral glycol auxiliary (which is recyclable) and raised the enantiomeric and diastereomeric purity to ≥99.5%; other solvents were not as effective (Table IV). The use of sodium percarbonate rather than sodium borate or hydrogen peroxide in the oxidation step of the work-up reduced the level of boron in the final product. Table V shows the resulting boron levels after one recrystallization from acetonitrile/water. Finally, the *t*-butyl ester was converted to the sodium salt by hydrolysis using NaOH in THF/H_2O or $EtOH/H_2O$, followed by freeze-drying.

Table IV: Effect of Solvent on Purification

starting ratio
(3*R*,5*S*):(3*S*,5*R*) = 93.2 : 6.8



11

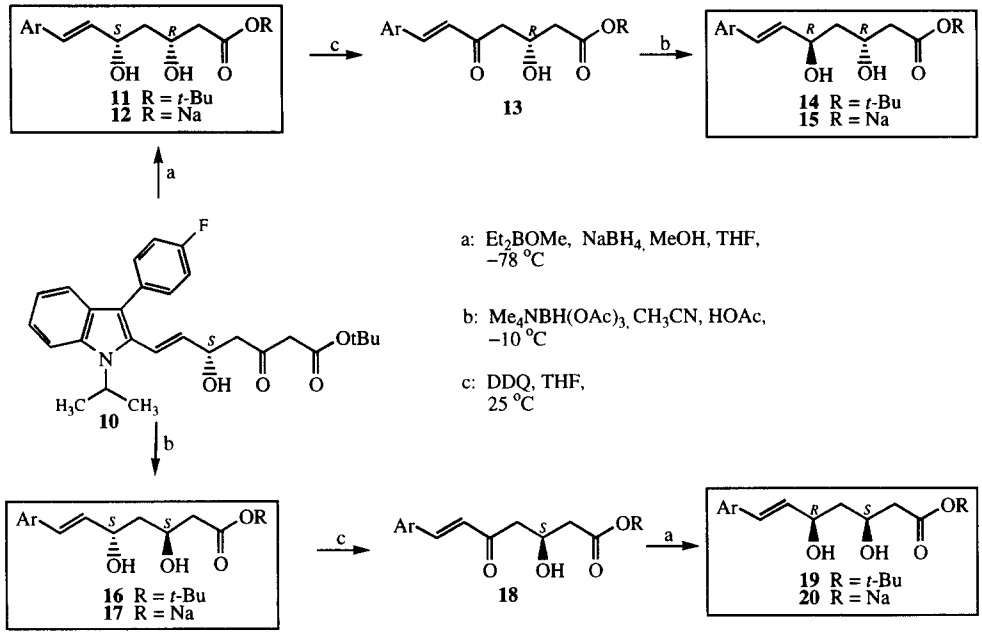
Entry	Solvent	Ratio of (3*R*,5*S*):(3*S*,5*R*)
1	EtOAc	95.5 : 4.5
2	CH_3CN[a]	97.5 :2.5
3	CH_3CN[b]	99.6 : 0.4
4	$(CH_3)_3COCH_3$	96.3 : 3.7
5	THF/hexane	95.4 : 4.6
6	9 :1 CH_3CN : H_2O[c]	99.7 : 0.3

[a]After one recrystallization; [b]after two recrystallizations; [c]crystallized hydroxyketoester was used in this reaction.

Table V: Effect of Oxidation Agent on Boron Impurities

Entry	Oxidizing Agent	Equivalents	Boron in Product [ppm]
1	H_2O_2	5	125-150
2	H_2O_2	10	124
3	$NaBO_3 \cdot H_2O$	1.3	78
4	$Na_2CO_3 \cdot 1.5\ H_2O_2$	1.3	25

We have also demonstrated that the remaining three stereoisomers (one *syn* and two *anti*) of the dihydroxyheptenoate family are also accessible from the same (*S*)-hydroxyketoester. Scheme V illustrates the application of this strategy to the preparation of both isomers of fluvastatin and the corresponding *anti* isomers. The DDQ oxidation of allylic alcohols to the unsaturated ketohydroxyesters was a pivotal step in these transformations, as were the *syn*[4] and *anti*-reduction[5] methodologies. Whereas the reduction using $Et_2BOMe/NaBH_4$ was completely *syn* selective, the *anti* selectivity using $Me_4NHB(OAc)_3$ was in the range of 90:10 to 96:4 but could be improved to >99:1 by crystallization from ethyl acetate and hexane. Thus, after basic hydrolysis of the *t*-butyl esters, all four isomers were accessible by utilizing this practical and flexible methodology.



