Inhibitors of Cholesterol Biosynthesis. 2. 3,5-Dihydroxy-7-(*N*-pyrrolyl)-6-heptenoates, a Novel Series of HMG-CoA Reductase Inhibitors

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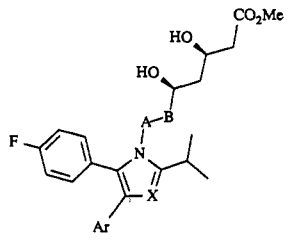
A series of 7-[2,3-diaryl-5-(1-methylethyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxy-6-heptenoates was prepared and evaluated for its ability to inhibit the enzyme HMG-CoA reductase *in vitro*. Maintaining a 5-(1-methylethyl) substituent found to be optimal in related studies, structure–activity relationships were established for compounds modified at positions 2, 3, and 4 of the pyrrole ring. The 4-fluorophenyl group was preferred at the pyrrole 2-position, while incorporation of a range of substituted phenyl groups and pyridyl substituents at the 3-position provided compounds with equivalent enzyme inhibitory activities and widely different lipophilicities. Pentasubstituted pyrrole **3h** was found to have a 10-fold greater potency than lovastatin.

In the preceding paper,[1] we described a series of novel tetrasubstituted imidazole 3,5-dihydroxy-6-heptenoic (**1**) and heptanoic (**2**) acid derivatives as highly potent inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. From the structure–activity relationships (SAR) derived for these series of compounds, heptenoates were shown to be more potent than the corresponding heptanoates. In particular, heptenoates having imidazoles incorporating the preferred 2-(1-methylethyl) substituent were shown to be more potent than the corresponding heptanoates by a factor of >150.

In our continued studies toward novel potent inhibitors of HMG-CoA reductase, we were interested in examining the effect of replacing the imidazole ring with less basic heterocycles. *N*-linked pyrrole 3,5-dihydroxyheptanoates have recently been reported.[2] This paper describes the synthesis and biological activity of a series of 3,5-dihydroxy-7-(*N*-pyrrolyl)-6-heptenoates.

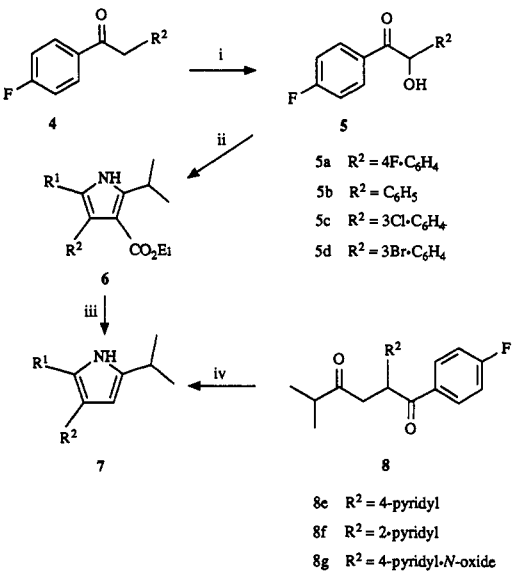


	A—B	X
1	(*E*) CH=CH	N
2	CH_2CH_2	N
3	(*E*) CH=CH	CH

Chemistry

Hydroxylation of the 4-fluorophenyl ketones **4** provided benzoins **5**, cyclocondensation of which with ethyl isobutyrylacetate in the presence of ammonium acetate in refluxing acetic acid gave 4,5-diarylpyrrole-3-carboxylate esters **6**.[3] When utilizing unsymmetrical benzoins **5**, both 5- and 4-(4-fluorophenyl)pyrroles **6** were formed, in an approximate ratio of 9:1 by NMR or GC; the major component was ascribed to the expected 5-(4-fluorophenyl) regioisomer.[4] Subsequent steps employed the mixture of isomers which were separated at the penultimate stage in the synthesis, at which point their regiochemical integrity was confirmed (*vide infra*). Decarboxylation of **6** by sulfuric acid gave the trisubstituted pyrrole **7** (Scheme I).

Scheme I[a]



4 **5**

5a $R^2 = 4F\text{-}C_6H_4$
5b $R^2 = C_6H_5$
5c $R^2 = 3Cl\text{-}C_6H_4$
5d $R^2 = 3Br\text{-}C_6H_4$

6 **7** **8**

8e R^2 = 4-pyridyl
8f R^2 = 2-pyridyl
8g R^2 = 4-pyridyl-*N*-oxide

[a](i) $NaN(TMS)_2$, THF; TMS-Cl; *m*-CPBA; H_3O^+; (ii) NH_4OAc, $^iPrCOCH_2CO_2Et$, AcOH, reflux; (iii) 80% H_2SO_4; (iv) NH_4OAc, AcOH, reflux.

Alternatively, 2-(4-fluorophenyl)pyrroles **7** were prepared free of the 3-(4-fluorophenyl) regioisomer by the Paal–Knorr synthesis using the appropriate 1,4-diketone **8**[2b] and ammonium acetate (Scheme I).

Pyrroles **7** were deprotonated by sodium hydride and reacted with methyl propiolate to give the (*N*-pyrrolyl) β-acrylate esters **9** as mixtures of geometrical isomers (Scheme II). Prior to undertaking a similar alkylation of the 3-[(4-pyridyl)pyrrole] **7e**, the pyridine nitrogen was protected as the *N*-oxide, by reacting **8e** with *m*-chloroperbenzoic acid, in order to avoid competitive side-reactions involving the pyridine ring. Protection of the pyridine