Scheme V

In summary, we have developed an efficient stereoselective approach to the family of 3,5-dihydroxyheptenoate-containing HMG-CoA reductase inhibitors. The synthesis exemplifies: 1) the use of Braun's chiral acetate for 'one-pot' conversion of the aldehyde to hydroxyketoester with high enantioselection, 2) recrystallization of the hydroxyketoester to improve the optical purity, 3) application of a highly *syn*-selective boron-mediated reduction for virtually complete diastereoselection, and 4) easy access to all four dihydroxyheptenoate stereoisomers. The methods described in this paper have made possible for the first time a practical, three-step, plant-scale asymmetric synthesis of the (3*R*,5*S*), biologically potent isomer of fluvastatin, a racemate.

EXPERIMENTAL

General: NMR spectra were recorded on a Bruker DPX-300 spectrometer with TMS as an internal standard. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. Thin layer chromatography was performed on 0.25-mm silica gel F254 plates (Merck). Flash chromatography was carried out on Merck silica gel, grade 9385, 230-400 mesh, 60 Å. Melting points were determined on a Büchi 535 instrument and are uncorrected. IR spectra were obtained on a BioRad FTS-40 FT-IR. High resolution mass spectra (FAB, NaI/MNBA matrix) were measured on a TSQ70 instrument. Freeze-drying of laboratory samples was carried out in a Virtis Genesis freeze-dryer.

[(*S*)-(*E*)]-7-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-5-hydroxy-3-oxo-6-heptenoic acid 1,1-dimethylethyl ester (10): Under a nitrogen atmosphere, a 3-L, 4-necked, round-bottomed flask equipped

with a mechanical stirrer, addition funnel, and low temperature thermometer was charged with 1,1,1,3,3,3-hexamethyldisilazane (193.7 g, 1.200 mol) and THF (1.0 L). The mixture was cooled to −10 °C with stirring, and *n*-butyllithium (200 mL of a 2.5-M solution in hexane, 0.500 mol) was added over 20 min (exothermic), keeping the temperature below 0 °C. The reaction mixture was stirred at −2 to −7 °C for 15 min, then cooled to −32 to −34 °C before adding 2-(*S*)-acetoxy-1,1,2-triphenylethanol (42.17 g, 0.127 mol) over 5 min. The internal temperature of the white suspension was raised to −15 °C, and the contents of the flask were stirred at this temperature for 45 min. The resulting homogeneous yellow solution was cooled to approximately −76 °C, and a solution of 3-[3-(fluorophenyl)-1-(methylethyl)-1H-indol-2-yl]-2-propenal (30.74 g, 0.1 mol) in THF (75 mL) was added over 35 min, maintaining the temperature at −75 to −78 °C. The reaction mixture was stirred for 40 min, then a second portion of *n*-butyllithium (280 mL of a 2.5-M solution in hexane, 0.7 mol) was added over 25 min, keeping the internal temperature below −70 °C. The dark reaction mixture was stirred for 5 min at −71 to −77 °C, then *t*-butyl acetate (81.3 g, 0.700 mol) was added over 25 min, maintaining the temperature at −76 to −78 °C. The dark reaction mixture was stirred for 1 h at this temperature. The temperature was then increased to 0-2 °C over 15 min, and the solution was stirred at 0-1 °C for 1.5 h.