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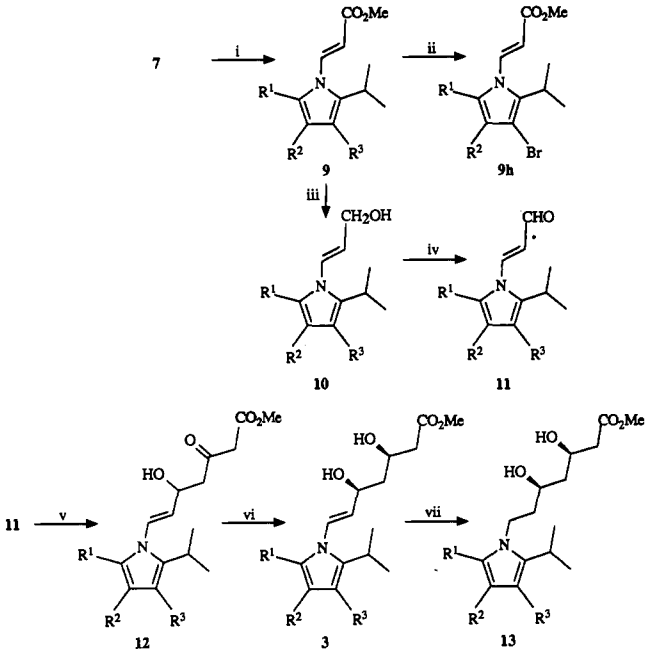
Scheme II[a]



[a](i) NaH, DMF; $HC{\equiv}CCO_2Me$; (ii) NBS, DMF; (iii) DIBAL-H, PhMe; (iv) MnO_2, CH_2Cl_2; (v) $CH_3COCH_2CO_2Me$, NaH, *n*-BuLi, THF; (vi) Et_3B, MeOH, THF; $NaBH_4$; (vii) PtO_2, H_2, EtOH.

nitrogen of the 3-[(2-pyridyl)pyrrole] **7f** was not necessary as the alkylation proceeded smoothly on the pyrrole nitrogen.

Bromination of **9a** with *N*-bromosuccinimide[5] in DMF gave the pentasubstituted pyrrole **9h**.

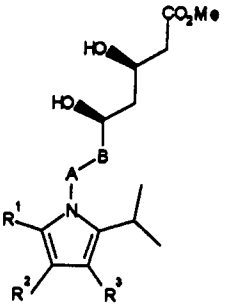
Diisobutylaluminum hydride (DIBAL-H) reduction of acrylates **9** gave the allylic alcohols **10**. Reduction of acrylate **9g** was achieved with concomitant reduction of the pyridine *N*-oxide. Oxidation of the allylic alcohols **10** with excess manganese dioxide gave the (*N*-pyrrolyl)-acroleins **11** as mixtures of geometrical isomers, which were readily separated by column chromatography. Furthermore, the *Z*-isomers were readily converted into the *E*-isomers using a catalytic amount of iodine in refluxing carbon tetrachloride.

Condensation of acroleins **11** with the dianion of methyl acetoacetate afforded the corresponding ketoalcohols **12** which were complexed with methoxydiethylborane and reduced with sodium borohydride in tetrahydrofuran–MeOH[6] at −73 °C to give the *syn*-3,5-diols **3** with excellent stereoselectivity (*syn*:*anti* ratio >20:1). In the three cases where regioisomeric mixtures of the 2,3-diarylpyrroles **7b**, **7c**, and **7d** were brought through the linear synthetic route, the derived regioisomeric diol esters were readily separated on a Zorbax-NH_2 column by normal phase HPLC, thereby providing 7-[3-aryl-2-(4-fluorophenyl)pyrrolyl]heptenoate **3** (R^1 = 4-fluorophenyl) and 7-[2-aryl-3-(4-fluorophenyl)-pyrrolyl]heptenoate **3** (R^2 =4-fluorophenyl) analogues. Their constitution was determined by NMR spectroscopy. It was observed that for the three pairs of regioisomers **3b–3l**, **3c–3j**, and **3d–3k**, the chemical shift of the triplet due to the 3- and 5-protons of the 4-fluorophenyl ring appeared in the range of 6.94–7.04 ppm for the major isomer and 6.80–6.89 ppm for the minor regioisomer. For any particular pair, the major isomer's triplet appeared 0.14 ppm downfield relative to that for the minor isomer. The triplet due to the same protons of 2-(4-fluorophenyl)-pyrroles **3e** and **3f** which were prepared by an unambiguous route appeared at 7.06 ppm. Therefore, the major isomers had the 4-fluorophenyl ring attached at the 2-position of the pyrrole ring. Moreover, irradiation of the 2- and 6-protons of the 4-fluorophenyl ring of the major isomers gave an NOE enhancement at the olefinic protons, whereas irradiation of the 2- and 6-protons of the other aryl ring had no effect, thus confirming that the major isomers were the 2-(4-fluorophenyl) substituted pyrroles.

The (*N*-pyrrolyl)heptanoate **13** was obtained by catalytic hydrogenation of the corresponding heptenoate **3a**.

The stability of the sodium salts of heptenoates **3** at 37 °C in pH 2 buffer was examined by TLC; only after 4 days were significant amounts of the parent pyrroles observed, indicating hydrolysis of the heptenoates. The carbon–carbon double bond of the heptenoate chain in the (*N*-imidazolyl)heptenoates **1** has been shown by X-ray crystallographic studies[1] to be substantially out of the plane of the imidazole ring; by analogy, the remarkable stability of the (*N*-pyrrolyl)heptenoates **3** is thought to arise through a similar lack of conjugation of the double bond with the pyrrole ring.

Table I. In Vitro HMG-CoA Reductase Activity[a] and log *D* Values



compd no.	A–B	R^1	R^2	R^3	IC_{50} (nM)	log *D*
3a	CH=CH	4F-C_6H_4	4F-C_6H_4	H	2	2.10
3b	CH=CH	4F-C_6H_4	C_6H_5	H	2	
3c	CH=CH	4F-C_6H_4	3Cl-C_6H_4	H	2	2.57
3d	CH=CH	4F-C_6H_4	3Br-C_6H_4	H	0.5	2.80
3e	CH=CH	4F-C_6H_4	4-pyridyl	H	5	0.90
3f	CH=CH	4F-C_6H_4	2-pyridyl	H	2	
3h	CH=CH	4F-C_6H_4	4F-C_6H_4	Br	0.3	
3i	CH=CH	C_6H_5	4F-C_6H_4	H	25	
3j	CH=CH	3Cl-C_6H_4	4F-C_6H_4	H	71	
3k	CH=CH	3Br-C_6H_4	4F-C_6H_4	H	69	
13	CH_2CH_2	4F-C_6H_4	4F-C_6H_4	H	105	
lovastatin					3	
pravastatin					5	

[a] All compounds in this table were tested after being converted to the sodium salts of the corresponding dihydroxy carboxylic acids. IC_{50} values were determined at least on two different occasions with five dose levels of each inhibitor at least in duplicate and are expressed as mean values, using pravastatin sodium salt as a reference. The variation for pravastatin was ±5%, and that for the inhibitors ±15%.

Biological Results and Discussion

The methyl esters listed in Table I were converted to the corresponding sodium salts and evaluated for their ability to inhibit rat liver microsomal HMG-CoA reductase. This assay procedure measured the direct conversion of DL-3-hydroxy-3-methyl[3-^{14}C]glutaryl-CoA to [^{14}C]mevalonolactone. The enzyme preparation and assay procedures used in this study were the same as those described in the preceding paper. The data in Table I clearly indicate that the heptenoate **3a** is more potent than the heptanoate **13**.

The 5-(1-methylethyl) substituent was found to afford optimum potency in our analogous imidazole series, and

it was therefore retained in the present study. The 4-fluorophenyl group is preferred at the 2-position of the pyrrole ring (cf. **3b**, **3c**, and **3d** with **3i**, **3j**, and **3k**) supporting our findings in the 7-(*N*-imidazolyl)heptenoate series[1] and also confirming the SAR reported for the related 7-(*N*-pyrrolyl)heptanoate series.[2] Incorporation of a range of substituted phenyl groups and pyridyl substituents at the pyrrole 3-position provided compounds with equivalent enzyme inhibitory activities and widely different lipophilicities (log*D* in the range of 0.9–2.8).

Interestingly, when a suitable substitution is made at the pyrrole 4-position as in the bromopyrrole **3h**, the inhibitory activity is increased providing the most potent compound in this study with an activity 10-fold greater than that of lovastatin, the potent hypocholesterolemic fungal metabolite in clinical use.

Heptenoate **3d** was tested for its ability to inhibit cholesterol biosynthesis in cultures of hepatic cells (HEP G2, a human hepatoma cell line), as determined by the inhibition of the incorporation of sodium [^{14}C]acetate into cholesterol. Racemic **3d** possessed an IC_{50} of 0.3 nM and was 23-fold more active than lovastatin sodium salt (IC_{50} 7 nM).

Conclusion

A series of 7-(*N*-pyrrolyl)heptenoates was prepared and evaluated for its ability to inhibit the enzyme HMG-CoA reductase *in vitro*. By focusing on compounds having the 5-(1-methylethyl) substituent found to be optimal in previous studies, several compounds were identified that were equipotent or more potent than lovastatin.

The remarkable acid stability of the 7-(1*H*-pyrrol-1-yl)heptenoates **3** is in marked contrast to that of the analogous 7-(1*H*-pyrrol-3-yl)heptenoates.[7] The instability of the latter series is thought to arise by protolytic removal of the 5-hydroxy group which leads to a cation that is highly conjugated with the pyrrole nitrogen.[6] The chemical stability of the (*N*-imidazolyl)heptenoates **1** and (*N*-pyrrolyl)heptenoates **3** is closely similar. The presence, however, in the pyrrole series of an additional position available for substitution resulted in inhibitors with enhanced potency. The *in vivo* evaluation of these compounds will be reported elsewhere.

Experimental Section

Tetrahydrofuran (THF) was distilled from sodium and benzophenone. Organic solutions were dried over $MgSO_4$, and column chromatography was performed on silica gel 60 (Merck, Art no. 7734 or 9385). Mp's were determined on a Reichert apparatus and are uncorrected. IR spectra were recorded on a Nicolet 5SXC FTIR spectrophotometer. NMR spectra were recorded on a Bruker AM 250 or Varian VXR 400 spectrometers. Chemical shifts are expressed as parts per million downfield from internal tetramethylsilane. High-resolution CI (ammonia) mass spectrometry was performed on a Kratos Concept 1H, and low-resolution mass spectrometry was performed on a Finnigan MAT 4600. Elemental analyses were determined with a Perkin–Elmer 240C or a Carlo-Erba 1106 elemental analyzer. HPLC analyses were performed on a Varian 5000 HPLC with a UV detector set at 255 nm. GC analyses were performed on a Hewlett Packard 5880 A instrument on a Quadrex MPS-5 15 m × 0.25 mm id column.