A separate 5-L, 4-necked, round-bottomed separatory funnel, equipped with mechanical stirrer and thermometer, was charged with 37% hydrochloric acid solution (300 mL), ice water (1.0 kg), and ethyl acetate (200 mL). To this rapidly stirred mixture was added the contents of the first flask over 20 min, keeping the temperature ≤5 °C. The temperature was moderated during this procedure by addition of ice (200 g). The reaction mixture was stirred vigorously for an additional 10 min, and the pH was adjusted to pH 5 using 2 N HCl. The layers were separated, and the upper organic layer was washed with saturated aqueous NaCl solution (1 x 500 mL, 1 x 350 mL). The combined aqueous phases were washed with ethyl acetate (400 mL). After separation of layers, the organic layer was washed with saturated aqueous NaCl solution (150 mL). The combined organic layers were evaporated under reduced pressure to give a yellow suspension, which was then co-evaporated with toluene (200 mL) under reduced pressure. Ethyl acetate (300 mL) was then added, and the yellow suspension was stirred at room temperature for 30 min. The solids were filtered and washed with ethyl acetate (2 x 50 mL). [The solids may be dried at high vacuum and 50 °C to recover slightly yellow 2-(*S*)-acetoxy-1,1,2-triphenylethanol.]

The resulting clear dark solution was evaporated under reduced pressure (200 to 30 mbar, 50 °C) to yield a dark oil (91.5 g). To this was added heptane (125 mL) and isopropanol (25 mL), and the resulting solution was cooled to −12 to −15 °C and kept for 2 h. The solids were filtered, and the filter cake was washed with cold (0 °C) 9:1 heptane/isopropanol (2 x 50 mL). The solids were dried under vacuum at 50 °C for 4 h to give the crude product (a mixture of **10** and triphenylglycol[10]) as a yellow powder (30.6 g) assayed at 49.6% purity for **10**. A second crop (9.6 g, 35.4% purity) brought the total yield to 40%. The following characterization was performed on **10** purified by column chromatography on silica (30-40% ethyl acetate in hexane). In practice this mixture was used as such in the following step. $[\alpha]_D$ −7.0 (*c* 0.8, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.65 (d, 6H, *J* = 7.0 Hz), 2.66 (dd, 2H, *J* = 2.4, 6.0 Hz), 3.08 (d, 1H, *J* = 3.8 Hz), 3.36 (s, 2H), 4.68 (br m, 1H), 4.82 (ddd, 1H, *J* = 7.0 Hz), 5.67 (dd, 1H, *J* = 5.2, 16.0 Hz), 6.73 (dd, 1H, *J* = 1.6, 16.0 Hz), 7.15 (overlapping m, 4H), 7.40 (dd, 2H, *J* = 5.6, 8.8 Hz), 7.54 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.1, 21.0, 21.7, 27.9, 47.7, 48.7, 51.0, 68.0, 82.4, 111.6, 114.6, 115.2 (d, *J* = 21 Hz), 119.0, 119.3, 119.6,

121.7, 128.2, 131.5, 131.8, 131.9, 134.9, 136.9, 164.5 (d, J = 218 Hz), 203.4; IR (KBr) 3443, 2979, 2934, 1733, 1713, 1546, 1501, 1458, 1369, 1221, 1155, 841, 743, 566 cm^{-1}; FABHRMS (NBA-NaI) *m/e* 488.2230 (M^+ + Na, $C_{28}H_{32}FNO_4Na$ requires 488.2213).