2-(3-Bromophenyl)-1-(4-fluorophenyl)-2-hydroxy-1-ethanone (5d). To a THF solution of sodium bis(trimethylsilyl)amide (1 M, 10 mL) at −70 °C under nitrogen was added a solution of 2-(3-bromophenyl)-1-(4-fluorophenyl)-1-ethanone **4d** (2.3 g, 7.85 mmol) in THF (10 mL), and the solution was stirred for 10 min. Chlorotrimethylsilane (2 mL, 15.7 mmol) was added, and the solution was stirred for a further 10 min at −70 °C and then allowed to warm to room temperature over 1 h. The mixture was diluted with cyclohexane, and the organic solution was washed once with aqueous $NaHCO_3$ solution, dried, and evaporated. The residue was diluted with cyclohexane (30 mL) and treated with *m*-chloroperbenzoic acid (50% pure, 3.0 g, 8.69 mmol). An exotherm was observed, a further quantity of cyclohexane was added, and the reaction was stirred at room temperature for 1.5 h. The reaction mixture was filtered and the residue was washed thoroughly with cyclohexane. The filtrate and washings were combined and concentrated, and the residue was dissolved in ether. Aqueous hydrochloric acid solution was added, and the two phase mixture stirred at room temperature for 70 h. The organic layer was washed with aqueous $NaHCO_3$ solution, brine, then dried, and evaporated. The residue was chromatographed on silica gel eluting with ethyl acetate–petroleum (40–60 °C) (1:9) to give **5d** (1.214 g, 50%) as a white solid: NMR ($CDCl_3$) δ 4.53 (d, 1H, J = 7 Hz), 5.87 (d, 1H, J = 7 Hz), 7.10 (t, 2H, J = 9 Hz), 7.23 (t, 1H, J = 7 Hz), 7.26 (d, 1H, J = 7 Hz), 7.42 (d, 1H, J = 7 Hz), 7.49 (s, 1H), 7.95 (dd, 2H, J = 6 and 9 Hz). Anal. ($C_{14}H_{10}BrFO_2$) C, H.

4,5-Bis(4-fluorophenyl)-2-(1-methylethyl)-1*H*-pyrrole-3-carboxylic Acid, Ethyl Ester (6a). A mixture of ethyl isobutyrylacetate (6.95 g, 44 mmol), ammonium acetate (8.95 g, 116 mmol), and 4,4′-difluorobenzoin **5a** (7.04 g, 28 mmol) in acetic acid (70 mL) was heated under reflux for 2 h. The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate. The organic solution was washed with water, saturated aqueous $NaHCO_3$ solution, and brine, dried, and evaporated to dryness. The residue was recrystallized from hot ethanol to give **6a** (7.23 g, 70%) as white crystals: mp 181–184 °C; NMR ($CDCl_3$) δ 1.05 (t, 3H, J = 7 Hz), 1.36 (d, 6H, J = 7 Hz), 3.85 (septet, 1H, J = 7 Hz), 4.08 (q, 2H, J = 7 Hz), 6.88–7.22 (m, 8H), 8.28 (br s, 1H). Anal. ($C_{22}H_{21}F_2NO_2$) C, H, N.

2,3-Bis(4-fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrole (7a). **6a** (9.8 g, 26.5 mmol) was suspended in sulfuric acid (80% v/v, 160 mL) and heated to 110 °C for 15 min. The mixture was allowed to cool, poured into ice–water, and extracted with ether. The organic solution was washed with water, saturated aqueous $NaHCO_3$ solution, and brine, dried, and evaporated to dryness to give **7a** (7.19 g, 91%) as a solid: NMR ($CDCl_3$) δ 1.32 (d, 6H, J = 7 Hz), 2.98 (septet, 1H, J = 7 Hz), 6.09 (d, 1H, J = 3 Hz), 6.94 and 6.99 each (t, 2H, J = 9 Hz), 7.27 (m, 4H), 7.9 (br s, 1H). Anal. ($C_{19}H_{17}F_2N$) C, H, N.

1-(4-Fluorophenyl)-5-methyl-2-(*N*-oxo-4-pyridyl)-1,4-hexanedione (8g). A solution of 1-(4-fluorophenyl)-5-methyl-2-(4-pyridyl)-1,4-hexanedione[2h] (**8e**) (1.2 g, 4 mmol) in $CHCl_3$ (12 mL) was treated with *m*-chloroperbenzoic acid (50% pure, 1.39 g, 4 mmol), and the mixture was stirred at 20 °C for 1.5 h. This was then diluted with $CHCl_3$, washed with aqueous $NaHCO_3$ solution, dried, and chromatographed on silica gel eluting with MeOH-$CHCl_3$ (1:19) to give **8g** (0.774 g, 61%) as a colorless oil: NMR ($CDCl_3$) δ 1.09 and 1.14 (2d, 6H, J = 7 Hz), 2.66 (septet, 1H, J = 7 Hz), 2.85 (dd, 1H, J = 17 and 4 Hz), 3.59 (dd, 1H, J = 17 and 9 Hz), 5.10 (dd, 1H, J = 9 and 4 Hz), 7.12 (t, 2H, J = 9 Hz), 7.22 (d, 2H, J = 7 Hz), 7.99 (dd, 2H, J = 9 and 6 Hz), 8.15 (d, 2H, J = 7 Hz); HRMS (CI) found 315.1280, calculated for $C_{19}H_{18}FNO_3$ 315.1271 (GC purity 97%).

2-(4-Fluorophenyl)-5-(1-methylethyl)-3-(*N*-oxo-4-pyridyl)-1*H*-pyrrole (7g). To a stirring solution of **8g** (0.761 g, 2.41 mmol) in acetic acid (12 mL) was added ammonium acetate (1.86 g, 24 mmol), and the mixture was heated at reflux for 2 h. The solvent was removed under reduced pressure, and the residue was diluted with ethyl acetate and aqueous $NaHCO_3$ solution. Solid sodium carbonate was added until effervescence ceased. The organic phase was washed with aqueous $NaHCO_3$ solution and brine, dried, and evaporated to give **7g** (0.520 g, 73%) as an off-white solid: NMR ($CDCl_3$) δ 1.33 (d, 6H, J = 7 Hz), 2.96 (septet, 1H, J = 7 Hz), 6.12 (d, 1H, J = 2 Hz), 7.06 (t, 2H, J = 9 Hz), 7.15 (d, 2H, J = 7 Hz), 7.32 (dd, 2H, J = 9 and 6 Hz), 7.97 (d, 2H, J = 7 Hz), 8.72 (br s, 1H). Anal. ($C_{16}H_{17}FN_2O\cdot0.25H_2O$) C, H, N.

2-(4-Fluorophenyl)-5-(1-methylethyl)-3-(2-pyridyl)-1*H*-pyrrole (7f). By a similar procedure to that described for **7g** yielded 98% as a brown solid: NMR ($CDCl_3$) δ 1.33 (d, 6H, J = 7 Hz), 2.97 (septet, 1H, J = 7 Hz), 6.44 (d, 1H, J = 2 Hz), 6.97–

7.48 (m, 7H), 8.00 (br s, 1H), 8.56 (d, 1H, J = 6 Hz). Anal. ($C_{18}H_{17}FN_2$) C, H, N.

(*E*)- and (*Z*)-[2,3-Bis(4-fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrol-1-yl]-2-propenoic Acid, Methyl Ester (9a). The pyrrole **7a** (7.07 g, 23.8 mmol) in DMF (35 mL) was added to a suspension of sodium hydride (60% oil dispersion, 0.96 g, 24 mmol) in DMF (30 mL) under nitrogen. After 10 min of stirring, methyl propiolate (19 mL, 213 mmol) was added cautiously, and the mixture was stirred for 1 h at 20 °C. The reaction mixture was diluted with ethyl acetate and brine, and the organic phase was washed thoroughly with brine, dried, and chromatographed on silica gel eluting with CH_2Cl_2–petroleum (40–60 °C) (1:2) to give **9a** (3.78 g, 41%) in a ratio of 2:1 (*E*:*Z*) as a white solid. The two isomers were separable by further careful chromatography to give the *E*-isomer: IR (Nujol) 1721, 1647, 1513, 841 cm^{-1}; NMR ($CDCl_3$) δ 1.37 (d, 6H, J = 7 Hz), 3.17 (septet, 1H, J = 7 Hz), 3.69 (s, 3H), 5.18 (d, 1H, J = 15 Hz), 6.25 (s, 1H), 6.88 (t, 2H, J = 9 Hz), 7.04 (dd, 2H, J = 9 and 6 Hz), 7.08 (t, 2H, J = 9 Hz), 7.22 (dd, 2H, J = 9 and 6 Hz). Anal. ($C_{23}H_{21}F_2NO_2$) C, H, N, F.

Z-Isomer: IR (Nujol) 1723, 1650, 1515, 836 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (d, 6H, J = 7 Hz), 2.87 (septet, 1H, J = 7 Hz), 3.49 (s, 3H), 5.79 (d, 1H, J = 9 Hz), 6.21 (s, 1H), 6.8–7.2 (m, 9H).

3-[3-Bromo-4,5-bis(4-fluorophenyl)-2-(1-methylethyl)-1*H*-pyrrol-1-yl]-2-propenoic Acid, Methyl Ester (9h). Pyrrole **9a** (*E*:*Z*, 3:1) (3.80 g, 9.6 mmol) in DMF (35 mL) was treated with *N*-bromosuccinimide (1.77 g, 9.96 mmol), and the mixture was stirred at 20 °C for 4 h. Further *N*-bromosuccinimide (440 mg, 2.47 mmol) was added, and the mixture was stirred for 15 min. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ solution and brine, dried, and chromatographed on silica gel eluting with ethyl acetate–cyclohexane (1:20) to give **9h** (3.47 g, 76%) in a ratio of 3:1 (*E*:*Z* isomers): NMR ($CDCl_3$) δ 1.42 and 1.48 (2d, 6H, J = 7 Hz), 3.22 and 3.49 (2 septets, 1H, J = 7 Hz), 3.52 and 3.69 (2s, 3H), 5.15 and 5.87 (2d, 1H, J = 15 and 8 Hz), 6.81–7.20 (m, 9H), 7.89 (d, 1H, J = 15 Hz). Anal. ($C_{23}H_{20}BrF_2NO_2$) C, H, N.

(*E*)-3-[2,3-Bis(4-fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrol-1-yl]-2-propenol (10a). Ester **9a** (*E*-isomer) (1.512 g, 3.96 mmol) in toluene (25 mL) was treated at −70 °C with DIBAL-H (1.5 M in toluene, 5.55 mL) under nitrogen. The mixture was stirred at −65 °C for 20 min and then allowed to warm to −5 °C. Water (1.4 mL) was added cautiously, followed by ethyl acetate (50 mL) and solid $NaHCO_3$ (3 g). The mixture was stirred vigorously for 30 min, filtered, and chromatographed on silica gel eluting with CH_2Cl_2 to give **10a** (1.363 g, 97%) as a white solid: IR (Nujol) 3409, 1668, 1514, 843 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (d, 6H, J = 7 Hz), 3.08 (septet, 1H, J = 7 Hz), 4.13 (t, 2H, J = 6 Hz), 5.38 (dt, 1H, J = 14 and 6 Hz), 6.19 (s, 1H), 6.70 (d, 1H, J = 14 Hz), 6.88 (t, 2H, J = 9 Hz), 6.95–7.25 (m, 6H). Anal. ($C_{22}H_{21}F_2NO \cdot 0.25H_2O$) C, H, N, F.

(*E*)-[2,3-Bis(4-fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrol-1-yl]-2-propenal (11a). Allylic alcohol **10a** (1.33 g, 3.76 mmol, as a 6:4 mixture of *E*:*Z* isomers) in CH_2Cl_2 (100 mL) was stirred with manganese(IV) oxide (18.6 g, 214 mmol) at 20 °C for 1 h. The reaction mixture was filtered through kieselguhr, and the filtrate was chromatographed on silica gel eluting with CH_2Cl_2–hexanes (1:1) to give the *Z*-isomer (267 mg, 20%): NMR ($CDCl_3$) δ 1.31 (d, 6H, J = 7 Hz), 2.96 (septet, 1H, J = 7 Hz), 5.83 (t, 1H, J = 8 Hz), 6.27 (s, 1H), 6.85–7.15 (m, 8H), 7.38 (d, 1H, J = 8 Hz), 9.37 (d, 1H, J = 8 Hz). Further elution of the column with neat CH_2Cl_2 gave the *E*-isomer (622 mg, 47%): IR (Nujol) 1676, 1667, 1637, 839 cm^{-1}; NMR ($CDCl_3$) δ 1.39 (d, 6H, J = 7 Hz), 3.18 (septet, 1H, J = 7 Hz), 5.63 (dd, 1H, J = 15 and 8 Hz), 6.34 (s, 1H), 6.90 (t, 2H, J = 9 Hz), 7.0–7.15 (m, 4H), 7.25 (m, 2H), 7.54 (d, 1H, J = 15 Hz), 9.30 (d, 1H, J = 8 Hz). Anal. ($C_{22}H_{19}F_2NO$) C, H, N, F.