[*R*-[(*R,*S**)-(*E*)]-7-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid 1,1-dimethylethyl ester (11):** A 500-mL, four-necked, round-bottomed flask equipped with a mechanical stirrer, addition funnel, and thermometer was charged with THF and cooled to −78 °C. Over 3 min, sodium borohydride (2.42 g, 64.0 mmol) was added, and the suspension was stirred for 5 min before the addition of diethylmethoxyborane (9.6 g, 48 mmol of a 50% solution in THF, 4.09 M) over 15 min. After stirring an additional 15 min, a solution of **10** (30.0 g, 49.6% purity, 32.0 mmol) in THF (43 mL) and MeOH (50 mL) was added over 45 min, maintaining the temperature of the reaction mixture below −75 °C. The reaction mixture was stirred an additional 45 min. A separate 5-L, 4-necked, round-bottomed separatory flask equipped with mechanical stirrer and thermometer was charged with saturated aqueous $NaHCO_3$ solution (150 mL) and ethyl acetate (150 mL). To this rapidly stirred mixture was added the contents of the first reactor over a period of 10 min. Water (150 mL) was added to dissolve precipitated salts. The upper organic layer was washed with brine (200 mL), then evaporated down to a brown oil, which was dissolved in ethyl acetate (200 mL). To this solution was slowly added hydrogen peroxide (21.67 g, 192 mmol of a 30% w/w solution in water), keeping the temperature below 30 °C. The dark, clear solution was stirred for 15 h at room temperature, before the addition of brine (150 mL). The separated organic phase was shaken with a 10% aq. solution of sodium sulfite (150 mL) until it tested negative for peroxides (peroxide test paper) at which point it was shaken again with brine (100 mL). The organic layer was evaporated to a brown oil which solidified on standing. This solid was transferred to a 250-mL, 4-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer, and condenser, and dissolved under reflux in acetonitrile (100 mL). After heating for 5 min, water (10 mL) was added, and heating was continued for 5 min. The solution was cooled to room temperature over 90 min, and the resulting suspension was stirred for 3.5 h. The solids were filtered and washed with 9:1 acetonitrile/water (3 x 25 mL) to yield a semi-dry white solid (19.3 g). This material was transferred to a similar flask and recrystallized as above from acetonitrile (80 mL) and water (8 mL). The resulting white solid was dried (50 °C, 10 mbar) for 6 h, giving the pure **11** as a white powder (10.5 g, 22.5 mmol, 70%).

The *syn/anti* ratio was determined by HPLC on a 150 x 4.6 mm stainless steel column packed with ZORBAX® silica, 5 μm particles, 70 Å pore size (e.g., MAC-MOD Analytical, Inc.); run time 20 min; flow rate 1.5 mL/min; λ = 305 nm; injection volume 15 μL; mobile phase hexane/ 2-propanol 97:3 (v/v); retention times 7.2 min (*anti*), 9.6 min (*syn*).

The ee of the *syn*-diol ester was determined by HPLC on a 250 x 4.6 mm stainless steel column packed with CHIRALCEL® OD [cellulose tris(3,5-dimethylbenzene carbamate) coated on silica gel], 10 μm particles (e.g., Chiral Technologies, Inc.); run time 20 min; flow rate 1.0 mL/min; λ = 305 nm; injection volume 10 μL; mobile phase hexane/ 2-propanol 90:10 (v/v); retention times 6.98 min (3*R*,5*S*), 13.25 min (3*S*,5*R*).

mp 141-143 °C; $[\alpha]_D$ −3.0 (*c* 1, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.60 (m, 2H), 1.66 (dd, 6H, J = 1.6, 7.0 Hz), 2.39 (dd, 2H, J = 6.1 Hz), 3.75 (br s, 1H), 3.87 (br s, 1H), 4.19 (m, 1H), 4.49 (m, 1H), 4.87 (ddd, 1H, J = 7.0 Hz), 3.69 (d, 1H, J = 5.4, 16.0 Hz), 6.70 (dd, 1H, J = 1.5, 16.0 Hz), 7.09 (m, 3H), 7.19

(m, 1H), 7.39 (m, 2H), 7.54 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 21.7, 28.0, 42.1, 47.6, 50.8, 68.6, 72.2, 81.7, 111.6, 114.3, 115.1 (d, J = 21 Hz), 118.1, 119.3, 119.5, 121.6, 128.3, 131.6, 131.9, 133.7, 134.9, 138.8, 161.4 (d, J =218 Hz), 172.1; IR (KBr) 3468, 3458, 3391, 2979, 1707, 1535, 1501, 1458, 1421, 1391, 1369, 1345, 1305, 1258, 1216, 1155, 1118, 1105, 839, 743, 564 cm^{-1}.

[*R*-[(*R,*S**)-(*E*)]-7-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt (12):** The dihydroxyester **11** (19.22 g, 41.10 mmol) was added to a 250-mL, 4-necked, round-bottomed flask equipped with a stirrer, addition funnel, and thermometer, and dissolved in 200-proof ethanol (95 mL). A solution of sodium hydroxide (1.58 g, 39.5 mmol) in water (33 mL) was added over 5 min while maintaining the temperature at 25 °C. The suspension was stirred for 1.5 h. The reaction mixture was then filtered, and diluted with water (120 mL) and MTBE (20 mL). The lower aqueous phase was washed with MTBE (75 mL), then concentrated under reduced pressure to a volume of about 100 mL. The heterogeneous mixture was then lyophilized to obtain the sodium salt **12** as a pale yellow powder (15.4 g, 35.5 mmol, 90%).

The *syn/anti* ratio of the sodium salt was determined by HPLC on a 50 x 4.6 mm Hypersil ODS column, 5 μm particles (e.g., Keystone Scientific, Inc.); mobile phase A: acetonitrile/methanol/water (4/6/90) with 0.5% (w/v) tetramethylammonium phosphate, pH 7.2; mobile phase B: acetonitrile/methanol/water (36/54/10) with 0.5% (w/v) tetramethylammonium phosphate, pH 7.2. Gradient: 0.0 min: 60% A, 40% B; 6.0 min: 60% A, 40% B; 20.0 min: 18% A, 82% B; 20.1 min: 60% A, 40% B. Reequilibration time 5 min; flow rate 3.0 mL/min; λ= 305 nm + 365 nm + 222 nm; column temperature 35 °C; injection volume 20 μL; retention times 4.8 min (*syn*), 5.8 min (*anti*).

The ee of the sodium salt was determined by CE on a Beckman P/ACE 5000 Series Capillary Electrophoresis System equipped with a fused silica capillary, 75 μm ID x 365 μm OD x 60 cm effective separation length (e.g., Polymicro Technologies, Inc.). Separation electrolyte 90% [75 mM sodium borate, pH 9.0; 25 mM sodium phosphate dibasic, pH 9.0; 50 mM SDS and 15 mM γ-cyclodextrin], 10% acetonitrile; λ= 214 nm; injection 5 s pressure (0.5 psi); run voltage 23.45 kV (350 V/cm); run time 50 min; polarity positive; capillary temperature 20 °C; migration times 41.9 min (3*R*,5*S*), 41.2 min (3*S*,5*R*).

$[\alpha]_D$ +26.3 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (300 MHz, CD_3OD) δ 1.52 (m, 1H), 1.65 (d, 6H, J = 7.0 Hz), 1.73 (m, 1H), 2.27 (dd, 1H, J = 7.7, 15.2 Hz), 2.35 (dd, 1H, J = 4.9, 15.2 Hz), 3.96 (m, 1H), 4.38 (m, 1H), 4.90 (m, 1H), 5.72 (dd, 1H, J = 6.5, 16.1 Hz), 6.70 (dd, 1H, J = 1.1, 16.1 Hz), 7.01 (m, 1H), 7.13 (m, 3H), 7.43 (m, 3H), 7.57 (m, 1H, J= 8.3 Hz); ^{13}C NMR (75 MHz, CD_3OD) 21.8, 44.7, 45.1, 68.4, 71.7, 112.6, 115.4, 115.9, 116.1, 119.7, 120.0, 120.5, 122.6, 133.0, 133.1, 133.2, 134.8, 136.4, 140.8, 162.6 (d, J = 244 Hz), 180.4; IR (KBr) 3407, 1573, 1346, 1216, 1107 cm^{-1}; Anal. calcd for $C_{24}H_{25}FNO_4Na$: C, 63.9; H, 6.0; N, 3.1. Found: C, 63.9; H, 5.4; N, 2.6.

[(*R*)-(*E*)]-7-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3-hydroxy-5-oxo-6-heptenoic acid 1,1-dimethylethyl ester (13): The dihydroxyester **11** (5.4 g, 12 mmol) was stirred with DDQ (5.8 g, 26 mmol) in THF (375 mL) at room temperature. The color of the solution changed from brown to green upon DDQ addition. The solution was allowed to stir overnight before addition of saturated aqueous $NaHCO_3$ (100 mL) and ethyl acetate (100 mL). The organic layers were shaken again with saturated aqueous $NaHCO_3$ and then with brine, followed by drying ($MgSO_4$) and evaporation to a red oil. Column chromatography on silica using 30-50% ethyl acetate in hexane gave the pure ketohydroxyester **13** as an orange oil (3.9 g, 8.4 mmol, 70%).