The *Z*-isomer (260 mg, 0.74 mmol) and iodine (2 mg) in carbon tetrachloride (30 mL) were stood over a 200W tungsten lamp for 42 h under nitrogen. The solvent was removed under reduced pressure, and the residue was chromatographed to give the *E*-isomer (212 mg, 81%).

(±)-(*E*)-7-[2,3-Bis(4-fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrol-1-yl]-5-hydroxy-3-oxo-6-heptenoic Acid, Methyl Ester (12a). Methyl acetoacetate (0.34 mL, 3.12 mmol) was added dropwise to a suspension of sodium hydride (60% oil dispersion, 291 mg, 7.28 mmol) in THF (3 mL) under nitrogen at 0 °C. After 5 min, *n*-butyllithium (1.6 M in hexanes, 2.11 mL) was added at 2 °C, and the mixture was stirred for 10 min. The aldehyde **11a** (913 mg, 2.6 mmol) in THF (20 mL) was added to the methyl acetoacetate dianion solution at 2 °C. After 15 min, the mixture was allowed to warm to 20 °C and stirred for 30 min. The mixture was then quenched with saturated aqueous NH_4Cl solution (50 mL) and extracted with ethyl acetate. The organic solution was washed with water and brine, dried, chromatographed on silica gel eluting with ethyl acetate–hexanes (1:3) and crystallized from MeOH to give **12a** (990 mg, 81%) as white needles: mp 120–121 °C; IR (Nujol) 3521, 1748, 1714, 1661, 1514, 839 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (d, 6H, J = 6 Hz), 2.58 (m, 2H), 2.70 (d, 1H, J = 4 Hz), 3.04 (septet, 1H, J = 7 Hz), 3.44 (s, 2H), 3.75 (s, 3H), 4.59 (m, 1H), 5.09 (dd, 1H, J = 14 and 6 Hz), 6.17 (s, 1H), 6.77 (d, 1H, J = 14 Hz), 6.87 (t, 2H, J = 9 Hz), 7.0–7.2 (m, 6H). Anal. ($C_{27}H_{27}F_2NO_4$) C, H, N, F.

(±)-*erythro*-(*E*)-7-[2,3-Bis(4-fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxy-6-heptenoic Acid, Methyl Ester (3a). Dry MeOH (4.6 mL) was added to a solution of triethylborane (1 M, 2.5 mL) in THF (12.5 mL) at 20 °C under nitrogen. The mixture was stirred for 1 h at 20 °C and then cooled to −73 °C. The hydroxy keto ester **12a** (923 mg, 1.97 mmol) in THF (18 mL) was added, and the mixture was stirred for 1.3 h at −73 °C. Sodium borohydride (88 mg, 2.32 mmol) was added, and the mixture was stirred at −73 °C for 5 h. The reaction was then quenched with saturated aqueous NH_4Cl solution (20 mL), and the mixture was allowed to warm to 20 °C overnight. The mixture was diluted with water (50 mL) and extracted with ethyl acetate. The extracts were dried and evaporated, and the residue was dissolved in MeOH (20 mL) and evaporated under reduced pressure. The residue was reevaporated with MeOH three more times. The residue was then chromatographed on silica gel eluting with ethyl acetate–hexanes (1:3 and 1:2) and finally crystallized from aqueous MeOH to give **3a** (613 mg, 66%) as white needles: mp 132–133 °C; IR (Nujol) 3475, 1723, 1513, 843 cm^{-1}; NMR ($CDCl_3$) δ 1.31 (d, 6H, J = 7 Hz), 1.35–1.59 (m, 2H), 2.45 (m, 2H), 2.5–3.2 (br, 2H), 3.06 (septet, 1H, J = 7 Hz), 3.74 (s, 3H), 4.15 (m, 1H), 4.40 (m, 1H), 5.14 (dd, 1H, J = 15 and 6 Hz), 6.17 (s, 1H), 6.72 (dd, 1H, J = 15 and 1 Hz), 6.88 (t, 2H, J = 9 Hz), 6.98–7.20 (m, 6H). Anal. ($C_{27}H_{29}F_2NO_4$) C, H, N, F.