$[\alpha]_D$ +16.7 (*c* 0.9, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.68 (d, 6H, *J* = 7.0 Hz), 2.44 (d, 2H, *J* = 6.4 Hz), 2.69 (dd, 2H, *J* = 3.3, 7.2 Hz), 3.56 (d, 1H, *J* = 3.6 Hz), 4.45 (br m, 1H), 4.94 (ddd, 1H, *J* = 7.0 Hz), 6.29 (d, 1H, *J* =16.1 Hz), 7.15 (m, 3H), 7.28 (m, 1H), 7.37 (m, 2H), 7.55 (m, 2H), 7.74 (d, 1H, *J* = 16.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 21.8, 28.1, 41.7, 46.9, 47.9, 64.8, 81.2, 112.1, 115.7 (d, *J* = 21 Hz), 120.3, 120.6, 121.1, 124.0, 127.6, 128.3, 130.6, 131.8, 131.9, 136.9, 160.4, 171.3, 198.4; IR (KBr) 3438, 2978, 2934, 1726, 1592, 1540, 1457, 1368, 1222, 1156, 840, 744 $^{-1}$; FABHRMS (NBA-NaI) *m/e* 488.2200 (M^+ + Na, $C_{28}H_{32}FNO_4Na$ requires 488.2213).

[*R*-[(*R*R)-(*E*)]-7-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid 1,1-dimethylethyl ester (14):** Tetramethylammonium triacetoxyborohydride (11.5 g, 43.7 mmol) was stirred in acetonitrile (30 mL) and acetic acid (30 mL) at room temperature for 2 h. The solution was cooled to −20 °C, and the (*R*)-ketohydroxyester **13** (2.9 g, 6.2 mmol) was added dropwise as a solution in acetonitrile (35 mL) and acetic acid (10 mL). The solution was stirred at −15 to −20 °C for 2 h, then diluted with saturated aqueous $NaHCO_3$ and ethyl acetate. The orange organic layer was washed twice with saturated aqueous $NaHCO_3$ and once with brine, then dried ($MgSO_4$) and evaporated to a dark oil. Column chromatography on silica using 30-60% ethyl acetate in hexane gave the dihydroxyester **14** as an orange oil which gradually solidified (2.4 g, 5.1 mmol, 82%). The initial ratio of (3*R*,5*R*):(3*R*,5*S*) diastereomers was shown to be 90:10 by HPLC. Upon recrystallization from ethyl acetate/hexane, the ratio was improved to >99:1; mp 95-98 °C; $[\alpha]_D$ +17.4 (*c* 0.9, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 9H), 1.66 (d, 6H, *J* = 7.0 Hz), 2.30 (dd, 1H, *J* = 3.4, 16.8 Hz), 2.41 (dd, 1H, *J* = 9.0, 16.8 Hz), 3.36 (d, 1H, *J* = 6.1 Hz), 3.74 (d, 1H, *J* = 2.2 Hz), 4.12 (m, 1H), 4.51 (br m, 1H), 4.87 (ddd, 1H, *J* = 7.0 Hz), 5.75 (dd, 1H, *J* = 4.9, 15.9 Hz), 6.75 (dd, 1H, *J* = 1.7, 15.9 Hz), 7.08 (m, 3H), 7.20 (m, 1H), 7.43 (m, 2H), 7.52 (t, 2H, *J* = 8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 21.7, 28.0, 41.1, 41.8, 47.7, 65.8, 69.8, 81.7, 111.5, 114.2, 115.1 (d, *J* = 21 Hz), 118.4, 119.3, 119.5, 121.6, 128.4, 131.7, 131.9, 133.9, 134.9, 139.5, 161.5 (d, *J*= 218 Hz), 172.3; IR (KBr) 3438, 2978, 2935, 1716, 1501, 1458, 1369, 1220, 1155, 839, 743, 565 cm^{-1}; FABHRMS (NBA-NaI) *m/e* 490.2361 (M^+ + Na, $C_{28}H_{34}FNO_4Na$ requires 490.2370).