(±)-*erythro*-(*E*)-7-[2(3)-(4-Fluorophenyl)-5-(1-methylethyl)-3(2)-phenyl-1*H*-pyrrol-1-yl]-3,5-dihydroxy-6-heptenoic Acid, Methyl Ester (3b and 3i). By a similar procedure to that described for the preparation of **3a**. The regioisomers were separated by HPLC (Zorbax-NH_2 column) eluting with 26% (cyclohexane–CH_2Cl_2–MeOH (75:20:5)): 74% (cyclohexane–CH_2Cl_2 (80:20)) to give **(±)-*erythro*-(*E*)-7-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-1*H*-pyrrol-1-yl]-3,5-dihydroxy-6-heptenoic acid, methyl ester 3b** (80%) as a cream-yellow solid: NMR ($CDCl_3$) δ 1.33 (d, 6H, J = 7 Hz), 1.13–1.52 (m, 2H), 2.46 (d, 2H, J = 7 Hz), 3.07 (septet, 1H, J = 7 Hz), 3.26 and 3.65 each (s, 1H), 3.74 (s, 3H), 4.16 (m, 1H), 4.41 (m, 1H), 5.15 (dd, 1H, J = 15 and 7 Hz), 6.24 (s, 1H), 6.74 (d, 1H, J = 15 Hz), 6.94 (t, 2H, J = 9 Hz), 6.97–7.17 (m, 7H); analytical HPLC (Spherisorb ODS-2 column) 50% CH_3CN–50% 0.05 M aqueous NH_4OAc solution RT = 11.88 min 97.9% pure; MS (CI) m/z 452 $(MH)^+$, 434 $(MH - H_2O)^+$, 416 $(MH - 2H_2O)^+$. Anal. ($C_{27}H_{30}FNO_4 \cdot 0.3H_2O$) C, H, N and **(±)-*erythro*-(*E*)-7-[3-(4-fluorophenyl)-5-(1-methylethyl)-2-phenyl-1*H*-pyrrol-1-yl]-3,5-dihydroxy-6-heptenoic acid, methyl ester 3i** (6%) as a cream-yellow solid: NMR ($CDCl_3$) δ 1.23 (d, 6H, J = 7 Hz), 1.0–1.5 (m, 2H), 2.36 (m, 2H), 3.00 (septet, 1H, J = 7 Hz), 3.49 and 3.57 each (br s, 1H), 3.66 (s, 3H), 4.06 (m, 1H), 4.31 (m, 1H), 5.07 (dd, 1H, J = 15 and 7 Hz), 6.12 (s, 1H), 6.67 (d, 1H, J = 15 Hz), 6.78 (t, 2H, J = 8 Hz), 7.03 (dd, 2H, J = 8 and 7 Hz), 7.10–7.28 (m, 5H); analytical HPLC (Zorbax-NH_2 column) eluting with hexane–CH_2Cl_2–MeOH (80:20:1.5) RT = 12.01 min 99.6% pure; MS (CI) m/z 452 $(MH)^+$, 434 $(MH - H_2O)^+$, 416 $(MH - 2H_2O)^+$.

(±)-*erythro*-(*E*)-7-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3-(4-pyridyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxy-6-heptenoic Acid, Methyl Ester (3e). By a similar procedure to that described for the preparation of **3a** yielded 75% as a white foam: NMR ($CDCl_3$) δ 1.31 (d, 6H, J = 7 Hz), 1.35–1.60 (m, 2H), 2.45 (m, 2H), 3.03 (septet, 1H, J = 7 Hz), 3.73 (s, 3H), 4.15 (m, 1H), 4.40 (m, 1H), 5.22 (dd, 1H, J = 14 and 6 Hz), 6.29 (s, 1H), 6.69 (d, 1H, J = 14 Hz), 7.00 (d, 2H, J = 6 Hz), 7.07 (t, 2H, J = 9 Hz), 7.21 (dd, 2H,

J = 9 and 6 Hz), 8.31 (d, 2H, J = 6 Hz). Anal. ($C_{26}H_{29}FN_2O_4$) H, N, C: Calcd, 69.01; found, 69.46.

(±)-*erythro*-(*E*)-7-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3-(2-pyridyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxy-6-heptenoic Acid, Methyl Ester (3f). By a similar procedure to that described for the preparation of **3a** yielded 83% as a cream-yellow foam: NMR ($CDCl_3$) δ 1.30 (d, 6H, J = 7 Hz), 1.20–1.71 (m, 2H), 2.45 (m, 2H), 3.02 (septet, 1H, J = 7 Hz), 3.72 (s, 3H), 4.13 (m, 1H), 4.38 (m, 1H), 5.18 (dd, 1H, J = 15 and 7 Hz), 6.57 (s, 1H), 6.67 (d, 1H, J = 15 Hz), 6.77 (d, 1H, J = 8 Hz), 6.97 (dd, 1H, J = 8 and 7 Hz), 7.06 (t, 2H, J = 7 Hz), 7.29 (m, 3H), 8.54 (d, 1H, J = 6 Hz); analytical HPLC (Hypersil SAS column) 50% MeOH–50% 0.2 M aqueous $NH_4H_2PO_4$ solution RT = 4.01 min 99.3% pure; HRMS (CI) found 453.2186, calculated for $C_{26}H_{30}FN_2O_4$ 453.2189.

(±)-*erythro*-(*E*)-7-[2(3)-(3-Chlorophenyl)-3(2)-(4-fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxy-6-heptenoic Acid, Methyl Ester (3c and 3j). By a similar procedure to that described for **3a**. The regioisomers were separated by HPLC (Zorbax-NH_2 column) eluting with 44% (cyclohexane–CH_2Cl_2–MeOH (75:20:5)):56% (cyclohexane–CH_2Cl_2 (80:20)) to give **(±)-*erythro*-(*E*)-7-[2-(3-chlorophenyl)-3-(4-fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxy-6-heptenoic acid, methyl ester 3j** (30 mg, 9%) as a gum: NMR ($CDCl_3$) δ 2.48 (d, 2H, J = 6 Hz), 3.07 (septet, 1H, J = 7 Hz), 3.39 (br s, 1H), 3.66 (br s, 1H), 3.74 (s, 3H), 4.18 (m, 1H), 4.44 (m, 1H), 5.12 (dd, 1H, J = 15 and 6 Hz), 6.16 (s, 1H), 6.76 (d, 1H, J = 15 Hz), 6.88 (t, 2H, J = 9 Hz), 7.04–7.25 (m, 6H); analytical HPLC (Zorbax-NH_2 column) eluting with hexane–CH_2Cl_2–MeOH (80:20:1.5) RT = 11.22 min 100% pure; MS (CI) m/z 486 $(MH)^+$, 468 $(MH - H_2O)^+$, 450 $(MH - 2H_2O)^+$ and **(±)-*erythro*-(*E*)-7-[3-(3-chlorophenyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxy-6-heptenoic acid, methyl ester 3c** (179 mg, 54%) as a white crystalline solid: NMR ($CDCl_3$) δ 1.17–1.62 (m, 2H), 1.31 (d, 6H, J = 7 Hz), 2.45 (m, 2H), 3.05 (septet, 1H, J = 7 Hz), 3.39 (br s, 1H), 3.67 (br s, 1H), 3.71 (s, 3H), 4.14 (m, 1H), 4.40 (m, 1H), 5.17 (dd, 1H, J = 14 and 7 Hz), 6.19 (s, 1H), 6.71 (d, 1H, J = 15 Hz), 6.89–7.25 (m, 8H); analytical HPLC (Zorbax-NH_2 column) eluting with hexane–CH_2Cl_2–MeOH (80:20:1.5) RT = 13.25 min 100% pure; MS (CI) m/z 486 $(MH)^+$, 468 $(MH - H_2O)^+$, 450 $(MH - 2H_2O)^+$. Anal. ($C_{27}H_{29}ClFNO_4 \cdot 0.3H_2O$) C, H, N.