[*R*-[(*R*R)-(*E*)]-7-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt (15):** The dihydroxyester **14** (0.8330 g, 1.782 mmol) was dissolved in THF (5 mL) and aqueous NaOH solution (1.7 mL, 1.8 mmol of a 1.066-M solution) at room temperature, and stirred overnight. Methanol (7 mL) was added, and the solution was evaporated to dryness. The solids were dissolved in water (20 mL), and this solution was washed with MTBE (3 x 20 mL). The aqueous layer was freeze-dried, giving the sodium salt **15** as a pale yellow solid (0.4125 g, 0.9517 mmol, 53%). $[\alpha]_D$ +2.9 (*c* 1, MeOH); ^1H NMR (300 MHz, DMSO-d_6) δ 1.35 (m, 2H), 1.59 (d, 6H, *J* = 7.0 Hz), 1.88 (dd, 1H, *J* = 8.9, 15.1 Hz), 2.06 (dd, 1H, *J* = 3.4, 15.1 Hz), 3.69 (m, 1H), 3.83 (m, 1H), 4.29 (br m, 1H), 4.92 (ddd, 1H, *J* = 7.0 Hz), 5.10 (br s, 1H), 5.77 (dd, 1H, *J* = 5.1, 16.1 Hz), 6.62 (dd, 1H, *J* = 1.2, 16.1 Hz), 7.02 (t, 1H, *J* = 8.7 Hz), 7.14 (t, 1H, *J* = 8.3 Hz), 7.25 (t, 2H, *J* = 8.9 Hz), 7.49 (m, 3H), 7.65 (d, 1H, *J* = 8.3 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) 21.7, 44.2, 44.9, 47.4, 65.1, 68.0, 112.3, 113.0, 115.6 (d, *J* = 21 Hz), 116.5, 118.9, 119.8, 121. 8, 127.9, 131.9, 134.6, 135.0, 143.0, 159.3, 160.7 (d, *J* = 218 Hz), 177.0; IR (KBr) 3428, 2974, 2935, 1577, 1500, 1457, 1403, 1346, 1219, 1156, 838, 741, 565 cm^{-1}; FABHRMS (NBA-NaI) *m/e* 456.1555 (M^+ + Na, $C_{24}H_{25}FNO_4Na$ requires 456.1563).

[*S*-[(*R*R**)-(*E*)]-7-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid 1,1-dimethylethyl ester (16):** Prepared from **10** using the representative procedure shown for **14**; $[\alpha]_D$ −24.5 (*c* 0.7, CH_2Cl_2).

[*S*-[(*R*R**)-(E)]-7-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt (17):** Prepared according to the procedure shown for **12**; $[\alpha]_D$ −0.34 (*c* 1.2, MeOH).

[(*S*)-(*E*)]-7-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3-hydroxy-5-oxo-6-heptenoic acid 1,1-dimethylethyl ester (18): Prepared using the procedure shown for **13**. $[\alpha]_D$ −15.6 (*c* 1.2, CH_2Cl_2).

[*S*-[(*R*S**)-(*E*)]-7-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid 1,1-dimethylethyl ester (19):** Sodium borohydride (142.5 mg, 3.767 mmol) was added to a mixture of THF (8 mL) and MeOH (2 mL) at −78 °C in a nitrogen-purged flask. Diethylmethoxyborane (50% w/w solution in THF, 4.09 M, 0.440 mL, 1.80 mmol) was added dropwise by addition funnel and stirred for 15 min. The ketohydroxyester **18** (0.80 g, 1.7 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 aqueous $NaHCO_3$ solution (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 ($MgSO_4$) and evaporated. The residue was co-evaporated with methanol three times for hydrolysis of the boronate. The *syn/anti* ratio of the resulting dihydroxyester was >99/1, by HPLC. Column chromatography on silica gel gave the pure dihydroxyester **19** (0.65 g, 1.4 mmol, 82%). $[\alpha]_D$ +2.8 (*c* 1, CH_2Cl_2).

[*S*-[(*R*S**)-(*E*)]-7-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, sodium salt (20):** Prepared from **19** following the procedure shown for **12**. $[\alpha]_D$ −21.3 (*c* 0.8, CH_2Cl_2).

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10. The optically pure triphenylglycol which is the by-product in this reaction was recovered as the acetyl derivative by treating the mother liquors with acetyl chloride and reused

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