(±)-*erythro*-(*E*)-7-[3(2)-(3-Bromophenyl)-2(3)-(4-fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxy-6-heptenoic Acid, Methyl Ester (3d and 3k). By a similar procedure to that described for **3a**. The regioisomers were separated by HPLC (Spherisorb ODS-2 column) eluting with CH_3CN–0.05 M aqueous NH_4OAc solution (3:2) to give **(±)-*erythro*-(*E*)-7-[2-(3-bromophenyl)-3-(4-fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxy-6-heptenoic acid, methyl ester 3k** (7 mg, 3%) as a white solid: NMR ($CDCl_3$) δ 1.31 (d, 6H, J = 7 Hz), 1.35–1.60 (m, 2H), 2.50 (d, 2H, J = 6 Hz), 3.05 (septet, 1H, J = 7 Hz), 3.43 (br s, 1H), 3.65 (br s, 1H), 3.74 (s, 3H), 4.19 (m, 1H), 4.43 (m, 1H), 5.11 (dd, 1H, J = 15 and 7 Hz), 6.15 (s, 1H), 6.75 (d, 1H, J = 15 Hz), 6.89 (t, 2H, J = 9 Hz), 7.05–7.15 (m, 4H), 7.37 (m, 2H); analytical HPLC (Spherisorb ODS-2 column) eluting with 30% 0.05 M aqueous NH_4OAc solution–70% CH_3CN–H_2O (95:5) RT = 3.06 min 97.4% pure; MS (CI) m/z 530 $(MH)^+$, 512 $(MH - H_2O)^+$, 494 $(MH - 2H_2O)^+$ and **(±)-*erythro*-(*E*)-7-[3-(3-bromophenyl)-2-(4-fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxy-6-heptenoic acid, methyl ester 3d** (114 mg, 57%) as a white solid: IR ($CHBr_3$) 3472, 1729, 1667, 843, 782 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (d, 6H, J = 7 Hz), 1.35–1.60 (m, 2H), 2.45 (m, 2H), 3.05 (septet, 1H, J = 7 Hz), 3.33 (br s, 1H), 3.63 (br s, 1H), 3.73 (s, 3H), 4.35 (m, 1H), 4.40 (m, 1H), 5.17 (dd, 1H, J = 14 and 6 Hz), 6.19 (s, 1H), 6.71 (d, 1H, J = 14 Hz), 6.94–7.05 (m, 2H), 7.04 (t, 2H, J = 9 Hz), 7.13–7.25 (m, 3H), 7.34 (s, 1H); analytical HPLC (Spherisorb ODS-2 column) eluting with 30% 0.05 M aqueous NH_4OAc solution-70% CH_3CN–H_2O (95:5) RT = 3.56 min 96.7% pure; MS (CI) m/z 530 $(MH)^+$, 512 $(MH - H_2O)^+$, 494 $(MH - 2H_2O)^+$; HRMS (CI) found 530.1337, calculated for $C_{27}H_{30}BrFNO_4$ 530.1343.

(±)-*erythro*-(*E*)-7-[3-Bromo-4,5-bis(4-fluorophenyl)-2-(1-methylethyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxy-6-heptenoic Acid, Methyl Ester (3h). By a similar procedure to that described for **3a** yielded 76% as a white solid: NMR ($CDCl_3$) δ 1.44 (d, 6H, J = 7 Hz), 2.43 (m, 2H), 3.36 (septet, 1H, J = 7 Hz), 3.48 (br s, 1H), 3.62 (br s, 1H), 3.73 (s, 3H), 4.12 (m, 1H), 4.43 (m, 1H), 5.20 (dd, 1H, J = 14 and 6 Hz), 6.92 (t, 4H, J = 9 Hz), 7.04 and 7.11 each (dd, 2H, J = 9 and 6 Hz). Anal. ($C_{27}H_{28}BrF_2NO_4$) C, H, N.

(±)-*erythro*-7-[2,3-Bis(4-fluorophenyl)-5-(1-methylethyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoic Acid, Methyl Ester (13). **3a** (100 mg, 0.21 mmol) was hydrogenated for 3 h over PtO_2 (100 mg) in MeOH (10 mL). The catalyst was collected by filtration and washed with MeOH. The filtrate was evaporated, and the residue was chromatographed on silica gel eluting with ethyl acetate–hexanes (1:1) to give **13** (46 mg, 46%): NMR ($CDCl_3$) δ 1.33 (d, 6H, J = 7 Hz), 2.40 (d, 2H, J = 6 Hz), 3.03 (septet, 1H, J = 7 Hz), 3.46 and 3.64 each (br s, 1H), 3.70 (s, 3H), 3.8–4.2 (m, 4H), 6.15 (s, 1H), 6.83 (t, 2H, J = 9 Hz), 7.07 (m, 4H), 7.27 (dd, 2H, J = 9 and 6 Hz). Anal. ($C_{27}H_{31}F_2NO_4 \cdot 0.25H_2O$) C, H, N.

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